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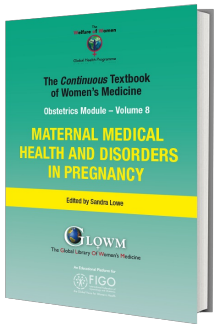

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Chapter

Inflammatory Bowel Disease and Pregnancy: A Comprehensive Review

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the bowel characterized by a relapsing and remitting course. It can be further subclassified as ulcerative colitis (UC), Crohn's disease (CD) or IBD-unclassified. UC is characterized by superficial inflammation from the rectum extending proximally and can present with bloody diarrhea and weight loss. CD on the other hand presents as transmural inflammation and endoscopically as patchy disease throughout the gastrointestinal tract, including the perianal region. However, regardless of these subtypes, there remains no cure for IBD and as such, many patients are managed with long-term immunosuppressive agents such as corticosteroids, immunomodulators, and biologics such as tumor-necrosis factor (TNF) antagonists.

IBD often affects young patients, with 50% of patients diagnosed prior to the age of 35.[1] This coincides with the peak of reproductive potential of young women, with up to 25% of women becoming pregnant after the diagnosis of IBD.[2] It is well-recognized that active IBD during pregnancy increases the risk of adverse maternal and neonatal outcomes (e.g. miscarriage, stillbirth, preterm birth, growth retardation, small for gestational age infants). The risk of disease relapse and adverse outcomes can be minimized with adequate pre-conception counseling and ensuring disease remission pre-conception and during all gestational periods.[3] As such, it is imperative that healthcare professionals understand the impact of this chronic disease on pregnancy in order to minimize adverse events and ensure a healthy pregnancy. This chapter reviews common issues that may arise when managing IBD during pregnancy and offershealthcare professionals a guide to refer to during routine counseling during all gestational periods.

PERCEPTIONS AND ATTITUDES DURING PREGNANCY

Chronic illnesses often provoke significant anxiety in vulnerable life stages, particularly during pregnancy. Women may fear the effects of their chronic disease on their unborn child which may in turn result in significant psychological distress. In fact, up to a quarter of women with IBD choose to tolerate disease-related symptoms rather that initiate medical therapy for flares during pregnancy, up to 36% believe all medications are harmful to their unborn child, and almost all worry about the effect of their chronic illness on pregnancy.[4,5] Almost half of all women with IBD may stop their prescribed IBD medication during pregnancy, a majority without consulting their physician.[6] This translates to an increased risk of medication discontinuation, disease relapse, and adverse pregnancy-related outcomes.[5,7]

FERTILITY AND FECUNDABILITY

Infertility is defined as an inability to become pregnant and produce offspring after 12 months of unprotected intercourse.[8,9] In patients with quiescent IBD, infertility rates appear to be similar to patients without the disease process.[10] However, those with active disease and those with history of surgical intervention may have an increased risk of infertility.[11,12,13] Specifically, proctocolectomy with ileal pouch anal anastomosis (IPAA) has been associated with up to a 4-fold increased risk of infertility in women with UC.[13] In this setting, deferring the completion stage of IPAA procedure until the patient has completed her pregnancy(ies) is a reasonable approach if clinically reasonable. If not possible, then consideration for *in vitro* fertilization can be made as success rates are similar in IBD to those without the disease.[14] Fecundability is defined as the probability of achieving a successful conception. Specifically, it is measured over one menstrual cycle and in the setting of no contraception and regular intercourse.[15] Unlike fertility, fecundability can be reduced in women with IBD, in large part due to voluntary childlessness.[16] In particular, rates of voluntary childlessness are as high as 18% in CD and 14% in UC, compared to 6.2% in the general population.[16] Factors that may contribute to this include underlying disease burden, poor disease-related knowledge, and fear of medication exposure to the fetus.[17]

EFFECT OF IBD ON PREGNANCY

The association of IBD with adverse pregnancy outcomes has been extensively studied. Patients with quiescent IBD do not appear to be at an increased risk of adverse maternal or neonatal outcomes.[18] However, those with active disease, particularly at time of conception, appear to be strongly at risk of certain adverse pregnancy-related outcomes other than major congenital abnormalities.[11,18,19,20,21,22,23,24,25,26,27,28,29] Numerous studies have demonstrated that compared to those with inactive disease, patients with active IBD are at an increased risk of ectopic pregnancy, pre-term birth and infants with small for gestational age and low birth weight.[11,18,19,20,21,22,23,24,25,26,27,28] Those with active disease upon conception may also have an increased risk of experiencing fetal loss.[23,30] A recent systematic review and meta-analysis concluded that the odds of developing preterm birth, small for gestational age, stillbirth was 1.85 (95% CI 1.67–2.05), 1.36 (95% CI 1.16–1.60), and 1.57 (95% CI 1.03–2.38), respectively.[31] As such, most healthcare providers, in line with current guideline recommendations, recommend delaying conception until the underlying IBD is in remission in order to prevent these adverse pregnancy outcomes.

Inflammatory bowel disease is also a risk factor for thromboembolism in pregnancy and postpartum with a systematic review estimating a pooled relative risk of 2.13 (95% CI 1.78–2.66, P <0.001) compared with normal pregnant women.[32]The risk is greater during flares of IBD during pregnancy and in the postpartum period. Thus, IBD should be taken into consideration when assessing the need for thromboprophylaxis, particularly during flares, postpartum or if the woman has any other additional risk factors for thromboembolism.

EFFECT OF PREGNANCY ON IBD

Alterations in pregnancy physiology may affect underlying disease activity in patients with IBD.[33,34] In particular, it is hypothesized that this may be due to a shift from a T helper 1 (Th1) to T helper 2 (Th2) immune response that occurs to

protect the fetus.[35,36] Traditionally, it is estimated that approximately up to 66% of patients with active disease at conception will have active disease throughout pregnancy, whereas only 33% with no disease activity at conception will experience a disease relapse.[37,38] A meta-analysis including 14 studies (1130 UC and 590 CD patients) demonstrated that the relative risk of active disease during pregnancy in those who had active disease at conception was 2.0 (95% CI 1.5–3, $p < 0.001$).[39] More recently, a large prospective multicenter cohort study concluded that pregnant women with UC were at higher risk of disease relapse during pregnancy compared to non-pregnant UC controls.[40] In particular, of the 117 pregnant patients with UC in remission at conception, only 65% remained in remission throughout pregnancy. With respect to patients with CD, of 92 pregnant women, 90% were in remission at conception, of which 81% remained in remission at the end of pregnancy. Longer duration of pre-conception CD (i.e. >5 years) and immunosuppressive therapy were risk factors for persistent peripartum disease activity in CD.[40]

MEASURING DISEASE ACTIVITY DURING PREGNANCY

Careful monitoring for and early detection of active IBD during pregnancy is critical in ensuring optimal maternal and neonatal outcomes. Routinely, non-invasive tests such as laboratory and fecal investigations are appropriate in follow-up of disease activity during pregnancy (Table 1). However, when appropriate, endoscopic assessments with sigmoidoscopy should be used if the yield will result in a significant change in the therapeutic management of the patient.

Table 1 Methods to assess inflammatory bowel disease activity in pregnancy.

Tests	
Laboratory	
Serum albumin	Decreases in normal pregnancy. Interpret with caution
C-reactive protein	Increases in normal pregnancy. Interpret with caution
Hemoglobin	Decreases in normal pregnancy. Interpret with caution
Platelet	Decreases in normal pregnancy. Interpret with caution
Stool tests	
Fecal calprotectin	Not affected by normal pregnancy. Useful to monitor disease activity throughout pregnancy. Consider trimester 3 fecal calprotectin to guide timing of last dose of biologic in pregnancy
Radiological tests	
Ultrasound	Safest imaging modality during pregnancy, and where available, small bowel ultrasound should be considered to assess for disease activity
Magnetic resonance imaging	Potential risk of placental transfer and fetal toxicity, avoid use of gadolinium contrast during pregnancy
Computed tomography	Potential fetal ionizing radiation exposure. Only use in the setting of an absolute indication and when results will alter the management plan
Radiography	Minimal fetal ionizing radiation exposure. Only use in the setting of an absolute indication and when results will alter the management plan
Endoscopy	
Flexible sigmoidoscopy	May perform without sedation throughout pregnancy if clinically indicated. Avoid supine position
Colonoscopy	If necessary, to complete, perform after 24 weeks gestational age and discussion

	of risks vs. benefits with patient. For sedation, meperidine preferred followed by small doses of midazolam. Propofol safe to administer by a trained anesthesiologist. Avoid supine position

Laboratory tests

Routine laboratory investigations commonly performed to monitor disease activity in the non-pregnant IBD patient include albumin, C-reactive protein (CRP), hemoglobin, and platelet levels. In particular, hypoalbuminemia, elevated CRP, anemia, and thrombocytosis may be indicators of underlying inflammation. However, during pregnancy, alterations in physiology result in hemodilution (i.e. increase in plasma volume by 50% by term) and in turn difficulty interpreting abnormalities in these markers. For example, pregnancy-related hemodilution may result in a decrease in serum albumin by 10 g/L, physiologic anemia, and gestational thrombocytopenia.[41]Most studies reported that C-reactive protein (CRP) levels remains unchanged during healthy pregnancy, though levels rise up to fourfold in the first 2 days postpartum.[42,43,44,45] These markers should be interpreted with caution and always in adjunct with other clinical symptoms to detect underlying disease activity.

Fecal tests

Fecal calprotectin (FCP) is another non-invasive tool to monitor disease activity. Calprotectin is released by activated colonic neutrophils and as such can correlate with luminal inflammation. In particular, in non-pregnant IBD patients, FCP is routinely used to detect active disease, with diagnostic accuracy as high as 80%.[46,47] FCP is not affected by pregnancy and several studies have demonstrated that it may be able to detect active disease in the IBD pregnant patient, regardless of gestational age.[48,49,50] As such, FCP, where available, should be used as an adjunctive tool in monitoring disease activity and detecting disease relapse in all gestational periods.[51]

Radiological tests

Imaging modalities remain essential in assessing for underlying small bowel disease activity as well as extra-intestinal complications of IBD, such as fistulas and abscesses. Ultrasound remains the safest imaging modality during pregnancy and should be considered when disease activity or complications are suspected in these patients. Magnetic resonance imaging is a reasonable alternative to detect disease activity during pregnancy, but gadolinium contrast is contraindicated.[52] Other imaging modalities such as traditional radiography and computed tomography (CT) imaging techniques may be ordered if clinically indicated (see Radiation in Pregnancy chapter).

Endoscopic assessment

Endoscopic assessment, via sigmoidoscopy or colonoscopy, remains the gold-standard method to monitor disease activity in non-pregnant IBD patients. Historically, given the concerns regarding intra-procedural maternal hypoxemia and hemodynamic instability, endoscopy in pregnancy has been limited, and suggested to be deferred to the second trimester if indicated.[53] However, recent evidence suggests that lower endoscopy may be safe in all trimesters of pregnancy, for both mother and fetus.[54] Lower endoscopy during pregnancy may result in fewer spontaneous abortions compared to those not undergoing endoscopy, possibly reflecting treatment modifications in response to disease activity detection.[54] Despite this, the literature on endoscopy safety during pregnancy remains limited. As such, it is recommended to follow recent guideline recommendations which suggest that a flexible sigmoidoscopy can be performed without sedation throughout gestation if clinically indicated.[53,55] If a full colonoscopy is necessary during pregnancy (i.e. diagnosis of de novo IBD during pregnancy), it should be performed after 24 weeks gestational age and only after a full discussion with the patient regarding the theoretical risks. As per the American Society of Gastrointestinal Endoscopy guidelines, if sedation is required for endoscopy during pregnancy, meperidine is preferred, followed by small doses of midazolam as required. Propofol is safe during pregnancy only if administered by a trained anesthesiologist who is aware of pregnancy-related hemodynamic changes.[56] The supine position should be avoided to prevent compression of the inferior vena cava and aorta which may result in maternal hypotension.[53,55,56]

MEDICATION USE FOR CONTROLLING IBD DURING PREGNANCY

As aforementioned, the chance of a successful, healthy pregnancy relies on effective preconception counseling, close monitoring of disease activity, and medication adherence. However, many patients fear the potential toxicities of immunosuppressive agents during pregnancy. As such, it is important for healthcare professionals to understand the potential risks and benefits of the routine medications used to maintain disease remission during pregnancy. A summary of the safety of the commonly used IBD-related therapies during pregnancy and breast-feeding is provided in Table 2.

Table 2 Safety of IBD-related therapies during pregnancy and lactation

Therapy	Pregnancy	Lactation	Comments
5-ASA therapy			
Sulfasalazine	Continue*	Continue*	Consider Folate 2mg per day during pregnancy. Prefer mesalamine for breastfeeding if possible.
Mesalamine	Continue*	Continue*	Asacol may contain dibutyl phthalate and may need to be switched.
Corticosteroids	Continue*	Continue*	Reserved for acute flares only. Avoid chronic exposure. Allow for 1-2 hours duration before breastfeeding
Thiopurines (Azathioprine, mercaptopurine)	Continue*	Continue*	Avoid combination therapy with biologics, if possible. Monitor for neonatal anemia post-delivery.
Methotrexate	Avoid	Avoid	Discontinue at least three months before pregnancy. High-dose folic acid supplementation, for at least three months before pregnancy
Metronidazole	Continue*	Avoid	Recommended for acute management of perianal disease or pouchitis. Not for chronic management
Ciprofloxacin	Continue*	Continue*	Recommended for acute management of perianal disease or pouchitis. Not for chronic management
Anti-TNF therapy			
Infliximab	Continue*	Continue*	Third trimester dosing should be discussed with prescribing physician
Adalimumab	Continue*	Continue*	Third trimester dosing should be discussed with prescribing physician
Golimumab	Continue*	Continue*	Third trimester dosing should be discussed with prescribing physician
Certolizumab	Continue*	Continue*	Third trimester dosing should be discussed with prescribing physician
Vedolizumab	Continue*	Continue*	Limited available data. Third trimester dosing should be discussed with prescribing physician
Ustekinumab	Continue*	Continue*	Limited available data. Third trimester dosing should be discussed with prescribing physician.
Tofacitinib	Avoid	Avoid	Avoid until further data available.

*Continue if needed to control disease process

Corticosteroids

Corticosteroids are used to induce remission in those with active IBD.[57] They can cross the placenta membrane though are inactivated by placental enzymes.[58] First-trimester use of corticosteroids has been reported in observational studies to increase the risk of cleft lip, with or without cleft palate, with an odds ratio up to 1.7 (95% CI 1.1–2.6).[59,60] However, larger cohort studies have not demonstrated this association.[61,62,63] In fact, a meta-analysis concluded that the overall risk of major malformations in first trimester corticosteroid use was not significant (OR 1.45, 95% CI 0.80–2.60), and that a potential association was only seen in four case–control studies (OR 3.35, 95% CI 1.97–5.69).[64] As such, current data remain conflicted but the overall risk of major malformations in the setting of first trimester corticosteroid use appears to be low. Corticosteroid use later in pregnancy may be associated with other adverse pregnancy outcomes such as low birth weight, preterm delivery, and fetal adrenal suppression.[65,66,67] Furthermore, corticosteroid use during pregnancy may also be associated with a non-significant trend towards an increased risk of infant infection in the first 4 months of life.[68,69] As such, corticosteroids should be reserved for those pregnant patients with acute disease flare requiring acute control of their disease process..[55] Similar to the non-pregnant IBD patient, they are not indicated as maintenance agents and should be tapered once disease control is achieved.

Antibiotics

Antibiotics are used to treat pouchitis and infectious complications of IBD such as perianal and intra-abdominal abscesses. Commonly used antibiotics in IBD include metronidazole and ciprofloxacin, which when used in combination, empirically cover against anaerobic and Gram-negative organisms. Metronidazole use in pregnancy is not associated with any increased risk of teratogenicity.[70,71] Similarly, though historically ciprofloxacin use in pregnancy was associated with fetal arthropathies and cartilage abnormalities, recent evidence suggests its use is safe with no increase in the risk of congenital abnormalities.[72] Despite this, a large nested case–control study within the Quebec Pregnancy Cohort demonstrated that the use of macrolides, quinolones, and metronidazole during early pregnancy may be associated with an increased risk of spontaneous abortion.[73] As such, it is important that there is a clinical indication for the use of antibiotics during pregnancy and that all risks are discussed with the patients.

Aminosalicylates

Aminosalicylate (5-ASA) agents are routinely used to induce and maintain remission in those with mild–moderate ulcerative colitis.[57] There are a number of specific 5-ASA agents that vary on their outer coating and route of administration (i.e. oral, suppository, enema). In IBD, the specific 5-ASA agents routinely used include sulfasalazine, mesalamine (i.e. Asacol®, Pentasa®, Mezavant®, Salofalk®), and olsalazine. In pregnancy, the safety of these 5-ASA agents has been extensively evaluated. In a meta-analysis of 642 patients treated with mesalamine or sulfasalazine and 1158 disease-matched controls, there was no significant difference in risk of preterm delivery, low birth weight, congenital abnormalities, stillbirth, and spontaneous abortion.[74] Similarly, the odds ratio of developing major congenital abnormalities due to 5-ASA use in the first trimester was 0.82 (95% CI 0.42–1.61).[75] As such, both sulfasalazine and mesalamine should be continued in IBD patients during pregnancy for induction and maintenance of clinical remission. However, some clinical pearls should be remembered with respect to their use. Those maintained on sulfasalazine should be prescribed high dose folic acid therapy (i.e. 2 mg per day) which has been demonstrated to reduce the risk of fetal toxicity when administered with other folate synthesis inhibiting drugs.[55,76] In addition, some mesalamine formulations such as Asacol® and Asacol HD® may contain an enteric coating of dibutyl phthalate (DBP). DBP has been associated with reduced skeletal, reproductive, and neurological fetal development in animal models.[77] Although this risk has not been replicated in the human population, current guidelines recommend avoiding (if possible) the use of these particular formulations in the organogenesis period of the first trimester.[53,77,78]

Immunomodulators

Thiopurines

Thiopurines, azathioprine and 6-mercaptopurine, are commonly used as maintenance agents in patients with IBD.[57] Specifically, in combination with anti-TNF therapy, thiopurine use improves rates of clinical response and remission in both UC and CD, in part by reducing the risk of antibody formation to the anti-TNF agents.[79,80] Similarly, thiopurine use in pregnancy is frequently reported to maintain clinical remission. Historically, its use has been associated with a possible increased risk of preterm birth.[81,82] However, recent studies have demonstrated that this increased risk of preterm birth may be a manifestation of active, flaring disease rather than the thiopurine exposure itself.[23,83] In a recent prospective study of women who visited an IBD preconception outpatient clinic, after correction for disease activity, thiopurine use in pregnancy was not associated with congenital abnormalities or spontaneous abortions.[83] Similar results were also reported in the pregnancy and neonatal outcomes in women with inflammatory bowel disease (PIANO) study.[84] As such, current evidence suggests that thiopurines may be continued during pregnancy to maintain clinical remission.[53,55] However, where possible, combination therapy should be avoided and thiopurine therapy should be discontinued to prevent an increased risk of infant infections.[55]

Thiopurine methyltransferase (TPMT) is the main enzyme regulator of thiopurine metabolism and its levels are often checked prior to the initiation of azathioprine or 6-mercaptopurine; low TPMT levels are associated with an increased risk of thiopurine-induced myelosuppression.[85] Thiopurine metabolism is significantly altered by pregnancy physiology and as such it is recommended to closely monitor thiopurine metabolite levels, 6-thioguanine (6-TG) and 6-methyl-mercaptopurine (6-MMP), during all stages of pregnancy.[86] The optimal frequency of testing in pregnancy remains unknown, but guidelines do recommend checking thiopurine metabolite levels in settings of concern for non-compliance or active disease to guide therapeutic decision making..[53] Newborns exposed to maternal thiopurine use may have anemia at birth and as such, screening neonatal complete blood cell counts should be considered.[86]

Methotrexate

Methotrexate inhibits purine biosynthesis via competitive inhibition of the dihydrofolate reductase enzyme.[87] It is widely used to treat chronic inflammatory conditions such as rheumatoid arthritis, psoriasis, and IBD. Particularly in the non-pregnant patient with Crohn’s disease, methotrexate can be used as an adjunct to anti-TNF therapy to reduce immunogenicity (i.e., antibody formation) and to maintain clinical remission.[88,89,90] It is often taken as a once a week oral, intramuscular, or subcutaneous administration with doses that range up to 25 mg per week. In pregnancy, methotrexate is absolutely contraindicated as it has been associated with congenital and craniofacial anomalies when taken in the first trimester[91] and risk of fetal demise when taken later in pregnancy.[92] As such, to minimize this risk of teratogenicity, some suggest the use of at least two contraceptive methods to prevent inadvertent conception.[93] When pregnancy is desired, it is recommended to withhold methotrexate for at least 3 months prior to conception.[53,55] High dose folic acid supplementation (i.e. 2 mg daily) should be prescribed for these patients, ideally starting at least 3 months prior to conception.[55] In addition, if pregnancy occurs while on methotrexate therapy, immediate therapy discontinuation and urgent referral to an obstetrician is recommended.[53]

Cyclosporine

Cyclosporine is a calcineurin inhibitor that is involved in the regulation of T-cell activation.

Its major mode of action is inhibition of the production of cytokines involved in the regulation of T-cell activation. It is recommended for use in the inpatient treatment of acute, severe ulcerative colitis as an alternative to anti-TNF therapy.[94] Solid organ transplant studies have demonstrated that cyclosporine crosses the human placenta, though the teratogenicity risk is low.[95,96,97] Particularly, the risk of major malformations with peripartum use of cyclosporine is approximately 4.1%, which is similar to the general population.[97,98] In IBD patients particularly, cyclosporine use during pregnancy has been reported to achieve successful control of severe colitis and preventing progression to colectomy.[99]

As such, cyclosporine therapy may be indicated in the setting of severe, hospitalized ulcerative colitis during pregnancy in order to avoid progression to an urgent colectomy.

Tacrolimus

Tacrolimus, traditionally used for allogenic liver or renal transplant, can also be used to treat severe ulcerative colitis.[100] In observational studies involving pregnant patients, tacrolimus therapy is associated with premature births but there does not appear to be an increased risk for congenital abnormalities.[101] During pregnancy, use of tacrolimus in IBD patients is limited to case reports but it's use appears to be safe.[102] However, given the limited evidence, a risk versus benefit discussion between the healthcare provider and the patient is necessary prior to its use during pregnancy.

Biologic agents

Biologic agents are the mainstay treatment for moderate–severe IBD and include anti-TNF medications (infliximab, adalimumab, golimumab, certolizumab), anti-integrin medications (vedolizumab), and anti-interleukin 12 and 23 agents (ustekinumab). With some exceptions, biologics can cross the placental membrane and as such, it is important to discuss the theoretical risks to the developing fetus.

Anti-tumor necrosis factors

Anti-TNF agents, infliximab, adalimumab and golimumab, are monoclonal antibodies that are routinely used as induction and maintenance agents in IBD.[57] In particular, they are considered first-line agents for the management of fistulizing/perianal CD and moderate–severe UC. They block the pro-inflammatory TNF-α molecule which has been implicated in activation of subsequent cytokine pathways and prostaglandin production. As monoclonal IgG antibodies, these agents actively cross the placental membrane, particularly in the third trimester.[103] This can result in detectable anti-TNF levels in the umbilical cord as well as the serum of the newborn.[104] Certolizumab, also an anti-TNF agent, is a PEGylated Fab fragment and as such does not actively transport through the placenta membrane.[105] Specifically, Mariette *et al.* demonstrated no quantifiable certolizumab drug levels in infants exposed to the agent *in utero* and as such concluded that it may be safe to continue this anti-TNF treatment during pregnancy.[105]

Evidence suggests that anti-TNF therapy is not teratogenic and is generally safe during pregnancy. In particular, rates of miscarriage and risk of congenital abnormalities and low birth weight appear to be similar in anti-TNF exposed patients compared to anti-TNF naïve patients during pregnancy.[69,84,106,107,108] There does not appear to be an increased risk of infection in children who were exposed to *in utero* anti-TNF therapy, at least within the first year of life.[109,110,111] Finally, achievement of developmental milestones is also similar in anti-TNF exposed children compared to anti-TNF naïve patients with respect to growth and mental development.[109]

However, recent evidence suggests anti-TNF exposure during pregnancy may be associated with an increased risk of maternal infections, particularly when combined with thiopurine therapy.[69] The recent EVASION study analyzed data from 11,275 pregnancies in 8276 women with IBD, of which 1457 were exposed to anti-TNF therapy.[69] Even after adjusting for disease activity, anti-TNF use during pregnancy was associated with a higher rate of maternal infections (OR 1.31, 95% CI 1.16–1.47). Interestingly, continuing anti-TNF therapy beyond the second trimester did not significantly increase this risk of maternal infections, but discontinuing therapy increased the risk of disease relapse.

As such, current recommendations are to continue anti-TNF therapy during pregnancy, especially in the setting of clinical remission.[55] However, given the persistence of anti-TNF levels up to 6 months of life in the neonate[104] and lack of long-term safety data, it is recommended to individualize the last pregnancy dose of anti-TNF agent in pregnancy to each clinical scenario with respect to underlying disease activity, therapeutic drug levels, and perhaps fecal calprotectin monitoring.[55] For example, if a patient remains in disease remission with undetectable fecal calprotectin levels, the final infliximab infusion may be scheduled 6–10 weeks before delivery (4–5 weeks prior if on every 4-week dosing), the final adalimumab injection may be scheduled 2–3 weeks before delivery (1–2 weeks prior if on every 1-week dosing) and the final golimumab injection should be scheduled 4–6 weeks before delivery. Finally, guidelines recommend that live vaccines (i.e. rotavirus (usually not given until after 6 months), oral polio, and the BCG vaccines) should be avoided for the first 6 months of life for the infant exposed to in utero anti-TNF agents.[12,53,55] Older studies have demonstrated that

infants with severe immunodeficiency are at a risk of severe reactions associated with live vaccines.[112] Furthermore, a fatal case of disseminated BCG infection in an infant exposed to in utero infliximab was reported following vaccination at 3 months.[113] However, more recent studies have demonstrated possible safety of live vaccines in infants exposed to in utero anti-TNF agents.[114] A recent multicenter study demonstrated that of 120 children exposed in utero to anti-TNF therapy, seven received the live rotavirus vaccine, five before six months of age. Only one child developed a fever.[114] Furthermore, of 43 infants exposed to in utero biologic therapy that received the rotavirus vaccine, less than 20% developed a minor reaction,[115] comparable to the rates reported in healthy infants.[116] Until further large, prospective studies are reported on the safety of live vaccines in infants exposed to in utero biologic therapy, we recommend continuing to avoid live vaccines for at least the first 6 months of life in infants exposed to in utero biologics.

Anti-integrin agents

Vedolizumab is a gut-specific, anti-integrin humanized monoclonal antibody used for the treatment of IBD. It selectively modulates the trafficking of gut lymphocytes and as such few systemic side-effects are reported in clinical studies.[117] Compared to placebo, patients treated with vedolizumab are more likely to achieve clinical response and remission and mucosal healing after 6 weeks of treatment (47.1% vs. 25.5%, p <0.001).[117] Durable clinical remission at week 52 occurs more significantly in patients treated with vedolizumab compared to placebo (24% vs. 8.7%, p = 0.008).[117] The use of vedolizumab in pregnancy, however, is quite limited.[118,119,120] In a retrospective study, 24 pregnancies in IBD exposed to vedolizumab were reported.[118] The rate of pregnancy related maternal and neonatal complications were 25% (i.e. pre-eclampsia, miscarriage, elective termination, stillbirth) and 35% (i.e. prematurity, IUGR, SGA, congenital malformations), respectively.[118] Of all patients enrolled in clinical IBD studies, 27 pregnancies in female and 19 pregnancies in partners of male participants exposed to vedolizumab were reported.[120] Only one case of congenital malformation (congenital corpus callosum agenesis anomaly) was reported. Limited by the small sample size, there did not appear to be any significant safety concerns for pregnancy outcomes related to vedolizumab use. However, given the lack of large-scale prospective safety data, vedolizumab use during pregnancy should be only prescribed when benefits outweigh the risks to both the mother and fetus. If prescribed during pregnancy, strict follow-up is required to ensure optimal maternal and neonatal outcomes.

Anti-interleukin 12 and 23 agents

Ustekinumab is an anti-interleukin 12 and 23 human monoclonal antibody currently indicated for moderate to severe active CD.[121] In patients with psoriasis, data on the use of Ustekinumab during pregnancy are limited to case reports/series and limited registry data.[122] Similarly, it's use in pregnancy for CD also remains limited.[123,124,125,126,127] In a study assessing women exposed to ustekinumab in five CD trials, only 26 maternal pregnancies were reported.[123] In all cases, ustekinumab was discontinued at first detection of pregnancy and the rates of spontaneous and elective abortions was 16.7% and 20.8%, respectively. There were no congenital abnormalities reported. Subsequently, in a larger safety database study comprising of patients with psoriatic arthritis and CD, of 206 reports of pregnancies exposed to ustekinumab, the rates of spontaneous abortions and congenital abnormalities were 17% and 4.4%, respectively, both comparable to the general population in the United States of America.[127] Finally, case reports have demonstrated that maternal trough levels of ustekinumab remain stable throughout pregnancy though cord blood levels may be as high as 2-fold higher than the maternal serum level.[125,126] Given these limited pregnancy data, a risk versus benefit discussion should be held with the patient, and if continued during pregnancy, the final dose should be administered 6–10 weeks prior to the estimated delivery date.[55]

Janus kinase inhibitors

Tofacitinib

Tofacitinib is an oral Janus kinase inhibitor that has been recently approved for the treatment of moderate to severe UC. In these patients, tofacitinib, 5–10 mg orally twice daily, significantly improves clinical response and achieves durable remission up to 52 weeks of follow-up.[128] During pregnancy, animal studies have raised concerns of potential

teratogenicity at doses exceeding 6.3 times the recommended maximum dose of 10 mg twice daily.[129] Such data are limited in the human population, particularly because contraceptive precaution was necessary in women of childbearing potential enrolled in clinical studies assessing tofacitinib in UC.[128] In these studies, if pregnancy inadvertently occurred, tofacitinib was discontinued. In a recent Pfizer safety database study, investigators identified 25 cases of pregnancy-related tofacitinib exposure; the rates of congenital malformations and spontaneous abortions were 1.0% and 10.8%, respectively, rates similar to that of the general population.[130] Despite this, until further prospective safety data are reported, tofacitinib should be avoided during pregnancy in IBD.[55]

MODE OF DELIVERY

Traditionally, rates of cesarean delivery are higher in patients with IBD compared to those without the disease process.[131,132] These rates are as high as 52% and 48% in patients with CD and UC, respectively, with over half of all these deliveries being performed emergently.[132] The presence of active perianal disease and prior history of colectomy with ileal pouch–anal anastomosis (IPAA) are risk factors for undergoing cesarean over vaginal delivery.[132,133] A past history of cesarean also increases the risk of the same during future pregnancies.[132]

In patients with CD, the presence of active perianal disease during pregnancy is an indication for cesarean delivery.[53] This stems from concern that vaginal delivery may result in inadvertent trauma and laceration leading to progressive perianal symptoms and de novo fistulizing disease. Although some studies have demonstrated this to be true,[134] others have demonstrated no increased risk of either de novo or progression of inactive perianal disease postvaginal delivery compared to cesarean.[135,136] As such, an individualized, multidisciplinary approach is necessary, involving the patient, gastroenterologist, and obstetrician, in order to determine the most appropriate mode of delivery in patients with perianal disease and CD.

In patients with UC on the other hand, there is risk that in women with IPAA, vaginal delivery may result in sphincter injury resulting in fecal incontinence and pouch dysfunction.[137] However, long-term pouch function does not seem to be affected in women with an IPAA that undergo vaginal delivery.[138] Since large-scale evidence remains lacking, current recommendations are for patients with an IPAA to be considered for a cesarean delivery. Again this decision should be made in consultation with the patient and obstetrician.[137]

BREASTFEEDING CONSIDERATIONS

Similar to concerns during pregnancy, women with IBD may also fear the effect of their medications on their newborn during lactation. Older studies have demonstrated rates of breastfeeding as low as 44%,[139] though recently this has improved to as high as 83.3%,[140] possibly due to improved patient awareness and counseling on the part of healthcare physicians. Since breastfeeding can improve newborn intestinal microbiota composition, some suggest it may also be associated with overall reduced risk of pediatric and adult onset IBD, particularly in those breastfeeding for at least 12 months.[141] (It is believed with respect to the current available data that breastmilk predominant affects the infant gut microbiome and passes beneficial immunity which reduces risk of childhood infections, both of which may be the reason for the apparent reduced risk of developing child and adult onset IBD in those infants that are breastfed.)

The majority of medications aforementioned are safe to continue during lactation as most are passed in minute concentrations into the breast milk and as such likely cause negligible harm to the infant.[55,142] In fact, results from the recent PIANO registry demonstrated similar milestone achievement and infection rates in breastfed infants exposed to immunomodulators, biologics, or combination of the both in the first 12 months of life.[143] As such, though traditionally the “pump and dump” approach was recommended for women lactating while on immunosuppressive agents, it is likely not necessary and is in fact discouraged by the recent American clinical care pathway recommendations.[55]

Most 5-ASA agents are safe to continue during lactation.[55] Two case reports have reported either bloody diarrhea[144] or watery diarrhea[145] in infants exposed to 5-ASA agents via breast milk, suggesting a possible hypersensitivity reaction or

reflecting the acetylation phenotype of the infant. Similarly, breast milk levels of thiopurines, anti-TNF agents, and vedolizumab are minimal and as such these agents should be continued during lactation.[143,146] Data on safety of tofacitinib and ustekinumab during lactation are lacking and as such current guidelines recommend avoiding lactation while on therapy.[55] Finally, though methotrexate levels in breast milk are likely clinically insignificant, due to lack of strong evidence, current recommendations also recommend not to breastfeed on methotrexate therapy.[147]

CONCLUSION

IBD is a chronic illness that poses a significant challenge for healthcare providers during pregnancy. Effective pre-conception counseling can reduce disease-related anxiety and improve medication adherence. Careful monitoring during all gestational periods for disease relapse is important in order to optimize treatment and prevent adverse maternal and neonatal outcomes. As we learn more about the interplay of IBD and pregnancy, it will be critical that collaboration between gastroenterologists and obstetricians occurs in order to achieve the healthiest pregnancy possible.

PRACTICE RECOMMENDATIONS

- **Patients with inflammatory bowel disease contemplating pregnancy should undergo a comprehensive pre-conception counseling appointment with a gastroenterologist with special training in managing the disease process during pregnancy.**
- **Lower endoscopy appears to be safe during pregnancy, particularly in the second trimester, and is recommended if results will significantly alter the management plan.**
- **Most medications used to treat inflammatory bowel disease appear to be safe, with the exception of methotrexate, and should not be withheld in the setting of disease remission.**
- **There remains limited evidence on the use of tofacitinib in pregnancy and as such its use should be avoided until further research is completed.**
- **In most clinical situations, the mode of delivery should be guided by obstetrical indications. Active perianal Crohn's disease and history of an ileal pouch–anal anastomosis (IPAA) may be indications for cesarean delivery.**
- **Breastfeeding should be encouraged in all patients and most immunosuppressive agents (with the exception of methotrexate and tofacitinib) can be continued.**

CONFLICTS OF INTEREST

The authors of this chapter declare that they have no interests that conflict with the contents of the chapter.

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