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ECCO Guidelines/Consensus Paper

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The Second European Evidenced-Based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease

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Abstract

Trying to conceive and being pregnant is an emotional period for those involved. In the majority of patients suffering from inflammatory bowel disease, maintenance therapy is required during pregnancy to control the disease, and disease control might necessitate introduction of new drugs during a vulnerable period. In this updated consensus on the reproduction and pregnancy in inflammatory bowel disease reproductive issues including fertility, the safety of drugs during pregnancy and lactation are discussed.

Keywords: Inflammatory bowel disease; pregnancy; reproduction; lactation; Crohn's disease; ulcerative colitis

1. Introduction

Inflammatory bowel diseases (IBD) have a high prevalence in young individuals, so that reproductive issues freqently arise. This updated consensus paper addresses these issues and is aimed to optimize preconceptional counseling in patients with inflammatory bowel disease and to promote a European perspective on the management of pregnancy in patients with IBD and its dilemmas.

This document is based on the European Consensus on reproduction in inflammatory bowel disease, reached by the European

Crohn's and Colitis Organization (ECCO) at a meeting held in Prague in February 2010.[1] The Consensus is grouped into four parts: fertility; pregnancy and delivery; outcome of children and management of IBD during pregnancy; and lactation. The strategy to reach the Consensus on the guideline revisions involved seven steps.

Guideline statements of the 2010 Consensus were analyzed systematically by the chairs of the working parties. After careful consideration the following chapters of the first Consensus were not addressed in this Consensus: influence of IBD on sexuality, oral contraceptive use in IBD, venous thromboembolism risk in pregnancy, cervical cancer screening, and endoscopy during pregnancy. Guideline statements selected for change and questions unresolved by the 2010 ECCO Consensus were distributed to the working party members.

In parallel, the working parties 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 (EL) was graded according to the Oxford Centre for Evidence Based Medicine of 2011.[2]

Provisional guideline statements on their topic were then written by the chairs of the working groups and posted on a web blog. Discussions and exchange of the literature evidence among the working party members was then performed on the web blog. This process was supervised by C.J.W. and F.M.

After agreement within the working parties, the statements were posted for review by the working parties and national representatives from 18 different countries (n = 25).

After the first voting, all consensus statements that did not reached the approval rate above 80% were revised.

On December 6th 2013, the working parties met in Vienna to agree the statements. Technically this was done by projecting the statements and revising them on screen until a consensus was reached. Consensus was defined as agreement by >80% of participants, termed a Consensus Statement and numbered for convenience in the document.

The final document on each topic was written by the chairs in conjunction with their working party. The final text was edited for consistency of style by C.J.W. and F.M. and then circulated and approved by the participants. In some areas the level of evidence is generally low, which reflects the paucity of evidence in reproduction-related issues. Consequently expert opinion is included where appropriate.

2. Fertility

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

ECCO Statement 2A

There is no evidence that ulcerative colitis or inactive Crohn's disease affect fertility [EL3]. However, active Crohn's disease may reduce fertility and hence it is advisable to strive for remission [EL3]. High levels of voluntary childlessness in women with Inflammatory bowel disease indicate the need for better education [EL4]

Patients with quiescent Inflammatory bowel disease (IBD) are as fertile as the general population.[3,4]

Patients with IBD have fewer children than the general population, but this is related to voluntary childlessness.[4,5] Patient's choice is reported to be the main reason for voluntary childlessness[6]; patient's knowledge of pregnancy in IBD is often poor,[7] which in itself is associated with negative views.[8] Crohn's disease (CD) might decrease fertility both directly, by inducing inflammation in the fallopian tubes and ovaries and by perianal disease causing dyspareunia,[9] and indirectly through surgical interventions and associated tubal adhesions. In addition there are recent data to suggest a reduction in ovarian reserve function as estimated by serum levels of anti-Müllerian hormone in CD, particularly in active disease and women over age 30.[10,11] Many women with IBD choose to stay childless voluntarily and this exceeds the number of those experiencing fertility issues, as also demonstrated in a recent meta-analysis.[12,13]

2.2. Influence of medication on fertility and conception

ECCO Statement 2B

There is no evidence that medication affects fertility in females [EL4]. In males sulphasalazine causes reversible oligospermia [EL3]

There are no data reporting the effects of medication on female fertility. In men, sulfasalazine therapy causes a reversible decrease in sperm motility and count.

The effect is dose related and it is unaffected by supplemental folic acid.[14–17] Azathioprine (AZA) did not influence sperm quality in 18 male IBD patients who used AZA for at least 3 months.[18] In addition, no effect was seen on the outcomes of pregnancies fathered by IBD patients on thiopurines.[19] Methotrexate (MTX) produces oligospermia, this will improve within a few months after stopping the drug.[20] MTX is however contraindicated for men aiming to father a child. Infliximab (IFX) seems to affect semen quality by reducing motility in a small group of patients; however data are contradictory as sperm concentration increased after infusion.[21,22] Furthermore, men with spondylarthropathies tended to have better sperm qualities when receiving anti-TNF therapy.[23] The outcome of 10 pregnancies indirectly exposed to IFX through the male partner resulted in nine live births, one miscarriage, and no congenital malformations were reported.[22]

2.3. The influence of abdominal surgery on fertility in males

ECCO Statement 2C

Pelvic surgery may lead to impotence or ejaculatory problems in men [EL4]

Men who undergo ileoanal pouch surgery for ulcerative colitis (UC) may experience retrograde ejaculation and erectile dysfunction.

However, overall no change or even an improvement in sexual function occurs after surgery.[24–27] The effect of surgery on fertility rates in men has not been studied.

2.4. The influence of abdominal surgery on fertility in females

ECCO Statement 2D

Pelvic and, to a lesser extent, abdominal surgery for IBD increases the risk of subfertility in females [EL1]. A laparoscopic approach to ileal pouch anal anastomosis may lower infertility rates compared with an open surgical approach [EL2]

Evidence suggests that subfertility (failure to conceive within a year) is increased amongst women with IBD who have undergone pouch surgery.[4,9,24,28–33]

Several meta-analyses found that ileal pouch-anal anastomosis (IPAA) conferred a 2-3-fold increased risk of infertility compared with medical management.[34–36] Higher rates of hydrosalpinx, destruction of fimbria, and tubal obstruction following pelvic surgery[37] are the most likely mechanisms for subfertility after surgery for IBD.

There is now some evidence from retrospective studies that infertility rates after laparoscopic IPAA surgery are lower than those seen after open IPAA surgery,[38,39] which may be primarily related to a reduction in adhesions.[40] There are, however, no data to support the approach of subtotal colectomy with rectal stump and ileostomy during the childbearing years followed by IPAA later in life to help reduce infertility rates. Relatively rare ileostomy complications could arise during pregnancy, such as obstruction or stoma-related problems.[41,42] Rates of successful in vitro fertilization after IPAA are similar to those in women without IBD and surgery.[43]

3. Pregnancy and delivery outcome of mothers

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

ECCO Statement 3A

If conception occurs at a time of quiescent disease, the risk of relapse is the same as in nonpregnant women [EL3]. Conception occurring at a time of active disease increases the risk of persistent activity during pregnancy [EL3]. Pregnancy may influence the course of inflammatory bowel disease [EL3]

When conception occurs during a period of remission, about a third of patients relapse during pregnancy which is similar to the relapse risk in non-pregnant CD patients.[44,45] On the other hand, if conception occurs at a time of active disease, two-thirds have ulcerative colitis (UC). In UC, females' higher relapse rates were observed during the first 2 trimesters. This underscores the importance of advising patients to conceive at a time of remission.[46–49] Pregnancy may influence the overall course of IBD positively; with increasing parity, 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.[32,50] 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.[51–53] A small retrospective study has demonstrated that quality of life determined by the Short Inflammatory Bowel Disease Questionnaire improved during pregnancy in 50% of women.[54] Pregnancy has an effect on the immune system, which may contribute to these findings.[55]

3.2. The mode of delivery and outcomes

ECCO Statement 3B

The mode of delivery is subject to a multidisciplinary approach and should primarily be governed by obstetric indications [EL5]

ECCO Statement 3C

Cesarean section is indicated in active perianal disease or active rectal involvement [EL5]. An ileoanal pouch or an ileorectal anastomosis in women with IBD is a relative indication for a cesarean section but the decision should be made on an individual basis [EL5]

The mode of delivery should primarily be dictated by obstetric necessity. Advice from a gastroenterologist and/or the colorectal surgeon should give the obstetrician and patient a balanced view on the consequences of a postpartum sphincter/pelvic floor impairment with respect to present and future bowel function. Cesarean section is recommended in patients with perineal disease or in case of active disease with rectal involvement. Although some clinicians advocate cesarean 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 in favour of either approach.[56,57] Episiotomy should be avoided if possible because a high rate of perianal involvement has been reported; nevertheless it is preferable to an uncontrolled laceration.[58] Vaginal delivery was not a risk factor for developing fecal incontinence in a large UK study.[59] In contrast, a much smaller survey of women with CD (likely subject to selection and response bias) found an increased risk of incontinence after vaginal delivery compared with healthy controls.[60] The risk of developing de novo perianal disease is not increased after vaginal delivery in comparison with women who underwent cesarean section.[61] A recent large retrospective review of 6 797 669 deliveries and 2882 (0.04%) deliveries among patients with concomitant diagnosis of CD showed that perianal disease predicts severe perianal laceration.[62]

IPAA is regarded as a relative indication for Caesarean section.[29,63–65] A person with an IPAA is deemed borderline incontinent and depends more on an intact sphincter and pelvic floor function for maintaining fecal continence. Some studies report worse physiological and/or clinical outcomes,[29,66] but the literature is not unanimous on this.[34,58,67–69] The choice of delivery method post IPAA should be made after careful consideration of the patient's situation and preferences, as data on continence post vaginal delivery are equivocal. Patients with an ileorectal anastomosis have an intact rectal function, but are at risk of recurrent disease and further surgery. There are no data to suggest that these patients would benefit from cesarean sections.

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. Counseling a patient with regard to mode of delivery must be on an individual basis, mainly adhering to obstetric principles. Those patients considered at particularly high risk for needing pouch surgery in the future (such as previous admission with acute severe colitis, or those needing biological therapy) might be a group for whom particularly careful discussion on the mode of delivery is

appropriate. 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 cesarean section.

3.3. The risk of relapse after delivery

ECCO Statement 3D

There is no increased risk of a flare in the postpartum period for women with CD remaining on their maintenance therapy [EL 2]. In women with UC the risk of a postpartum flare may be increased [EL4]

About a third of IBD mothers experience a flare after delivery[47] but this risk is not significantly higher when compared with the risk of having a flare while not pregnant. A recent prospective study has suggested that in contrast to women with CD, women with UC may have higher rates of flares postpartum,[49] but these results require verification. 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.[63,68,70,71]

4. Pregnancy and delivery: outcome of children

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

ECCO Statement 4A

Children of parents with IBD have an increased risk of developing inflammatory bowel disease. The risk is higher for Crohn's disease, and if both parents are affected [EL 3]. In Crohn's disease, transmission is more common from mother to child than from father to child, and female offspring are at higher risk than male offspring [EL 3]

Positive family history is an important predictor of the lifetime risk for acquiring IBD.[72–74] Around 5.5-22.5% of patients with IBD have another family member also affected with the disease.[75,76] The overall risk for children with one parent affected with IBD is 2–13 times higher than in the general population.[77,78] For children among whom both parents have IBD, the risk of disease occurrence during their lifetime rises above 30%.[79,80] The relative risk for a sibling of a CD patient to become affected is 13 to 36 higher than the general population, and for a sibling of a UC patient the relative risk is 7 to 17 higher compared with the general population. Translating 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 2–3% for a sibling of a CD patient and 0.5–1% for a sibling of a UC patient.[81] Risk increases significantly if the parent affected with CD is the mother, and if the offspring is female.[82,83] Transmission of CD from the affected mother to daughter, in the familial IBD population, implies a specific female sex inheritance pattern, which could not be demonstrated for UC, for the affected fathers or for the affected male offspring.[83] Patients with IBD and a family history tend to present at an earlier age, and show an increased concordance in disease type (CD or UC) and probably in disease location. In contrast, the severity of the disease does not differ between familial or sporadic disease.[73]

4.2. Outcome of pregnancy and adverse outcome of offspring

ECCO Statement 4B

Cesarean delivery is more frequent in women with IBD; and there is an increased risk of low birthweight and preterm birth [EL2]. Disease activity at conception or during the pregnancy is associated with preterm birth and low birthweight [EL 3]

ECCO Statement 4C

Adverse fetal outcomes such as low APGAR scores, seizures or admission to an intensive care unit and death, are not increased in babies born at term [EL2]. The risk of congenital abnormalities in offspring from women with inflammatory bowel disease does not seem to be increased [EL2]

Women with IBD have an increased overall risk for adverse pregnancy outcomes. The most consistently described are preterm delivery (before 37 weeks of gestation), low birthweight (LBW) (<2500 g) and small for gestational age (SGA) birth.[73,84–90]

Concerning delivery mode, most studies have shown significantly increased frequency of cesarean section, both elective and performed as an emergency intervention.[44,86,89–91] The risk of adverse pregnancy outcome seems to be similarly increased in UC and CD.[85,89,90,92,93]

Very few studies have evaluated whether there is an effect of IBD on first-trimester outcome of pregnancy (i.e. increased chance of miscarriage or an ectopic pregnancy) and whether there is an effect on the rate of complications of pregnancy (placental abruption, chorioamnionitis, preeclampsia/eclampsia, placenta previa, premature and prolonged rupture of membranes). However, a few studies report there is an increased rate of miscarriage, both spontaneous and induced. Additional data on the frequency of complications of pregnancy and labour are very inconsistent, precluding a meaningful conclusion.[44,89–91,93]

Disease activity at conception and during pregnancy seems to be an important risk factor for adverse pregnancy outcomes. Several recent studies have examined the impact of disease activity on pregnancy outcomes using proxy measures such as IBD-related surgery and hospitalization before and during pregnancy, change of IBD medication, and low weight gain during pregnancy.[85–87,89,90,93–95] The majority have revealed that IBD mothers with active disease at conception and during pregnancy have a higher risk of preterm birth, low birthweight and small for gestational age birth compared with IBD mothers with disease in remission. Other predictors of adverse pregnancy outcomes in IBD, besides disease activity, include familial history of IBD, disease localization and IBD surgery.[84,86,88]

Maternal IBD seems to have no major adverse effects on the infant born at term. In these infants, low APGAR (Appearance, Pulse, Grimace, Activity, Respiration) scores and presence of seizures were not more common in the offspring of mothers with IBD. For these infants there is no increased risk of neonatal death rates and admission on an intensive care unit.

Although some studies revealed an association between congenital malformations and maternal UC, particularly limb deficiencies and urinary malformation,[74,96,97] this has not been replicated in large studies, regardless of disease activity.[86,88–90,95]

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

ECCO Statement 4D

Fetal exposure to most IBD medications is considered of low risk to the child, except for methotrexate and thalidomide [EL2]. Fetal exposure to thiopurines is not associated with an increased risk of infections in the first year [EL3]. The risk of infection with anti-TNF agents alone or in combination with immunomodulators is controversial [EL4]

ECCO Statement 4E

Since detectable levels of anti-TNF in the offspring are present in the first 6 months at least, live vaccines should be avoided in this period [EL5]. Current vaccination strategies with non-live vaccines do not differ from those for infants unexposed in utero to anti-TNF agents [EL4]

ECCO Statement 4F

Timing of the last dose of the anti-TNF drug should consider both maternal disease activity and drug placental transfer. When considered appropriate by the clinician and the patient, to limit the transport of the anti-TNF to fetus, the anti-TNF drug should be discontinued around gestational week 24–26 [EL3]

Several studies have demonstrated that mothers with IBD using thiopurines during pregnancy have an increased risk of preterm birth, LBW and SGA.[74,98–101] However, the investigators failed to take disease activity into consideration, which is the risk factor most commonly associated with these adverse pregnancy outcomes.

In contrast to these findings, a number of recent cohort studies revealed that thiopurine use during pregnancy does not affect the risk of preterm birth, low birthweight or SGA.[92,102–105] Moreover, long-term follow-up studies (3–4 years) reported that offspring exposed to thiopurines during pregnancy had normal mental and physical development and no increased risk of infections during childhood.[106,107] However, with respect to congenital anomalies, the safety of thiopurines during pregnancy is still being debated.[108] Although some studies have demonstrated an association between intrauterine thiopurine exposure and congenital abnormalities,[96,99,109] this has not been replicated in several larger studies.[100,103,104,107,110,111]

One prospective investigation, which included 28 pregnant IBD mothers on thiopurines, revealed that 60% of the offspring were born with anemia (hemoglobin level below 10 mmol/l). Further studies are needed to clarify this association.[104]

The incidence of childhood malignancies or risk for other specific disorders due to long-term fetal exposure to IBD medication remains unknown.

With respect to medications used by fathers with IBD, no increase in major malformations was found (3 vs 2.2 %) in offspring from 115 pregnancies where the fathers were exposed to thiopurines at the time of conception.[19]

With respect to biological agents, several studies have shown that treatment with anti-TNF drugs does not increase the risk of adverse pregnancy outcomes.[102,112–114] As IFX has been detected in infants up to 6 months after birth, there are concerns about immune system development, rate of infections and also possible negative implications on the response to vaccination. For non-live vaccines there have been no reported adverse events,[115] and immune responses to routine childhood vaccinations were appropriate.[116] Similarly, the response of adult patients treated with adalimumab (ADA) to pneumococcal and influenza vaccinations was normal in rheumatoid arthritis patients.[117] 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 to live vaccines such as rotavirus, oral polio and Bacille Calmette–Guerin (BCG) vaccinations which are contraindicated in immune-suppressed individuals. There is a single case report of a child, from a mother exposed to IFX during pregnancy, that died at 4.5 months due to disseminated BCG infection after receiving the vaccination at 3 months.[118] Live vaccines should only be given to infants in the second half of the first year, when it is expected that no detectable IFX or ADA should be present,or no detectable anti-TNF is found when measured. Also, timing of the last dose of IFX and ADA should be as late in the second trimester as possible (around 24–26 weeks of gestation), to maintain remission but to limit the transport of the drug to the fetus.[119–123] Whether this applies to certolizumab pegol needs to be investigated, since this medication is not actively transported across the placenta. The levels of other drugs used for IBD treatment in infants (such as AZA) 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 5A

Appropriate treatment of IBD should be maintained in those patients who wish to conceive, in order to reduce the risk of flares during pregnancy [EL5]. Acute flares during pregnancy carry a high risk of adverse maternal and fetal outcome, and are best treated appropriately and without delay to prevent these complications [EL3]

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.[124–126] A meta-analysis by Miller in more than 1300 female UC patients and 700 CD patients 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).[127] Malformations were observed in about 1% of all pregnancies, and the frequency of spontaneous miscarriages and stillbirths was 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.[128–132] However,

increased rates of preterm birth and low birthweight in IBD patients also occur unrelated to disease activity.[92] Moreover, compared with pregnant IBD patients with inactive disease, women with a relapse during pregnancy have infants with significantly shorter gestation time and lower birthweight,[84,95,130,131,133] increased neonatal intensive care unit admission, and low APGAR score.[87] In addition, disease activity increases the risk for thromboembolic events and emergency cesarian delivery.[134] Therefore, conception should take place during disease remission and active disease should be treated aggressively.

5.2. Medical treatment of IBD and adverse pregnancy outcomes

ECCO Statement 5B

Most drugs used for the treatment of IBD are considered to be of low risk during pregnancy [EL3]. However, methotrexate and thalidomide, are contraindicated [EL3]

ECCO Statement 5C

In cases of relapse, depending on the disease phenotype and activity, 5-ASA or corticosteroids are the preferred therapies [EL5]. Anti-TNF agents can be considered to treat flares in appropriate situations [EL5]

ECCO Statement 5D

Infliximab and adalimumab cross the placenta and their use beyond the second trimester results in neonatal levels exceeding maternal levels [EL3]. This exposure can be limited by stopping the treatment around gestational week 24–26 when considered appropriate by the clinician and the patient [EL3]

The use of 5-ASA derivatives (with the exception of formulation with dibutylphthalate coating), corticosteroids, thiopurines, and biologicals is not associated with significant maternal or neonatal adverse outcomes in pregnant IBD patients. For a summary of the risks of frequent IBD medications used during pregnancy and current ECCO recommendations, see Table 1.

5.2.1. Aminosalicylates, sulfasalazine

Case series, population-based cohort studies,[47,135–138] and two meta-analyses[139,140] 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 birthweight; however, the confounding factor of active disease is difficult to delineate.[135] Animal and human data and the recent meta-analysis[140] did not demonstrate teratogenic effect. A small increase in the risk for congenital malformations has only been shown in the meta-analysis by Cornish et al., but could have been the result of active disease.[139] As sulfasalazine treatment interferes with folate absorption, supplementation is recommended with a higher dose of folic acid than recommended in general (2 mg/day of folate).

Table 1. ECCO overview on drug risk during pregnancy and lacatation.

Drug	During pregnancy	During lactation
Mesalazine	Low risk	Low risk
Sulfasalazine	Low risk	Low risk
Corticosteroids	Low risk	Low risk, 4 h delay before breastfeeding is advised
Thiopurines	Low risk, limited data on 6-TG	Low risk
Anti-TNF agents	Low risk, consider stopping around week 24 in patients with sustained remission. See text	Probably low risk, limited data
Methotrexate	Contraindicated	Contraindicated
Thalidomide	Contraindicated	Contraindicated
Metronidazole	Avoid first trimester	Avoid
Ciprofloxacin	Avoid first trimester	Avoid

6-TG: 6-thioguanine

The mesalazine formulation Asacol® (Procter & Gamble Pharmaceuticals, OH, USA) with dibutyl phthalate coating has been recently downgraded from FDA Category B to C. Dibutyl phthalate has been found in increased concentrations in a patient using the drug,[141] and in animal studies an increased risk of malformations in the male urogenital tract has been observed, but this has not been described in a humans.[142] Nevertheless, high level of phthalates exposure is possibly associated with precocious puberty in humans[143] and, therefore, a switch to a different 5-ASA should be considered for a pregnant IBD patient.

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 fetal 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.[47,86,144] However, the risk for orofacial malformations (cleft lip/palate) is increased in offspring of mothers receiving steroids in the first trimester of pregnancy,[145,146] though this increased risk is small and not confirmed by all studies.[147] In addition, a recent large population-based study comprising 51 973 pregnancies exposed to corticosteroids during the first trimester also failed to find an increased risk of orofacial malformations.[148] Also, there are case reports of neonatal adrenal suppression due to the use of corticosteroids in the late pregnancy of womwn with IBD.[149] There is just one case series of eight CD patients treated with budesonide, which did not find an increased risk of adverse pregnancy outcome.[150] Nevertheless, it remains important to always consider the risks and benefits when prescribing steroids for the mother. Although not clearly demonstrated in IBD patients, the risk of maternal complications such as hypertension, diabetes and preeclampsia seems to be increased during pregnancy,[151,152] which in turn can be associated with an unfavorable pregnancy outcome.

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 its metabolites have been determined in fetal red blood cells.[153] In a recent study evaluating prospectively the pharmacokinetics of thiopurines during 30 pregnancies, a metabolic shift towards higher 6-methylmercaptopurine (6-MMP) production was shown in mothers but without clinically relevant toxicity. In cord blood, thiopurines' active metabolites (6-TG) were detected in levels reaching on average 50% of maternal levels.[104] In this study, 60% of infants had anemia and, therefore, immediate postnatal blood count assessment of children exposed to thiopurines in utero might be considered. Fetal exposure to AZA and 6-MP has been reported in several hundreds of cases.[99,100,136,154] The adverse pregnancy outcomes described in these studies were an increased rate of spontaneous miscarriage, preterm delivery and low birthweight,[99,155] which could have been caused by the underlying disease rather than by the use of thiopurines.[156] More recent controlled studies[102,103,106,111] and a meta-analysis[157] reported no increased risk for adverse pregnancy outcome in IBD patients treated during pregnancy with thiopurines, compared with pregnancy outcomes of IBD patients without this treatment. An association with preterm birth, but no congenital malformations, and low birthweight was shown in one recent meta-analysis.[98] A few cases of immunologic and hematologic abnormalities and chromosomal aberrations in newborns and infants, probably caused by immunosuppression, have been described.[100] However, a prospective study following 30 children exposed to thiopurines in utero revealed neither developmental nor immunologic abnormalities in these children during a median follow-up of 3.8 years.[107]

It has been reported that 6-T6 passes through the placenta,[158] and in the absence of further safety data it should not be used during pregnancy.

5.2.4. Ciclosporin and tacrolimus

Both ciclosporin and tacrolimus are widely used for treatment and prevention of graft vs host reaction after bone marrow transplantations, and to inhibit rejection after solid organ transplantation. Therefore most of the data on pregnancy outcome are derived from these patients.

For ciclosporin, a meta-analysis of 15 studies with 410 pregnant patients did not find an increased rate of congenital malformations.[159] Similar, but fewer, data exist for tacrolimus.[160]

Evidence on the use of ciclosporin in IBD is limited to small series of women who had severe relapses during pregnancy.[133,148,161] With tacrolimus just a single case report of UC patient was published.[162] No congenital malformations were described; the outcomes were complicated with prematurity and low birthweight, but it is very difficult to differentiate the impact of severe disease from the effect of drug itself.

5.2.5. Methotrexate (MTX) 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,[163] exposure to MTX, particularly during the first trimester, may result in miscarriage, growth retardation, fetal loss and congenital malformations, including craniofacial anomalies, limb defects and CNS abnormalities.[164] If conception should accidentally occur, termination of pregnancy 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 6 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 fetal malformations involving limbs, ears, eyes, and neural tube defects, and with neonatal mortality rate of 40%.[165] There are no data on the recommended wash-out period prior to conception for thalidomide.

5.2.6. Biological therapy

IFX and ADA both are IgG1 antibodies and can cross the placenta, particularly in the second and third trimester.[120] Concerning IFX, detectable levels were documented in one case report[166] and in three studies comprising 11, 12 and 11 infants, respectively.[121,123] At birth levels were, as expected, higher in infants and were measurable for 2 to 7 months.[167] Although data are still limited, there is growing evidence that IFX exposure is of low risk in pregnancy, at least for the early outcomes including the absence of teratogenic effects.[112] In addition, the preliminary data from the PIANO study also suggest that the use of anti-TNF agents is safe during pregnancy. In this multicenter, prospective study, pregnancy outcomes of 797 pregnancies of IBD patients exposed, respectively, to thiopurines monotherapy, anti-TNF agents monotherapy, and combination therapy, were compared with a control group of IBD patients without immune-suppressive medication or anti-TNF treatment. No differences in the rate of congenital malformations and other short-term adverse pregnancy outcomes were found between the pregnancies exposed to thiopurines or anti-TNF monotherapy and the control group. However, an increased infection rate during the first year of life has been reported in the group of infants exposed in utero to the combination of thiopurines and anti-TNF agents [relative risk (RR) 1.5; 95% confidence interval (CI) 1.08–2.09].[168]

For ADA, fewer data are available. Placental transfer has been shown in small studies.[121,123] Pregnancy outcomes in these studies were available for only a limited number of pregnancies and, together with the report from PIANO study, no increased rate of adverse pregnancy outcomes has been documented for pregnancies exposed to ADA.[168] Interestingly, ADA 40 mg every other week or weekly was administered to 14 women with recurrent miscarriage to prevent a new miscarriage. Four pregnancies resulted in miscarriage; in the other 10 pregnancies no abnormalities occurred.[169]

Although intra-uterine exposure to IFX or ADA does not seem to increase the risk of adverse pregnancy outcomes, the long-term effect on the developing immune system remains unknown. Therefore, in specific cases, discontinuation of the treatment during pregnancy might be considered to limit the intra-uterine exposure to these agents. A prospective study comprising 29 pregnancies with intentional discontinuation of anti-TNF agents during the second trimester demonstrated that this early discontinuation does not increase the risk of the flare of maternal disease and results in significantly lower levels of IFX in cord blood.[123]

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 with 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 with the full antibody.[170] In the human situation, a study including 10 pregnancies exposed to certolizumab showed very low (less than 2 μg/ml) to undetectable levels of certolizumab in cord blood.[173] Experiences with the use of certolizumab pegol during

pregnancy are more limited than with IFX or ADA, but experimental data in animals and first clinical data do not reveal an increased teratogenic risk in humans.[121,168,171]

Data on the initiation of anti-TNF treatment during pregnancy are scarce. Seven cases of infliximab initiation during pregnancy as part of two retrospective cohort studies,[112] and one case report of successful treatment of steroid-refractory disease with infliximab during pregnancy[172] have been reported thus far. Despite the lack of data, keeping in mind the maternal and fetal risks related to active disease, in specific cases of steroid-refractory disease or in case of significant adverse events of steroids, the initiation of an anti-TNF agent should be considered. Since certolizumab has very limited placental transfer, this agent may be preferred in case of initiation of anti-TNF treatment during pregnancy.

5.2.7. Metronidazole, ciprofloxacin

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 miscarriage or congenital anomalies,[173,174] 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. However, a recent cohort study with 922 pregnant women treated with metronidazole at different stages of pregnancy showed no adverse pregnancy outcomes, including congenital malformations, related to metronidazole.[175]

Human studies with ciprofloxacin have not shown an increase in spontaneous miscarriage or congenital abnormality incidence.[176] However, animal studies demonstrate musculoskeletal abnormalities induced by this medication class.[177] Fluoroquinolones 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

There are no specific nutritional recommendations in pregnant women with IBD beyond those of a 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 according to national guidelines should be commenced in all IBD patients in anticipation of a pregnancy[178–184] and, although data are lacking, higher doses could be administered to women with known small bowel disease. Nutritional deficiencies should be assessed and treated as required. World Health Organization recommendations for pregnancy should be followed.[185]

5.4. Surgery during pregnancy

ECCO Statement 5E

Indications for surgery in pregnant women with IBD are the same as for non-pregnant patients. In the severely ill patient, continued illness is a greater risk to the fetus than surgical intervention [EL4]

Indications for surgery in pregnant women with IBD do not differ from nonpregnant women. In severely ill patients, continued illness is a greater risk to the fetus than surgical intervention.[186] In women with CD, obstruction, perforation, hemorrhage, abscess, or ongoing disease activity despite medical treatment, are indications for surgery and are no different to those for nonpregnant women.[125,186–188] In UC, the main indication would be severe colitis not responding to medical therapy. 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.[188] In the case of UC, the indications for surgery are 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 are some limited series reporting on spontaneous miscarriage in the first trimester and on preterm labour when operation in the third trimester.[188]

5.5. Counseling during pregnancy

ECCO Statement 5F

Discontinuation of maintenance therapy may result in disease relapse and appropriate counseling of the patient, ideally prior conception, is helpful in preventing non adherence to the treatment due to fear of potential harm to the unborn child [EL5]

Studies evaluating the impact of medication discontinuation on the relapse rate of pregnant IBD patients are lacking. Only two studies evaluated adherence to maintenance therapy during pregnancy and reported rates of 59% and 72% among pregnant women with UC and with CD, respectively.[189,190] The most frequent reason for non-compliance during pregnancy is the fear of medication adverse effects on the fetus.[7,189,191–193] Recently, it has been shown that patient knowledge of reproductive aspects of IBD improves after a single education session[194] but, thus far, no studies have evaluated the real impact of the counseling on medication adherence and relapse rate during pregnancy. However, it has been documented that a tailored approach in counseling in general results in an increased adherence in the long term,[195] and thus this approach might be useful in maintaining adherence among pregnant IBD patients as well.

6. Lactation

6.1. Influence of lactation on disease activity and child outcome

ECCO Statement 6 A

Lactation does not independently affect disease activity in IBD [EL 2]

Women with IBD are as likely as the general population to breastfeed their infants; the mean duration of the breastfeeding period is shorter than in the general population.[196,197] Breastfeeding is not associated with an increased risk of disease flare and may even provide a protective effect against disease flare in the postpartum year.[70,198–201] However, in one study, lactation was associated with an increase in disease activity; but medication cessation was a relevant confounding factor.[202]

It is reported that breastfeeding might be protective against the development of early onset of IBD in children.[201] Thus, breastfeeding is suggested when possible, as it may have a protective effect against development of IBD in the offspring; however, the quality of existing

data is generally poor. These findings need to be investigated in well-designed prospective studies.

There is also limited evidence that breastfeeding may be associated with a more beneficial gut microbe profile, as it seems to be associated with highest numbers of bifidobacteria and lowest numbers of C. difficile and E. coli,[203,204] which may help protect against the development of IBD. Formula milk feeding or breastfeeding do not seem to differ in terms of onset of intestinal inflammation,[205] but controversial data exist.[206]

6.2. Medical treatment during lactation

ECCO Statement 6B

5-ASA derivatives [EL3], thiopurines [EL3], anti-TNFs [EL4], and corticosteroids [EL4] are of low risk for breast-fed infants

For a summary of risks of frequent IBD medications used during lactation, see Table 1.

Sulfasalazine is of low risk during breastfeeding. The sulfapyridine moiety is absorbed in minimal amounts and is excreted in milk, but the milk/serum ratio is acceptable.[207] This low risk of aminosalicylates has been confirmed in prospective trials.[208–210]

As metronidazole[211] and ciprofloxacin[212] are excreted into breast milk, neither drug is considered appropriate during the breastfeeding period.

Prednisone and prednisolone result in low human breast milk concentrations. To minimize exposure, a 4-h delay after oral dosing could be recommended.[213,214]

Very small amounts of AZA/6-MP metabolites (nanomolar concentrations of 6-methyl mercaptopurine and thiouric acid) appear in breast milk as reported in several case reports.[215–217] There is a great inter-individual variability in the absorption and metabolism of AZA and 6- MP,[218,219] which influences the exposure of the individual child. Investigation of a group of 11 mothers taking AZA during pregnancy and lactation, and another of 12 patients without using any immunosuppressive therapy, showed that in the 15 breast-fed babies followed up to 4.7 years of age, no increased infection risks for the children were observed.[220]

Limited data suggest that infant exposure to tacrolimus via breast milk is low and therefore this should be discussed.[221] There are no data to support the use of ciclosporin in breastfeeding because therapeutic blood concentrations in the breastfed infant are described.[222] 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 three infants.[223,224] Interestingly, in one observation 6 weeks after delivery, the breastfed infant's serum infliximab level was 39.5 µ/ml after the mother had received IFX until 2 weeks before delivery, but IFX was not detected in the breast milk.[166] In more recent reports, IFX was detected in the breast milk obtained postpartum from three breastfeeding patients with Crohn's disease, but at doses 200 times lower than serum levels. No impact on the infection rate in the newborn was found.[225] 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.[226]

Data on the effects of maternal biologicals on the breast-fed infant are scarce, but until now no adverse effects have been reported. As for all drugs, the unknown long-term side effects of the drugs should be discussed with the patient. IFX can be detected in the breast milk of nursing mothers, but the level of oral absorption by the infant is unclear. Drug and antibody monitoring in breast milk and infants are possible; however, the relevance of those levels remains unclear.

7. Special considerations

7.1. Influence of IBD on sexuality

ECCO Statement 7A

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

There are conflicting data on the impact of IBD on sexuality.[227,228] 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.[229]

Psychological factors may also play a role and depression has been found to be more prevalent among people with IBD[230] and is a predictor for low sexual function.[231] Women with IBD report significantly reduced sexual activity and libido compared with men.[232] There is conflicting evidence on the effect 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[233] and other studies reporting no difference despite an increase in dyspareunia.[232–234] In men, sexuality seems to be less affected.[231,234] Rare complications, particularly from pelvic surgery, include loss of or retrograde ejaculation. However, sexual function seems to be preserved or even increased after surgery.[27,234,235] 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.[236,237]

7.2. Oral contraceptive use in IBD

ECCO Statement 7B

There are no data to support an effect of IBD on the efficacy of oral contraceptives [EL4]. Oral contraceptives do not aggravate the activity of IBD [EL3]

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 thiss 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, who have been vomiting or have had severe diarrhoea for more than

24 h, is to follow instructions for missed pills.[238] One large prospective cohort study and some case-control studies showed no effect of OCs on the activity of IBD.[238–240]

ECCO Statement 7C

IBD is a thrombophilic condition, however the effect is modest [EL3]. Oral contraceptives place patients with thrombophilic conditions such as IBD and smoking at higher risk for thromboembolism [EL1]

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.[241] 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.[242] 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,[243] increase levels of procoagulant proteins (factors II, VII, VIII, and fibrinogen),[244] decrease levels of antithrombin, protein S, tissue factor pathway inhibitor, and fibrinolytic proteins, and increase markers of coagulation and fibrinolysis activation.[244–246] 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.[246,247] 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.[248–251] Inflammation is a thrombophilic condition, due to elevated factor VIII. IBD specifically is considered a thrombophilic condition.[252] 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 7D

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

Pregnancy increases the risk of venous thromboembolism (VTE) by 4–6 fold[253] and is a leading cause of direct maternal death in developed countries.[254] The time of highest risk is in the first 6 weeks of the postnatal period.[255] IBD patients, particularly those hospitalized with active disease, are at increased risk for VTE.[93,256] Hospitalized pregnant IBD patients have an increased risk of VTE compared with their non-IBD pregnant controls: for CD, odds ratio (OR) 6.12 (95% CI, 2.91–12.9) and for UC, 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%.[257] Low molecular weight heparin has been shown to be safe and efficacious in the pregnant population.[258] Therefore consideration of the use of prophylactic low molecular weight heparin in 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.[259]

7.4. Cervical cancer screening: please see guidelines on opportunistic infections statement (OI 4F)

ECCO Statement 7E / OI 4F

Regular gynecologic screening for cervical cancer is strongly recommended for women with IBD, especially if treated with immunomodulators [EL2]. In patients with extensive cutaneous warts and/or condylomata, discontinuation of immunomodulator therapy should be considered [EL5]. Routine prophylactic HPV [human papillovirus] vaccination is recommended for females and males according to national guidelines [EL2]. Current or past infection with HPV is not a contraindication for immunomodulator therapy [EL2]

For text please see Second European Evidence-based Consensuson the prevention, diagnosis, and managementof opportunistic infections in inflammatory bowel disease.[260]

7.5. Endoscopy during pregnancy

ECCO Statement 7G

Gastroscopy [EL3], sigmoidoscopy/colonoscopy, and ERCP [endoscopic retrograde cholangiopancreatography] [EL4] 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]. Hemostasis measures are safe and should be carried out with precautions [EL5]

ECCO Statement 7H

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

ECCO Statement 7I

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]. Sedative drugs should be administered to provide patient comfort, while avoiding over-sedation [EL 5]

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 due to lower esophageal 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 second or third 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.[261–264] Case series and case-controlled studies have shown that gastroscopy is safe and effective, with no evidence for this procedure inducing labor.[265,266] Likewise, small case series of colonoscopy in pregnancy showed no evidence of adverse outcome.[267,268]

Endoscopic retrograde cholangiopancreatography (ERCP) in pregnancy has been reported in several case series.[269–271.] These studies suggest that ERCP is safe in pregnancy, with no increased incidence of congenital malformations, fetal distress, or incidence of precipitating labor. However, there may be a higher risk of post-ERCP associated pancreatitis,[269,272–274] although this did not alter the overall pregnancy outcome in these studies. Radiation dose should clearly be kept to a minimum; in the majority of studies the dose did not exceed the accepted threshold of 10 mGy, but this was not always the case. Recently several case reports and a small study on six pregnant women described the successful application of ERCP without radiation.[275]

The benefit of epinephrine, electricity and contrast dye[276] in the appropriate situation outweigh the risks. The risk of use of polyethelene glycol for preparation is considered low.[277] Sodium phosphate preparations have no data but are a potential harm and should be avoided.[278]

Meperidine is commonly used in endoscopy for analgesia and sedation. It is rapidly transferred across the placenta, but in two large studies of 268 mothers[279] and 62 newborns,[280] respectively, no teratogenicity from meperidine administration during the first trimester was reported. Meperidine can cause diminished fetal beat-to-beat cardiac variability that lasts for approximately 1 h after maternal intravenous administration.[281] This can also be interpreted as a sign of fetal 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 breastfeeding mothers.

Fentanyl is commonly administrated during labor and is considered safe, although case reports note neonatal respiratory depression, muscle rigidity,[282] and opioid withdrawal[283] as potential side effects. Fentanyl is excreted in breast milk, but its low bioavailability to the breastfeeding infant makes it acceptable to breast feed following its use.[284]

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.[285] 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-hirds of maternal serum levels after oral, intramuscular, or intravenous maternal administration.

Midazolam and its metabolite are excreted into milk, but there was minimal exposure if breastfeeding was held for 4 h after administration of a 15-mg dose.[285,286]

8. Recommendations from the Consensus group

ECCO Statement 8A

Appropriate referral for pre-pregnancy and pre-conception counseling should be available for all patients with IBD, to advise and optimize management before conception [EL5]

ECCO Statement 8B

If steroids and biological therapy are required in the third trimester, women should receive multidisciplinary care by a team with experience in treating active IBD in pregnancy [EL5]

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 peri-conceptional use is available.[287] In addition, reproductive wishes lead to medication changes in one-third of these patients. Therefore the working group feel it is important to counsel all IBD patients wishing to conceive. Furthermore, if a flare occurs in the third trimester, the working group feel 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.[287].

Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests (CoI). The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors (ICMJE). The CoI statement is not only stored at the ECCO Office and the editorial office of JCC but also open to public scrutiny on the ECCO website (https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html), providing a comprehensive overview of potential conflicts of interest of authors.

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The ECCO Consensus Guidelines are based on an international Consensus process. Any treatment decisions are a matter for the individual clinician and should not be based exclusively on the content of the ECCO Consensus Guidelines.

The European Crohn´s and Colitis Organization and/or any of its staff members and/or any Consensus contributor may not be held liable for any information published in good faith in the ECCO Consensus Guidelines.

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