Journal of Crohn's and Colitis (2010) 4, 493–510

available at www.sciencedirect.com

SPECIAL ARTICLE

European evidenced-based consensus on reproduction in inflammatory bowel disease

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Received 7 July 2010; accepted 12 July 2010

KEYWORDS
Inflammatory bowel disease;
Pregnancy;
Reproduction;
Lactation;
Crohn's disease;
Ulcerative colitis

Contents

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1873-9946/$ - see front matter
doi:10.1016/j.crohns.2010.07.004

1. Introduction

Inflammatory bowel diseases (IBD) typically affect patients in their reproductive years. It has been shown that reproductive issues are of key concern to IBD patients,[1] especially women.[2] In this respect, it is important to note that IBD patients remain voluntary childless more frequently than non-IBD controls.[1,3,4] A recent study reported that IBD patients refrain from having children due the concerns about the adverse reproductive outcome.[1] Fear of side-effects of the medication on the child and medical advice given by physicians, were the most important reasons for voluntary childlessness in this study.

The treatment of IBD patients wishing to conceive is surrounded with uncertainties both for the parents to be and the treating physician. This guideline is developed to address these uncertainties and to promote a European perspective on reproduction in inflammatory bowel disease patients.

The strategy to reach consensus involved the following steps:

1. The development of questions that should be covered by these pregnancy guidelines. Participants were asked to review these questions and when necessary to adjust or add questions.
2. The participants met in London in November to agree on the questions
3. The participants performed a systematic literature search of their topic with the appropriate key words using Medline/Pubmed and the Cochrane database, as well as their own files. The evidence level was graded (Table 1) according to the Oxford Centre for Evidence-Based medicine [5].
4. Provisional statements of the participants were written and the participants met in Prague in February 2010 to agree on the statements. This was done by projecting the statements and revising them on screen until a consensus was reached. Consensus was defined as agreement by

Table 1 Safety of IBD drugs in pregnancy (ECCO rating).

Safe	Probably safe	Contraindicated
Oral 5-Aminosalicylates	Infliximab	Methotrexate
Topical 5-Aminosalicylates	Adalimumab	Thalidomide
Sulfasalazine	Certolizumab	6-thioguanine
Corticosteroids	Cyclosporin	(no data)
Azathioprine	Tacrolimus	
6-Mercaptopurine	Budesonide	
	Metronidazole	
	Ciprofloxacin	

>80% of the participants. Each recommendation was graded as stated above.

5. The final document on each topic was written by the designated participants. Consensus guideline statements in bold are followed by comments on the evidence and opinion. Statements are intended to be read in context with qualifying comments and not to read in isolation. The final document was edited by the first author. In some areas the level of evidence is generally low, which reflects the lack of prospective trials in this specific area. Consequently expert opinion is included where appropriate.
6. This document includes the ECCO opinion on drug safety during pregnancy and lactation. This approach is carefully chosen because the FDA made an announcement in May 2008, stating that they will replace the A, B, C, D, and X classification system with a narrative framework consisting of 3 sections although the system is easy to use, it might oversimplify the complexity of weighing risks to the fetus against the need to adequately manage maternal medical conditions [6]. The system does not fully address the fact that the benefits of treatment of some conditions (e.g., diabetes, asthma, pregnancy-induced hypertension, and psychiatric conditions) might outweigh the risk of fetal drug exposure.

2. Fertility in IBD

2.1. Influence of disease activity on fertility in females and males

ECCO Statement 2 A
There is no evidence that ulcerative colitis or inactive Crohn's disease affects fertility [EL3a, RG B]; however active Crohn's disease may lead to reduced fertility. Therefore it is advisable to strive for clinical remission to optimise the chances of conception [EL3b, RG B].

Patients with quiescent IBD are as fertile as the general population. Patients with IBD have fewer children than the general population, but this may partly be because of voluntary childlessness.[7,8] It is suggested that active Crohn's disease (CD) reduces fertility by several mechanisms, including inflammation involving the fallopian tubes and ovaries and perianal disease causing dyspareunia.[9]

2.2. Influence of medication on fertility and conception in IBD patients

ECCO Statement 2 B
There is no evidence that medication for IBD affects fertility in females [EL4, RG C]. In males sperm quality may be affected by sulphasalazine, methotrexate, and infliximab [EL4, RG C].

Sulfasalazine therapy causes a reversible decrease in sperm motility and count in male patients. The effect is dose related and it is unaffected by supplemental folic acid.[10–13] Azathioprine (AZA) did not influence sperm quality in 18 male IBD patients who used AZA at least 3 months.[14] Methotrexate (MTX) given for psoriasis produces oligospermia, this will improve within a few months after stopping the drug.[15]

Infliximab (IFX) seems to affect semen quality by reducing motility in a small group of patients; however sperm concentration increased after infusion.[16,17] The outcome of 10 pregnancies indirectly exposed to IFX through the male partner resulted in 9 lives births, 1 miscarriage and no congenital malformations were reported.[17]

For anti-TNF alpha it is unknown whether the fetus will be affected by exposure to anti-TNF alpha through semen and therefore barrier methods are advised during pregnancy [EL 5, RG D].

2.3. The influence of abdominal surgery on fertility in males

ECCO Statement 2 C
Pelvic surgery may lead to impotence or ejaculatory problems in men [EL4, RG C].

Men who undergo ileoanal pouch surgery for ulcerative colitis (UC) may experience retrograde ejaculation and erectile dysfunction.[18–20] However, these studies have shown that overall there is no change or even an improvement in sexual function post surgery.[18–21] The effect of preservation or improvement of sexual function after surgery on fertility rates in men has not been studied.

2.4. The influence of abdominal surgery on fertility in females

ECCO Statement 2 D
Pelvic, and to a lesser extent, abdominal surgery for IBD increases the incidence of subfertility in females [EL2a, RG B].

There is evidence to suggest that subfertility (unsuccessful to conceive within a year) has an increased incidence amongst women with IBD who have undergone surgery.[8,9,18,22–26] A systematic review concluded that the fertility of women with UC was reduced after restorative proctocolectomy[27] and a meta-analysis found that ileal pouch-anal anastomosis (IPAA) conferred a three-fold increased risk of infertility compared to medical management.[28] Studies have demonstrated a high rate of hydrosalpinx, destruction of fimbria, and tubal obstruction following pelvic surgery[29] and this is the most likely mechanism for subfertility after surgery. There is a large amount of literature on the use of laparoscopic IPAA, however, there are no studies that show improved fertility following a laparoscopic rather than a conventional approach. Likewise there are no data to support the approach of subtotal colectomy with rectal stump and ileostomy during the childbearing years and then creating an IPAA later in life to help reduce infertility rates. The drawbacks of the latter procedure include rare ileostomy complications during pregnancy such as obstruction and stoma related problems.[30,31]

3. Pregnancy and delivery outcome of mothers

3.1. The influence of pregnancy on the activity of inflammatory bowel diseases

ECCO Statement 3 A
If conception occurs at a time of quiescent disease the risk of relapse is the same as in non-pregnant women [EL5, RG D]. Conception occurring at a time of active disease is associated with persistent activity during pregnancy [EL3b, RG B]. Pregnancy might affect the natural course of IBD [EL2, RG B].

When conception occurs during a period of remission about a third of patients relapse during pregnancy which is similar to that expected in non-pregnant CD patients over a period of nine months.[32–35] On the other hand, if conception occurs at a time of active disease, two thirds have persistent activity and of these, two thirds will deteriorate. This underscores the importance of advising patients to conceive at a time when disease is in remission.[36–38] It seems that pregnancy influences the overall course of IBD positively, because as parity increases, the need for surgical intervention decreases. Furthermore patients with a previous pregnancy require fewer resections and the interval between operations tends to be longer when compared with nulliparous women with CD.[39,40] Mothers with CD seem also to have a lower relapse rate in the years after pregnancy, compared with the years before pregnancy but specific confounders such as smoking have not been investigated or ruled out in multivariate analyses.[41,42] Pregnancy has an effect on the immune system, which may contribute to these findings.[35]

3.2. The mode of delivery and outcomes

ECCO Statement 3 B
The mode of delivery should primarily be governed by obstetric necessity and indications. However, a multidisciplinary approach involving the gastroenterologist and/or the colorectal surgeon is advocated [EL 5, RG D].

ECCO Statement 3 C
An ileoanal pouch or an ileorectal anastomosis in women with IBD is regarded as a relative indication for a caesarean section but the decision should be made on an individual basis [EL 4, RG D]. Caesarean section should be preferred in active perianal disease or recto-vaginal involvement [EL4, RG C].

The mode of delivery should primarily be dictated by obstetric necessity, but the decision should be combined with the gastroenterologist and/or the colorectal surgeon to give the obstetrician and patient a balanced view on the consequences of a post partum sphincter/pelvic floor impairment with respect to present and future bowel function. Caesarean section is recommended in patients with perineal disease or in case of rectal involvement. Although some clinicians advocate caesarean section for all CD patients it seems reasonable to allow vaginal delivery for women with quiescent or mild disease as no evidence can be found in the literature for either approach.[43,44] Episiotomy should be avoided if possible because a high rate of perianal involvement has been reported, but is better than an uncontrolled laceration.[45] IPAA is regarded as an indication for caesarean section.[46–49] The reason being that a person with an IPAA is borderline incontinent and depends much more on an intact sphincter and pelvic floor function for maintaining faecal continence compared with a person having intact rectal functions. The reasoning could also be applied to patients with an ileorectal anastomosis although they have an intact rectal function they could have loose stools and are at risk of recurrent disease and further surgery. The literature is not unanimous on this.[45,50,51,52] There is a one in five risk that a woman with UC will need a colectomy and may be a candidate for an ileal pouch anal anastomosis during her fertile period. The risk of sphincter injuries is highest at the first delivery. Counselling a non-operated UC patient with regard to mode of delivery must be on an individual basis mainly adhering to obstetric principles. Patients with a colostomy, ileostomy or continent ileostomy can deliver vaginally, but if the obstetric risk is increased for other reasons, there should be a low threshold for caesarean section. A recent patient survey has indicated that IBD patients have more problems with persisting

faecal incontinence after vaginal delivery compared with controls.[53]

3.3. The risk of relapse after delivery

ECCO Statement 3 C
There is no increased risk of a flare in the postpartum period if women remain on their maintenance therapy [EL 2c, RG C].

About a third of IBD mothers experience a flare after delivery[54] but this risk is not significantly higher when compared to the risk of having a flare while not having a child. Patients with IPAA have a 20–30% chance of developing disturbances of pouch function (increased bowel frequency and a decrease in continence) in pregnancy and particularly in the third trimester. These changes usually resolve completely during the puerperium.[46,51,55,56]

4. Outcome of children

4.1. Risk of developing IBD with one or both parents having IBD

ECCO Statement 4 A
Children from parents with IBD have an increased risk of developing IBD. The risk is higher for Crohn's disease (2–3%) than for ulcerative colitis (0.5–1%) [EL3, RG B]. The highest risk appears for children of whom both parents have IBD [EL4, RG C].

The familial occurrence of IBD is well-known. Around 5.5% to 22.5% of patients with IBD have another family member also affected with the disease.[57,58] In fact, the most important risk factor for IBD is having a family member with the disease. The relative risk for a sibling of a CD patient to become affected is 13 to 36, and for a sibling of a UC patient this relative risk is 7–17. Translating this into absolute numbers, hereby assuming an overall incidence in Europe and North-America of 10 new cases per 100,000 for UC and 5–6 new diagnoses per 100,000 for CD, this gives a risk of only 2–3% for a sibling of a CD patient and 0.5–1% for a sibling of a UC patient.[59] The greatest risk appears for children of whom both parents have IBD and was shown to be above 30% at the age of 28 years.[60] Patients with IBD and a familial history tend to get their disease at an earlier age than patients without a familial history and show an increased concordance in disease type (CD or UC) and probably also disease location.[60-62] In contrast, the severity of the disease does not differ between familial or sporadic disease.

4.2. Outcome of pregnancy and adverse outcome of offspring

ECCO Statement 4 B
Women with IBD and in particular with Crohn's disease may have an increased risk of adverse pregnancy outcome [EL 2b, RG C]. These adverse outcomes include low birth weight, preterm delivery, and an increased frequency of Caesarean section [EL 2, RG B]. Increased risk for adverse pregnancy outcome is regardless of disease activity [EL 2b, RG B] although in Crohn's disease the rate of preterm delivery correlates with the severity of the disease [EL 3b, RG D].

ECCO Statement 4 C
Adverse outcomes such as death, low APGAR scores, seizures or admission to an intensive care unit [EL 2b, RG B] are not significantly increased in babies born at term. Whether the risk for congenital anomalies is increased remains controversial due to large discrepancies in the literature [EL 2b, RG D].

Women with IBD have an increased overall risk for adverse pregnancy outcomes. The most consistently described are preterm delivery (before 37 weeks of gestation) with a relative risk of 1.87, and low birth weight (less than 2700 g) with a relative risk of 2.1.[38,61,63] Concerning delivery mode, most studies have also shown significantly increased frequency of Caesarean section, but is it not consistently clear whether this is predominantly due to elective or emergency intervention by caesarean section.[33,37,38,64,65] Adverse pregnancy outcomes are more frequent in pregnant women with CD, compared to UC.

Only few studies have looked at the influence of IBD on a conception outcome (miscarriage) and on the rate of complications of pregnancy and labour (abruption of placenta, chorioamnionitis, eclampsia, placenta praevia, premature and prolonged membrane rupture, ectopic pregnancy). While the rate of abortion is increased, both, spontaneous and induced, data on the frequency of complications of pregnancy and labour are very inconsistent, precluding a meaningful conclusion.[33,37,64,65]

Disease severity probably does have an impact on pregnancy outcome. However, most of the studies did not evaluate this effect, and the only recent studies that specifically addressed the influence of CD activity, found the 3.4 fold increase in the risk of preterm birth, but not in low birth weight, low birth weight at term and in congenital anomalies in women with active disease.[66]

Except for the prematurity (infants delivered before 37 weeks) and low birth weight, maternal IBD seems to have no major adverse effects on the infant born at term. In these infants the APGAR scores, death rate, hospitalization in the intensive care unit, and seizures were not more common in offspring of mothers with IBD. Concerning the rate of congenital malformations, data is equivocal, mostly due to inconsistencies in the diagnoses included and the

confounding influence of the used medications. However, UC might carry a higher risk for congenital anomalies compared to CD, particularly for selected anomalies such as: limb deficiencies (OR 6.2), obstructive urinary malformations (OR 3.3), and multiple congenital anomalies (OR 2.6).[38,67-69]

4.3. Effect of medication used for IBD treatment during pregnancy on the health and development of the infant, including the vaccination programme

ECCO Statement 4 D
There are no published long term data on infant health outcomes such as neurodevelopment, incidence of childhood malignancies or increased risk for other specific disorders with respect to foetal *in utero* drug exposure [EL 5, RG D].

ECCO Statement 4 E
Current vaccination strategies with non-live vaccines for infants who have been exposed *in utero* to anti-TNF do not differ from those for unexposed infants as no adverse effects have been reported, and responses to vaccination were appropriate [EL4 RG D].

ECCO Statement 4 F
Live vaccines such as rotavirus, oral polio virus and Bacille Calmette–Guerin (BCG) vaccination should be provided when there is no detectable anti-TNF in the blood — which is expected in most infants in the second half of the first year [EL5 RG D]. To limit the transport of the drug to foetus, timing of the last dose of anti TNF therapy should be as early in the third trimester of pregnancy as possible [EL5 RG D].

As IFX is present in the circulation through the first 6 months of life, there are concerns about the immune system development, rate of infections, and also possible implications for the response to vaccination. So far, there have been no reported adverse infectious events,[70] and immune responses to routine childhood vaccinations were appropriate,[71] as well as the response of adult patients treated with adalimumab (ADA) to vaccination with pneumococcal and influenza vaccination.[72] Therefore, current vaccination strategies with non-live vaccines for infants who have been exposed to anti-TNF *in utero* do not differ from those for unexposed infants. This does not apply for live vaccines such as rotavirus, oral polio and Bacille Calmette–Guerin (BCG) vaccinations which are contraindicated in immune suppressed individuals. So far one case was reported of a child from a mother exposed to IFX during pregnancy that died at 4.5 months due to disseminated BCG infection after receiving a vaccination at 3 months.[73] Live vaccines can be provided to infants only in the second half of the first year, when it is expected that no detectable IFX or ADA are present, or when there are no detectable anti-TNF levels measured in the infant. Also, timing of the last dose of IFX and ADA should be as early in the third trimester as possible to maintain remission but to limit transport to the fetus.[69,74,75] Whether this applies for Certulizumab pegol needs to be investigated. The levels of other drugs used for IBD treatment in infants (such as azathioprine) are probably not elevated and will not influence vaccination programs, however data are lacking.

5. Management of IBD during pregnancy

5.1. The influence of IBD activity on IBD management

ECCO Statement 5 A
Acute flares during pregnancy carry a high risk of adverse outcome, and are best treated aggressively to prevent these complications [EL 3a, RG C]. Appropriate medical treatment of IBD (Table 1) should be continued in those patients who wish to conceive in order to reduce the risk of flares during pregnancy [EL 5, RG D].

Several studies have demonstrated that most pregnancies in women with IBD will be uncomplicated, if the patient is in remission or has only minor disease activity at the time of conception.[76–78] A meta-analysis by Miller with more than 1300 female patients with UC and over 700 patients with CD clearly demonstrated that normal pregnancies are observed in 83% of women with CD (71–93% in individual studies) and in 85% of women with UC (76–97% in individual studies).[79] Malformations were observed in about 1% of all pregnancies and also the frequency of spontaneous abortions and still births were in the same range as observed in the healthy normal population. In contrast, several studies demonstrate that the frequency of normal pregnancies is reduced and the frequency of adverse outcomes of pregnancy is increased, when pregnancies take place in phases with active inflammatory bowel disease.[80–84] Moreover, compared to pregnant IBD patients with inactive disease, women with a relapse during pregnancy have infants with significantly shorter gestation time and lower birth weight.[32,62,82,83] Therefore, the flares of active disease in pregnant patients have to be treated aggressively, and it is best if conception occurs during remission.

5.2. Medical treatment of IBD and congenital malformations

ECCO Statement 5 B
Most drugs used for the treatment of IBD are considered to be of low risk during pregnancy; however, methotrexate and thalidomide, are contraindicated [EL3, RGB].

ECCO Statement 5 C
The use of 5-ASA derivatives, corticosteroids and biologicals is not significantly associated with malformations or adverse outcomes in pregnant IBD patients and their offspring [EL3, RG C]. Patients treated with sulfasalazine should be supplemented with folic acid [EL3, RG C]. In cases of relapse, 5-ASA and corticosteroids are preferred therapy.

ECCO Statement 5 D
Due to lack of potential adverse drug effects, exclusive enteral nutrition can be considered as an option [EL5 RG D].

ECCO Statement 5 E
In the majority of patients, maintaining remission with medical treatment outweighs the potential risks of adverse drug effects (EL3, RGB). However, the benefits and the risks must be discussed with the patient and management decisions have to made on an individual basis [EL5, RGD].

For a summary of safety aspects of frequent IBD medications used during pregnancy[84,85] and current ECCO recommendation categories see Table 1.

5.2.1. Aminosalicylates, sulfasalazine

Sulfasalazine and all aminosalicylates are considered safe. Case series, population-based cohort studies,[37,86–89] and two meta-analysis[39,90] did not demonstrate an increased risk for early pregnancy adverse outcomes such as miscarriage and ectopic pregnancy. Some trials have demonstrated a higher rate of premature birth, stillbirth, and low birth weight, however, the confounding factor of active disease is difficult to delineate. Both animal and human data and the recent meta-analysis[90] did not demonstrate teratogenic effect. A small increase in risk of congenital malformations has only been shown in the meta-analysis by Cornish et al., whereby it could have been the result of disease itself.[39] As sulfasalazine treatment interferes with folate absorption, supplementation is recommended (2 mg/day of folate).

5.2.2. Corticosteroids

All corticosteroids (systemic, oral and topical) can cross the placenta to the fetus but are rapidly converted by placental 11-hydroxygenase to less active metabolites, resulting in low foetal blood concentration. As short-acting prednisone, prednisolone and methylprednisolone are more efficiently metabolized by the placenta and therefore reach lower concentrations in the fetus than the longer-acting dexamethasone and betamethasone, the former molecules are preferred for the treatment of maternal conditions necessitating glucocorticosteroids. Adverse effects on pregnancy outcome, shown in animal studies, have not been confirmed in humans.[33,37,38] However, the risk for orofacial malformations (cleft lip/palate) is increased in offspring of mothers receiving steroids in the first trimester of pregnancy,[91-93] though this increased risk is small, and not confirmed by all studies.[94] Also, there are case reports of neonatal adrenal suppression due to the use of corticosteroids in the late pregnancy of woman with IBD.[95] There is just one case series of eight CD patients treated with budesonide which did not find an increased risk of adverse pregnancy outcome.[96]

5.2.3. Azathioprine (AZA) and 6-mercaptopurine (6-MP)

AZA and its metabolite 6-MP are purine analogues which interfere with the synthesis of adenine and guanine ribonucleotides. AZA crosses the placenta, and though it hardly enters fetal circulation, metabolites have been determined in comparable levels in maternal and foetal red blood cells.[97,98]

Fetal exposure to AZA and 6-MP has been reported in several hundreds of cases. Most studies demonstrated the safety of thiopurines in females and males as no increased risk of malformations in the newborn occurred.[37,87,99–101] The most commonly cited pregnancy adverse outcomes are increased rate of spontaneous abortions, preterm delivery and low birth weight.[99,102] Again, in the majority of studies the adverse birth outcome could have been caused by the underlying disease rather than by the use of AZA or 6-MP.[103] Further risks for newborns and infants, described in a few cases, are immunological and haematological abnormalities, and chromosomal aberrations, caused probably by immunosuppression.[100] For 6-thioguanine (6-TG) it is reported that it passes the placenta,[104] further safety data are not available and therefore 6-TG during pregnancy in IBD is not advised.

5.2.4. Cyclosporin and tacrolimus

Both, cyclosporin and tacrolimus are widely used for treatment and prevention of graft *versus* host reaction after bone marrow transplantations, and to restrain rejection after solid organ transplantation. Therefore most of data on pregnancy outcome are derived from these patients. For cyclosporin, a meta-analysis of 15 studies with 410 pregnant patients did not find an increased rate of congenital malformations.[105] Similar, but fewer, data exist for tacrolimus.[106]

Evidence on the use of cyclosporin in IBD is limited to small series of women that had severe relapses during pregnancy.[32,107] With tacrolimus just a single case report of UC patient was published.[108] No congenital malformations were described; the outcomes were complicated with prematurity and low birth weight, but it is very difficult to differentiate the impact of severe disease from the effect of drug itself.

5.2.5. Methotrexate and thalidomide

Both drugs are teratogenic and contraindicated in pregnancy and therefore barrier methods to prevent pregnancy during therapy with MTX are advised.

Though normal pregnancy outcomes were reported,[109] exposure to MTX, particularly during the first trimester, may result in abortions, growth retardation, foetal loss, and congenital malformations, including craniofacial anomalies, limb defects and CNS abnormalities.[110] If conception should accidentally occur, therapeutic abortion should be discussed, but not necessarily performed. Prospective mothers should be instructed to stop MTX immediately and start high dose folate replacement. The intracellular metabolites of MTX, methotrexate polyglutamates, have a long half life and take about six weeks to reach steady state or to completely

wash out. To avoid exposure to MTX it should be stopped in both females and males, at least for 3–6 months before trying to conceive. Use of thalidomide has been associated with major foetal malformations involving limbs, ears, eyes, neural tube defects, and with neonatal mortality rate of 40%.[111]

5.2.6. Biologic therapy

IFX and ADA both are IgG1 antibodies, and can cross placenta, particularly in the second and third trimester.[74] Therefore, IFX and ADA are expected to be present in fetal circulation and in infants for several months after birth. For ADA this has not been documented yet, but seems presumable. Concerning IFX, detectable levels were found in a case report[112] and also in 8 healthy infants delivered after pregnancies during which mothers were receiving IFX every 8 weeks, with the last infusion being delivered at the mean time of 66 days before birth. At birth, levels were, as expected, higher in infants, and were measurable for 2 to 7 months.[113] This case series, as well as the evidence coming from the TREAT registry with 117 pregnant mothers exposed to IFX[114] and from IFX Safety Database where data are available for 96 women with direct exposure to IFX[17] suggest that IFX is of low risk in pregnancy, both for the early and late outcomes, and does not seem to be a teratogenic.

For ADA three case reports were published on 3 pregnancies in patients with CD. No complications occurred in any of these pregnancies and all the babies were developing normally at 6 months.[115–117] Interestingly adalimumab 40 mg every other week or weekly was administered in 14 women with previous recurrent spontaneous abortion to prevent miscarriage. Four pregnancies resulted in miscarriage; in the other 10 pregnancies no abnormalities 1occurred.[118]

Certolizumab pegol is a PEGylated Fab′ fragment of a humanized anti-TNFα monoclonal antibody. Fab′ fragments cross the placenta by passive diffusion, unlike the active transfer of IgG1 antibodies, so the rates of transfer across the placenta in the third trimester are likely to be lower than IFX or ADA. A study of pregnant rats receiving a murinized IgG1 antibody of TNFα and a PEGylated Fab′ fragment of this antibody, demonstrated much lower drug concentrations in the infant rat and breast milk with the Fab′ fragment, compared to the full antibody.[119] The experiences with certolizumab pegol are more limited, but experimental data in animals and first clinical data do not reveal an increased teratogenic risk in humans.[120]

5.2.7. Metronidazole, cipropfloxacin

Metronidazole and the quinolones have limited benefit for long term treatment of IBD. Short courses of these medications may be beneficial in the treatment of pouchitis and perianal disease and are low risk in the pregnant patient.

Metronidazole is used for treatment of active CD as well as perianal disease. This medication does not increase risk of spontaneous abortion or congenital anomalies,[121,122] although infants of women exposed to metronidazole in the second to third months of pregnancy have shown higher rates of cleft lip with or without cleft palate.

Human studies with ciprofloxacin have not shown an increase in spontaneous abortion or congenital abnormality incidence.[123] However, animal studies demonstrate musculoskeletal abnormalities induced by this medication class.[124] Fluroquinolones have a high affinity for bone tissue and cartilage, and may cause arthropathies in children. Although they are thought to have minimal risk overall, they should be avoided in the first trimester.

5.3. Nutritional deficiencies

ECCO Statement 5 I
Nutritional deficiencies such as folate [EL 1a, RG A], B12, iron and vitamin D [EL2a, RG B] should be assessed and treated as required. Folic acid 1 mg should be commenced in all IBD patients in anticipation of a pregnancy [EL1a, RG A].

There are no specific nutritional recommendations in pregnant women with IBD beyond control population or specific situations (such as an obstructed CD patient). Scarce reports in older literature addressed hyperalimentation as a method of sustaining pregnancy in IBD patients. The data do not justify specific recommendations. Folic acid supplementation before conception is recommended for all women[125–131] and although data are lacking higher doses could be given in women with known small bowel disease.

5.4. Surgery during pregnancy

ECCO Statement 5J
Indications for surgery in pregnant women with IBD are the same as for non-pregnant patients: In UC the main indication would be severe colitis not responding to medical therapy. In Crohn's disease obstruction, perforation, haemorrhage, and abscess. In the severely ill patient, continued illness is a greater risk to the foetus than surgical intervention [EL4, RG C].

Indications for surgery in pregnant women with IBD do not differ much from non pregnant women. In severely ill patients, continued illness is a greater risk to the foetus than surgical intervention.[132] In women with CD obstruction, perforation, haemorrhage, or abscess are indications for surgery and are no different to those for non-pregnant women.[77,132–134] Procedures have included proctocolectomy, hemicolectomy, segmental resection, and ileostomy. A temporary ileostomy is generally preferred, to reduce the risk of postoperative complications after primary anastomosis.[134] In the case of ulcerative colitis the indication for surgery is severe disease not controlled by medical therapy and urgent premalignant or malignant disease discussed on an individual basis. With respect to timing of surgery during pregnancy there is seldom room for a choice. Surgery is relatively safe in all trimesters but there is some limited series reporting on spontaneous abortion in the first trimester and preterm labour when operation in the third trimester.[134]

6. Lactation

6.1. Influence of lactation on disease activity

ECCO Statement 6 A
Lactation does not independently affect disease activity in IBD [EL 2C RG C].

Lactation was associated with an increase in disease activity in one study; however medication cessation was a confounding factor.[135] More recently lactation was not associated with an increased risk for a flare in either CD or UC.[54]

6.2. Medical treatment during lactation

ECCO Statement 6 B
5-ASA derivates are considered to be safe [EL 3b, RGB]. Corticosteroids are considered to be safe [EL 4, RG C]. Thiopurines are excreted in small amounts in the breast milk. Thiopurines are probably safe; however lactation needs to be discussed because of unknown long-term side effects in the newborn with immature liver metabolism. [EL4, RG C].

ECCO Statement 6 C
All anti-TNFs are likely to be excreted in the breast milk in very small amounts. However, no adverse effects have been reported in the small number of infants breastfed by mothers on this therapy. With such little data, the use of anti-TNFs in the breastfeeding mother needs to be carefully discussed and if available consider drug and antibody monitoring in milk and infants [EL5, RG C].

For a summary of safety aspects of frequent IBD medications used during lactations and current ECCO recommendation categories see Table 2.

Sulfasalazine is safe for breast feeding. The sulfapyridine moiety is absorbed in minimal amounts and is excreted in milk, however the milk: serum ratio is acceptable.[136] The safety of aminosalicylates has been confirmed in prospective trials.[137–139]

As *metronidazole*[140] and *ciprofloxacin*[141] are excreted into milk both drugs are not considered as appropriate during the breastfeeding period.

Prednisone and prednisolone result in low human breast milk concentrations. To minimise exposure, a 4 hour delay after oral dosing could be recommended.[142,143]

Very small amounts of *AZA/6-MP* metabolites (nanomolar concentrations of 6-methyl mercaptopurine and thiouric acid) appear in breast milk a reported in several case reports.[144-146] There is a great interindividual variability in the absorption and metabolism of azathioprine and 6-MP[147,148] that influences the exposure of the individual child.

Limited data suggest that infant exposure to *tacrolimus* via milk is low and therefore this should be discussed.[149]

There are no data to support the use of *cyclosporin* in breastfeeding because therapeutic blood concentrations in the breastfed infant are described.[150] It is not known whether *thalidomide* is excreted in breast milk.

In 4 women treated with *IFX* while breastfeeding, the IFX antibody could not be detected in breast milk and the IFX was also not detectable in the sera of 3 infants.[151,152]

ADA has been reported to be excreted in low levels in the milk of a nursing mother; however no data are available about serum levels in infants.[153]

7. Special considerations

7.1. Influence of IBD on sexuality

ECCO Statement 7 A
Data on the effect of IBD on the sexual function are conflicting [EL4 RG C]. A negative effect on sexual function is associated with low mood, but disease activity is also implicated [EL4 RG C]. In males and females sexual function seems to be preserved or even increased after surgery [EL 2a, RG B].

There are conflicting data of the impact of IBD of sexuality.[154,155] It is likely that symptoms and disease activity can affect sexuality, and female patients with IBD are reported to have a higher likelihood of symptoms such as penetration pain, low libido, and menstrual abnormalities.[156] Psychological factors may also play a role and depression has been found to be more prevalent among people with IBD[157] and is a predictor for low sexual function.[158] Women with IBD report significantly reduced sexual activity and libido compared to men.[159] There is conflicting evidence on the affect of surgery on the sexual function of women with IBD with some studies reporting a significant reduction in libido, body image and sexual activity after surgery[160]; and other

Table 2 Safety of IBD drugs during lacatation (ECCO rating).

Safe	Probably safe	Unknown safety	Contraindicated
Oral 5-aminosalicylates	Infliximab	Metronidazole	Methotrexate
Topical 5-aminosalicylates	Adalimumab	Ciprofloxacin	Thalidomide
Sulfasalazine	Certolizumab	Budesonide	Cyclosporin
Corticosteroids (4 hour delay)	Azathioprine		
	6-Mercaptopurine		
	Tacrolimus		

studies reporting no difference despite an increase in dyspareunia.[159–161] In men, sexuality seems to be less affected.[158,161] Rare complications, from particularly pelvic surgery, include loss or retrograde ejaculation, however, sexual function seems to be preserved or even increased after surgery.[161–163] This can be attributed to improvements in general health after therapeutic surgery and/or improvements in psychosexual health leading to increased sexual desire following, for example, reversal of stoma which has been shown to have a negative impact on sexual function.[164,165]

7.2. Oral contraceptive use in IBD

ECCO Statement 7 B
There are no data to support an effect of IBD on the efficacy of oral contraceptives [EL4 RG D]. Oral contraceptives do not aggravate the activity of IBD [EL3B RG C].

There are no studies assessing the efficacy of oral contraceptives (OCs) in women with IBD. OC steroids are mainly absorbed from the small bowel, and contraceptive efficacy depends on its absorptive capacity. Enhanced passage of gastrointestinal contents or impaired absorption may thus contribute to contraceptive failures in patients who have chronic inflammatory disease, diarrhea, or jejunoileal bypass. Therefore it can be hypothesized that the efficacy of OCs may be reduced in women with CD who have small bowel disease and malabsorption. The general advice for women using OCs that have been vomiting or severe diarrhoea for more than 24 h is to follow instructions for missed pills.[166] One large prospective cohort study and some case-control studies showed no effect of OCs on the activity of IBD.[166–169]

ECCO Statement 7 C
IBD is a thrombophilic condition however the effect is modest [EL3B RG C]. Oral contraceptives place patients with thrombophilic conditions such as IBD and smoking at higher risk for thromboembolism [EL1B RG A]. Contraception is highly efficient and safe in preventing unwanted pregnancy. In an IBD patient a clinical decision regarding the use of contraceptives should be made on an individual basis

Using OCs has long been associated with a modest increase in the chance of developing IBD, specifically CD.[170] In the older literature a hypothesis was raised that OCs may play a role in the etiology of IBD through a process of multifocal, microvascular gastrointestinal infarction.[171] Evidence regarding the effect of thrombosis risk that would be specific to IBD patients is vague. Hormonal therapy is one of the most significant prothrombotic risk factors. OCs induce resistance to activated protein C,[172] increase levels of procoagulant proteins (factors II, VII, VIII, and fibrinogen),[173] decrease levels of antithrombin, protein S, tissue factor pathway inhibitor, and fibrinolytic proteins; and increase markers of coagulation and fibrinolysis activation.[173–175] The thrombotic risk associated with OC use varies with the time interval since starting treatment but is highest in the first year of use, especially in women who have a prothrombotic defect.[175,176] Adolescent girls who have coexisting thrombophilic conditions, such as systemic lupus erythematosus, a history of thromboembolism (TE), or other conditions, have relative contraindications to combination hormonal contraceptive methods, because these medications place them at higher risk for TE.[177–180] Inflammation is a thrombophilic condition, due to elevated factor VIII. IBD specifically is considered a thrombophilic condition.[181] Thus, in an IBD patient a clinical decision regarding the use of OCs should be made on an individual basis.

7.3. Venous thromboembolism risk in pregnancy

ECCO Statement 7 D
Risk assessment for VTE should be performed in the pregnant patient with IBD [EL 4 RG C] Consideration of prophylactic low molecular weight heparin should be given for any pregnant IBD patient experiencing a relapse, admitted to hospital or if additional risk factors are identified [EL3 RG B].

Pregnancy increases the risk of venous thromboembolism (VTE) by 4–6 fold[182] and is a leading cause of direct maternal death in developed countries.[183] The time of highest risk is in the first 6 weeks of the postnatal period.[184] IBD patients, particularly hospitalised with active disease, are at increased risk for VTE.[185,186] Hospitalised pregnant IBD patients have an increased risk of VTE compared to their non-IBD pregnant controls; for CD aOR, 6.12 (95% CI, 2.91–12.9) and for UC an OR, 8.44 (95% CI, 3.71–19.2). Low molecular weight heparin in a prophylactic dose reduces the risk of VTE in medical and surgical patients by 60–70%.[187] Low molecular weight heparin has been shown to be safe and efficacious in the pregnant population.[188] Therefore consideration of the use of prophylactic low molecular weight heparin is pregnant IBD patients experiencing a relapse and/or admitted to hospital, is strongly recommended. All women should undergo a documented assessment of risk factors for venous thromboembolism (VTE) in early pregnancy or before pregnancy. This assessment should be repeated if the woman is admitted to hospital for any reason and again after delivery.[189]

7.4. Cervical cancer screening

ECCO Statement 7 E
It is imperative that all women with IBD utilize their national screening programmes and ensure they have regular (as per national guideline) surveillance [EL 2a RG B]. Humane papilloma virus vaccination should be given to all women with IBD, ideally prior to starting immunosuppression [EL 5 RG D].

There is evidence of an increase in incidence of humane papilloma virus (HPV)-associated cervical dysplasia in the renal

transplant population[190,191] and cervical intra-epithelial neoplasia (CIN) in human immunodeficiency virus (HIV) patients.[192] Therefore it has been extrapolated that women with IBD who are on immunomodulatory therapy maybe at similar risk.[193,194] There is conflicting data to support this assumption. Evidence for a higher incidence of cervical dysplasia was demonstrated in an age-matched case controlled study where 18% of women with IBD were found to have abnormal Pap smears compared to 5% of controls.[195] This was confirmed by another case controlled study which found abnormal Pap smears in 42.5% of women with IBD compared to 7% of age and parity-matched controls ($P<0.001$) [196]. This study implicated immunosuppressive therapy by showing an increased incidence in abnormal Pap smears in those on immunomodulators for >6 months compared to those not taking such agents (OR 1.5 (1.2–7.1, $P=0.021$). Immunomodulators were again implicated in a large retrospective case-controlled study which showed higher hazard ratio with increasing numbers of medications.[197] However, the increase in cervical dysplasia in these studies did not translate to an increase in cervical neoplasms. More recently 2 large case-controlled studies showed no increase in cervical dysplasia associated with IBD with or without immunosuppressive therapy.[198,199] The only significant predictor of cervical dysplasia in this population was current smoking (OR2.95, CI 1.55–5.50, $P=0.001$).[198] While there is no consensus on the necessary frequency of Pap smears, it is imperative that women with IBD are counselled about the potential risks and receive regular screening as per the national guideline. Many countries have now adopted a policy of universal vaccination for the certain types of HPV virus that are associated with 70% of cervical cancers.[200] It is therefore reasonable that women with IBD, in particular should be advised to have this vaccination, ideally before starting immunosuppressant therapy.[200] See for further recommendations ECCO statement OI 4E in Consensus on the prevention, diagnosis and management of infections in inflammatory bowel diseases.[201]

7.5. Endoscopy during pregnancy

ECCO Statement 7 G
Gastroscopy [EL3b RG B], sigmoidoscopy/colonoscopy and ERCP [EL4 RG C] are generally considered to be safe in pregnancy, however, these procedures should only be done when there is a strong indication and should be performed in the second trimester whenever possible [EL5 RG D]. Haemostasis measures are safe and should be carried out with precautions [EL3, RG C].

ECCO Statement 7 H
Procedure time and radiation exposure should be kept to a minimum [EL4 RG C]. Endoscopic procedures should be managed in conjunction with specialists in obstetrics and obstetric anesthesia [EL5 RG D]. Pregnant patients should be placed in left pelvic tilt or left lateral position before, during and after the endoscopic procedure, to avoid vena caval compression [EL5 RG D]. Presence of fetal heart sounds should be confirmed before sedation is begun and after the endoscopic procedure [EL5 RG D].

ECCO Statement 7 I
Close attention should be paid to appropriate drug selection using drugs most tried and tested in pregnancy and using the minimum dose possible to achieve the desired effect [EL4 RG C]. Sedative drugs should be administered to provide patient comfort, while avoiding over sedation [EL 5, RG D].

Limited evidence exists regarding the utility and safety of endoscopy in the pregnant woman with IBD. Maternal considerations include the increased risk of aspiration following gastroscopy (OGD) due to lower oesophageal sphincter incompetence. Fetal considerations include the preservation of adequate maternal oxygenation and blood pressure to allow optimal placental perfusion. Therefore pregnant women undergoing endoscopy should have their saturations monitored throughout the procedure and the minimum dose of sedating drug necessary for an adequate effect should be used. Pregnant patients in the 2nd or 3rd trimester should be placed in the left pelvic tilt to reduce the risk of vena caval compression and thus minimize hypotension. Due to these potential complications, endoscopy in pregnancy should be reserved for strong indications however; endoscopy does appear to offer a relatively safe alternative to radiologic or surgical intervention.[202–205] Case series and case-controlled studies have shown that OGD is safe and effective, with no evidence for this procedure inducing labour.[206,207] Likewise, small case series of colonoscopy in pregnancy showed no evidence of adverse outcome.[208,209]

Endoscopic retrograde cholangiopancreatography (ERCP) in pregnancy has been reported in several case series.[210–212] These studies suggest that ERCP is safe in pregnancy with no increased incidence of congenital malformations, fetal distress or incidence of precipitating labour. However, there may be a higher risk of post-ERCP associated pancreatitis,[210,213–215] although this did not alter the overall pregnancy outcome in these studies. Radiation dose should clearly be kept to a minimum and in the majority of studies the dose did not exceed the accepted threshold of 10 mGy however this was not always the case and recently several case reports and a small study on 6 pregnant women has described the successful application of ERCP without radiation.[216]

The benefit of epinephrine, electricity and contrast dye[217] in the appropriate situation outweigh the risks.

The risk of use of polyethelene glycol for preparation is considered low.[218] Sodium phosphate preparations have no data but a potential harm and should be avoided.[219]

7.5.1. Sedation

Meperidine is commonly used in endoscopy for analgesia and sedation. It is rapidly transferred across the placenta but two large studies of 268 mothers[220] and 62 newborns,[221] respectively; no teratogenicity from meperidine administration during the first trimester was reported. Meperidine can cause diminished foetal beat-to-beat cardiac variability that lasts for approximately 1 h after maternal intravenous administration.[222] This can also be interpreted as a sign of foetal distress; however this side effect is reversible, transient, and not a poor prognostic indicator. Meperidine, when used sparingly, is approved by the American Academy of Pediatrics for use in breast-feeding mothers.

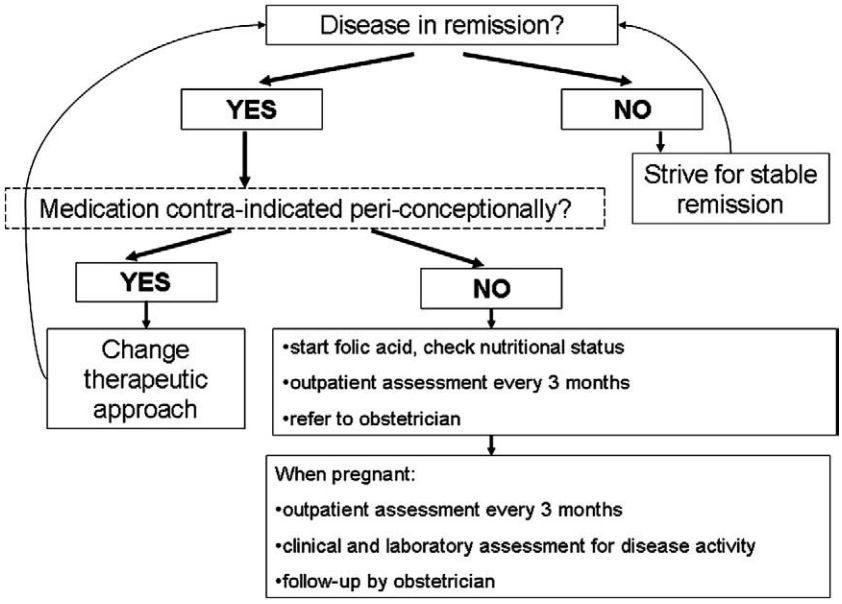

Figure 1 Algorithm for counseling females who wish to conceive.

Fentanyl is commonly administrated during labour and is considered safe although case reports note neonatal respiratory depression, muscle rigidity,[223] and opioid withdrawal[224] as potential side effects. Fentanyl is excreted in breast milk, but its low bioavailability to the breast-feeding infant makes it acceptable to breast-feed following its use.[225]

Propofol use during endoscopy is increasingly common. However, it has not been extensively studied in women in the first and second trimesters and therefore is not recommended for use during this time. Small amounts of propofol are excreted into breast milk and colostrum, but the concentration is considered negligible.[226]

The benzodiazepines, diazepam and midazolam should be avoided particularly during the first trimester. Midazolam, the preferred benzodiazepine for endoscopy, crosses the human placenta, but fetal serum levels increase to only about one to two thirds of maternal serum levels after oral, intramuscular, or intravenous maternal administration. Midazolam and its metabolite are excreted into milk, but there is minimal exposure if breast-feeding was held for 4 h after administration of a 15 milligram dose.[226,227]

8. Recommendations from the consensus group

ECCO Statement 8 A
Appropriate referral for pre-pregnancy and pre-conception counseling should be available for all patients with IBD to advise and optimise management before conception [EL5 RG D].

ECCO Statement 8 B
If steroids and biological therapy is required in third trimester, women should receive multidisciplinary care by a team with experience in treating active IBD in pregnancy [EL5 RG D].

It was shown in a small case series that the majority of IBD patients with conception plans require medication for which limited information on the safety of the peri-conceptional use is available.[228] In addition, reproductive wish lead to the medication changes in one third of these patients. Therefore the working group feel it is important to counsel all IBD-patients wishing to conceive (see for suggested algorithm in females; Fig. 1). Furthermore if a flare occurs in the third trimester the working group feels that these women are in need of specialized multidisciplinary care by a team with experience in treating active IBD in pregnancy. This team should include gastroenterologists, obstetricians and pediatricians.

Acknowledgements

The authors would like to disclose the following potential conflict of interest.

The following authors have given lectures supported by the following companies:

Van der Woude: Abbott, Schering-Plough, Centocor, UCB, Falk Foundation.

Kolacek: Neste, Abbott Ross Lab, Roche, Schering, SHS – Danone, Fresenius Kabi.

Vermeire: Ferring, Abbott, MSD, Centocor, Falk Foundation, UCB.

Munkholm: unknown.

Oresland: none.

Dotan: ABBOTT MSD GIVEN IMAGING.

Mahadevan: none.

Mckillop: none.

Dignass: Ferring, Astellas, Falk Foundation, Essex Pharma, Merckle Recordati, Abbott, UCB, Shire, Otsuka, Fresenius, Vifor, Ardeypharm, Immundiagnostik GmbH.

The following authors have received study/travel grants form the following companies:

Van der Woude: none.

Kolacek: Nestle.
Vermeire: none.
Dotan: TEVA.
Munkholm: unknown.
Oresland: none.
Mahadevan: Abbott.
Mckillop: none.
Dignass: Astellas, Falk Foundation, PDL, Otsuka, Fresenius; Asahi, Ferring.

The following authors have received an unrestricted educational grant from the following companies:

Van der Woude: Ferring, Abbott, Schering-Plough.
Kolacek: Abbott, Dukat, Nestle, Podravka, SHS/Danone.
Vermeire: UCB.
Dotan: none.
Munkholm: unknown.
Oresland: none.
Mahadevan: none.
Mckillop: none.
Dignass: none.

The following aurthors have served as paid consultant for the following companies:

Van der Woude: Abbott, Shire.
Kolacek: Abbott, Nestle, Fresenius Kabi.
Vermeire: Astra-Zeneca, Ferring, Pfizer, Shire.
Dotan: CENTOCOR MILLENIUM TEVA.
Munkholm: unknown.
Oresland: Abbott, Ferring.
Mahadevan: Abbott, UCB, Centocor, Elan, Shire, Biogen, Takeda.
Mckillop: none.
Dignass: Ferring, Astellas, Essex Pharma, Schering Plough, Centocor, Abbott, UCB, PDL, Shire, Genentech, Genzyme.

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