European Crohn's and Colitis Guidelines on Sexuality, Fertility, Pregnancy, and Lactation

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Inflammatory bowel disease has a high incidence and prevalence especially in young individuals in their reproductive years. 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. Therefore, the management of patients with a wish to conceive and during pregnancy requires specialized counselling and appropriate management including a multidisciplinary approach and close involvement of the prospective parents under a shared decision-making model. This updated consensus paper addresses these issues and is aimed to optimize pre-conceptional, pregnancy and post pregnancy counselling, including the monitoring and therapeutic management of patients with IBD patients with a wish to conceive.

Keywords: Guidelines, Pregnancy, Fertility, Inflammatory Bowel Disease

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1. INTRODUCTION

Inflammatory bowel disease [IBD] has a high incidence and prevalence in young individuals, affecting people in their reproductive years.[1, 2] The diagnosis of IBD raises many questions; these include concerns about sexuality, disease heritability, and the impact of medications and disease activity on fertility, pregnancy outcomes, and lactation.[3, 4] Uncertainty about the health of the offspring may influence patients' choices in family planning. Therefore, the management of patients who wish to conceive or who are pregnant requires specialized counselling and appropriate management. This involves a multidisciplinary approach and close involvement of the prospective parents under a shared decision-making model. These updated consensus guidelines address these issues and are aimed to optimize and harmonize pre-conceptional, pregnancy, and post-pregnancy IBD management and counselling.

2. METHODS

This document represents the third version of the European Consensus on reproduction in IBD. The development of this consensus included the formulation of population, intervention, control, and outcomes [PICO] questions that were raised by the coordinators [JT and CJvW] that addressed clinically relevant questions in sexuality, fertility, pregnancy, and lactation in patients with IBD. While these PICOs were partly based on the previous guidelines from 2010 and 2015, new relevant clinical questions were also added. The working group consisted of gastroenterologists, an obstetrician, a paediatrician, a surgeon, a dietitian, a clinical epidemiologist, and patient representatives from EFCCA [European Federation of Crohn's and Ulcerative Colitis Associations]. Each PICO question was assigned to two working group members. In an initial web-based conference held in October 2020, all participants discussed the PICO questions, adjusted them where needed, added new questions, and agreed on the final set of 27 questions. The questions were classified into the following four major topics: 1) sexuality, fertility, and counselling patients with IBD considering starting a family; 2) management of IBD during pregnancy; 3) the impact of IBD on pregnancy and the baby's outcomes; and 4) management of IBD postpartum, including the lactation period.

A team of professional librarians performed a comprehensive literature search on EMBASE, PubMed/Medline, and Cochrane Central databases using specific search strings for each PICO question. Two independent working group members [one assigned to the PICO and another from the same group as a second reviewer] assessed the relevance of each

abstract to the PICO and included all relevant papers for final data extraction and analysis. Subsequently, the working group members assigned to each PICO question systematically reviewed and summarized the evidence on every outcome to compile an Evidence Table and to formulate statements. Whenever possible, recent high-quality systematic reviews and meta-analyses of clinical trials were preferentially used to create the statements. When these were unavailable, individual randomized clinical trials [RCTs] followed by observational studies were reviewed. Due to limited randomized controlled trials, it was decided to grade the evidence level [EL] according to the 2011 Oxford Centre for Evidence-Based Medicine [http://www.cebm.net]. All statements were subject to online voting by the panel members, the ECCO National Representatives [two for each country affiliated with ECCO], and 28 additional reviewers from a list of ECCO members who applied to the open call but were not selected to be part of the Working Groups [see acknowledgments section]. The final version of all statements/recommendations was discussed among panel members during a final online consensus meeting held in December 2021 and put to a vote; final recommendations were approved if at least 80% of the panellists agreed with the statement and its associated strength grading. The draft of the manuscript was critically reviewed by two external Guideline Committee members and by the ECCO Governing Board members, who also approved the final version of these Guidelines. The final document on each topic was written by the workgroup leader and their working party. Statements are intended to be read in context with supporting comments and not read in isolation. To ensure consistency, the statements and recommendations were rearranged and merged in the final manuscript by the coordinators. The final manuscript was edited for consistency of style before being circulated and approved by the participants. The final manuscript is divided into different sections that follow in a clinically relevant order but are not necessarily reflective of the order of the initial PICO questions.

3. SEXUALITY, CONTRACEPTION, COUNSELLING, AND FERTILITY IN IBD

3.1. Sexual dysfunction in patients with IBD

Sexual dysfunction refers to any physical or psychological perturbation of sexual health, defined as a state of physical, emotional, mental, and social well-being in relation to sexuality.[5] There is an increased prevalence of sexual dysfunction in patients with IBD. Multiple factors may be responsible, including disease flares, psychosocial factors, pelvic-floor disorders, and side effects of drugs.[6]

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A systematic review with meta-analysis addressed the association between IBD and sexual dysfunction.[7] Pooling together eight observational studies, a significantly higher risk of sexual dysfunction both in men (7 studies, relative risk [RR]: 1.41, 95% confidence interval [95% CI]: 1.09–1.81; $p = 0.008$] and in women [5 studies, RR: 1.76, 95% CI: 1.28–2.42; $p < 0.001$] with IBD was reported. Males <50 years and females <40 years were found to be particularly at risk of sexual dysfunction.[7] In two other systematic reviews, it was also noted that the influence of IBD on sexual health was greater in females than in males,[8, 9] although this was confirmed only for patients with Crohn's disease [CD] in a large population study from Denmark.[10]

Disease activity may impair sexual function due its association with fatigue, discomfort, objective limitations [such as active inflammation or perianal disease], and patient's concerns about body image and intimacy.[6] As an example, erectile function and overall sexual functioning were found to be compromised in males with active IBD.[11, 12] In the IMPACT study, a large survey conducted across Europe with the goal of understanding the impact of IBD on patients' lives, 40% of patients reported that disease activity negatively impacted intimate relationships.[13]

Furthermore, overall sexual quality of life was shown to be significantly lower in patients with IBD; importantly, depression was an independent predictor of lower sexual quality of life.[14, 15] This was confirmed in a survey of German patients with IBD, where females with IBD and depression had reduced pleasure, orgasm, libido, and intercourse frequency.[16]

The possible association between IBD medications, surgery, and sexual dysfunction has not been fully elucidated. Steroids may aggravate sexual dysfunction due to side effects such as weight gain, acne, and hypertrichosis. Some case reports have shown an association between erectile dysfunction and methotrexate [MTX] and sulfasalazine use.[17, 18] Immunosuppressants and biologics have no supporting data in this context. Conflicting data exist on the association between surgery and sexual function.[8, 9, 19-22] Although some studies have shown no difference in sexual health after proctocolectomy with J-pouch anastomosis in ulcerative colitis [UC],[23] there are reports claiming improvement in sexual function after surgery.[22, 24] Other studies have revealed deterioration in many of the associated items,[25, 26] such as injury to the autonomic nerves resulting in erectile dysfunction in males.[27]

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Statement 1

In patients with IBD there is an increased risk of sexual dysfunction, particularly in females and in those with active disease or perianal disease [EL3].

3.2. Contraception in IBD

Absorption of oral contraceptives [OC] mostly occurs in the small bowel.[28] However, it is unknown if having IBD impacts the efficacy of contraception. In a systematic review, two pharmacokinetic reports in women with UC were found. These reports concluded that circulating hormone concentration after OC ingestion was similar between healthy controls and patients with mild activity or ileostomy following proctocolectomy.[29] Nevertheless, it is possible and plausible that OC efficacy may be reduced in patients with CD who have extensive small bowel active disease or have extensive resections.

The association between OC use and disease flares in women with IBD was addressed in one systematic review of five cohort studies.[29] No increased risk of relapse was found in current or previous users of OC when compared with patients that never took hormonal contraception. The strength of this analysis was low due to small sample size and absence of details on OC formulations.[29] In another study on 6104 women with UC from the national Swedish registry, OC use was not associated with UC progression, both in terms of risk of surgery and need for steroids or anti-TNF treatment.[30] In contrast to these findings, a prospective study on a large cohort of 4036 Swedish women with CD revealed a positive correlation between use of combination OC and risk of surgery, particularly with longer use [>3 years] and higher doses.[31] On the other hand, no significant association was found for progestin-only contraceptives.[31]

The safety of OC regarding the predisposition to venous thromboembolism has been poorly addressed in patients with IBD. In a retrospective study, oestrogen-based contraceptives were not associated with an additional risk for thromboembolism in women with IBD in remission when compared to controls.[32] As IBD is considered a thrombophilic condition, particularly when disease is active,[33] a careful assessment of thrombotic risk before OC prescription is recommended. To summarize all available evidence, the United States Centers for Disease Control released the updated *Medical Eligibility Criteria for*

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Contraceptive Use in 2016.[34] This document placed the use of combined hormonal therapy in IBD into a 'grey area', as they are generally regarded as safe except for women with an increased risk of venous thromboembolism, in whom the risks may outweigh the benefits. On the other hand, the benefits seem to outweigh the risks in the case of progestin-only contraceptives, including depot medroxyprogesterone acetate [DMPA] injection. In the latter case, prescription should be avoided in patients with osteopenia or osteoporosis, as DMPA is associated with slight changes in bone mineral density. No restrictions for the use of emergency contraception or an intrauterine device have been reported for women with IBD.[34]

Statement 2

The efficacy of oral contraceptives does not seem to be reduced in women with IBD [EL5]. Oral contraceptives do not seem to be associated with increased probability of IBD flares [EL2]. Oral contraceptives are generally low risk in women with IBD; nevertheless, a careful assessment of thrombotic risk is recommended before prescription [EL5].

3.3. The impact of paternal or maternal IBD on the risk of IBD in the offspring

Studies have consistently described an increased risk of UC and CD in first-degree relatives [FDRs] of affected IBD cases; approximately 12–20% of patients with IBD report family history of disease.[35, 36] Indeed, a positive family history for IBD, especially in FDRs, is considered the strongest risk factor for developing IBD.[37-39] Therefore, it is unsurprising that patients with IBD have a fear of transmitting the disease to their offspring, thus warranting special advice and discussion.

Risk estimates depend on the background population, ethnicity, and type of kinship. Overall, the risk is higher in white versus non-white populations, in Ashkenazy Jewish populations, in CD versus UC, in infants and young adults, in children born to couples with IBD, and in families with multiple members affected.[40-42]

Population-based studies in white populations have shown that the risk of CD in FDRs of a CD case is almost 8-fold increased, whereas the risk of UC in FDRs of a UC case is 4-fold increased.[35] The risk for an offspring of developing the same type of IBD as the parent is significantly higher. In some studies, the highest risk observed was for CD among offspring

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of patients with CD. While the relative risk is increased, it may be useful to communicate risk estimates with prospective parents in terms of absolute risk; overall, the prevalence of IBD in FDRs of a CD and UC proband can reach up to 5% and 3%, respectively.[35, 39, 40, 43]

Although not universally confirmed, some studies have reported a higher risk of IBD in the offspring when the mother is affected as compared to the father.[44, 45] 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 or for affected fathers or for the affected male offspring.[45]

When both parents have IBD, the risk of developing IBD in the offspring was approximately 30% in a population-based study.[46] A more recent survey reported that the cumulative probability of developing IBD is 16% when both parents have disease, although this study was not population-based.[47]

Studies in multiplex families with IBD [>2 FDRs affected] revealed a 57-fold increase in the incidence of IBD compared to the general population. A cumulative effect of the number of family members affected with an increased risk for CD per additional FDR with the disease was reported.[40]

Overall, studies have not shown an association between disease characteristics in the proband and disease course or severity in the offspring. There is no strong evidence to suggest that familial IBD may have a more aggressive clinical course.[48, 49]

Statement 3

Paternal or maternal IBD increases the risk of IBD development for the offspring [EL3]. The risk is greater for CD and is much greater when both parents are affected [EL3].

3.4. Pre-conception counselling in patients with IBD who want to become pregnant

Ideally, all patients with IBD who are planning pregnancy should receive pre-conception counselling, including general and IBD-specific peri-conceptional information. However, not all pregnancies are planned, and therefore physicians should discuss conception and pregnancy with all women of childbearing age with IBD. This will provide an opportunity to discuss parental concerns [including disease heritability], to aim for disease remission, to

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assess anaemia or other deficiencies, to ensure adequate nutritional status, and to discontinue any potentially teratogenic medication.

Prior to conception, women should be up-to-date with healthcare maintenance, including cervical cancer screening and vaccinations. Smoking cessation and alcohol, opiate, and recreational drug use should be addressed.[50] Patients planning pregnancy should be advised to take supplemental folic acid. Higher dosages of folic acid supplementation should be prescribed [2 mg/day] for women taking sulfasalazine.

Active disease at conception increases the risk of adverse birth outcomes, such as preterm birth, low birth weight [LBW], and small for gestational age [SGA]. Conversely, quiescent IBD at conception is associated with pregnancy outcomes similar to the non-IBD population. Therefore, all efforts should be made to achieve disease remission before pregnancy.[51] If possible, disease remission before conception should be assessed through clinical, biomarker(s), and endoscopic or cross-sectional methods. Assessing drug levels before conception provides an opportunity for drug optimization before pregnancy, and should be pursued if available and indicated.

Patient education on IBD and pregnancy increases patient knowledge and promotes IBD medication adherence during pregnancy.[52-54] An educational intervention improved pregnancy-related knowledge and emotional health in pregnant women with IBD and in women with IBD wishing to conceive.[55] Many mothers experience anxiety related to pregnancy and these fears can be addressed with appropriate counselling. Male patients may have similar concerns regarding medication safety and fatherhood in IBD.

Two studies have directly addressed the impact of pre-conception care on pregnancy-related outcomes. One study in IBD patients compared outcomes in 155 patients with an active pregnancy desire who were referred to a dedicated IBD pre-conception clinic to 162 patients who attended the clinic only after they became pregnant. Counselling improved medication compliance, smoking cessation, reduced flares during pregnancy, and lowered the risk of delivering a LBW infant.[56] Another study reported outcomes from a multidisciplinary, single-centre clinic created to manage women with IBD and their neonates ['IBD MOM' clinic]. Patients with severe IBD were more likely to be referred to the clinic. Outcomes of 90 women who attended the clinic were compared to 206 IBD patients who attended community clinics and 61 689 controls. Pregnant women with moderate or severe IBD who attended the 'IBD MOM' clinic achieved similar perinatal outcomes as women with milder forms of IBD and were comparable to the general population regarding pregnancy complications, birth weight, and C-section rates but had significantly higher rates of preterm delivery, likely attributable to disease severity.[57] Based on these studies, early referral to specialist centres

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with a multidisciplinary team [including IBD physicians, maternal-foetal medical specialists, psychologists, and colorectal surgeons] should be considered.

Figure 1 summarizes essential aspects of IBD counselling during the pre-conceptional period, pregnancy, and the postpartum period.

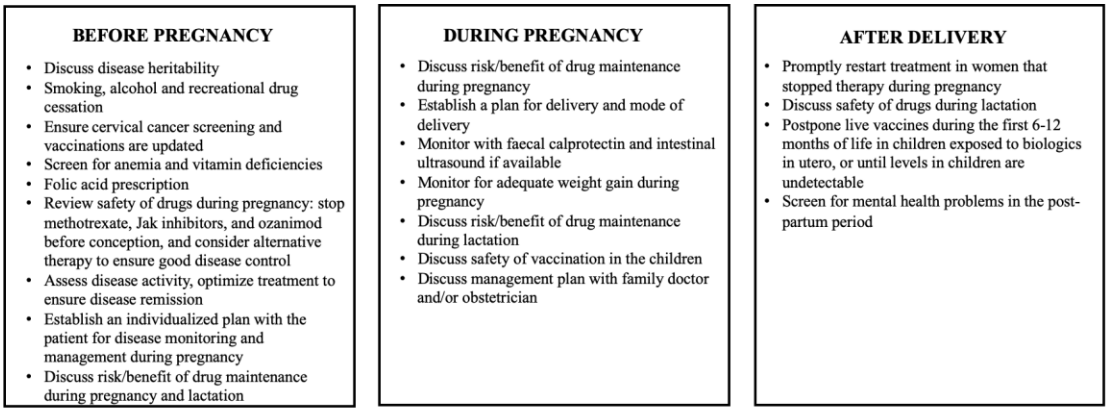

Figure 1 – Management of patients with IBD before, during, and after pregnancy

Statement 4

Pre-conception counselling in IBD is associated with improved pregnancy outcomes [EL3].

Individuals with IBD who are planning pregnancy should undergo pre-pregnancy counselling to address parental concerns, to aim for disease remission, and to discuss medication use during pregnancy [EL5].

3.5. Voluntary childlessness in IBD

Voluntary childlessness refers to the decision not to parent. Patients with IBD have higher rates of voluntary childlessness than controls, with a prevalence of 17–38%. A systematic review described higher rates of voluntary childlessness in CD than in UC and with increasing age.[58 59]

Patients with voluntary childlessness have significantly lower pregnancy-specific IBD knowledge than patients without voluntary childlessness. Having pregnancy-specific IBD knowledge and attendance at a dedicated IBD-pregnancy clinic are significant negative

predictors of voluntary childlessness.[60] Therefore, pre-conception counselling for all IBD patients of childbearing age allows these patients to make informed decisions on family planning and parenting.

Statement 5

Patients with IBD, particularly with CD, are more likely to choose voluntary childlessness than healthy controls [EL2]. Lack of pregnancy-specific IBD knowledge may impact voluntary childlessness. Therefore, appropriate education on pregnancy and family planning for all patients with IBD of childbearing age is recommended [EL5].

3.6. Fertility in IBD

a) Impact of disease activity

Women with IBD are less likely to have biological children,[58, 61] in part due to voluntary childlessness,[62] disease-related psychosocial reasons,[11] and reduced fertility and fecundity rates due to abdominal and pelvic surgery.[61] When patients present with active disease, systemic inflammation can lead to adverse conditions for successful conception and symptoms may lead to less frequent sexual activity. In a population-based study from the UK on 9639 women with IBD, overall fertility rate was significantly reduced in the 9-month period following a flare. After adjustment for contraceptive use, this association was interpreted as inability to conceive rather than voluntary childlessness.[61] While many systematic reviews report reduced female fertility during active disease,[61, 63, 64] we acknowledge that the evidence from original studies supporting these findings remains poor [old studies, small sample sizes, no reports on more objective markers of disease activity].

Male patients with active disease were more likely to report difficulties conceiving [45%, OR: 2.62; 95% CI: 1.34–5.13] in contrast to those in remission [21%, OR: 0.93; 95% CI: 0.37–2.33].[65] A study examining sperm quality in severely active IBD provided further support to this observation by revealing increased sperm motility [28.4% to 37.4%] in patients who achieved remission.[66]

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Statement 6

Active disease is associated with decreased fertility in women with IBD [EL3]. Achieving clinical remission may increase the probability of successful conception. Active disease is also associated with decreased fertility in men with IBD [EL4].

b) Impact of IBD drugs on fertility

Several studies assessed impairment of spermatogenesis due to medications used for IBD. For mesalazine compounds, phthalate-containing tablets should be avoided based on one recent study that revealed an impact on sperm quality in addition to the already known risk of urogenital tract malformations.[67] The strongest evidence for sperm abnormality (lower spermatozoa count, lower sperm motility [asthenozoospermia], and higher risk of oligospermia) has emerged according to a meta-analysis based on four studies comparing 2–4 g/d sulfasalazine to mesalazine.[68] Male patients on sulfasalazine may therefore be switched to mesalazine. Studies on thiopurines were too heterogeneous to perform a meta-analysis. However, no concerns were raised in the 14 observational studies reported in a systematic review.[69] MTX can induce aberration in sperm DNA via oxidative stress in animal studies,[70] although a very recent study did not reveal any DNA aberrations with low-dose MTX.[71] A systematic review on the effect of MTX on male fertility did not reveal a direct influence on sperm integrity or on fertility or risks associated with conception.[72] A systematic review did not find evidence that use of anti-TNF agents affects sperm motility or vitality.[73] Anti-TNF agents are excreted in negligible amounts in semen.[66] Patients who started anti-TNF agents had a statistically significant, but clinically irrelevant, reduction in sperm DNA fragmentation index after treatment initiation [12.8% vs 10.0%; p = 0.02].[66] All other semen parameters were unaffected by therapy. To our knowledge, limited data have not revealed any signals for other classes of drugs used to treat IBD, such as steroids, thiopurines,[74] anti-integrins,[75] calcineurin inhibitors, or anti-IL12/23 inhibitors.[76] In rat studies, tofacitinib at supratherapeutic levels reduced female fertility due to increased post-implantation loss. There was no impairment of female rat fertility at exposure levels of tofacitinib equal to the recommended dose of 5 mg twice daily, and at approximately 0.5 times the 10 mg twice daily dose.[77] Tofacitinib exposure at supratherapeutic levels had no effect on male fertility, sperm motility, or sperm concentration.[77] Studies in filgotinib-treated rats revealed decreased male fertility, impaired spermatogenesis, and histopathological effects on male reproductive

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organs. There was no impact on female fertility.[78] The final results from clinical studies evaluating the impact on male fertility are pending [clinicaltrials.gov NCT03201445]. Ozanimod had no effect on male or female fertility.[79]

Statement 7

Most of the commonly used IBD drugs have no demonstrated impact on fertility, in particular sperm quality [EL4].

Sulfasalazine is associated with reversible oligospermia and asthenozoospermia [EL2].

c) Impact of surgery on fertility

There is evidence that fertility and fecundity rates may be reduced in female patients with IBD following open pouch surgery.[61, 80-92] The impact of surgical interventions other than ileal pouch-anal anastomosis [IPAA] on fertility is unknown. There is an association between IBD-related surgery and miscarriage rates, C-section delivery, and use of assisted reproductive technologies.[82]

Several meta-analyses and studies have shown that IPAA resulted in a 2- to 5-fold increase in infertility rate;[80-82, 86] this risk is even higher in the first year after surgery.[81] Increasing age is also a risk factor associated with reduced fertility.[88]

Laparoscopic IPAA seems to be associated with lower infertility rates compared to open surgeries,[83, 84] likely due to reduced pelvic adhesions.[82] No difference was found in fertility rates between patients who had laparoscopic appendectomy and laparoscopic IPAA.[83] Laparoscopic colectomy and ileorectal anastomosis may be discussed in suitable patients as this alternative procedure avoids pelvic dissection and reconstruction, thus averting pelvic adhesions seen in open pouch surgery.

After an IPAA procedure, reduction in fertility is more distinct in female patients when compared to male patients.[92] There is a more pronounced reduction in fertility for patients with pouch failure, especially in female patients.[91]

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Statement 8

IBD-related pelvic surgeries lead to decreased fertility and fecundity rates in women [EL2]. Laparoscopic surgical approaches may lower the risk of infertility [EL2].

d) In vitro fertilisation (IVF) treatment in patients with IBD

Cohort studies reported that the incidence of pregnancy and live births after IVF in patients with UC and CD are comparable with controls.[93,94] However, one nationwide study showed that the chance of a live birth following an IVF treatment was lower in women with UC [OR: 0.73; 95% CI:0.58–0.92] but not in women with CD [OR: 0.77; 95% CI:0.52–1.14]. However, in this study, prior surgery in women with CD led to reduced probability of a live birth for each embryo transfer [OR: 0.51; 95% CI:0.29–0.91].[95] Corticosteroids prior to assisted reproductive technology in women with CD and UC did not increase the probability of a live birth.[96]

Females with restorative proctocolectomy for UC have a 3-fold increased use of *in vitro* fertilization [IVF] than female IBD patients without restorative proctocolectomy.[97] Nonetheless, the probability of having a live birth after IVF are comparable to those of the general IVF population and to those of patients with UC without IPAA.[97, 98]

Consistent with the general infertile population, younger age and lower BMI [22.5 kg/m2 vs 24.0 kg/m2; p = 0.06] are associated with the likelihood of achieving a live birth following IVF in patients with IBD.[99] Although disease activity is not associated with reduced probability of achieving a live birth following IVF, in most studies patients were mostly in remission.[99]

Statement 9

In women who have had restorative proctocolectomy with IPAA for UC, IVF procedures are three times more likely than in women without restorative proctocolectomy. However, both groups have a similar probability of having a live birth after IVF [EL3].

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4. MANAGEMENT OF IBD DURING PREGNANCY

Pregnancy is a highly emotional and vulnerable period, especially for those diagnosed with a chronic disease. To ensure a stable environment for patients, a dedicated multidisciplinary team of specialists with IBD knowledge should be involved in management and should maintain a close relationship with the prospective parents. Ideally, pregnant patients, particularly those presenting features associated with poor disease course, should be discussed regularly in a multidisciplinary team including a gastroenterologist, obstetrician, paediatrician, psychologist, dietitian, and a surgeon, depending on the trimester and the patient's personal situation. Although many of the important aspects that may impact pregnancy outcome, such as smoking cessation, vaccination, a healthy diet, and lifestyle are preferably already discussed in the pre-conception period, continuous education and reassurance remains of utmost importance to ensure patient adherence to the IBD management plan [**Figure 1**]. Another important aspect of managing IBD during pregnancy is stringent monitoring of disease activity to allow timely interventions and adjustments to IBD therapy if warranted. Pregnant women with IBD should be given special attention regarding nutritional requirements. Gaining weight during pregnancy is critical, as inadequate weight gain is associated with poor outcomes for the offspring.[100, 101] Although most IBD pregnancies have excellent outcomes, being pregnant with IBD can bring an extra layer of fear and anxiety. Attention should be given to the mental and psychological health of women with IBD, as an increased risk of new-onset psychiatric diagnosis in the postpartum period has been described in this population.[102, 103] Special circumstances during pregnancy include carrying an ostomy and perianal fistulizing disease. The pregnant IBD patient with an ostomy warrants specialized care as there may be a higher risk of preterm birth and LBW babies. Major stoma complications, such as stoma prolapse, parastomal hernias, and small-bowel obstruction may complicate pregnancy; regular monitoring and specialized counselling is warranted in these situations.[104] Patients with perianal fistulizing disease require timely consultation on the mode of delivery to discuss the patient's preferences and the risk of sphincter injury balanced with risk of C-section.

4.1. Impact of pregnancy on IBD course

Pregnancy coincides with hormonal, immunological, microbial, and immunological changes, all of which may interact with the pathophysiology of IBD.[105] An ECCO-EpiCom observational study on 209 pregnant patients with IBD compared with 209 non-pregnant IBD patients showed that pregnant women with CD had a similar disease course both during pregnancy and after delivery as non-pregnant women with CD. In contrast, pregnant women

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with UC were at higher risk of relapse during pregnancy and in the postpartum period than non-pregnant women with UC.[106] In a long-term observational study on 310 patients with a total of 597 pregnancies, disease course was worse in non-pregnant patients than in pregnant patients with IBD.[106] This association was statistically significant in patients with UC only. The number of pregnancies did not affect long-term disease course in patients with UC or with CD.[106]

In a retrospective study of patients with CD, pregnancy was independently associated with higher rates of surgical disease [OR: 2.9, 95% CI: 2.3–3.7; $p < 0.001$], defined in this study as peritonitis, gastrointestinal haemorrhage, intra-abdominal abscess, toxic colitis, anorectal suppuration, intestinal-intestinal fistulae, intestinal-genitourinary fistulae, obstruction or stricture [or both], perforation, anorectal suppuration, and intestinal-genitourinary fistulae.[107] In contrast, having an IPAA does not impact pregnancy outcomes.[108]

A meta-analysis of 14 studies revealed that patients with IBD who conceive when their disease is active [based on clinician's assessment or Harvey-Bradshaw Index in patients with CD, and clinician's assessment, Truelove criteria, or Simple Colitis Clinical Activity Index in patients with UC] are more likely to have active disease during pregnancy than those who conceive when in remission. However, these studies had a high risk of bias that limited data quality.[51] Nonetheless, these findings were confirmed by two observational studies. Active disease at conception in a prospective cohort was strongly associated with disease relapse during pregnancy (odds ratio [OR]: 7.66; 95% CI: 3.77–15.54). Patients with UC experienced relapse during pregnancy more often than patients with CD [OR: 3.71; 95% CI: 1.86–7.40] independent of maternal age, smoking, peri-conceptional disease activity, previous IBD surgery, and use of immunosuppressive or anti-TNF agents.[109] Another report revealed that active disease at conception and history of disease flare during previous pregnancy were the only independent predictors of disease relapse in current pregnancy. The risk of disease relapse was higher in those with UC than in those with CD [48.1% vs 31.8%; $p = 0.005$]. Rates of hospitalization during pregnancy [14.7% vs 0%; $p = 0.02$] and preterm delivery [32.4% vs 5.7%, $p = 0.006$] were higher and neonatal birth weight was lower [median 3039 vs 3300 g, $p = 0.03$] with those with disease flare than for patients who maintained remission during pregnancy.[110]

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Statement 10

Pregnancy may increase the risk of relapse or worsening disease in patients with UC and complications in patients with CD, especially if disease is active at conception [EL3]. IBD remission before conception is recommended [EL2].

4.2. Monitoring IBD during pregnancy

It is important to note that physiologic adaptations associated with pregnancy can alter serum biomarkers, including haemoglobin, albumin, and C-reactive protein [CRP]. In normal pregnancy, haemoglobin and albumin concentrations decrease, while CRP can increase.[111] A systematic review concluded that haemoglobin, albumin, and CRP do not correlate with clinical disease activity in pregnancy.[112] Although CRP may be higher in pregnant patients with active IBD than in those with inactive disease, CRP does not consistently correlate with clinical disease activity indices or physician global assessment.[112-115] Nonetheless, it may be useful to monitor trends in these biomarkers.

Faecal calprotectin does not appear to be affected by pregnancy. In two studies including healthy pregnant women without IBD, no changes in faecal calprotectin concentrations during pregnancy were observed.[115, 116] A systematic review that included seven studies assessing faecal calprotectin concentrations during pregnancy in women with IBD concluded that faecal calprotectin appears to correlate with active disease throughout pregnancy.[112] A subsequent prospective study that included 157 pregnancies in women with IBD revealed that faecal calprotectin correlated with disease activity as measured by physician global assessment and clinical disease scores in all trimesters.[113]

Statement 11

Faecal calprotectin can reliably monitor disease activity during pregnancy [EL2]. Some blood parameters, such as haemoglobin and CRP, are impacted by pregnancy and may not be reliable, although trends can be helpful [EL5].

Reports on the use of endoscopy and cross-sectional imaging in pregnant women with IBD are very limited. In a registry-based study, delivery outcome in 3052 pregnant women undergoing endoscopy between 1992 and 2011 was compared with 1 589 173 pregnancies

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without endoscopy during pregnancy.[117] Endoscopy during pregnancy was associated with an increased risk of preterm birth, SGA, and LBW. No increased risk was found regarding congenital malformations or stillbirth. When only a subset of women with IBD undergoing endoscopy was examined, the risk was increased for preterm birth and LBW, while no increased risk was observed for SGA, neonatal death, or malformations.[117] These findings should be interpreted with caution, as the impact of disease activity in these outcomes may be a confounder.

A prospective cohort study showed no significant differences in gestational age at birth, congenital abnormalities, or APGAR scores in 42 pregnant women with IBD who underwent endoscopy who were matched 1:1 with pregnant patients with IBD who did not undergo endoscopy.[118] These outcomes were confirmed by an uncontrolled study in 48 pregnant patients.[119] No hospitalizations or adverse obstetric events temporally associated with sigmoidoscopy were found; in 78% of cases, performing the procedure led to therapeutic adjustment. Three other multicentre retrospective studies found no increased risk of stillbirth, congenital abnormalities, or induced deliveries in patients who underwent either sigmoidoscopies or colonoscopies. In 63% of patients, the findings led to therapeutic adjustment.[120-122] In these studies, stillbirths were reported but were within the expected range of the overall population.[117-122] Even if considered safe, endoscopy during pregnancy should be reserved for situations where there is a strong indication that may impact clinical decisions. Procedure time should be minimized, the lowest effective dose of sedative medications is recommended, and patient should be kept in left pelvic tilt or left lateral position to avoid vena cava or aortic compression. The decision and the methods used to monitor foetal heart rate depend on gestational age of the foetus and available resources.[123]

There are no published data on outcomes of capsule endoscopy in pregnant women with IBD. Two cases reported in pregnant patients without IBD were uneventful.[124] However, pregnancy is considered as a [relative] contraindication by the capsule manufacturers given the unknown risks of the electromagnetic field of the capsule recorder.[124]

To avoid radiation exposure, magnetic resonance imaging [MRI] is preferred over computed tomography [CT] during pregnancy. However, use of gadolinium is not recommended due to unknown effects on the child in utero.[125-127] Nevertheless, use of a CT scan during pregnancy with a low radiation dose [<50 mGy] may be considered if required by the clinical situation and if alternatives are limited.[127]

Intestinal ultrasound [IUS] can objectively and effectively assess disease activity in pregnant patients with IBD.[128, 129] A study including 127 IUS examinations in pregnant IBD patients

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revealed that IUS is accurate in assessing disease activity in the setting of pregnancy when compared with faecal calprotectin and had a high sensitivity and specificity [74% and 83%, respectively].[128] In this study, there was also a significant association between physician global assessment and active disease on IUS. Colonic views were feasible in almost all cases up to the early third trimester, while terminal ileal views were feasible in almost all patients up to gestational week [GW] 20. Ileal views are possible beyond GW 20, but the terminal ileum becomes more difficult to assess with IUS due to the gravid uterus.[128]

As part of the monitoring strategy, therapeutic drug monitoring in pregnancy, as in the non-pregnant patient, may be needed to adjust therapy or to interpret flares. Three studies have reported on anti-TNF trough levels during pregnancy. While adalimumab levels remain stable throughout pregnancy, infliximab clearance decreases in the second and third trimester, leading to increased trough levels.[130-132]

Statement 12

During pregnancy, endoscopy can be performed when needed to guide clinical decision making [EL3].

Capsule endoscopy during pregnancy is considered a contraindication [EL5].

Ultrasonography [EL4] and MRI without the use of gadolinium [EL4] are radiation-free and are recommended instead of a CT scan [EL5].

4.3. Monitoring and managing thromboembolic complications during pregnancy

Patients with IBD have a higher risk for thromboembolic complications. As pregnancy is also related to a higher risk of thromboembolic complications, especially if disease is active, it is recommended to screen for any additional risk factors before conception. Thromboprophylaxis should be initiated if a patient is considered to be at high risk for thromboembolic complications.[133]

A systematic review with meta-analysis evaluated the venous thromboembolic [VTE] risk in patients with IBD compared with healthy controls during pregnancy and postpartum.[134] Four of these studies evaluated UC and CD risk separately, three differentiated between deep venous thromboses [DVT] and pulmonary embolism [PE], and two addressed VTE events in the context of disease flares. Overall, 17 636 pregnant women with IBD and 11 251 778 pregnant women without IBD were included. The VTE risk during pregnancy was higher in patients with IBD (relative risk [RR]: 2.13; 95% CI: 1.78–2.66), with a higher risk of DVT [RR:

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2.73; 95% CI:1.78–2.66] but without a significant increase of PE. Both patients with UC [RR: 2.24; 95% CI: 1.61–3.11] and CD [RR: 1.87; 95% CI: 1.09–3.19] had an increased risk of VTE. Furthermore, there was a trend towards a higher risk of pregnancy-associated VTE during disease flares [RR: 7.81; 95% CI: 0.90–67.78]. Even though significant differences were not observed in the meta-analysis, previous studies have found that IBD flare during pregnancy increased the risk of VTE [RR: 2.64; 95% CI: 1.69–4.14].[135] VTE risk persisted in pregnant women with IBD after adjusting for smoking, BMI >30 kg/m², and maternal age.[135] During the postpartum period, the risk of VTE was also higher in patients with IBD [RR: 2.61; 95% CI:1.84–3.69], especially in UC [RR: 2.85; 95% CI: 1.79–4.52] when compared with CD [RR: 1.69; 95% CI: 0.85–3.38].[134]

A study comparing obstetric outcomes in patients with and without IBD also found a higher risk of VTE during pregnancy [UC, OR: 8.44, 95% CI: 3.71–19.20; CD, OR: 6.12, 95% CI: 2.91–12.9). Moreover, C-sections [OR: 1.68; 95% CI: 1.51–1.87] and hospital admission were associated with an increased risk of VTE [CD, 1.5% vs 0.2%; UC, 2.1% vs 0.2%; $p < 0.001$].[136]

Use of low molecular weight heparins [LMWH] appear to be safe during pregnancy.[133] There is no support for routine use of vitamin K antagonists, direct oral thrombin, or factor Xa inhibitors, fondaparinux, or danaparoid in uncomplicated pregnancy-related VTE. In lactating women, an overlapping switch from LMWH to warfarin is possible. Overall, anticoagulation should be continued for 3 months and until at least 6 weeks postpartum when indicated.[137]

Statement 13

Pregnancy and IBD increase the risk of VTE events [EL2]. VTE risk assessment should be performed before conception and during pregnancy, especially in patients with active disease [EL5]. LMWH is recommended after C-section, during hospital admission for disease flares, or when other risk factors of VTE are present [EL5].

4.4. Managing IBD flares during pregnancy

Given the low risk of adverse pregnancy outcomes associated with antibiotics, 5-aminosalicylates [5-ASA], corticosteroids, and anti-TNF agents, pregnant women experiencing a flare can in general be managed according to current guidelines for non-pregnant patients.[138, 139] The choice of therapy should be individualized and should consider disease severity and gestational age. After a multidisciplinary discussion considering the

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patient's preference, delivery induction may be preferable before initiating therapy in those who are at least at GW 37.[140] Considering the potential adverse events associated with corticosteroids [infections, hypertension, diabetes, and preeclampsia], anti-TNF agents are preferred over prolonged corticosteroid use. Budesonide in patients with mild disease may be an alternative to avoid exposure to systemic corticosteroids. Although limited data are available on the use of budesonide in pregnancy, budesonide is considered to be low risk. Similarly, although older data with ciclosporin suggest a benefit in treating pregnant patients with UC, anti-TNF agents offer the option of maintenance treatment. Initiation of thiopurine therapy is generally not recommended because of the risk of idiosyncratic adverse reactions and slow onset of action. Vedolizumab may be considered to treat a flare during pregnancy but could be combined with a faster acting agent, such as corticosteroids. Limited data are available for ustekinumab, and very limited for enteral feeding. Currently, use of JAK inhibitors and S1P receptor modulators should be avoided during pregnancy. MTX is contraindicated during pregnancy.

Although IBD flares are at least as common in pregnant woman as in non-pregnant woman, robust data on optimal management are limited to case series. In an American case-control study, 15 out of 18 pregnant patients treated with intravenous steroids for a severe UC flare [including five patients who received rescue therapy with cyclosporine] achieved clinical response, while three patients required a colectomy.[141] Similar efficacy was shown in the retrospective GETAID study, which included 8 pregnant patients requiring intravenous steroids followed by ciclosporin for severe UC.[142] All 8 patients achieved clinical response, although 1 patient required rescue therapy with infliximab. In a Czech retrospective study, 6 out of 9 pregnant patients achieved clinical remission after initiation of anti-TNF therapy for a flare.[143] In the retrospective CONCEIVE study, 3 pregnant patients initiated vedolizumab for a flare, 1 in combination with mesalazine and 2 in combination with steroids.[144] All patients achieved clinical remission.

In general, if a pregnant patient with IBD develops a flare, follow up by a multidisciplinary team including a gastroenterologist, an obstetrician, a paediatrician, and an experienced surgeon should be sought to optimize outcomes. The risks of active disease should be weighed against the risks of surgery throughout pregnancy, and urgent surgery should be performed if clinically indicated, regardless of the gestational age.

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Statement 14

A multidisciplinary team that includes an experienced gastroenterologist, obstetrician, and surgeon may be valuable in helping to optimize outcomes in pregnant women with a disease flare [EL5]. The choice of therapy for a flare during pregnancy should consider the severity of disease activity and the gestational age [EL5].

Statement 15

Pregnant women experiencing a flare should be managed according to current guidelines for non-pregnant patients with 5-ASA, steroids, cyclosporine, anti-TNF agents [EL4], ustekinumab, or vedolizumab [EL5].

Initiating monotherapy with a thiopurine is generally not recommended due to the slow onset of action and the potential risk of adverse events [EL5]. Currently, JAK inhibitors and S1P receptor modulators should be avoided during pregnancy [EL5].

Statement 16

In case of a flare beyond gestational week 37, early delivery could be considered prior to initiation of medical therapy [EL5].

4.5. Surgery in pregnant women with IBD

There is little information in the literature on IBD-related surgery during pregnancy, and much of what is available predates the availability of biologic therapy or minimally invasive surgery. In a systematic review, optimal surgical management strategies for complicated and medically refractory IBD during pregnancy and the puerperium were identified.[145] A total of 32 articles reporting 86 cases over a 60-year period [1950-2015] were included. The most common indications for IBD-related surgery during pregnancy were refractory UC and perforated small bowel in patients with CD. In the older literature, surgical interventions during the third trimester of gestation universally required C-section or resulted in premature delivery due to the onset of labour; these findings led some authors to recommend a synchronous C-section and colectomy preferably after 28 weeks.

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More recently, a report described 15 patients with CD who underwent surgery between 1992 and 2015.[146] Most of the surgeries were performed due to penetrating or stricturing disease and the surgical approach was mainly through laparotomy [11 cases]. Seven surgeries were performed during the first trimester, seven during the second trimester, and one during the third trimester. Delivery was vaginal in half of the cases. Four C-sections were performed concomitantly with CD surgery.[146] An Ecco Confer multicentre case series reported on 44 IBD patients that had surgery during pregnancy, 55% in the 2nd trimester; while no patient died, 27% had post-surgical complications, and 4 miscarriages/stillbirths occurred, 2 during and 2 after surgery. Among the 40 newborns 42% needed hospitalisation, of which 25% required intensive care.[147]

A recently published nationwide registry-based cohort study including women identified in the Danish National Patient Registry and the Danish Medical Birth Registry examined the association between non-obstetric abdominal surgery during pregnancy and birth outcomes [SGA, preterm birth, and miscarriage].[148] Over 1 200 000 pregnancies were analysed [4490 had undergone surgery]. The highest risk of miscarriage was observed in the week following surgery. Over 80% of the miscarriages occurred after non-obstetric abdominal surgery during the first trimester of pregnancy. There were 8556 patients with IBD in the study cohort [137 had undergone surgery]. Although there was an increased risk of SGA [only in births that occurred at least 14 days after surgery], preterm delivery, and miscarriages among patients operated on during pregnancy, there was not a specific sub-analysis that focused on patients with IBD. These undesired outcomes of surgery should be interpreted with caution, as these may relate to the underlying disease, the patient's condition, and inflammatory mediators.

Statement 17

Indications for surgery in pregnant women with IBD are the same as for non-pregnant patients [EL5]. The indication for IBD-related surgery during pregnancy should be determined promptly based on IBD severity and general maternal conditions. Urgent surgery should be performed if clinically indicated, regardless of the gestational age [EL5].

The surgical management should be discussed in a multidisciplinary team involving gastroenterologists, colorectal surgeons, obstetricians, and neonatal specialists, as required [EL5].

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4.6. Drug discontinuation during pregnancy

a) Thiopurines

In a small registry-based case-control study, the odds of preterm birth were significantly higher among women with IBD who stopped thiopurine therapy either 90 days before or during the first trimester of pregnancy [n=14, OR: 6.56; 95% CI: 1.44–29.82] than in women with IBD who continued thiopurine therapy throughout pregnancy [n=2, OR: 2.15; 95% CI: 1.25–3.72).[149] However, the investigators did not consider disease activity at the time of thiopurine discontinuation.

It is unknown whether a short thiopurine cessation period during pregnancy in women in remission on thiopurine monotherapy or combination therapy with a biologic is associated with an increased risk of relapse, adverse pregnancy outcomes, or both. In the absence of data in pregnancy, data on non-pregnant patients may provide guidance. Withdrawal of thiopurine monotherapy is associated with a higher risk of relapse, whereas withdrawal of the thiopurine from combination therapy with biologics does not appear to increase clinical or endoscopic relapse rates up to 2 years of follow up.[150] However, it should be noted that discontinuing thiopurines may lead to lower anti-TNF trough levels.[151] Assessing trough levels may be considered before thiopurine discontinuation to ensure adequate levels to maintain remission.

Two prospective cohort studies assessing thiopurine metabolites in pregnant patients with IBD reported pregnancy-related shunting of metabolites, with a decrease in 6-TGN and increase in 6-MMP levels by the second trimester.[152, 153] Rarely, this can result in maternal thiopurine hepatotoxicity, which may be difficult to distinguish from intrahepatic cholestasis of pregnancy. Therefore, measurement of thiopurine metabolite levels [liver function tests at a minimum should be measured during the different trimesters] should be considered in pregnant women on thiopurine therapy.[152]

Statement 21

Patients on thiopurine monotherapy can continue treatment throughout pregnancy [EL5].

When thiopurines are used as combination therapy with biologics, thiopurine discontinuation may be considered on an individual basis if the patient is in long-term remission [EL5]. Demonstration of adequate serum anti-TNF levels may be helpful in this setting [EL5].

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a) Biologics

Biologics for the treatment of IBD are immunoglobulin G1 [IgG1] full monoclonal antibodies. In early pregnancy, insignificant amounts of IgG are transported by passive diffusion. However, starting at week 13–17 and increasing significantly thereafter, maternal transfer of IgG1 through placental Fc neonatal receptors occurs,[154-156] which may result in cord blood levels in infants that may be up to 4-fold higher than in maternal serum.[157]

Cord blood levels depend on type of anti-TNF agent [higher for infliximab than adalimumab, approximately 2.6 and 1.5 foetal:maternal ratio, respectively][158-160] and on the duration of exposure during pregnancy [significantly lower in those who discontinue anti-TNF before GW 30].[132, 160] Detectable anti-TNF agents may persist in the infant's blood for up to 12 months.[160] An exception is certolizumab pegol, which contains a polyethylene glycol [PEG] moiety and as such is not transported across the placenta.[156] Infant vedolizumab levels at birth are lower than maternal levels, suggesting more rapid clearance when compared with anti-TNF agents.[132, 161] A recently published prospective study on patients exposed to vedolizumab during pregnancy showed that the median infant:mother vedolizumab ratio at birth was 0.44, with a mean time to clearance of 3.8 months and no detectable levels in infants by 6 months of age.[161] Similar to anti-TNF agents, the cord blood concentration of ustekinumab is higher than the measured maternal serum drug level.[157, 162-164]

Acknowledging the active transfer of biologics and potential exposure of infants in utero and in early life [a sensitive period for immune system programming and development], there is a theoretical concern that exposure to biologics may disturb the child's immunity. Therefore, discontinuing a biologic drug before the third trimester [T3] will limit the drug exposure of the foetus.[158, 160, 165] However, discontinuing a biologic drug that has induced remission may increase the chances of relapse, with negative consequences for the mother and foetus. Likewise, it is plausible that a long drug holiday may increase the chances of secondary loss of response in the postpartum period.

Several studies have investigated the relapse rates following anti-TNF discontinuation during pregnancy and compared maternal and child outcomes between those exposed to the drug during the three trimesters of pregnancy with those where drug was discontinued before T3.[166-172] In a prospective cohort study, 51 patients who were in remission for more than 8 months discontinued anti-TNF before week 25 of pregnancy. There was a 9.8% relapse rate by the end of pregnancy and 15.7% by 3 months postpartum; this was similar to the 15.6% in the 32 women who continued treatment because of active disease [p = 0.14].[173] In a prospective survey that included 169 pregnant women with IBD, 54 [35%] discontinued anti-TNF before GW 30 and 99 patients continued beyond GW 30. Subgroup analysis for women

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in remission during T1 and T2 showed no differences in self-reported rates of relapse [defined as treatment intensification] between those who discontinued or continued treatment [RR: 0.20, 95% CI: 0.02–1.56; $p = 0.08$].[168] These results were confirmed in other studies, where there was no difference between infliximab and adalimumab in relapse rates.[160,158] Few studies have reported on the post-pregnancy relapse rate in women who discontinued anti-TNF before T3 when compared with those who continued. In the Pregnancy in IBD and Neonatal Outcomes [PIANO] study, discontinuation of a biologic in T3 was not associated with an increased risk of subsequent flare at 4, 9, and 12 months postpartum.[157] However, in a recently published meta-analysis, therapy discontinuation during pregnancy was identified as one of the risk factors for postpartum disease activity.[174]

Large cohort studies have been published recently. Using data from the large Truven Health Analytics MarketScan database, 68 deliveries in women who discontinued treatment before GWs 30–32 were compared to 318 deliveries who continued infliximab at least until T3, 90 days or less before delivery.[175] The single factor associated with risk of flare [defined as need for new steroid prescription, patient hospitalization, or emergency room visits] was early infliximab discontinuation [OR: 5.98; 95% CI: 1.83–19.5].[175] In the largest study reported to date,[176] data from a French national health system database reported on 1457 pregnancies exposed to anti-TNF agents. There was a significantly greater risk of relapse [defined as steroid initiation in steroid-naïve women] in women who discontinued anti-TNF before GW 24 [60/131, 45.8%] than in those who continued anti-TNF beyond GW 24 [63/206, 30.6%; $p = 0.005$], even after adjusting for disease severity, age, IBD type and duration, and concomitant thiopurine use [OR: 1.98; 95% CI: 1.25-3.15].[176]

When compared with earlier anti-TNF discontinuation, most studies show no negative impact of the use of anti-TNF agents throughout the three trimesters of pregnancy on pregnancy outcomes (C-sections, intrauterine growth retardation [IUGR], congenital malformations)[175, 177] or on birth outcomes [LBW, preterm birth, SGA, stillbirth].[168, 175, 178, 179] In one study, a reduction in birth weight of 300 g was reported [albeit not meeting criteria for LBW] in women in remission who continued anti-TNF agents during T3 when compared with those who stopped before GW 30.[168] In contrast, another study reported a higher rate of preterm births in women who discontinued infliximab earlier during pregnancy.[176] Stopping anti-TNF agents during T1 showed a higher incidence of unfavourable global pregnancy outcomes [69% vs 25%; $p < 0.05$] and higher frequency of spontaneous abortions [46% vs 0%; $p = 0.001$] when compared with continuation of anti-TNF therapy throughout T3.[172] Continuing anti-TNF therapy during T3 as opposed to earlier discontinuation does not seem to be associated with an increased risk of maternal complications or maternal infections during pregnancy.

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Follow up of children exposed to anti-TNF agents in utero revealed no differences in the overall rate of infections requiring hospital admission, milestone developments, autoimmunity, or other negative outcomes between exposure only during early trimesters of pregnancy or exposure during the full three trimesters.[158, 160, 167, 176, 177, 180] The impact on the newborn's outcomes after intrauterine exposure to biologics is discussed in more detail in the next section.

Decisions on stopping or continuing anti-TNF agents should be made on an individual basis and always discussed with the patient. To reduce foetal exposure, the timing of the last dose of an anti-TNF agent in T3 may be administered in accordance with the presumed due date. If the drug is stopped during pregnancy, it should be started as soon as possible after delivery to minimize the risk of relapse and to avoid a protracted drug holiday.[181]

Data on the effects of stopping or continuing vedolizumab or ustekinumab during pregnancy are scarce and limited by small sample size and brief follow-up time. A retrospective, observational study reported on relapse rates following early discontinuation of vedolizumab or ustekinumab during pregnancy. Fifty percent of women who stopped vedolizumab during T1 had a relapse as compared with 8% for those who continued the drug. In contrast, in a prospective study of 50 vedolizumab-exposed pregnant women, those who stopped treatment prior to T3 [n=13] were not at increased risk of relapse during the postpartum period [6 months] compared with women who continued treatment in T3 [n=30, RR: 0.85; 95% CI: 0.23–3.14].[161] Relapse was reported in 31% of patients who stopped ustekinumab and in 33% of those where ustekinumab was continued.[182] It is likely that stopping vedolizumab and ustekinumab during pregnancy may increase the risk of relapse or may lead to worsening disease activity, as these agents are currently mostly used in case of anti-TNF failure. Therefore, careful judgment is required before discontinuing treatment. Factors to consider include risk of relapse, prior disease history, patient preferences, the limited evidence and follow up on the child's outcomes, and the half-life of these agents and their lower immunogenicity when compared to anti-TNF agents [rendering secondary loss of response less likely in the context of a drug holiday].

Statement 18

For women with active disease just before or during pregnancy, or with disease that is difficult to control, continuation of anti-TNF [EL3] or non-TNF biologics [EL5] throughout pregnancy is recommended. The last dose of anti-TNF in the third trimester should be timed in accordance with the presumed due date to reduce foetal exposure [EL5].

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Statement 19

For women in remission discontinuing anti-TNF prior to the third trimester is not recommended, as it may increase the risk of relapse [EL3] and lead to unfavourable pregnancy outcomes [EL3]. However, if a pregnant patient in long-term remission wishes to discontinue anti-TNF prior to the third trimester, resumption of anti-TNF shortly after delivery is recommended [EL5].

Statement 20

For women in remission treated with non-TNF biologic agents [ustekinumab, vedolizumab], an individualized decision on discontinuing treatment should be made, considering the risk of relapse and the limited data on the consequences of foetal exposure [EL5].

5. IMPACT OF IBD AND IBD MEDICATIONS ON PREGNANCY AND NEONATAL OUTCOMES

5.1. Impact of IBD on pregnancy outcome

Two meta-analyses evaluated the risk of adverse outcomes during pregnancy in patients with IBD.[183, 184] One report included 23 cohort studies.[183] Overall, 15 007 pregnancies in women with IBD and 4 614 271 pregnancies in women without IBD were evaluated. Women with IBD were more likely to have preterm delivery [OR: 1.85; 95% CI: 1.67–2.05], stillbirth [OR: 1.57; 95% CI 1.03–2.38], SGA, or LBW newborns than healthy controls [OR: 1.36; 95% CI: 1.16–1.60].[183] This meta-analysis considered SGA separately from LBW and did not find significant results in SGA.[183] Nevertheless, in a sensitivity analysis with higher quality studies, a higher risk of SGA was observed for patients with IBD [OR: 1.96; 95% CI: 1.01–3.81].[184] Observational studies concluded that pregnant women with IBD have a higher risk of preterm birth,[185-189] LBW,[185-187, 190, 191] and SGA.[187, 188, 192]

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A recent meta-analysis that included 7917 IBD pregnancies and 3253 healthy pregnancies evaluated the risk of adverse pregnancy outcomes.[193] Gestational diabetes was more frequent in patients with IBD [OR 2.96; 95% CI: 1.47–5.98] regardless of corticosteroid use. The risk of preterm prelabour rupture of membranes [PPROM] was increased in patients with IBD [OR: 12.10; 95% CI: 2.15–67.98].[193] Pregnant women with IBD were more likely to undergo C-section [OR: 1.79; 95% CI: 1.16–2.77] than healthy controls; this was significant for patients with UC [OR: 1.80; 95% CI: 1.21-2.90] but not CD [OR: 1.48, 95% CI: 0.94-2.34]. Predictors of C-section in patients with UC included smoking, pancolitis, and IPAA; predictors for those with CD were previous intestinal or perianal surgery and active perianal disease.[193]

Patients with IBD do not seem to have an increased rate of voluntary abortion or abortion due to medical reasons, ectopic pregnancy, early pregnancy loss, placenta previa, placental abruption, preeclampsia, or chorioamnionitis.[193] Nevertheless, a recent population-based cohort study that included 6731 CD pregnancies and 1 832 732 control pregnancies revealed that CD was associated with a small but increased risk of ectopic pregnancy [OR: 1.23; 95% CI: 1.01–1.49] regardless of previous surgeries.[194] A single cohort study of 86 792 women that included 666 diagnosed with IBD reported a higher risk of severe preeclampsia in patients with IBD (Hazard ratio [HR]: 2.24; 95% CI: 1.05–4.80), even though no increased risk of overall pre-eclampsia was observed [HR: 1.21; 95% CI: 0.76–1.95].[186]

Only two studies[186, 195] reported a higher risk of 5-minute Apgar score <7 in pregnant women with IBD, but this was not concordant among the studies.[187, 191, 196-198] Five studies[187, 191, 192, 195, 199] evaluated the risk of neonatal intensive unit care admission. Two studies reported a higher risk of admission for newborns from mothers with IBD, although a higher rate of newborn deaths was not observed.[187, 195, 199, 200] In a population-based study with 2637 UC and 868 942 control pregnant women, a higher risk of death for newborns from women with UC was reported [OR: 1.93; 95% CI: 1.04–3.60]. Risk factors included previous surgery and <5 years of disease. Importantly, the number of events was low [n=11] and results should be interpreted with caution.[198] A nationwide cohort study that included 7250 UC pregnancies, 6559 CD pregnancies, and 1 691 857 non-IBD pregnancies found no differences in voluntary abortion.[201]

Having a disease flare during pregnancy increased the risk of PPROM [UC, OR: 2.82, 95% CI: 1.87–4.26; CD, OR: 2.82, 95% CI: 1.87–4.26], preterm birth [UC, OR: 2.72, 95% CI: 2.12–3.48; CD, OR: 2.72, 95% CI: 2.12–3.48], and LBW [UC, OR: 1.92, 95% CI: 1.37–2.70; CD, OR: 2.10, 95% CI: 1.51–2.90]. Moreover, patients with active CD also had an increased risk for stillbirth [OR: 4.48; 95% CI: 1.67–11.9], SGA [OR: 2.75; 95% CI: 1.72–4.38], and 5-minute Apgar score <7 [OR: 2.21; 95% CI: 1.24–3.93].[196] Other observational studies

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revealed similar results in active disease, with a lower rate of live births and an increased risk of miscarriage, C-section, foetal growth restriction,[190] and LBW.[189]

Although a significantly higher risk of congenital anomalies [OR: 1.29; 95% CI: 1.05–1.58] was observed in a meta-analysis, there was publication bias and no reliable conclusions could be made.[183] Moreover, in a multicentre prospective study including 159 mothers with IBD and 175 healthy controls, a higher rate of congenital anomalies was observed, but results were limited by a small number of events and no definitive conclusions could be made.[200]

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Pregnant women with IBD seem to have a higher risk of gestational diabetes, stillbirth, preterm prelabour rupture of membranes, preterm delivery, small for gestational age, and low birth weight newborns [EL2].

Disease activity during pregnancy is a risk factor, as it is associated with preterm prelabour rupture of membranes, preterm birth, and low birth weight in IBD pregnant women. Disease activity during pregnancy also increases the risk of stillbirth and low Apgar score in CD [EL3].

5.2. Risks of IBD drugs during pregnancy

Most IBD drugs are considered low risk during pregnancy and can be used, although exceptions exist. At the time of this review, many novel biologics and small molecules are being tested in phase 3 RCTs and results are becoming available. In these guidelines, only drugs that were licensed at the time of our literature review and consensus meeting were included [**Table 1**].

Statement 23

Most drugs used for the treatment of IBD are considered low risk during pregnancy [EL3].

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a) 5-aminosalicylates, sulfasalazine

Treatment with 5-ASA and sulfasalazine during pregnancy is not associated with an increased risk for adverse pregnancy outcomes or malformations.[184, 201-205] Although a higher rate of premature birth, stillbirth, and LBW was observed in some studies, it seems plausible that these results were due to the confounding factor of active disease.[203] Teratogenic effects have not been demonstrated.[205] To prevent toxicity of sulfasalazine treatment preventing folate absorption, supplementation with folate 2 mg/day is recommended. If using an aminosalicylate with dibutyl coating, switching to a different 5-ASA formulation should be considered for the pregnant IBD patient due to the possibility of urogenital malformations in the offspring.{Zhu, 2016 #1720}

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5-ASA is regarded as low risk during pregnancy [EL3].

b) Corticosteroids

Short-term use of corticosteroids is generally not associated with adverse pregnancy outcomes. Although some small studies suggested a possible risk for orofacial malformations in offspring of mothers receiving steroids in the T1, a large study did not reveal any increased risk of orofacial malformations.[206-209] Neonatal adrenal suppression due to corticosteroid use in late pregnancy has been described in one infant exposed in utero and may be dependent on the type of corticosteroid used.[210] On the other hand, budesonide and budesonide MMX were not associated with an increased risk of adverse pregnancy outcomes in two case series.[211, 212] It should be noted that the risk for maternal complications during pregnancy, such as hypertension, diabetes, and preeclampsia, may be increased due to corticosteroid use and thus increase the risk of an unfavourable pregnancy outcome.[213, 214] A recent analysis from the prospective PIANO registry reported on 432 mothers who were exposed to steroids during pregnancy. After adjusting for other variables, corticosteroid use was associated with increased risk of preterm birth, LBW, IUGR, and neonatal intensive care unit admission. Exposure to corticosteroids during T2 or T3 was associated with serious infections in infants at 9 and 12 months. A limitation of this cohort study is that disease activity was monitored using self-reported questionnaires and not objective markers of inflammation, thus making it difficult to separate the contribution of disease activity itself from

steroid exposure.[215] Nonetheless, these data emphasize the importance of adequate disease control during pregnancy and steroid-sparing strategies.

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Although short-term corticosteroids, including budesonide, can in general be regarded as low risk during pregnancy for managing flares, the risk of maternal-foetal complications should be considered [EL3].

c) Antibiotics

The role of antibiotic therapy in the treatment of IBD is very limited. Metronidazole and ciprofloxacin are the most frequently used antibiotics in the treatment of selected clinical conditions, such as pouchitis and perianal or abdominal sepsis in patients with CD.[216]

There are minimal data on the efficacy and safety of antibiotic use in pregnant patients with IBD. In fact, in this specific situation, this use is largely based only on data from series that do not include pregnant patients with IBD.

Although a case-control study reported cleft defects associated with metronidazole exposure,[217] two historical meta-analyses[218, 219] and a retrospective cohort study[220] showed no association between metronidazole treatment at different trimesters with development of preterm birth, LBW, or congenital anomalies.[220] A review of evidence, including cohort studies, case-control studies, and meta-analyses confirmed no relationship between metronidazole exposure during pregnancy and risk of preterm delivery and birth defects.[221]

An association between quinolones and musculoskeletal abnormalities has been shown in animal studies. Moreover, due to their high affinity for bone and cartilage, fluoroquinolones may cause arthropathy in children. For this reason, this class of antibiotics should be avoided during the first 3 months of pregnancy. However, as reported by three meta-analyses,[222-224] exposure to quinolone, fluoroquinolone, or ciprofloxacin was not associated with a significant increase in major congenital malformations and adverse pregnancy outcomes during T1. Moreover, in a small case series of pregnant patients with IBD, both metronidazole and ciprofloxacin were not associated with poor pregnancy outcomes.[224] Thus, considering the limited available data, a short course of ciprofloxacin may be considered if needed during T1.

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In case of perianal or abdominal sepsis or pouchitis, metronidazole and ciprofloxacin can be administered in patients with IBD during pregnancy. However, given the risk of arthropathies in children, ciprofloxacin should be avoided if possible during the first trimester of pregnancy [EL4].

d) Thiopurines

Controlled trials and meta-analyses have not reported an increased risk for adverse pregnancy outcomes in patients with IBD treated during pregnancy with thiopurines compared with pregnancy outcomes of patients with IBD not treated with thiopurines.[172, 180, 201, 225-233] The PIANO study also revealed that thiopurine therapy or combination therapy with biologics during pregnancy was not associated with increased adverse maternal or foetal outcomes at birth.[158] An association with preterm birth [but not with congenital malformations] and LBW was shown in only one meta-analysis.[234] Reported adverse pregnancy outcomes, such as an increased rate of spontaneous miscarriage, preterm delivery, and LBW, may instead be caused by the underlying disease than by thiopurine use.[225, 235, 236] A small number of cases of immunologic and hematologic abnormalities in newborns and infants, probably caused by immunosuppression, have been described.[152, 226, In a prospective study that followed 30 children exposed to thiopurines in utero, no developmental or immunologic abnormalities were observed, although 60% of infants presented with anaemia at birth.[153, 237]

Only minimal data from case series or case reports are available on combined use of thiopurines and allopurinol during pregnancy. These data do not suggest any important safety signal regarding risk of malformations.[238-240] However, the available data are insufficient to be conclusive.

e) Calcineurin inhibitors

Data for ciclosporin and tacrolimus on pregnancy outcomes are mostly derived from transplant patients. Ciclosporin is not associated with an increased rate of congenital malformations.[241] Similar but more limited data exist for tacrolimus.[242] Evidence on the use of ciclosporin in pregnant IBD patients is limited to a small series of women who had severe

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relapses during pregnancy.[142, 243] A single case report of a patient with UC treated with tacrolimus has been published.[244] No congenital malformations were described; the outcomes were complicated by prematurity and LBW. However, it is difficult to differentiate the impact of severe disease from the effect of the drug itself. Due to its known side-effect profile, ciclosporin use during pregnancy may be considered only after careful risk and benefit assessment.

f) Methotrexate and thalidomide

Both MTX and thalidomide are teratogenic and contraindicated in pregnancy. Therefore, barrier methods to prevent pregnancy during MTX therapy are advised. Particularly during T1, MTX use may result in miscarriage, IUGRI, foetal loss, congenital malformations [including craniofacial anomalies], limb defects, and central nervous system abnormalities.[245] If conception accidentally occurs, termination of pregnancy should be discussed, but not necessarily performed. Use of thalidomide is associated with major foetal malformations involving limbs, ears, eyes, and neural tube defects. The neonatal mortality rate associated with thalidomide use is 40%.[246] Thus, thalidomide use is strongly contraindicated during pregnancy.

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Thiopurines are not associated with significant neonatal adverse outcomes in pregnant patients with IBD [EL3]. Methotrexate [EL3], thalidomide [EL3], JAK inhibitors and ozanimod are contraindicated during pregnancy [EL5]. Data for ciclosporin and tacrolimus in patients with IBD during pregnancy are limited.

g) Biologics

Existing data suggest that use of anti-TNF agents is low risk in pregnancy and is not associated with adverse pregnancy outcomes, congenital abnormalities, preterm birth, LBW, or teratogenicity.[160, 173, 176, 179, 247-252] The PIANO study demonstrated that the use of anti-TNF agents either as monotherapy or in combination with thiopurines had no impact on adverse pregnancy outcomes in patients with IBD. In this prospective registry study, drug exposure did not increase the rate of congenital malformations, spontaneous abortions, preterm birth, LBW, or infant infections in the first year of life. However, the study also confirmed that a higher disease activity was associated with risk of spontaneous abortion.[157] Although the

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data exist mainly for infliximab, adalimumab, certolizumab pegol, and golimumab also do not seem to have a different safety profile during pregnancy.[157, 171] Though some studies reported adverse events, such as LBW, this might rather be due to the underlying disease activity than the anti-TNF agent.[168, 253, 254]

Animal studies show no evidence of adverse effects on pre- or post-natal development after administration of vedolizumab and ustekinumab.[255, 256] Few studies including patients treated with vedolizumab or ustekinumab during pregnancy have been published; pregnancies were uneventful pregnancies in most cases.[132, 144, 157, 161, 164, 257-259] A retrospective cohort study including 73 pregnancies in patients receiving vedolizumab or ustekinumab did not reveal a negative signal on maternal or neonatal outcomes.[182] These data were confirmed for vedolizumab in the prospective NOVA study among 50 vedolizumab-exposed pregnancies and the retrospective CONCEIVE study [n=79].[144, 161] Nevertheless, due to limited data, careful follow up of pregnant patients treated with vedolizumab or ustekinumab is advised.

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Anti-TNF antibodies are regarded as low risk during pregnancy [EL3]. Data for vedolizumab and ustekinumab are limited, but no increased risk of adverse pregnancy outcomes has been identified [EL4].

h) Small molecules

Tofacitinib is teratogenic in rats and rabbits and induced external and soft-tissue malformations and skeletal malformations or variations. However, applied doses were 73 times and 6.3 times greater, respectively, than the human dose of 10 mg twice daily, which makes the relevance of these findings to human data difficult to determine.[260] Reported outcomes of pregnancy cases identified from tofacitinib RCTs, post-approval and non-interventional studies, and spontaneous adverse-event reporting appear similar to those observed in the general population.[257] Overall, no firm conclusions can be drawn, as only very few women were actually exposed early in T1 to tofacitinib and only very few birth outcomes have been reported.[260] Thus, due to the very limited data available in pregnant patients with IBD, use of tofacitinib during pregnancy is contraindicated at this stage. Based on findings in animals, filgotinib may cause foetal harm and is therefore contraindicated during pregnancy.[78] This recommendation likely applies to other JAK inhibitors.

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There are only very limited data about pregnancy from patients treated with ozanimod from the trials on multiple sclerosis[261] and UC.[262] Thus, ozanimod is also contraindicated during pregnancy due to lack of human data.

Table 1. ECCO overview of risks of drugs during pregnancy and lactation

Drug	During pregnancy	During lactation
Mesalazine	Low risk	Low risk
Sulfasalazine	Low risk	Low risk
Corticosteroids	Low risk	Low risk
Metronidazole	Low risk *	Avoid
Ciprofloxacin	Avoid in T1*	Low risk*
Thiopurines	Low risk	Low risk
Thiopurines + allopurinol	Limited data	Limited data
Ciclosporin **Tacrolimus**	Low risk, limited data	Limited data
Anti-TNF	Low risk	Low risk
Vedolizumab	Low risk, limited data	Low risk, limited data
Ustekinumab	Low risk, limited data	Low risk, limited data
Methotrexate	Contraindicated	Contraindicated
Thalidomide	Contraindicated	Contraindicated
Tofacitinib	Contraindicated	No data; avoid
Filgotinib	Contraindicated	No data; avoid
Ozanimod	Contraindicated	No data; avoid

**May be considered for short-term course for perianal disease; if possible consider other alternatives*

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5.3. Mode of delivery in women with IBD

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The mode of delivery does not seem to influence outcome of patients with IBD regarding development or worsening of inactive perianal disease [EL2] and anal sphincter damage [EL2].

The outcome of delivery in patients with IBD has been subject to two systematic reviews that focused primarily on pouch failure in patients after restorative proctocolectomy and worsening of pre-existing perianal CD or development of de novo perianal disease. [80,263]

In these two systematic reviews, 25 studies of UC patients after restorative proctocolectomy were included. The outcomes of vaginal versus C-section delivery were mainly evaluated by faecal incontinence questionnaires. In only one study on 97 patients with UC, where objective anal sphincter measures such as anal manometry and endo-anal ultrasound were used,[264] a higher risk of anal sphincter damage was reported in patients following vaginal delivery. However, both systematic reviews overall found no differences in the risk for damage of the anal sphincter with regard to delivery mode in UC patients after restorative proctocolectomy. [80,263 264]

A systematic review analysed seven studies of CD patients with perianal disease and found no increased risk of relapse of perianal disease in those with inactive disease, or de novo perianal disease following vaginal delivery.[263] In addition, two other prospective-retrospective cohort studies that used self-reported faecal incontinence outcomes and included patients with CD and perianal disease, respectively, found no increased risk of faecal incontinence associated with vaginal delivery.[136, 265] Thus, the overall evidence does not support specific preference of C-section over vaginal delivery in patients with IBD regarding damage of the anal sphincter in case of restorative proctocolectomy or development of de novo perianal disease. Therefore, choice of delivery mode in these patients should be based on a multidisciplinary discussion involving the gastroenterologist, obstetrician, and in patients with perianal disease, an IBD surgeon. The final mode of delivery should be discussed with the obstetrician and should be agreed upon with the patient based on shared decision making. Considering the impact on quality of life of even a minor perineal trauma caused by vaginal delivery in UC patients after restorative proctocolectomy, or in patients with CD and active perianal disease or history of rectovaginal fistula, a C-section as the preferred mode of delivery should be discussed with the obstetrician in these settings. Given the increased

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future risk of restorative proctocolectomy in UC patients with chronically active disease, in whom a colectomy is likely foreseen, a C-section as the preferred mode of delivery should also be discussed for these patients.

One retrospective study based on a nationwide register that included over 3000 deliveries of patients with IBD found an overall increased risk of VTE in IBD patients postpartum; after adjustment for demographic covariates and C-section delivery, the OR for developing VTE was 6.12 [95% CI: 2.91–12.9] for women with CD and 8.44 [95% CI: 3.71–19.20] for women with UC. C-section itself was an independent risk factor for increased risk of VTE [OR: 1.68; 95% CI: 1.51–1.87].[136]

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Mode of delivery should be guided by obstetric considerations. In patients with active perianal disease, prior rectovaginal fistula, and after restorative proctocolectomy, C-section is recommended after multidisciplinary discussion involving gastroenterologists, obstetricians, and IBD surgeons [EL5].

5.4. Effect on in utero exposure of IBD drugs on health and development of the offspring

Several cohort studies on infants exposed to anti-TNF agents and thiopurines in utero [all trimesters] have been published, sometimes with conflicting results. The risk of [parent-reported] serious infections requiring hospital admission or antibiotic treatment in the first year of life of these children did not appear to be increased in most of these studies.[167 157, 160, 173, 176, 177, 180, 235, 237, 250, 252, 266-271] However, some studies reported an increased risk of paediatric infections, particularly for children exposed to combination therapy, even if lack of adjustment for confounding by disease severity and healthcare-seeking behaviour could not be excluded.[272, 273 160, 270]

A large multicentre retrospective study compared the outcomes of children up to 5 years of age born to mothers with IBD. In total, 196 [20%] had intrauterine exposure to anti-TNF agents [60 with concomitant thiopurine], 240 [24%] were exposed to thiopurine monotherapy, and 564 children [56%] were not exposed to anti-TNF agents or thiopurines and served as a control group. Overall, no associations between in utero exposure to anti-TNF agents, thiopurines, or both and antibiotic-treated infections, severe infections requiring

hospital admission, adverse reactions to vaccinations, growth failure, autoimmune diseases, or malignancies were observed.[180, 274] Likewise, a large study from France found no increased risk for serious infections during the first 5 years of life after in utero exposure to thiopurines and anti-TNF monotherapies. However, there was a higher risk for children exposed to combination therapy [aHR: 1.36; 95% CI: 1.04-1.79].[270]

Consistent with these reports, most studies failed to reveal an association between anti-TNF cord blood levels at birth and number of infections requiring antibiotic treatment after birth, hospital admission, development of allergies, or adverse reactions to vaccinations during the first year of life.[157, 160, 176, 268]

However, effects on the developing immune system, particularly from drugs transferred across the placenta, cannot be excluded. One infant died after Bacillus Calmette-Guérin [BCG] vaccination[275] and some cases of neutropenia with skin infections requiring granulocyte colony stimulating factor have been reported after exposure to anti-TNF agents.[276] Small studies have shown subtle changes in T and B cell subsets,[277, 278] decreased response after mycobacterial challenge,[277] and vaccine response rates lower than historically reported [see section on vaccination].[250, 279] Furthermore, the reassuring data on infection rates are mostly regarding serious infections requiring hospitalization and have been generated in a population with high vaccination coverage.

Thiopurine exposure may be associated with neonatal anaemia,[153] although this was not observed in the recent Australian PICCOLO study.[152] Another small study did not show anaemia of exposed children at the age of 1 year.[233] Thiopurines in combination with anti-TNF agents may increase the risk of neonatal infections,[160, 272, 273] although this has not been consistently shown.[157, 270, 280] However, the body of long-term safety data with up to 5 years of follow up after intrauterine exposure to biologics in combination with thiopurines is increasing; overall, no increased risk of major infant infections, no increased risk of malignancy, and no psychiatric diagnoses or autism were observed.[160, 180, 273, 280] Data on growth and neurodevelopment are also limited, but follow up of psychomotor development in children in the first year of life[157, 250, 267] and quality of life assessments in children up to 5 years of age did not raise concerns thus far.[237, 281]

Safety data on children exposed to vedolizumab, ustekinumab, and tofacitinib are limited;[132, 144, 161, 164] data up to 1 year of life from vedolizumab-exposed children has shown no increased risk of infections.[157,162]

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The risk of serious infections requiring hospital admission in the first 5 years of life does not seem to be increased in children exposed to anti-TNF agents or thiopurines during pregnancy [EL4]. However, there are no data beyond 5 years of follow up on the effect of in utero exposure of IBD drugs on the developing immune system and neurodevelopment [EL4]. Safety data on children exposed to vedolizumab, ustekinumab, and tofacitinib are limited [EL5].

6. MANAGEMENT OF IBD IN THE POSTPARTUM AND DURING THE LACTATION PERIOD

6.1. Risk of postpartum flare

Studies on the risk of postpartum relapse in patients with IBD are scarce and differ in methodology and outcomes. One retrospective-prospective study including 37 patients with IBD with assessment of clinical activity prior to pregnancy and up to 3 years postpartum found a significantly lower rate of both CD and UC relapses in the postpartum period.[282] On the other hand, a prospective, multicentre study that included 209 pregnant IBD patients matched by age, disease location, and activity to non-pregnant patients with IBD found no increased risk of CD relapse postpartum but an increased risk of UC flare both during pregnancy and postpartum.[106] Another prospective study that included 46 pregnant patients with IBD that assessed faecal calprotectin and clinical activity prior to conception, in each trimester, and 6 months postpartum found no difference in disease activity at these five timepoints.[115]

Overall, the relapse rate postpartum varies significantly across studies and ranges from 25–50%.[283-285] The predictors of postpartum relapse include disease activity during T3, therapy de-escalation during and after pregnancy,[285] and longer duration of disease, specifically in CD.[106] A recent meta-analysis aiming to assess risk factors for postpartum disease activity that pooled results from 27 observational studies [3825 patients] reported stricturing or penetrating phenotype in CD, active disease at conception and during pregnancy, and biologic discontinuation in T3 as risk factors for postpartum disease activity.[174]

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There is no increased risk of postpartum relapse in patients with CD compared with non-pregnant patients with CD. In UC, there may be an increased risk of relapse postpartum [EL3].

6.2. Restarting biologics in the postpartum period

Given the risk of a postpartum flare [section 4.1], biologics will be continued throughout pregnancy and in the postpartum phase in many cases unless there is a complication postpartum [e.g., infection that serves as a contraindication to biologic therapy]. There is a low risk of transmission of biologics in breast milk. The low levels of biologic drugs transferred through breast milk in the postpartum period do not appear to lead to negative outcomes in infants, and the benefits of breastfeeding overall outweigh this low risk.[286, 287]

If biologics were paused earlier in pregnancy, for example in T2 or T3 due to patient choice or well controlled disease, they can be restarted in the postpartum period with clinical benefit to the mother. Ideally, the biologic should be resumed as soon as possible after delivery.

Although there are data on the risk of flare after discontinuing anti-TNF agents outside the context of pregnancy, there are minimal data on the risk of a short drug holiday as is the case with cessation during pregnancy. Reintroducing the same anti-TNF agent after a short period of cessation [such as after stopping during pregnancy] appears to be effective in most patients.[173] No data are available to guide the best approach to restarting the drug after a drug holiday. Therefore, either reinduction or resuming the same maintenance regimen is a case-by-case decision and should consider duration of drug holiday, disease activity, concomitant immunomodulators, and type of biologic.

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For patients who continue biologics during the entire pregnancy, the treatment should be continued uninterrupted in the postpartum phase, unless there is a contraindication to their use [EL5].

For patients who interrupted treatment during pregnancy, the treatment should be resumed after delivery as soon as possible [EL5]. Reinduction or continuation of previous maintenance therapy is dependent on clinical circumstances [EL5].

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6.3. Impact of in utero exposure to IBD drugs on schedule, effectiveness and safety of vaccinations in the first year of life

Several small studies have been conducted to evaluate the efficacy and safety of vaccines in infants who were exposed in utero to anti-TNF agents and azathioprine. In most studies, vaccine response was measured cross-sectionally at different ages, which makes interpretation of results difficult.[250, 267, 271, 288-290] Although two studies indicated inadequate response to vaccination in some children, conclusions could not be drawn due to the small study size.[279, 291] One study compared vaccination response to *Haemophilus influenzae type B* and tetanus between 42 children exposed to biologics and 8 children exposed to either other immunosuppressive drugs or to no immunosuppressive drugs. No significant differences were found, but overall response rates were lower than historically reported.[279] A study on the effectiveness of hepatitis B vaccination in children born to mothers with IBD did not reveal a difference between response to hepatitis B vaccination in 15 children exposed to anti-TNF agents compared with 12 children not exposed to anti-TNF agents.[292] In a recent retrospective cohort study, the response to routinely administered *Haemophilus influenzae* type B, pneumococcal, and pertussis vaccinations in 27 children exposed to anti-TNF agents during pregnancy was measured. The overall vaccination response seemed comparable for children exposed to anti-TNF agents and healthy infants after booster vaccination at 12 months of age. However, after the primary vaccination series at 6 months of age, inadequate response was observed in some infants and may be related to anti-TNF exposure.[292]

No adverse events regarding vaccination safety were shown for children exposed to thiopurines and biologic therapy in cohort studies and in one large multicentre retrospective study.[173, 180, 232] However, the 2022 European Medicines Agency recommendation stated that 'no live attenuated vaccines should be administered during the first year of life in infants exposed to infliximab, but live attenuated vaccination can be considered if there is a clear benefit and infant infliximab level is undetectable'.[293] This recommendation follows some case reports of fatal disseminated BCG infection after the live BCG vaccination[275, 294] and the presence of detectable infliximab levels for up to 1 year after exposure in utero. [160, 295] Few studies have investigated the safety of live attenuated vaccination during the first year of life after exposure to biologics in utero.[160, 267, 279] A study in 90 anti-TNF exposed infants where BCG vaccination was administered at a median age of 6 months [range 0.25–11 months] revealed a very low rate of minor adverse events [3.3%].[296] A recent systematic review that assessed live vaccine outcomes in infants [276 in utero exposures to adalimumab, certolizumab, etanercept, infliximab, golimumab, tocilizumab, and ustekinumab] reported

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eight reactions to BCG, namely four fatal disseminated BCG infections in infants exposed to TNF agents in utero, including infliximab, adalimumab, and one unspecified anti-TNF agent.[294]

In conclusion, no adverse events for inactivated vaccines have been reported. However, based on current evidence it is not possible to make a conclusive statement on the effectiveness of vaccination in children from women with IBD exposed to immunomodulators or biologics in utero. Given the few case reports of fatal outcomes after BCG vaccination, there is insufficient evidence to change the current recommendation to withhold live vaccines within the first 6–12 months of life or until biologics are no longer detectable in the infant's blood. Two recent studies showed very rapid neonatal clearance of vedolizumab, suggesting live vaccines from 6 months of age in vedolizumab-exposed children may be considered safe.[132, 161] A small study indicated that the median time for ustekinumab clearance from infant blood [n=9] was 9 weeks [range 6–19] weeks.[164]

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Inactivated vaccines are recommended according to national guidelines. In children exposed in utero to biologics, live attenuated vaccines should be withheld within the first year of life or until the biologic is no longer detectable in the infant's blood [EL3].

6.4. Breastfeeding with IBD

a) Safety of IBD drugs during breastfeeding

Breastfeeding is important to child health and development and is the preferred method of feeding. A summary of the risks of IBD medications used during lactation is shown in Table 1.

Aminosalicylates are considered low risk during breastfeeding,[297] although some cases of diarrhoea have been reported in infants.[298]

Sulfasalazine is considered low risk during breastfeeding. Although the sulfapyridine moiety is absorbed in minimal amounts and is excreted in breast milk, the milk:serum ratio is acceptable.[299]

Corticosteroids are found in very low concentrations in breast milk.[300, 301] In case of high maternal doses, avoiding breastfeeding for 4 hours after a dose should markedly decrease

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the dose received by the infant. However, this recommendation is only necessary in case of long-term, high-dose treatment.

Minimal amounts of azathioprine or mercaptopurine metabolites are detectable in breast milk.[302, 303] A multicentre prospective observational study of women with IBD and their breastfed infants reported rates of infections and developmental milestones that did not differ among infants whose mothers received immunomodulators or combination therapy [immunomodulators and biologics] compared with unexposed infants.[286] This study corroborates smaller studies that indicated no increased risk of infections or global medical and psychosocial health status in babies born to mothers exposed to azathioprine during pregnancy and breastfeeding.[229, 237] The data indicate that biologic drugs and immunomodulators are compatible with breastfeeding.

In breast milk, immunoglobulins are predominantly of the secretory IgA class; transfer of IgG immunoglobulins occurs in minimal quantities. Given that the biologic drugs used to treat IBD [infliximab, adalimumab, certolizumab pegol, golimumab, ustekinumab, vedolizumab] are IgG1 monoclonal antibodies, secretion and transfer in breast milk should be minimal. Indeed, only very low levels of infliximab[286], adalimumab[286], certolizumab pegol[178, 286, 304], ustekinumab,[286] and vedolizumab[287, 305] have been detected in the breast milk of mothers who received these biologic drugs. The peak biologic milk concentration is less than 1% of the concentration of maternal serum.[287, 305-308] This is well under the recommended arbitrary cut-off values of 10% for excretion of drugs into breast milk.[309] Consistent with these results, no adverse outcomes have been reported in breastfed infants of mothers treated with biologics. In a multicentre prospective observational study of women with IBD and their infants, the risk of infant infections and the achievement of milestones at 12 months was similar between breastfed infants who were exposed to biologic drugs, infants who had not been exposed to biologic drugs, and non-breastfed infants.[286] Further, neonatal clearance of anti-TNF agents and vedolizumab after exposure in utero was similar among breastfed and non-breastfed infants.[161,161]

MTX is contraindicated in breast feeding as it is partially metabolized to the active metabolite 7-hydroxymethotrexate, which is detectable in breast milk.[310] No data are available on the use of tofacitinib during breastfeeding in women with IBD, but the manufacturer recommends that breastfeeding should be discontinued during tofacitinib therapy for at least 18 hours after the last dose.[311] Similarly, breastfeeding during filgotinib treatment is not recommended.[78] According to the manufacturer's labelling, there is no recommendation

against breastfeeding with ozanimod use. However, no experience with ozanimod and breastfeeding has been reported.[312]

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Drugs that are considered low risk during pregnancy are also considered low risk during breastfeeding and thus can be continued [EL3].

b) Breastfeeding and disease activity

Lactation leads to increased levels of prolactin, a hormone that upregulates TNF production and could in theory lead to increased disease activity in women who breastfeed.[313] Data on the impact of breastfeeding on disease activity of women with IBD are limited. One retrospective study on 105 patients with IBD found a protective effect of breastfeeding on disease activity in puerperium based on data from medical databases and self-reported disease activity.[284] In contrast, another retrospective study[314] found an increased relapse rate in breastfeeding patients with CD. However, this association was not significant when corrected for medication cessation. Two other retrospective studies that included 258 and 132 patients with IBD found no association between breastfeeding and self-reported disease activity.[315, 316] These studies differ in breastfeeding rate in patients with IBD and in the methodology of disease activity assessment. In addition, these studies were retrospective and thus were prone to recall bias.

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Breastfeeding does not seem to influence disease activity of patients with IBD [EL4].

c) Breastfeeding and risk of IBD

Some studies have suggested that breastfeeding may protect from IBD development. No study has focused specifically on the high-risk population of offspring of patients with IBD. Two case-control studies found a protective effect of any breastfeeding on IBD development.[317, 318]. In four studies, the protective effect was significant only for a breastfeeding duration greater than 3, 6, or 12 months.[319-322] Two case-control studies

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concluded that breastfeeding was a risk factor for CD.[323, 324] Three prospective cohort studies analysed the effect of breastfeeding on subsequent IBD development.[325-327] These three studies found no association between having ever or never been breastfed and subsequent IBD. A 2019 meta-analysis of 13 case-control studies concluded that evidence examining ever versus never being breastfed and IBD was inconclusive,[328] and found limited evidence suggesting that among breastfed infants, shorter versus longer durations of breastfeeding were associated with higher risk of IBD. This meta-analysis pointed out the lack of data available on the duration of exclusive breastfeeding in most case-control studies. Moreover, no articles examined the impact of the amount of human milk for mixed-fed infants.[328] A review of two older meta-analyses revealed a protective effect of breastfeeding on IBD development. However, the overall confidence in the results of the two meta-analyses was rated as low and critically low, respectively.[329] To conclude, the data currently available on the relationship between breastfeeding and IBD development is not sufficient to develop a specific recommendation for IBD patients.

CONCLUSIONS

Conception and pregnancy are important life events for patients, and a concomitant diagnosis of IBD brings an additional layer of concern and anxiety. This consensus attempted to address the most common aspects of IBD management during this period of life, particularly regarding disease monitoring and treatment during pregnancy and lactation. Achieving and maintaining disease remission is key for a successful and uneventful pregnancy. We recognize that evidence is minimal for some situations and multidisciplinary management is therefore advised.

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Figure 1