

EXPERT
REVIEWSInflammatory bowel disease
and pregnancy: an update*Expert Rev. Clin. Immunol.* 6(4), 643–657 (2010)Lola Y Kwan¹ and
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Women with inflammatory bowel disease have similar rates of conception to the general population unless they have had pelvic surgery. Once pregnant, regardless of disease activity, they have an increased risk of adverse pregnancy outcome and should be followed as high-risk obstetric patients. Most medications are compatible with pregnancy and lactation, as described in this article. Ideally, women should discuss their plans for pregnancy with their physician prior to conception so that risks and benefits can be reviewed, medications adjusted and healthcare maintenance updated. Once pregnant, a multidisciplinary team of gastroenterologists, obstetricians and pediatricians should help to ensure the best care for the mother and child.

KEYWORDS: adalimumab • certolizumab • Crohn's disease • inflammatory bowel disease • infliximab • pregnancy • ulcerative colitis

Inflammatory bowel disease (IBD) affects women during their childbearing years, with the peak age of onset between 15 and 30 years of age [1]. Concerns over fertility, disease activity during pregnancy and inheritance of disease in the offspring are common prior to conception, along with anxiety over the safety of IBD medications during pregnancy and breastfeeding. Given the limited data and known adverse outcomes, pregnant women with IBD require an interdisciplinary approach to therapy, with close monitoring and counseling to optimize their clinical disease course and neonatal outcomes. This article will present the best evidence to date on fertility and pregnancy in women with IBD.

Inheritance/anticipation

There is a higher risk for Crohn's disease (CD) and ulcerative colitis (UC) in the offspring of patients with IBD. A child born to a parent with IBD is 2–13-times more likely to develop IBD in their lifetime compared with the general population [2]. A child has a 5% chance of developing IBD if one parent has CD; the chance is 1.6% if one parent has UC. If both parents have IBD, a child's risk is as high as 35% for IBD development [3]. However, inheritance is multifactorial with a role for as yet undefined environmental triggers. Familial CD has earlier onset than sporadic cases at an average age of 22 years versus 27 years, respectively [4].

Fertility: the role of surgery, sexual dysfunction & inflammation

The overall infertility rate in the USA is 13.8% [5]. Fertility, or the ability to conceive within a year of unprotected intercourse, is similar among women with IBD and their age-matched peers, unless they have had pelvic surgery for their disease [6–8], or possibly an acute flare of disease [7,9]. Prior to surgery, age is the only independent factor affecting fertility rates, as is seen in the general population [10]. However, voluntary childlessness, dyspareunia and fear of reproduction have resulted in smaller families and an increased use of contraception after diagnosis of IBD (82%) compared with the general population (76%) [11]. Many couples have concerns over heritability, teratogenicity of medications and maintaining a healthy pregnancy without disease activity or systemic effects [12]. In Australia, a questionnaire study with 255 responders reported a 42.7% fear of infertility [13]. Couples affected with IBD tend to seek fertility experts and/or *in vitro* fertilization (IVF) at a higher rate than the general population (24–40 vs 10–13%) [14,15], especially postoperatively.

Fertility and fecundity (rate of conception per menstrual cycle) is decreased after surgery for CD [7] and colectomy with ileal pouch anal anastomosis (IPAA) for UC, with infertility rates of 26–48% compared with 12–15% for IBD patients without surgery [8,16]. Extensive

dissection during removal of the rectum and creation of the J pouch may lead to pelvic scarring, adhesions and tubal infertility [17,18]. However, the majority of these patients can still conceive with IVF. Colectomy with ileostomy and rectal stump may be an option for preserving female fertility but many patients are reluctant to have an ostomy, even temporarily. The potential role of laparoscopic or robotic surgery in reducing adhesions is not known at this time but is worthy of further investigation.

Sexual dysfunction also plays a role in decreased conception rates and thus smaller families for couples with IBD [13]. A total of 60–75% of Australian women with IBD versus 40% of the general population reported sexual difficulties [19]. Living with IBD can diminish one's body image and libido. In addition, disease-related effects of fatigue, infection and adverse effects of steroid use can lead to sexual difficulties. Finally, dyspareunia can occur post-IPAA due to anatomical changes to the posterior vaginal wall and loss of anatomical support after rectal excision. Fluid retention can also occur in the vagina [20]. A systematic review of seven studies with 419 women found an estimated 25% incidence of sexual dysfunction postoperatively after restorative proctocolectomy versus 8% preoperatively, without long-term follow up [16].

Women with IBD may have an elevated ratio of Th1/Th2 cytokines, contributing to difficulties in conception and pregnancy loss [21]. Protection of the fetus from maternal attack has been correlated with a shift toward a Th2 cytokine profile in the general population [22]. This may explain why some women feel their IBD disease activity is the lowest during pregnancy. It also raises the possibility that anti-TNF- α agents can improve fertility. Winger *et al.* significantly improved IVF outcomes and implantation rates by the use of adalimumab (ADA) and intravenous immunoglobulin (IVIG) in a study enrolling 75 subfertile women without IBD from an assisted reproductive facility in London (UK), all of whom had elevated Th1/Th2 cytokine ratios [23]. Implantation rates were 59% using ADA and IVIG, versus 47% using IVIG alone and 0% with neither. The role of anti-TNF agents in improving fertility in women with IBD may be related to both improving disease activity and shifting the Th1/Th2 balance.

Pregnancy outcomes

There is an increased risk for preterm birth, low birth weight (LBW) and being small for gestational age (SGA) among infants of women with IBD. Adverse outcomes have been significantly demonstrated in several European-based population studies [24–26]. Recently, a Taiwanese population database study compared infants of 196 women with UC to 1568 unaffected women matched by age and hospital of delivery from 2001–2003 [27]. This study consistently found an increased risk of preterm birth (11.73 vs 6.25%; $p = 0.004$) and LBW (12.76 vs 5.55%; $p < 0.001$), controlling for maternal characteristics including age, parity and education level. This is the first study evaluating pregnancy outcomes of women with UC in an Asian population, suggesting that an increased risk for preterm birth and LBW infants in women with UC is not specific to women of European descent.

There is no clear evidence for an increased risk of congenital anomalies. Only one study found a significant increase in overall congenital anomalies in offspring of women with IBD. This cohort study reviewed electronic birth records in the state of Washington (USA), including infants born to 107 UC women and 155 CD women, and found an odds ratio (OR) of 3.8 (95% CI: 1.5–9.8) for infants of UC women [28]. However, this study did not control for disease activity or medication use. In a Hungarian case–control surveillance queried from 1980–1996 [29], there is a nonsignificant trend towards an increased risk of congenital anomalies in UC women versus controls (OR: 1.3; 95% CI: 0.9–1.8), while there is some evidence for an increased risk for isolated anomalies in infants of women with UC: limb deficiencies (OR: 6.2; 95% CI: 2.9–13.1), obstructive urinary congenital abnormalities (OR: 3.3; 95% CI: 1.1–9.5), and multiple congenital abnormalities (OR: 2.6; 95% CI: 1.3–5.4) [29]. This study controlled for age, parity and medication use.

In the Northern California Kaiser population, a cohort study compared women with IBD ($n = 461$) matched to controls ($n = 495$) by age and hospital of delivery [30]. The findings demonstrated that women with IBD were more likely to have a spontaneous abortion (OR: 1.65; 95% CI: 1.09–2.48); an adverse pregnancy outcome (stillbirth, preterm birth or SGA infant; OR: 1.54; 95% CI: 1.00–2.38); or a complication of labor (OR: 1.78; 95% CI: 1.13–2.81). The study did not find a difference in the rate of congenital malformations in control versus IBD patients, either as a group or for UC and CD separately.

A recent retrospective study suggested that the offspring of mothers with IBD may have higher rates of developmental delay and reduced height and weight later in childhood [31]. Further research in this area is also greatly needed.

Disease activity: effect of disease activity on pregnancy

Disease activity at conception has been associated with a higher rate of fetal loss [32] and preterm birth [33], while disease activity during pregnancy was associated with LBW and preterm birth [34,35]. Other potential predictors of an adverse outcome include ileal CD and previous bowel resection [30,36]. The Northern California Kaiser population study, however, did not have an increased risk of adverse events associated with disease activity, even when limited to moderate-to-severe disease activity [30]. The majority of patients in this cohort had inactive or mild disease throughout pregnancy. The use of medication during pregnancy also did not have a statistical impact on outcomes in this population. A population study from Denmark reported that women with active disease had adjusted risks of LBW, LBW at term, preterm birth and congenital anomalies of 0.2 (95% CI: 0.0–2.6), 0.4 (95% CI: 0.0–3.7), 2.4 (95% CI: 0.6–9.5) and 0.8 (95% CI: 0.2–3.8), respectively, similar to women with inactive IBD. However, the crude risk of preterm birth was increased with an OR of 3.4 (95% CI: 1.1–10.6) in those with moderate-to-high disease activity. Overall, these data suggest that women with IBD, either with active disease or in remission, have higher rates of adverse outcomes compared

with the general population. However, the limitations of these studies are that they are retrospective and electronic record-based, so flares that did not require hospitalization or a physician visit may be missed.

Effect of pregnancy on IBD

Pregnant women with either CD or UC are as likely to flare (34% per year) as nonpregnant women with UC (32% per year) [33,37]. Some studies have linked lower disease activity during pregnancy to reduced tobacco use [38,39]. Two studies found lower rates of relapse at 3 years postpartum including a large European cohort study with comparable use of medications before and after pregnancy [40,41]. The cohort study also reports lower rates of stenosis and bowel resection in a 10-year follow-up from diagnosis of CD.

Some women with IBD and other autoimmune diseases report that their disease is most quiescent during pregnancy. Physiologic explanations for this phenomenon include the hypothesis that HLA class II disparity between the mother and paternal alloantigens in the fetus induces a protective downregulation of the immune system. This has been demonstrated in pregnant women with rheumatoid arthritis [42] and nonpregnant UC patients post-liver transplantation for primary sclerosing cholangitis (PSC) who have donor/native HLA-DR and -DQ disparity [43]. A chart review of 50 pregnancies in 38 women with IBD found that women with disparity in both DRβ1 and DQ loci, but not individual loci, had a statistically significant difference in overall disease activity before and during pregnancy (OR: 8.4; 95% CI: 1.5–14; $p = 0.01$) [44].

Postpartum period

The postpartum period brings about several shifts in hormone balance and physical changes. Postpartum flares of disease are common in autoimmune disorders for many reasons. Among women with IBD, discontinuation of medication to breastfeed seems to be the most common cause of flares [45]. Other presumptive etiologies include resumption of smoking [39] and hormonal changes following delivery [46]. Changes in anti-inflammatory cytokines, which increase in pregnancy and decrease postpartum in patients with rheumatic disease based on plasma levels of IFN- γ and IL-10 markers, may also play a role [47]. In general, for patients with IBD who remain on stable medical therapy, the postpartum period does not appear to constitute a time of risk for disease flare compared with the general IBD population.

Breastfeeding

Breastfeeding provides an ideal form of nutrition, a transfer of immunity to the infant and an important source of bonding between the infant and mother. However, concern about transfer of drugs via breast milk to the infant leads women to either avoid breastfeeding or stop their medication. Compared with the general population (60%), patients with IBD (44%) or CD alone (29%) have lower rates of breastfeeding [45].

Breastfeeding may have an effect on IBD disease activity in the nursing mother, as has been demonstrated in other autoimmune disorders [48,49]. One hypothesis is the role of prolactin,

which is increased during lactation and possesses proinflammatory properties, including upregulation of TNF [50]. The limited data in IBD do not suggest a role for breastfeeding in increased disease activity independent of medication cessation prior to breastfeeding [45]. Recently, a population-based study from the University of Manitoba IBD research registry (Winnipeg, Canada) questioned 132 women (90 CD and 39 UC) who had 156 births [51]. Of the women with IBD, 56.1% breastfed for more than 24 weeks versus 44.4% of controls ($p = 0.02$). The OR of disease flare postpartum for those who breastfed versus those who did not was 0.58 (95% CI: 0.24–1.43) for IBD; 0.84 (95% CI: 0.19–9.87) for CD; and 0.51 (95% CI: 0.12–2.2) for UC. Results were adjusted for age at pregnancy, duration of disease and socioeconomic status. This study suggests a protective effect of breastfeeding rather than increased disease flare among women with IBD, although the results must be interpreted with caution as the flare may be leading to avoidance of breastfeeding rather than breastfeeding leading to the flare.

It has been suggested that breastfeeding is protective against the development of IBD. A meta-analysis of breastfeeding and the development of IBD reported a protective effect for CD (OR: 0.45; 95% CI: 0.26–0.79) and for UC (OR: 0.56; 95% CI: 0.38–0.81) [52]. The limitations to this meta-analysis were that only eight studies were of high methodological quality and the details of breastfeeding were not always known. By contrast, a subsequent study deemed to be of high methodological quality suggested that breastfeeding, partial or exclusive, was a risk factor for CD (OR: 2.1; 95% CI: 1.3–3.4; $p = 0.003$) based on 222 cases. Breastfeeding had no effect, however, on the risk of UC (OR: 1.07; 95% CI: 0.52–2.22; $p = 0.85$) based on 60 cases [53]. The mothers in these studies did not have IBD. The impact of breastfeeding by a mother with IBD on her child's risk of developing IBD is not known. While breastfeeding will not be harmful, given the potential immunologic changes that occur in the mother with or without medical therapy, the immunological benefit to the child may be less than in the general population.

Pregnancy & surgery

A pregnant woman with IBD can rarely develop severely active disease resulting in complications, hospitalization and the need for surgery. As in nonpregnant patients, medical therapy is the first approach. When the disease is refractory to medical therapy and in life-threatening conditions such as toxic megacolon, intestinal obstruction or significant gastrointestinal hemorrhage, urgent surgery is indicated.

Nonobstetrical surgeries in a pregnant woman are generally well tolerated, with the ideal window in the second trimester [54]. There is cumulative evidence that colectomy during the third trimester is also low risk without significant adverse pregnancy outcomes [55,56]. The use of Turnbull–Blowhole colostomy for colonic decompression and ileal diversion with delayed restorative proctocolectomy and IPAA has been suggested for mothers at less than 28 weeks gestation. Alternatively, a synchronous cesarean section with subtotal colectomy, if possible, is suggested for patients at greater than 28 weeks gestation [56].

Mode of delivery

There is a higher rate of cesarean section in IBD patients compared with the general population, with reported rates as high as 44% [57]. Studies suggest that the majority of cesarean sections are due to patient or physician preference rather than true obstetrical indication. A meta-analysis of six studies found an OR of 1.5 (95% CI: 1.26–1.79). The risk of cesarian section for CD was significant, with an OR of 1.65 (95% CI: 1.19–2.29), but was not significant for UC [58]. Concerns for vaginal delivery are anal sphincter or perineal damage, leading to development or worsening of perianal disease in CD [59], or pouch dysfunction in patients with IPAA prior to pregnancy. Small studies show that vaginal delivery in patients with inactive perianal disease does not lead to exacerbation or progression of perianal disease [60,61]. There are also data to suggest that vaginal delivery is low risk for those with a pouch as there is a return to pre-pregnancy function within 6 months [62]. Current recommendations are delivery by cesarian section for those with active perianal disease at the time of delivery or (perhaps) with an ileoanal pouch, otherwise the mode of delivery is at the discretion of the obstetrician.

Medications

Medication use during pregnancy is a concern for women with IBD who are planning families or have conceived, and many patients will change or discontinue medication if not properly counseled. A Dutch study found that 61% (51 out of 61) of women with plans for conception consulted a physician, and about a third of these patients underwent a medication change [63]. Women who are aware of medication risks compared with the risk of disease activity on pregnancy outcomes may be more likely to continue appropriate medication during pregnancy. Good communication between the patient, gastroenterologist, obstetrician and pediatrician is important for a healthy pregnancy and healthy infant. Despite limited data, most IBD medications are considered low risk during conception, pregnancy and lactation. The exception is methotrexate, which is an absolute contraindication.

The US FDA classification of drugs offers a guide to the use of medications during pregnancy. The FDA categories are listed in TABLE 1 and are noted for each drug discussed. TABLE 2 summarizes the safety of IBD medications for pregnancy and breastfeeding.

Aminosalicylates

Aminosalicylates are considered low risk for use in pregnancy. Most are pregnancy category B (sulfasalazine, mesalamine and balsalazide) with the exception of olsalazine, which is category C. Despite initial case reports of cardiovascular, genitourinary and neurologic defects [64–66], a cohort study from Denmark [67] and a prospective controlled trial of 165 women exposed to mesalamine (2G daily) did not find aminosalicylates teratogenic [68]. Sulfasalazine is 5-aminosalicylic acid azo-bonded to sulfapyridine. To confer potential anti-folate effects of the drug, it is recommended that women take at least folic acid 2 mg daily in the prenatal period and throughout pregnancy. Breastfeeding is also considered low risk with exposure to sulfasalazine and

probably negligible levels of transfer to breast milk. There is a rare association with diarrhea in the infant and thus should be monitored for persistent stool changes if the mother continues on aminosalicylates [69]. Unlike other sulfonamides, bilirubin displacement, and therefore kernicterus, does not occur in the infant [70].

Antibiotics

Metronidazole

Metronidazole is pregnancy category B and a low-risk drug during pregnancy. Prenatal use is not associated with birth defects, supported by two meta-analyses [71,72], two retrospective cohort studies [73,74] and a prospective controlled study of 228 women exposed to metronidazole during pregnancy [75]. A population-based case-control study of infants of women exposed to metronidazole in the first trimester of pregnancy had slightly higher rates of cleft lip with or without cleft palate, but overall teratogenic risk was low [76].

Metronidazole transfers to breast milk. The American Academy of Pediatrics recommends that breastfeeding be withheld for 12–24 h if a single dose of metronidazole is given [77]. Longer-term use of metronidazole should be avoided owing to potential toxic effects.

Quinolones

Quinolones (e.g., ciprofloxacin, levofloxacin and norfloxacin) are pregnancy category C drugs. Quinolones are associated with potential damage to joints of immature rats, dogs and children. This drug has a high affinity for bone tissue and cartilage, leading to arthropathies in children [78]. However, several human studies failed to show an increased risk of congenital malformations in infants born to women exposed to quinolones [79,80]. Overall, quinolones are believed to be of minimal risk. The risk/benefit ratio must be reviewed for indication of use. There is limited evidence of benefit of quinolones for treatment of IBD and they usually require an extended treatment course; given the safer alternatives, quinolones should generally be avoided during pregnancy. Short courses for the treatment of pouchitis can be considered. There are limited data in breastfeeding, but quinolones are probably safe to use if necessary [81].

Amoxicillin/clavulanic acid

Amoxicillin/clavulanic acid is a pregnancy category B drug and a safer alternative antibiotic for treatment of pouchitis. A population-based case-control study [82] and a prospective controlled study [83] did not show evidence of increased teratogenic risk and the drug is safe to use during breastfeeding.

Corticosteroids

Corticosteroids are classed as pregnancy category C drugs. To date, evidence suggests that use in the first trimester should be with caution, owing to a low risk associated with oral clefts in the newborn [84]. A meta-analysis from the year 2000 reports a summary OR for case-control studies examining the risk of oral clefts (OR: 3.35; 95% CI: 1.97–5.69) [85]. However, for

major malformations, the overall risk was low (OR: 1.45; 95% CI: 0.80–2.60). A total of 311 women who received glucocorticosteroids during the first trimester were enrolled in a prospective controlled study. An increased rate of major anomalies above 2.5-fold as powered by this study was not found and no cases of oral cleft were noted [86]. Premature rupture of membranes and adrenal insufficiency of the newborn were noted in a study of post-transplant recipients exposed to corticosteroids during pregnancy [87]. Notably, a neonate born to a mother with CD who ingested 32 mg oral prednisone and used 100 mg hydrocortisone enemas daily in the last month prior to delivery was found to develop adrenal insufficiency within 3 h after birth [88]. An additional concern involves the development of gestational diabetes. Overall, it can be concluded that corticosteroid use poses a small risk to the

developing infant; however, the mother needs to be informed of both the benefits and the risks of therapy. With regard to breastfeeding, another possible concern, data support prednisone and prednisolone as compatible.

There are very little data on the safety of budesonide. A case series of eight patients with CD treated with budesonide did not find an increased risk of adverse outcomes [89]. Inhaled or intranasal budesonide is not associated with adverse fetal outcomes based on large clinical series [90,91] and safety in lactation is not known.

Immunomodulators

Methotrexate

Methotrexate, a pregnancy category X drug, is clearly teratogenic and should not be used in women considering conception. Methotrexate is a folic acid antagonist and use during the critical period of organogenesis (6–8 weeks postconception) is associated with multiple congenital anomalies collectively called methotrexate embryopathy or the fetal aminopterin–methotrexate syndrome [81]. The syndrome is characterized by intrauterine growth retardation, decreased ossification of the calvarium, hypoplastic supraorbital ridge, small, low-set ears, micrognathia, limb abnormalities and occasional mental retardation [92]. Exposure in the second and third trimesters may be associated with fetal toxicity and mortality [81]. Methotrexate may persist in tissues for long periods, and it is suggested that patients wait at least 6 months from the discontinuation of the drug before attempting conception.

Methotrexate is excreted in breast milk and may accumulate in neonatal tissues. The American Academy of Pediatrics classifies methotrexate as a cytotoxic drug with the potential to interfere with cellular metabolism [93] and it is consequently contraindicated in breastfeeding.

Table 1. US FDA categories for the use of medications in pregnancy.

Category	Definition
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

Data taken from [150].

Azathioprine/6-mercaptopurine

6-mercaptopurine (6MP) and its prodrug azathioprine (AZA) are pregnancy category D drugs. To date, these are the most controversial drugs to use in pregnancy with conflicting data, but are widely used for patients with IBD, rheumatoid arthritis and transplantation. 6MP/AZA are teratogenic in animal studies with increased frequencies of cleft palate, open-eye and skeletal anomalies seen in mice exposed to AZA, and cleft palate, skeletal anomalies and urogenital anomalies seen in exposed rats [94]. In humans, transplacental and transamniotic transmission of AZA and its metabolites from the mother to the fetus can occur [95]. However, there is no consistent evidence for an increased risk of teratogenicity. For AZA and 6MP, the oral bioavailability is low (47 and 16%, respectively) [94]. The early fetal liver lacks inosinate pyrophosphorylase, the enzyme required to convert AZA to 6MP, and this may limit the toxic exposure of the drug to the fetus during the crucial period of organogenesis. While theoretically reassuring, large population safety data are needed to confirm that thiopurines are low risk for use in pregnancy.

The largest evidence on safety comes from transplantation studies where rates of congenital anomalies ranged from 0 to 11.8% without recurrent patterns [94]. A population-based cohort study from Denmark compared 11 women exposed to AZA or 6MP with the general population [96]. The adjusted OR for congenital malformations was 6.7 (95% CI: 1.4–32.4). However, when a single severely ill patient with autoimmune hepatitis and multiple other medications was removed from the cohort, the OR was 3.4 (95% CI: 0.4–27.3).

In IBD, multiple case series have not noted an increase in congenital anomalies [97–100], although one study did report a higher incidence of fetal loss in women with IBD with prior treatment on 6MP compared with those who had never had

Table 2. Medication recommendations for pregnancy and breastfeeding.

Drug	US FDA pregnancy category	Recommendations for pregnancy	Recommendations for breastfeeding
Aminosalicylates			
Balsalazide	B	Low risk	No human data; potential diarrhea
Mesalamine	B	Low risk	Limited human data; potential diarrhea
Olsalazine	C	Low risk	Limited human data; potential diarrhea
Sulfasalazine	B	Low risk; give 2 mg folate daily	Limited human data; potential diarrhea
Antibiotics			
Amoxicillin/clavulanic acid	B	Low risk	Probably compatible
Quinolones: ciprofloxacin	C	Avoid	Limited human data; avoid prolonged courses
Metronidazole	B	Low risk; avoid T1	Limited human data; potential toxicity
Rifaximin	C	No human data; animal teratogen	No human data
Biologics			
Adalimumab	B	Low risk	Limited human data; probably compatible
Certolizumab	B	Low risk	Limited human data; probably compatible
Infliximab	B	Low risk	Limited human data; probably compatible
Natalizumab	C	Limited human data	Limited human data; probably compatible
Corticosteroids			
All corticosteroids, including budesonide	C	Low risk; avoid T1	Compatible
Immunomodulators			
Azathioprine/6MP	D	Animal teratogen; low risk	Low risk; probably compatible
Cyclosporine	C	Low risk	Limited human data; potential toxicity
Methotrexate	X	Contraindicated	Contraindicated
Tacrolimus	C	Low risk	Limited human data; potential toxicity
Thalidomide	X	Contraindicated	No human data

T1: Trimester 1.

Modified with permission from [151].

6MP exposure [101]. A French study of 86 women with IBD exposed to thiopurines during pregnancy versus 129 who were unexposed did not find a difference in the rate of congenital

anomalies [102]. A Danish cohort study by Norgard *et al.* found that women with CD exposed to corticosteroids and AZA/6MP were more likely to have preterm birth (12.3 and 25% respectively) compared with non-IBD controls (6.5%) [103]. There was an increased rate of congenital anomalies among women exposed to AZA/6MP compared with the control group (15.4 vs 5.7%) with an OR of 2.9 (95% CI: 0.9–8.9), although the exposed group was small (n = 26) compared with the control group (n = 628). Furthermore, based on disease activity, only the most severe patients were included in this study. On the contrary, a study by Goldstein did not find an increased rate of major malformations between neonates exposed to AZA and a control group, with six neonates in each group (3.5 vs 3.0%; p = 0.775; OR: 1.17; 95% CI: 0.37–3.69) [104].

Finally, the largest single study to date used the Swedish population-based medical birth registry to identify 476 women who were exposed to AZA during early pregnancy [105]. Approximately 300 had IBD and the rest other conditions. There was a threefold increased risk for ventricular/atrial septal defects with exposure to AZA in early pregnancy, adjusted for maternal characteristics (adjusted OR: 3.18; 95% CI: 1.45–6.04). The overall rate of congenital malformations was 6.2% in the AZA group compared with 4.7% among all infants born (adjusted OR: 1.41; 95% CI: 0.98–2.04). However, the data should be interpreted with caution as the majority of the cardiac defects were in non-IBD patients, suggesting a possible disease-specific risk.

Breastfeeding is now considered compatible with AZA use as there is little or no exposure of the drug to the fetus. Data are limited by small studies. Moretti *et al.* reported that two of four women breastfeeding on AZA did not have detectable levels of drug by high-performance liquid chromatography, and none of them had any complications [106]. Drug metabolite levels are negligible or undetectable in the breastfeeding infant as reported by three studies. Gardiner *et al.* reported

four infants with undetectable metabolite levels despite mothers whose levels were in the therapeutic range [107]. A study by Sau found that only two of 31 samples of breast milk collected from

ten lactating women had low levels of 6MP (1.2 and 7.6 ng/ml in one patient vs a serum level of 50 ng/ml), and metabolites (6-thioguanine nucleotides or 6-methylmercaptopurine) were not detectable in all ten infants [108]. There were no reports of hematologic or clinical immunosuppression. Finally, an elegant study by Christensen *et al.* addressed the timing of drug excretion into breast milk [109]. Milk and plasma samples obtained from eight lactating women on AZA at 30 and 60 min after drug administration and hourly for the following 5 h demonstrated peak excretion of 6MP in breast milk in the first 3 h after drug intake, with a wide range of peak plasma values corresponding to the variation in bioavailability of the drug. At 4 h, a similar curve of variable drug levels at much lower levels ranging from 2 to 50 µg/l was measured in maternal milk. On the basis of maximum concentration measured, an infant ingested less than 0.008 mg/kg bodyweight/24 h of 6MP. At this time there is no absolute contraindication to breastfeeding while on AZA/6MP, although the risks and benefits of breastfeeding while on AZA/6MP must be assessed carefully. Lactating mothers are advised to wait 4 h after dosing to feed.

Cyclosporine & tacrolimus

Cyclosporine

Cyclosporine is a pregnancy category C drug and overall is low risk to use during pregnancy. This drug is not a major human teratogen as evidenced by several studies. A meta-analysis of 15 studies of pregnancy outcomes after cyclosporine therapy reported no significant increase in major malformations of 410 patients at 4.1% compared with the general population [110]. In the obstetric literature [111], a retrospective review of 38 pregnancies in 29 post-transplant recipients between 1992 and 2002 reported four spontaneous abortions and ten first-trimester terminations for worsening liver function. There were no intrauterine or neonatal deaths, five minor congenital anomalies were noted and the mean gestational age was 36.4 weeks. The study by Nagy *et al.* found that in women on chronic immunosuppression at least 2 years after liver transplantation with stable allograft function, planned pregnancies were seen to have excellent maternal and neonatal outcomes [111].

There are several case reports demonstrating efficacy of cyclosporine use during pregnancy to control disease activity of UC allowing completion of pregnancy [112–115]. Cyclosporine is also an effective option for treatment and deferral of colectomy during pregnancy in the setting of corticosteroid-refractory fulminant UC [116]. Colectomy can pose substantial risk to the mother and fetus at the time of pregnancy and, while feasible, medical therapy is usually a better option.

The American Academy of Pediatrics considers cyclosporine contraindicated during breastfeeding owing to the potential for immunosuppression and neutropenia. Cyclosporine is excreted into breast milk in high concentrations.

Tacrolimus

Tacrolimus is also a pregnancy category C drug. The limited data on drug safety are reported from several studies on the post-transplant recipient population. The earliest report in 1997 describes

experience with 27 pregnancies exposed to tacrolimus with mean gestational age at 36.6 weeks [117]. Two infants died at weeks 23–24, 36% had transient perinatal hyperkalemia and one newborn had unilateral polycystic renal disease. A study in Germany on 100 pregnancies of transplant recipients (1992–1998) reported 68% live birth rate, 12% spontaneous abortion rate, 3% stillbirth rate and 59% preterm birth rate [118]. Four neonates had malformations with no pattern.

Subsequently, Jain *et al.* prospectively followed 49 pregnancies in 37 women over 13 years [119]. There were two preterm births of 36 women who survived the pregnancy. One infant died of Alagille syndrome; the rest survived and 78% were of normal birth weight. No other congenital abnormalities were noted.

As for tacrolimus exposure in IBD patients, there is a single case report of a UC patient who had a successful pregnancy on maintenance tacrolimus [120]. Tacrolimus is contraindicated in breastfeeding owing to the potential toxicity of high concentrations found in breast milk.

Biologic therapy

Infliximab

Infliximab (INF) is a pregnancy category B drug. It is a chimeric anti-TNF monoclonal IgG₁ antibody used for the induction and maintenance of CD [121] and UC [122]. It does not cross the placenta in the first trimester, protecting the infant from exposure during the critical period of organogenesis. INF does, however, cross very efficiently in the second and third trimester [123] and is detectable in the infant several months after birth [124,125].

There is cumulative evidence for INF as a low-risk drug during pregnancy. The two largest studies are the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) Registry [126] and the INF Safety Database [127] maintained by Centocor (Malvern, PA, USA). The TREAT Registry is a prospective registry of patients with CD [126]. Of the greater than 6200 patients enrolled, 117 of 168 reported pregnancies were exposed to INF. There was no difference in the rates of miscarriage (10 vs 6.7%) and neonatal complications (6.9 vs 10%) between those treated with INF and those who were not, respectively.

The INF Safety Database is a retrospective data collection instrument. It shows that 96 women (82 CD, one UC, ten rheumatoid arthritis and three unknown) with direct exposure to INF gave birth to 100 infants [127]. There was no difference in pregnancy outcomes in these women compared with what is expected in that population.

There are two case series reporting on the use of INF during pregnancy. The first describes ten women maintained on INF throughout pregnancy. All ten ended in live births with no reported congenital malformations [128]. The second describes a series of 22 patients with exposure to INF within 3 months of conception that continued until 20 weeks of gestation, at which time the drug was stopped to minimize placental transfer [129]. In this series, during the third trimester, several of the patients were seen to flare, there were three spontaneous abortions, one missed abortion, one stillbirth at 36 weeks (umbilical strangulation), two preterm births, three LBW infants and no congenital anomalies.

Placental transfer of INF in the second and third trimesters results in drug levels detectable in the infant up to 6 months after birth. A case report noted higher than detectable INF levels in an infant born to a mother who was on INF therapy every 4 weeks [124]. The mother breastfed and continued to receive INF but the infant's INF level dropped over 6 months, suggesting placental rather than breast milk transfer. In a case series of eight patients receiving INF during pregnancy, all eight patients delivered a healthy infant [125]. Mean time between delivery and the last infusion was 66 days (range: 2–120 days). The INF level at birth was always higher in the infant and cord blood than in the mother and remained detectable 2–7 months after birth. Perhaps the infant reticuloendothelial system is too immature to clear the antibody as efficiently as the adult mother. INF has not been detected in breast milk [130,131].

The effect of exposure of INF on the infant's developing immune system is unknown, although abnormal immunological development leading to increased risk of infection, autoimmune disease and malignancy is theoretically possible. In adults, anti-TNF treatment has been shown to disrupt germinal center reactions at least in part via effects on follicular dendritic cells, suggesting the same may occur in newborns [132]. There are also three case reports of malignancies in children exposed to infliximab *in utero*: one sacrococcygeal teratoma in a 3-week-old male, one neuroblastoma of the liver, kidneys and stomach in a 2-month-old female, and one leukemia in a 4-year-old child [CENTOCOR, DATA ON FILE]. While these malignancies may also occur in the unexposed population, further observation is needed in larger populations to ensure that this is not causal. Thus far, there has been no reported adverse event associated with elevated INF levels in newborns, although there is no long-term follow-up. In our experience, infants exposed to INF *in utero* have appropriate responses to standard early vaccinations [133]. In adults receiving a similar agent, ADA, pneumococcal and influenza vaccinations were given safely and effectively [134]. However, in adults maintained on combination immunomodulator (6MP/AZA) and biologic (ADA/INF) therapy, there is a recent report of a lower response to pneumococcus vaccine (PSV-23) by measured antibody titers [135]. Live vaccinations, such as varicella, smallpox and so on, are contraindicated in immunosuppressed patients on anti-TNF therapy. In the past, live virus was first encountered by infants during vaccination at 1 year of age (varicella and measles–mumps–rubella), at which point INF levels would be undetectable. However, currently, rotavirus live vaccine is given orally at 2 months of age. Despite its mode of administration and being significantly attenuated, the safety of this virus in this setting is not known and the mother and pediatrician should be cautioned against its use if either INF or ADA levels may be present.

Adalimumab

Adalimumab is a pregnancy category B drug and is FDA approved for induction and maintenance of remission in CD. Three case reports [136–138] document the successful use of ADA to treat CD during pregnancy, including one in which the patient received

weekly dosing throughout pregnancy for a total of 38 doses [138]. The Organization for Teratology Information Specialists reports 27 women enrolled in a prospective study of ADA in pregnancy and an additional 47 ADA-exposed pregnant women in a registry [CHAMBERS CD, JOHNSON D, JONES KL, PERS. COMM.]. There was no difference in the rate of spontaneous abortion and stillbirth for those with CD compared with the general population and the rates of congenital malformation and preterm delivery are also within the expected range.

Adalimumab, an IgG1 antibody, would be expected to cross the placenta in the third trimester as INF does. However, as ADA levels cannot be checked commercially, this has not been confirmed. ADA is considered compatible with breastfeeding, although there are no data in humans.

Certolizumab pegol

Certolizumab pegol (CZP) is a PEGylated Fab fragment of a humanized anti-TNF- α monoclonal antibody that is efficacious in the treatment of CD [139]. It does not have an Fc portion and therefore is not expected to be actively transported across the placenta as INF and ADA are. In a study of pregnant rats, much lower levels of the drug were found in the infant and in breast milk when the PEGylated Fab fragment of this antibody versus the murinized IgG1 antibody of TNF- α was administered [140]. Similarly, in humans, a series of ten patients with CD receiving CZP during pregnancy up to 2 weeks prior to delivery describes high levels of the drug in the mother's serum but low levels in the infants and their cord blood on the day of birth [141]. It is hypothesized that the Fab fragment may cross the placenta passively in low levels in the first trimester during the period of organogenesis. However, this may be true for all anti-TNF agents, and further data are clearly needed to establish safety.

Timing of anti-TNF therapy in pregnancy

Infliximab, CZP and ADA should be continued through conception and the first and second trimester on schedule. If the patient is in remission, the last dose of INF is given in our practice at around week 30 of gestation and then immediately after delivery. We give the last dose of ADA at approximately week 32 of gestation and then immediately after delivery. While the half-life of ADA is similar to INF, given the biweekly dosing of ADA, we stop it later in the course to reduce the risk of flares in the mother. The risks to the mother include a flare of disease prior to delivery and the development of antibody to the anti-TNF agent. For INF, the dose will be delayed by 2–4 weeks, which should not significantly increase antibody risk. For ADA, this may be more of a concern. In some instances, the mother may flare during this time period. In these cases, the available options include either restarting anti-TNF therapy or using steroids to manage the patient until the time of delivery; the decision is made depending on how far the mother is from delivery. In our practice, we refrain from administering INF at week 39 of gestation, however, a mother experiencing flaring at week 34 on ADA would probably benefit from continuing dosing on schedule. Given its minimal placental transfer, CZP

is continued on schedule until delivery. Rotavirus vaccine can be given to the infant on schedule if there is no INF detectable in their blood at the time of vaccination or if the mother received CZP as that does not cross the placenta in significant amounts. As testing for ADA levels is not commercially available, we advise mothers not to have their child vaccinated against rotavirus.

Fish oil supplements

Fish oil supplementation is not FDA regulated and is purchased over the counter. Women with IBD who may be at an increased risk for preterm birth and miscarriage may find some benefit from fish oil supplementation. The limited data thus far suggest it is low risk for use in pregnancy. Fish oil supplementation may play a role in preventing miscarriage associated with the antiphospholipid antibody syndrome [142]. In addition, a randomized controlled trial of fish oil supplementation demonstrated a prolongation of pregnancy without detrimental effects on the growth of the fetus or on the course of labor [143].

Bisphosphonates

Bisphosphonates (alendronate and risedronate) are pregnancy category C drugs and often used to prevent bone loss in IBD patients, especially if treated with corticosteroids. Animal studies demonstrate placental transfer and storage in fetal bone, resulting in anatomic changes [144]. Alendronate, in particular, has a long half-life (up to 10 years) and should be given with caution to women of childbearing age. Despite the theoretical concern, there were no reported adverse effects of exposure to alendronate in 24 pregnancies, 6 months before conception or in the first 8 weeks of gestation [145]. In another cohort study, the risk of abortion, birth defects or growth retardation was not increased with various bisphosphonate exposures (12 with alendronate, five with etidronate, two with risedronate and two with pamidronate) [146]. Hypocalcemia can occur in neonates exposed to infused or injected bisphosphonates, but not oral formulations [145]. It is recommended that bisphosphonates be discontinued once a patient conceives. There are no data on the use of bisphosphonates during breastfeeding.

Diagnostic testing in the pregnant patient

Laboratory studies

Patients on immunomodulators and biologics should continue to receive regular laboratory monitoring. With disease exacerbation, the initial diagnostic workup includes laboratory studies aimed at evaluation of inflammation, and stool studies to rule out infection. One must keep in mind normal physiologic changes of pregnancy when evaluating laboratory test results for status of IBD. Blood volume increases progressively from 6–8 weeks to 32–34 weeks gestation resulting in an expected hemodilution of pregnancy. Overall, there is an increase in red-cell mass, leukocyte counts are variable, and platelet counts rise but remain within normal limits. Liver function tests, particularly alkaline phosphatase, may be elevated [147]. C-reactive protein may be elevated as early as 4 weeks.

Imaging

Radiographic studies are best avoided for pregnant IBD patients to minimize exposure to ionizing radiation, but may need to be used to rule out life-threatening complications, such as toxic megacolon, bowel obstruction and appendicitis. The fetus is at greatest susceptibility for teratogenicity when exposed to ionizing radiation at 2–20 weeks gestation above an estimated 0.15 Gy threshold. Iodinated contrast is not teratogenic in animal studies; however, there is a theoretical risk for fetal hypothyroidism with exposure. Magnetic resonance imaging avoids fetal exposure to ionizing radiation and is the imaging modality of choice for any pregnant patient. Gadolinium, however, is teratogenic in animal studies and should be avoided in the first trimester. Advances in imaging techniques offer magnetic resonance enterography as an attractive alternative approach to evaluating small bowel inflammation and is the preferred modality in pregnancy.

Endoscopy

Endoscopic evaluation for disease activity in the pregnant IBD patient is seldom necessary, but may be helpful in new diagnoses of IBD, suspected distal bowel disease flare or significant rectal bleeding. Unsedated flexible sigmoidoscopy is the lowest risk procedure. If sedation is needed, meperidine (category B) alone is recommended and preferred over fentanyl (category C). Midazolam (category D) should be avoided. Bipolar cautery poses less risk than monopolar cautery. If unavailable, then the grounding pad must be placed away from the uterus. The patient should always be positioned in the left lateral decubitus position to avoid compression of the vena cava and aorta, which can exacerbate hypotension [148]. Obstetric anesthesia assistance should be considered.

Health maintenance

One area often overlooked in patients with IBD is healthcare maintenance. Prior to attempting conception, women with IBD should be counseled on ways to maximize their overall health and achieve a durable remission.

All immunizations (hepatitis A, hepatitis B, influenza, pneumococcal, Td/Tdap, human papillomavirus and live vaccines [measles–mumps–rubella and varicella/zoster]) should be up to date. Any live vaccines needed should be given prior to conception if the patient is not on an anti-TNF agent. For IBD patients, there is an increased risk of cervical dysplasia (which can impact fertility), particularly if they are exposed to an immunomodulator or biologic. Pap smears should be up to date and human papillomavirus vaccine should be encouraged in women 9–26 years of age. Levels of B12, folate and vitamin D should be checked and supplemented as appropriate. Surveillance colonoscopy should also be up to date.

Expert commentary

Women with IBD have similar fertility rates to the general population, except when they have had pelvic surgery or have very active disease. Once pregnant, regardless of disease activity, they

have a higher rate of adverse outcomes and should be followed as high-risk pregnancies. However, most women will have a healthy pregnancy and healthy infant, and should not be discouraged from childbearing.

The majority of IBD medications are low risk for use during conception and pregnancy, with the exception of methotrexate and thalidomide. There is no significant evidence for an association with congenital anomalies among other standard IBD medications thus far, although larger studies are needed. Any concerns about medication risk for an adverse fetal event must be carefully weighed against the benefit to the health of the mother and minimizing disease activity. Discontinuation of medications at conception or for breastfeeding is often a cause for disease flare. While appropriate imaging, endoscopy, surgery and administration of new medications can be safely carried out during pregnancy, avoiding them by keeping the patient stable during pregnancy is the best course.

Current evidence suggests that a woman with IBD contemplating pregnancy should optimize her disease status and overall health. Low-risk, effective medication regimens should allow a durable remission and health maintenance should be kept up to date. Methotrexate should be discontinued 6 months prior to attempting conception. Aminosalicylates, AZA/6MP and anti-TNF agents are continued during conception and pregnancy. There are two potential nuances to this policy: a patient on sulfasalazine may be switched to a mesalamine agent (if tolerated) to minimize anti-folate effects, and a stable patient on combination AZA/6MP and an anti-TNF agent may consider discontinuing the AZA/6MP prior to conception to minimize risk to the fetus. While this may seem inconsistent since data suggest that continuing AZA/6MP during pregnancy is low risk, at every opportunity we want to maintain the mother's health and minimize risk to the fetus. Discontinuing AZA/6MP in a patient stable on INF has not been associated with an increase in adverse events [149]. Corticosteroids and antibiotics should be avoided in the first trimester to avoid the small risk of congenital malformations. However, if a patient is flaring, steroids may be used at any point in pregnancy. A patient naive to AZA/6MP should not receive

it for the first time during pregnancy as the risk of leukopenia and pancreatitis is unpredictable. Anti-TNFs can be started in the appropriate naive patient during pregnancy. Use of INF and ADA should be minimized in the third trimester (we stop dosing of INF at week 30 and ADA at week 32 of gestation if tolerated) given the high rates of placental transfer. If an anti-TNF agent is to be given for the first time during pregnancy, CZP may be the ideal choice given the low rate of placental transfer.

Five-year view

Advances in medical therapy for IBD have allowed more women to be in remission and consider pregnancy. However, the safety of these medications has not been fully established with respect to birth defects as well as to long-term consequences to the infant with respect to infections and developmental delay. A current 1000-patient prospective registry is underway among women with IBD that will follow them throughout pregnancy and the first 4 years of the infant's life. This will provide critical and statistically significant information on the safety of IBD medications during pregnancy and the risk to the child both *in utero* and during early childhood. In addition, several new medications for IBD will be released in the next 5 years and their safety during pregnancy will also need to be established. By better understanding the transfer of antibodies across the placenta, the safety of new biologic medications can be established more quickly. In the future, all women with IBD will be followed as high-risk obstetric patients and their offspring will be monitored for developmental delay if appropriate. Early intervention for any potential problems will be provided to improve outcome.

Financial & competing interests disclosure

Uma Mahadevan serves as a consultant for Abbott, Centocor, UCB, Elan, and Proctor and Gamble. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Fertility in women with inflammatory bowel disease (IBD) is similar to the general population unless they have had pelvic surgery.
- Women with IBD have higher rates of adverse pregnancy outcomes compared with the general population, even if their disease is in remission.
- The majority of medications for IBD are low risk during pregnancy and breastfeeding, with the exception of methotrexate, which is absolutely contraindicated.
- Infliximab and adalimumab are low risk for use throughout pregnancy and during breastfeeding. However, given transfer across the placenta during the third trimester, dosing can be suspended after week 30–32 of gestation.
- Certolizumab has minimal transfer across the placenta and is the biologic of choice for an IBD patient planning to conceive imminently or needing initiation of a biologic during pregnancy.
- Radiocontrast imaging and endoscopic studies should be avoided during pregnancy unless absolutely indicated. Magnetic resonance imaging is the modality of choice to avoid exposure to ionizing radiation.
- Prior to conception, patients should ideally be in remission, have been counseled about the use of medications in pregnancy and be up to date with respect to their healthcare maintenance.

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