REVIEW ARTICLE

Inflammatory bowel disease and pregnancy: fertility, complications and treatment

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Abstract   Inflammatory bowel disease (IBD) is commonly diagnosed and treated in the young population. Therefore, it is common that women anticipating or undergoing pregnancy will have to cope with the additional burden of their IBD. Pregnancy in an IBD patient also presents challenges for the practitioner, in that the usual diagnostic and therapeutic armamentarium of potential tests and therapies is disrupted. This review covers the implications of IBD for fertility, pregnancy and offspring, and discusses the management of IBD in pregnancy.

Keywords Inflammatory bowel disease, pregnancy, ulcerative colitis, Crohn's disease, pregnancy complications

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Introduction

There are currently an estimated 1-1.3 million people suffering from inflammatory bowel disease (IBD) in the United States [1,2]. Ulcerative colitis (UC) is more common in men and Crohn's disease (CD) is more common in women. Although CD and UC can occur at any age, people are frequently diagnosed between the ages of 15 and 35 years. According to the Olmsted County study, which examined a well-defined US population from 1970-2010, the adjusted annual incidence of CD from 2000-2010 was 10.7 cases per 100,000 person-years, while that of UC was 12.2 per 100,000 person-years. The median age of diagnosis of UC and CD was 34.9 years and 29.5 years, respectively [3]. For women, this age range encompasses the child-bearing years and therefore has implications for fertility, pregnancy, offspring health and treatment.

IBD and effects on fertility

Fertility rates in women with IBD depend on disease activity and therapeutic strategy. Those with quiescent or

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medically treated IBD and no prior pelvic surgery have similar infertility rates to the general population, ranging between 5 and 14% [4-6]. Conversely, active disease can impair fertility, probably via multifactorial mechanisms including pelvic inflammation of the fallopian tubes and ovaries, dyspareunia secondary to perianal disease, and adhesions or scarring from previous surgeries [7]. Voluntary nulliparity due to fear of intimacy and disease transmission to offspring, poor body image (ostomy, perianal disease), and depression are also significant [8].

Pelvic surgery, specifically in UC, can significantly increase female infertility via scarring, adhesions, or injury to the reproductive organs. A meta-analysis of ileal pouch anal anastomosis (IPAA) surgery in UC found a 48% postoperative infertility rate, 3 times higher than in medically treated patients [9-12]. Delaying abdominal surgeries that spare the pelvis, such as colectomy with ileorectal anastomosis/subtotal colectomy, rectal stump creation and ileostomy, until childbearing is complete are temporizing measures that may preserve female fertility.

IBD also decreases the efficacy of assisted reproductive technology (ART) treatments in women with infertility. Women with CD should initiate ART treatment before surgery is required for CD. In women with UC and using ART, the risk of preterm birth is increased 5-fold and thus there should be increased prenatal observation in this population [13].

Data concerning the effects of IBD on male fertility are in shorter supply. Sulfasalazine is known to cause reversible infertility in men, due to dose-dependent oligospermia, reduced sperm motility and altered sperm morphology [14]. Analogously, methotrexate (MTX) may adversely affect sperm morphology, although as with sulfasalazine, such effects are reversible upon medication discontinuation. It is recommended that men stop MTX 3-6 months before conception [15].

IBD and effects on preconception and pregnancy

Women with IBD are more likely to experience pregnancy complications compared to age-matched controls. These include spontaneous abortion, infants small for gestational age (SGA), preterm birth, and labor and delivery complications. They are correlated with disease activity.

Large community-based studies, like the one published by Mahadevan *et al* in 2007, revealed that women with IBD are more likely to have adverse conception outcomes or pregnancy complications (odds ratios of 1.65 and 1.78 respectively) [16]. Independent predictors of adverse outcomes include a history of surgery for IBD and non-Caucasian ethnicity. Separate studies have further examined the associations between IBD and pregnancy complications such as preterm birth, low birth weight (LBW) and preterm premature rupture of membranes [17-20]. It was shown that disease activity is a strong predictor of these adverse pregnancy outcomes [21-23]. These findings were subsequently confirmed by O'Toole *et al* in a meta-analysis. Compared with non-diseased controls, data pooled from multiple studies show that women with IBD were at greater risk for preterm birth, SGA, LBW, stillbirth and congenital anomalies [24]. However, the authors did find evidence of publication bias for the link between IBD and congenital anomalies and that association may not be reliable.

Moreover, disease activity at the time of conception influences whether a patient will have an IBD flare during pregnancy. For active UC, roughly 45% will worsen, a quarter will remain the same and a quarter will improve. In active CD, a third will probably worsen, a third will stay the same (active, stable disease) and one third will improve (remission) [25]. Of women with IBD in remission at the time of conception, 80% remain in remission and 20% will experience a disease flare [26-28]. In light of the evidence associating active IBD disease and pregnancy complications, controlling disease activity and suppressing disease flares is the priority in managing IBD in pregnancy. The current Toronto Consensus statements and the European Crohn's and Colitis Organization (ECCO) guidelines were generated accordingly [29,30].

Given the importance of controlling disease activity during conception, preconception counseling becomes crucial. A prospective study of 149 IBD women of childbearing age from 2008-2013 demonstrated that those who received 30 min of preconception IBD point-of-care counseling were more likely to adhere to IBD medications and prenatal vitamins, cease smoking and achieve more controlled perinatal IBD disease activity [31].

Preconception management of women with IBD should include reviewing and optimizing medications, confirming disease remission (fecal calprotectin/colonoscopy) and ensuring standard health care maintenance, such as surveillance colonoscopies, pap smears, vaccinations and blood monitoring, including vitamin D and iron studies.

IBD and mode of delivery

Cesarean section rates as high as 44% have been reported in IBD patients [32]. Only a minority of these are likely to be due to true obstetrical indications. A meta-analysis of 6 studies by Cornish *et al* in 2007 retrospectively examined case-control studies from 1980-2006 and found that the higher rate of cesarean section was significant for CD but not UC [33]. Vaginal delivery has risks for anal sphincter or perineal damage, which lead to worsening perianal disease in CD or pouch dysfunction in patients with IPAA prior to pregnancy. However, some studies show that vaginal delivery is feasible in patients with inactive disease [34-36]. In fact, data suggest that vaginal delivery is of low risk for those with a pouch, with a return to pre-pregnancy function within 6 months [37]. Therefore, delivery by cesarean section is currently recommended for those with active perianal disease at the time of delivery, or with an ileo-anal pouch. Otherwise, the mode of delivery is at the discretion of the obstetrician.

Effects of pregnancy on medical management of IBD patients

Antibiotics

Perianal disease and intraabdominal abscesses due to fistulizing CD are often treated with a combination of metronidazole and ciprofloxacin (FDA category B and category C, respectively). The goal is to provide sufficient anaerobic and gram-negative coverage. Metronidazole, especially for a short course of 5-7 days, is considered safe in pregnancy [38]. Koss *et al* studied 922 women treated with metronidazole for clinical indications in an urban New York State hospital to compare rates of preterm, birth, LBW or major congenital anomalies [39,40]. No association was found between metronidazole treatment and these conditions.

Though fluoroquinolone use was thought to increase the risk of arthropathies in the offspring, studies have not confirmed any associations between ciprofloxacin use and major congenital anomalies, including musculoskeletal complications [41]. A meta-analysis by Bar-Oz *et al* concluded that fluoroquinolone use during the first trimester of pregnancy does not appear to increase the risk of major malformations, stillbirths, preterm births or LBW [42]. However, given the known potential effect of ciprofloxacin on bone and cartilage, avoidance during pregnancy is recommended [43]. After birth, breastfeeding is discouraged while on either of these antibiotics. Therefore, ECCO guidelines have categorized metronidazole and ciprofloxacin as low risk for short-term use but with limited benefit from long-term treatment [30].

Other antibiotics used in IBD may require alteration in pregnancy. Rifaximin, an FDA category C medication in pregnancy, has been used to treat pouchitis but has not been well studied in IBD [44]. Amoxicillin/clavulanate is also used to treat pouchitis and is considered an FDA category B medication [45]. As an alternative, penicillins are considered first-line therapy in pregnancy and have not been shown to cause fetal malformations or adverse pregnancy outcomes [31].

Finally, the use of peripartum broad-spectrum antibiotics has been studied in animals. Chang *et al* published results suggesting that broad-spectrum peripartum antibiotics

(cefoperazone specifically) promote offspring gut dysbiosis, immune dysfunction and IBD progression. Antibiotic-perturbed maternal microbiota probably contribute to neonatal gut dysbiosis [46]. More investigation into this question is warranted.

Aminosalicylates (5-ASA)

The safety of 5-ASA compounds was studied in several trials [47,48]. Women taking 5-ASA for IBD do not have a higher incidence of fetal abnormalities than the general population.

The various formulations of mesalamine are generally FDA category B medications, except for Asacol, a category C drug. This label was due to the presence of dibutyl phthalate (DBP) in the coating of Asacol and Asacol HD, which has been associated with urogenital defects in male offspring: nonsignificant adjusted odds ratio (OR) of 1.32 (0.18-9.63) [49]. Notably, these complications only arose with DBP doses of greater than 190 times the human dose in animal studies [50]. Pregnant women should be advised of the potential risk to the fetus and the limitations of the current literature.

Sulfasalazine is a category B drug and is safe to continue peripartum. Pregnant patients treated with sulfasalazine should also have folic acid supplementation at a dose of 1 mg of oral folic acid twice daily in the pre- and perinatal period to avoid fetal neural tube defects [51].

In conclusion, mesalamine and sulfasalazine are safe in pregnancy. A meta-analysis by Rahimi et al, following 2200 pregnant women with IBD, revealed no significant association between the use of mesalamine or sulfasalazine and a greater incidence of congenital malformations, stillbirth, spontaneous abortion, preterm delivery, or LBW [52]. Pregnant patients should be assured of these data.

Immunomodulators

Previously, thiopurine immunomodulators such as azathioprine (AZA) and mercaptopurine (6-MP) were classified as category D because of the teratogenic effects at high doses observed in animal models. However, the current consensus is that thiopurines are safe during pregnancy [53].

A retrospective study by Francella et al revealed no significant differences in spontaneous abortion, birth defects, congenital malformations, neoplasias or increased infections in patients taking 6-MP compared with controls. 6-MP use appeared to be safe, whether taken before or during pregnancy. Medication discontinuation during those time periods is therefore not indicated [54]. Nevertheless, these medications remain classified as category D.

When the outcomes of 115 pregnancies with paternal exposure to AZA or 6-MP were prospectively analyzed by Hoeltzenbein et al, the rate of major malformations was not increased. There were no birth defects or chromosomal aberrations in the exposed group. However, a higher rate of elective terminations was noted. The authors recommended

further prospective studies to explore the possible association with an increased risk of spontaneous abortion [55].

A meta-analysis by Akbari et al answered that question. It included 5 studies comprising women and men exposed to immunomodulators within 3 months of conception and/or during pregnancy. They analyzed 66 exposed pregnancies with 60 live pregnancies. There was no increased risk of spontaneous abortion, congenital anomalies, LBW or preterm birth (although studies were not adjusted to disease activity) [56]. Casanova et al also showed that the rate of pregnancy complications was similar among the thiopurines (21%) and non-exposed (28%) groups (Table 1) [57].

Similarly, the Pregnancy in IBD And Neonatal Outcome (PIANO study) by Mahadevan et al yielded the same results in a prospective setting [16]. PIANO is a prospective registry of pregnancy outcomes in women with IBD, involving 30 IBD centers in the US with over 1500 patients categorized based on drug exposure between conception and delivery. The groups included unexposed patients vs. patients exposed to AZA/6-MP, biologics, or any combination of the two. Relative risks of spontaneous abortion, preterm birth, LBW, intrauterine growth restriction (IUGR), cesarean section, neonatal intensive care unit (ICU) stays, and congenital anomalies were not significant.

However, there is evidence that immunomodulators and their metabolites are transferred from mother to fetus [58,59]. DeBoer et al measured thiopurine metabolites 6-thioguaninenucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP) in the red blood cells (RBCs) of mothers and neonates after delivery. 6-TGN concentrations, which correlate with therapeutic doses of immunomodulators, were detected in the RBCs of both the infant and mother. 6-MMP, a marker for immunomodulator hepatotoxicity and myelotoxicity, was not detected in the infants. Therefore, thiopurines should be continued in pregnancy with metabolite monitoring, especially in women with active disease [60].

Jharap et al performed a prospective study examining the effects of pregnancy on thiopurine metabolism and the effect of thiopurine use on exposed fetuses. At birth, all newborns had a normal Apgar score and none had major congenital abnormalities. However, 60% of the newborns had anemia [61]. Newborns to mothers exposed to thiopurines should have blood counts monitored.

Small studies have examined AZA and 6-MP in lactating women (in both plasma and breast milk). Concentrations of 6-MP in breast milk peaked within the first 4 h after drug intake with the infant ingesting <0.008 mg/kg bodyweight/24 h or <1% maternal dose [62]. Pumping and discarding 4 h after taking the drug could be a possibility. There was no increase in infections or hospitalizations and all offspring showed age-appropriate mental and physical development [63].

Biologics

Tumor necrosis factor inhibitors (anti-TNFs)

Anti-TNFs are generally considered safe during pregnancy and are category B medications. In the PIANO trial to date, more

Table 1 Summary of studies and evidence of medications

Study	Year	Disease	Medication	# of exposed pregnancies/live births	Complications	Congenital abnormalities
Katz/ IFX Safety Database [68]	2004	CD and UC	IFX	131[1]/64	Miscarriages 15% Therapeutic termination 19%; Same as general population	1
Schnitzler [69]	2011	CD and UC	IFX and ADA	42/32	7 premature deliveries; 6 LBW; 1 stillbirth and 1 death; outcomes no different compared to no or indirect anti-TNF	1
Johnson [76]	2011	CD	ADA	95/95	No difference in preterm delivery, birth weight in full term infants or serious infections;	11 major birth defects: 4.5% in ADA-exposed vs. 5.2% in disease-matched pregnancies vs. 6.6% in healthy pregnancies
Lichtenstein/ TREAT [67]	2013	CD	IFX	105/80	16.3% spontaneous abortion; clinical condition of infants born to IFX exposed women is comparable to those exposed to other CD treatments.	1
Casanova [57]	2013	CD and UC	IFX, ADA and CZP	66/60	The rate of pregnancy complications was similar among the anti-TNF (30%) vs. thiopurines (21%) vs. non-exposed (28%) groups	1
Mahadevan [80]	2013	CD and UC	IFX, ADA and CZP	31/33	None reported	0
Lin [95]	2014	CD and UC	Glucocorticoid	969[2]	Glucocorticoid use may increase risk for preterm birth, gestational diabetes, and LBW	82
Zelinkova [81]	2013	CD and UC	IFX and ADA	31/28	3 miscarriages	0
Seirafi [75]	2014	CD, UC and undetermined	IFX, ADA and CZP	133/119	Complications in 35% women and 20% newborns; safety profile similar to control group	2
Diav-Citrin [72]	2014	CD and UC	IFX and ADA	83/65	No cases of VATER/ VACTERL association	3
Clowse [86]	2015	CD	CZP	192/150	32 miscarriages; 10 induced abortions	5
De Lima [74]	2016	CD and UC	IFX and ADA	106/83	No difference in IBD relapse rate between women in deep remission who stopped IFX and those who did not in after week 22. Similar birth outcomes	0
Naureckas [90]	2016	CD and UC	UST	87/57	16 spontaneous abortions, 14 elective terminations, comparable to general population rates	1

(Contd...)

Table 1 *(Continued)*

Study	Year	Disease	Medication	# of exposed pregnancies/live births	Complications	Congenital abnormalities
Mahadevan [88]	2017	CD and UC	VDZ	24/11	One corpus callosum agenesis abnormality reported in a patient with extensive obstetric history	1
Chaparro [71]	2018	CD and UC	IFX	841[3]	No increase in infection rates in childhood in children exposed to anti-TNFs	
Mahadevan [93]	2018	UC	TOF	25/15[4]	No fetal deaths, neonatal deaths. Adverse events analogous to general population	0
Bar-Gil Shitrit [89]	2019	CD and UC	VDZ	24/15	Higher abortion rate in pregnant women taking VDZ compared to women taking ADA, IFX which may be confounded by baseline disease activity. Rates of IBD flares and steroid usage was significantly decreased	0

[1]Data obtained from 96 of 131 patients

[2]Study of infants after birth whose mothers required glucocorticoids perinatally

[3]Study of 841 children, half with mothers exposed to anti-TNFs and half without

[4]6 patients were lost to follow up; pregnancy and birth status is unknown for them

CD, Crohn's disease; UC, ulcerative colitis; IFX, infliximab; ADA, adalimumab; CZP, certolizumab pegol; anti-TNF, tumor necrosis factor inhibitor; SGA, small for gestational age; LBW, low birth weight

than 500 women have been exposed to anti-TNF medications during pregnancy, including approximately 260 to infliximab (IFX), 150 to adalimumab (ADA), 65 to certolizumab pegol (CZP), and 29 to a combination of agents. No increased rates of congenital anomalies were observed compared with the unexposed IBD cohort.

Similarly, a systematic review by Nielsen *et al* of more than 1500 anti-TNF-exposed pregnancies and a meta-analysis by Narula *et al*, comprising more than 1200 participants, found no pattern of adverse pregnancy outcomes (preterm delivery, abortion, LBW), congenital anomalies or immunosuppression [64,65].

Additional investigations studying anti-TNFs during pregnancy include the TREAT registry, which examined 117 pregnancies in CD patients on IFX and other therapies, the IFX Safety Database, which followed 96 women with CD and rheumatoid arthritis, and a large single-center study with 212 women on IFX and ADA (Table 1) [66-69]. In all these studies, there were no differences in the rates of miscarriage, neonatal complications, fetal malformation, live births, miscarriages, therapeutic terminations or general pregnancy outcomes between exposed and non-exposed individuals.

The PIANO registry, however, indicated that combination therapy with anti-TNFs and thiopurines may be associated with 2.4-fold greater odds of preterm birth and 1.7-fold greater odds of general pregnancy complications and delayed infant infections: relative risk 1.35 (1.01-1.80). Julsgaard *et al* also demonstrated a nearly 3-fold elevated risk of infection in infants born to women who were on this combination therapy during pregnancy compared to those on anti-TNF therapy alone [70]. However, this finding was challenged in the multicenter European TEDDY study, where 841 children were studied; approximately half had anti-TNF exposure (with or without thiopurine combination therapy) *in utero* and the other half did not. The 2 groups were compared and the incidence of severe infections were found to be similar (Table 1) [71]. Because of these conflicting data, the current guidelines state that anti-TNFs should be continued, especially in patients with more severe disease activity, as maintaining remission is paramount. [29].

Research has also been focused on the impact of anti-TNFs on fetuses (Table 1) [72-76]. As depicted in Fig. 1, immunoglobulins, and particularly all 4 subclasses of IgG (1-4), are detectable in the umbilical circulation. IgG transferred via the placenta persists longer in the newborn than in the mother, with a half-life of 48.4 days [77-79]. Anti-TNFs was found to actively traverse the placenta via the FcRn receptor, starting as early as the 2nd trimester, with the majority occurring in the 3rd trimester. Drug levels of IFX, ADA and CZP measured in a study by Mahadevan *et al* in mothers at birth, cord blood, infants, and then followed monthly in the infant until they were undetectable, showed wide ranges for IFX and ADA (2.9-39.5 µg/mL and 4.28-17.7 µg/mL respectively), along with significant median cord-to-maternal drug level ratios (Table 1) [80]. The median level of IFX in the cord was 160% that of the mother and the median level of ADA in the cord was 153% that of the
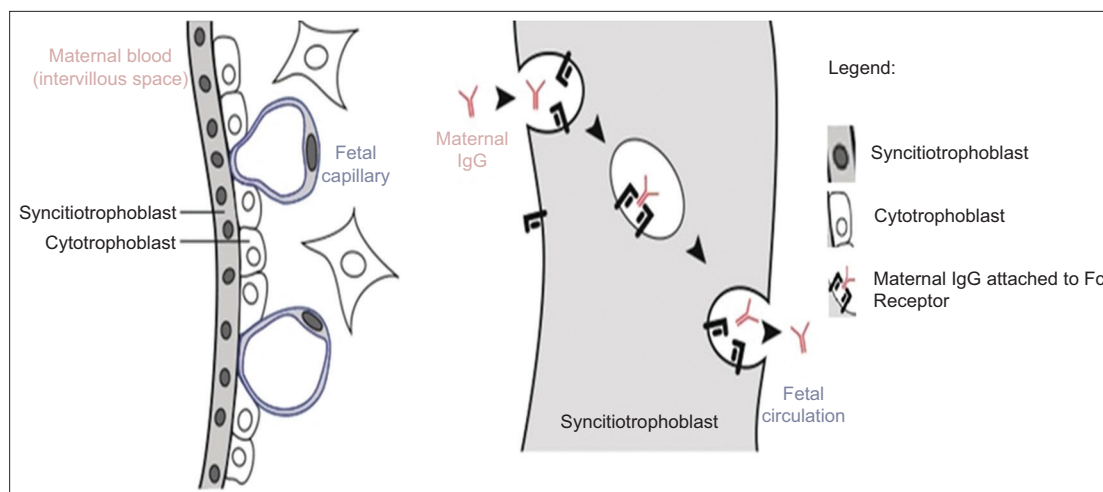
Figure 1 Active transplacental transport of immunoglobulin G (IgG). Reproduced with permission, Oxford University Press (http://creativecommons.org/licenses/by-nc/4.0), Hazes JM, Coulie PG, Geenen V, et al. Rheumatoid arthritis and pregnancy: evolution of disease activity and pathophysiological considerations for drug use. *Rheumatology (Oxford)* 2011;**50**:1955-1968.

mother. IFX levels were detectable for 2-7 months in the infant. ADA levels were detectable for 3 months. CZP had the lowest level of placental transfer, based on levels measured in cords and infants at birth, probably because it lacks an Fc portion. The median level of CZP in the cord was 3.9% that of the mother.

Subsequently, Julsgaard *et al*, in a prospective study, measured the umbilical cord and infant blood concentrations of IFX and ADA in women exposed to anti-TNF agents during pregnancy. They found that the IFX and ADA levels in the cord and infant blood were greater than that in the mother, as reflected by the median ratio of infant-to-mother drug concentration at birth (1.21 for ADA, 95% confidence interval [CI] 0.94-1.49; 1.97 for IFX, 95%CI 1.50-2.43). Interestingly, IFX was cleared more slowly than ADA from the infants and drugs were detected in infants until 12 months of age. The significance of this is not yet known [70].

The PIANO registry data did not show any association between biologic exposure in the third trimester and preterm birth, infections after 1 year of age, or disease activity in the third trimester or 4 months post-partum. Third trimester anti-TNF exposure did not detrimentally affect infant growth rate, immune development, number of infections or achievement of developmental milestones. Zelinkova *et al* also published data comprising 31 pregnancies in 28 women with IBD, observing the consequences of stopping anti-TNFs in the 3rd trimester (Table 1) [81]. All patients who stopped taking IFX (12 of 17, 71%) before gestational week 30 remained in remission, whereas 2 of 11 patients taking ADA who discontinued treatment before gestational week 30 had relapses of IBD. Of the 28 live births, there was 1 miscarriage in the IFX cohort and 2 miscarriages in the ADA cohort. There were no congenital malformations. Of these patients, 22% (5/23) had a flare or required therapy alteration postpartum. The investigators concluded that discontinuation of anti-TNF therapy appears to be safe for pregnant women with quiescent IBD.

Given that anti-TNF medications are transferred from mother to infant and that holding the medications in the 3rd trimester is found to be relatively safe, women in sustained remission should consider 3rd trimester anti-TNF dosing adjustments to minimize neonatal exposure [15]. Serum trough concentrations enable therapeutic drug monitoring and should help guide dosing in the late 2nd or early 3rd trimester of pregnancy.

Finally, extrapolating from the ongoing PIANO registry and controlling for drug exposure, breastfeeding in mothers on biologic therapy has not been associated with infection risk, abnormal height or weight, or deviations in achievement of developmental milestones. While disease activity and immunomodulator use has been inversely associated with breastfeeding, there is no such correlation with biologics. Beaulieu *et al* also analyzed PIANO, looking at serum samples collected from infants at least 7 months old for antibody titers to *Haemophilus influenzae* B or tetanus toxin in mothers exposed to biologic therapy and compared them to infants born to unexposed mothers [82]. They concluded that the use of biologic therapy does not affect the infant's response to vaccines.

A study by Benhorin revealed that, although IFX levels in breast milk increased to 101 ng/mL within 2-3 days of the infusion, these levels were roughly 1/200th of the level in blood (i.e., 0.5% plasma concentration) [83]. Likewise, ADA levels in breast milk were roughly 1/200th of the level in blood [84,85]. Since there is minimal if any placental transfer of CZP, none was detected in breastmilk (Table 1) [86].

In conclusion, anti-TNF agents are safe to use during pregnancy to induce and sustain disease control. Based on available safety data, there is no increased risk of congenital anomalies among infants exposed to these medications [87]. Consensus guidelines support continuing anti-TNFs throughout pregnancy. The decision to hold anti-TNFs in situations such as strong patient preferences to limit fetal exposure should be made on an individual case-by-case basis with extensive counseling. Holding the medication should only be considered in patients with a low risk of relapse: sustained

symptomatic remission for at least a year before conception, no evidence of active disease on imaging or endoscopy, documented therapeutic drug levels, no prior dose escalation, no intestinal resections, and no hospitalizations within the last 36 months for IBD flare. Guidelines suggest administering the last dose of anti-TNFs at 22-24 weeks gestation. With regard to postnatal care, these immunosuppressants are detectable in infants up to 6 months after birth. Therefore, current guidelines recommend delaying live vaccines for 6-12 months, with anti-TNF drug levels measured and drug clearance documented to help inform decisions [29,30].

Anti-integrins

Vedolizumab (VDZ) is a monoclonal antibody that provides gut-selective anti-inflammatory activity by blocking the α4β7 integrin. Vedolizumab is an FDA category B medication. Available data concerning its safety in pregnancy are limited. Mahadevan *et al* reported 27 pregnancies in 24 VDZ-treated females as well as 19 pregnant partners of males with IBD treated with VDZ across 6 studies (Table 1) [88]. Analysis of the female group showed a correlation between the severity of disease activity and pre-term live birth or spontaneous abortions. The data did not associate VDZ with any new safety concerns. Analysis of the partner group showed a similar trend. It seems that VDZ displays a similar pregnancy safety profile to that of anti-TNF medications and that the use of VDZ is not associated with more adverse outcomes, though this study was limited by small sample sizes and incomplete follow up.

Shitrit *et al* prospectively followed 330 pregnancies, of which 20 were in the setting of VDZ use at least 3 months before conception and continued throughout the third trimester (Table 1) [89]. They were compared to patients treated with TNF inhibitors, as well as those treated with 5-ASA and thiopurines. The abortion rate was significantly higher than that of the other groups. A possible confounder to this is the fact that patients on VDZ have already failed one or more biologics and therefore have more refractory and severe disease at baseline, which independently leads to worse pregnancy outcomes. Conversely, the rate of flares and corticosteroid usage in the VDZ group was significantly lower.

Based on the available evidence, VDZ appears safe to use in pregnancy and adverse pregnancy outcomes correlate with baseline IBD disease activity. These studies are currently limited by small sample sizes and larger studies with longer follow-ups are needed.

Anti-interleukin (IL) 12/23 agents

Ustekinumab (UST) is a humanized IgG1 that binds and inhibits IL-12 and IL-23 and is an FDA category B medication. Data regarding the safety of these drugs in pregnant IBD patients have been extrapolated from studies in patients with psoriasis. Naureckas *et al* studied pregnancy outcomes in pregnant women with psoriasis (plaque psoriasis or psoriatic arthritis) exposed to UST (Table 1) [90]. Eighty-seven pregnancy reports were

identified, predominantly in patients with plaque psoriasis. Average maternal age was 31 years. Most pregnancies (57/87; 65.5%) resulted in live births. There was one congenital anomaly (1.2%), 16 spontaneous abortions (18.4%), and 14 elective terminations (16.1%). In 16 of 87 pregnancies there was exposure to UST in all 3 trimesters whereas 37 reported exposure in the first trimester. In both these instances, the rates of spontaneous abortions and elective terminations were comparable to those reported in the general population (15-20%).

Similarly, Schaufelberger *et al* studied pregnancies with maternal use of UST from 4 phase 2 and 3 plaque psoriasis studies (ACCEPT and PHOENIX trials) [91]: 981 female patients received ≥1 dose of UST and 29 pregnancies were reported. The mean maternal age was 30 years and the mean duration of UST exposure prior to the reported pregnancy was 72±61 weeks. Pregnancy outcomes were reported for 26 of 29 pregnancies, including 14 (54%) live births, 5 (19%) spontaneous abortions and 7 (27%) elective abortions. All 5 spontaneous abortions occurred in the 1st trimester. Neonatal outcomes were generally healthy. Longer duration of UST exposure prior to the reported pregnancy was not associated with adverse outcomes. Even though the limited available data suggest that UST exposure may not impact pregnancy outcomes, the evidence is weak, and it is not recommended throughout pregnancy.

In a prospective multicenter study by Matro *et al* of women with IBD and their infants, the authors analyzed collected breast milk samples from patients receiving biologic therapy including UST, IFX, ADA, CZP, and natalizumab [92]. They reported low concentrations of these medications in the breast milk samples, with levels of UST ranging between 0.72 and 1.57 μg/mL. Breastfed infants of these mothers being treated with biologics and/or immunomodulators had infection risks and rates of milestone achievement comparable to those of non-breastfed infants and infants not exposed to these drugs. Maternal use of biologic therapy appears compatible with breastfeeding.

Janus kinase inhibitor

Outcome data following tofacitinib, a Janus kinase inhibitor, for UC in pregnancy are ongoing but limited. It is an FDA category C medication. Mahadevan *et al* recently reported outcomes of pregnancies with maternal and paternal exposure to tofacitinib in 5 UC interventional studies (Table 1)[93]. Eleven cases of maternal and 14 cases of paternal exposure to tofacitinib prepartum and peripartum were identified among 301 women of childbearing age. The pregnancy outcomes were 15 healthy newborns, 2 spontaneous abortions, and 2 medical terminations. No fetal deaths, neonatal deaths, or congenital malformations were noted. The adverse events were analogous to those reported for tofacitinib use in populations with rheumatologic disorders and to the background risks in the general population. It should be noted that tofacitinib was found to be teratogenic in animal models, with malformations such as omphalocele, ventricular septal defects and cranial abnormalities, though this was only observed at drug exposure levels of 70-140 times the recommended human drug dosing [94]. Given the lack of robust evidence and the small

sample sizes in available studies, general recommendations at the current time suggest avoiding use in pregnant women until additional information is available.

MTX

MTX is absolutely contraindicated in pregnancy (FDA Class X). It is an abortifacient and teratogen and post-conception use has been clearly linked to abortions and major birth defects [15]. Women of childbearing age should be on 1-2 forms of contraception and should wait at least 3-6 months after stopping MTX before attempting conception. MTX is also contraindicated in breastfeeding. Although excreted at levels <10% of maternal plasma concentration, its long half-life allows accumulation in neonatal tissue.

Table 2 summarizes the current recommendations for each class of medication.

Glucocorticoids

Glucocorticoids are FDA Class C. Data from the PIANO registry indicates that corticosteroid use during pregnancy is associated with preterm birth (OR 1.8, 95%CI 1.0-1.31), LBW (OR 2.8, 95%CI 1.3-6.1), and gestational diabetes (OR 2.8, 95%CI 1.3-6.0). There were no associations with infection, congenital malformation, cleft palate or developmental delay. Adjusted analysis found no difference in spontaneous abortions, IUGR, cesarean section, congenital malformations, neonatal ICU stays, or infections between exposed and unexposed patients.

Corticosteroids may be used to treat disease flares, despite their association with an increased risk of pregnancy complications. Their use during pregnancy should be restricted to the lowest effective dose for the shortest duration. In a separate retrospective study, these risks were not seen specifically with budesonide. Prednisone and budesonide are both compatible with breastfeeding. Their drug levels in breast milk are less than 0.05% of maternal dose (Table 1) [95].

Management of an IBD flare during pregnancy

Prior to diagnosing a flare during pregnancy, infection should always be ruled out with stool studies (including *Clostridium difficile* toxin polymerase chain reaction). Since erythrocyte sedimentation ratio and C-reactive protein are

Table 2 Summary of inflammatory bowel disease medications and recommendations in pregnancy

Medication	FDA Category	Recommendations for women in conception & pregnancy	Breast milk drug concentration	Breastfeeding Recommendations
MTX	X	Contraindicated; Teratogen and abortifacient. Stop 3-6 months before conception	Low: <10% of plasma concentration	Contraindicated
AZA/6-MP	D	Monotherapy: may continue during conception and pregnancy; Combination therapy with biologic: consider stopping thiopurine before conception in quiescent disease	Clinically insignificant: peak excretion 4 h after ingestion	Compatible: wait 4 h after ingestion if possible
IFX	B	Possible risk of infant infection when combined with thiopurine. Give last dose in the third trimester (week 30-32). Consider measuring trough levels in second trimester.	Clinically insignificant: 0.5% of plasma concentration (ng/mL) peak excretion 24-96 h after infusion	Compatible: doubtful oral bioavailability in infant
ADA	B	Possible risk of infant infection when combined with thiopurine. Give last dose in the 3rd trimester (week 36-38). Consider measuring trough levels in second trimester.	Clinically insignificant: <1% of plasma concentration (ng/mL) peak excretion 1-6 d after injection	Compatible: doubtful oral bioavailability in infant
CZP	B	May continue throughout pregnancy without dosing adjustment.	Clinically insignificant: peak excretion 12-48 h after injection	Compatible: doubtful oral bioavailability in infant
VDZ	B	Give last dose in the third trimester (week 30-32)	Unknown	Compatible: doubtful oral bioavailability in infant
UST	B	Limited human data	Clinically insignificant: peak excretion 24 h after injection	Compatible: doubtful oral bioavailability in infant
TOF	C	Limited human data	Unknown	No human data

MTX, methotrexate; AZA, azathioprine; 6-MP, 6-mercaptopurine; IFX, infliximab; ADA, adalimumab; CZP, certolizumab pegol; VDZ, vedolizumab; UST, ustekinumab; TOF, tofacitinib

usually elevated in pregnancy, fecal calprotectin should be monitored and trended to rule in a flare. The gastroenterologist should ensure that there is a baseline fecal calprotectin measured before conception. Magnetic resonance imaging is the imaging modality of choice (gadolinium contraindicated in the 1st trimester), but ultrasound can also be used. Flexible sigmoidoscopy without sedation can be considered (in any semester) to rule out cytomegalovirus, for which pregnant patients are at higher risk. Deep vein thrombosis prophylaxis is also important. Indications for surgery are similar to those in non-pregnant patients (2nd trimester is optimal).

There is a general reluctance to perform radiation-based procedures and endoscopies during pregnancy, because of concerns about sedation and hemodynamic fluctuations with the latter that may be deleterious for the fetus. In general, all endoscopic procedures should only be performed if the potential findings would change perinatal management and preferably in the second semester. Flexible sigmoidoscopies are preferred over pan-colonoscopy. Less invasive monitoring, such as inflammatory markers and fecal calprotectin, is preferred.

For targeted treatment, mesalamine can be initiated at any time during pregnancy for patients with UC. Biologics can be initiated in the first or second trimester with modification of dosage and frequency as necessary. New AZA and 6-MP should be avoided in the first trimester. If necessary, glucocorticoids can be used cautiously at this time in disease flares, as inducing remission and suppressing disease activity are of utmost importance [29].

In rare cases, pregnant women with severely active IBD might require surgery to treat life-threatening conditions refractory to medical therapy, such as toxic megacolon, intestinal obstruction and significant gastrointestinal hemorrhage. Colectomy during the second and third trimester is low-risk without significant adverse pregnancy outcomes [96]. If necessary, mothers with less than 28 weeks gestation can opt for the Turnbull-Blowhole colostomy for colonic decompression and ileal diversion with delayed restorative proctocolectomy and IPAA. On the other hand, for patients with more than 28 weeks gestation, a synchronous cesarean section with subtotal colectomy is a feasible alternative [97]. Surgery for perineal fistulas is usually postponed until after delivery. Non-obstetric surgeries are generally well tolerated and should ideally be performed in the second trimester [98].

A systematic review of 3 databases of women who underwent IBD surgery during pregnancy noted that there were no maternal or fetal mortalities, but there was an almost 50% preterm delivery rate [99]. Approximately 18% of cases were *de novo* presentations and the most common reasons were refractory UC and small bowel perforations.

Concluding remarks

Many women of child-bearing age are newly diagnosed with IBD every year. The addition of biologics to the armamentarium of 5-ASA and immunomodulators has provided more treatment options, but their impact on pregnancy outcomes (from the perspective of both mother and child) have yet to be fully understood. However, the growing body of research into this field has revealed some important insights. Firstly, maintaining control of IBD before and during pregnancy is paramount. Active disease increases the risk of complications such as stillbirth, premature delivery, and LBW. In addition to appropriate medical therapy, high quality prenatal education and counseling are crucial. Secondly, current data suggest that biologics can be used safely in pregnant women. Although medications like IFX and ADA are IgG1 antibodies that can cross the placenta and have been detected in breastmilk and infants post-delivery, no obvious harm has been reported. More data are required for the anti-integrins and IL-12/23 agents before definitive recommendations can be made. Immunomodulators should be continued given the risk of flare on discontinuation. However, one must consider the possibility of adverse outcomes (e.g., preterm birth) when biologics are used in combination with anti-TNF agents. 5-ASA appear to be safe in pregnancy and breast feeding. Finally, the value of a detailed discussion with the patient and shared decision making cannot be emphasized enough because all decisions should be taken with the overall risks vs. benefits kept in mind.

Future directions

As we delve deeper into the molecular and genetic mechanisms underlying the pathogenesis of IBD and develop novel treatments, e.g., Janus kinase inhibitors, anti-SMAD 7 oligonucleotides and cell-based therapies, more therapeutic options will become available to pregnant women with CD and UC. Additionally, our growing insight into the seminal role of the gut microbiome in the pathogenesis of IBD will enable the development of new efficacious medications that can be tailored to the specific individual.

Acknowledgments

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