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ECCO Guideline/Consensus Paper

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

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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 specialised 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 aim to optimise and harmonise 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] and that addressed clinically relevant questions in sexuality, fertility, pregnancy, and lactation in patients with IBD. These PICOs were partly based on the previous guidelines from 2010 and 2015, and 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 summarised 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 randomised clinical trials [RCTs] followed by observational studies were reviewed. Due to limited randomised 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]

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 (seven studies, relative risk [RR]: 1.41, 95% confidence interval [95% CI]: 1.09–1.81; $p = 0.008$) and in women [five 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 affected 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 sulphasalazine 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]

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 affects 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 who 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, in terms of risk of surgery and need for steroids or anti-tumour necrosis factor [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, estrogen-based contraceptives were not associated with an additional risk for thromboembolism in women with IBD in remission when compared with 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 summarise all available evidence, the United States Centers for Disease Control released the updated *Medical Eligibility Criteria for 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 of patients with CD. Whereas 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 with 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 [more than two FDRs affected] revealed a 57-fold increase in the incidence of IBD compared with 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 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 health care 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 sulphasalazine.

Active disease at conception increases the risk of adverse birth outcomes, such as preterm birth, low birthweight [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 optimisation 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, with 162 patients who attended the clinic only after they became pregnant. Counselling improved medication compliance and 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 with 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, birthweight, and caesarean section [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 with a multidisciplinary team [including IBD physicians, maternal-fetal medical specialists, psychologists, and colorectal surgeons] should be considered.

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

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 on voluntary childlessness. Therefore, appropriate education on pregnancy and family planning for all patients with IBD of childbearing age is recommended[EL5]

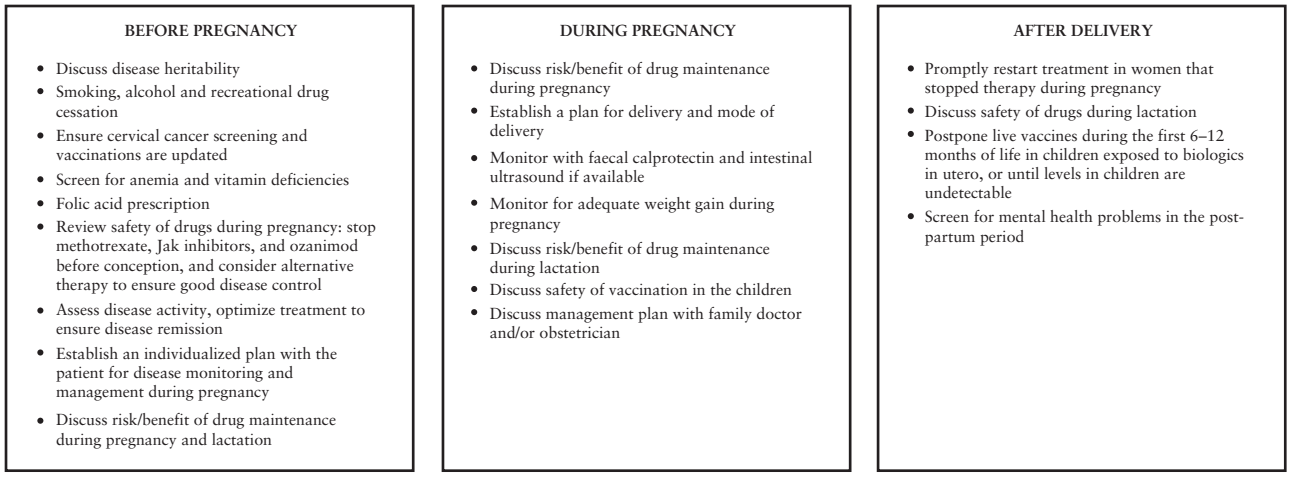

Figure 1. Management of patients with IBD before, during, and after pregnancy.

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] Many systematic reviews report reduced female fertility during active disease,[61,63,64] but 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%, odds ratio [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]

Statement 6

Active disease is associated with decreased fertility in women with IBD [EL3]. Achieving clinical remission may increase the probabilityof 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 as 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/day sulphasalazine with mesalazine.[68] Male patients on sulphasalazine 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] Methotrexate [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 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]. Sulphasalazine 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 with 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 with male patients.[92] There is a more pronounced reduction in fertility for patients with pouch failure, specially in female patients.[91]

Statement 8

IBD-related pelvic surgeries lead to decreased fertilityand fecundityrates in women [EL2]. Laparoscopic surgical approaches may lower the risk of infertility [EL2]

d] In vitro fertilisation treatment in patients with IBD

Cohort studies reported that the incidence of pregnancy and live births after *in vitro* fertilisation [IVF] in patients with UC and CD are comparable to 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 is comparable to that 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/m^2 vs 24.0 kg/m^2; $p = 0.06$] 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]

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 surgeon, depending on the trimester and the patient's personal situation. Although many of the important aspects that may impact on 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 remain 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 fistulising disease. The pregnant IBD patient with an ostomy warrants specialised 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 specialised counselling are warranted in these situations.[104] Patients with perianal fistulising 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 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 affect 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 [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 hospitalisation during pregnancy [14.7% vs 0%; p = 0.02] and preterm delivery [32.4% vs 5.7%; p = 0.006] were higher and neonatal birthweight was lower [median 3039 vs 3300 g, p = 0.03] with those with disease flare than for patients who maintained remission during pregnancy.[110]

Statement 10

Pregnancy may increase the risk of relapse or worsening disease in patients with UC and complications in patients with CD, specially 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 physiological adaptations associated with pregnancy can alter serum biomarkers, including haemoglobin, albumin, and C-reactive protein [CRP]. In normal pregnancy, haemoglobin and albumin concentrations decrease whereas 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 affected 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 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, but 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 and 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 hospitalisations 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 affect clinical decisions. Procedure time should be minimised, the lowest effective dose of sedative medications is recommended, and the 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 fetal heart rate depend on gestational age of the fetus 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 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, and 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. Whereas 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 [RR: 2.13, 95% CI: 1.78–2.66], with a higher risk of DVT [RR: 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], specially 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] appears 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 individualised and should consider disease severity and gestational age. After a multidisciplinary discussion considering the 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 the pregnant woman as in the 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 ciclosporin] achieved clinical response; the remaining three patients required colectomy.[141] Similar efficacy was shown in the retrospective GETAID study, which included eight pregnant patients requiring intravenous steroids followed by ciclosporin for severe UC.[142] All eight patients achieved clinical response, although one patient required rescue therapy with infliximab. In a Czech retrospective study, six out of nine pregnant patients achieved clinical remission after initiation of anti-TNF therapy for a flare.[143] In the retrospective CONCEIVE study, three pregnant patients initiated vedolizumab for a flare, one in combination with mesalazine and two 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 optimise 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.

Statement 14

A multidisciplinary team that includes an experienced gastroenterologist, obstetrician, and surgeon may be valuable in helping to optimise 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, ciclosporin, 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.

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 who had surgery during pregnancy, 55% in the second trimester; whereasfour no patient died, 27% had post-surgical complications, and miscarriages/stillbirths occurred, two during and two after surgery. Among the 40 newborns, 42% needed hospitalisation, of whom 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]

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-thioguanine [6-TGN] and increase in 6-mercaptopurine [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 18

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]

b] 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 fetal: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 fetus.[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 fetus. 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.[149,166–171] 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 [$p = 0.14$].[172] 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 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; $p = 0.08$].[167] These results were confirmed in other studies, where there was no difference between infliximab and adalimumab in relapse rates.[158,160] 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, or 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.[173]

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 with 318 deliveries who continued infliximab at least until T3, 90 days or less before delivery.[174] The single factor associated with risk of flare [defined as need for new steroid prescription, patient hospitalisation, or emergency room visits] was early infliximab discontinuation [OR: 5.98, 95% CI: 1.83–19.5].[174] In the largest study reported to date,[175] 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].[175]

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][174,176] or on birth outcomes [LBW, preterm birth, SGA, stillbirth].[167,174,177,178] In one study, a reduction in birthweight 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.[167] In contrast, another study reported a higher rate of preterm births in women who discontinued infliximab earlier during pregnancy.[175] 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.[171] 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.

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.[158,160,166,175,176,179] 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 fetal 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 minimise the risk of relapse and to avoid a protracted drug holiday.[180]

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; 50% 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.[181] 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 with anti-TNF agents [rendering secondary loss of response less likely in the context of a drug holiday].

Statement 19

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]

Statement 20

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 21

For women in remission treated with non-TNF biologic agents [ustekinumab, vedolizumab], an individualised decision on discontinuing treatment should be made, considering the risk of relapse and the limited data on the consequences of fetal 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.[182,183] One report included 23 cohort studies.[182] 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].[182] 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].[183] Observational studies concluded that pregnant women with IBD have a higher risk of preterm birth,[184–188] LBW,[184–186,189,190] and SGA.[186,187,191]

A recent meta-analysis that included 7917 IBD pregnancies and 3253 healthy pregnancies evaluated the risk of adverse pregnancy outcomes.[192] 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 pre-labour rupture of membranes [PPROM] was increased in patients with IBD [OR: 12.10, 95% CI: 2.15–67.98].[192] 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.[192]

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 praevia, placental abruption, preeclampsia, or chorioamnionitis.[192] 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.[193] 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 preeclampsia was observed [HR: 1.21, 95% CI: 0.76–1.95].[185]

Only two studies[185,194] reported a higher risk of 5-min Apgar score <7 among pregnant women with IBD, but this was not concordant among the studies.[186,190,195–197] Five studies[186,190,191,194,198] 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.[186,194,198,199] 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.[197] 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.[200]

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-min Apgar score <7 [OR: 2.21, 95% CI: 1.24–3.93].[195] Other observational studies revealed similar results in active disease, with a lower rate of live births and an increased risk of miscarriage, C-section, fetal growth restriction,[189] and LBW.[188]

Although a significantly higher risk of congenital anomalies [OR: 1.2, 95% CI: 1.05–1.58] was observed in a meta-analysis, there was publication bias and no reliable conclusions could be made.[182] 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.[199]

Statement 22

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

Disease activity during pregnancy is a risk factor, as it is associated with preterm pre-labour rupture of membranes, preterm birth, and low birthweight 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]

a] 5-aminosalicylates, sulphasalazine

Treatment with 5-ASA and sulphasalazine during pregnancy is not associated with an increased risk for adverse pregnancy outcomes or malformations.[183,200–204] Although higher rates of premature birth, stillbirth, and LBW were observed in some studies, it seems plausible that these results were due to the confounding factor of active disease.[202] Teratogenic effects have not been demonstrated.[204] To prevent toxicity of sulphasalazine 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}

Statement 24

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 T1, a large study did not reveal any increased risk of orofacial malformations.[205–208] 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.[209] On the other hand, budesonide and budesonide MMX were not associated with an increased risk of adverse pregnancy outcomes in two case series.[210,211] 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

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

Drug	During pregnancy	During lactation
Mesalazine	Low risk	Low risk
Sulphasalazine	Low risk	Low risk
Corticosteroids	Low risk	Low risk
Metronidazole	Low risk*	Avoid
Ciprofloxacin	Avoid in T1*	Low risk[a]
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

TNF, tumour necrosis factor.
[a]May be considered for short-term course for perianal disease; if possible consider other alternatives.

thus increase the risk of an unfavourable pregnancy outcome.[212,213] 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.[214] Nonetheless, these data emphasise the importance of adequate disease control during pregnancy and steroid-sparing strategies.

Statement 25

Although short-term corticosteroids, including budesonide, can in general be regarded as low-risk during pregnancy for managing flares, the risk of maternal-fetal 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.[215]

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,[216] two historical meta-analyses[217,218] and a retrospective cohort study[219] showed no association between metronidazole treatment in different trimesters with development of preterm birth, LBW, or congenital anomalies.[219] 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.[220]

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,[221–223] 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.[223] Thus, considering the limited available data, a short course of ciprofloxacin may be considered if needed during T1.

Statement 26

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.[171,179,200,224–232] The PIANO study also revealed that thiopurine therapy or combination therapy with biologics during pregnancy was not associated with increased

adverse maternal or fetal outcomes at birth.[158] An association with preterm birth [but not with congenital malformations] and LBW was shown in only one meta-analysis.[233] Reported adverse pregnancy outcomes, such as an increased rate of spontaneous miscarriage, preterm delivery, and LBW, may instead be caused by the underlying disease rather than by thiopurine use.[224,234,235] A small number of cases of immunological and haematological 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 immunological abnormalities were observed, although 60% of infants presented with anaemia at birth.[153,236]

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.[237–239] 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.[240] Similar but more limited data exist for tacrolimus.[241] Evidence on the use of ciclosporin in pregnant IBD patients is limited to a small series of women who had severe relapses during pregnancy.[142,242] A single case report of a patient with UC treated with tacrolimus has been published.[243] 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, IUGR, fetal loss, congenital malformations [including craniofacial anomalies], limb defects, and central nervous system abnormalities.[244] If conception accidentally occurs, termination of pregnancy should be discussed, but not necessarily performed. Use of thalidomide is associated with major fetal malformations involving limbs, ears, eyes, and neural tube defects. The neonatal mortality rate associated with thalidomide use is 40%.[245] Thus, thalidomide use is strongly contraindicated during pregnancy.

Statement 27

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.[160,172,175,178,246–251] 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 data exist mainly for infliximab, adalimumab, certolizumab pegol, and golimumab also do not seem to have a different safety profile during pregnancy.[157,170] Though some studies reported adverse events such as LBW, this might rather be due to the underlying disease activity than to the anti-TNF agent.[167,252,253]

Animal studies show no evidence of adverse effects on pre- or postnatal development after administration of vedolizumab and ustekinumab.[254,255] Few studies including patients treated with vedolizumab or ustekinumab during pregnancy have been published; pregnancies were uneventful pregnancies in most cases.[132,144,157,161,164,256–258] A retrospective cohort study including 73 pregnancies in patients receiving vedolizumab or ustekinumab did not reveal a negative signal on maternal or neonatal outcomes.[181] These data were confirmed for vedolizumab in the prospective NOVA study among 50 vedolizumab-exposed pregnancies, and in 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.

Statement 28

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.[259] 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.[256] 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.[259] 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 fetal harm and is therefore contraindicated during pregnancy.[78] This recommendation likely applies to other JAK inhibitors.

There are only very limited data about pregnancy from patients treated with ozanimod from the trials on multiple sclerosis[260] and UC.[261] Thus, ozanimod is also contraindicated during pregnancy due to lack of human data.

5.3. Mode of delivery in women with IBD

Statement 29

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.[80,262]

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,[263] 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.[80,262,263]

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, nor *de novo* perianal disease following vaginal delivery.[262] 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.[136,264] 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 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]

Statement 30

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.[160,172,175,176,179,234,236,249,251,265–270,166,157] 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 health care-seeking behaviour could not be excluded.[166,269,271,160]

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.[179,272] 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 (adjusted HR [aHR]: 1.36, 95% CI: 1.04-1.79).[269]

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.[157,160,175,267]

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,[273] and some cases of neutropenia with skin infections requiring granulocyte colony stimulating factor have been reported after exposure to anti-TNF agents.[274] Small studies have shown subtle changes in T and B cell subsets,[275,276] decreased response after mycobacterial challenge,[275] and vaccine response rates lower than historically reported [see section on vaccination].[249,277] Furthermore, the reassuring data on infection rates are mostly regarding serious infections requiring hospitalisation 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.[232] Thiopurines in combination with anti-TNF agents may increase the risk of neonatal infections,[160,166,271] although this has not been consistently shown.[157,269,278] 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.[160,179,271,278] Data on growth and neurodevelopment are also limited, but follow-up of psychomotor development in children in the first year of life[157,249,266] and quality of life assessments in children up to 5 years of age did not raise concerns thus far.[236,279]

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 have shown no increased risk of infections.[157,162]

Statement 31

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.[280] 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, which 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 time points.[115]

Overall, the relapse rate postpartum varies significantly across studies and ranges from 25% to 50%.[281–283] The predictors of postpartum relapse include disease activity during T3, therapy de-escalation during and after pregnancy,[283] and longer duration of disease, specifically in CD.[106] A recent meta-analysis aiming to assess risk factors for postpartum disease activity, which 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.[173]

Statement 32

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 [eg 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.[284,285]

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.[172] No data are available to guide the best approach to restarting the drug after a drug holiday. Therefore, either re-induction 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.

Statement 33

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]. Re-induction or continuation of previous maintenance therapy is dependent on clinical circumstances [EL5]

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.[249,266,270,286–288] Although two studies

indicated inadequate response to vaccination in some children, conclusions could not be drawn due to the small study size.[277,289] One study compared vaccination response to *Haemophilus influenzae* type B and tetanus between 42 children exposed to biologics and either 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.[277] 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.[290] 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.[290]

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.[172,179,231] 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'.[291] This recommendation follows some case reports of fatal disseminated BCG infection after the live BCG vaccination[273,292] and the presence of detectable infliximab levels for up to 1 year after exposure *in utero*.[160,293] Few studies have investigated the safety of live attenuated vaccination during the first year of life after exposure to biologics *in utero*.[160,266,277] 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%].[294] 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 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.[292]

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]

Statement 34

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,[295] although some cases of diarrhoea have been reported in infants.[296]

Sulphasalazine is considered low-risk during breastfeeding. Although the sulphapyridine moiety is absorbed in minimal amounts and is excreted in breast milk, the milk:serum ratio is acceptable.[297]

Corticosteroids are found in very low concentrations in breast milk.[298,299] In case of high maternal doses, avoiding breastfeeding for 4 h after a dose should markedly decrease 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.[300,301] 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.[284] 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.[228,236] 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,[284] adalimumab,[284] certolizumab pegol,[177,284,302] ustekinumab,[284] and vedolizumab[285,303] 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 in maternal serum.[285,303–306] This is well under the recommended arbitrary cut-off values of 10% for excretion of drugs into breast milk.[307] 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.[284] Further, neonatal clearance of anti-TNF agents and vedolizumab after exposure *in utero* was similar among breastfed and non-breastfed infants.[161]

MTX is contraindicated in breast feeding as it is partially metabolised to the active metabolite 7-hydroxymethotrexate, which is detectable in breast milk.[308] 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 h after the last dose.[309] 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.[310]

Statement 35

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.[311] 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 the puerperium, based on data from medical databases and self-reported disease activity.[282] In contrast, another retrospective study[312] 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.[313,314] 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.

Statement 36

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..[315,316] In four studies, the protective effect was significant only for a breastfeeding duration greater than 3, 6, or 12 months.[317–320] Two case-control studies concluded that breastfeeding was a risk factor for CD.[321,322] Three prospective cohort studies analysed the effect of breastfeeding on subsequent IBD development.[323–325] 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,[326] 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.[326] 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.[327] To conclude, the data currently available on the relationship between breastfeeding and IBD development are not sufficient to develop a specific recommendation for IBD patients.

7. 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 recognise that evidence is minimal for some situations and multidisciplinary management is therefore advised.

References

1. Torres J, Mehandru S, Colombel JF, *et al*. Crohn's disease. *Lancet* 2017;**389**:1741–55. doi:10.1016/S0140-6736[16]31711-1.
2. Ungaro R, Mehandru S, Allen PB, *et al*. Ulcerative colitis. *Lancet* 2017;**389**:1756–70. doi:10.1016/S0140-6736[16]32126-2.
3. Gallinger ZR, Rumman A, Nguyen GC. Perceptions and attitudes towards medication adherence during pregnancy in inflammatory bowel disease. *J Crohns Colitis* 2016;**10**:892–7. doi:10.1093/ecco-jcc/jjw052.
4. Selinger CP, Eaden J, Selby W, *et al*. Inflammatory bowel disease and pregnancy: lack of knowledge is associated with negative views. *J Crohns Colitis* 2013;**7**:e206–13. doi:10.1016/j.crohns.2012.09.010.
5. World Health Organization. *Sexual Health, Human Rights and the Law*. 2015. https://www.who.int/publications/i/item/9789241564984.
6. Ghazi LJ, Patil SA, Cross RK. Sexual dysfunction in inflammatory bowel disease. *Inflamm Bowel Dis* 2015;**21**:939–47. doi:10.1097/MIB.0000000000000260.
7. Zhao S, Wang J, Liu Y, *et al*. Inflammatory bowel diseases were associated with risk of sexual dysfunction in both sexes: a meta-analysis. *Inflamm Bowel Dis* 2019;**25**:699–707. doi:10.1093/ibd/izy345.
8. Mantzouranis G, Fafliora E, Glanztounis G, *et al*. Inflammatory bowel disease and sexual function in male and female patients: an update on evidence in the past 10 years. *J Crohns Colitis* 2015;**9**:1160–8. doi:10.1093/ecco-jcc/jjv140.
9. Jedel S, Hood MM, Keshavarzian A. Getting personal: a review of sexual functioning, body image, and their impact on quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2015;**21**:923–38. doi:10.1097/MIB.0000000000000257.
10. Nøhr EA, Nielsen J, Nørgård BM, *et al*. Sexual health in women with inflammatory bowel disease in the Danish National Birth Cohort. *J Crohns Colitis* 2020;**14**:1082–9. doi:10.1093/ecco-jcc/jjaa038.

11. Timmer A, Bauer A, Dignass A, *et al*. Sexual function in persons with inflammatory bowel disease: a survey with matched controls. *Clin Gastroenterol Hepatol* 2007;**5**:87–94. doi:10.1016/j.cgh.2006.10.018.
12. Timmer A, Bauer A, Kemptner D, *et al*. Determinants of male sexual function in inflammatory bowel disease: a survey-based cross-sectional analysis in 280 men. *Inflamm Bowel Dis* 2007;**13**:1236–43. doi:10.1002/ibd.20182.
13. Ghosh S, Mitchell R. Impact of inflammatory bowel disease on quality of life: results of the European Federation of Crohn's and Ulcerative Colitis Associations [EFCCA] patient survey. *J Crohns Colitis* 2007;**1**:10–20. doi:10.1016/j.crohns.2007.06.005.
14. Roseira J, Magro F, Fernandes S, *et al*. Sexual quality of life in inflammatory bowel disease: a multicenter, national-level study. *Inflamm Bowel Dis* 2020;**26**:746–55. doi:10.1093/ibd/izz185.
15. Ateş Bulut E, Törüner M. The influence of disease type and activity to sexual life and health quality in inflammatory bowel disease. *Turk J Gastroenterol* 2019;**30**:33–9. doi:10.5152/tjg.2018.18250.
16. Timmer A, Kemptner D, Bauer A, *et al*. Determinants of female sexual function in inflammatory bowel disease: a survey based cross-sectional analysis. *BMC Gastroenterol* 2008;**8**:45. doi:10.1186/1471-230X-8-45.
17. Blackburn WD, Alarcón GS. Impotence in three rheumatoid arthritis patients treated with methotrexate. *Arthritis Rheum* 1989;**32**:1341–2. doi:10.1002/anr.1780321029.
18. Ireland A, Jewell DP. Sulfasalazine-induced impotence: a beneficial resolution with olsalazine? *J Clin Gastroenterol* 1989;**11**:711.
19. Purewal S, Chapman S, Czuber-Dochan W, *et al*. Systematic review: the consequences of psychosocial effects of inflammatory bowel disease on patients' reproductive health. *Aliment Pharmacol Ther* 2018;**48**:1202–12. doi:10.1111/apt.15019.
20. O'Toole A, Winter D, Friedman S. Review article: the psychosexual impact of inflammatory bowel disease in male patients. *Aliment Pharmacol Ther* 2014;**39**:1085–94. doi:10.1111/apt.12720.
21. Hor T, Lefevre JH, Shields C, *et al*. Female sexual function and fertility after ileal pouch-anal anastomosis. *Int J Colorectal Dis* 2016;**31**:593–601. doi:10.1007/s00384-015-2497-y.
22. Wang JY, Hart SL, Wilkowski KS, *et al*. Gender-specific differences in pelvic organ function after proctectomy for inflammatory bowel disease. *Dis Colon Rectum* 2011;**54**:66–76. doi:10.1007/DCR.0b013e3181fd48d2.
23. Cornish J, Wooding K, Tan E, *et al*. Study of sexual, urinary, and fecal function in females following restorative proctocolectomy. *Inflamm Bowel Dis* 2012;**18**:1601–7. doi:10.1002/ibd.21910.
24. Davies RJ, O'Connor BI, Victor C, *et al*. A prospective evaluation of sexual function and quality of life after ileal pouch-anal anastomosis. *Dis Colon Rectum* 2008;**51**:1032–5. doi:10.1007/s10350-008-9248-x.
25. Ogilvie JW, Goetz L, Baxter NN, *et al*. Female sexual dysfunction after ileal pouch-anal anastomosis. *Br J Surg* 2008;**95**:887–92. doi:10.1002/bjs.6072.
26. Yoshida K, Araki T, Uchida K, *et al*. Sexual activity after ileal pouch-anal anastomosis in Japanese patients with ulcerative colitis. *Surg Today* 2014;**44**:73–9. doi:10.1007/s00595-013-0505-9.
27. Picaud O, Beyer-Berjot L, Parc Y, *et al*. Laparoscopic rectal dissection preserves erectile function after ileal pouch-anal anastomosis: a two-centre study. *Colorectal Dis* 2021;**23**:123–31. doi:10.1111/codi.15383.
28. Victor A, Odlind V, Kral JG. Oral contraceptive absorption and sex hormone binding globulins in obese women: effects of jejunoileal bypass. *Gastroenterol Clin North Am* 1987;**16**:483–91.
29. Zapata LB, Paulen ME, Cansino C, *et al*. Contraceptive use among women with inflammatory bowel disease: a systematic review. *Contraception* 2010;**82**:72–85. doi:10.1016/j.contraception.2010.02.012.
30. Khalili H, Neovius M, Ekbom A, *et al*. Oral contraceptive use and risk of ulcerative colitis progression: a nationwide study. *Am J Gastroenterol* 2016;**111**:1614–20. doi:10.1038/ajg.2016.464.
31. Khalili H, Granath F, Smedby KE, *et al*. Association between long-term oral contraceptive use and risk of Crohn's disease complications in a nationwide study. *Gastroenterology* 2016;**150**:1561–7.e1. doi:10.1053/j.gastro.2016.02.041.
32. Pellino G, Sciaudone G, Caprio F, *et al*. Hormonal contraceptives and venous thromboembolism: Are inflammatory bowel disease patients at increased risk? A retrospective study on a prospective database. *Ann Med Surg [Lond]* 2015;**4**:462–6. doi:10.1016/j.amsu.2015.10.020.
33. Cheng K, Faye AS. Venous thromboembolism in inflammatory bowel disease. *World J Gastroenterol* 2020;**26**:1231–41. doi:10.3748/wjg.v26.i12.1231.
34. Curtis KM, Tepper NK, Jatlaoui TC, *et al*. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep* 2016;**65**:1–103. doi:10.15585/mmwr.rr6503a1.
35. Moller FT, Andersen V, Wohlfahrt J, *et al*. Familial risk of inflammatory bowel disease: a population-based cohort study 1977-2011. *Am J Gastroenterol* 2015;**110**:564–71. doi:10.1038/ajg.2015.50.
36. Lashner BA, Evans AA, Kirsner JB, *et al*. Prevalence and incidence of inflammatory bowel disease in family members. *Gastroenterology* 1986;**91**:1396–400. doi:10.1016/0016-5085[86]90193-9.
37. Orholm M, Munkholm P, Langholz E, *et al*. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991;**324**:84–8. doi:10.1056/nejm199101103240203.
38. Loftus EV. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004;**126**:1504–17. doi:10.1053/j.gastro.2004.01.063.
39. Peeters M, Nevens H, Baert F, *et al*. Familial aggregation in Crohn's disease: increased age-adjusted risk and concordance in clinical characteristics. *Gastroenterology* 1996;**111**:597–603. doi:10.1053/gast.1996.v111.pm8780562.
40. Joossens M, Van Steen K, Branche J, *et al*. Familial aggregation and antimicrobial response dose-dependently affect the risk for Crohn's disease. *Inflamm Bowel Dis* 2010;**16**:58–67. doi:10.1002/ibd.20985.
41. Basu D, Lopez I, Kulkarni A, *et al*. Impact of race and ethnicity on inflammatory bowel disease. *Am J Gastroenterol* 2005;**100**:2254–61. doi:10.1111/j.1572-0241.2005.00233.x.
42. Yang H, McElree C, Roth MP, *et al*. Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews. *Gut* 1993;**34**:517–24. doi:10.1136/gut.34.4.517.
43. Santos MPC, Gomes C, Torres J. Familial and ethnic risk in inflammatory bowel disease. *Ann Gastroenterol* 2018;**31**:14–23. doi:10.20524/aog.2017.0208.
44. Akolkar PN, Gulwani-Akolkar B, Heresbach D, *et al*. Differences in risk of Crohn's disease in offspring of mothers and fathers with inflammatory bowel disease. *Am J Gastroenterol* 1997;**92**:2241–4.
45. Zelinkova Z, Stokkers PC, van der Linde K, *et al*. Maternal imprinting and female predominance in familial Crohn's disease. *J Crohns Colitis* 2012;**6**:771–6. doi:10.1016/j.crohns.2012.01.002.
46. Laharie D, Debeugny S, Peeters M, *et al*. Inflammatory bowel disease in spouses and their offspring. *Gastroenterology* 2001;**120**:816–9. doi:10.1053/gast.2001.22574.
47. Costa-Santos MP, Frias-Gomes C, Oliveira A, *et al*. Conjugal inflammatory bowel disease: a systematic review and European survey. *Ann Gastroenterol* 2021;**34**:361–9. doi:10.20524/aog.2021.0598.
48. Carbonnel F, Macaigne G, Beaugerie L, *et al*. Crohn's disease severity in familial and sporadic cases. *Gut* 1999;**44**:91–5. doi:10.1136/gut.44.1.91.
49. Andreu M, Marquez L, Domenech E, *et al*. Disease severity in familial cases of IBD. *J Crohns Colitis* 2014;**8**:234–9. doi:10.1016/j.crohns.2013.08.010.
50. Mahadevan U, Robinson C, Bernasko N, *et al*. Inflammatory bowel disease in pregnancy clinical care pathway: a report from the American Gastroenterological Association IBD parenthood project working group. *Gastroenterology* 2019;**156**:1508–24. doi:10.1053/j.gastro.2018.12.022.
51. Abhyankar A, Ham M, Moss AC. Meta-analysis: the impact of disease activity at conception on disease activity during pregnancy in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2013;**38**:460–6. doi:10.1111/apt.12417.

52. Mountifield R, Andrews JM, Bampton P. It IS worth the effort: patient knowledge of reproductive aspects of inflammatory bowel disease improves dramatically after a single group education session. *J Crohns Colitis* 2014;**8**:796–801. doi:10.1016/j.crohns.2013.12.019.
53. Julsgaard M, Nørgaard M, Hvas CL, *et al*. Self-reported adherence to medical treatment prior to and during pregnancy among women with ulcerative colitis. *Inflamm Bowel Dis* 2011;**17**:1573–80. doi:10.1002/ibd.21522.
54. Nielsen MJ, Nørgaard M, Holland-Fisher P, *et al*. Self-reported antenatal adherence to medical treatment among pregnant women with Crohn's disease. *Aliment Pharmacol Ther* 2010;**32**:49–58. doi:10.1111/j.1365-2036.2010.04318.x.
55. Flanagan E, Wright EK, Sparrow MP, *et al*. A single educational intervention improves pregnancy-related knowledge and emotional health among women with IBD who are pregnant or wish to conceive. *Inflamm Bowel Dis* 2021. doi:10.1093/ibd/izab021.
56. de Lima A, Zelinkova Z, Mulders AG, *et al*. Preconception care reduces relapse of inflammatory bowel disease during pregnancy. *Clin Gastroenterol Hepatol* 2016;**14**:1285–92.e1. doi:10.1016/j.cgh.2016.03.018.
57. Shitrit AB, Cohen Y, Hassin O, *et al*. Antenatal management for women with inflammatory bowel disease: experience from our 'IBD MOM' clinic. *Dig Dis Sci* 2018;**63**:1774–81. doi:10.1007/s10620-018-5048-x.
58. Tavernier N, Fumery M, Peyrin-Biroulet L, *et al*. Systematic review: fertility in non-surgically treated inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;**38**:847–53. doi:10.1111/apt.12478.
59. Walldorf J, Brunne S, Gittinger FS, *et al*. Family planning in inflammatory bowel disease: childlessness and disease-related concerns among female patients. *Eur J Gastroenterol Hepatol* 2018;**30**:310–5. doi:10.1097/meg.0000000000001037.
60. Laube R, Yau Y, Selinger CP, *et al*. Knowledge and attitudes towards pregnancy in females with inflammatory bowel disease: an international, multi-centre study. *J Crohns Colitis* 2020;**14**:1248–55. doi:10.1093/ecco-jcc/jjaa047.
61. Ban L, Tata LJ, Humes DJ, *et al*. Decreased fertility rates in 9639 women diagnosed with inflammatory bowel disease: a United Kingdom population-based cohort study. *Aliment Pharmacol Ther* 2015;**42**:855–66. doi:10.1111/apt.13354.
62. Selinger CP, Ghorayeb J, Madill A. What factors might drive voluntary childlessness [VC] in women with IBD? Does IBD-specific pregnancy-related knowledge matter? *J Crohns Colitis* 2016;**10**:1151–8. doi:10.1093/ecco-jcc/jjw078.
63. Lamah M, Scott HJ. Inflammatory bowel disease and pregnancy. *Int J Colorectal Dis* 2002;**17**:216–22. doi:10.1007/s00384-001-0365-4.
64. Palomba S, Sereni G, Falbo A, *et al*. Inflammatory bowel diseases and human reproduction: a comprehensive evidence-based review. *World J Gastroenterol* 2014;**20**:7123–36. doi:10.3748/wjg.v20.i23.7123.
65. Ananthakrishnan AN, Martin C, Kane S, *et al*. Paternal disease activity is associated with difficulty in conception among men with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2019;**17**:203–4. doi:10.1016/j.cgh.2018.04.001.
66. Grosen A, Bungum M, Christensen LA, *et al*. Semen quality and sperm DNA integrity in patients with severe active inflammatory bowel disease and effects of tumour necrosis factor-alpha inhibitors. *J Crohns Colitis* 2019;**13**:564–71. doi:10.1093/ecco-jcc/jjy198.
67. Nassan FL, Coull BA, Skakkebaek NE, *et al*. A crossover-crossback prospective study of dibutyl-phthalate exposure from mesalamine medications and semen quality in men with inflammatory bowel disease. *Environ Int* 2016;**95**:120–30. doi:10.1016/j.envint.2016.08.006.
68. Banerjee A, Scarpa M, Pathak S, *et al*. Inflammatory bowel disease therapies adversely affect fertility in men: a systematic review and meta-analysis. *Endocr Metab Immune Disord Drug Targets* 2019;**19**:959–74. doi:10.2174/1871530319666190313112110.
69. Simsek M, Lambalk CB, Wilschut JA, *et al*. The associations of thiopurines with male fertility and paternally exposed offspring: a systematic review and meta-analysis. *Hum Reprod Update* 2018;**24**:192–206. doi:10.1093/humupd/dmx034.
70. Ley D, Jones J, Parrish J, *et al*. Methotrexate reduces DNA integrity in sperm from men with inflammatory bowel disease. *Gastroenterology* 2018;**154**:2064–7.e3. doi:10.1053/j.gastro.2018.02.025.
71. Grosen A, Bellaguarda E, Nersting J, *et al*. Low-dose methotrexate therapy does not affect semen parameters and sperm DNA. *Inflamm Bowel Dis* 2021. doi:10.1093/ibd/izab205.
72. Grosen A, Kelsen J, Hvas CL, *et al*. The influence of methotrexate treatment on male fertility and pregnancy outcome after paternal exposure. *Inflamm Bowel Dis* 2017;**23**:561–9. doi:10.1097/MIB.0000000000001064.
73. Puchner R, Danninger K, Puchner A, *et al*. Impact of TNF-blocking agents on male sperm characteristics and pregnancy outcomes in fathers exposed to TNF-blocking agents at time of conception. *Clin Exp Rheumatol* 2012;**30**:765–7.
74. Grosen A, Nersting J, Bungum M, *et al*. Sperm DNA integrity is unaffected by thiopurine treatment in men with inflammatory bowel disease. *J Crohns Colitis* 2019;**13**:3–11. doi:10.1093/ecco-jcc/jjy086.
75. Grosen A, Bungum M, Hvas CL, *et al*. Vedolizumab does not impair sperm DNA integrity in men with inflammatory bowel disease. *Gastroenterology* 2019;**156**:2342–4. doi:10.1053/j.gastro.2019.02.041.
76. Grosen A, Bellaguarda E, Liljeqvist-Soltic I, *et al*. Normal sperm DNA integrity in patients with inflammatory bowel disease on ustekinumab maintenance therapy. *Inflamm Bowel Dis* 2022. doi:10.1093/ibd/izac028.
77. Xeljanz Nonclinical toxicology. https://www.pfizermedicalinformation.com/en-us/xeljanz/nonclinical-toxicology. Accessed September 15, 2022.
78. Assessment report Jyseleca. https://www.ema.europa.eu/en/documents/assessment-report/jyseleca-epar-public-assessment-report_en.pdf. Accessed September 15, 2022.
79. Assessment report Zeposia. https://www.ema.europa.eu/en/documents/assessment-report/zeposia-epar-public-assessment-report_en.pdf. Accessed September 15, 2022.
80. Cornish JA, Tan E, Teare J, *et al*. The effect of restorative proctocolectomy on sexual function, urinary function, fertility, pregnancy and delivery: a systematic review. *Dis Colon Rectum* 2007;**50**:1128–38. doi:10.1007/s10350-007-0240-7.
81. Lee S, Crowe M, Seow CH, *et al*. The impact of surgical therapies for inflammatory bowel disease on female fertility. *Cochrane Database Syst Rev* 2019;**7**:CD012711. doi:10.1002/14651858.CD012711.pub2.
82. Rajaratnam SG, Eglinton TW, Hider P, *et al*. Impact of ileal pouch-anal anastomosis on female fertility: meta-analysis and systematic review. *Int J Colorectal Dis* 2011;**26**:1365–74. doi:10.1007/s00384-011-1274-9.
83. Beyer-Berjot L, Maggiori L, Birnbaum D, *et al*. A total laparoscopic approach reduces the infertility rate after ileal pouch-anal anastomosis: a 2-center study. *Ann Surg* 2013;**258**:275–82. doi:10.1097/SLA.0b013e3182813741.
84. Bartels SA, D'Hoore A, Cuesta MA, *et al*. Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy: a cross-sectional study. *Ann Surg* 2012;**256**:1045–8. doi:10.1097/SLA.0b013e318250caa9.
85. Olsen KO, Joelsson M, Laurberg S, *et al*. Fertility after ileal pouch-anal anastomosis in women with ulcerative colitis. *Br J Surg* 1999;**86**:493–5. doi:10.1046/j.1365-2168.1999.01076.x.
86. Friedman S, Nielsen J, Nøhr EA, *et al*. Comparison of time to pregnancy in women with and without inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2020;**18**:1537–44.e1. doi:10.1016/j.cgh.2019.08.031.
87. Gorgun E, Cengiz TB, Aytac E, *et al*. Does laparoscopic ileal pouch-anal anastomosis reduce infertility compared with open approach? *Surgery* 2019;**166**:670–7. doi:10.1016/j.surg.2019.04.045.
88. Johnson P, Richard C, Ravid A, *et al*. Female infertility after ileal pouch-anal anastomosis for ulcerative colitis. *Dis Colon Rectum* 2004;**47**:1119–26. doi:10.1007/s10350-004-0570-7.

89. Ørding Olsen K, Juul S, Berndtsson I, *et al*. Ulcerative colitis: female fecundity before diagnosis, during disease, and after surgery compared with a population sample. *Gastroenterology* 2002;**122**:15–9. doi:10.1053/gast.2002.30345.
90. Lepistö A, Sarna S, Tiitinen A, *et al*. Female fertility and childbirth after ileal pouch-anal anastomosis for ulcerative colitis. *Br J Surg* 2007;**94**:478–82. doi:10.1002/bjs.5509.
91. Pachler FR, Bisgaard T, Mark-Christensen A, *et al*. Impact on fertility after failure of restorative proctocolectomy in men and women with ulcerative colitis: a 17-year cohort study. *Dis Colon Rectum* 2020;**63**:816–22. doi:10.1097/DCR.0000000000001640.
92. Pachler FR, Brandsborg SB, Laurberg S. Paradoxical impact of ileal pouch-anal anastomosis on male and female fertility in patients with ulcerative colitis. *Dis Colon Rectum* 2017;**60**:603–7. doi:10.1097/DCR.0000000000000796.
93. Hernandez-Nieto C, Sekhon L, Lee J, *et al*. Infertile patients with inflammatory bowel disease have comparable in vitro fertilization clinical outcomes to the general infertile population. *Gynecol Endocrinol* 2020;**36**:554–7. doi:10.1080/09513590.2019.1684465.
94. Oza SS, Pabby V, Dodge LE, *et al*. In vitro fertilization in women with inflammatory bowel disease is as successful as in women from the general infertility population. *Clin Gastroenterol Hepatol* 2015;**13**:1641–6.e3. doi:10.1016/j.cgh.2015.03.016.
95. Nørgård BM, Larsen PV, Fedder J, *et al*. Live birth and adverse birth outcomes in women with ulcerative colitis and Crohn's disease receiving assisted reproduction: a 20-year nationwide cohort study. *Gut* 2016;**65**:767–76. doi:10.1136/gutjnl-2015-311246.
96. Nørgård BM, Larsen MD, Friedman S, *et al*. Corticosteroids prior to embryo transfer in assisted reproduction in women with Crohn's disease and ulcerative colitis: a nationwide cohort study. *Clin Epidemiol* 2020;**12**:317–26. doi:10.2147/clep.S234996.
97. Pachler FR, Toft G, Bisgaard T, *et al*. Use and success of in vitro fertilisation following restorative proctocolectomy and ileal pouch-anal anastomosis. A nationwide 17-year cohort study. *J Crohns Colitis* 2019;**13**:1283–6. doi:10.1093/ecco-jcc/jjz055.
98. Pabby V, Oza SS, Dodge LE, *et al*. In vitro fertilization is successful in women with ulcerative colitis and ileal pouch anal anastomosis. *Am J Gastroenterol* 2015;**110**:792–7. doi:10.1038/ajg.2014.400.
99. Oza SS, Pabby V, Dodge LE, *et al*. Factors associated with the success of in vitro fertilization in women with inflammatory bowel disease. *Dig Dis Sci* 2016;**61**:2381–8. doi:10.1007/s10620-016-4076-7.
100. Bengtson MB, Aamodt G, Mahadevan U, *et al*. Inadequate gestational weight gain, the hidden link between maternal IBD and adverse pregnancy outcomes: results from the Norwegian Mother and Child Cohort Study. *Inflamm Bowel Dis* 2017;**23**:1225–33. doi:10.1097/mib.0000000000001123.
101. Bengtson MB, Martin CF, Aamodt G, *et al*. Inadequate gestational weight gain predicts adverse pregnancy outcomes in mothers with inflammatory bowel disease: results from a prospective US pregnancy cohort. *Dig Dis Sci* 2017;**62**:2063–9. doi:10.1007/s10620-017-4547-5.
102. Vigod SN, Kurdyak P, Brown HK, *et al*. Inflammatory bowel disease and new-onset psychiatric disorders in pregnancy and post partum: a population-based cohort study. *Gut* 2019;**68**:1597–605. doi:10.1136/gutjnl-2018-317610.
103. Flanagan EK, Richmond J, Thompson AJ, *et al*. Addressing pregnancy-related concerns in women with inflammatory bowel disease: Insights from the patient's perspective. *JGH Open* 2021;**5**:28–33. doi:10.1002/jgh3.12442.
104. Blackwell S, Selinger C, Brookes M, *et al*. PMO-32 pregnancy outcomes after stoma surgery for IBD: the results of a multi-centre retrospective audit. *Gut* 2021;**70**:A93. doi:10.1136/gutjnl-2021-BSG.171.
105. van der Giessen J, Huang VW, van der Woude CJ, *et al*. Modulatory effects of pregnancy on inflammatory bowel disease. *Clin Transl Gastroenterol* 2019;**10**:e00009–e00009. doi:10.14309/ctg.0000000000000009.
106. Pedersen N, Bortoli A, Duricova D, *et al*. The course of inflammatory bowel disease during pregnancy and postpartum: a prospective European ECCO-EpiCom Study of 209 pregnant women. *Aliment Pharmacol Ther.* 2013;**38**:501–12. doi:10.1111/apt.12412.
107. Hatch Q, Champagne BJ, Maykel JA, *et al*. The impact of pregnancy on surgical Crohn disease: an analysis of the Nationwide Inpatient Sample. *J Surg Res* 2014;**190**:41–6. doi:10.1016/j.jss.2014.03.028.
108. Hahnloser D, Pemberton JH, Wolff BG, *et al*. Pregnancy and delivery before and after ileal pouch-anal anastomosis for inflammatory bowel disease: immediate and long-term consequences and outcomes. *Dis Colon Rectum* 2004;**47**:1127–35. doi:10.1007/s10350-004-0569-0.
109. de Lima-Karagiannis A, Zelinkova-Detkova Z, van der Woude CJ. The effects of active IBD during pregnancy in the era of novel IBD therapies. *Am J Gastroenterol* 2016;**111**:1305–12. doi:10.1038/ajg.2016.254.
110. Rottenstreich A, Fridman Lev S, Rotem R, *et al*. Disease flare at prior pregnancy and disease activity at conception are important determinants of disease relapse at subsequent pregnancy in women with inflammatory bowel diseases. *Arch Gynecol Obstet* 2020;**301**:1449–54. doi:10.1007/s00404-020-05557-8.
111. Klajnbard A, Szecsi PB, Colov NP, *et al*. Laboratory reference intervals during pregnancy, delivery and the early postpartum period. *Clin Chem Lab Med* 2010;**48**:237–48. doi:10.1515/CCLM.2010.033.
112. Tandon P, Leung K, Yusuf A, *et al*. Noninvasive methods for assessing inflammatory bowel disease activity in pregnancy: a systematic review. *J Clin Gastroenterol* 2019;**53**:574–81. doi:10.1097/MCG.0000000000001244.
113. Rottenstreich A, Mishael T, Granovsky SG, *et al*. Clinical utility of fecal calprotectin in monitoring disease activity and predicting relapse in pregnant patients with inflammatory bowel diseases. *Eur J Intern Med* 2020;**77**:105–10. doi:10.1016/j.ejim.2020.03.015.
114. Kammerlander H, Nielsen J, Kjeldsen J, *et al*. Fecal calprotectin during pregnancy in women with moderate-severe inflammatory bowel disease. *Inflamm Bowel Dis* 2018;**24**:839–48. doi:10.1093/ibd/izx055.
115. Julsgaard M, Hvas CL, Gearry RB, *et al*. Fecal calprotectin is not affected by pregnancy: clinical implications for the management of pregnant patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2017;**23**:1240–6. doi:10.1097/mib.0000000000001136.
116. Balint A, Berenyi A, Farkas K, *et al*. Pregnancy does not affect fecal calprotectin concentration in healthy women. *Turk J Gastroenterol* 2017;**28**:171–5. doi:10.5152/tjg.2017.16711.
117. Ludvigsson JF, Lebwohl B, Ekbom A, *et al*. Outcomes of pregnancies for women undergoing endoscopy while they were pregnant: a nationwide cohort study. *Gastroenterology* 2017;**152**:554–63 e559. doi:10.1053/j.gastro.2016.10.016.
118. Ko MS, Rudrapatna VA, Avila P, *et al*. Safety of flexible sigmoidoscopy in pregnant patients with known or suspected inflammatory bowel disease. *Dig Dis Sci* 2020;**65**:2979–85. doi:10.1007/s10620-020-06122-8.
119. de Lima A, Zelinkova Z, van der Woude CJ. A prospective study of the safety of lower gastrointestinal endoscopy during pregnancy in patients with inflammatory bowel disease. *J Crohns Colitis* 2015;**9**:519–24. doi:10.1093/ecco-jcc/jjv079.
120. Cappell MS, Colon VJ, Sidhom OA. A study at 10 medical centers of the safety and efficacy of 48 flexible sigmoidoscopies and 8 colonoscopies during pregnancy with follow-up of fetal outcome and with comparison to control groups. *Dig Dis Sci* 1996;**41**:2353–61. doi:10.1007/BF02100127.
121. Cappell MS, Fox SR, Gorrepati N. Safety and efficacy of colonoscopy during pregnancy: an analysis of pregnancy outcome in 20 patients. *J Reprod Med* 2010;**55**:115–23.
122. Cappell MS, Sidhom O. Multicenter, multiyear study of safety and efficacy of flexible sigmoidoscopy during pregnancy in 24 females

with follow-up of fetal outcome. *Dig Dis Sci* 1995;**40**:472–9. doi:10.1007/BF02065437.
123. Shergill AK, Ben-Menachem T, Chandrasekhara V, *et al*. Guidelines for endoscopy in pregnant and lactating women. *Gastrointest Endosc* 2012;**76**:18–24. doi:10.1016/j.gie.2012.02.029.
124. Bandorski D, Kurniawan N, Baltes P, *et al*. Contraindications for video capsule endoscopy. *World J Gastroenterol* 2016;**22**:9898–908. doi:10.3748/wjg.v22.i45.9898.
125. Stern MD, Kopylov U, Ben-Horin S, *et al*. Magnetic resonance enterography in pregnant women with Crohn's disease: case series and literature review. *BMC Gastroenterol* 2014;**14**:146. doi:10.1186/1471-230X-14-146.
126. Birchard KR, Brown MA, Hyslop WB, *et al*. MRI of acute abdominal and pelvic pain in pregnant patients. *AJR Am J Roentgenol* 2005;**184**:452–8. doi:10.2214/ajr.184.2.01840452.
127. Woussen S, Lopez-Rendon X, Vanbeckevoort D, *et al*. Clinical indications and radiation doses to the conceptus associated with CT imaging in pregnancy: a retrospective study. *Eur Radiol* 2016;**26**:979–85. doi:10.1007/s00330-015-3924-8.
128. Flanagan E, Wright EK, Begun J, *et al*. Monitoring inflammatory bowel disease in pregnancy using gastrointestinal ultrasonography. *J Crohns Colitis* 2020;**14**:1405–12. doi:10.1093/ecco-jcc/jjaa082.
129. Leung Y, Shim HH, Wilkens R, *et al*. The role of bowel ultrasound in detecting subclinical inflammation in pregnant women with Crohn's disease. *J Can Assoc Gastroenterol* 2019;**2**:153–60. doi:10.1093/jcag/gwy062.
130. Seow CH, Leung Y, Vande Casteele N, *et al*. The effects of pregnancy on the pharmacokinetics of infliximab and adalimumab in inflammatory bowel disease. *Aliment Pharmacol Ther* 2017;**45**:1329–38. doi:10.1111/apt.14040.
131. Grisic AM, Dorn-Rasmussen M, Ungar B, *et al*. Infliximab clearance decreases in the second and third trimesters of pregnancy in inflammatory bowel disease. *United Eur Gastroenterol J* 2021;**9**:91–101. doi:10.1177/2050640620964619.
132. Flanagan E, Gibson PR, Wright EK, *et al*. Infliximab, adalimumab and vedolizumab concentrations across pregnancy and vedolizumab concentrations in infants following intrauterine exposure. *Aliment Pharmacol Ther* 2020;**52**:1551–62. doi:10.1111/apt.16102.
133. Bates SM, Rajasekhar A, Middeldorp S, *et al*. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv* 2018;**2**:3317–59. doi:10.1182/bloodadvances.2018024802.
134. Kim YH, Pfaller B, Marson A, *et al*. The risk of venous thromboembolism in women with inflammatory bowel disease during pregnancy and the postpartum period: A systematic review and meta-analysis. *Medicine [Baltimore]* 2019;**98**:e17309. doi:10.1097/MD.0000000000017309.
135. Hansen AT, Erichsen R, Horváth-Puhó E, *et al*. Inflammatory bowel disease and venous thromboembolism during pregnancy and the postpartum period. *J Thromb Haemost* 2017;**15**:702–8. doi:10.1111/jth.13638.
136. Nguyen GC, Boudreau H, Harris ML, *et al*. Outcomes of obstetric hospitalizations among women with inflammatory bowel disease in the United States. *Clin Gastroenterol Hepatol* 2009;**7**:329–34. doi:10.1016/j.cgh.2008.10.022.
137. Beyer-Westendorf J, Tittl L, Bistervels I, *et al*. Safety of direct oral anticoagulant exposure during pregnancy: a retrospective cohort study. *Lancet Haematol* 2020;**7**:e884–91. doi:10.1016/s2352-3026[20]30327-6.
138. Torres J, Bonovas S, Doherty G, *et al*. ECCO Guidelines on Therapeutics in Crohn's Disease: medical treatment. *J Crohn's Colitis* 2020;**14**:4–22. doi:10.1093/ecco-jcc/jjz180.
139. Raine T, Bonovas S, Burisch J, *et al*. ECCO Guidelines on Therapeutics in Ulcerative Colitis: medical treatment. *J Crohns Colitis* 2021:jjab178. doi:10.1093/ecco-jcc/jjab178.
140. Vermeire S, Carbonnel F, Coulie PG, *et al*. Management of inflammatory bowel disease in pregnancy. *J Crohns Colitis* 2012;**6**:811–23. doi:10.1016/j.crohns.2012.04.009.
141. Reddy D, Murphy SJ, Kane SV, *et al*. Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes. *Am J Gastroenterol* 2008;**103**:1203–9. doi:10.1111/j.1572-0241.2007.01756.x.
142. Branche J, Cortot A, Bourreille A, *et al*. Cyclosporine treatment of steroid-refractory ulcerative colitis during pregnancy. *Inflamm Bowel Dis* 2009;**15**:1044–8. doi:10.1002/ibd.20858.
143. Bortlik M, Machkova N, Duricova D, *et al*. Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF-α therapy during pregnancy: three-center study. *Scand J Gastroenterol* 2013;**48**:951–8. doi:10.3109/00365521.2013.812141.
144. Moens A, van der Woude CJ, Julsgaard M, *et al*. Pregnancy outcomes in inflammatory bowel disease patients treated with vedolizumab, anti-TNF or conventional therapy: results of the European CONCEIVE study. *Aliment Pharmacol Ther* 2020;**51**:129–38. doi:10.1111/apt.15539.
145. Killeen S, Gunn J, Hartley J. Surgical management of complicated and medically refractory inflammatory bowel disease during pregnancy. *Colorectal Dis* 2017;**19**:123–38. doi:10.1111/codi.13413.
146. Germain A, Chateau T, Beyer-Berjot L, *et al*. Surgery for Crohn's disease during pregnancy: A nationwide survey. *United Eur Gastroenterol J* 2020;**8**:736–40.doi:10.1177/2050640620921060.
147. Chaparro M, Kunovský L, Aguas M, *et al*. Surgery due to inflammatory bowel disease during pregnancy: mothers and offspring outcomes from an ECCO CONFER Multicentre Case Series [Scar Study]. *J Crohns Colitis* 2022;**16**:1428–35. doi:10.1093/ecco-jcc/jjac050.
148. Rasmussen AS, Christiansen CF, Ulrichsen SP, *et al*. Non-obstetric abdominal surgery during pregnancy and birth outcomes: a Danish registry-based cohort study. *Acta Obstet Gynecol Scand* 2020;**99**:469–76. doi:10.1111/aogs.13775.
149. Bröms G, Granath F, Stephansson O, *et al*. Preterm birth in women with inflammatory bowel disease: the association with disease activity and drug treatment. *Scand J Gastroenterol* 2016;**51**:1462–9. doi:10.1080/00365521.2016.1208269.
150. Chapman TP, Gomes CF, Louis E, *et al*. De-escalation of immunomodulator and biological therapy in inflammatory bowel disease. *Lancet Gastroenterol Hepatol* 2020;**5**:63–79. doi:10.1016/s2468-1253[19]30186-4.
151. Roblin X, Boschetti G, Williet N, *et al*. Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: an open-label, prospective and randomised clinical trial. *Aliment Pharmacol Ther* 2017;**46**:142–9. doi:10.1111/apt.14106.
152. Flanagan E, Wright EK, Hardikar W, *et al*. Maternal thiopurine metabolism during pregnancy in inflammatory bowel disease and clearance of thiopurine metabolites and outcomes in exposed neonates. *Aliment Pharmacol Ther* 2021;**53**:810–20. doi:10.1111/apt.16294.
153. Jharap B, de Boer NK, Stokkers P, *et al*. Intrauterine exposure and pharmacology of conventional thiopurine therapy in pregnant patients with inflammatory bowel disease. *Gut* 2014;**63**:451–7. doi:10.1136/gutjnl-2012-303615.
154. Lozano NA, Lozano A, Marini V, *et al*. Expression of FcRn receptor in placental tissue and its relationship with IgG levels in term and preterm newborns. *Am J Reprod Immunol* 2018;**80**:e12972. doi:10.1111/aji.12972.
155. Beltagy A, Aghamajidi A, Trespidi L, *et al*. Biologics during pregnancy and breastfeeding among women with rheumatic diseases: safety clinical evidence on the road. *Front Pharmacol* 2021;**12**. Review. doi:10.3389/fphar.2021.621247.
156. Mariette X, Förger F, Abraham B, *et al*. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. *Ann Rheum Dis* 2018;**77**:228–33. doi:10.1136/annrheumdis-2017-212196.
157. Mahadevan U, Long MD, Kane SV, *et al*. Pregnancy and neonatal outcomes after fetal exposure to biologics and thiopurines among

women with inflammatory bowel disease. *Gastroenterology* 2021;**160**:1131–9. doi:10.1053/j.gastro.2020.11.038.
158. Kanis SL, De Lima-Karagiannis A, Van Der Ent C, *et al*. Anti-TNF levels in cord blood at birth are associated with anti-TNF type. *J Crohns Colitis* 2018;**12**:839–947. doi:10.1093/ecco-jcc/jjy058.
159. Mahadevan U, Wolf DC, Dubinsky M, *et al*. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013;**11**:286–92; quiz e224. doi:10.1016/j.cgh.2012.11.011.
160. Julsgaard M, Christensen LA, Gibson PR, *et al*. Concentrations of Adalimumab and Infliximab in mothers and newborns, and effects on infection. *Gastroenterology* 2016;**151**:110–9. doi:10.1053/j.gastro.2016.04.002.
161. Julsgaard M, Baumgart DC, Baunwall SMD, *et al*. Vedolizumab clearance in neonates, susceptibility to infections and developmental milestones: a prospective multicentre population-based cohort study. *Aliment Pharmacol Ther* 2021;**54**:1320–9. doi:10.1111/apt.16593.
162. Klenske E, Osaba L, Nagore D, *et al*. Drug levels in the maternal serum, cord blood and breast milk of a ustekinumab-treated patient with Crohn's disease. *J Crohns Colitis* 2019;**13**:267–9. doi:10.1093/ecco-jcc/jjy153.
163. Rowan CR, Cullen G, Mulcahy HE, *et al*. Ustekinumab drug levels in maternal and cord blood in a woman with Crohn's disease treated until 33 weeks of gestation. *J Crohns Colitis* 2018;**12**:376–8. doi:10.1093/ecco-jcc/jjx141.
164. Flanagan E, Prentice R, Wright EK, *et al*. Ustekinumab levels in pregnant women with inflammatory bowel disease and infants exposed in utero. *Aliment Pharmacol Ther* 2022;**55**:700–4. doi:10.1111/apt.16739.
165. Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. *Am J Gastroenterol* 2009;**104**:228–33. doi:10.1038/ajg.2008.71.
166. Broms G, Kieler H, Ekbom A, *et al*. Paediatric infections in the first 3 years of life after maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther* 2020;**52**:843–54. doi:10.1111/apt.15971.
167. Julsgaard M, Hvas CL, Gearry RB, *et al*. Anti-TNF therapy in pregnant women with inflammatory bowel disease: effects of therapeutic strategies on disease behavior and birth outcomes. *Inflamm Bowel Dis* 2020;**26**:93–102. doi:10.1093/ibd/izz110.
168. Argüelles-Arias F, Castro-Laria L, Barreiro-de Acosta M, *et al*. Is safety infliximb during pregnancy in patients with inflammatory bowel disease? *Rev Esp Enferm Dig* 2012;**104**:59–64. doi:10.4321/s1130-01082012000200003.
169. Seirafi M, De Vroey B, Amiot A, *et al*. Factors associated with pregnancy outcome in anti-TNF treated women with inflammatory bowel disease. *Aliment Pharmacol Ther* 2014;**40**:363–73. doi:10.1111/apt.12833.
170. Zelinkova Z, van der Ent C, Bruin KF, *et al*. Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. *Clin Gastroenterol Hepatol* 2013;**11**:318–21. doi:10.1016/j.cgh.2012.10.024.
171. Casanova MJ, Chaparro M, Domenech E, *et al*. Safety of thiopurines and anti-TNF-alpha drugs during pregnancy in patients with inflammatory bowel disease. *Am J Gastroenterol* 2013;**108**:433–40. doi:10.1038/ajg.2012.430.
172. de Lima A, Zelinkova Z, van der Ent C, *et al*. Tailored anti-TNF therapy during pregnancy in patients with IBD: maternal and fetal safety. *Gut* 2016;**65**:1261–8. doi:10.1136/gutjnl-2015-309321.
173. Malhi G, Tandon P, Perlmutter JW, *et al*. Risk factors for postpartum disease activity in women with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2021. doi:10.1093/ibd/izab206.
174. Truta B, Leeds IL, Canner JK, *et al*. Early discontinuation of infliximab in pregnant women with inflammatory bowel disease. *Inflamm Bowel Dis* 2020;**26**:1110–7. doi:10.1093/ibd/izz250.
175. Luu M, Benzenine E, Doret M, *et al*. Continuous anti-TNFalpha use throughout pregnancy: possible complications for the mother but not for the fetus. A retrospective cohort on the French National Health Insurance Database [EVASION]. *Am J Gastroenterol* 2018;**113**:1669–77. doi:10.1038/s41395-018-0176-7.
176. Geldhof A, Slater J, Clark M, *et al*. Exposure to infliximab during pregnancy: post-marketing experience. *Drug Saf* 2020;**43**:147–61. doi:10.1007/s40264-019-00881-8.
177. Clowse MEB, Scheuerle AE, Chambers C, *et al*. Pregnancy outcomes after exposure to Certolizumab Pegol: updated results from a pharmacovigilance safety database. *Arthritis Rheumatol* 2018;**70**:1399–407. doi:10.1002/art.40508.
178. Kammerlander H, Nielsen J, Knudsen T, *et al*. Anti-TNF-alpha use during the third trimester of pregnancy in women with moderate-severe inflammatory bowel disease and the risk of preterm birth and low birth weight. *Inflamm Bowel Dis* 2017;**23**:1916–23. doi:10.1097/MIB.0000000000001234.
179. Kanis SL, Modderman S, Escher JC, *et al*. Health outcomes of 1000 children born to mothers with inflammatory bowel disease in their first 5 years of life. *Gut* 2021;**70**:1266–74. doi:10.1136/gutjnl-2019-319129.
180. Nguyen GC, Seow CH, Maxwell C, *et al*. The Toronto consensus statements for the management of inflammatory bowel disease in pregnancy. *Gastroenterology* 2016;**150**:734–57.e731. doi:10.1053/j.gastro.2015.12.003.
181. Wils P, Seksik P, Stefanescu C, *et al*. Safety of ustekinumab or vedolizumab in pregnant inflammatory bowel disease patients: a multicentre cohort study. *Aliment Pharmacol Ther* 2021;**53**:460–70. doi:10.1111/apt.16192.
182. O'Toole A, Nwanne O, Tomlinson T. Inflammatory bowel disease increases risk of adverse pregnancy outcomes: a meta-analysis. *Dig Dis Sci* 2015;**60**:2750–61. doi:10.1007/s10620-015-3677-x.
183. Cornish J, Tan E, Teare J, *et al*. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007;**56**:830–7. doi:10.1136/gut.2006.108324.
184. Abdul Sultan A, West J, Ban L, *et al*. Adverse pregnancy outcomes among women with inflammatory bowel disease: a population-based study from England. *Inflamm Bowel Dis* 2016;**22**:1621–30. doi:10.1097/mib.0000000000000802.
185. Boyd HA, Basit S, Harpsøe MC, *et al*. Inflammatory bowel disease and risk of adverse pregnancy outcomes. *PLoS One* 2015;**10**:e0129567. doi:10.1371/journal.pone.0129567.
186. Shand AW, Chen JS, Selby W, *et al*. Inflammatory bowel disease in pregnancy: a population-based study of prevalence and pregnancy outcomes. *BJOG* 2016;**123**:1862–70. doi:10.1111/1471-0528.13946.
187. Bandoli G, Singh N, Strouse J, *et al*. Mediation of adverse pregnancy outcomes in autoimmune conditions by pregnancy complications: a mediation analysis of autoimmune conditions and adverse pregnancy outcomes. *Arthritis Care Res [Hoboken]* 2020;**72**:256–64. doi:10.1002/acr.24037.
188. Bortoli A, Pedersen N, Duricova D, *et al*. Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003-2006. *Aliment Pharmacol Ther* 2011;**34**:724–34. doi:10.1111/j.1365-2036.2011.04794.x.
189. Lee HH, Bae JM, Lee BI, *et al*. Pregnancy outcomes in women with inflammatory bowel disease: a 10-year nationwide population-based cohort study. *Aliment Pharmacol Ther* 2020;**51**:861–9. doi:10.1111/apt.15654.
190. Lavie I, Lavie M, Doyev R, *et al*. Pregnancy outcomes in women with inflammatory bowel disease who successfully conceived via assisted reproduction technique. *Arch Gynecol Obstet* 2020;**302**:611–8. doi:10.1007/s00404-020-05644-w.
191. Moser MA, Okun NB, Mayes DC, *et al*. Crohn's disease, pregnancy, and birth weight. *Am J Gastroenterol* 2000;**95**:1021–6. doi:10.1111/j.1572-0241.2000.01852.x.
192. Tandon P, Govardhanam V, Leung K, *et al*. Systematic review with meta-analysis: risk of adverse pregnancy-related outcomes in inflammatory bowel disease. *Aliment Pharmacol Ther* 2020;**51**:320–33. doi:10.1111/apt.15587.

193. de Silva PS, Hansen HH, Wehberg S, *et al*. Risk of ectopic pregnancy in women with inflammatory bowel disease: a 22-year nationwide cohort study. *Clin Gastroenterol Hepatol* 2018;**16**:83–9. e81. doi:10.1016/j.cgh.2017.06.054.
194. Oron G, Yogev Y, Shcolnick S, *et al*. Inflammatory bowel disease: risk factors for adverse pregnancy outcome and the impact of maternal weight gain. *J Matern Fetal Neonatal Med* 2012;**25**:2256–60. doi:10.3109/14767058.2012.684176.
195. Bröms G, Granath F, Linder M, *et al*. Birth outcomes in women with inflammatory bowel disease: effects of disease activity and drug exposure. *Inflamm Bowel Dis* 2014;**20**:1091–8. doi:10.1097/mib.0000000000000060.
196. Stephansson O, Larsson H, Pedersen L, *et al*. Congenital abnormalities and other birth outcomes in children born to women with ulcerative colitis in Denmark and Sweden. *Inflamm Bowel Dis* 2011;**17**:795–801. doi:10.1002/ibd.21369.
197. Stephansson O, Larsson H, Pedersen L, *et al*. Crohn's disease is a risk factor for preterm birth. *Clin Gastroenterol Hepatol* 2010;**8**:509–15. doi:10.1016/j.cgh.2010.02.014.
198. Mahadevan U, Sandborn WJ, Li DK, *et al*. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. *Gastroenterology* 2007;**133**:1106–12. doi:10.1053/j.gastro.2007.07.019.
199. Dotan I, Alper A, Rachmilewitz D, *et al*. Maternal inflammatory bowel disease has short- and long-term effects on the health of their offspring: a multicentre study in Israel. *J Crohns Colitis* 2013;**7**:542–50. doi:10.1016/j.crohns.2012.08.012.
200. Norgard B, Pedersen L, Christensen LA, *et al*. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish nationwide cohort study. *Am J Gastroenterol* 2007;**102**:1406–13. doi:10.1111/j.1572-0241.2007.01216.x.
201. Mogadam M, Dobbins WO 3rd, Korelitz BI, *et al*. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. *Gastroenterology* 1981;**80**:72–6.
202. Norgard B, Fonager K, Pedersen L, *et al*. Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish cohort study. *Gut* 2003;**52**:243–7. doi:10.1136/gut.52.2.243.
203. Norgard B, Czeizel AE, Rockenbauer M, *et al*. Population-based case control study of the safety of sulfasalazine use during pregnancy. *Aliment Pharmacol Ther* 2001;**15**:483–6. doi:10.1046/j.1365-2036.2001.00962.x.
204. Rahimi R, Nikfar S, Rezaie A, *et al*. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. *Reprod Toxicol* 2008;**25**:271–5. doi:10.1016/j.reprotox.2007.11.010.
205. Park-Wyllie L, Mazzotta P, Pastuszak A, *et al*. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000;**62**:385–92. doi:10.1002/1096-9926[200012]62:6<385::AID-TERA5>3.0.CO;2-Z.
206. Carmichael SL, Shaw GM, Ma C, *et al*. Maternal corticosteroid use and orofacial clefts. *Am J Obstet Gynecol* 2007;**197**:e581–7. doi:10.1016/j.ajog.2007.05.046.
207. Gur C, Diav-Citrin O, Shechtman S, *et al*. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. *Reprod Toxicol* 2004;**18**:93–101. doi:10.1016/j.reprotox.2003.10.007.
208. Hviid A, Molgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. *CMAJ* 2011;**183**:796–804. doi:10.1503/cmaj.101063.
209. Homar V, Grosek S, Battelino T. High-dose methylprednisolone in a pregnant woman with Crohn's disease and adrenal suppression in her newborn. *Neonatology* 2008;**94**:306–9. doi:10.1159/000151652.
210. Beaulieu DB, Ananthakrishnan AN, Issa M, *et al*. Budesonide induction and maintenance therapy for Crohn's disease during pregnancy. *Inflamm Bowel Dis* 2009;**15**:25–8. doi:10.1002/ibd.20640.
211. Vestergaard T, Jorgensen SMD, Christensen LA, *et al*. Pregnancy outcome in four women with inflammatory bowel disease treated with budesonide MMX. *Scand J Gastroenterol* 2018;**53**:1459–62. doi:10.1080/00365521.2018.1533583.
212. Martel MJ, Rey E, Beauchesne MF, *et al*. Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. *BMJ* 2005;**330**:230. doi:10.1136/bmj.38313.624352.8F.
213. Pang S, Clark AT, Freeman LC, *et al*. Maternal side effects of prenatal dexamethasone therapy for fetal congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 1992;**75**:249–53. doi:10.1210/jcem.75.1.1619017.
214. Odufalu F-D, Long M, Lin K, *et al*. Exposure to corticosteroids in pregnancy is associated with adverse perinatal outcomes among infants of mothers with inflammatory bowel disease: results from the PIANO registry. *Gut* 2021:gutjnl-2021-325317. doi:10.1136/gutjnl-2021-325317.
215. Gionchetti P, Dignass A, Danese S, *et al*. Third European evidence-based consensus on the diagnosis and management of Crohn's disease 2016. Part 2: surgical management and special situations. *J Crohns Colitis* 2017;**11**:135–49. doi:10.1093/ecco-jcc/jjw169.
216. Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. *Br J Obstet Gynaecol* 1998;**105**:322–7. doi:10.1111/j.1471-0528.1998.tb10094.x.
217. Burtin P, Taddio A, Ariburnu O, *et al*. Safety of metronidazole in pregnancy: a meta-analysis. *Am J Obstet Gynecol* 1995;**172**:525–9. doi:10.1016/0002-9378[95]90567-7.
218. Caro-Patón T, Carvajal A, Martin de Diego I, *et al*. Is metronidazole teratogenic? A meta-analysis. *Br J Clin Pharmacol* 1997;**44**:179–82. doi:10.1046/j.1365-2125.1997.00660.x.
219. Koss CA, Baras DC, Lane SD, *et al*. Investigation of metronidazole use during pregnancy and adverse birth outcomes. *Antimicrob Agents Chemother* 2012;**56**:4800–5. doi:10.1128/aac.06477-11.
220. Sheehy O, Santos F, Ferreira E, *et al*. The use of metronidazole during pregnancy: a review of evidence. *Curr Drug Saf* 2015;**10**:170–9. doi:10.2174/1574886310021505151245548.
221. Bar-Oz B, Moretti ME, Boskovic R, *et al*. The safety of quinolones: a meta-analysis of pregnancy outcomes. *Eur J Obstet Gynecol Reprod Biol* 2009;**143**:75–8. doi:10.1016/j.ejogrb.2008.12.007.
222. Yefet E, Schwartz N, Chazan B, *et al*. The safety of quinolones and fluoroquinolones in pregnancy: a meta-analysis. *BJOG* 2018;**125**:1069–76. doi:10.1111/1471-0528.15119.
223. Moskovitz DN, Bodian C, Chapman ML, *et al*. The effect on the fetus of medications used to treat pregnant inflammatory bowel-disease patients. *Am J Gastroenterol* 2004;**99**:656–61. doi:10.1111/j.1572-0241.2004.04140.x.
224. Cleary BJ, Kallen B. Early pregnancy azathioprine use and pregnancy outcomes. *Birth Defects Res A Clin Mol Teratol* 2009;**85**:647–54. doi:10.1002/bdra.20583.
225. Goldstein LH, Dolinsky G, Greenberg R, *et al*. Pregnancy outcome of women exposed to azathioprine during pregnancy. *Birth Defects Res A Clin Mol Teratol* 2007;**79**:696–701. doi:10.1002/bdra.20399.
226. Norgard B, Hundborg HH, Jacobsen BA, *et al*. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. *Am J Gastroenterol* 2007;**102**:1947–54. doi:10.1111/j.1572-0241.2007.01355.x.
227. Coelho J, Beaugerie L, Colombel JF, *et al*. Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines: cohort from the CESAME Study. *Gut* 2011;**60**:198–203. doi:10.1136/gut.2010.222893.
228. Angelberger S, Reinisch W, Messerschmidt A, *et al*. Long-term follow-up of babies exposed to azathioprine in utero and via breastfeeding. *J Crohns Colitis* 2011;**5**:95–100. doi:10.1016/j.crohns.2010.10.005.
229. Shim L, Eslick GD, Simring AA, *et al*. The effects of azathioprine on birth outcomes in women with inflammatory bowel disease [IBD]. *J Crohns Colitis* 2011;**5**:234–8. doi:10.1016/j.crohns.2011.01.009.

230. Hutson JR, Matlow JN, Moretti ME, *et al*. The fetal safety of thiopurines for the treatment of inflammatory bowel disease in pregnancy. *J Obstet Gynaecol* 2013;**33**:1–8. doi:10.3109/01443615.2012.716106.
231. Kanis SL, de Lima-Karagiannis A, de Boer NKH, *et al*. Use of thiopurines during conception and pregnancy is not associated with adverse pregnancy outcomes or health of infants at one year in a prospective study. *Clin Gastroenterol Hepatol* 2017;**15**:1232–41 e1231. doi:10.1016/j.cgh.2017.02.041.
232. Koslowsky B, Sadeh C, Grisaru-Granovsky S, *et al*. Thiopurine therapy for inflammatory bowel disease during pregnancy is not associated with anemia in the infant. *Dig Dis Sci* 2019;**64**:2286–90. doi:10.1007/s10620-019-05555-0.
233. Akbari M, Shah S, Velayos FS, *et al*. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;**19**:15–22. doi:10.1002/ibd.22948.
234. Francella A, Dyan A, Bodian C, *et al*. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. *Gastroenterology* 2003;**124**:9–17. doi:10.1053/gast.2003.50014.
235. Langagergaard V, Pedersen L, Gislum M, *et al*. Birth outcome in women treated with azathioprine or mercaptopurine during pregnancy: a Danish nationwide cohort study. *Aliment Pharmacol Ther* 2007;**25**:73–81. doi:10.1111/j.1365-2036.2006.03162.x.
236. de Meij TG, Jharap B, Kneepkens CM, *et al*. Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;**38**:38–43. doi:10.1111/apt.12334.
237. Fazal MW, Doogue MP, Leong RW, *et al*. Allopurinol use in pregnancy in three women with inflammatory bowel disease: safety and outcomes: a case series. *BMC Gastroenterol* 2013;**13**:172. doi:10.1186/1471-230X-13-172.
238. Hoeltzenbein M, Stieler K, Panse M, *et al*. Allopurinol use during pregnancy: Outcome of 31 prospectively ascertained cases and a phenotype possibly indicative for teratogenicity. *PLoS One* 2013;**8**:e66637. doi:10.1371/journal.pone.0066637.
239. Sheikh M, Nelson-Piercy C, Duley J, *et al*. Successful pregnancies with thiopurine-allopurinol co-therapy for inflammatory bowel disease. *J Crohns Colitis* 2015;**9**:680–4. doi:10.1093/ecco-jcc/jjv072.
240. Bar Oz B, Hackman R, Einarson T, *et al*. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. *Transplantation* 2001;**71**:1051–5. doi:10.1097/00007890-200104270-00006.
241. Jain AB, Reyes J, Marcos A, *et al*. Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. *Transplantation* 2003;**76**:827–32. doi:10.1097/01.TP.0000084823.89528.89.
242. Korelitz BI. Inflammatory bowel disease and pregnancy. *Gastroenterol Clin North Am* 1998;**27**:213–24. doi:10.1016/s0889-8553[05]70354-x.
243. Baumgart DC, Sturm A, Wiedenmann B, *et al*. Uneventful pregnancy and neonatal outcome with tacrolimus in refractory ulcerative colitis. *Gut* 2005;**54**:1822–3. doi:10.1136/gut.2005.078972.
244. Kozlowski RD, Steinbrunner JV, MacKenzie AH, *et al*. Outcome of first-trimester exposure to low-dose methotrexate in eight patients with rheumatic disease. *Am J Med* 1990;**88**:589–92. doi:10.1016/0002-9343[90]90522-f.
245. Smithells RW, Newman CG. Recognition of thalidomide defects. *J Med Genet* 1992;**29**:716–23. doi:10.1136/jmg.29.10.716.
246. Schnitzler F, Fidder H, Ferrante M, *et al*. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. *Inflamm Bowel Dis* 2011;**17**:1846–54. doi:10.1002/ibd.21583.
247. Shihab Z, Yeomans ND, De Cruz P. Anti-tumour necrosis factor alpha therapies and inflammatory bowel disease pregnancy outcomes: a meta-analysis. *J Crohns Colitis* 2016;**10**:979–88. doi:10.1093/ecco-jcc/jjv234.
248. Broms G, Granath F, Ekbom A, *et al*. Low risk of birth defects for infants whose mothers are treated with anti-tumor necrosis factor agents during pregnancy. *Clin Gastroenterol Hepatol* 2016;**14**:234–41 e231-5. doi:10.1016/j.cgh.2015.08.039.
249. Duricova D, Dvorakova E, Hradsky O, *et al*. Safety of anti-TNF-alpha therapy during pregnancy on long-term outcome of exposed children: a controlled, multicenter observation. *Inflamm Bowel Dis* 2019;**25**:789–96. doi:10.1093/ibd/izy294.
250. Kawai Y, Tsuchiya T, Aoki S. Pregnancy outcomes of patients exposed to Adalimumab in Japan. *Dig Dis* 2019;**37**:123–30. doi:10.1159/000493462.
251. Chambers CD, Johnson DL, Xu R, *et al*. Birth outcomes in women who have taken adalimumab in pregnancy: a prospective cohort study. *PLoS One* 2019;**14**:e0223603. doi:10.1371/journal.pone.0223603.
252. Kammerlander H, Nielsen J, Kjeldsen J, *et al*. The effect of disease activity on birth outcomes in a nationwide cohort of women with moderate to severe inflammatory bowel disease. *Inflamm Bowel Dis* 2017;**23**:1011–8. doi:10.1097/MIB.0000000000001102.
253. Lichtenstein GR, Feagan BG, Mahadevan U, *et al*. Pregnancy outcomes reported during the 13-year TREAT registry: a descriptive report. *Am J Gastroenterol* 2018;**113**:1678–88. doi:10.1038/s41395-018-0202-9.
254. Mahadevan U, Vermeire S, Lasch K, *et al*. Vedolizumab exposure in pregnancy: outcomes from clinical studies in inflammatory bowel disease. *Aliment Pharmacol Ther* 2017;**45**:941–50. doi:10.1111/apt.13960.
255. Martin PL, Sachs C, Imai N, *et al*. Development in the cynomolgus macaque following administration of ustekinumab, a human anti-IL-12/23p40 monoclonal antibody, during pregnancy and lactation. *Birth Defects Res B Dev Reprod Toxicol* 2010;**89**:351–63. doi:10.1002/bdrb.20250.
256. Gisbert JP, Chaparro M. Safety of new biologics [Vedolizumab and Ustekinumab] and small molecules [Tofacitinib] during pregnancy: a review. *Drugs* 2020;**80**:1085–100. doi:10.1007/s40265-020-01346-4.
257. Terjung B, Schmelz R, Ehehalt R, *et al*. Safety of vedolizumab in the treatment of pregnant women with inflammatory bowel disease: a targeted literature review. *Therap Adv Gastroenterol* 2020;**13**:1756284820952592. doi:10.1177/1756284820952592.
258. Bar-Gil Shitrit A, Ben Ya'acov A, Livovsky DM, *et al*. Exposure to Vedolizumab in IBD pregnant women appears of low risk for mother and neonate: a first prospective comparison study. *Am J Gastroenterol* 2019;**114**:1172–5. doi:10.14309/ajg.0000000000000186.
259. Mahadevan U, Dubinsky MC, Su C, *et al*. Outcomes of pregnancies with maternal/paternal exposure in the Tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis* 2018;**24**:2494–500. doi:10.1093/ibd/izy160.
260. Selmaj KW, Cohen JA, Comi G, *et al*. Ozanimod in relapsing multiple sclerosis: Pooled safety results from the clinical development program. *Mult Scler Relat Disord* 2021;**51**:102844. doi:10.1016/j.msard.2021.102844.
261. Sandborn WJ, Feagan BG, Hanauer S, *et al*. Long-term efficacy and safety of ozanimod in moderately to severely active ulcerative colitis: results from the open-label extension of the randomised, phase 2 TOUCHSTONE study. *J Crohns Colitis* 2021;**15**:1120–9. doi:10.1093/ecco-jcc/jjab012.
262. Foulon A, Dupas JL, Sabbagh C, *et al*. Defining the most appropriate delivery mode in women with inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis* 2017;**23**:712–20. doi:10.1097/mib.0000000000001112.
263. Remzi FH, Gorgun E, Bast J, *et al*. Vaginal delivery after ileal pouch-anal anastomosis: a word of caution. *Dis Colon Rectum* 2005;**48**:1691–9. doi:10.1007/s10350-005-0124-7.
264. Cheng AG, Oxford EC, Sauk J, *et al*. Impact of mode of delivery on outcomes in patients with perianal Crohn's disease. *Inflamm Bowel Dis* 2014;**20**:1391–8. doi:10.1097/MIB.0000000000000093.

265. Nielsen OH, Loftus EV, Jess T. Safety of TNF-alpha inhibitors during IBD pregnancy: a systematic review. *BMC Med* 2013;**11**:174. doi:10.1186/1741-7015-11-174.
266. Bortlik M, Duricova D, Machkova N, *et al*. Impact of anti-tumor necrosis factor alpha antibodies administered to pregnant women with inflammatory bowel disease on long-term outcome of exposed children. *Inflamm Bowel Dis* 2014;**20**:495–501. doi:10.1097/01.MIB.0000440984.86659.4f.
267. Kanis SL, de Lima-Karagiannis A, van der Ent C, *et al*. Anti-TNF levels in cord blood at birth are associated with anti-TNF type. *J Crohns Colitis* 2018;**12**:939–47. doi:10.1093/ecco-jcc/jjy058.
268. Tsao NW, Lynd LD, Sayre EC, *et al*. Use of biologics during pregnancy and risk of serious infections in the mother and baby: a Canadian population-based cohort study. *BMJ Open* 2019;**9**:e023714. doi:10.1136/bmjopen-2018-023714.
269. Meyer A, Taine M, Drouin J, *et al*. Serious infections in children born to mothers with inflammatory bowel disease with in utero exposure to thiopurines and anti-tumor necrosis factor. *Clin Gastroenterol Hepatol* 2021. doi:10.1016/j.cgh.2021.07.028.
270. Sheibani S, Cohen R, Kane S, *et al*. The effect of maternal peripartum Anti-TNFalpha use on infant immune response. *Dig Dis Sci* 2016;**61**:1622–7. doi:10.1007/s10620-015-3992-2.
271. Nørgård BM, Nielsen J, Friedman S. In utero exposure to thiopurines/anti-TNF agents and long-term health outcomes during childhood and adolescence in Denmark. *Aliment Pharmacol Ther* 2020;**52**:829–42. doi:10.1111/apt.15956.
272. Long MD, Siegel CA, Abraham BP, *et al*. Day care attendance and infectious complications in children born to mothers with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2022;**20**:706–8.e701. doi:10.1016/j.cgh.2021.02.003.
273. Cheent K, Nolan J, Shariq S, *et al*. Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J Crohns Colitis* 2010;**4**:603–5. doi:10.1016/j.crohns.2010.05.001.
274. Guiddir T, Fremond ML, Triki TB, *et al*. Anti-TNF-alpha therapy may cause neonatal neutropenia. *Pediatrics* 2014;**134**:e1189–93. doi:10.1542/peds.2014-0054.
275. Esteve-Sole A, Deya-Martinez A, Teixido I, *et al*. Immunological changes in blood of newborns exposed to Anti-TNF-alpha during pregnancy. *Front Immunol* 2017;**8**:1123. doi:10.3389/fimmu.2017.01123.
276. Kattah MG, Milush JM, Burt T, *et al*. Anti-TNF and thiopurine therapy in pregnant IBD patients does not significantly alter a panel of B-cell and T-cell subsets in 1-year-old infants. *Clin Transl Gastroenterol* 2018;**9**:143. doi:10.1038/s41424-018-0018-3.
277. Beaulieu DB, Ananthakrishnan AN, Martin C, *et al*. Use of biologic therapy by pregnant women with inflammatory bowel disease does not affect infant response to vaccines. *Clin Gastroenterol Hepatol* 2018;**16**:99–105. doi:10.1016/j.cgh.2017.08.041.
278. Chaparro M, Verreth A, Lobaton T, *et al*. Long-term safety of in utero exposure to Anti-TNFalpha drugs for the treatment of inflammatory bowel disease: results from the Multicenter European TEDDY Study. *Am J Gastroenterol* 2018;**113**:396–403. doi:10.1038/ajg.2017.501.
279. van der Giessen J, Wieringa JW, Kanis SL, *et al*. Health-related quality of life in the first 5years of the children born to mothers with IBD does not differ from children born to healthy mothers. *J Psychosom Res* 2019;**127**:109840. doi:10.1016/j.jpsychores.2019.109840.
280. Castiglione F, Pignata S, Morace F, *et al*. Effect of pregnancy on the clinical course of a cohort of women with inflammatory bowel disease. *Ital J Gastroenterol* 1996;**28**:199–204.
281. Woolner JT, Hunter JO. Is dietary treatment of Crohn's disease safe in pregnancy? A retrospective study. *e-SPEN Journal* 2014;**9**:e173–7. doi:10.1016/j.clnme.2014.07.001.
282. Julsgaard M, Nørgaard M, Hvas CL, *et al*. Self-reported adherence to medical treatment, breastfeeding behaviour, and disease activity during the postpartum period in women with Crohn's disease. *Scand J Gastroenterol* 2014;**49**:958–66. doi:10.3109/00365521.2014.920913.
283. Yu A, Friedman S, Ananthakrishnan AN. Incidence and predictors of flares in the postpartum year among women with inflammatory bowel disease. *Inflamm Bowel Dis* 2020;**26**:1926–32. doi:10.1093/ibd/izz313.
284. Matro R, Martin CF, Wolf D, *et al*. Exposure concentrations of infants breastfed by women receiving biologic therapies for inflammatory bowel diseases and effects of breastfeeding on infections and development. *Gastroenterology* 2018;**155**:696–704. doi:10.1053/j.gastro.2018.05.040.
285. Julsgaard M, Kjeldsen J, Bibby BM, *et al*. Vedolizumab concentrations in the breast milk of nursing mothers with inflammatory bowel disease. *Gastroenterology* 2018;**154**:752–4.e751. doi:10.1053/j.gastro.2017.08.067.
286. Vasiliauskas EA, Church JA, Silverman N, *et al*. Case report: evidence for transplacental transfer of maternally administered infliximab to the newborn. *Clin Gastroenterol Hepatol* 2006;**4**:1255–8. doi:10.1016/j.cgh.2006.07.018.
287. Zelinkova Z, de Haar C, de Ridder L, *et al*. High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther* 2011;**33**:1053–8. doi:10.1111/j.1365-2036.2011.04617.x.
288. Steenholdt C, Al-Khalaf M, Ainsworth MA, *et al*. Therapeutic infliximab drug level in a child born to a woman with ulcerative colitis treated until gestation week 31. *J Crohns Colitis* 2012;**6**:358–61. doi:10.1016/j.crohns.2011.10.002.
289. de Lima A, Kanis SL, Escher JC, *et al*. Hepatitis B vaccination effective in children exposed to anti-tumour necrosis factor alpha in utero. *J Crohns Colitis* 2018;**12**:948–53. doi:10.1093/ecco-jcc/jjy053.
290. Wieringa JW, van Beek RHT, Rövekamp LW, *et al*. Response to vaccination in infants exposed to antitumor necrosis factor alpha In Utero. *Pediatr Infect Dis J* 2021;**40**:912–6. doi:10.1097/inf.0000000000003271.
291. https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-infliximab-remicade-flixabi-inflectra-remsima_en.pdf.
292. Goulden B, Chua N, Parker E, *et al*. A systematic review of live vaccine outcomes in infants exposed to biologic disease modifying anti-rheumatic drugs in utero. *Rheumatology* 2022. doi:10.1093/rheumatology/keac141.
293. Vestergaard T, Kammerlander H, Brock B, *et al*. Immunoglobulin and infliximab concentrations in dichorionic twins exposed to infliximab in utero. *J Crohns Colitis* 2017;**11**:1152–3. doi:10.1093/ecco-jcc/jjx034.
294. Park SH, Kim HJ, Lee CK, *et al*. Safety and optimal timing of BCG vaccination in infants born to mothers receiving anti-TNF therapy for inflammatory bowel disease. *J Crohns Colitis* 2020;**14**:1780–4. doi:10.1093/ecco-jcc/jjaa099.
295. Ambrosius Christensen L, Rasmussen SN, Hansen SH, *et al*. Salazosulfapyridine and metabolites in fetal and maternal body fluids with special reference to 5-aminosalicylic acid. *Acta Obstet Gynecol Scand* 1987;**66**:433–5. doi:10.3109/00016348709022049.
296. Nelis GF. Diarrhoea due to 5-aminosalicylic acid in breast milk. *Lancet* 1989;**1**:383. doi:10.1016/s0140-6736[89]91754-6.
297. Esbjörner E, Järnerot G, Wranne L. Sulphasalazine and sulphapyridine serum levels in children to mothers treated with sulphasalazine during pregnancy and lactation. *Acta Paediatr Scand* 1987;**76**:137–42. doi:10.1111/j.1651-2227.1987.tb10430.x.
298. Ost L, Wettrell G, Björkhem I, *et al*. Prednisolone excretion in human milk. *J Pediatr* 1985;**106**:1008–11. doi:10.1016/s0022-3476[85]80259-6.
299. Greenberger PA, Odeh YK, Frederiksen MC, *et al*. Pharmacokinetics of prednisolone transfer to breast milk. *Clin Pharmacol Ther* 1993;**53**:324–8. doi:10.1038/clpt.1993.28.

300. Christensen LA, Dahlerup JF, Nielsen MJ, *et al*. Azathioprine treatment during lactation. *Aliment Pharmacol Ther* 2008;**28**:1209–13. doi:10.1111/j.1365-2036.2008.03843.x.
301. Gardiner SJ, Gearry RB, Roberts RL, *et al*. Exposure to thiopurine drugs through breast milk is low based on metabolite concentrations in mother-infant pairs. *Br J Clin Pharmacol* 2006;**62**:453–6. doi:10.1111/j.1365-2125.2006.02639.x.
302. Clowse ME, Förger F, Hwang C, *et al*. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. *Ann Rheum Dis* 2017;**76**:1890–6. doi:10.1136/annrheumdis-2017-211384.
303. Lahat A, Shitrit AB-G, Naftali T, *et al*. Vedolizumab levels in breast milk of nursing mothers with inflammatory bowel disease. *J Crohns Colitis* 2017;**12**:120–3. doi:10.1093/ecco-jcc/jjx120.
304. Ben-Horin S, Yavzori M, Katz L, *et al*. Adalimumab level in breast milk of a nursing mother. *Clin Gastroenterol Hepatol* 2010;**8**:475–6. doi:10.1016/j.cgh.2009.11.023.
305. Ben-Horin S, Yavzori M, Kopylov U, *et al*. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. *J Crohns Colitis* 2011;**5**:555–8. doi:10.1016/j.crohns.2011.05.006.
306. Grosen A, Julsgaard M, Kelsen J, *et al*. Infliximab concentrations in the milk of nursing mothers with inflammatory bowel disease. *J Crohn's Colitis* 2014;**8**:175–6. doi:10.1016/j.crohns.2013.09.003.
307. Begg EJ. Determinants of drug transfer into human milk. In: Bennett PN, editor. *Drugs and Human Lactation*. 2nd edn. Amsterdam: Elsevier Science B.V.; 1996: 47–58.
308. Johns DG, Rutherford LD, Leighton PC, *et al*. Secretion of methotrexate into human milk. *Am J Obstet Gynecol* 1972;**112**:978–80. doi:10.1016/0002-9378[72]90824-1.
309. Drugs and Lactation Database, National Library of Medicine.. *Tofacitinib*. 2020. https://www.ncbi.nlm.nih.gov/books/NBK500664/.
310. Drugs and Lactation Database, National Library of Medicine [US]. *Ozanimod*. 2021. https://www.ncbi.nlm.nih.gov/books/NBK562678/.
311. Tang C, Li Y, Lin X, *et al*. Prolactin increases tumor necrosis factor alpha expression in peripheral CD14 monocytes of patients with rheumatoid arthritis. *Cell Immunol* 2014;**290**:164–8. doi:10.1016/j.cellimm.2014.06.005.
312. Kane S, Lemieux N. The role of breastfeeding in postpartum disease activity in women with inflammatory bowel disease. *Am J Gastroenterol* 2005;**100**:102–5. doi:10.1111/j.1572-0241.2005.40785.x.
313. Mañosa M, Navarro-Llavat M, Marín L, *et al*. Fecundity, pregnancy outcomes, and breastfeeding in patients with inflammatory bowel disease: a large cohort survey. *Scand J Gastroenterol* 2013;**48**:427–32. doi:10.3109/00365521.2013.772229.
314. Moffatt DC, Ilnyckyj A, Bernstein CN. A population-based study of breastfeeding in inflammatory bowel disease: initiation, duration, and effect on disease in the postpartum period. *Am J Gastroenterol* 2009;**104**:2517–23.
315. Corrao G, Tragnone A, Caprilli R, *et al*. Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. Cooperative Investigators of the Italian Group for the Study of the Colon and the Rectum [GISC]. *Int J Epidemiol* 1998;**27**:397–404. doi:10.1093/ije/27.3.397.
316. Rigas A, Rigas B, Glassman M, *et al*. Breast-feeding and maternal smoking in the etiology of Crohn's disease and ulcerative colitis in childhood. *Ann Epidemiol* 1993;**3**:387–92. doi:10.1016/1047-2797[93]90066-d.
317. Gearry RB, Richardson AK, Frampton CM, *et al*. Population-based cases control study of inflammatory bowel disease risk factors. *J Gastroenterol Hepatol* 2010;**25**:325–33. doi:10.1111/j.1440-1746.2009.06140.x.
318. Hlavaty T, Toth J, Koller T, *et al*. Smoking, breastfeeding, physical inactivity, contact with animals, and size of the family influence the risk of inflammatory bowel disease: A Slovak case-control study. *United Eur Gastroenterol J* 2013;**1**:109–19. doi:10.1177/2050640613478011.
319. Ko Y, Kariyawasam V, Karnib M, *et al*. Inflammatory bowel disease environmental risk factors: a population-based case-control study of Middle Eastern migration to Australia. *Clin Gastroenterol Hepatol* 2015;**13**:1453–63.e1451. doi:10.1016/j.cgh.2015.02.045.
320. Ng SC, Tang W, Leong RW, *et al*. Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific. *Gut* 2015;**64**:1063. doi:10.1136/gutjnl-2014-307410.
321. Baron S, Turck D, Leplat C, *et al*. Environmental risk factors in paediatric inflammatory bowel diseases: a population based case control study. *Gut* 2005;**54**:357–63. doi:10.1136/gut.2004.054353.
322. Strisciuglio C, Giugliano F, Martinelli M, *et al*. Impact of environmental and familial factors in a cohort of pediatric patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2017;**64**:569–74. doi:10.1097/mpg.0000000000001297.
323. Khalili H, Ananthakrishnan AN, Higuchi LM, *et al*. Early life factors and risk of inflammatory bowel disease in adulthood. *Inflamm Bowel Dis* 2013;**19**:542–7. doi:10.1097/MIB.0b013e31828132f8.
324. Voutilainen M, Hutri-Kähönen N, Tossavainen P, *et al*. Low childhood high density lipoprotein cholesterol levels and subsequent risk for chronic inflammatory bowel disease. *Dig Liver Dis* 2018;**50**:348–52. doi:10.1016/j.dld.2018.01.121.
325. Thompson NP, Montgomery SM, Wadsworth ME, *et al*. Early determinants of inflammatory bowel disease: use of two national longitudinal birth cohorts. *Eur J Gastroenterol Hepatol* 2000;**12**:25–30. doi:10.1097/00042737-200012010-00006.
326. Güngör D, Nadaud P, Dreibelbis C, *et al*. Infant milk-feeding practices and diagnosed celiac disease and inflammatory bowel disease in offspring: a systematic review. *Am J Clin Nutr* 2019;**109**:838s–51s. doi:10.1093/ajcn/nqy371.
327. Piovani D, Danese S, Peyrin-Biroulet L, *et al*. Environmental risk factors for inflammatory bowel diseases: an umbrella review of meta-analyses. *Gastroenterology* 2019;**157**:647–59.e644. doi:10.1053/j.gastro.2019.04.016.