Insights into the treatment of inflammatory bowel disease in pregnancy

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***Abstract*:** Patients diagnosed with inflammatory bowel disease (IBD) are most commonly diagnosed in late adolescence or early adulthood, with half of patients being diagnosed before age 32, thus impacting peak years of reproduction and family planning. While controlled IBD has no negative effects on the ability to conceive, there is overall a trend towards voluntary childlessness due to patients' concerns for adverse fetal outcomes from underlying IBD and from adverse medication effects. Active disease at the time of conception is associated with worsening disease activity during pregnancy and carries a higher risk of poor fetal outcomes. It is therefore important to maintain remission during pregnancy, which is often achieved with pharmacologic therapy. The goal of this paper is to provide a comprehensive review of the current literature and safety data for pharmacologic treatment of IBD in pregnancy, in breastfeeding women, and in men planning to have children.

Keywords: Crohn's disease, fertility, inflammatory bowel disease, pregnancy, ulcerative colitis

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Introduction

The prevalence of inflammatory bowel disease (IBD) is high, exceeding 0.3% in North America and many countries in Europe, with many patients diagnosed in early adulthood, thus impacting peak years of reproduction and family planning.[1–3] While there is no difference in the ability to conceive in patients with well-controlled IBD, several reports have indicated that men and women with IBD tend to have fewer overall pregnancies.[4,5] The reason for this observation is multifactorial, stemming from poor knowledge of the disease, fears around pregnancy, and voluntary childlessness.[6,7] Conversely, active disease may reduce fertility, and disease activity serves as the strongest predictor of adverse pregnancy outcomes.[5] To help control disease activity prior to conception and during pregnancy, the majority of patients will require maintenance therapy.[8]

In 2013, Tavernier and colleagues performed a systematic review evaluating the effects of non-surgically treated IBD on overall fertility. A total of 11 studies were reviewed, and there was found to be a 17–44% reduction in fertility in women with Crohn's Disease (CD) as compared with controls. In men with CD, there was a 18–50% reduction in fertility as compared with controls. There was no difference in fertility seen in either men or women with ulcerative colitis (UC).[9] However, when evaluated further, there did not appear to be a physiological reason for decreased fertility, and these changes were attributed to voluntary childlessness.[9] The reason for voluntary childlessness is multifactorial. The predominant factors are felt to be the perceived increased risk of complications in pregnancy either due to the underlying disease or secondary to adverse side effects from IBD-related medications. This fear is common, and ultimately has been demonstrated to impact family-planning decisions.[10–15] A survey study of 145 women with IBD found that one-fourth believed it is more important to tolerate symptoms than to expose the fetus to IBD medications, one-third believed that all medications for IBD were harmful to the fetus, and nearly half were worried about infertility.[15] In 2012, Selinger and colleagues evaluated how women with IBD make decisions about family planning, evaluating their attitudes towards pregnancy, medication-use during pregnancy, and breastfeeding. This group found that half of women with IBD had

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poor medical knowledge, thereby identifying a need to improve patient education around actual risks prior to, and during, pregnancy.[7]

While quiescent disease does not impact the overall ability to conceive, women with IBD do experience a higher rate of adverse pregnancy outcomes than the general population. The risk during pregnancy is the greatest in those patients with active disease at the time of conception or in those where disease was difficult to control during pregnancy. This emphasizes the importance of achieving remission ideally prior to conception. Active disease has been shown to increase the risk for preterm birth, small for gestational age, and low birth weight.[4,16–19] One Swedish study, which evaluated over 470,000 singleton births between 2006 and 2010, including 1833 women with UC and 1220 with CD, found that there was an increased risk of preterm birth for UC with an adjusted odds ratio (aOR) of 1.78 [95% confidence interval (CI), 1.49–2.13], and CD with an aOR of 1.65 [95% CI, 1.33–2.06], and that risks were more pronounced in women who were flaring during pregnancy.[18] Of note, while many studies have found an increased risk for preterm birth, defined as birth prior to 37 weeks, the majority of these deliveries occur after 35 weeks gestation with favorable outcomes.[8,20] There does not appear to be a significant increased risk for congenital abnormalities.[8,21,22]

For patients with controlled disease at the time of conception, the overall course of their disease is similar to that of nonpregnant patients with IBD, and pregnancy does not appear to exacerbate IBD.[8] It has been shown that women who have active disease at the time of conception, however, are more likely to flare throughout their pregnancy.[23] A 2013 meta-analysis examining 14 studies, including patients with UC and CD, demonstrated that women with active disease at conception had twice the risk of having active disease during pregnancy than those who conceived when in remission.[23] Another prospective cohort study looking at 298 pregnancies found that active disease at conception was strongly associated with disease relapse during pregnancy, with an aOR of 7.66 [95% CI, 3.77–15.54].[24] Patients with longer disease duration of CD also have an increased risk of flare during pregnancy.[25]

Given the importance of clinical remission, both in influencing a patient's ability to conceive and in pregnancy outcomes, and data that demonstrate a knowledge gap of many patients about their IBD, the goal of this paper was to provide a comprehensive review of the current literature and safety data for pharmacologic treatment of IBD in pregnancy, breastfeeding, and in men planning to have children, and to provide recommendations based on the Toronto Consensus and European Crohn's and Colitis Organisation (ECCO) guidelines to assist physicians in patient counselling.

Methods

A PubMed search of the published literature was performed using search terms of 'inflammatory bowel disease,' 'Crohn's disease,' 'ulcerative colitis,' 'inflammatory bowel disease and pregnancy,' 'fertility and inflammatory bowel disease,' 'fertility and Crohn's disease,' 'fertility and ulcerative colitis,' 'aminosalicylates and pregnancy,' 'aminosalicylates and lactation,' 'paternal exposure of aminosalicylates,' 'corticosteroids and pregnancy,' 'corticosteroids and lactation,' 'paternal exposure of corticosteroids,' 'azathioprine and pregnancy,' 'azathioprine and lactation,' 'paternal exposure of azathioprine,' '6-mercaptopurine and pregnancy,' '6-mercaptopurine and lactation,' 'paternal exposure of 6-mercaptopurine,' 'methotrexate and pregnancy,' 'methotrexate and lactation,' 'paternal exposure of methotrexate,' 'cyclosporine and pregnancy,' 'cyclosporine and lactation,' 'paternal exposure of cyclosporine,' 'infliximab and pregnancy,' 'infliximab and lactation,' 'paternal exposure of infliximab,' 'adalimumab and pregnancy,' 'adalimumab and lactation,' 'paternal exposure of adalimumab,' 'golimumab and pregnancy,' 'golimumab and lactation,' 'paternal exposure of golimumab,' 'certolizumab and pregnancy,' 'certolizumab and lactation,' 'paternal exposure of certolizumab,' 'vedolizumab and pregnancy,' 'vedolizumab and lactation,' 'paternal exposure of vedolizumab,' 'ustekinumab and pregnancy,' 'ustekinumab and lactation,' 'paternal exposure of ustekinumab,' 'tofacitinib and pregnancy,' 'tofacitinib and lactation,' and 'paternal exposure of tofacitinib.' Key articles that were published in the English language were reviewed. Additional articles were found through review of reference lists of select articles.

Pharmacologic therapies

Most medications used to treat inflammatory bowel disease, with the exception of methotrexate,

are safe or low-risk in pregnancy, and use outweighs the risk of active disease.[8,10] Preconception counseling has been associated with improved medication compliance and reduced disease relapses during pregnancy, and is important in optimizing disease management.[26,27] The authors of this paper recommend that all gastroenterologists have a discussion with their patients of reproductive age regarding the risk and benefit of medications prior to conception, during pregnancy, and during breastfeeding. The goal of treatment in patients with IBD is remission. If clinical remission is achieved during pregnancy, it is likely to be sustained throughout the remainder of the pregnancy, thereby reducing risks to the fetus as outlined above. The risks and benefits of common medications used in IBD are outlined below.

Aminosalicylates

Sulfasalazine is a prodrug composed of 5-ASA linked to sulfapyridine through an azo bond. 5-ASA is the primary active ingredient of the aminosalicylates and has many different formulations to target the location of disease. 5-ASA acts topically as an anti-inflammatory compound by preventing formation of prostaglandin and leukotrienes and increasing the expression of peroxisome proliferator-activated receptor-gamma (PPAR-gamma) gene activity.[28–30]

While there are no well-controlled studies of sulfasalazine and 5-aminosalicyclic acid (5-ASA) use in pregnancy, reproductive studies performed in rats and rabbits revealed no increased risk for impaired fertility or harm to the fetus.[31] Sulfasalazine can cross the placenta and can be found in umbilical cord blood; however, overall rates of decreased birth weight, prematurity, spontaneous abortions, or birth defects are similar as compared with mothers not taking sulfasalazine.[32,33] As sulfasalazine interferes with the absorption of folic acid, mothers should increase their intake from the recommended 800 mg daily to 2 mg orally (po) daily.

5-ASA drugs have also been found to be safe to use during pregnancy. A meta-analysis of seven studies that followed 2200 pregnant women with IBD found that exposure to 5-ASA drugs (including mesalazine, sulfasalazine, balsalazide, and olsalazine) was not associated with a significantly increased risk of congenital abnormalities (OR, 1.16 [95% CI, 0.76–1.77]), stillbirth (OR, 2.38 [95% CI, 0.65–8.72]), spontaneous abortion (OR, 1.14 [95% CI, 0.65–2.01]), or preterm delivery (OR, 1.35 [95% CI, 0.85–2.13]).[34]

Some formulations of 5-ASA drugs include dibutyl phthalate (DBP) in the enteric coating, which had been associated with skeletal formations and urogenital defects in male offspring of exposed female rates.[35,36] In a report of six cases, urinary concentrations of phthalate metabolites in patients treated with DBP-containing 5-ASA formulations were 50 times higher than those not treated with these formulations.[37] The effects seen in animal models have not been seen in humans. However, given the overall limited data and uncertainty of the safety of DBP exposure during pregnancy, The Toronto Consensus Statement recommends that women contemplating pregnancy and taking 5-ASA formulations containing DBP should switch to an alternative formulation of 5-ASA that does not contain DBP.[26] Ideally this change should occur months prior to conception given the risk of possible flare while changing agents. If a patient has already conceived on a DBP-containing 5-ASA agent, the decision to change agents should be individualized to the patient.[26]

Paternal exposure. In men, sulfasalazine has been shown to cause oligospermia, abnormal sperm morphology, and decreased sperm motility in several studies.[38,39] These effects are fully reversible, and generally resolve a few months after discontinuation.[40] The sulfapyridine metabolite is felt to be responsible for these effects on sperm; therefore, it is recommended to transition patients to an alternative 5-ASA agent, such as mesalazine, at least 4 months prior to planned conception.[41,42]

Lactation. Sulfasalazine and 5-ASA are excreted in breast milk in small concentrations.[43] There have been case reports of breastfeeding infants developing diarrhea while their mothers were on 5-ASA and sulfasalazine, which resolved upon discontinuation.[44,45] The sulfapyridine metabolite can also be found in breast milk and infant serum, and may result in hemolysis in newborn infants with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[46] Using an alternative 5-ASA agent, such as mesalazine, is preferred for this reason over sulfasalazine, and is felt to be safe in breastfeeding.[47]

Corticosteroids

Corticosteroids, including prednisone and budesonide, are commonly used to induce remission during IBD flares. Corticosteroids decrease the migration of polymorphonuclear leukocytes, downregulate inflammatory cytokines, and reverse capillary permeability, thus decreasing inflammation in IBD.[48] Budesonide undergoes about 90% first-pass metabolism in the liver, and therefore acts topically with fewer systemic effects when compared to prednisone.[49]

Clinical practice guidelines recommend the use of corticosteroids or anti-TNF alpha agents in patients with IBD who flare while on optimal 5-ASA or thiopurine maintenance therapy.[26,50,51] It should be noted, however, that, while budesonide is felt to be safe to use in pregnancy, there is a limited amount of published safety data. A meta-analysis performed in 2011 found that corticosteroids were superior to placebo in inducing clinical remission in UC, and likely were also useful in CD. Budesonide was not as effective at inducing clinical remission in UC as standard glucocorticoids.[52] A small case-control study evaluated 18 pregnant patients with IBD hospitalized for disease relapse between 1989–2001, and found that 15 of the 18 patients were able to avoid colectomy with intravenous hydrocortisone or intravenous cyclosporine.[53]

Risk of congenital malformations with steroid use is controversial. A meta-analysis published in 2000 found a 3.4-fold increased incidence of cleft palate associated with maternal exposure to corticosteroids. This risk is seen most often when steroids are given during the first trimester.[54] There are conflicting studies, however, with a large Danish trial with over 50,000 infants born to mothers on corticosteroids showing no increased risk of orofacial cleft development.[55] Even in those studies that suggest an increased risk, the absolute incidence of cleft palate in infants born to mothers on corticosteroids is still quite low.[56,57]

Long-term use of high dose steroids (greater than 20 mg/day) has been associated with adrenal insufficiency of the fetus, which requires close neonatal monitoring.[58] However, data on this are also somewhat conflicting.[59] There are also associated risks to the mother with increased rates of gestational diabetes.[60,61] In the PIANO registry, corticosteroid use was associated with gestational diabetes with OR 2.8 [95% CI, 1.3–6.0], preterm birth with OR 1.8 [95% CI, 1.0–3.1), and low birth weight with OR 2.8 [95% CI, 1.3–6.1], although this was difficult to separate from activity of disease.[62] These results were not seen with budesonide in a separate study.[63] Furthermore, Leung and coworkers found not only an increased risk for gestational diabetes in patients exposed to corticosteroids during pregnancy, but, in a subgroup analysis that did not achieve statistical significance, they found a higher rate of gestational diabetes in pregnant women with IBD independent of corticosteroid exposure.[61]

Despite the risks listed above, the low risk of adverse pregnancy outcomes associated with corticosteroid use, and increased risk of adverse fetal outcome with active disease, the benefit of achieving clinical remission with corticosteroid use likely exceeds the risks associated with corticosteroid exposure. This is also in line with the Toronto consensus statement.[26]

Paternal exposure. The use of paternal corticosteroids may result in decreased sperm concentrations, and therefore should be used for only short periods of time if possible. In rat models, Lerman and colleagues demonstrated reduced fertility with no effects on sperm count or motility. These effects were reversible with cessation of steroid use.[64]

Lactation. Overall breastfeeding while on corticosteroids is felt to be safe. Corticosteroids are excreted into breast milk in low concentrations.[65]

Immunomodulators

Azathioprine and 6-mercaptopurine. Thiopurines, including azathioprine (AZA) and 6-mercaptopurine (6-MP) are used in maintenance therapy in IBD. AZA is a prodrug that is converted to 6-MP, and this is further metabolized by hypoxanthine-guanine-phosphoribosyltransferase into the active metabolite 6-thioguanine nucleotides (6-TGN). 6-TGN acts as an immunosuppressant, inhibiting protein synthesis in lymphocytes and inhibiting the proliferation of T and B lymphocytes.[66]

Women who are well-controlled on AZA and 6-MP for IBD maintenance therapy should be continued on their treatment throughout pregnancy.[26] AZA does cross the placenta, and use during pregnancy is controversial. A 2013 meta-analysis of over 3000 women with IBD found that

thiopurines were associated with preterm births with an aOR of 1.67 [95% CI, 1.26–2.20]; however, there were no increased rates of congenital abnormalities (aOR, 1.45 [95% CI, 0.99–2.13]), or low birth weight (aOR, 1.01 [95% CI, 0.96–1.06]). Discontinuing therapy, however, was associated with a high rate of relapse.[67] A large Swedish health registry study, found a slight increased risk of preterm birth with thiopurines with an aOR of 2.41 [95% CI, 1.05–5.51]); however, this risk was substantially increased in those patients with active disease with an aOR of 4.90 [95% CI, 2.76–8.69], which suggests that this increased risk seen with thiopurine use may be more reflective of underlying IBD rather than due to thiopurine exposure itself.[18] Even with a possible increased risk of preterm birth in active IBD, the risk of active disease is likely greater than the risk associated with use of AZA and 6-MP.

It is important to note that maternal metabolism of thiopurines is altered during pregnancy. One study published in 2014 found that, in 30 patients on AZA or 6-MP, during pregnancy the metabolites of these drugs changed with median 6-TGN levels decreasing over time, and 6-methylmercaptopurine (6-MMP) concentrations increasing. No major congenital abnormalities were seen in infants at birth; however, 60% were anemic.[68] These authors, along with Toronto consensus guidelines, recommend considering measuring 6-TGN and 6-MMP levels during pregnancy in patients with active disease, and checking a complete blood cell count of the infants at birth.[26]

Paternal exposure. Paternal use of AZA and 6-MP is safe during conception. This recommendation had previously been controversial with conflicting data. In 2000, Rajapakse and colleagues published a retrospective cohort study that evaluated fetal outcomes of fathers taking 6-MP compared with those who were not taking 6-MP, and found that the incidence of pregnancy-related complications was significantly increased, including spontaneous abortions and congenital abnormalities in fathers who used 6-MP within 3 months of conception.[69] Follow-up studies have not demonstrated similar findings, however. One study of 130 conceptions by Teruel and colleagues in 2010 found no increased risk of spontaneous abortion, fetal deaths, preterm births, low birth weight, or congenital malformations. They recommended no alterations to treatment regimens in male patients taking thiopurines who are attempting to conceive.[70] A large nationwide cohort study out of Denmark looking at children fathered by men who used AZA or 6-MP 3 months prior to conception between the years of 1997 and 2013 found no significantly increased risk of congenital abnormalities (aOR 0.82 [95% CI, 0.53–1.28]), preterm birth (aOR 1.17 [95% CI, 0.72–1.92]), or small for gestational age (aOR 1.38 [95% CI, 0.76–2.51]).[71] Given little evidence of increased risk, the recommendation is for men to continue on AZA or 6-MP if well controlled.

Lactation. It is generally considered acceptable to continue AZA or 6-MP while breastfeeding.[26] AZA is rapidly metabolized to 6-MP, which can be found in breast milk. However, the enzyme to metabolize 6-MP to 6-TGN is found in red blood cells, and therefore significant levels of the active metabolite are not seen in infants after breastfeeding.[72] One small study found no difference in newborn infections, and similar age-appropriate mental and physical development in newborns exposed to AZA either in-utero or while breastfed.[73] Based on available data, breastfeeding is likely safe and can be continued while mothers are taking AZA or 6-MP.[8]

Methotrexate

Methotrexate (MTX) is used to induce and maintain clinical remission in CD and works by inhibiting dihydrofolate reductase, preventing the formation of reduced folates, and therefore DNA synthesis. In CD, it is felt to have anti-inflammatory effects.[74] In pregnancy, MTX is a known potent teratogen and abortifacient, and thus must be discontinued prior to conception. For this reason, women in their reproductive years who are initiated on MTX are placed on a form of medical contraception. Women who plan to conceive should discontinue MTX and use contraception for at least 3 months, and ideally 6 months, prior to conception.[16] In addition to loss of pregnancy, there are also increased findings of congenital malformations including skeletal abnormalities and MTX-induced developmental toxicity.[75]

Paternal exposure. MTX use in men who are planning to have children is highly controversial; however, more recent data suggest that it is likely safe for use in men prior to planned conception. There are some studies that suggest MTX use may contribute to impotence in men and has

been associated with reversible oligospermia, with a recommendation to discontinue use 3 months prior to planned conception.[76,77] There have been no data linking male use of MTX to birth defects.[78] A nationwide register study in Denmark performed in 2017 evaluated all live births in Denmark between 1997 and 2011, and found no association between paternal exposure to MTX within 90 days before pregnancy and congenital malformations (aOR 1.01 [95% CI, 0.37–2.74]) or preterm births (aOR 1.31 [95% CI, 0.66–2.59]).[79] A prospective cohort study performed in 2013 evaluated pregnancies fathered by men on low-dose MTX, and found no increased risk of adverse pregnancy outcomes.[80]

Lactation. Breastfeeding is contraindicated as methotrexate is excreted into breast milk and can accumulate in neonatal tissues.[81]

Cyclosporine

Cyclosporine is often used in steroid-refractory UC and can be quite effective. It is a fungal metabolite that acts as an immunosuppressor of T cells by blocking interleukin-2 (IL-2) gene transcription.[82]

The lowest effective dose of cyclosporine should be used in pregnancy. While data from rheumatology patients have reported no increased risk of congenital malformations associated with exposure during pregnancy, a meta-analysis in 2001 evaluating women taking cyclosporine, found an associated increased risk for prematurity with OR 1.52 [95% CI, 1.00–2.32]. It was unclear, however, if this was attributed to medication effect or due to the mother's underlying disease.[83] Ultimately the known side effects of cyclosporine to the patient including paresthesia, tremors, hypertension, renal dysfunction, hypomagnesemia, and gastrointestinal upset may limit acceptability of use during pregnancy.[26,51]

Paternal exposure. Data for cyclosporine in men are somewhat limited. In mice models, cyclosporine has been shown to be associated with decreased testis weight, decreased testosterone concentrations, abnormal sperm, abnormal sperm motility, and oligospermia.[84] Using higher doses of 10 mg/kg/day has demonstrated decreased sperm motility and sex hormone levels, although this is much higher than the regular dose used for IBD, and no studies have evaluated effects at lower doses.[76] Cyclosporine may therefore be continued in men if needed.

Lactation. Cyclosporine is excreted in breast milk and concentrations can vary widely. It is therefore not recommended in breastfeeding due to the potential for serious adverse events in infants.[85]

Tumor necrosis factor alpha inhibitors

Anti-tumor necrosis factor alpha (anti-TNF alpha) medications were the first of the newer 'biologic therapies' approved to treat IBD and have revolutionized how IBD is managed. These agents, which include the commonly used infliximab (IFX) and adalimumab (ADA), as well as golimumab (GLM) and certolizumab pegol (CZP), are monoclonal antibodies that suppress the systemic inflammatory cascade by inhibiting tumor necrosis factor alpha. These monoclonal antibodies are actively transported across the placenta starting in the second trimester, increasing as the pregnancy progresses. CZP is an exception to this, as it lacks the Fc portion of the IgG necessary for transport, and thus has almost no to minimal placental transfer.[86] Serum levels of IFX and ADA have been found to be higher, and circulate longer, in infants than in their mothers who are receiving treatment, which suggests the infants' reticuloendothelial system is too immature to clear the antibody effectively.[87] Recent studies examining anti-TNF alpha levels in maternal and cord blood have found that maternal IFX levels and transportation across the placenta rise more dramatically as the pregnancy progresses compared to ADA.[88,89] ADA has also been shown to be cleared more quickly than IFX in exposed newborns, with a mean time to drug clearance of 4.0 and 7.3 months, respectively.[90] Despite these higher drug concentration levels found in the infants, there were no differences regarding growth or infection rate between the two groups.[89] Some have suggested that, given the change in maternal drug levels as pregnancy progresses, there may be benefit to monitoring drug levels to assist with possible dose adjustment.[88,89]

While the lack of transport across the placenta during the first trimester may protect against exposure during organogenesis, the increased transfer in the third trimester has raised concerns about immune system development and risk of infections. For this reason, in the past, organizations recommended

that pregnant women discontinue anti-TNF agents before the third trimester. More recently, the Toronto and ECCO consensus statements recognize that the benefits of disease control outweigh the risks, and that continuation of anti-TNF agents even throughout the third trimester is advisable for patients in clinical remission, as most studies have shown these agents to be safe in pregnancy.[8,26,86,91–93] In the large PIANO registry, use of anti-TNF alpha antibodies was not associated with increased congenital anomalies, preterm births, or other adverse events.[60] Additionally, there was no evidence that exposure led to developmental delay, as developmental scores in the exposed group were similar, and, in some categories, higher than the nonexposed cohort.[94] The authors also assessed the risk of those exposed to anti-TNF alpha agents, specifically in the third trimester, and did not find any association in rates of preterm birth or infection rates in infants.[95]

In the prospective, observational TREAT registry, which compared outcomes of 162 pregnancies with maternal exposure to IFX with 90 pregnancies receiving other, nonbiologic therapy, the vast majority (87.3%) of pregnancies resulted in live births. While there was a nonstatistically significant increase in spontaneous abortions amongst the women exposed to IFX compared with the nonexposed, these patients had more severe disease and were more likely to receive concomitant immunosuppressive therapy. Additionally, the spontaneous abortion rate was consistent with that of the general population. The overall clinical condition of the neonates was similar across groups and the rate of congenital abnormalities was similar to the general population. Interestingly, there was a trend towards fewer neonatal complications and fewer prolonged hospital stays amongst the exposed group, which likely reflects the importance of better disease control during pregnancy.[96]

In a study of the French national insurance database, Luu and colleagues analyzed 1457 pregnancies of mothers with IBD exposed to anti-TNF alpha agents during pregnancy, of whom about one-half were exposed during the third trimester and about one-third at delivery. The study demonstrated that pregnant women exposed to anti-TNF alpha medications had a higher rate of infections, although there was no increased risk of infection in the offspring during the 1st year of life. Additionally, they showed that for women exposed to anti-TNF alpha agents during pregnancy, pursuing treatment beyond 24 weeks did not increase the risk of adverse events for the women or for their children, while discontinuing therapy was associated with an increased risk of disease relapse.[97] In a commentary of this study, Mao and Mahadevan explain that the increased infection rate in the exposed pregnant mothers is similar to that of nonpregnant women on anti-TNF alpha agents. Additionally, the decreased risk of disease relapse and lack of negative effect on the infant of continuing TNF alpha inhibitors throughout the pregnancy provided enough evidence to support the idea that these agents should be continued throughout all trimesters.[98]

The European retrospective multicenter TEDDY study, which compared 388 children who had been exposed to anti-TNF alpha drugs in utero to 453 children of IBD mothers who had not been exposed, also found that the exposed pregnant women had higher rates of infections but no difference was found with respect to premature rupture of membranes, placenta previa, chorioaminitis, eclampsia, and fetal growth. Similar to the Luu trial, children who were exposed in utero did not have an increase in serious infections when compared with unexposed children born to mothers with IBD with a mean follow up of 4 years. Additionally, the authors did not find any difference in infection rates between exposure in the third trimester and those with nonexposure.[99]

In another study focused on long-term outcomes, Duricova and coworkers found no difference in congenital abnormalities, perinatal complication and percentage of infants with low birth weight, when comparing IBD mothers exposed to anti-TNF alpha agents with healthy, non-IBD mothers. They found that children exposed to anti-TNF alpha therapy in utero had similar risks of infections and allergy, growth, and psychomotor development compared to unexposed children of non-IBD mothers, with a median follow-up of 36 months.[100]

Despite the theoretical decreased immune response to vaccination, studies have shown that infants exposed to anti-TNF alpha agents during pregnancy mount adequate serological responses when compared with nonexposed counterparts.[100] A recent study by Beaulieu and colleagues showed no difference in the rates of serologic response to

HiB and tetanus vaccines in infants of women who used biologics during pregnancy and those who did not, regardless of the biologic used and cord concentration at the time of birth.[101] Controversy continues regarding the timing of live vaccines for exposed infants, as there have been case reports of newborns having adverse reactions to live immunizations, including one child who died from disseminated BCG.[102] A newer French study questions the risk of giving live vaccinations within 6 months, as they found that only 1 in 19 infants had an adverse reaction (abscess with favorable evolution), and 7 children received rotavirus vaccination with only one fever reported.[103] Of the 40 infants of exposed mothers who received the rotavirus vaccine in the Beaulieu study above, there were no serious adverse reactions and mild events occurred at a similar rate to the general population.[101] Despite these findings, we support current guideline recommendations of waiting until 6–12 months of age to give live vaccinations.

Paternal exposure. There have been several small cohort studies and case reports regarding paternal exposure to anti-TNF alpha agents. While there were some small initial studies that suggested decreased sperm motility with their use,[104,105] most studies have shown no relationship between anti-TNF alpha use and sperm health, and a few studies have shown improvement in sperm function with treatment, believed to be due to reduction in disease activity.[106–108] In addition, their use does not appear to adversely affect pregnancy outcomes when compared with the general population.[109–111]

Lactation. In one study, IFX was found in breast milk in about two-thirds of women who submitted samples while ADA was found in only 5%. This same study showed minimal to no amount of CZP transferred from serum to breast milk, and that no infants being breast fed by mothers receiving CZP had detectable blood levels.[112–114] Despite the presence of detectable levels in breast milk, anti-TNF alpha agents are large protein molecules and are unlikely to be absorbed from the GI tract; therefore, breast milk levels and exposure are unlikely to correlate with infant serum drug levels. In addition, studies have not shown any association with breastfeeding, infant infection and achievement of developmental milestones, and therefore it does not need to be avoided.[112]

Integrin inhibitors

Vedolizumab. Vedolizumab (VDZ) is an IgG1 monoclonal antibody approved for the treatment of UC and CD. VDZ acts on $\alpha 4\beta 7$ integrin, which is selective in blocking gut lymphocyte transport, and therefore avoids many undesirable systemic effects. Mahadevan and coworkers analyzed data from six initial clinical trials with VDZ, which included 27 pregnancies with exposure during pregnancy and did not show any adverse effect on pregnancy outcomes.[115] In a more recent retrospective observational study, Moens and colleagues identified 23 pregnancies in patients with VDZ exposure, including three patients who continued VDZ throughout the pregnancy. There were 18 live births, which included two congenital abnormalities, as well as one case of intrauterine growth retardation and two cases of premature rupture of the membranes, and five pregnancies that were still ongoing at the time of the study.[116] Given the number of congenital abnormalities and complications amongst the small number of identified pregnancies, more research needs to be conducted to help determine the safety of VDZ in pregnancy and strict monitoring for any pregnant patient receiving VDZ is recommended.

Paternal exposure. In the same study of the clinical trials, there were 15 pregnancies in partners of male participants with no clear evidence that VDZ negatively affected pregnancy outcomes.[115]

Lactation. VDZ has been found in small amounts in breast milk of patients who breastfed while receiving treatment. One study found detectable levels from 30 min to 14 days after receiving a dose with a peak around 5–7 days, but in very small concentrations, which the authors concluded would likely be degraded by gastric proteolysis. The children who were breastfed had normal developmental milestones from age 3.5 to 10 months.[117] Therefore, breastfeeding can be considered safe while mothers are receiving VDZ.

Interleukin-12 and interleukin-23 inhibitors

Ustekinumab. Ustekinumab (UST) is an IgG1 monoclonal antibody against interleukin-12 (IL-12) and interleukin-23 (IL-23) that is approved for treatment of CD. These cytokines are known to play an important role in uterine physiology and pregnancy, but the nature of that role is not completely understood.[118] While data are scarce, two case reports of pregnant women with CD

who took UST into the third trimester showed elevated cord blood levels in comparison with maternal drug levels. In both cases, the children had no congenital abnormalities.[119,120]

While there have not been many studies evaluating the effects of UST on pregnancy, the available data from the clinical development programs for psoriasis and CD showed that the rate of spontaneous abortion was similar to that of the general population and was associated with older maternal age. There was only one congenital abnormality amongst the 111 pregnancies between the two studies.[121,122] An updated analysis from the safety database included 206 pregnancies from clinical trials, registries, and spontaneous reports of maternal UST use for psoriasis, psoriatic arthritis, and CD during pregnancy or within 2 months of conception, 13% of which having exposure in the third trimester. This study, which included both prospectively and retrospectively reported cases found similar rates of spontaneous abortions and congenital abnormalities between the exposed group and the general population.[123]

Paternal exposure. There are no published data on the effect of male exposure on pregnancy outcome.

Lactation. Ustekinumab has been found in breast milk at low levels and breastfeeding is believed to be safe.[112]

Janus kinase inhibitors

Tofacitinib. Tofacitinib is an oral janus kinase (JAK)-inhibitor that is approved for the treatment of UC. As this drug has been recently approved, there are few studies involving patients with UC. A small study by Clowse and colleagues analyzed patients enrolled in rheumatoid arthritis and psoriasis randomized controlled trials who received tofacitinib while pregnant, and concluded that exposure to tofacitinib appears neither to be associated with increased risks to the fetus when compared with the general population nor different from rates specifically reported in rheumatoid arthritis and psoriasis patients.[124] Mahadevan and coworkers analyzed the UC safety database and identified a total of 11 maternal exposures during pregnancy, all of whom were exposed during the first trimester. Of the 11 pregnancies, there were four healthy newborns, two medical terminations, two spontaneous abortions and 3 pregnancies whose outcomes were unknown.[123] The authors also performed an updated analysis across the entire tofacitinib program in UC, rheumatoid arthritis, psoriasis, and psoriatic arthritis, and identified 74 cases of maternal exposure during pregnancy. There was one reported case of a congenital abnormality (pulmonary valve stenosis) and 10 spontaneous abortions, which the authors concluded were consistent with the background rates in the general population.[125] Given the paucity of pregnancies with tofacitinib exposure, a definitive conclusion cannot be made regarding its safety in pregnancy.

Paternal exposure. There were a total of 44 pregnancies fathered by men in the rheumatoid arthritis and psoriasis randomized controlled trials with no association between tofacitinib exposure and adverse effects on pregnancy outcome.[126] The Mahadevan study mentioned above also identified 14 cases of paternal exposure in UC trials, of which there were no cases of congenital abnormalities and spontaneous abortion.[123]

Lactation. There have been no reports describing the use of tofacitinib during breastfeeding, although the small molecular weight and moderate plasma protein binding are suggestive that the drug will be excreted in breast milk. Tofacitinib has been found to be in the milk of lactating rats at a concentration approximately two times higher than that found in the maternal serum. While the effect of tofacitinib on breastfed infants is unknown, given the serious adverse reactions seen in adults treated with tofacitinib, the manufacturers recommend against breastfeeding for at least 18 h after the last dose of immediate release, and 36 h after extended release forms of the drug.[126]

Conclusion

In summary, pregnant women with active IBD prior to conception have a higher risk of flaring throughout pregnancy, which in turn is associated with worse fetal outcomes with an increased risk of preterm birth, small for gestational age, and low birth weight. Overall, apart from MTX use, the risks of discontinuing IBD-related medication prior to conception, during pregnancy, or during breastfeeding generally outweigh the risk of the medications themselves. Preconception counseling is essential given the overall concerns that patients have regarding their underlying disease and medication exposure on their infants.

In line with the Toronto and ECCO consensus statements, we would agree that women well-controlled on maintenance therapy with 5-ASA, thiopurines, or anti-TNF alpha agents should continue therapy throughout pregnancy. Our authors would also recommend continuing maintenance therapy with ustekinumab if disease is well controlled. There is a paucity of data regarding the use of vedolizumab and tofacitinib in pregnancy, and more studies are needed for improved guidance on use during pregnancy. During mild-to-moderate flares on maintenance 5-ASA or thiopurines, treatment should be optimized with either corticosteroids or anti-TNF alpha agents. In addition, while the data on use of tofacitinib during breastfeeding are lacking, the use of 5-ASA, systemic corticosteroid, thiopurine, anti-TNF alpha, vedolizumab, or ustekinumab therapy should not influence the decision to breastfeed, nor should breastfeeding influence the decision to continue these medications.[27]

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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