

# Managing inflammatory bowel disease in pregnancy: current perspectives

Matthew Pinder<sup>1</sup>

Katie Lummis<sup>1</sup>

Christian P Selinger<sup>1,2</sup>

<sup>1</sup>Leeds Gastroenterology Institute,  
Leeds Teaching Hospitals NHS Trust,

<sup>2</sup>University of Leeds, Leeds, UK

**Abstract:** Inflammatory bowel disease (IBD) affects many women of childbearing age. The course of IBD is closely related to pregnancy outcomes with poorly controlled IBD increasing the risk of prematurity, low weight for gestation, and fetal loss. As such, women with IBD face complex decision making weighing the risks of active disease versus those of medical treatments. This review summarizes the current evidence regarding the safety and efficacy of IBD treatments during pregnancy and lactation aiming to provide up-to-date guidance for clinicians. Over 50% of women have poor IBD- and pregnancy-related knowledge, which is associated with views contrary to medical evidence and voluntary childlessness. This review highlights the effects of poor patient knowledge and critically evaluates interventions for improving patient knowledge and outcomes.

**Keywords:** pregnancy, breast feeding, nursing, inflammatory bowel disease, Crohn's disease, ulcerative colitis

## Introduction

Crohn's disease (CD) and ulcerative colitis (UC) have a high prevalence in young adults.<sup>1</sup> As such, they often present in women of childbearing age. Given that inflammatory bowel disease (IBD) can significantly affect quality of life, many women have concerns about the effects of pregnancy on their disease control and, in turn, how their disease may affect their fertility, ability to carry a pregnancy to term, and subsequent effects on their children.<sup>2,3</sup>

However, with appropriate therapy and close medical supervision, most women can have a normal pregnancy and deliver a healthy baby. While women with IBD should obviously follow general medical advice given to all women contemplating conception, there are specific issues pertaining to pregnancy in IBD, from preconception through the pregnancy itself and continuing into the postpartum period.

As such, women and their physicians can face some complex decisions when contemplating pregnancy. This review aims to highlight particular issues faced by women with IBD and summarize the current guidance, evidence, and experience available to aid in decision making.

## Preconception

Many women with IBD face challenging decisions when contemplating having children. Active IBD symptoms may negatively impact on body image and libido while anemia and fatigue may reduce the quality of life.<sup>4</sup> These direct effects of IBD may influence

Correspondence: Christian P Selinger  
Leeds Gastroenterology Institute, Leeds  
Teaching Hospitals NHS Trust, St James  
University Hospital, Bexley Wing, Beckett  
Street, Leeds LS9 7TF, UK  
Tel +44 113 206 8768  
Email [Christian.selinger@web.de](mailto:Christian.selinger@web.de)

women's wishes regarding reproduction regardless of their biological ability to have children. Overall, women with IBD are more likely to be childless than the general population.<sup>5</sup>

Cohort studies have demonstrated that women greatly overestimate the effects of IBD on fertility.<sup>3</sup> Many fear infertility despite having not tried to conceive and few actively seek medical advice on fertility.<sup>3</sup> This is also highlighted by the fact that up to 18% of women with IBD remain voluntarily childless (VC) as compared with only 6% of the general population. A novel, validated assessment tool of patient knowledge of pregnancy-related issues in IBD found that nearly half of those surveyed had poor knowledge of such issues.<sup>6</sup> A recent study of 1,324 women has sought to establish the reasons for VC: CCPKnow scores were found to be significantly lower in those patients with IBD who remained VC as compared to those who contemplated having children (5.98 vs 7.47).<sup>7</sup>

The exact etiology of voluntary childlessness is complex. In a survey of 145 women with IBD, 46% of participants expressed concerns regarding reduced rates of fertility associated with the condition and 75% of respondents were concerned regarding the potential for passing their condition to their offspring.<sup>8</sup> Concerns regarding the effects of disease on a successful pregnancy and the effects of pregnancy on disease course were almost universally held. Furthermore, greater than a third of women included considered all medication used in the treatment of IBD to be harmful in pregnancy.<sup>8</sup> As such, there is a clear link between poor patient knowledge of IBD- and pregnancy-related issues and views contrary to medical guidance as well as voluntary childlessness.

Current consensus is that there is no significantly increased rate of involuntary childlessness among most IBD populations.<sup>1</sup> A systematic review of eleven studies into fertility in nonsurgically treated CD and UC patients found that a perceived 17%–44% reduction in rates of fertility could not be explained by fecundability or fertility issues.<sup>9</sup> In the case of active CD, fertility is reduced, possibly owing to transmural inflammation or systemic effects of the disease, such as anemia.<sup>10–15</sup> Rates of fertility are comparable to the general population when clinical remission is achieved and this phenomenon is not noted in UC where fertility mirrors that in non-IBD populations.<sup>4,10,16</sup>

It is however accepted that patients who have undergone surgical procedures related to CD and UC are at a greater risk of infertility.<sup>16–24</sup> The greatest risk would appear to be associated with ileal pouch-anal anastomosis (IPAA) procedures for UC. A meta-analysis of six studies demonstrated a relative risk of infertility after such procedures of 3.91 (95%

confidence interval [CI]: 2.06–7.44) and reported infertility rates varying between 40% and 80% depending on the study cohort.<sup>25</sup> This increased risk is likely secondary to tubal dysfunction related to pelvic adhesions. Laparoscopic approaches for IPAA have become more widely adopted and these seem to be associated with lower infertility rates than those seen with traditional open surgery.<sup>26,27</sup> While many studies have shown increased rates of physical infertility after surgery (by reporting only patients attempting pregnancy), other factors may also influence the rates of children born after women experienced surgery for IBD. Some women especially those with UC may delay surgery until they have completed their family planning. Indeed, some clinicians advise women with UC who plan to have children to delay pouch surgery after a colectomy until they have had children. On the other hand, surgery may sway women (potentially unnecessarily) toward voluntary childlessness as documented by a recent study.<sup>7</sup>

While the development of IBD has a strong hereditary basis, the condition is not inherited in a Mendelian fashion, with variation in multiple genes contributing modestly to overall risk. Furthermore, many nonhereditary factors are required for IBD to develop.<sup>28,29</sup> Rates of inheritance vary by type of IBD as parental UC leads to an increased relative risk for the offspring developing CD of 2.6 and UC of 5.1, respectively.<sup>30</sup> Conversely, parental CD poses a relative risk for the development of CD or UC in the offspring of 12.8 and 4.0, respectively.<sup>30</sup> The absolute risk of a child developing IBD when one parent is affected by either CD or UC is between 4% and 11%, although this rises to 35% when conception occurs between two parents suffering from IBD. It is important to note that the fear of passing on IBD to offspring is often in excess of the reported evidence and appropriate reassurance is required for women contemplating motherhood.<sup>2</sup> Absolute risk may better help patients understand that the risk of offspring developing IBD is actually relatively low.

Preconception counseling in the general population has been persistently shown to promote healthier behaviors and improve pregnancy outcomes. The proven negative effect of misunderstanding fertility- and pregnancy-related issues in IBD has also been shown to be mitigated to some extent by preconception counseling.<sup>31</sup> Both improved adherence to treatment and reduced relapse rates have been found in IBD patients who received IBD-specific counseling preconception when compared to those who did not.<sup>31</sup> Furthermore, it has been shown that preconception discussion with a gastroenterologist improves CCPKnow scores, which, as discussed, are associated with reduced odds of voluntary childlessness.<sup>32</sup>

## Disease behavior during and after pregnancy

In general, the course of IBD during pregnancy mirrors that of the nonpregnant IBD population and most women will experience a quiescent course of disease during their pregnancies.<sup>33–35</sup> However, the recent pan-European EPICOM study has suggested increased flare rates for women with UC (relative risk 2.19; 95% CI: 1.25–3.97,  $P=0.004$ ).<sup>36</sup>

Reports of the disease course in the postpartum period are conflicting. While many women experience reduced disease activity,<sup>37,38</sup> some studies suggest that women with UC are more likely to experience flares postpartum.<sup>36,39</sup> Among the theories for a more benign course of IBD during and post-pregnancy, the interplay between maternal and fetal immune systems seems most important. Immuno-tolerance is required to overcome the disparity between maternal and fetal HLA class II antigens. This may in turn alter the intestinal inflammation levels and thereby affect the clinical disease course of IBD.<sup>40</sup> On the other hand, increased disease activity has been linked to nonadherence to IBD medication in breastfeeding mothers.<sup>39</sup> Similarly, it is known that adherence to 5-ASA is generally poor in nonpregnant<sup>41,42</sup> but also in pregnant patients,<sup>43</sup> which could lead to more flares in women with IBD.

## Effects of IBD and IBD disease activity on pregnancy

IBD can have a profound effect on the course of a pregnancy and pregnancy outcomes. It can, however, be difficult to disentangle what effects stem from having IBD itself (for example, mediated through genes and microbiome), what effects stem from IBD disease activity (mediated through cytokines and the effect of flares on the mother), and what effects are solely related to medication used for the treatment of IBD. Clinicians and patients are faced with complex decisions around medication during pregnancy and breast feeding. This process needs to involve a balancing of the risks associated with a flare of IBD and the risks associated with maintenance medication. To aid this decision making, the implications of any disease flares in the antenatal period need to be understood by both physicians and patients.

While women with quiescent disease can expect normal pregnancy outcomes, this cannot be said for those experiencing active disease during pregnancy. Adverse pregnancy outcomes, including low birth weight, preterm birth, and even fetal loss, have been reported in women with active IBD and especially CD.<sup>34,44–47</sup> Three recent studies have reported conflicting results: A Danish population-based study confirmed

the association of disease activity with preterm birth.<sup>48</sup> The results of an American population-based study demonstrating no association between disease activity with pre-term birth needs to be treated with caution as the number of patients with active disease was rather small in the study.<sup>33</sup> The latest study from the Netherlands clearly demonstrates that even in the biological treatment age, active disease is associated with worse pregnancy outcomes.<sup>49</sup> Interestingly, patients with UC experienced more active disease than those with CD.<sup>49</sup>

It remains unclear whether a risk of preterm birth relates to IBD overall or just CD. While a meta-analysis reported a significant risk of preterm births in all IBD patients,<sup>33,50</sup> this effect disappears for UC when stratifying by disease type. The main association with preterm birth is seen in CD.<sup>51,52</sup> Consequently, a link between CD and a lower birth weight has also been found.<sup>51,52</sup> As such, there is strong evidence to recommend that efforts are made to achieve clinical remission prior to conception and maintain a symptom-free status for the antenatal period. With the exception of mild or quiescent disease, most women will require medication to achieve this. Poorly controlled IBD can have devastating consequences on a pregnancy. The risk of adverse pregnancy outcomes appears to be greatest in those women who have active disease at the time of conception. As such, treatment to avoid and/or treat active disease is vital to ensure a safe and successful pregnancy course.

## Congenital abnormalities in offspring of mothers with IBD

Congenital abnormalities or birth defects can occur in up to 3%–7% of mothers without chronic conditions. As such, they are a worry to any expectant mother, but this also is the case for women with IBD.<sup>53</sup> Physicians need to know the risks for any congenital abnormalities in offspring to mother with IBD to reassure patients. Unfortunately, due to conflicting evidence, the question over any increased risk of congenital abnormalities in babies to mother with IBD remains difficult to answer.

An American study in Washington showed that maternal UC was associated with an increased risk of malformations (7.9% vs 1.7%;  $P<0.001$ ), while no increased risk for CD patients was seen (3.4%;  $P=$  not significant).<sup>51</sup> Due to a lack of adjustment for medication use, the study could not provide any insight into effects related to medication rather than disease.<sup>51</sup> Better quality evidence arises from the large Hungarian Case Control Surveillance of Congenital Anomalies (1980–1996) study. The investigators collected comprehensive data and were able to adjust for parity, age,

and medication use. Importantly, the study reported no overall increase for any malformations (odds ratio [OR]: 1.2, 95% CI: 0.9–1.8) for UC.<sup>54</sup> However, when specific types of malformations were examined, a number of significant relationships were found: The risks for limb (OR: 6.2, 95% CI: 2.9–13.1), urinary tract (OR: 3.3, 95% CI: 1.1–9.5), and multiple malformations (OR: 2.6, 95% CI: 1.3–5.4) were significantly increased.<sup>54</sup> In the overall analysis, however, this effect was offset by lower risks for other abnormalities and the any malformation risk was similar to that in the comparator group.

An Italian case-control study reported a 5.5% risk of any malformation in offspring to mothers with IBD patients in contrast to a matched control (0%) group.<sup>52</sup> Usually, congenital abnormalities occur in up to 7% in offspring to healthy mothers. The study has, therefore, a very unusual control rate and the result should be treated with extreme caution due to this bias.<sup>53</sup>

Summary data from a meta-analysis of four studies show the risk of giving birth to offspring with congenital abnormalities was increased for mothers with UC (OR: 2.37, 95% CI: 1.47–3.82), while for mothers with CD the risk increase did not reach statistical significance (OR: 2.14, 95% CI: 0.97–4.74;  $P=0.06$ ).<sup>50</sup>

In conclusion, while the data remain difficult to interpret, there seems to be a small increase in congenital malformations in infants born to mothers with UC. Further studies are required to determine the risk for CD and IBD overall.

## Safety of IBD medication use during pregnancy

The principle underlying the use of IBD medication during pregnancy is the weighing of risks associated with active disease versus any potential or real risk associated with specific IBD medications. Many patients feel that any medication use

could be harmful.<sup>8</sup> This perception needs to be acknowledged and set into context with appropriate counseling with regard to the adverse effects associated with untreated disease. The European Crohn's and Colitis Organisation (ECCO) has recently published the second version of their extensive guidelines on the management of IBD during pregnancy.<sup>1</sup> The principle underlying medication recommendations in the guidelines is that the risk of active disease usually outweighs any risk from medication (notable exception methotrexate).<sup>1</sup> Table 1 is an overview of treatment recommendations.

## Aminosalicylates

Aminosalicylates are indicated to treat mild-to-moderate UC. Aminosalicylates are generally considered safe for use in pregnancy as per the ECCO guidelines.<sup>1</sup>

There are a number of studies that have demonstrated the safety of mesalazine use during pregnancy.<sup>55</sup> There have been no reports that mesalazine increases the risk of congenital abnormalities.<sup>56</sup> A population-based study that showed an increased incidence of stillbirth and preterm birth in those with Crohn's is likely a result of the underlying disease as opposed to the medication as patients were compared to healthy women.<sup>56</sup> Asacol was temporarily reclassified by the American Food and Drug Administration as it contained small quantities of phthalates in its coating. Both European and American regulators have suggested removing phthalates from any pharmaceutical agent based on concerns over a potential risk of congenital abnormalities. Asacol preparations for the European and American markets have been changed subsequently and no longer contain phthalates.

Initial reports suggested that sulfasalazine was teratogenic,<sup>57</sup> but this has since been refuted.<sup>48,58</sup> Sulfasalazine does interfere with folate absorption, which is essential for neural tube development. Folic acid supplementation is therefore always required.<sup>1</sup>

**Table 1** ECCO guidance regarding medication use in pregnancy

Drugs	ECCO	Potential risks
5-ASA	Low risk	Theoretically: stillbirth, preterm birth (confounder in studies: not controlled for disease activity)
Thiopurines	Probably low risk	Low risk of spontaneous miscarriage, preterm labor, and low birth weight (confounder in studies: not controlled for disease activity)
Methotrexate	Contraindicated	High risk of fetal mortality and numerous fetal abnormalities
Anti-TNF	Probably low risk	Main risk relates to drug levels in newborn with potential increased risk of infections; need to avoid live vaccinations
Prednisolone	Low risk	Low risk of orofacial malformations
Anti-integrin	Not included in ECCO guidance	Too few data
Anti-IL-23	Not included in ECCO guidance	Too few data
Budesonide	Too few data	Too few data

**Abbreviations:** ECCO, European Crohn's and Colitis Organisation; TNF, tumor necrosis factor; IL-23, interleukin-23.

## Antibiotics

Antibiotics have a role in the management of both peri-anal CD and pouchitis. The ECCO guidelines have categorized antibiotics, specifically metronidazole and ciprofloxacin, as low risk for short-term use as there is limited benefit from long-term treatment.<sup>1</sup>

A population-based case control study showed that metronidazole exposure during the second or third trimester was associated with cleft defects.<sup>59</sup> However, other studies, including a cohort study<sup>60</sup> with 922 pregnant women and two meta-analysis,<sup>61,62</sup> have found no increased risk of congenital abnormalities or spontaneous miscarriage relating to metronidazole use.

Quinolones have a high affinity for bone and cartilage and in some animal studies they have been shown to induce arthropathy.<sup>63,64</sup> However, studies in humans have not shown any increased risk of spontaneous miscarriage or congenital abnormality associated with the use of ciprofloxacin.<sup>65</sup>

## Corticosteroids

Steroids remain the drug of choice for an acute flare of IBD and are recommended for use in the ECCO guidelines.<sup>1</sup> All corticosteroids cross the placenta and some data show adverse effects in humans. Although a number of studies have shown no increased risk of major congenital malformations associated with the use of steroids, there is an increased risk of orofacial malformations if steroids are used in the first trimester.<sup>66,67</sup> However, not all studies have confirmed these findings, including a large population-based study which included 51,973 pregnancies.<sup>68,69</sup>

There is a single retrospective study looking specifically at the use of budesonide in pregnancy. The study included eight patients who received oral budesonide for CD. The study did not report any adverse pregnancy outcomes associated with its use.<sup>70</sup> Given its high first-pass metabolism, it is at least in theory unlikely that sufficient quantities of budesonide get transferred across the placenta to exert any pharmacological effect on the fetus.

## Thiopurines

Thiopurines, both azathioprine and 6-mercaptopurine, are indicated for maintenance of remission for both UC and CD. The ECCO guidelines consider thiopurines to be low risk and well tolerated during pregnancy.<sup>1</sup>

A number of studies have shown adverse outcomes associated with fetal exposure to thiopurines, including increased rate of spontaneous miscarriage, preterm labor, and low birth weight.<sup>71,72</sup> It is suggested, however, that these outcomes may

be a consequence of the underlying IBD rather than due to exposure to thiopurines as exposed patients were compared to a disease-free population.

More recent studies,<sup>73–75</sup> including a meta-analysis which included 494 patients with IBD,<sup>76</sup> reported no increased risk for adverse pregnancy outcome in IBD patients treated during pregnancy with thiopurines compared with pregnancy outcomes of IBD patients without this treatment. Interestingly, in a Spanish study, patients on thiopurines had better outcomes than those not exposed to thiopurines, thereby highlighting the importance of disease control throughout pregnancy.<sup>75</sup>

## Methotrexate

Methotrexate is absolutely contraindicated during pregnancy as it is teratogenic.<sup>1</sup> Methotrexate acts as a folate antagonist and is therefore associated with a high risk of fetal mortality as well as numerous fetal abnormalities.<sup>77</sup> Current ECCO advice is to stop methotrexate for at least 3–6 months in both men and women before any attempt to conceive is made.<sup>1</sup>

There has been some controversy over the safety of methotrexate in men trying to father a child. While a study of 40 pregnancies with paternal methotrexate exposure found no increased levels of adverse outcomes,<sup>78</sup> current consensus remains that the potential risk associated with paternal methotrexate should be avoided.<sup>1</sup>

## Biologic agents

In the treatment of IBD, biological agents are used for the treatment of moderate-to-severe CD and UC. In addition to the antitumor necrosis factor (anti-TNF) class of biologics, which have been widely used for 2 decades, newer biological agents targeting alpha-4-beta-7 integrin and interleukin (IL)-23 have recently entered or about to enter the market.

## Anti-TNF agents

Anti-TNF agents used for IBD include infliximab, adalimumab, golimumab, and in some countries certolizumab. These agents are large molecules, which cannot passively cross the placenta. However, at the end of the second trimester, infliximab and adalimumab are actively transported across the placenta as they resemble maternal immunoglobulins, which are actively transported to help develop the fetal immune system.<sup>79</sup> As such, fetus is not only exposed to these agents but fetal anti-TNF concentrations often exceed maternal concentrations at birth.<sup>80</sup> In a recent Australasian study, it took an average of 4 months to achieve full adalimumab clearance and 7 months for full infliximab clearance.<sup>80</sup> Detectable drug levels were found up to the age of 12 months.<sup>80,81</sup> It is

therefore important for safety data to include developmental and infective outcomes in infants in addition to the usual data on pregnancy complications and neonatal outcomes. In contrast to infliximab and adalimumab, certolizumab has a pegylated molecular structure and no placental transfer occurs with either very low or no detectable fetal drug levels at birth.<sup>81</sup>

The ECCO guidelines recommend that anti-TNF agents are probably of low risk during pregnancy.<sup>1</sup> The safety of infliximab in pregnant women is IBD, which has been assessed by four larger scale studies reporting no significant concerns over maternal or fetal outcomes.<sup>81–84</sup> Further safety data are emerging from the ongoing “Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes” (PIANO) study assessing maternal, fetal, developmental, and infective outcomes in the newborn in over 1,000 cases.<sup>85</sup> These data are only available as conference abstracts at present but suggest that anti-TNF exposure does not lead to developmental problems.<sup>85</sup> Data on childhood infections remain inconclusive with borderline risk increases. Combination therapy with anti-TNF and thiopurines seems to carry a small increased risk of benign infections in the infant though.<sup>80</sup> There are fewer data on adalimumab, but these again show no specific safety concern.<sup>81,84,86</sup> The importance of striking a balance between disease control and drug exposure is highlighted by a Spanish study showing no difference between pregnancy outcomes of mothers with IBD on anti-TNF therapy compared to mothers with IBD neither exposed to biological agents nor thiopurines.<sup>75</sup> Interestingly, the best outcomes were seen in the group exposed to thiopurines suggesting that the anti-TNF group may have had more severe disease but also that the completely unexposed group may have had worse disease control.<sup>75</sup> The limited data available on certolizumab are reassuring.<sup>81,85</sup> Data on golimumab exposure are scarce and stem from clinical trials largely, where patients discontinue the drug immediately when pregnancy occurs.<sup>87</sup>

The detectable drug levels in infants to mothers exposed to anti-TNF therapy have implications on the infant’s health care. Health care professionals attending the infant should be made aware of the anti-TNF exposure. It would seem sensible to apply lower thresholds for investigations and/or treatment of infective complications where appropriate. The other area of interest is the vaccination program for the new born. At least in theory any live vaccination can pose a risk. There has unfortunately been a death of a 3-month-old child who had been exposed to anti-TNF in utero due to disseminated bacillus Calmette–Guérin (BCG) after receiving the live BCG vaccination.<sup>88</sup> Based on studies showing detectable drug

levels for up to 12 months, it seems prudent to delay any live vaccination until the infant has reached an age of at least 12 months. Rotavirus vaccinations have recently become part of the standard vaccination program in the UK and need to be given before the infant has reached 24 weeks of age. The risk from this live vaccine is unclear, but the PIANO study has reported on a small number of cases with no adverse effects.<sup>85</sup> For the time being at least, standard advice is, however, to avoid the rotavirus vaccine.

Due to the active placental transfer of biological agents in the third trimester, anti-TNF should be discontinued around 24–26 weeks of gestation if clinical remission has been achieved.<sup>1</sup> Patients are unlikely to experience a third trimester flare in this setting.<sup>89</sup> In the case of active disease, however, anti-TNF can safely be continued throughout the third trimester.<sup>89</sup>

### Anti-integrin agents

The alpha-4-beta-7 anti-integrin vedolizumab is a gut-specific agent restricting lymphocyte migration to the gut. It is indicated for moderate-to-severe UC and CD. The currently available limited data stem from the clinical trials program.<sup>90</sup> While the agent is gut-specific and should have little effect on systemic development, it might in theory have implications for the development of the fetal intestinal immune system. Clinical data are needed urgently to inform clinicians on the safety during pregnancy.

### Anti-IL-23 agents

The blockade of IL-23 has shown good results in patients with CD and the agent ustekinumab is expected to be licensed for this indication next 12 months. Ustekinumab has been used in the treatment of psoriasis and psoriatic arthritis for a number of years, but safety data for pregnancy are limited with only a handful of case reports.<sup>91</sup>

### Medication adherence

Adherence to IBD medication is often poor outside pregnancy with 30%–45% of patients not taking medication as prescribed.<sup>92</sup> Given the high concerns expressed by many women with IBD regarding medication during pregnancy<sup>2</sup> and the extent of views in contrast to medical guidelines,<sup>8</sup> clinicians must assume that a significant proportion of pregnant women may not adhere to their medication. While two Danish population-based studies report adherence levels just below of those expected in nonpregnant women,<sup>43,93</sup> a recent survey reported that 47% of respondents stopped IBD medication (half on their own accord) when trying to conceive.

## Monitoring of and investigations for IBD during pregnancy

### Noninvasive monitoring

Wherever possible, clinical observation and/or noninvasive monitoring is preferred over invasive tests during pregnancy. However, many IBD patients experience physiological changes in their bowel function during pregnancy as expected in healthy women.<sup>94</sup> CRP can, however, be influenced by many obstetric conditions<sup>95</sup> and levels may not reflect IBD activity. Fecal calprotectin may offer a better way of monitoring intestinal inflammation, but the test has not been validated during pregnancy yet and small studies have reported conflicting results regarding its accuracy in the antenatal phase.<sup>96,97</sup>

### Imaging during pregnancy

The decision to proceed to imaging tests needs to incorporate potential harmful effects of radiation and the effects that results of any imaging test may have on treatment decisions. The use of nonionizing radiation imaging is preferred as ultrasound and magnetic resonance imaging are considered safe in pregnancy.<sup>98</sup> In emergency situations or the absence of a viable alternative, a single exam with ionizing radiation is considered acceptable.<sup>98</sup>

### Endoscopy during pregnancy

Endoscopy can be undertaken during pregnancy provided that it is instrumental for clinical decision making. While ECCO guidance recommends fetal monitoring,<sup>99</sup> this may not be feasible in many settings. A small Dutch study has shown that maternal and fetal outcomes in patients requiring lower gastrointestinal endoscopy during pregnancy were similar to those not exposed to endoscopy.<sup>100</sup> Clinicians should review the need for sedation during endoscopy as this could place an independent, albeit probably very small, risk to the fetus. It is advisable to limit endoscopic examination to the least invasive option offering the required diagnostic value. For example, disease assessment in UC can usually be achieved with a less invasive (and potentially lower risk) sigmoidoscopy rather than a full colonoscopy.

### Delivery

The choice between vaginal delivery and cesarean section is influenced by obstetric and sometimes IBD-related considerations. While women with UC have a cesarean section rate comparable with the general population, women with CD are more likely to have a cesarean section.<sup>50</sup> IBD can influence the choice of delivery method in a number of ways. Preservation

of anal sphincter function and maintenance of continence are clearly the long-term aim and fears over negative effects on both may occur in some women. There is also at least in theory a risk of developing de novo perianal disease after a traumatic birth. The rate of this occurring remains unclear. A small Canadian study reported only one case of perianal disease after vaginal delivery and episiotomy in 27 women,<sup>101</sup> while a self-report survey of 179 women found an 18% rate postnatal perianal disease.<sup>102</sup> There was a, however, a high risk of recall and selection bias.<sup>102</sup>

Women with CD without active perianal disease, including those with currently inactive perianal disease, can have a vaginal delivery and episiotomy as they are unlikely to experience postnatal perianal complications.<sup>101,103,104</sup> When active perianal disease is present during pregnancy, the risk of complications is much higher and cesarean sections should be considered mandatory according to ECCO guidance.<sup>105</sup> The main concern for women with active perianal disease is that wound healing in an inflamed or even infected perineum will be severely impaired.

In the setting of UC, a vaginal delivery is usually advised with the notable exception for women with previous IPAA surgery.<sup>105</sup> While it has been established that vaginal delivery is associated with pathophysiological changes in anal sphincter function, it remains unclear whether this leads to problems with long-term pouch function.<sup>20,22,106</sup> Anorectal physiology is often impaired (lower squeeze pressure) and anorectal sonography shows more anal sphincter defects, but this was not associated with differences in clinical outcomes.<sup>107</sup> A large study of 232 women who gave birth after IPAA surgery found, however, no differences in functional outcomes.<sup>108</sup> This finding is further supported by a survey comparing 85 women with vaginal deliveries after IPAA to 343 age-matched women who did not have children after IPAA.<sup>109</sup> No differences in outcomes were found similar to a smaller Finnish study of 39 women.<sup>110</sup>

ECCO guidance, however, suggests that cesarean section may be preferable after IPAA surgery as women are likely to have borderline continence in the first instance.<sup>105</sup>

### Breast feeding

During pregnancy, women with IBD face the dilemma of weighing the risk of flares against the risks of medication without the option of avoiding these risks completely. The choice between breast feeding and bottle feeding allows, however, the chance to avoid any drug exposure in the newborn completely. As breast feeding has several advantages over bottle feeding, the mother with IBD is forced to make a choice

between the potential benefits of breast feeding versus the risk of exposure to small amounts of drug.

A number of health benefits derive from breast milk, including the provision of complete, tailored nutrition and maternal immunoglobulins. These help to develop the infant's immune system.<sup>111</sup> Breast milk may also provide protective effects in reducing the incidence of atopic diseases and even IBD, but most studies are of low quality with recall bias and lack of standardization of duration of breast feeding.<sup>112</sup> A meta-analysis of 17 studies showed that breast feeding reduced the risk of IBD developing in offspring to healthy mothers (OR: 0.67 [95% CI: 0.52–0.86] for CD and OR: 0.77 [95% CI: 0.61–0.96] for UC). It is, however, unclear whether breast feeding has any protective effect in offspring to mothers with IBD, where genetic factors may play a greater role in the development of IBD.

Breastfeeding rates in women with IBD are lower than expected,<sup>39</sup> which may be explained by fears over medication effects. In a recent study, 56% of women believed that all IBD medication would be a barrier to breast feeding.<sup>8</sup>

While small quantities of IBD medication can often be detected in breast milk, this does not necessarily exert any biological effects on the infant. Table 2 contains the ECCO guidance on IBD medication and breast feeding. Based on only two cases of bloody diarrhea, the American Academy of Pediatrics classed aminosalicylates as a contraindication to breast feeding.<sup>113–115</sup> ECCO guidance judges aminosalicylates as low risk in view of low drug levels in breast milk and infants' blood.<sup>1,116–118</sup>

For women with corticosteroid exposure, ECCO guidance suggests leaving a 4-hour gap between medication and feeding to reduce drug levels.<sup>1,105,119</sup> Thiopurine metabolites (ECCO: low risk) are often undetectable or found in extremely low quantities in breast milk<sup>120–122</sup> and are usually not detectable in infants.<sup>123,124</sup>

Adalimumab and infliximab can be detected in breast milk in very small concentrations,<sup>125,126</sup> but usually require parenteral rather than enteral administration to exert an effect (ECCO: probably risk<sup>1</sup>). Methotrexate is again considered contraindicated.<sup>1</sup>

**Table 2** ECCO guidance on medication use while breast feeding

Medication	ECCO guidance
Mesalazine/sulfasalazine	Low risk
Corticosteroids	Low risk
Thiopurines	Low risk
Anti-TNF	Probably low risk
Methotrexate	Contraindicated

**Abbreviations:** ECCO, European Crohn's and Colitis Organisation; TNF, tumor necrosis factor.

## Conclusion

Women with IBD face complex decisions when contemplating having children and many remain childless. To help them achieve their life ambitions, these patients should be supported by appropriate prepregnancy counseling, and antenatal IBD care focused on maintaining remission, specialist obstetric input, and a pregnancy plan that includes advice on delivery methods and breast feeding.

## Author contributions

MP and KL reviewed the literature and wrote the draft manuscript. CPS reviewed the literature and critically reviewed the manuscript.

## Disclosure

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