Review

# IBD in pregnancy: recent advances, practical management

Christian P Selinger ,[1] Catherine Nelson-Piercy,[2] Aileen Fraser,[3] Veronica Hall,[4] Jimmy Limdi,[5,6] Lyn Smith,[7] Marie Smith,[8] Reem Nasur,[8] Melanie Gunn,[9] Andrew King ,[9] Aarthi Mohan,[10] Khasia Mulgabal,[11] Alexandra Kent,[12] Klaartje Bel Kok,[13] Tracey Glanville[14]

For numbered affiliations see end of article.

**Correspondence to**
Dr Christian P Selinger, Leeds Gastroenterology Institute, Leeds Teaching Hospitals NHS Trust, Leeds LS9 7TF, UK; christian.selinger@web.de

Received 21 November 2019
Revised 27 April 2020
Accepted 4 May 2020
Published Online First 19 May 2020

## ABSTRACT

Inflammatory bowel disease (IBD) poses complex issues in pregnancy, but with high-quality care excellent pregnancy outcomes are achievable. In this article, we review the current evidence and recommendations for pregnant women with IBD and aim to provide guidance for clinicians involved in their care. Many women with IBD have poor knowledge about pregnancy-related issues and a substantial minority remains voluntarily childless. Active IBD is associated with an increased risk of preterm birth, low for gestation weight and fetal loss. With the exception of methotrexate and tofacitinib the risk of a flare outweighs the risk of IBD medication and maintenance of remission from IBD should be the main of care. Most women with IBD will experience a normal pregnancy and can have a vaginal delivery. Active perianal Crohn's disease is an absolute and ileal pouch surgery a relative indication for a caesarean section. Breast feeding is beneficial to the infant and the risk from most IBD medications is negligible.

The management of inflammatory bowel disease (IBD) poses a particular challenge during pregnancy. Here, we give an overview of the current evidence and guidance regarding best practice for managing patients with IBD who want to become pregnant or are pregnant.

## FERTILITY IN IBD

Fertility rates for women with Crohn's disease (CD) and ulcerative colitis (UC) in remission without prior surgery are equal to those in the general population.[1] Women with active IBD may have decreased fertility and symptoms may negatively impact on body image and libido.[2 3] There is no evidence that medical therapy for IBD decreases fertility. Women may have decreased fertility after pelvic surgery due to inflammation and scarring of the fallopian tubes. Laparoscopic rather than open ileoanal pouch surgery may improve fertility rates.[4 5] Some clinicians advise women with UC who plan to have children to delay pouch surgery until they have had children. Patients who have tried unsuccessfully to conceive for 6–12 months should be referred for fertility evaluation.[6 7]

Seventeen per cent of women with IBD are voluntarily childless (VC) compared with 6% of women in the general population.[8] It is associated with disease burden, poor knowledge or incorrect information about pregnancy and IBD.

## PRECONCEPTION COUNSELLING AND EDUCATION IN IBD

Preconception counselling is persistently shown to promote healthier behaviours and improve pregnancy outcomes, mitigating the negative effect of misunderstanding fertility and pregnancy-related issues. Objective disease evaluation before conception can optimise disease management. In-person preconception care is associated with improved adherence to medications, enhanced smoking-cessation efforts, reduced relapses and decreased risk of low birthweight infants.[9] Such care should focus on optimising nutritional status, maintaining iron and folic acid supplementation and achieving an ideal weight.[9 10]

Patient education programmes and counselling in IBD clinic at induction of all medications, could help to reduce the rate of VC in women with IBD, through education, correcting misconceptions and alleviating patient concerns.[11]

## THE GENETIC RISK OF IBD

The genetic risk of IBD in offspring is often overestimated by prospective



**To cite:** Selinger CP, Nelson-Piercy C, Fraser A, *et al*. *Frontline Gastroenterology* 2021;**12**:214–224.

parents. Cohort studies have demonstrated the genetic risk of CD is higher than that of UC. Absolute risk is an easier and more understandable concept to discuss with patients. In the setting of maternal CD, the absolute risk of an offspring developing CD is 2.7%, whereas the risk of UC in the setting of maternal UC is 1.6%.[12] The risk of IBD can exceed 30% when both parents have the disease and these rates may be increased in cases of multiple affected family members, young age at diagnosis and in certain ethnic groups.[13 14]

The risk of IBD is twofold to fourfold higher in Ashkenazi Jews compared with non-Jewish ethnic groups, although the risk among non-European populations has not been well-characterised amid rising global incidence.[14] Numerous genetic associations with IBD have been identified, but as yet there are no genetic tests available to predict whether offspring will develop IBD.

## THE EFFECT OF PREGNANCY ON IBD AND VICE VERSA

Complex interplay between pregnancy, disease activity and medication result in difficulty interpreting pregnancy-related outcomes, with many studies showing conflicting results and little consistency in measured variables.

### The effect of IBD on pregnancy outcomes

Most pregnancies in IBD will have favourable outcomes, with an uncomplicated pregnancy in 80%.[15] Active IBD is a strong predictor of adverse outcomes, including preterm birth, low birth weight and small for gestational age (SGA).[16 17] There is limited evidence regarding the risk of stillbirth although two population studies found an elevated risk of stillbirth in women with CD, particularly those who flared during pregnancy and those with active UC.[18 19] An increased risk of congenital malformations has not been shown in large cohort studies, regardless of disease activity.[16 20]

Other factors affecting outcomes include venous thromboembolism (VTE), active perianal Crohn's and surgical intervention during pregnancy. Pulmonary embolism remains a leading cause of maternal death and is a recognised complication in IBD, especially in those hospitalised with a flare.[21 22] Active perineal disease, in particular perianal fissures, fistulae, abscess and anal stenosis, is associated with up to a 10-fold increased risk of significant perianal damage.[23] Patients with ileal pouch–anal anastomosis (IPAA) have a reported 20%–30% risk of pouch dysfunction during pregnancy, usually resolving post partum.[24] Surgical intervention for IBD in pregnancy is based on the same principles as in non-pregnant patients with IBD. In severely ill patients with active disease despite medical treatment, continued illness is a greater risk to the fetus than surgical intervention.[15] Surgery is reasonably safe in all trimesters but there are some limited series reporting increased spontaneous miscarriage in the first trimester and preterm labour in the third trimester.[25 26] Limited series report increased spontaneous miscarriage in the first trimester and preterm labour in the third trimester after IBD surgery but no increased maternal death or fetal loss. While surgery could be complex, there are no studies assessing outcomes of not doing surgery under the same circumstances and surgery is hence considered relatively safe in all trimesters. Stoma complications may occur with increasing abdominal girth, including displacement, enlargement, retraction, stenosis and prolapse. These complications require coordination with obstetric and colorectal teams.[27] Overall there is an increase in the rate of caesarean section in patients with IBD.[28]

### The effect of pregnancy on IBD outcomes

UC patients in remission have no greater risk of flare during pregnancy than seen in the non-pregnant population.[29] Active disease at the time of conception is associated with a higher risk of activity or flares during the pregnancy and/or postpartum period.[30 31] A higher risk of relapse is seen in UC compared with CD, with a prospective study showing that patients with CD have no increased risk of flare compared with non-pregnant patients.[31 32] Preconception care, including education and counselling, has been shown to reduce the risk of relapse, mainly related to drug adherence and smoking cessation.[9] Pregnancy has been associated with an increased quality of life, and shown to reduce the risk of flares for up to 10 years post partum in UC and CD.[33 34] Management of active IBD in a pregnant patient requires specialist multidisciplinary care in order to minimise adverse outcomes.

## THE SAFETY OF IBD MEDICATION DURING PREGNANCY

### Mesalazine and sulfasalazine

There is no evidence that sulfasalazine or 5-ASA are associated with adverse outcomes in pregnancy.[10 35] In a large primary care cohort, the adjusted OR of a major congenital anomaly associated with 5-aminosalicylate use was 0.82 (95% CI 0.42 to 1.61).[36] All international guidelines recommend that sulfasalazine and mesalazine should be continued in pregnancy.[10 15] Sulfasalazine has antifolate actions so should be supplemented with 5 mg of folic acid for 3 months prior to conception, and for the first 12 weeks of pregnancy, to reduce the risk of neural tube defects.

### Corticosteroids

Rectal, oral and intravenous corticosteroids should not be withheld in pregnancy if indicated. Steroids have been used to treat multiple conditions in pregnancy for many decades. Prednisolone is preferred as it is metabolised by the placenta and only 10% crosses into the fetal circulation.[37] Retrospective studies suggested an association between corticosteroid exposure in the first trimester and an increased risk of cleft lip/

palate.[38 39] However, this link has not been substantiated in prospective case–control or large cohort studies.[40–42] Ban *et al*, using a primary care database, found the adjusted OR for congenital malformations in fetuses exposed to corticosteroids was 0.48 (95% CI 0.15 to 1.50).[36] Corticosteroid use is associated with an increased risk of gestational diabetes mellitus (GDM), elevations in blood pressure, urinary tract and other infections and preterm delivery.[43] Screening for GDM is recommended at 28 weeks gestation, or sooner if there are other risk factors. Pregnant women receiving more than 5 mg prednisolone per day for more than 3 weeks prior to delivery should receive parenteral steroids to cover the physiological stress of delivery as per National Institute for Health and Care Excellence guideline NG211. When corticosteroids to treat IBD are required in the third trimester a focus should be placed on fetal growth monitoring.

### Thiopurines

Azathioprine is low risk during pregnancy and breast feeding.[44 45] The fetal liver does not express inosinate pyrophosphorylase, the enzyme that converts azathioprine to its active metabolites, protecting the fetus from clinical effects of the drug. Studies in women receiving thiopurines for renal disease, IBD and connective tissue disease do not demonstrate an increased risk of prematurity, congenital malformations or childhood neoplasia when data are corrected for underlying maternal disease.[45] A meta-analysis reporting outcomes in pregnancy in patients receiving thiopurines included nine studies (494 exposed patients and 2782 IBD controls). When compared with healthy women, those receiving thiopurines had an increased risk for congenital malformations (RR 1.45; 95% CI 1.07 to 1.96; p=0.02). When compared with IBD controls, there was no increased risk (RR 1.37; 95% CI 0.92 to 2.05; p=0.1).[45] Concerns about neonatal anaemia/cytopenias have not been consistent.[46 47] A small case series is also reassuring about the use of allopurinol when used in conjunction with azathioprine to potentiate the effect of a low dose in women unable to tolerate therapeutic doses.[48]

### Methotrexate

Methotrexate is teratogenic and associated with an increased risk of miscarriage.[49] Counselling regarding contraception is essential when prescribing methotrexate to women of childbearing age. Methotrexate should be discontinued 3 months prior to conception. In one study, the risk of miscarriage in women exposed to methotrexate after conception was 20.7% compared with 8.7% in those exposed preconception and 7.1% in non-autoimmune disease-matched controls. However, if inadvertent conception occurs and the woman does not miscarry then the risk of major congenital malformations is 6.6%, compared with a back ground risk of 3%.[49] Urgent referral to obstetric services for counselling regarding risks and detailed fetal scanning is recommended if women conceive before discontinuing methotrexate.

### Biologic agents

IgG is actively transported across the placenta from the second trimester until delivery, with most antibodies being transferred during the third trimester. This is facilitated by the neonatal Fc receptor on the placenta.[50] Infliximab, adalimumab, golimumab, vedolizumab and ustekinumab are all $IgG_1$ monoclonal antibodies. Certolizumab does not have an Fc portion and has very low levels of passive placental transfer.[51]

### Antitumour necrosis factors: Safety

Most data regarding antitumour necrosis factor (TNF) safety in pregnancy come from studies in patients treated with infliximab and adalimumab. The use of anti-TNFs in the third trimester results in fetal exposure. Anti-TNF cord levels correlate with gestational week at the last drug administration with fetal concentrations often exceeding maternal levels at birth.[51–53] Clearance of anti-TNFs can take 6 months or more, with slower clearance for infliximab than adalimumab, although infliximab has been detected up to 12 months after birth.[51 52] Anti-TNF therapy has no negative impact on pregnancy or newborn outcomes. A meta-analysis and systematic review, assessing >300 and >1500 anti-TNF exposed pregnancies, respectively, showed no increased risk of unfavourable pregnancy outcomes, miscarriage, preterm birth, low birthweight or congenital malformations.[54 55] Studies have found no harmful effect of maternal certolizumab or golimumab exposure on pregnancy outcomes.[56 57]

### Third trimester cessation: risks versus benefits

Uncontrolled IBD is associated with poor pregnancy outcomes. One-third of non-pregnant patients in sustained remission flare within 12 months of withdrawal of anti-TNF therapy.[58] Data in pregnant women are very similar. Active disease and relapse rates are higher in pregnant and peripartum women who discontinue anti-TNFs (36%–39%) compared with in women continuing anti-TNF treatment throughout pregnancy (25%–26%).[59 60] Discontinuation may also lead to immunogenicity.[58] The EVASION cohort study reported pregnancy and neonatal outcomes of 1457 anti-TNF-treated women, demonstrating that anti-TNF exposed mothers had higher rates of infection. Stopping therapy prior to 24 weeks gestation led to a higher rate of disease flares in the mother with no benefit to the infant compared with continued therapy. EVASION and other recent large observational and cohort studies show no increased short-term or long-term severe infection in anti-TNF exposed children.[61–63] Anti-TNF and thiopurine combination therapy carries increased risk of benign infant infections compared

**Box 1 Summary of current guidance third trimester cessation**

All major European and North American guidance considers antitumour necrosis factors (TNFs) of low risk in pregnancy.[10 15 106]

The European Crohns and Colitis Organisation (ECCO) 2015 consensus advise that 'to minimise neonatal anti-TNF exposure, discontinuation of a-TNF can be considered for women in sustained remission, if deemed appropriate by the treating clinician, around week 24–26 weeks gestation'.[15]

Putting more emphasis on maternal relapse risk, the 2016[10] consensus strongly recommend continuation of anti-TNF treatment throughout pregnancy stating that 'cessation should only be considered in patients at low risk of relapse'.[10]

Taking into consideration the newer, larger cohort studies showing no increased infection risk and confirming no adverse pregnancy or neonatal outcomes[61–63] the American Gastroenterology Association (AGA) inflammatory bowel disease parenthood working group 2019 recommends continuation of anti-TNFs throughout pregnancy, without interruption in the third trimester, only adjusting last dose timings to achieve the lowest possible trough levels during delivery, with final infliximab infusion given 6–10 weeks before estimated date of confinement (EDC), final adalimumab injection 2–3 weeks before EDC (1–2 weeks if weekly dosing) and final golimumab injection given 4–6 weeks before EDC.[106]

with anti-TNF monotherapy although this is not consistently reported.[52 55]

### Vedolizumab

Animal studies show no adverse effects from vedolizumab at supraphysiological doses on prenatal or postnatal development.[64] The limited human data available are mainly from abstracts and small cohorts. Vedolizumab cord levels are lower than maternal levels.[65 66] Retrospective study,[67] small prospective study[68] and pregnancy data collected during the clinical trials programme and from postmarketing reports[69] did not identify safety concerns for pregnancy outcomes in females directly or indirectly exposed to vedolizumab. The current data do not allow for general recommendations, and advice for any individual patient needs to carefully consider potential risks and benefits.[70]

### Ustekinumab

In animal studies exposure to ustekinumab had no adverse effects on prenatal and postnatal development.[71] In a case report, cord blood ustekinumab levels were markedly higher than the measured maternal serum drug level.[72] Data on the effects of ustekinumab in pregnancy are limited to isolated case reports, mainly of patients treated for psoriasis or psoriatic arthritis.[73] Notably ustekinumab for these indications is given at a lower dose than in IBD. Twenty-six maternal exposures in the CD clinical trials programme were reported, with drug stopped when pregnancy was confirmed.[74] From these reports, ustekinumab does not appear to negatively impact pregnancy outcomes but more data are needed. Advice for any individual patient needs to carefully consider potential risks and benefits.

### Tofacitinib

Tofacitinib is a small molecule that likely can cross the placenta. At doses exceeding human dose, it has demonstrated teratogenicity in animal models.[75] There are a limited number of maternal and paternal exposures from clinical trials programmes and postapproval safety studies with no increased risk identified compared with general population and in patients treated with biologic therapies.[76 77] The current manufacturer recommendation is to use contraception during treatment with tofacitinib and 4–6 weeks after the last dose.

## INVESTIGATING IBD DURING PREGNANCY

When managing IBD during pregnancy clinicians need to consider changes in normal values and risk of radiation and endoscopy.

### Blood markers

Pregnancy induces haemodilution which results in a fall in serum albumin by 1 mg/dL towards the end of the first trimester. Pregnancy also increases the Erythrocyte sedimentation rate (ESR) from rising fibrinogen levels, which may increase 2–3 times the upper limit of normal by the end of the first trimester.[78] As such, a fall in albumin or elevated ESR should not be directly attributed to IBD activity and should be interpreted in context and with the use of other clinical and biochemical parameters.[78] C reactive protein (CRP) is a useful biomarker of inflammation and may reflect IBD activity although it may also be influenced by obstetric conditions.[78 79] A study examining the association of an elevated CRP with IBD activity in pregnancy suggested that CRP is useful for assessing IBD disease activity in the early trimesters of pregnancy but may not accurately reflect the disease activity in later trimesters.[80]

### Faecal calprotectin

Faecal calprotectin (FCP) is a useful surrogate marker of gut inflammation with a good correlation with endoscopic inflammation in CD and UC.[81 82] Recent studies assessing its utility in IBD during the pregnancy have shown conflicting results with some studies showing good correlation between FCP and non-invasive disease scores and others suggesting that it may be a poor predictor of relapse.[83–85] In the absence of a clear consensus and limited data, clinicians need to be aware of potential limitations of the use of FCP during the pregnancy.

### Endoscopy

Endoscopy is generally safe in pregnancy and may be performed if it alters management decisions and is in the best interests of the mother.[10 15 86 87] The major theoretical concerns with endoscopy in pregnancy are maternal and fetal hypoxia, aspiration, teratogenicity of medications such as colon-cleansing agents, sedatives and antibiotics.[10 15 86 87] A recent systematic review reported outcomes of 100 lower gastrointestinal endoscopies (sigmoidoscopy and colonoscopy) performed in pregnancy with six adverse events related to endoscopy, and concluded that lower gastrointestinal endoscopy is likely safe in all three trimesters.[88] A subsequent prospective study of 42 pregnant patients undergoing lower gastrointestinal endoscopy reported no adverse outcomes relating to endoscopy.

With regard to sedation, a meta-analysis of over 1 million pregnancies suggested that benzodiazepines do not appear to pose teratogenic risk although case–control studies suggest a twofold increased risk of cleft palate.[89] Single-dose administration of a sedative and analgesic is very unlikely to result in harm. Where appropriate unsedated endoscopy is preferred. Midazolam is the preferred sedative.[10 15] Although it crosses the placenta fetal levels increase by one to two thirds of maternal serum levels.[15] Midazolam is excreted through breast milk so breast feeding should be withheld for 4 hours after administration.[90]

Fentanyl (commonly administered in labour) is also excreted through breast milk, but with low bioavailability it is acceptable to breastfeed after administration.[90] Case reports on neonatal respiratory depression, muscle rigidity[91] and opioid withdrawal[92] have been noted. A joint statement from the American Society of Anaesthesiologists and the American College of Obstetrics and Gynaecology states that none of the currently used anaesthetic agents, when used in standard concentrations at any gestational age, have been shown to have any teratogenic effect in humans.[93] Polyethylene glycol electrolyte cathartics have not been studied in pregnancy. Sodium phosphate-based preparations may cause fluid and electrolyte imbalance and should be used with caution.[10 15 86 87]

Whenever possible endoscopy should be performed in the second trimester of pregnancy. Patients should be carefully placed in a left pelvic tilt or left lateral position to avoid vena caval or aortic compression, which may lead to maternal hypotension and reduce placental perfusion.[10 15 86 87] Flexible sigmoidoscopy is preferred without sedation or bowel preparation, throughout gestation.[10 15 86 87]

### Radiological investigations

Radiation exposure in pregnant women with IBD should be avoided, but performed in cases of diagnostic necessity when the risk of misdiagnosis outweighs the potential risk.[10 86 87 94] Abdominal plain films and CT are generally avoided due to exposure to ionising radiation. Abdominal X-ray results in exposure to 0.1 rad of radiation.[95] The maximal risk of 1 rad exposure (0.003%) is thousands of times smaller than the risk of spontaneous miscarriage, malformations or genetic disease.[96] Likewise, CT imaging is also acceptable if absolutely necessary with a single procedure unlikely to result in exposure of more than 50 mGy and adverse effects to the fetus unlikely to occur at a cumulative radiation exposure of less than 100 mGy.[10 94]

Ultrasound and MRI have the advantage of not using ionising radiation. A meta-analysis and systematic review showed similar diagnostic accuracy between ultrasound, CT and MRI.[97 98] Contrast-enhanced ultrasound is an emerging technique to evaluate disease activity, differentiate between inflammatory and fibrotic small bowel strictures and assessment of response to therapy.[99] Sensitivity in pregnancy needs to be investigated. The practical application of ultrasound after 28–30 weeks may be limited by the fetus obscuring views.

MRI does not pose the risks of ionising radiation but its safety has not been established with concerns around a static magnetic field, tissue heating effects and high acoustic noise levels.[94] There are concerns around the use of gadolinium as contrast medium. Gadolinium chelates may accumulate in amniotic fluid with the potential for the dissociation of the toxic-free gadolinium ion. This may enter the fetal circulation possibly conferring risk to the fetus.[100] No well controlled study of the teratogenic effects of these media has been performed and the fetal risk is unknown.[100] The consensus is that gadolinium should be avoided during the first trimester and only used in a pregnant woman if it significantly improves diagnostic performance to improve fetal or maternal outcome, outweighing the possible, but unknown risk of free gadolinium ions.[10 87]

## OBSTETRIC CONSIDERATIONS IN ANTENATAL CARE

At booking comorbidities and risk factors will be taken into account when planning care for the remainder of her pregnancy. Prevention and screening strategies need to be considered to mitigate risks. Obstetric factors that will influence growth include age, smoking, previous SGA babies and previous poor pregnancy outcomes such as stillbirth.[101] Other medical factors will also increase risk, including medical disorders such as hypertension and autoimmune disorders. Factors that will influence risk of preterm birth include previous cervical surgery, history of previous preterm births.[102]

In accordance with guidance for any pregnant woman consideration should be given to pre-eclampsia prophylaxis with aspirin 75–150 mg ideally at 12 weeks gestation but at least by 16 weeks gestation.[103]

Women should have symphysial-fundal height plotted against a growth chart to assess fetal growth. If there are concerns formal fetal scans for growth should be initiated. There are screening strategies to assess risks of growth restriction that may include uterine artery Doppler in mid-trimester.[101] Frequency of growth scans can be determined by risk stratification. For those at high risk, including active IBD, growth velocity should be assessed at a minimum of two growth scans, for example, 30 and 36 weeks.[101] Growth scans may need to be initiated at earlier gestations depending on other risk factors. For those with well-controlled IBD growth scans are not essential. Each obstetric unit needs to consider risk stratification and frequency of growth scanning taking into account availability of appropriately trained sonographers, obstetric staff and local resources. Strategies for prevention of preterm birth will include consideration of cervical scanning, especially in women with a history of preterm birth before 32 weeks.

Patients with active IBD are at higher risk of VTE and pregnancy further increases this risk.[104] The Royal College of Obstetrics and Gynaecology guidelines recommend that patients with significant risk factors should be offered prophylaxis against VTE.[105]

## BIRTH

In the majority of pregnant women with IBD, their mode of birth should be discussed according to usual obstetric indications.[15] There are a number of instances when IBD-related factors will influence the decision. Women with IBD are concerned regarding their long-term anal sphincter function and the effect of the birth on their IBD. Women with active perianal CD, including anorectal fistulae/abscesses, rectovaginal fistulae, anal fissures or anal stenosis present at the time of birth, should be recommended to have an elective caesarean section.[10 15] A concern for women with active perianal disease is that wound healing in an inflamed or infected perineum will be compromised.

For pregnant women who have undergone IPAA surgery, recent guidance suggests this is a relative indication for an elective caesarean and the risks and benefits of each mode of delivery need to be carefully considered.[10 15 106] Women who have an IPAA may have borderline continence to begin with, and depend on an intact sphincter and pelvic floor function to maintain faecal continence. A study of 232 women who had vaginal births after IPAA surgery found no differences in functional outcomes, but data in other studies are conflicting.[107 108] In patients for whom the need for pouch surgery in the future is high, the decision regarding mode of birth should be made on an individual basis after counselling by a maternal medicine obstetrician. If a caesarean section is needed, a planned procedure is preferred over an emergency procedure.

A stoma does not preclude vaginal delivery. If patients with an ostomy require a caesarean section for obstetric reasons, then covering the ostomy with sterile gauze should be adequate to protect the operative field and should not affect the operation.[27 109] Instrumental deliveries (forceps or vacuum) and episiotomies, for women with IBD without active perianal disease, should be reserved for the usual obstetric indications. It is important not to forget the increased risk of VTE in pregnant patients with IBD, especially during a disease flare, in the postpartum period and after a caesarean section.

A multidisciplinary team approach to looking after these women throughout their pregnancy and around the time of delivery should be encouraged, with the patient and her wishes kept at the centre of the care throughout. Gastroenterologists should consider that caesarean sections are major abdominal surgeries with a risk of VTE, wound healing problems and increased risk of adverse pregnancy outcomes, including stillbirth in subsequent pregnancies.[104 110]

## INFANT FEEDING

The exposure of the infant to any drug can be completely avoided by bottle feeding. The main choice depends on the potential benefits of breast milk over formula feeding compared with any risk due from drug exposure. The key benefits of breast milk over formula feeding include complete and tailored nutrition including maternal immunoglobulins, which may in turn positively affect the infant's immune system.[111] Breast milk feeding may protect against the development of IBD in the infant although data stem from non-IBD mothers and it is unclear whether these results apply to a more high-risk group with genetic predisposition. A meta-analysis of 17 studies reported a lower risk with ORs of 0.67 (95% CI 0.52 to 0.86) for CD and 0.77 (95% CI 0.61 to 0.96) for UC.[112] Breast milk feeding rates in IBD are lower than the general population, which may relate to unwarranted fears over medication effects on the infant.[113] In a survey 56% of women with IBD believed that all IBD medication should be avoided while breast milk feeding.[114] While many IBD medications can be detected in breast milk, the level is frequently considered too low to exert biological effects in the infant. Studies examining concentrations of aminosalicylates in breast milk or infant's blood are reassuring and[115] breast milk feeding while exposed to aminosalicylates is endorsed by ECCO guidance.[116]

As corticosteroids are found in low concentrations in breast milk ECCO guidelines classify these as low risk and suggest leaving 4 hours between medication intake and breast milk feeding.[117 118] The suggested gap may, however, not be practical in mothers using exclusive breast feeding. Thiopurines are of low risk in breast milk feeding with extremely low or even undetectable

metabolite levels in breast milk[119] and undetectable levels in breast milk fed infants.[120]

Biologics can be found in very low concentrations in breast milk as demonstrated for adalimumab and infliximab.[121 122] Oral ingestion of biologics in the infant is unlikely to lead to significant systemic absorption and ECCO guidance classifies anti-TNF biological agents as probably safe.[15] There is little data on newer biologics (vedolizumab, ustekinumab) but similar principle to anti-TNFs likely apply. Methotrexate is considered contraindicated and should be avoided.[123] Sufficient data for a recommendation on tofacitinib are lacking.

## VACCINATION

Neonatal vaccinations are essential for the prevention of a number of serious and potentially fatal infections.[124] Anti-TNF's may be detected in infants up to 6 months after birth.[10 15 86 87] In utero exposure of biological therapy has not been shown to affect antibody titre concentrations against inactivated (non-live) vaccinations which should be given on schedule.[124 125] If the mother has been exposed to biological therapy (with the exception of certolizumab) during the third trimester of pregnancy, live vaccines including Bacille Calmette-Guérin, rotavirus, oral polio (but not intramuscular), measles, mumps, rubella and varicella vaccine should not be administered until at least 6 months after birth.[10 15 86 87] The Pregnancy in IBD and neonatal outcomes (PIANO) registry did not find any risk of serious infections in children exposed to anti-TNF therapy in utero, at 12 months follow-up.[126] Reassurance from such data notwithstanding, the potential for serious harm and relative dearth of data have steered consensus opinion to defer live vaccinations until after 6 months of age. The rotavirus (live) vaccine is administered in two doses, at 2 and 4 months. To be effective the vaccine needs to be administered by 15 weeks of age, so infants exposed to anti-TNF in utero should not be administered the rotavirus at all.[86 87] Other live vaccines, namely varicella, measles, mumps and rubella are administered at 1 year of age and are acceptable to administer even while the infant is breast feeding.[87]

With respect to non-anti TNF biologics and tofacitinib, no evidence-based recommendations can be made at the present time.

## SERVICE SET UP

Traditionally pregnant patients with IBD received separate care from IBD and obstetric services with great variation in care and service set up. Due to the complexity of caring for pregnant patients with IBD, the care needs to be coordinated between services and provision by staff with relevant experience and expertise of IBD and pregnancy. Specific IBD antenatal services can facilitate coordinated high quality care.[9]

As patients with IBD are at a higher risk of adverse pregnancy outcomes an assessment by a consultant obstetrician is preferable with subsequent follow-up determined by a risk assessment at the first consultation. IBD disease activity should be monitored actively throughout pregnancy by a suitably experienced member of the IBD team.

## CONCLUSION

Pregnant women with IBD require specialist joined-up care for a complex disease to avoid the adverse outcomes associated with active disease. With the exception of Methotrexate and tofacitinib all IBD medications provide more benefit than risk in pregnancy especially give the risk associated with active disease. Most women can have a vaginal delivery and breast feeding is generally encouraged on most IBD medications.

It is vital to ensure continuity of care for the IBD aspects post partum to allow for recommencing medication where required and potential flare management.

**Author affiliations**
[1]Leeds Gastroenterology Institute, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[2]Obstetric Medicine, Guy's and Saint Thomas' Hospitals NHS Trust, London, UK
[3]Gastroenterology, United Hospitals Bristol, Bristol, UK
[4]Gastroenterology, Royal Bolton Foundation NHS Trust, Bolton, UK
[5]Section of iBD- Division of Gastroenterology, The Pennine Acute Hospitals NHS Trust, Manchester, UK
[6]Gastroenterology, Manchester Academic Health Science Centre, Manchester, UK
[7]Gastroenterology, NHS Greater Glasgow and Clyde North Glasgow University Hospitals Division, Glasgow, UK
[8]Obstetrics, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK
[9]Gastroenterology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[10]Obstetrics, United Hospitals Bristol, Bristol, UK
[11]Obstetrics, Royal Bolton Foundation NHS Trust, Bolton, UK
[12]Gastroenterology, King's College Hospital NHS Foundation Trust, London, UK
[13]Gastroenterology, Barts and The London NHS Trust, London, UK
[14]Obstetrics, Leeds Teaching Hospitals NHS Trust, Leeds, UK

**Contributors** CPS, CN-P, AF, VH, JL, LS, MS, RN, MG, AK, AM, KM, AK, KBK and TG all wrote parts of the manuscript and critically reviewed the draft manuscript. CPS joined the parts together and wrote abstract and conclusion. CPS, CN-P, AF, VH, JL, LS, MS, RN, MG, AK, AM, KM, AK, KBK and TG all critically reviewed the draft and the final manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** CPS has received unrestricted research grants from Warner Chilcott, Janssen and AbbVie, has provided consultancy to Warner Chilcott, Falk, AbbVie, Takeda, Fresenius Kabi and Janssen, and had speaker arrangements with Warner Chilcott, Falk, AbbVie, MSD, Pfizer and Takeda. CN-P had speaker arrangements with Falk, UCB, Sanofi, Alliance and Alexion. KBK has provided consultancy to Amgen and PredictImmune, and had speaker arrangements with Janssen and Takeda. JL has received research grants from Takeda, consultancy and speaker fees from Abbvie, Janssen, MSD, Pfizer and Takeda. AK has provided consultancy to Abbvie, and had speaker arrangements with Pfizer, Janssen and Takeda.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**ORCID iDs**
Christian P Selinger http://orcid.org/0000-0003-2022-5859
Andrew King http://orcid.org/0000-0002-5002-4751

## REFERENCES

1 Hudson M, Flett G, Sinclair TS, *et al*. Fertility and pregnancy in inflammatory bowel disease. *Int J Gynaecol Obstet* 1997;58:229–37.
2 Dubinsky M, Abraham B, Mahadevan U. Management of the pregnant IBD patient. *Inflamm Bowel Dis* 2008;14:1736–50.
3 Ban L, Tata LJ, Humes DJ, *et al*. Decreased fertility rates in 9639 women diagnosed with inflammatory bowel disease: a United Kingdom population-based cohort study. *Aliment Pharmacol Ther* 2015;42:855–66.
4 Bartels SAL, D'Hoore A, Cuesta MA, *et al*. Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy: a cross-sectional study. *Ann Surg* 2012;256:1045–8.
5 Beyer-Berjot L, Maggiori L, Birnbaum D, *et al*. A total laparoscopic approach reduces the infertility rate after ileal pouch-anal anastomosis: a 2-center study. *Ann Surg* 2013;258:275–82.
6 Cornish JA, Tan E, Teare J, *et al*. The effect of restorative proctocolectomy on sexual function, urinary function, fertility, pregnancy and delivery: a systematic review. *Dis Colon Rectum* 2007;50:1128–38.
7 Waljee A, Waljee J, Morris AM, *et al*. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. *Gut* 2006;55:1575–80.
8 Selinger CP, Ghorayeb J, Madill A. What factors might drive voluntary childlessness (vc) in women with IBD? does IBD-specific pregnancy-related knowledge matter? *J Crohns Colitis* 2016;10:1151–8.
9 de Lima A, Zelinkova Z, Mulders AGMGJ, *et al*. Preconception care reduces relapse of inflammatory bowel disease during pregnancy. *Clin Gastroenterol Hepatol* 2016;14:1285–92.
10 Nguyen GC, Seow CH, Maxwell C, *et al*. The Toronto consensus statements for the management of inflammatory bowel disease in pregnancy. *Gastroenterology* 2016;150:734–57.
11 Mountifield R, Andrews JM, Bampton P. It is worth the effort: patient knowledge of reproductive aspects of inflammatory bowel disease improves dramatically after a single group education session. *J Crohns Colitis* 2014;8:796–801.
12 Moller FT, Andersen V, Wohlfahrt J, *et al*. Familial risk of inflammatory bowel disease: a population-based cohort study 1977-2011. *Am J Gastroenterol* 2015;110:564–71.
13 Bennett RA, Rubin PH, Present DH. Frequency of inflammatory bowel disease in offspring of couples both presenting with inflammatory bowel disease. *Gastroenterology* 1991;100:1638–43.
14 Yan B, Panaccione R, Sutherland L. I am Jewish: what is my risk of developing Crohn's disease? *Inflamm Bowel Dis* 2008;14 Suppl 2:S26–7.
15 van der Woude CJ, Ardizzone S, Bengtson MB, *et al*. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. *J Crohns Colitis* 2015;9:107–24.
16 Bortoli A, Pedersen N, Duricova D, *et al*. Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003-2006. *Aliment Pharmacol Ther* 2011;34:724–34.
17 Molnár T, Farkas K, Nagy F, *et al*. Pregnancy outcome in patients with inflammatory bowel disease according to the activity of the disease and the medical treatment: a case–control study. *Scand J Gastroenterol* 2010;45:1302–6.
18 Ujihara M, Ando T, Ishiguro K, *et al*. Importance of appropriate pharmaceutical management in pregnant women with ulcerative colitis. *BMC Res Notes* 2013;6:210.
19 Bröms G, Granath F, Linder M, *et al*. Birth outcomes in women with inflammatory bowel disease: effects of disease activity and drug exposure. *Inflamm Bowel Dis* 2014;20:1091–8.
20 Stephansson O, Larsson H, Pedersen L, *et al*. Congenital abnormalities and other birth outcomes in children born to women with ulcerative colitis in Denmark and Sweden. *Inflamm Bowel Dis* 2011;17:795–801.
21 Novacek G, Weltermann A, Sobala A, *et al*. Inflammatory bowel disease is a risk factor for recurrent venous thromboembolism. *Gastroenterology* 2010;139:779–87. 87 e1.
22 RCoOa G. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top guideline No. 37A 2015.
23 Hatch Q, Champagne BJ, Maykel JA, *et al*. Crohn's disease and pregnancy: the impact of perianal disease on delivery methods and complications. *Dis Colon Rectum* 2014;57:174–8.
24 Hahnloser D, Pemberton JH, Wolff BG, *et al*. Pregnancy and delivery before and after ileal pouch-anal anastomosis for inflammatory bowel disease: immediate and long-term consequences and outcomes. *Diseases of the Colon & Rectum* 2004;47:1127–35.
25 Killeen S, Gunn J, Hartley J. Surgical management of complicated and medically refractory inflammatory bowel disease during pregnancy. *Colorectal Dis* 2017;19:123–38.
26 Visser BC, Glasgow RE, Mulvihill KK, *et al*. Safety and timing of nonobstetric abdominal surgery in pregnancy. *Dig Surg* 2001;18:409–17.
27 Aukamp V, Sredl D. Collaborative care management for a pregnant woman with an ostomy. *Complementary Therapies in Nursing and Midwifery* 2004;10:5–12.
28 Nguyen GC, Boudreau H, Harris ML, *et al*. Outcomes of obstetric hospitalizations among women with inflammatory bowel disease in the United States. *Clin Gastroenterol Hepatol* 2009;7:329–34.
29 Nielsen OH, Andreasson B, Bondesen S, *et al*. Pregnancy in ulcerative colitis. *Scand J Gastroenterol* 1983;18:735–42.
30 Abhyankar A, Ham M, Moss AC. Meta-Analysis: the impact of disease activity at conception on disease activity during pregnancy in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;38:460–6.
31 Pedersen N, Bortoli A, Duricova D, *et al*. The course of inflammatory bowel disease during pregnancy and postpartum: a prospective European ECCO-EpiCom study of 209 pregnant women. *Aliment Pharmacol Ther* 2013;38:501–12.
32 de Lima-Karagiannis A, Zelinkova-Detkova Z, van der Woude CJ. The effects of active IBD during pregnancy in the era of novel IBD therapies. *Am J Gastroenterol* 2016;111:1305–12.
33 Riis L, Vind I, Politi P, *et al*. Does pregnancy change the disease course? A study in a European cohort of patients with inflammatory bowel disease. *Am J Gastroenterol* 2006;101:1539–45.
34 Ananthakrishnan AN, Zadvornova Y, Naik AS, *et al*. Impact of pregnancy on health-related quality of life of patients with inflammatory bowel disease. *J Dig Dis* 2012;13:472–7.
35 Rahimi R, Nikfar S, Rezaie A, *et al*. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. *Reprod Toxicol* 2008;25:271–5.

36 Ban L, Tata LJ, Fiaschi L, *et al*. Limited risks of major congenital anomalies in children of mothers with IBD and effects of medications. *Gastroenterology* 2014;146:76–84.
37 Benediktsson R, Calder AA, Edwards CRW, *et al*. Placental 11β-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. *Clin Endocrinol* 1997;46:161–6.
38 Park-Wyllie L, Mazzotta P, Pastuszak A, *et al*. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000;62:385–92.
39 Carmichael SL, Shaw GM, Ma C, *et al*. Maternal corticosteroid use and orofacial clefts. *Am J Obstet Gynecol* 2007;197:585.e1–7. discussion 683-4, e1-7.
40 Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. *Br J Obstet Gynaecol* 1998;105:322–7.
41 Tata LJ, Lewis SA, McKeever TM, *et al*. Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study. *Thorax* 2008;63:981–7.
42 Hviid A, Molgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. *Can Med Assoc J* 2011;183:796–804.
43 Laskin CA, Bombardier C, Hannah ME, *et al*. Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. *N Engl J Med* 1997;337:148–54.
44 Cleary BJ, Källén B. Early pregnancy azathioprine use and pregnancy outcomes. *Birth Defects Res A Clin Mol Teratol* 2009;85:647–54.
45 Hutson JR, Matlow JN, Moretti ME, *et al*. The fetal safety of thiopurines for the treatment of inflammatory bowel disease in pregnancy. *J Obstet Gynaecol* 2013;33:1–8.
46 Jharap B, de Boer NKH, Stokkers P, *et al*. Intrauterine exposure and pharmacology of conventional thiopurine therapy in pregnant patients with inflammatory bowel disease. *Gut* 2014;63:451–7.
47 Wiles K, Chandiramani M, Jiwani S, *et al*. A retrospective study of anaemia in neonates exposed to thiopurines in utero. *Gut* 2016;65:886–7.
48 Sheikh M, Nelson-Piercy C, Duley J, *et al*. Successful pregnancies with Thiopurine-Allopurinol Co-Therapy for inflammatory bowel disease. *ECCOJC* 2015;9:680–4.
49 Weber-Schoendorfer C, Chambers C, Wacker E, *et al*. Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy: a prospective multicenter cohort study. *Arthritis Rheumatol* 2014;66:1101–10.
50 Simister N. Placental transport of immunoglobulin G. *Vaccine* 2003;21:3365–9.
51 Mahadevan U, Wolf DC, Dubinsky M, *et al*. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013;11:quiz e24:286–92.
52 Julsgaard M, Christensen LA, Gibson PR, *et al*. Concentrations of Adalimumab and Infliximab in Mothers and Newborns, and Effects on Infection. *Gastroenterology* 2016;151:110–9.
53 Bortlik M, Machkova N, Duricova D, *et al*. Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF-α therapy during pregnancy: three-center study. *Scand J Gastroenterol* 2013;48:951–8.
54 Narula N, Al-Dabbagh R, Dhillon A, *et al*. Anti-TNFα therapies are safe during pregnancy in women with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2014;20:1862–9.
55 Nielsen OH, Loftus EV, Jess T. Safety of TNF-α inhibitors during IBD pregnancy: a systematic review. *BMC Med* 2013;11:174.
56 Clowse MEB, Wolf DC, Förger F, *et al*. Pregnancy outcomes in subjects exposed to Certolizumab pegol. *J Rheumatol* 2015;42:2270–8.
57 Wieringa JW, Driessen GJ, Van Der Woude CJ. Pregnant women with inflammatory bowel disease: the effects of biologicals on pregnancy, outcome of infants, and the developing immune system. *Expert Rev Gastroenterol Hepatol* 2018;12:811–8.
58 Kennedy NA, Warner B, Johnston EL, *et al*. Relapse after withdrawal from anti-TNF therapy for inflammatory bowel disease: an observational study, plus systematic review and meta-analysis. *Aliment Pharmacol Ther* 2016;43:910–23.
59 Seirafi M, de Vroey B, Amiot A, *et al*. Factors associated with pregnancy outcome in anti-TNF treated women with inflammatory bowel disease. *Aliment Pharmacol Ther* 2014;40:363–73.
60 Casanova MJ, Chaparro M, Domènech E, *et al*. Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease. *Am J Gastroenterol* 2013;108:433–40.
61 Luu M, Benzenine E, Doret M, *et al*. Continuous Anti-TNFα use throughout pregnancy: possible complications for the mother but not for the fetus. A retrospective cohort on the French National health insurance database (evasion). *Am J Gastroenterol* 2018;113:1669–77.
62 Lichtenstein GR, Feagan BG, Mahadevan U, *et al*. Pregnancy outcomes reported during the 13-year treat registry: a descriptive report. *Am J Gastroenterol* 2018;113:1678–88.
63 Chaparro M, Verreth A, Lobaton T, *et al*. Long-Term safety of in utero exposure to Anti-TNFα drugs for the treatment of inflammatory bowel disease: results from the multicenter European TEDDY study. *Am J Gastroenterol* 2018;113:396–403.
64 Crawford D, Friedman M. Evaluation of the Developmental Toxicity of Vedolizumab, an $\alpha_4\beta_7$ Receptor Antagonist, in Rabbit and Nonhuman Primate. *Int J Toxicol* 2019;38:395–404.
65 Julsgaard M, Kjeldsen J, Brock B, *et al*. Letter: vedolizumab drug levels in cord and maternal blood in women with inflammatory bowel disease. *Aliment Pharmacol Ther* 2018;48:386–8.
66 Mahadevan U, Vermeire S, Lasch K, *et al*. Letter: vedolizumab drug levels in cord and maternal blood in women with inflammatory bowel disease-authors' reply. *Aliment Pharmacol Ther* 2018;48:388–9.
67 Moens A, van Hoeve K, Humblet E, *et al*. Outcome of pregnancies in female patients with inflammatory bowel diseases treated with Vedolizumab. *J Crohns Colitis* 2019;13:12–18.
68 Bar-Gil Shitrit A, Ben Ya'acov A, Livovsky DM, *et al*. Exposure to Vedolizumab in IBD pregnant women appears of low risk for mother and neonate: a first prospective comparison study. *Am J Gastroenterol* 2019;114:1172–5.
69 Mahadevan U, Vermeire S, Lasch K, *et al*. Vedolizumab exposure in pregnancy: outcomes from clinical studies in inflammatory bowel disease. *Aliment Pharmacol Ther* 2017;45:941–50.
70 Moens A, van der Woude CJ, Julsgaard M, *et al*. Pregnancy outcomes in inflammatory bowel disease patients treated with vedolizumab, anti-TNF or conventional therapy: results of the European CONCEIVE study. *Aliment Pharmacol Ther* 2020;51:129-138.
71 Martin PL, Sachs C, Imai N, *et al*. Development in the cynomolgus macaque following administration of ustekinumab, a human anti-IL-12/23p40 monoclonal antibody, during pregnancy and lactation. *Birth Defects Res B Dev Reprod Toxicol* 2010;89:351–63.
72 Klenske E, Osaba L, Nagore D, *et al*. Drug levels in the maternal serum, cord blood and breast milk of a

Ustekinumab-Treated patient with Crohn's disease. *J Crohns Colitis* 2019;13:267–9.
73 Gerosa M, Argolini LM, Artusi C, *et al*. The use of biologics and small molecules in pregnant patients with rheumatic diseases. *Expert Rev Clin Pharmacol* 2018;11:987–98.
74 Al see. A109 abtract. *Journal of the Canadian Association of Gastroenterology*;1:166.
75 Picardo S, Seow CH. A pharmacological approach to managing inflammatory bowel disease during conception, pregnancy and breastfeeding: biologic and oral small molecule therapy. *Drugs* 2019;79:1053–63.
76 Mahadevan U, Dubinsky MC, Su C, *et al*. Outcomes of pregnancies with Maternal/Paternal exposure in the tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis* 2018;24:2494–500.
77 Clowse ME, Feldman SR, Isaacs JD, *et al*. Pregnancy outcomes in the tofacitinib safety databases for rheumatoid arthritis and psoriasis. *Drug Saf* 2016;39:755–62.
78 Tandon P, Leung K, Yusuf A, *et al*. Noninvasive methods for assessing inflammatory bowel disease activity in pregnancy. *J Clin Gastroenterol* 2019;53:574–81.
79 Watts DH, Krohn MA, Wener MH, *et al*. C-Reactive protein in normal pregnancy. *Obstet Gynecol* 1991;77:176–80.
80 J FR B, Ambrosio L, Kroeker KI, *et al*. P247 C-Reactive protein is elevated with clinical disease activity during pregnancy in women with inflammatory bowel disease. *J Crohns Colitis* 2015
81 Sipponen T, Karkkainen P, Savilahti E, *et al*. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. *Aliment Pharmacol Ther* 2008;28:1221–9.
82 Schoepfer AM, Beglinger C, Straumann A, *et al*. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflamm Bowel Dis* 2009;15:1851–8.
83 Huang V, Bal J, Foshaug R, *et al*. *Fecal calprotectin is elevated with clinical disease activity during pregnancy in women with inflammatory bowel disease European Crohns and colitis organisation*. Barcelona, 2015.
84 Shitrit A, Granovsky- Grisaru S, Adar T, *et al*. *Limitations in using fecal calprotectin as a biomarker of IBD disease activity during pregnancy European Crohns and colitis organisation*. Barcelona, 2015.
85 dLA KSL, Oorschot V V, Van Der Woude CJ. Fecal Calprotectine is a poor predictor of IBD relapse during pregnancy. *Gastroenterology* 2016;150:S556.
86 Lamb CA, Kennedy NA, Raine T, *et al*. British Society of gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;68:s1–106.
87 Mahadevan U, Robinson C, Bernasko N, *et al*. Inflammatory bowel disease in pregnancy clinical care pathway: a report from the American gastroenterological association IBD parenthood project Working group. *Inflamm Bowel Dis* 2019;25:627–41.
88 De Lima A, Galjart B, Wisse PHA, *et al*. Does lower gastrointestinal endoscopy during pregnancy pose a risk for mother and child? – a systematic review. *BMC Gastroenterol* 2015;15:15.
89 Enato E, Moretti M, Koren G. The fetal safety of benzodiazepines: an updated meta-analysis. *J Obstet Gynaecol Can* 2011;33:46–8.
90 Nitsun M, Szokol J, Saleh H, *et al*. Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006;79:549–57.
91 Lindemann R. Respiratory muscle rigidity in a preterm infant after use of fentanyl during caesarean section. *Eur J Pediatr* 1998;157:1012–3.
92 Regan J, Chambers F, Gorman W, *et al*. Neonatal abstinence syndrome due to prolonged administration of fentanyl in pregnancy. *BJOG* 2000;107:570–2.
93 Anesthesiologists CoOPASo. Nonobstetric surgery during pregnancy 2019;775.
94 Tremblay E, Thérasse E, Thomassin-Naggara I, *et al*. Quality initiatives: guidelines for use of medical imaging during pregnancy and lactation. *RadioGraphics* 2012;32:897–911.
95 Hufton AP. Radiation dose to the fetus in obstetric radiography. *Br J Radiol* 1979;52:735–40.
96 Brent RL. The effect of embryonic and fetal exposure to X-ray, microwaves, and ultrasound: counseling the pregnant and nonpregnant patient about these risks. *Semin Oncol* 1989;16:347–68.
97 Horsthuis K, Bipat S, Bennink RJ, *et al*. Inflammatory bowel disease diagnosed with us, Mr, scintigraphy, and CT: meta-analysis of prospective studies. *Radiology* 2008;247:64–79.
98 Panés J, Bouzas R, Chaparro M, *et al*. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. *Aliment Pharmacol Ther* 2011;34:125–45.
99 Maaser C, Sturm A, Vavricka SR, *et al*. ECCO-ESGAR guideline for diagnostic assessment in IBD Part 1: initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019;13:144–64.
100 De Santis M, Straface G, Cavaliere AF, *et al*. Gadolinium periconceptional exposure: pregnancy and neonatal outcome. *Acta Obstet Gynecol Scand* 2007;86:99–101.
101 Salomon LJ, Alfirevic Z, Da Silva Costa F, *et al*. ISUOG practice guidelines: ultrasound assessment of fetal biometry and growth. *Ultrasound Obstet Gynecol* 2019;53:715–23.
102 Goldenberg RL, Culhane JF, Iams JD, *et al*. Epidemiology and causes of preterm birth. *Lancet* 2008;371:75–84.
103 Atallah A, Lecarpentier E, Goffinet F, *et al*. Aspirin for prevention of preeclampsia. *Drugs* 2017;77:1819–31.
104 Kim YH, Pfaller B, Marson A, *et al*. The risk of venous thromboembolism in women with inflammatory bowel disease during pregnancy and the postpartum period: a systematic review and meta-analysis. *Medicine* 2019;98:e17309.
105 N-P C. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. *London* 2015.
106 Mahadevan U, Robinson C, Bernasko N, *et al*. Inflammatory bowel disease in pregnancy clinical care pathway: a report from the American gastroenterological association IBD parenthood project Working group. *Gastroenterology* 2019;156:1508–24.
107 Remzi FH, Gorgun E, Bast J, *et al*. Vaginal delivery after ileal pouch-anal anastomosis: a word of caution. *Dis Colon Rectum* 2005;48:1691–9.
108 Hahnloser D, Pemberton JH, Wolff BG, *et al*. Pregnancy and delivery before and after ileal pouch-anal anastomosis for inflammatory bowel disease: immediate and long-term consequences and outcomes. *Dis Colon Rectum* 2004;47:1127–35.
109 Whiteley I, Gullick J. The embodied experience of pregnancy with an ileostomy. *J Clin Nurs* 2018;27:3931–44.
110 Sandall J, Tribe RM, Avery L, *et al*. Short-term and long-term effects of caesarean section on the health of women and children. *Lancet* 2018;392:1349–57.
111 Jackson KM, Nazar AM. Breastfeeding, the immune response, and long-term health. *J Am Osteopath Assoc* 2006;106:203–7.
112 Klement E, Cohen RV, Boxman J, *et al*. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. *Am J Clin Nutr* 2004;80:1342–52.

113 Kane S, Lemieux N. The role of breastfeeding in postpartum disease activity in women with inflammatory bowel disease. *Am J Gastroenterol* 2005;100:102–5.
114 Selinger CP, Eaden J, Selby W, *et al*. Inflammatory bowel disease and pregnancy: lack of knowledge is associated with negative views. *J Crohns Colitis* 2013;7:e206-13.
115 Silverman DA, Ford J, Shaw I, *et al*. Is mesalazine really safe for use in breastfeeding mothers? *Gut* 2005;54:170–1.
116 van der Woude CJ, Kolacek S, Dotan I, *et al*. European evidenced-based consensus on reproduction in inflammatory bowel disease. *J Crohns Colitis* 2010;4:493–510.
117 Van Assche G, Dignass A, Reinisch W, *et al*. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: special situations. *J Crohns Colitis* 2010;4:63–101.
118 Ost L, Wettrell G, Björkhem I, *et al*. Prednisolone excretion in human milk. *J Pediatr* 1985;106:1008–11.
119 Christensen LA, Dahlerup JF, Nielsen MJ, *et al*. Azathioprine treatment during lactation. *Aliment Pharmacol Ther* 2008;28:1209–13.
120 Sau A, Clarke S, Bass J, *et al*. Azathioprine and breastfeeding: is it safe? *BJOG* 2007;114:498–501.
121 Ben-Horin S, Yavzori M, Katz L, *et al*. Adalimumab level in breast milk of a nursing mother. *Clin Gastroenterol Hepatol* 2010;8:475–6.
122 Ben-Horin S, Yavzori M, Kopylov U, *et al*. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. *J Crohns Colitis* 2011;5:555–8.
123 Johns DG, Rutherford LD, Leighton PC, *et al*. Secretion of methotrexate into human milk. *Am J Obstet Gynecol* 1972;112:978–80.
124 de Lima A, Kanis SL, Escher JC, *et al*. Hepatitis B vaccination effective in children exposed to anti-tumour necrosis factor alpha in utero. *J Crohns Colitis* 2018;12:948–53.
125 Beaulieu DB, Ananthakrishnan AN, Martin C, *et al*. Use of biologic therapy by pregnant women with inflammatory bowel disease does not affect infant response to vaccines. *Clin Gastroenterol Hepatol* 2018;16:99–105.
126 Mahadevan U, Martin CF, Dubinsky M, *et al*. 960 exposure to Anti-TNFα therapy in the third trimester of pregnancy is not associated with increased adverse outcomes: results from the piano registry. *Gastroenterology* 2014;146:S-170.