Updates on the management of inflammatory bowel disease from periconception to pregnancy and lactation

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Inflammatory bowel disease (IBD) affects reproductive planning due to psychological effects and mechanical problems related to surgery. Children of people with IBD have an increased risk of about 10% if one parent has IBD and up to 33% if both parents have IBD. The fertility of people with IBD is similar to the general population, but fertility might be reduced in individuals with active IBD, ileal pouch-anal anastomosis, or perianal Crohn's disease. Flaring disease during pregnancy increases complications, such as preterm birth. Thus, disease management with appropriate medications can optimise outcomes. As most medications have minimal fetal risks, people with IBD should be informed about the risks of stopping medications and the importance of maintaining remission. A period of disease remission is advisable before pregnancy and could reduce the risks for both the pregnant person and the fetus. Flexible endoscopy, intestinal ultrasound, and gadolinium-free magnetic resonance enterography are safe during pregnancy. We provide state-of-the-art knowledge on the basis of the latest evidence to ensure successful pregnancy outcomes in controlled IBD.

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Introduction

The global incidence and prevalence of inflammatory bowel disease (IBD) are increasing.[1,2] Most people are diagnosed between the ages of 15 years and 30 years.[3] As more individuals with IBD reach their reproductive age, concerns about medication safety and the effects of the disease on pregnancy and lactation are likely to become more important. Optimising therapy to control disease activity is essential to support conception and healthy pregnancies. Communicating the complex interplay of disease activity, pharmacotherapy, and pregnancy risks to people with IBD is essential to supporting informed decision making,[4] and improved knowledge of the disease could further reduce morbidity and enhance IBD management during pregnancy.[5–7]

Given the range of new therapies and research evaluating pregnancy outcomes in people with IBD, this Seminar aims to update care providers on the latest evidence regarding issues to be considered for optimal pregnancy outcomes in people with IBD (panel 1).

Counselling and education

Knowledge gaps have been associated with pregnancy avoidance, voluntary childlessness, and inappropriate IBD medication changes.[8] Therefore, counselling regarding medication management; avoidance of tobacco, cannabis,[9] and alcohol; promotion of physical activity; and nutritional planning should start in the preconception period. Preconception counselling provides the opportunity to discuss fertility concerns, review medications for fetal safety, and discuss IBD heritability. Importantly, in-person preconception care has been associated with improved clinical outcomes,[10] with a single educational intervention improving not only pregnancy-related knowledge but also emotional wellbeing.[11] However, health-care providers who possess adequate knowledge about IBD and pregnancy issues tend to apply this knowledge inconsistently, as shown in a 2023 study from the UK and Australia.[12] This inconsistent application might reflect the demands of covering complex gastrointestinal and therapeutic issues within a short timeframe, as well as gaps in reproductive health-care professional education, particularly in trainees and those not seeing many people with IBD.

During the past decade, improved access to preconceptual IBD digital tools could reduce the need for in-person resources.[13] Internet-based pregnancy-decision aids, including the American Gastroenterological Association IBD Parenthood Project[14] or the Pregnancy in IBD Decision Aid,[15,16] provide person-specific education for patients and support individuals during their reproductive journey.

A study involving anonymous surveys of female patients with IBD aged 18–45 years assessed their knowledge of IBD and pregnancy through the validated Crohn's Disease and Ulcerative Colitis Pregnancy Knowledge questionnaire (CCPKnow).[17] In a different study, only 33% of male and female patients with IBD reported previous reproductive health counselling; 31% of female patients and 15% of male patients reported considering not having children due to IBD.[18] A minority of patients had an adequate CCPKnow score (45% of female patients and 17% of male patients). A third of female patients either stopped or changed their medication; within this subgroup, 40% did so without

Search strategy and selection criteria

We searched MEDLINE with "inflammatory bowel disease (IBD)" as the main search term and "periconception", "pregnancy", "lactation", "fertility", "medication", "newborn", "infections", and "delivery" as key subsection headings. The search focused on publications from Jan 1, 2018, to Dec 22, 2023, and was expanded retrospectively to include contributions to the literature considered relevant for IBD management from periconception through pregnancy and lactation. Only publications in English were included.

Panel 1: **Checklist of major issues to be considered for a healthy pregnancy in people with inflammatory bowel disease**

- Childlessness
- Small for gestational age
- Preterm delivery
- Pre-eclampsia
- Prematurity
- Venous thromboembolism
- Mode of delivery (eg, perianal disease, ileal pouch-anal anastomosis, and at risk for future pouch surgery)
- Perinatal therapy (eg, pharmacotherapy and medical procedures)
- Increased postpartum complications after caesarean delivery
- Vaccinations

	Pooled odds ratio (95% CI)
Low birthweight	3·8 (1·8–8·0)
Small for gestational age	1·5 (1·2–1·9)
Preterm birth	2·4 (1·7–3·4)
Pre-eclampsia	2·8 (0·7–11·6)
Early pregnancy loss	1·9 (1·2–3·0)
Stillbirth	2·3 (1·0–5·0)

Table 1: **Risks of pregnancy-outcome complications in people with active versus inactive inflammatory bowel disease during periconception and pregnancy**

consulting a physician.[18] Overall, 67% of patients who completed the survey expressed a desire for additional information on IBD and reproductive health.[18]

Risk of disease among children

IBD involves a complex interplay between environmental factors, genetic susceptibility, and immune responsiveness to microbes. Addressing misconceptions about the heritability is essential, as people might be worried about passing their disease to future generations.[4,19] A family history is an important risk factor for developing IBD, which has been reported in up to 12% of patients with Crohn's disease and up to 9% in people with ulcerative colitis.[20,21] The risk of paediatric-onset IBD is highly influenced by a family history of the disease, and it is higher among children with multiple family members diagnosed with IBD than in children with no family members diagnosed with IBD, and is increased up to 33% if both parents are affected.[20,22,23] However, thus far genetic testing has been ineffective, as more than 240 gene loci have been associated with IBD.[24]

Fertility

Fertility care and voluntary and involuntary infertility are important considerations for people living with IBD and represent a knowledge gap for many clinicians.[25] These concerns can often be addressed in consultation with assisted-reproductive-technology specialists.[25]

Epidemiological studies do not typically distinguish between voluntary and involuntary childlessness. However, voluntary childlessness is more common in female individuals with IBD compared with the general public, with an increased prevalence of involuntary infertility reported in up to 17% of female individuals with IBD versus 6% in the general population.[8,26,27] Overall, involuntary infertility rates of up to 14% in people with Crohn's disease and 15% in people with ulcerative colitis have been reported, similar to rates observed in individuals without IBD.[27–29] However, reduced fertility can occur with periconceptually active IBD,[30] after restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA),[31] or with perianal complications of Crohn's disease,[32] without any proven fecundity reduction.[32]

As surgery after IPAA might negatively affect fertility,[31] elective IPAA formation in female individuals is recommended to be delayed until desired pregnancies have been completed. Moreover, to improve fertility, a laparoscopic IPAA approach is preferred to minimise complications, including inflammation and scar formation.[33]

In male individuals with IBD, fertility is mostly unaffected, with slightly reduced pregnancy rates attributable to voluntary childlessness.[34–36] Sulfasalazine exposure is known to reduce fertility in male individuals, as sulfapyridine can impair sperm maturation and reduce sperm motility and count.[37,38] Sperm recovery requires approximately 3 months after sulfasalazine discontinuation.[39] Although male fertility is not affected by an IPAA, a total laparoscopic approach, including rectal dissection, is recommended to preserve erectile function.[40]

Success rates of artificial reproductive technology with euploid single-embryo transfer in people with IBD are similar to those in the general population,[41] except in the subgroups of female individuals undergoing surgery for Crohn's disease or IPAA failure.[30]

Consequently, if a female individual with IBD older than 35 years is unable to conceive after 6 months or more of regular unprotected sexual activity, clinicians should consider referring them for an infertility evaluation.[42]

Periconception

As IBD activity during the periconception period is predictive of disease activity during pregnancy,[43–51] ensuring disease remission before conception is recommended to reduce the risk of adverse outcomes. A systematic review and meta-analysis of 28 studies reported an association between IBD flares during the periconception and pregnancy periods and a higher risk of pregnancy complications compared with people who had quiescent IBD (table 1).[50]

On the basis of a 2023 cohort study, female individuals with IBD are recommended to be in remission for at least 6 months before attempting conception.[51] Moreover, they are advised to effectively use contraception and seek pre-pregnancy multidisciplinary counselling, including obstetric providers and gastroenterologists, to optimise timing and reduce risks of pregnancy complications.[52,53]

The risk of increased activity during pregnancy for people with IBD who were in remission at conception is 38%,[54,55] similar to that reported in people who are not pregnant.[43,48] However, the risk of continued disease activity throughout pregnancy is nearly doubled among people with active IBD at conception.[43,45,47,48,50,56,57] In people who previously had flaring disease during pregnancy, the risk of active IBD during subsequent gestations might be increased as well,[49,58] emphasising the importance of good clinical disease control.[49,51]

An important consideration for people with IBD who are not in remission is seeking appropriate contraceptive counselling to avoid unplanned pregnancies at periods of increased morbidity. The approach to contraception should be adapted to each person.[53]

Female individuals with IBD might exhibit symptoms of sexual dysfunction, including reduced sex drive, dyspareunia related to perineal or pelvic disease, scar tissue, and pelvic-floor dysfunction. People should be asked questions about sexual function, and their concerns should be addressed with the help of a gynaecologist.[59]

Prophylactic measures during pregnancy

All pregnant people with IBD should receive regular prenatal care by an obstetric provider with knowledge of how IBD affects pregnancy,[60] in collaboration with the gastroenterology team.[61] People should have their iron, vitamin B12, and folic-acid concentrations assessed at conception and during the first trimester.[62–64] Increased daily doses of 2–5 mg of folic acid throughout pregnancy are recommended for those taking sulfasalazine, which impairs folic-acid metabolism and absorption.[65,66] Moreover, a minimum vitamin D serum concentration of 20 ng/mL is recommended.[67]

Beyond standard prenatal visits and fetal ultrasonography, additional monitoring in the third trimester is recommended given the potential for IBD-specific or pregnancy-related complications. The relationship between IBD and complications, such as gestational hypertensive disorders, including pre-eclampsia, remains unclear. As low-dose aspirin is routinely used in the prevention of gestational hypertension, data published in 2013 suggested that low-dose aspirin use in pregnancy does not increase the risk of IBD flares.[68] For female individuals with risk factors, including corticosteroid use by their birthing parent, advanced reproductive age, previous hypertension, or diabetes, low-dose aspirin prophylaxis is therefore recommended.[69–72] Aspirin-prophylaxis initiation involves administering enteric-coated aspirin at doses of 81–162 mg after the twelfth week, usually discontinued at week 36.[73] The prenatal visit at week 36 provides a convenient point for the person with IBD and obstetrician to review the pregnancy progress, medications, and aspirin cessation and to discuss a birth plan. Furthermore, postpartum-care issues such as lactation, neonatal vaccination, perineal care, mental health, and gastroenterology follow-up care can be addressed.

Controlling disease during pregnancy

During pregnancy, biochemical marker testing should be done on a regular basis. However, common symptoms and signs during pregnancy can be challenging to interpret. Haemoglobin and albumin concentrations are usually reduced, whereas the erythrocyte sedimentation rate and alkaline-phosphatase levels might increase due to physiological changes during pregnancy.[74] By contrast, faecal calprotectin and C-reactive protein (CRP) levels are mainly unaffected—although CRP might be slightly increased—during pregnancies in people with IBD.[75] Symptoms often associated with pregnancy, including abdominal discomfort, constipation, and haemorrhoids, complicate the assessment of gastrointestinal symptoms that might represent an IBD flare during pregnancy. For this reason, proactive monitoring of disease activity via faecal calprotectin and CRP is recommended in both early and late pregnancy. As point-of-care intestinal ultrasound becomes more available, this test can safely provide real-time disease activity assessment as well.[76]

With careful monitoring and active treatment of inflammation, the majority of pregnant people with IBD will not have increased disease activity or pregnancy complications.[6,37] However, if thiopurines are prescribed, regularly monitoring thiopurine-metabolite levels is advised[77] to optimise treatment and detect the potential development of intrahepatic cholestasis of pregnancy, a hormone-influenced, reversible type of cholestasis.[78] Caution should be used as dose escalation of thiopurines during pregnancy could substantially increase the levels of the 6-methylmercaptopurine metabolite and the risk of atypical liver function.[79] Furthermore, given the risks associated with intrahepatic cholestasis, laboratory testing in the late second or early third trimester should be done in pregnant people with pruritus.

Among pregnant female individuals with IBD, non-adherence to medications might be related to misconceptions about pregnancy and fetal risk and occur more frequently for those not attending specialised IBD centers.[80–82] On the basis of the latest recommendations, various medications with distinct safety profiles are being used for IBD during preconception, pregnancy, and lactation (table 2).[37,83–88] Medication adherence should be reviewed at all visits, remembering that mesalazine, immunomodulators, and self-administered biologics are the agents most often discontinued by people with IBD,[80] which increases the risks of flaring disease and adverse pregnancy outcomes.[80,82,89] Notably, IBD flares are related

	Periconception	Pregnancy	Lactation
Mesalazine	Compatible	Compatible	Compatible
Sulfasalazine	Avoid in male individuals for a minimum 3 months before conception; compatible in female individuals	Compatible, but extra folic acid supplementation (ie, 2 mg per day) is recommended	Compatible
Glucocorticoids	Compatible	Compatible for short-term use	Compatible
Thiopurines	Compatible	Compatible	Compatible
Allopurinol used with a thiopurine	Not recommended	Not recommended	Not recommended
Ciclosporin	Compatible	Compatible	Probably safe
Methotrexate	Compatible in male individuals, but avoid in female individuals for 3–6 months before conception	Avoid	Unclear
Thalidomide	Contraindicated	Contraindicated	Contraindicated
Tumour necrosis factor inhibitors (eg, infliximab, adalimumab, golimumab, and certolizumab pegol)	Compatible	Compatible	Compatible
Anti-integrin (ie, vedolizumab)	Compatible	Compatible	Compatible
Anti-IL-12 and IL-23 (eg, ustekinumab)	Compatible	Compatible	Compatible
Janus kinase inhibitors	Avoid due to sparse evidence	Avoid due to sparse evidence	Avoid due to sparse evidence
Sphingosine-1-phosphate receptor modulators	Avoid due to sparse evidence	Avoid due to sparse evidence	Avoid due to sparse evidence

Table 2: **Safety of medications used for the management of inflammatory bowel disease during periconception, pregnancy, and lactation based on published data**

Panel 2: **Risks of complications observed in moderate to severe inflammatory bowel disease during pregnancy**

- Early pregnancy loss: risk is increased
- Preterm birth: risk is increased
- Low birthweight: risk is increased
- Small for gestational age: risk is increased
- Caesarean delivery: risk is increased
- Pre-eclampsia: risk is unchanged

to increased incidence of preterm birth, low birthweight, and infants who are small for gestational age (SGA; panel 2).[50,90–92] Severe disease activity might also be associated with early pregnancy loss and caesarean delivery, whereas its correlation with gestational hypertension remains uncertain.[50] Crohn's-disease activity can lead to malnutrition, resulting in impaired gestational weight gain, which is associated with intrauterine-growth restriction and adverse fetal outcomes.[90,93] However, in people with quiescent Crohn's disease, outcomes are similar to those in the general population.[93,94]

In people with ulcerative colitis, flares occur more often in the first and second trimesters and postpartum periods than in the third trimester.[45,48] The risk of flares during pregnancy is higher in people with ulcerative colitis than in people with Crohn's disease. This increased risk of flaring disease might be ascribed to the fact that female individuals with Crohn's disease receive biologic therapy more often than female individuals with ulcerative colitis.[51] A prospective study of the US Pregnancy Inflammatory Bowel Disease and National Outcomes (PIANO) registry identified that inadequate gestational weight gain predicted adverse pregnancy outcomes in mothers with IBD.[95]

Medications during pregnancy and safety for the offspring

The classic therapies used to treat IBD, including corticosteroids, mesalazine, and thiopurines, have minimal risk during pregnancy and lactation (table 2).[37,96] Although corticosteroids cross the placenta, they are rapidly metabolised. The PIANO registry associated use of corticosteroids in 1490 pregnant women with gestational diabetes (odds ratio [OR] 2·8, 95% CI 1·3–6·0).[97] There were also associations between corticosteroid use (n=432) and preterm birth (1·79, 1·18–2·73), low birthweight (1·76, 1·07–2·88), and admission to neonatal intensive care units (1·54, 1·03–2·30).[98] However, there was no association with congenital malformations (10% in the corticosteroid group and 9% in the non-exposed group; p=0·37) or impaired cognitive development.[98] Separating the effects of the drugs from those caused by active IBD is not possible.

Biologics, including tumour necrosis factor-α (TNFα) inhibitors,[99] integrin antagonists,[100] and cytokine blockers,[101] are increasingly used to treat IBD. The safety of TNFα-inhibitor exposure has been assessed in infants up to the first year of life via the French national health system database Système National d'Information Inter-Régimes de l'Assurance Maladie, which involved 8726 pregnant women with IBD between 2011 and 2014.[102]

Maintaining TNFα inhibitors after 24 weeks of pregnancy did not increase the risk of maternal complications, whereas discontinuation before week 24 was associated with an increased risk of flaring disease. Moreover, no increased infection risk was observed in children born to mothers exposed to TNFα inhibitors during pregnancy (adjusted OR [aOR] 0·89, 95% CI 0·76–1·05).[102] Another nationwide population-based study conducted in France, via the Système National des Données de Santé (SNDS), identified 5293 people with IBD who were pregnant and received treatment with TNF inhibitors between 2010 and 2020.[103] In this study, TNF-inhibitor treatment was discontinued before 24 weeks for 2890 expecting parents but continued beyond 24 weeks for 2403. Continued therapy was associated with a reduced frequency of IBD relapse in the birthing parent and prematurity. No differences were detected for stillbirth, SGA, or serious infections among the children.[103] This study emphasises the importance of disease control and appropriate medical therapy during pregnancy in people with IBD.

The most vulnerable period for drug-induced fetal-developmental disorders during organogenesis is between the fourth and the eighth week of gestation. A systematic review and meta-analysis of 48 studies, including 6963 people with IBD who received biologics during pregnancy, reported that the prevalence of congenital malformations, early pregnancy loss, preterm birth, stillbirth, and low birthweight in people exposed to biologics was similar to the general population.[85] Furthermore, the data suggested that continued therapy with biologics (ie, both TNF inhibitors and non-TNF agents) throughout the third trimester of pregnancy was not associated with adverse pregnancy outcomes.[85,104] Another meta-analysis evaluating women with IBD identified the discontinuation of biologic therapy in the third trimester and biologic therapy de-escalation after delivery as risk factors for flaring disease postpartum.[105] Together, these results provide compelling evidence for the maintenance of biologic therapy throughout pregnancy to manage IBD and decrease complications.

In another study of the French SNDS database, the safety of thiopurine monotherapy was evaluated in 3554 people who were pregnant, of TNF inhibitor monotherapy was evaluated in 3525 people who were pregnant, and of combination therapy was evaluated in 829 people who were pregnant compared with 19 811 unexposed people who were pregnant between 2010 and 2018.[106] Compared with unexposed people who were pregnant, women who received concomitant thiopurine and biologic therapy more often had preterm birth or delivered infants who were large for gestational age (LGA; ie, fetal weight higher than the 90th percentile), with no difference in stillbirth rate.[106] However, thiopurine monotherapy was associated with higher frequencies of stillbirth, preterm birth, and LGA and with a lower frequency of SGA compared with unexposed people who were pregnant. By contrast, people who were pregnant and exposed to monotherapy with TNF inhibitors had similar rates to unexposed people who were pregnant.[106] A nationwide Danish cohort study examined the association between in-utero exposure to thiopurines and pregnancy outcomes, including all 1 308 778 liveborn children from 1995 to 2015. Of this cohort, 1047 children born to birthing parents with IBD were eligible. Children exposed to thiopurines during gestation were observed for a median of 8·9 years (IQR 5·5–12·4).[107] This study reported that offspring exposed to thiopurines in utero did not have an increased risk of congenital malformations or of Crohn's disease or ulcerative colitis during childhood or adolescence.[107]

Therefore, caution should be used when establishing whether thiopurines should be prescribed during pregnancy in people with IBD. However, the regimen of combined allopurinol with low-dose thiopurine therapy for people with IBD who are pregnant[108] is not recommended, as allopurinol might be a risk to the fetus.[86]

Data on the safety of vedolizumab, a monoclonal antibody directed against α4β7-integrin; ustekinumab, an anti-cytokine targeting both IL-12 and IL-23; novel selective IL-23 inhibitors; and small molecules of Janus kinase (JAK) inhibitors or sphingosine-1-phosphate receptor modulators for offspring are still scarce. Regarding biologics, there are no alarming signals related to safety.[85] However, three studies in small cohorts reported congenital malformations associated with vedolizumab exposure ranging from 6% to 13% of participants.[109–111] Of the seven infants with congenital malformations identified in these studies, four exhibited hip dysplasia. No such findings were observed in infants exposed to ustekinumab.[104,112]

Unlike monoclonal antibodies, orally administered small molecules might cross the placenta during organogenesis, and teratogenic effects have been reported in animal studies.[113] Due to sparse evidence, further data are needed, and these drugs are currently not recommended during pregnancy (table 2).[114]

Influence of in-utero exposure to medications on the offspring

A multicentre retrospective study conducted in the Netherlands included 1000 children born to 625 mothers with Crohn's disease, 225 with ulcerative colitis, and 20 with unclassified IBD. No association was noted between in-utero exposure to TNF inhibitors with or without a thiopurine and severe infections (ie, requiring admission to hospital), adverse reactions to vaccinations, not thriving, or other diseases occurring during the first 5 years of life.[115] A systematic review and meta-analysis including 8013 women with IBD who gave birth to 8490 infants evaluated the risk of infections after in-utero exposure to biologics in the infants. Biologics were not

associated with an increased risk of serious infections necessitating antibiotics or admission to hospital. However, they were related to a minor risk of mild respiratory infections in the first year of life; continued biologic therapy throughout the third trimester did not confer additional infection risks.[84] By contrast, data obtained from the French SNDS database between 2010 and 2018 encompassing 26 561 children born to mothers with IBD revealed that exposure to thiopurine or TNF-inhibitor monotherapy during gestation did not enhance the risk of serious infections in the first 5 years of life. However, the combined treatment showed an increased risk of developing serious infections in the first year (adjusted hazard ratio 1·36, 95% CI 1·04–1·79).[116] Exposure to corticosteroids in utero in a cohort of 1431 neonates born to mothers with IBD did not increase risk of infections during the first year of life, unless the exposure occurred in the second or third trimester, in which case it was associated with increased infection requiring admission to hospital of the infant at 9 months and 12 months (second trimester 4% *vs* 2%; p=0·03; third trimester 5% *vs* 2%; p=0·001).[98] To date, there is no evidence that intrauterine exposure to biologics can affect the development of the immune system of the infant.[84,117]

Evaluation of a Danish population-based cohort of all liveborn singleton neonates during 1995–2016 (n=1 343 960) revealed that maternal Crohn's disease, but not ulcerative colitis, was associated with an increased risk of infections in offspring younger than 5 years but was not associated with TNF inhibitors or adverse birth outcomes.[118] A study of the SNDS database between 2010 and 2020 did not detect any signs of early-life malignant diseases in offspring exposed to TNF inhibitors or thiopurines in utero.[119] To address the safety of IBD drugs during pregnancy and breastfeeding, the ongoing multicentre Spanish Safety of IBD Drugs During Pregnancy and Breastfeeding: Mothers' and Babies' Outcomes (DUMBO) registry is following up pregnant mothers during a 5-year period, with subsequent follow-up of infants up to age 4 years.[120] Results reported so far show no increase in risk of adverse events in offspring exposed to immunomodulators or biologics during pregnancy.[33,121]

Management of disease exacerbations in pregnancy

Flares of IBD during pregnancy might require endoscopy or radiographic imaging; guidelines addressing this topic were published in 2023.[122] Available data on endoscopy during pregnancy are encouraging, although increased risks of preterm birth and low birthweight have been described.[123] Nonetheless, flaring disease is a substantial confounding factor. The guidelines conclude that endoscopy with minimal time and sedation can be done when necessary, preferably in the second trimester.[122] To avoid ionising-radiation exposure, ultrasonography and MRI can be conducted, preferably at 1·5 T according to available safety data, although 3-T MRI might be acceptable.[124] Gadolinium contrast should be avoided due to potential teratogenic effects on the fetus.[125] CT scans with low radiation dose (ie, <50 mGy) should be done only when no alternatives are available.[122] Regarding capsule endoscopy, due to a potential risk of gastrointestinal-tract compression by the gravid uterus and still unclarified effects of the electromagnetic field of the capsule device on the fetus,[126] this procedure is currently contraindicated during pregnancy.[122]

There is little information on the management of acute, severe ulcerative colitis (ASUC) during pregnancy, which generally conforms to the treatment of non-pregnant people. Induction therapy with TNF inhibitors administered to people with active IBD during pregnancy, including in the third trimester, has been reported to be safe.[127] In a cohort of 20 pregnant women with ASUC, all women responded to standard therapies (ie, glucocorticoids and TNF inhibitors) and most women were able to avoid colectomy in the observation period (up to 4 years).[128] The majority had livebirths without serious fetal complications.[128]

Delivery modes

Selecting an appropriate delivery mode for people with IBD should be a shared decision-making process with obstetric indication and patient preference deciding the choice in the majority of people with IBD.[129] Expecting birthing parents should be reassured that the mode of birth does not influence the risk of developing IBD later in life.[130]

Vaginal delivery

Vaginal delivery is appropriate for most people with IBD. Long-term risk of injury to the anal sphincter or pelvic-floor dysfunction, including subsequent bowel function and faecal continence, should be considered in conjunction with disease type and activity. Contentious areas include vaginal delivery combined with an episiotomy in people with Crohn's disease, for whom existing perianal complications could induce fistula formation.[131] In people with active perianal Crohn's disease at time of delivery, a vaginal delivery is considered a major risk factor for new complications.[129] Moreover, in people with perianal disease with or without Crohn's disease, significantly higher risk of fourth-degree tears was observed after vaginal delivery (12·3%) compared with women with Crohn's disease but without perianal disease (1·4%; p<0·001).[132] In people with Crohn's disease and no previous perineal involvement, vaginal delivery did not affect the development of subsequent perineal involvement.[133]

Caesarean delivery

The risk of caesarean delivery is increased in people with IBD (29–34%) and is higher than that observed in the general public (16–22%) for elective and emergency indications.[56,131,134–139] Planned caesarean delivery for people

with IBD is usually recommended for people with active perianal disease associated with high risk of perianal injury;[61,140] people with IPAA, as they are reliant on an intact pelvic floor function and anal sphincter to avoid faecal incontinence;[141] and people with anticipated future IPAA surgery.[141] Pregnant people with active IBD should always be considered for referral to high-risk pregnancy clinics.[142]

In a 2022 Danish study including all liveborn singleton births between 1997 and 2015, 3255 women with IBD had caesarean delivery (*vs* 207 608 women without IBD) and 6425 women with IBD had vaginal delivery (*vs* 874 242 women without IBD). Caesarean delivery rate was 33·6% in women with IBD versus 19·2% in women without IBD.[138] Women with IBD—subanalyses for Crohn's disease or ulcerative colitis were not available—with caesarean delivery more often had subsequent surgery of the ileum and colon than women without IBD (aOR 5·00, 95% CI 2·00–12·51).[138] In women with IBD, 2·1% of those with caesarean delivery versus 0·3% of those with vaginal delivery had a 30-day postpartum complication necessitating surgery. Compared with vaginal delivery, the risk of surgical complications after caesarean delivery increased in women with IBD regardless of indications or immunosuppressive medication.[138] Therefore, physicians should consider caesareans primarily for obstetric indications in the absence of perianal Crohn's disease and an IPAA history.[138]

Wound healing

Postpartum wound healing and ongoing biologic therapy are a concern for people with IBD and obstetricians. A single-centre study including 87 people with IBD experiencing 100 births (58 caesarean and 42 vaginal deliveries) between August, 2015, and February, 2020, evaluated whether peripartum biologic agents affected wound healing.[143] Peripartum biologic exposure occurred in 72% of people after caesarean delivery and 57% of people after vaginal delivery. Time from last dose to parturition had a median of 6 weeks (IQR 4–8), and 21 people (32%) restarted biologic therapy within 72 h after labour. Seven infections occurred after caesarean delivery in five people with Crohn's disease. However, biologic exposure in pregnancy did not influence the risk of infections (6% *vs* 9% in unexposed birthing parents; p=0·68) or IBD activity (p=1·00).[143] Thus, the authors concluded that peripartum biologic exposure did not influence wound infections or postpartum wound healing after caesarean delivery or vaginal delivery.[143]

Vascular complications

As pregnancy increases venous thromboembolism risk, especially among people with active IBD,[144] proactive risk assessment is recommended, particularly after caesarean delivery.[61] In people with IBD undergoing emergency caesarean delivery or with one or more risk factors for venous thromboembolism, thromboprophylaxis should be considered and clinicians should review the recommendations on the basis of regional guidelines.[6,145]

Delivery complications

When planning for birth, some features of IBD require attention because of the increased risk for adverse outcomes for the birthing parent and the neonate.[92] These features include a combination of penetrating, stricturing, or perianal disease; surgical history with resection of the ileum or colon; protein-calorie malnutrition; and ongoing parenteral nutrition.[92] In a US study of 73 109 790 delivery admissions to hospital, the 2000–18 National Inpatient Sample characterised IBD trends and associated risks during delivery admissions to hospital.[92] Of all delivery admissions, 89 965 (1·2%) people had a diagnosis of IBD. People with IBD more often had adverse outcomes such as preterm delivery, need for transfusion, sepsis, stroke, shock, heart failure, venous thrombosis, and surgical complications compared with people without IBD.[92]

Additional considerations for obstetric outcomes

Preterm birth has been reported to occur up to 4-times more in women with active IBD than in women in the general public (5–9%).[136,146] The risk of preterm birth is higher than the general public for maternal IBD (OR 2·15, 95% CI 1·36–3·39) and for paternal IBD (3·02, 1·82–5·01), as well as for parents who also have at least one first-degree relative with IBD (4·29, 1·59–11·63).[147] A shared genetic susceptibility for IBD and preterm birth has been proposed as the underlying mechanism.[147]

5–7% of infants born to people with IBD are SGA, compared with 4% in the general population of Sweden.[56,135,136] A study based on the French SNDS database included 36 654 people with IBD who were pregnant and 8 595 562 people without IBD who were pregnant between 2010 and 2018. Women with IBD, especially those with flaring IBD before and during pregnancy, exhibited moderately increased risks of prematurity (aOR1·51, 1·45–1·58), SGA (1·15, 1·10–1·20), and caesarean delivery (1·39, 1·35–1·42).[148]

Lactation

Lactation in the postpartum period offers several benefits, including diminished risk of gastrointestinal infections[149] and a possible decreased risk of IBD development in the neonate.[150] However, many people with IBD are concerned about pharmacological exposure and safety for their nursing infants.[151] Breastfeeding-safety data are reassuring for most IBD medications except methotrexate, ciclosporin, allopurinol, thalidomide, and newer small molecules (eg, JAK inhibitors or sphingosine-1-phosphate receptor agonists; table 2).[37,63,86,152–157] The risk of postpartum IBD flares is unaffected by lactation.[151] For people

	Information	Reference
US Pregnancy Inflammatory Bowel Disease and National Outcomes (PIANO) registry	Outcomes after vedolizumab or ustekinumab in utero	Chugh et al (2023)[104]
European Pregnancy in Crohn's and Colitis—Observations, Levels and Outcomes (PICCOLO) registry	Pharmacokinetics of vedolizumab and ustekinumab in pregnant people with inflammatory bowel disease	Prentice et al (2023)[111]
Spanish Safety of IBD Drugs During Pregnancy and Breastfeeding: Mothers' and Babies' Outcomes (DUMBO) registry	Safety of live vaccines in children exposed to biologics for inflammatory bowel disease in utero or during breastfeeding	Chaparro et al (2023)[121]

Table 3: **Emerging work from prospective registries evaluating the safety of medications in people with inflammatory bowel disease during pregnancy and outcomes for offspring**

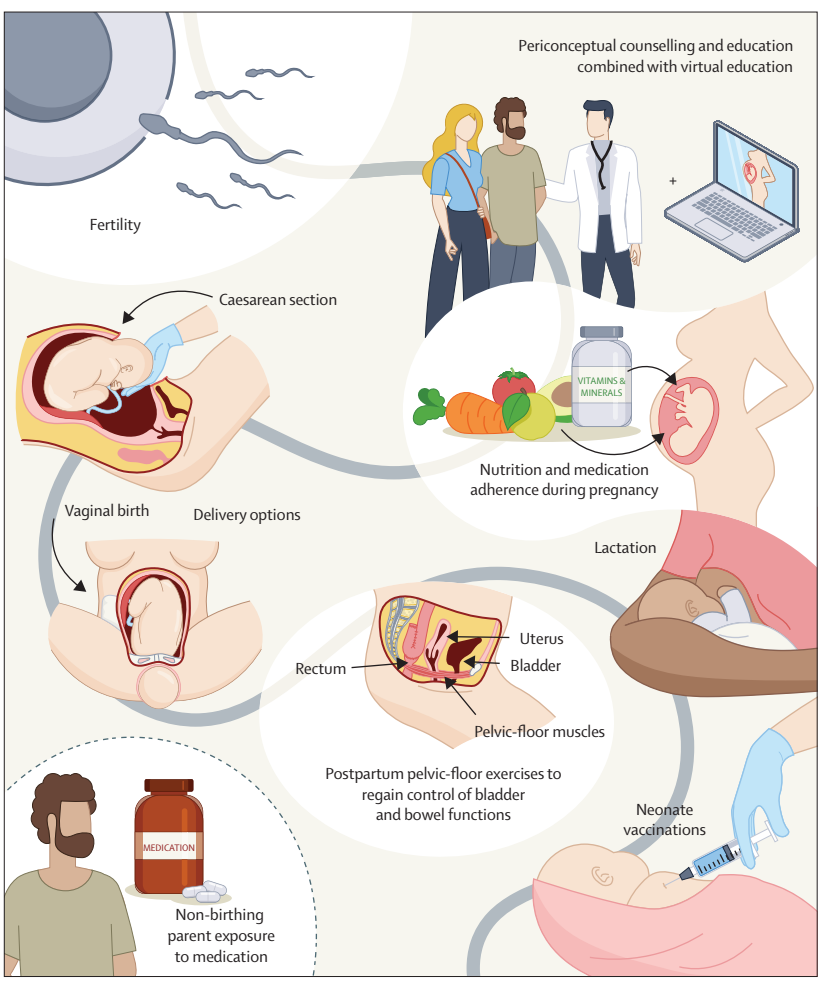

Figure: **Healthy patient trajectory ensuring optimised management of inflammatory bowel disease in parents from periconception through pregnancy and lactation, with appropriate educational support**

receiving biologic therapy, these drugs can be resumed 1 day after vaginal delivery, 2 days after caesarean delivery,[158] and during lactation. According to global guidelines, people with IBD are also recommended to lactate for at least 6 months, and preferably 12 months.[159–161]

Vaccinations

Most vaccinations used are non-live vaccines that do not increase risk of viral reactivation and can safely be offered to infants exposed to biologics or thiopurines in utero.[79,114,158,159,162] Live vaccines can also be administered to infants exposed in utero to non-biologic therapy or certolizumab pegol, a drug with minimal or no placental transfer.[158,163,164] Infants clear vedolizumab rapidly, resulting in lower vedolizumab concentrations compared with circulation in the birthing parent, which might be undetectable at week 15.[109,111] Ustekinumab has a higher placental transfer than vedolizumab, and the clearance of ustekinumab occurs in most infants during the first 15 weeks.[111] Notably, cord-blood concentrations of biologics other than certolizumab pegol and vedolizumab might be higher than in birthing-parent serum in infants exposed during pregnancy,[111,165] and drug concentrations of TNF inhibitors might be detectable up to age 6–12 months.[166–168] Therefore, live vaccines are a potential risk for infants exposed to such biologics because of the potential for altered immune function; they should be deferred for the first 6 months of life or used only after consultation with an infection-medicine specialist or paediatrician. However, emerging data suggest that inoculation against rotavirus, which is a live vaccine, can be administered without complications.[121,169] Moreover, in a DUMBO study, 40 of 205 neonates were exposed to biologics either in utero, during breastfeeding, or both. 11 children received all three doses of rotavirus vaccine and no adverse events were identified during a mean follow-up of 12 months.[121]

Exposure to IBD medications from the non-birthing parent

A 2021 retrospective cohort study assessed the periconceptional use of immunosuppressives or biologic agents among male individuals with chronic inflammatory diseases and risk to the offspring.[170] In total, 7453 expectant fathers with IBD and other chronic diseases were identified with periconception medication exposure 38–60 weeks before the birth, with a follow-up period of the first 3 months of infant life.[170] The unexposed cohort had chronic immune diseases without exposure to medications. Primary exposures included thiopurines, methotrexate, TNF inhibitors (ie, infliximab, adalimumab, certolizumab pegol, and golimumab), and non-TNF inhibitor biologics (ie, vedolizumab and ustekinumab). Concomitant therapy

with biologics and immunosuppressives was investigated as a secondary exposure. No increased risk of congenital malformations was found after exposure to thiopurines, methotrexate, TNF inhibitors, or non-TNF inhibitor biologics, with a 3·4% prevalence of major congenital malformations reported.[170] Similarly, preterm birth and low birthweight were not increased.[170] A Danish nationwide cohort study examined mesalazine, including sulfasalazine, in 2168 children fathered by men taking this medication versus 7732 unexposed children and did not identify increased adverse outcomes in offspring.[171] A 2023 meta-analysis of paternal medications in IBD and male reproductive outcomes from 16 studies, encompassing more than 25 000 people, concluded that exposure to biologics, thiopurines, or methotrexate among male individuals with IBD was not associated with alterations in sperm variables (ie, surrogate or fertility) or adverse pregnancy or neonatal outcomes, including preterm birth or congenital malformations.[83] A 2023 nationwide, multiregister cohort study of fathers in the general population of Sweden with periconceptional methotrexate exposure showed that paternal use of this drug was not associated with increased risk of congenital anomalies, preterm birth, or SGA in offspring, but might temporarily reduce fertility (defined by need for intracytoplasmic sperm injection).[172] There are no clear guidelines regarding the management of methotrexate in male individuals with IBD before conception. Due to the low risk of adverse pregnancy outcomes, male individuals with IBD who want to conceive can continue methotrexate in the preconception stage.[173] However, if male individuals have difficulty conceiving while taking methotrexate, the medication can be discontinued 60–90 days (ie, the duration of human spermatogenesis) before reattempting conception.[174]

Future directions

Fertility, pregnancy, and childbirth are pivotal life events that are affected by IBD. People living with these chronic diseases and considering parenthood should receive support from a multidisciplinary team based on the latest evidence to provide current recommendations, aid in dispelling myths, and empower them to make informed choices while pregnant and during lactation. This support is particularly important considering the emergence of a wide range of new IBD therapeutics, with additional promising medications in development. In this context, data collected via prospective registries (eg, PIANO, European Pregnancy in Crohn's and Colitis—Observations, Levels and Outcomes [PICCOLO], and DUMBO) evaluating medication safety in people with IBD who are pregnant and offspring outcomes are crucial for future rational decision making (table 3). Moreover, optimising nutritional care and choosing an appropriate mode of delivery are other complex issues that need to be addressed (figure). Prioritising the person's perspective when discussing risks and benefits is crucial. The provision of multidisciplinary support should extend into the postpartum period, a time of intense life changes in which fatigue, medication non-adherence, and disease flares might be additional challenges.

Contributors

OHN was the coordinator. All authors contributed equally to conceptualisation, the literature search, revisions, tables, the figure, and writing or editing of the manuscript; had full access to all the data in the manuscript; and had final responsibility for the decision to submit for publication.

Declaration of interests

SES holds stocks in Merk and Johnson & Johnson and is a consultant for Janssen, Takeda, Bristol Myers Squibb, Gilead, Prometheus, and Surrozen. All other authors declare no competing interests.

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