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Supplement Article

Navigating Reproductive Care in Patients With Inflammatory Bowel Disease: A Comprehensive Review

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Abstract

Inflammatory bowel disease [IBD] is often diagnosed in patients during their reproductive years. It is crucial that both healthcare providers and patients are adequately informed to avoid misguided decisions regarding family planning.

One of the most important aspects during conception and pregnancy is to maintain disease remission, as disease activity is associated with adverse pregnancy outcomes. Apart from methotrexate, most conventional drugs used in IBD are considered low risk during conception and pregnancy. For newer agents, evidence is still limited. If needed, surgery must not be postponed and should ideally be performed in specialized centres.

In most patients, delivery should be vaginal except for patients with complex perianal disease, with an ileoanal pouch anastomosis, or if there is an obstetric contraindication.

In children exposed to biological treatments during pregnancy, the risk of infections appears to be low, and psychomotor development is probably not affected. Regarding immunizations, the standard vaccination schedule for inactivated vaccines should be followed for children exposed to biologics *in utero*. In the case of live vaccines, such as rotavirus, decisions should be individualized and take into consideration the risk–benefit ratio, particularly in developing countries.

In this review, we provide a comprehensive and updated overview of aspects related to fertility, pregnancy, breastfeeding, and the impact on the care of children born to mothers with IBD. Both the available evidence and areas of uncertainty are discussed, with the goal of assisting healthcare professionals caring for IBD patients during this important stage of their lives.

Key Words: Fertility; pregnancy; gestation; offspring; lactation; breastfeeding; Crohn's disease; ulcerative colitis; inflammatory bowel disease.

1. Introduction

Inflammatory bowel diseases [IBD], which mainly include Crohn's disease [CD] and ulcerative colitis [UC], are chronic pathologies that primarily affect the digestive tract but are systemic in nature. In most cases, IBD is diagnosed in childhood and young adults, during the crucial stages of personal and professional development. Sexuality and reproduction are crucial aspects for full personal development, and therefore also for patients with IBD.[1]

In the past, lack of knowledge about reproductive aspects often led to a significant proportion of patients foregoing the opportunity to have children, sometimes advised by the attending physician. Currently, the exponential growth of therapeutic options for IBD, coupled with increasingly ambitious goals in controlling the disease, makes it more complex to make decisions about the risks of different diagnostic or therapeutic interventions during pregnancy, lactation, or preventive measures for newborns exposed to IBD drugs.[2] This is especially challenging for professionals not specifically dedicated to IBD.

However, it is our duty as healthcare professionals responsible for the care of these patients to enable them to lead a completely normal life in all aspects, including legitimate aspects such as sexuality and reproduction. The aim of the present article is to comprehensively and critically review aspects related to fertility, pregnancy, breastfeeding, and the impact on the care of children born to mothers with IBD; this involves presenting both the available evidence and areas where uncertainty still exists. The final goal is to assist healthcare

professionals responsible for patient care in making informed decisions that improve patients' lives.

2. Fertility in IBD

Infertility is defined as a disease of the reproductive system characterized by the failure to achieve a clinical pregnancy after 12 or more months of regular unprotected intercourse.[3] Many studies suggest that patients with IBD have fewer biological children than the general population, with multiple explanations beyond physiological causes of infertility [Figure 1].[3]

IBD may impact sexual activity due to debilitating symptoms of diarrhoea and fatigue, poor body image, decreased libido, and dyspareunia.[1,3] Both female and male patients with IBD have an increased prevalence of sexual dysfunction, frequently associated with depression.[4–6]

Voluntary childlessness, i.e. the decision not to parent, is more prevalent in patients with IBD than in healthy controls [17–38% vs. 6%].[1,3,7] Although it can be a positive choice for many individuals, it becomes a problem when it is based on misguided beliefs, as many patients commonly have poor knowledge of pregnancy-related topics.[8,9]

In a recent systematic review, the infertility rate of UC female patients with no history of surgical treatment was similar to controls, ranging from 1.7% to 15%.[3] In women with non-operated CD, results are more heterogeneous, with some studies demonstrating no differences in the rate of infertility between female CD patients and the control population, while others showed a slightly higher infertility rate, varying from 3% to 42%.[3] As opposed to UC, there is some evidence that fertility may be reduced in CD, even when the effects of voluntary childlessness are considered.[3,10–12]

In male IBD patients, data on infertility are even more limited.[6] In a large Swedish nation-based registry study, fertility was slightly reduced in all IBD subtypes.[13]

2.1. Impact of disease activity

Disease activity is reported to be associated with lower female fertility rates in both CD and UC, but the quality of the evidence is poor.[1,3] A chronic pelvic inflammatory status may affect fallopian tubes and ovaries.[3] A systemic inflammatory state may affect ovarian reserve function and increase the levels of reactive oxygen species and oxidative stress, negatively affecting semen parameters.[13,14] Active disease may also be associated with poor nutritional status.[15]

In male IBD patients, active disease has been associated with higher rates of erectile dysfunction than patients in remission or controls, and male IBD patients reporting difficulty or delay in conceiving were more likely to have active disease.[6,16] Semen quality is also impaired in IBD patients with severe disease, with significant improvements during remission.[17]

2.2. Impact of surgery

IBD surgery is often cited as a risk factor for infertility in both genders, due to adhesions, damage to autonomic nerves, altered anatomy, and psychological factors.[18] Accordingly, a population-based cohort study reported a reduced number of children in female IBD patients following surgery.[12] However, a Cochrane systematic review could not conclude on the effect of surgery due to poor quality of existing literature.[19] Most evidence refers to ileal pouch-anal anastomosis [IPAA], with several studies demonstrating a 2- to 5-fold increase in infertility rates.[1] This risk is probably lower in laparoscopic IPAA due to reduced pelvic adhesions. In men, IPAA can cause sexual dysfunction, but the impact of surgery on fertility rates seems to be lower than in women.[1,6]

In a recent Swedish nationwide cohort study, women with IBD had a lower fertility rate after colectomy when compared to a matched reference cohort, particularly when associated with proctectomy and IPAA.[18] In men, there was only a marginal impact on fertility rates following colectomy, regardless of reconstruction. The authors concluded that in selected female IBD patients, ileorectal anastomosis might be considered as the preferred reconstruction after colectomy [postponing proctectomy] to preserve fertility. For other surgical procedures the effect remains unknown.[1,19]

2.3. Impact of IBD drugs

Generally, none of the drugs used in IBD treatment have been associated with reduced fertility in female patients.[8] In men, although most of the commonly used therapies have no impact on fertility, some may cause abnormal semen parameters. Sulfasalazine causes reversible oligospermia and reduced sperm motility when compared to mesalazine.[20] Male IBD

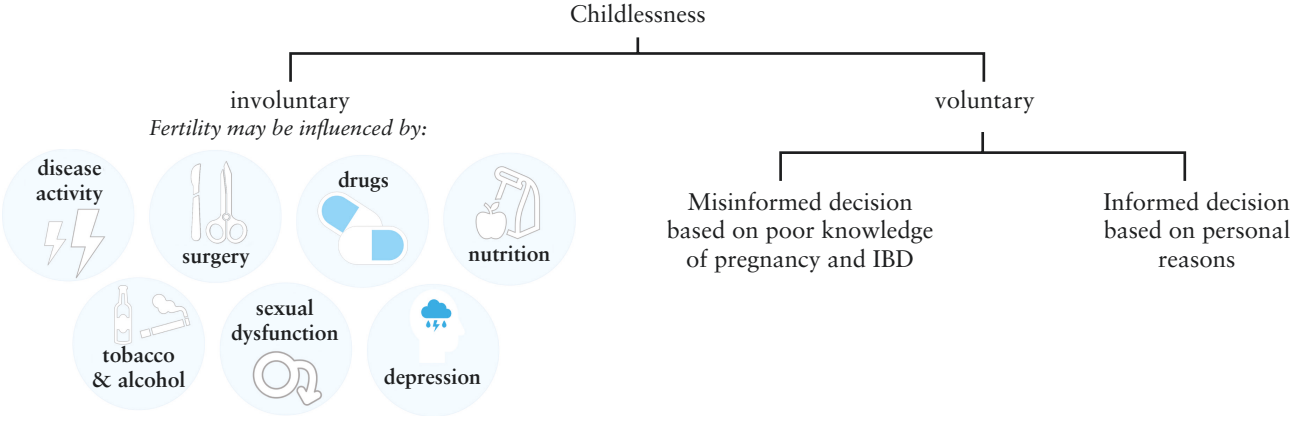

Figure 1. Reasons for childlessness in inflammatory bowel disease [IBD]. It is important to establish if childlessness in IBD patients is voluntary or not. In the former, healthcare professionals should ascertain if the decision was based on correct information, and not misguided by inadequate understanding. In the case of involuntary childlessness, reasons for infertility should be sought and managed as appropriate, and referral for assisted reproductive technologies should be considered. Image credits: Flaticon.com.

patients on sulfasalazine are usually recommended to switch to mesalazine before attempting conception.[1,6]

Methotrexate should be avoided in women attempting to conceive due to its teratogenic effects, but the data in men are more controversial.[6] A systematic review concluded that it is not certain if methotrexate influences male fertility and sperm DNA integrity; thus, current evidence suggests that male patients can continue methotrexate when aiming to father a child.[21–24]

Thiopurines, corticosteroids, calcineurin inhibitors, and biologics appear compatible with use in male IBD patients considering conception.[1,6] For newer drugs such as Janus kinase [JAK] inhibitors and sphingosine-1-phosphate [S1P] receptor modulators, data on the impact on fertility in humans remain limited. Tofacitinib and ozanimod did not impair fertility in animal models.[25] Although filgotinib was associated with decreased male fertility and impaired spermatogenesis in animal models, in the MANTA and MANTA-Ray studies, filgotinib had no measurable impact on semen parameters or sex hormones in men with active inflammatory diseases.[25–27]

2.4. Assisted reproductive technologies

When patients have difficulties conceiving naturally, they may require assisted reproductive technologies [ART]. In the PIANO registry, 13% of female IBD patients required ART to conceive, similar to reported rates in the general population.[28]

Although the data are scarce, the evidence suggests that, in most cases, ART success rates in patients with UC and CD patients who did not undergo surgery are similar to those of the general population.[29,30]

There is no evidence that ART increases the risk of IBD flares or maternal–fetal complications in IBD women.[8,31] IBD drugs do not seem to affect ART success.[29,32]

3. Inheritability of IBD

A positive family history of IBD is one of the strongest risk factors for IBD.[33] The risk of heritability seems lower in UC than in CD, given the lower rates of concordance in monozygotic and dizygotic twins.[34,35]

First-degree relatives of patients with CD have an almost 8-fold higher risk of developing IBD, whereas first-degree relatives of patients with UC have approximately a 4-fold higher risk.[33,36] In terms of absolute risk, first-degree relatives of patients with CD and UC have a prevalence of up to 5% and 3%, respectively.[1,33,37,38] Offspring of two affected parents have a higher risk of developing IBD, with an overall prevalence of ~30%.[39]

While heritability is generally used in the context of genetic inheritance from previous generations, environmental factors can also contribute to clustering of traits within families.[40] Indeed, the effect of early life non-genetic exposures such as tobacco, infections, and antibiotics must also be considered.[41,42] A cohort study using data from the UK Biobank evaluated the associations between genetic susceptibility, modifiable lifestyle factors, and risk of IBD.[43] While both a high genetic risk and an unfavourable lifestyle were associated with an increased risk of developing IBD, for participants with a high genetic risk a favourable lifestyle was associated with a nearly 50% risk reduction.

4. Preconception counselling

Family planning is a critical topic to be discussed with any person of reproductive age, but in the setting of IBD it is particularly relevant. Dedicated preconception education has been associated with improved patient knowledge, greater adherence to medication and better birth outcomes.[44,45]

Preconception counselling should begin at diagnosis in patients of childbearing age, and 3–6 months prior to attempts at conception.[45] In addition to general advice [Figure 2], IBD-specific peri-conceptional information should be provided, such as advice to plan pregnancy while in remission, as active disease is associated with worse birth outcomes, including preterm birth and low birthweight. Ideally, patients should have at least 3 months of steroid-free remission prior

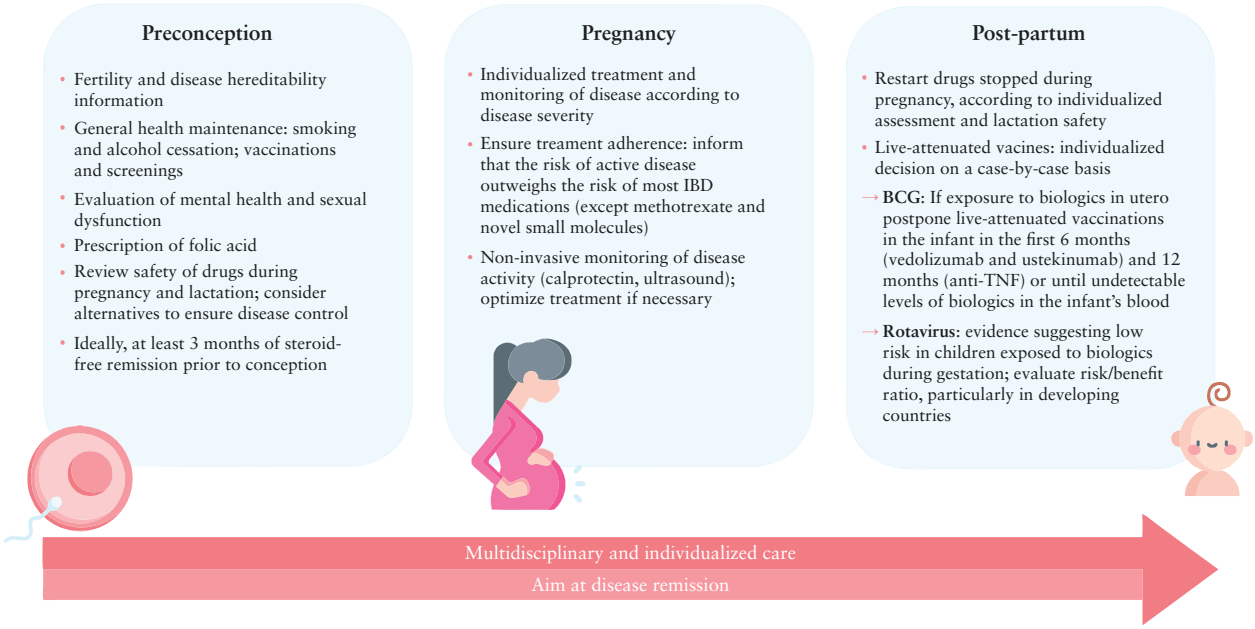

Figure 2. Pregnancy care pathway in inflammatory bowel disease [IBD], from preconception to post-partum. Image credits: Flaticon.com.

to conception.[1,15,45] Preconception management should also include nutritional screening and supplementation, and medication revision and optimization, with suspension of potential teratogenic drugs. Women taking sulfasalazine should be prescribed higher doses of folic acid [2 mg/day].[1]

In male patients with IBD, lifestyle factors and nutritional status should be optimized, and disease remission should be sought. Medications associated with infertility should be replaced.[6] In patients undergoing proctocolectomy, sperm banking can be discussed due to the real [~3%] risk of postoperative anejaculation or retrograde ejaculation.[46,47] In these cases, ART can also be an option.

5. IBD monitoring during pregnancy

IBD pregnancies should preferably be managed by a multidisciplinary IBD-pregnancy team, and adherence to recommendations and guidelines optimize outcomes in IBD pregnant women.[48] Clinical evaluations by a gastroenterologist should be done during pregnancy as appropriate for the patient's disease severity and pregnancy status. However, symptoms such as fatigue, abdominal cramps, and rectal bleeding from haemorrhoids can occur during pregnancy and be misinterpreted as active IBD.[49] Clinical indices such as Harvey–Bradshaw Index and Simple Clinical Colitis Index have not been validated for pregnant women.[50]

Laboratory markers, such as as erythrocyte sedimentation rate, C-reactive protein [CRP], and albumin are altered by the physiological adaptations in pregnancy. By contrast, faecal calprotectin is apparently not affected by pregnancy, making it a good indicator of active disease in pregnant IBD patients.[49] In a systematic review, only faecal calprotectin appeared to correlate with IBD activity through all gestational periods; CRP, haemoglobin, and albumin did not correlate with active disease.[51] Still, European Crohn's and Colitis Organisation [ECCO] guidelines suggest that it may be useful to monitor tendencies in these biomarkers.[1]

Endoscopy and imaging techniques are key elements of disease activity assessment in IBD. Although ECCO guidelines state that endoscopy is generally considered safe in pregnancy, existing data are very limited.[52,53] As such, endoscopic procedures should only be performed when an impact on patient management is expected.[1,53]

Concerning imaging procedures, ultrasonography and magnetic resonance imaging [MRI] are of choice in the pregnant patient.[54] However, the use of gadolinium contrast with MRI should be limited as possible risks to the fetus are uncertain.[53,54]

Intestinal ultrasound is increasingly used in IBD management, and it is also accurate in evaluating disease activity in pregnant patients.[55,56] Flanagan *et al*. demonstrated that intestinal ultrasound is feasible in pregnant UC and CD patients and adequate intestinal views can be obtained in most patients up to the early third trimester. Beyond 20 weeks of gestation, the terminal ileum is more difficult to visualize.[55]

Radiation exposure examinations, such us computed tomography, should be used only in cases where ultrasound or MRI are not available or in addition to these, if needed.[54] ECCO guidelines recommend against computed tomography and any other X-ray techniques unless potential risks are outweighed by clinical need.[53]

Capsule manufacturers consider pregnancy a contraindication to capsule endoscopy as current evidence is too limited to establish the safety of this procedure during pregnancy.[49,57]

6. Considerations on Treatment During Pregnancy

Active inflammation from IBD is associated with an increased risk of adverse pregnancy outcomes. IBD drugs cross the placenta either by passive transfer [small molecules] or by a transport [biological agents]; thus, fetuses are exposed to the drugs while the mother is receiving them during pregnancy. However, as most IBD medication is of low risk during pregnancy, the benefit of maintaining the treatment outweighs the risk of most IBD medications.[1]

7. Small-molecule Agents

7.1. Aminosalicylates

Aminosalicylates [including sulfasalazine] are generally considered low risk during pregnancy as several studies have demonstrated a benign profile during pregnancy with no reports of an increased risk of congenital abnormalities with mesalazine.[1,58,59]

7.2. Corticosteroids

Acute flares of IBD often require steroid treatment. Some studies from the past reported the risk of major congenital malformations associated with the use of steroids, but these findings have not been confirmed by more recent and better controlled studies.[60–63]

There is an increased risk of pregnancy complications including gestational diabetes and pre-mature labour in women exposed to steroids during pregnancy, though it is hard to differentiate between the effects of active disease and those of steroids.[64–66] There may also be increased infant infection risk associated with *in utero* exposure to steroids.[66] Budesonide has a high first-pass metabolism and hence systemic levels are low, making it unlikely that fetal exposure is significant.[67]

Although there might be some complications associated with systemic steroid treatment during pregnancy, when necessary, the benefits outweigh the potential risks.

7.3. Thiopurines

Azathioprine and mercaptopurine are considered low risk but initiation during pregnancy is discouraged due a slow onset of action and risk of first-use side effects.[1,68,69] However, maintenance of thiopurines during pregnancy is important to reduce the risk of flares.[1,70]

7.4. Methotrexate

Methotrexate is teratogenic and must be avoided during pregnancy.[71] Due to its folate antagonism there is a high risk of fetal mortality and fetal abnormalities.[72] Methotrexate should be stopped at least 3–6 months before any attempt to conceive.[1] If conception accidentally occurs, termination of pregnancy should be discussed, but patients and clinicians should weight the options including the potential chance for a healthy pregnancy outcome. Male patients can continue methotrexate when aiming to father a child as semen parameters and sperm DNA remain similar to those of healthy volunteers and population-based paternal exposure studies have not found an increased risk of adverse pregnancy outcomes.[21–23]

7.5. JAK inhibitors

JAK inhibitors are small molecules whose passive transfer through the placenta leads to early pregnancy exposure, in

contrast to biologics. Based on animal studies, there are serious concerns over teratogenicity.[73] Preclinical animal studies revealed that tofacitinib was feticidal and teratogenic in rabbits at a dosage 6.3 times the maximum human dose of 10 mg twice daily.[74] Doses equivalent to the human dose of 200 mg of filgotinib were associated with fetal death and serious malformations in rats and rabbits.[75] Upadacitinib was associated with musculoskeletal and cardiovascular malformations in pregnant rats and rabbits at doses equivalent to those used in humans.[76] Limited human data revealed two serious congenital malformations in 55 live births exposed to tofacitinib, one serious malformation in 21 live births exposed to filgotinib, and no malformations in 30 live births exposed to upadacitinib.[73] Based on these results, JAK inhibitors should be avoided during pregnancy; the maintenance of these agents during pregnancy should be extensively discussed with the patients in selected cases. Manufacturers recommend patients should stop these medications at least 4 weeks prior to planned conception for tofacitinib and upadacitinib, and at least 1 week prior for filgotinib.[74,76,77] Patients aiming to father a child do not have to interrupt the treatment.

7.6. S1P receptor modulators

Ozanimod and etrasimod are the S1P receptor modulators currently approved for IBD treatment. Animal studies have shown their teratogenicity.[73] Ozanimod was associated with fetal death and serious malformations in rabbits at a dose matching those in humans [0.92 mg/day].[78] For etrasimod, animal data have shown concerns regarding including embryo lethality and fetal malformations at doses 5–6 times that used in human exposure.[79]

Limited human data reported one congenital malformation of a duplex kidney in 31 live births exposed to ozanimod.[73] There are no published human data on etrasimod. For the time being they are contraindicated during pregnancy.

8. Monoclonal antibodies

8.1. Placental transport of monoclonal antibodies

Fetal immunity is acquired by transfer of antibodies such as immunoglobulin G [IgG] from the maternal to the fetal circulation during pregnancy. There is limited transport of IgG1 during the first trimester.[80] Between gestational week 17 and 22 the fetal IgG concentration is 5–10% of the maternal concentration, and by term it exceeds the maternal concentration by 3-fold.[81] The vast majority of IgG is actively transported across the placenta by a specific receptor-mediated binding of the Fc receptor. IgG1 exhibits preferential transport, followed by IgG4 and IgG3 with IgG2 being the least detected.[80]

8.2. Anti-TNF agents

Anti-tumour necrosis factor [anti-TNF] agents [infliximab, adalimumab, golimumab, and certolizumab] are large IgG1 molecules unable to passively cross the placenta. Active transport across the placenta occurs from the second trimester onwards.[82] Cord blood levels reveal significant exposure of the fetus for adalimumab and infliximab at birth.[83] Median time to clearance is 4 months for adalimumab and 7 months for infliximab [Table 1].[84,85] This has implications for infants in terms of infections and vaccinations as highlighted in subsequent sections of this review. Due to the pegylated molecular structure of certolizumab, no placental transfer occurs.[84]

Table 1. Cord/maternal ratio of biologics and time to infant clearance*

Drug	Cord/maternal concentration ratio, median	Mean time to infant clearance, months [95% CI]	Maximum time to clearance, months
Infliximab	2.4 [range, 0.7–8.0][92]	7.3 [6.2–8.3][85]	12[83]
Adalimumab	1.3 [range, 0.4–5.4][92]	4.0 [2.9–5.0][85]	9[83]
Certolizumab pegol	0.0 [range, 0.0–5.1][92]	n/a	n/a
Golimumab	1.5 [range, 0.0–2.2][92]	?	?
Vedolizumab	0.4 [95% CI, 0.3–0.6][99]	3.8 [3.1–4.4][99]	6[99]
Ustekinumab	2.2 [95% CI, 1.7–2.8][103]	6.7 [6.1–7.3][103]	?[103**]

*Data shown are based on the largest cohorts published to date.
**No detectable concentrations found after 7 months of age, but 11 infants did not have a control blood sample collected before 12 months of life after the 6-month sample showing a very low concentration.

Pharmacokinetic studies of infliximab during pregnancy show that maternal infliximab concentrations increase in the second and third trimester due to reduced clearance.[86–88] Maternal adalimumab clearance is unchanged during pregnancy and levels remain static through all three trimesters.[86,88]

A recent meta-analysis including data on 6963 patients from 48 studies reported pregnancy outcomes similar to those seen in the general population.[89] Furthermore, the PIANO study reported that 642 IBD patients exposed to biologics [mainly anti-TNF] had comparable outcomes to non-exposed IBD patients, findings further supported in two large European retrospective anti-TNF studies.[90–92]

Previously, guidelines advised the cessation of anti-TNF drugs during the third trimester to reduce infant exposure.[71] In this respect, a large French study of 1457 women exposed to anti-TNF therapy during pregnancy showed that cessation prior to gestational week 24 was associated with higher maternal relapse risks but had no effect on the infant infection risk.[93] However, other authors did not find an increased maternal flare risk for those stopping in the third trimester.[92,94] On balance, it is advisable not to interrupt anti-TNF therapy during pregnancy to avoid adverse maternal outcomes, and current guidance classifies anti-TNF therapy as low risk during pregnancy and recommends continuation throughout pregnancy.[1,48]

8.3. Anti-integrin [vedolizumab]

Vedolizumab is a humanized monoclonal IgG1 antibody that blocks the $\alpha_4\beta_7$–integrin–mucosal vascular addressing cell adhesion molecule-1 [MAdCAM-1] interaction in the gut vessels, inhibiting the trafficking of gut-homing lymphocytes, but may also impact the innate immune system.[95]

A meta-analysis published in 2021, including four studies with a total of 213 vedolizumab-exposed pregnancies, revealed an increased risk of early pregnancy loss (odds ratio [OR] 1.79) and preterm birth [OR 2.16].[96] Similar risks were found in another meta-analysis including four studies with a total of 150 vedolizumab-exposed pregnancies.[89] Of note, the retrospective European CONCEIVE study [$n = 79$] was included in both meta-analysis.[97] However, as highlighted

by the authors to the meta-analysis, a probable explanation could be the small number of vedolizumab-exposed studies compared with substantially larger anti-TNF exposure studies resulting in an overestimation of adverse pregnancy outcome among vedolizumab-exposed pregnancies.[89] Further, active disease and/or older age of the women probably also increased the risk of adverse pregnancy outcome among women exposed to vedolizumab compared with controls.[89,96] More recent prospective studies showed no increased risk of adverse pregnancy outcome [including congenital malformations] in vedolizumab-exposed pregnancies.[88,98–100] Induction treatment with vedolizumab during the first and second trimester has been described in a limited number of patients [n = 11] without any signals of increased risk of adverse pregnancy outcome.[88,97,99]

Whether pregnancy influences the pharmacokinetics of vedolizumab is yet to be fully elucidated. However, in a cohort of 12 women with at least two measured vedolizumab concentrations in pregnancy, analysis indicated that vedolizumab concentrations may decrease during pregnancy.[88]

Across four prospective studies, vedolizumab-exposed infants were born with an ~50% lower vedolizumab concentration than those in their respective mothers, and the vedolizumab concentration correlated with duration since the last drug exposure in pregnancy.[88,98–100] In the Danish–Canadian study the median ratio in 40 infant–mother pairs was 0.44 and a similar ratio of 0.69 was seen in the US PIANO registry among 37 infant-mother pairs.[98,99] The lower placental transport is in contrast to other types of biologics and may be explained, as highlighted by Julsgaard *et al*., that during the engineering of vedolizumab point mutations were introduced to the Fc receptor-binding motif, replacing leucine-239 and glycine-241 with alanine to diminish vedolizumab's binding to the Fc receptor.[99,101]

Rapid infant clearance of vedolizumab was seen in 40 Danish and Canadian infants exposed *in utero*, with a mean time to clearance of 3.8 months, and 100% clearance by 6 months.[99] Of note, neither breastfeeding, umbilical cord vedolizumab concentration, nor infant birthweight influenced time to clearance.[99] A similar clearance rate was found in a smaller Australian cohort.[88]

In conclusion, knowledge on the safety of vedolizumab exposure in pregnancy is constantly increasing, and its continuation during pregnancy seems of low risk. As with other drugs, the benefits of preventing flares during pregnancy outweigh the potential risks. The final dose of vedolizumab to be administered during pregnancy can be planned according to its half-life.

8.4. Anti-IL-12/23 and anti-IL-23 [ustekinumab, risankizumab, and mirikizumab]

Ustekinumab is a humanized monoclonal IgG1 antibody targeting the p40 subunit of interleukin [IL]-12 and IL-23. The existing evidence on the safety of ustekinumab during pregnancy is gradually advancing. No increased risk of adverse pregnancy outcome including congenital malformations has been found among ustekinumab-exposed IBD pregnancies in a French retrospective study, and in five prospective studies with a total of 225 infants.[98,100,102–105] These findings are in line with a review of cases reported to the manufacturers global safety database comprising a total of 681 ustekinumab-exposed pregnancies [65% only first trimester exposure] where rates of adverse pregnancy outcomes after exposure to ustekinumab *in utero* were similar with rates reported for the general population in the USA.[106] In a recently published European study among 78 ustekinumab *in utero* exposed infants, 15 [20%] were exposed to ustekinumab induction therapy due to maternal disease activity in the first, second, or third trimester of pregnancy.[103] Despite maternal disease activity, infants exposed to induction therapy were not at a substantial increased risk of adverse pregnancy outcome [preterm, low birthweight, small for gestational age, and/or congenital malformations] compared to maintenance exposure. No studies have investigated if pregnancy influences the pharmacokinetics of ustekinumab.

Risankizumab and mirikizumab are both humanized monoclonal antibodies, with risankizumab being an IgG1 antibody and mirikizumab an IgG4 antibody. Both risankisumab and mirikizumab selectively inhibit IL-23. There are currently no available pregnancy and risankizumab or mirikizumab exposure studies. However, since mirikizumab is an IgG4 antibody, transport across placenta will probably be lower than seen for the IgG1 antibody risankizumab, in line with the normal placental transport of IgG.[80] Further, their safety profiles in pregnancy probably also resemble the findings of other types of biologics, allowing for their use in pregnancy.

A recent review showed exposure data from clinical trials of risankizumab, including 60 pregnancies with exposure around conception/first trimester [26 in CD]. Among these, there were 11 spontaneous abortions and two elective terminations for disorders. No major congenital malformations were observed among the 18 live births.[107]

Exposure data from clinical trials shared by Lilly Pharmaceuticals in a physician communication revealed 28 pregnancies in mothers with CD, UC, or psoriasis on mirikizumab. Among these, three spontaneous abortions and six elective terminations occurred. Eight infants were born without major congenital abnormalities, with one born preterm at 34 weeks. The outcomes of four pregnancies were unknown, and seven were still *in utero* at the data cutoff [Lilly Pharmaceuticals, physician communication]. Future prospective studies are needed to investigate the safety of using risankizumab and mirikizumab during pregnancies.

In a European study among 78 infant–mother pairs, the ustekinumab concentration in cord blood surpassed the concentration of their mothers at the time of delivery, with a median infant-to-maternal ratio of 2.18.[103] This is consistent with the usual characteristics of IgG1 molecule transportation during the progression of pregnancy, and the uniform finding in three other studies compromising a total of 46 infant–mother pairs.[80,98,100,102] Across all ustekinumab and pregnancy studies the ustekinumab birth concentrations correlated with time since last drug exposure in pregnancy.[98,100,102,103]

Clearance of ustekinumab in infants exposed *in utero* closely mirrored that in non-pregnant adult patients in the study by Julsgaard *et al*.[103] Unlike anti-TNF and vedolizumab, the offspring's ustekinumab clearance was significantly correlated with the concentration in the infant's cord blood at the time of delivery. The mean time to clearance in infants exposed to ustekinumab in pregnancy was 6.7 months. Of note, the concentration was minuscule in the infants with detectable concentrations at 6 months.[103]

In summary, data on the safety of ustekinumab exposure in pregnancy are steadily accumulating. Across studies, the safety of its use in pregnancy has been highlighted. Continuation of ustekinumab throughout pregnancy seems of low risk and the

overall benefits of maintaining maternal remission outweigh any hypothetical risk of the treatment. To minimize transfer to the infant, the final dose in pregnancy can be planned according to the half-life of ustekinumab. Regarding anti-IL-23 agents, we do not have enough data yet and the decision should be made on a case-by-case basis.

9. IBD Surgery in Pregnant Patients

In general, the indications for emergency surgery for IBD are the same for pregnant and non-pregnant women. However, the decisions regarding timing, approach, and the appropriateness of surgery are often challenging.[1] In this respect, there is little information in the literature on surgery for IBD during pregnancy and much of what is available pre-dates the availability of biological therapy or minimally invasive surgery.[108–113] Some authors have suggested that surgery is of lowest risk when undertaken during the second trimester—there are higher risks of miscarriage in the first trimester and increased risks of maternal/fetal morbidity and mortality during the third trimester.[111,113] Nevertheless, and despite these considerations, once the indication of surgery is established, it should not be delayed, as this might be associated with worse outcomes.[1]

With respect to the surgical approach, a minimally invasive approach is advocated by several authors from extrapolation from general surgical procedures during pregnancy or from surgery in non-pregnant IBD patients and it would be the operative approach of choice mainly during the first and second trimester, being technically more difficult during the third trimester.[111,114–116]

In previous series, many authors favour subtotal colectomy and end-ileostomy in UC pregnant patients regardless of the indication.[111] Some indications might require proctectomy; however, removing the rectum is not without risk to the mother and the fetus. If a major haemorrhage occurs from the engorged pelvic venous plexus during a surgery involving the rectum, an emergency hysterectomy may even be necessary. Furthermore, dehiscence of a close rectal stump also has devastating consequences. With respect to CD, the preferred surgical approach is influenced by the type of complication and disease location besides factors due to the pregnancy.

Finally, the risk for miscarriage was highest in the first week after surgery and levelled out after 2 weeks.[108,113] These findings suggest that stricter fetal monitoring should be done during the first 2 weeks after surgery to detect complications as early as possible. Surgical and obstetric management should consider maternal and fetal status; however, during the third trimester of gestation delivery by Caesarean section [C-section] before surgery might be preferred and should be discussed in a multidisciplinary team including the patient's opinion.[1]

10. Mode of delivery

In general, vaginal delivery is recommended as long as there are no obstetric contraindications. C-section would only be considered in situations where vaginal delivery may pose a risk to the mother's faecal continence. This would focus primarily on two circumstances: the presence of an ileoanal pouch anastomosis in patients with UC, and complex perianal disease in the case of CD.

In two reviews encompassing 25 studies involving UC patients post-proctocolectomy, the comparison between vaginal and C-section deliveries relied primarily on faecal incontinence questionnaires.[117,118] Only one study, which included 97 UC patients, utilized objective anal sphincter measures, revealing a higher risk of sphincter damage after vaginal delivery.[119] Nevertheless, the overall findings from both reviews indicated no significant differences in the risk of anal sphincter damage based on the mode of delivery in UC patients post-proctocolectomy.

A systematic review by Foulon *et al.*, analysing seven studies involving CD patients with perianal disease, found no increased risk of perianal disease worsening or *de novo* perianal fistula development following vaginal delivery.[117] Furthermore, two prospective–retrospective cohort studies in CD patients with perianal disease demonstrated no increased risk of faecal incontinence associated with vaginal delivery.[120,121]

The decision regarding the mode of delivery in these cases should involve multidisciplinary discussions with gastroenterologists, obstetricians, and, in cases of perianal disease, an IBD surgeon. The ultimate mode of delivery should be determined through shared decision-making with the patient, taking into account factors such as perineal trauma and quality of life, where a C-section might be considered as a preferred option in specific scenarios.[1]

11. Neonatal outcomes in children exposed to biologics

11. 1. Infant infections

11.1.1. Anti-TNF

While there were concerns over detectable drug concentrations in infants to mothers exposed to biologics in general, anti-TNF monotherapy has not been associated with an increased infant infection risk.[90–92] Data regarding risk of infant infections after intrauterine exposure to combination therapy with anti-TNF and thiopurine are conflicting. In the large US PIANO-registry, among 1490 infants, combination therapy of a biologic and thiopurine [where the vast majority of biologic-exposed infants were exposed to anti-TNF] found no increased risk of infant infection during the first year of life.[92] This finding is substantiated by findings in two large European retrospective studies. A Dutch and the Spanish TEDDY study examined 1000 and 841 infants born to mothers with IBD who received anti-TNF monotherapy, combination therapy, or no therapy. Both studies revealed no variation in infection rates among these groups.[90,91] Conversely, Bröms *et al.* compared 1027 Nordic infants exposed to anti-TNF with 1 617 886 infants of the general population and found an increased risk of infant infections during the first year of life (relative risk [RR] 1.43; 95% confidence interval [CI], 1.23–1.67).[122] Of importance, no increased risk of infections was found in later life. A prospective international multicentre study in 80 infants exposed to anti-TNF monotherapy or in combination with azathioprine revealed an increased risk of infant infections in those exposed to combination vs. monotherapy [RR 2.7; 95% CI, 1.09-6.78].[85] As noted by some authors, the finding of increased infant infections after exposure to combination therapy with anti-TNF and thiopurine may be a true risk but could also be confounded by difference in healthcare-seeking behaviour including reporting of infections.[122] Importantly, in the study of 80 anti-TNF *in utero* exposed infants, the anti-TNF concentration at birth did not

correlate with risk of infant infections during the first year of life.[85] Hence, discontinuing anti-TNF in the third trimester does not reduce the infant infection risk.[85,93] Of great importance, a uniform finding across anti-TNF studies has been no sequela after infant infections.[85,90–92,122]

11.1.2. Anti-integrin and anti-IL-12 & anti-IL-23

The US PIANO registry, including 1669 offspring of mothers with IBD of whom 66 were exposed to vedolizumab and 47 to ustekinumab, investigated overall infection rates during the first year of life [serious infections resulting in hospitalization and non-serious infections]. Overall, the prevalence of infant infection at 1 year after *in utero* exposure to vedolizumab [43%] was similar to the prevalence reported among infants exposed to anti-TNF monotherapy [45%], combination therapy [anti-TNF + thiopurine] [46%], immunomodulators [43%], and no exposure [48%]. The prevalence of infections was significantly lower in the ustekinumab-exposed cohort [20%].[98] These findings are in line with studies by Julsgaard *et al*., who among 43 vedolizumab- and 78 ustekinumab-exposed infants reported a prevalence of infant infections at 1 year of life equivalent to 40% and 23%, respectively.[99,103] Of note, neither vedolizumab nor ustekinumab concentration at birth correlated with risk of infant infections during the first year of life.[99,103]

12. Development

12.1. Anti-TNF, anti-integrin, and anti-IL-12 & anti-IL-23

In the US PIANO registry, no difference was found in developmental milestones in respect to communication, gross motor function, fine motor function, problem-solving, and personal-social at 12 months of life by exposure status among all cohorts of biological therapy (anti-TNF monotherapy [$n = 302$], combination therapy, biologic plus thiopurine [$n = 77$], vedolizumab [$n = 22$], and ustekinumab [$n = 12$]) and when compared with the validated background population of 18 572 children [ASQ-3®].[92] Similar reassuring developmental data have been shown in European and Australian/New Zealand cohorts among 72 anti-TNF-, 34 vedolizumab-, and 63 ustekinumab-exposed infants.[85,99,103]

13. Lactation

Most conventional drugs [including aminosalicylates, corticosteroids, and thiopurines] are safe during breastfeeding; only methotrexate is contraindicated. The safety of targeted therapies on breastfeeding is reviewed below.

13.1. Anti-TNFs

Given that the biological drugs used to treat IBD [infliximab, adalimumab, certolizumab pegol, golimumab, ustekinumab, and vedolizumab] are IgG1 monoclonal antibodies, secretion and transfer through breast milk is minimal.[1] In particular, infliximab levels in breast milk rose to ≈100 ng/mL within 2–3 days of the infusion; this level was roughly 1/200th of the level in blood.[123,124]

The miniscule amounts of infliximab [or adalimumab] transferred in breast milk are unlikely to result in systemic immunosuppression of the infant. Moreover, because this minute quantity is also anticipated to undergo proteolysis in the stomach and intestine after ingestion, it probably exerts a negligible impact on the systemic immune response of the suckling infant. Accordingly, the 2022 pregnancy guideline from the ECCO concludes, in agreement with other international guidelines, that anti-TNF treatment is compatible with breastfeeding.[1,48,125]

13.2. Vedolizumab

The first study reporting that vedolizumab, similarly to infliximab and adalimumab, was excreted into women's breast milk—at low concentrations—was conducted by Julsgaard *et al*. in 2018.[126] This study with five IBD patients demonstrated detectable vedolizumab in milk at various concentrations in samples collected between 30 min and 14 days after vedolizumab administration. The peak concentration was only 0.318 µg/mL, equivalent to less than 1% of the corresponding serum concentration.[126] This is well under the recommended arbitrary cut-off value of 10% for excretion of drugs into breast milk. If the highest vedolizumab milk concentration measured in any of the samples [0.318 mg/mL] is multiplied by the amount of milk ingested by the infant, ~150 mL per kilogram of bodyweight per day, the infant is estimated to receive only 0.048 mg vedolizumab per kilogram bodyweight per day. As expected, normal developmental milestones were recorded in all infants at the age of 3–10 months.[126]

More recently, Lahat *et al*. measured vedolizumab in five lactating women who received this treatment.[127] Daily sequential vedolizumab measurement in breast milk following drug infusion allowed for a broader understanding of vedolizumab breast milk levels. Levels peaked at 3–4 days following infusion to maximal levels of 480 ng/mL, and then slowly subsided. Notably, milk drug levels were minute and more than two orders of magnitude lower than its level in serum.[127,128]

Furthermore, as was the case with anti-TNF drugs, the minute quantity of vedolizumab in breast milk is anticipated to undergo proteolysis in the stomach, and it may undergo degradation and finally excretion through the IgG Fc binding protein in the gastrointestinal tract, thereby exerting a negligible impact on the infant's immune system.[126,127] However, this assertion was not directly assessed in these studies, so further studies are warranted to address systemic effects, if any, of oral vedolizumab exposure on the suckling infant.

13.3. Ustekinumab

A study conducted in humans detected low ustekinumab levels [maximum 1.57 µg/mL] in the breast milk of four of six women treated with this drug for IBD.[129] In a woman with CD who was treated with ustekinumab until week 30 of pregnancy, the trough level in the breast milk after re-initiating post-partum ustekinumab therapy was initially in the same range as the corresponding serum trough level, and then decreased during maintenance therapy.[130] Finally, the most recent study on breast milk concentrations showed that the maximum ustekinumab concentration was 13.6 ng/mL at 9 days after the last maternal dose.[131] The ratio of the calculated areas under the time–concentration curves of ustekinumab in breast milk and maternal serum was 0.0008, which was comparable with previous human studies.[131]

As was stated for vedolizumab, the minute quantity of ustekinumab in breast milk is assumed to undergo proteolysis in the stomach, and it may undergo degradation in the gastrointestinal tract, thus exerting an insignificant impact on the infant's immune system. However, as was also the case with

vedolizumab, this conclusion is speculative and has not been proven by specifically designed studies.

13.4. Small molecules

Recently, tofacitinib was detected in breast milk of a lactating woman with UC on tofacitinib 10 mg BID.[132] The ratio of milk-to-plasma tofacitinib concentration increased by the hour after oral intake of 10 mg tofacitinib, and the milk concentration was 54% higher than the plasma concentration at 8 h after oral intake.[132] A similar pattern was found among lactating rats where the concentration of tofacitinib was two times higher than plasma concentrations.[133] Similarly, upadacitinib can be found in milk when administered to lactating rats, with 30-fold higher concentration in milk compared to plasma.[133] Filgotinib was detected in nursing pups following its administration to lactating rats.[133] Being orally administered drugs with a high gastrointestinal absorption, it is likely that infants will be exposed to effective concentrations of JAK inhibitors; therefore, breastfeeding should be avoided in women treated with JAK inhibitors.

The effects in the nursing infant of S1P receptor modulators are unknown. Animal studies revealed that ozanimod was detected in the milk of lactating animals at levels higher than those in maternal plasma. There is no information of excretion of the drug in humans. Due to the potential for serious adverse reactions to S1P receptor modulators in nursing infants, women receiving ozanimod should avoid breastfeeding.[133]

14. Vaccines

14.1. Inactivated vaccines

Both the efficacy and safety of inactivated vaccines [Table 2] are similar [i.e. adequate] in infants exposed to conventional treatments *in utero*, and therefore the vaccination schedule for these vaccines does not need to be modified in these cases; this recommendation is also valid for small molecules.

The efficacy of inactivated vaccines given to infants exposed to biologics *in utero* has been assessed in a recent review.[99,131,134–144] These studies suggest that the response [seroprotection] to inactivated vaccines could be considered adequate in most infants exposed to anti-TNF agents *in utero* [the experience regarding vedolizumab or ustekinumab is still too limited to draw reliable conclusions].[145–147] Similarly, a meta-analysis of studies assessing pregnancy and neonatal outcomes of women with immune-mediated inflammatory diseases [including IBD, rheumatoid arthritis, and psoriasis] exposed to anti-TNF agents during pregnancy demonstrated an adequate immune response to tetanus, *Streptococcus pneumoniae*, diphtheria, and hepatitis B virus.[148]

On the other hand, no relevant adverse events for non-live inactivated vaccines have been reported in newborns exposed *in utero* to biological agents [mainly anti-TNF agents], as has been recently reviewed.[91,134,136,144–146,149] Accordingly, the aforementioned meta-analysis of studies assessing children from mothers with immune-mediated inflammatory diseases exposed to anti-TNF agents during pregnancy reported only minor adverse events to vaccinations including tetanus, *Streptococcus pneumoniae*, diphtheria, hepatitis B virus, and *Haemophilus influenzae* B.[148] Again, the experience with other biologics different from anti-TNFs is too limited to draw reliable conclusions.

In summary, newborns born to IBD mothers should follow a standard vaccination schedule for non-live inactivated vaccines, as their effectiveness and safety seem to be favourable.[150]

Table 2. Commonly recommended vaccines for children.

Non-live inactivated vaccines	Live-attenuated vaccines
Hepatitis A	Measles
Hepatitis B	Mumps
Haemophilus influenzae	Rubella
Tetanus	Smallpox
Diphtheria	Varicella
Streptococcus pneumoniae	Yellow fever
	Oral polio
	Live varicella-zoster
	Rotavirus
	Bacillus Calmette-Guerin [BCG]

Live-attenuated vaccine administration time: during the first 12 months of life, live vaccines administered in clinical practice include mainly the rotavirus vaccine [generally given at 2 and 4 months], and, in some countries, also the BCG vaccine. As the first MMR [measles, mumps, rubella] vaccination dose is recommended between 12 and 15 months, there is in general no reason to delay vaccination in infants exposed to biologics *in utero* in this case.

15. Live-attenuated vaccines

Live-attenuated vaccines [Table 2] typically elicit a stronger antibody response compared to non-live inactivated vaccines.[151] The vaccination schedule for these vaccines does not need to be modified in infants exposed to conventional treatments [aminosalicylates, corticosteroids, thiopurines] *in utero*. Studies assessing the efficacy of live vaccines given to infants exposed to biologics *in utero* have been recently reviewed, demonstrating an adequate immunological response in most of the cases exposed to anti-TNF agents [the experience regarding vedolizumab and ustekinumab, although encouraging, is insufficient to draw any conclusion].[97,99,100,135,139,141,142,144,152–155]

In summary, although the experience is quite limited, it may be concluded that anti-TNF treatment does not seem to significantly reduce the immunogenicity of live-attenuated vaccinations in infants exposed to biologics *in utero*.

Because live-attenuated vaccines may cause disease by uncontrolled replication, severe immunosuppression is generally considered as a contraindication to this type of vaccine.[156] During the first 12 months of life, live-attenuated vaccination in clinical practice includes mainly the rotavirus vaccine and, in some countries, also the Bacillus Calmette-Guerin [BCG] vaccine. Studies assessing the safety of live-attenuated vaccines [including BCG and rotavirus] given to infants exposed to biologics *in utero* have reported no serious adverse events in most cases.[135,136,139,141,142,144,148,153–155,157,158] However, it should be noted that five fatal disseminated BCG infections in infants exposed to anti-TNF agents *in utero*, including infliximab and adalimumab, have been reported.[144]

In the most recent systematic review assessing live-attenuated vaccine outcomes in infants exposed to biological agents *in utero*, including BCG vaccinations administered at <12 months of age, only eight reactions were identified in 215 patients [3.7%], including one death.[159] All infants with an adverse reaction to BCG had been exposed to infliximab *in utero*, and six had received BCG in the first month of life. Most included studies reported outcomes in women with underlying IBD, so the majority of exposures were to infliximab and adalimumab.[159]

Regarding rotavirus vaccination, in the DUMBO Spanish registry, a prospective, observational, and multicentre registry, which enrols pregnant women with IBD over 5 years in 70 centres, 65 infants who had been exposed *in utero* to biologics during the third trimester of gestation received at least the first dose of rotavirus vaccine, and no serious adverse events were observed.[158,160] A recent review of studies of infants exposed to biological agents [mostly anti-TNFs] *in utero* who were given live-attenuated vaccines included 56 infants who had received rotavirus vaccine at <6 months of age.[157] Anti-TNF agents were stopped either in the second or third trimester. No serious adverse events were experienced by any of the infants. Similarly, in the most recent systematic review performed to date, the authors evaluated live-attenuated vaccine outcomes in infants <12 months of age exposed to biological agents *in utero*, including 46 rotavirus vaccinations, and only seven mild reactions to this vaccine were reported.[159] Finally, in a study conducted later, Fitzpatrick *et al.* prospectively examined whether rotavirus vaccine could be administered safely to 168 infants exposed to biological agents [including anti-TNFs, vedolizumab, and ustekinumab], and no serious adverse events after immunization were reported.[161]

It is challenging to decide if live-attenuated vaccines should be postponed during the first year of life in infants exposed *in utero* to biologics. On the one hand, the protection afforded by the vaccination may be reduced if not given according to vaccination schedules but, on the other hand, administering a live-attenuated vaccine to an infant with detectable biological agents levels may place the infant at risk of disseminated [mainly for tuberculosis] disease.[144]

In accordance with the ECCO and the European Medicines Agency [EMA] recommendations, we think that, given the few but definite case reports of fatal outcomes after BCG vaccination, there is insufficient evidence to change the current recommendation of withholding live-attenuated vaccines within the first 6–12 months of life or until biologics are no longer detectable in the infant's blood.[1,144,162] However, although avoiding BCG vaccine may not be relevant in most developed countries, it may be a difficult decision in countries with a high incidence of tuberculosis, where the determination of serum levels of biological drugs in the child may be difficult or impossible to perform. Therefore, the decision should always be individualized and taken on a case-by-case basis.[144]

With respect to rotavirus vaccination, given the exceptional nature of severe rotavirus disease in developed countries, vaccination would probably not be recommended either in infants whose mothers received anti-TNFs [or any other biological agent] during pregnancy.[144] The attitude in developing countries, where mortality due to rotavirus infection is relevant, is not so clear, as postponing rotavirus vaccine is not without risks, while the risk of this vaccination in infants exposed *in utero* to biological agents seems to be minimal. In this last scenario [developing countries], the risk–benefit ratio must be carefully considered.[144]

Finally, it remains unknown whether a mother who is taking a small molecule [such as JAK inhibitors or S1P receptor modulators] and breastfeeding at the time the live-attenuated vaccines are due should hold off the medication for a short period of time to minimize any immunosuppressant effect on the child who is receiving the vaccine. More data are needed before any recommendation can be made with regard to the interaction of small molecules with live vaccines.

16. Conclusions

The management of patients with IBD of childbearing age, during pregnancy and lactation, poses a challenge today. It is crucial to maintain remission of IBD during pregnancy, as disease activity correlates with the occurrence of complications during pregnancy and in the newborn. Most conventional drugs, except methotrexate, are low risk during conception and pregnancy. Regarding anti-TNF drugs, available evidence supports their use during pregnancy and lactation.

In recent years, there has been an increase in therapeutic resources for IBD, demonstrating efficacy and being used earlier in the course of the disease. However, information on the long-term safety of these new biological drugs in children remains limited, although they are expected to have a low risk.

The use of small molecules such as JAK inhibitors or S1P modulators for IBD treatment has recently been approved. These drugs have been shown to be teratogenic in animals, and, therefore, obtaining evidence on their use in humans may be delayed. It is crucial for pharmaceutical companies to promptly disclose safety data for molecules developed during pregnancy and support the creation of safety registries for these drugs. In cases where treatments do not control the disease, and surgery is necessary during pregnancy, it should be performed in specialized centres with surgeons experienced in IBD and with obstetric and neonatal support, but without unnecessary delay. During the third trimester of gestation, a C-section before the surgery should be considered to avoid fetal complications.

Regarding delivery, it should be vaginal unless there is an obstetric contraindication or in patients with IPAA or complex perianal disease. Most drugs for IBD are compatible with breastfeeding, although caution is needed regarding new biological drugs and contraindications for certain molecules.

With respect to the impact of biological treatments on the risk of infections in children, it appears to be low and, although less studied, they do not seem to affect psychomotor development. On the other hand, children exposed to biologics during pregnancy should follow current vaccination recommendations. The live virus vaccines recommended in the early months of life, when biological drugs may still be detectable in the newborn's blood, are the BCG vaccine [in some countries] and the rotavirus vaccine. BCG vaccine should be avoided the first 6 months of life in children exposed *in utero* to ustekinumab and vedolizumab and the first 12 months in children exposed to anti-TNF agents. Regarding rotavirus vaccine, its benefit in developed countries is questionable, but available evidence suggests that it would be of low risk in children exposed to biologics during gestation.

Finally, it has been observed that knowledge about managing IBD during pregnancy, as well as the impact of the disease and treatments, is limited among both professionals and patients. Efforts should be made to improve the training of professionals caring for these patients during this crucial stage of their lives.

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Author Contributions

MCh conceived and designed the review. PS, JPG, MJ, CPS, and MCh wrote part of the review. MCh and PS integrated different parts of the manuscript. PS designed the figures. All authors critically revised the manuscript for important intellectual property and approved its submission.

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