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Pregnancy and Inflammatory Bowel Disease

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Women with inflammatory bowel disease (IBD) often deal with the illness and its consequences during their childbearing years. Most will have safe pregnancies and healthy children, but there remains significant anxiety and misperceptions about fertility, pregnancy complications and medication toxicities. While IBD increases the risk of certain pregnancy complications and adverse pregnancy outcomes, active disease further increases these risks while sustained remission maximizes maternal and fetal health. A multidisciplinary team should emphasize the importance of medication adherence to achieve preconception disease control and maintain remission throughout pregnancy. Most medications, including aminosalicylates, thiopurines, and biologic agents, are low risk during pregnancy and compatible with breastfeeding. Medication adjustments to reduce fetal exposure may be considered on an individualized basis in quiescent disease. The mode of delivery is determined by obstetrical indications, except for women with active perianal disease who should consider cesarean delivery.

INTRODUCTION

The incidence of inflammatory bowel disease (IBD) peaks during the childbearing years, and the complexities of family planning and IBD management often coincide. Although most patients with IBD have successful pregnancies, anxiety and misconceptions about fertility, medication safety and the potential for adverse pregnancy outcomes are very common. Knowledgeable providers can positively impact IBD pregnancy outcomes by optimizing disease control, reducing medication-related risks and enhancing patient education. As always, a multidisciplinary team including the primary care provider, gastroenterologist, obstetrician, colorectal surgeon and pediatrician should be involved in the care of pregnant women with IBD.

FERTILITY

Though fear of infertility is common among IBD patients, women with quiescent disease and no prior pelvic surgery actually have similar infertility rates to the general population. Active disease, however,

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impairs fertility through a variety of mechanisms including pelvic inflammation, decreased ovarian reserve, poor nutrition, decreased libido, dyspareunia and depression. One well-established risk factor for infertility is prior pelvic surgery – which results in both scarring and adhesions. The post-operative infertility rate in ulcerative colitis patients who have undergone an ileal pouch anal anastomosis (IPAA) surgery is 48%, threefold higher than the 15% rate in medically treated patients.[1] Compared to open surgery, laparoscopic total proctocolectomy with IPAA may preserve fertility. Women of childbearing potential should be aware of the infertility risk of IPAA, and less invasive procedures may be considered.

Women who experience spontaneous abortion or difficulty conceiving should be assessed for other known risk factors for infertility, including vitamin D deficiency and celiac disease. If a woman remains unable to conceive after six months of calculated attempts, a reproductive endocrinology referral is warranted.

Less is known about male fertility in IBD, although certain medications have been shown to affect sperm quantity and quality. Sulfasalazine causes reversible infertility due to dose-dependent oligospermia and altered sperm motility and morphology. Methotrexate may reduce sperm quality, though this is reversible when the drug is discontinued. We recommend that men stop methotrexate at least 3 months before attempting conception though there have been no association with birth defects when the male has taken methotrexate prior to conception.

COMPLICATIONS

Women with IBD, independent of disease activity, experience higher rates of adverse pregnancy outcomes compared to age matched controls. A meta-analysis including more than 15,000 women with IBD found increased odds of preterm birth, small for gestational age infants and still birth.[2] Multiple population-based studies, however, have not detected an increased risk of congenital anomalies in IBD pregnancies. IBD is associated with higher rates of labor and delivery complications, including pre-eclampsia, preterm premature rupture of membranes and venous thromboembolism. Inadequate maternal weight gain has been identified as a predictor of adverse outcomes, and factors such inflammation, anemia, hypoalbuminemia and poor nutrition may also increase risk. Based on these findings, a maternal-fetal medicine specialist should monitor all pregnant patients with IBD, and serial ultrasonography for the assessment of fetal growth should be considered in the third trimester.

The Impact of Disease Activity on Pregnancy

Disease activity is the strongest predictor of adverse pregnancy outcomes. Active disease at conception increases the risk of spontaneous abortion and preterm birth, and disease flares during pregnancy increase the risk of preterm birth, still birth and low birth weight. An ulcerative colitis flare doubles the risk of low birth weight, and a Crohn's flare triples it. These observations emphasize the critical importance of maintaining remission throughout pregnancy, beginning in the preconception period.

When patients conceive during disease remission and maintain quiescent disease throughout pregnancy, the risks of preterm birth and low birth weight are similar to matched non-IBD controls. Therefore, it is recommended that women achieve and sustain remission for at least three to six months before conception to maximize the chances of a successful and healthy pregnancy. Disease remission should be confirmed prior to conception using laboratory analysis, a fecal calprotectin and/or a colonoscopy or flexible sigmoidoscopy.

The Impact of Pregnancy on Disease Activity

It is unclear whether pregnancy itself adversely affects the course of IBD. Among women in remission at conception, the risk of subsequent disease exacerbation during pregnancy is higher in ulcerative colitis (33%) than in Crohn's disease (20%).[3] The reason for the higher rate of flare in ulcerative colitis is unclear, although overlapping immune pathways and less-aggressive disease management may contribute. A meta-analysis of more than 1,700 IBD patients found that disease activity at conception is strongly correlated with more flares during pregnancy.[4] In this analysis, disease flares affected nearly half of pregnancies conceived during active disease, compared with approximately one-quarter of pregnancies conceived during remission.

It is important to note that inappropriate discontinuation of maintenance medications during pregnancy and the post-partum period increases the risk of disease flare. Patients should be educated about the importance of medication adherence to optimize preconception disease control and maintain remission throughout pregnancy.

Mode of Delivery

The mode of delivery in IBD pregnancies should largely be determined by patient preference and obstetric indications. Multiple studies have shown that cesarean delivery is more common among women with IBD compared to the general population due to concerns that vaginal delivery might trigger perianal disease. In reality, there is no association between mode of delivery and IBD natural history, and cesarean delivery should typically be recommended only for women with active perianal disease. While some colorectal surgeons also recommend cesarean delivery following IPAA to protect the pouch and preserve anal sphincter integrity, this has not fully been supported by the literature.

With regards to the risk of childhood IBD, there appears to be no link to the mode of delivery. Rather, studies estimate that a child has a 2-5% chance of developing IBD if a single parent has the disease and a 36% chance when both parents have IBD.[5-6]

TREATMENT

Prior to initiating IBD therapy in a woman of childbearing age, the patient's plans for pregnancy should be discussed and considered. Women should be aware

Table 1. Managing IBD Exacerbations During Pregnancy

EVALUATION

- **Lab Tests**
  - Rule out Clostridium difficile (more prevalent in the peripartum period)
  - Remember: low albumin, low hemoglobin, and elevated ESR* are common in pregnancy and may not reflect inflammation
- **Endoscopy**
  - A flexible sigmoidoscopy (without sedation) to assess disease severity can be performed safely in any trimester
  - Full colonoscopy (rarely necessary) requires anesthesia with fetal monitoring
- **Imaging**
  - Magnetic resonance imaging is preferred over computed tomography to avoid fetal radiation exposure
  - Gadolinium is a potential teratogen and should be avoided in the first trimester.

TREATMENT

- **Steroids**
  - Use corticosteroids at the lowest effective dose for the shortest duration
  - Consider budesonide if clinically appropriate
  - Stress dosing may be necessary during labor and delivery to avoid adrenal insufficiency
- **Aminosalicylates, corticosteroids, and biologics**
  - May be used for induction therapy in pregnancy
- **Antibiotics**
  - Amoxicillin-clavulanic acid has a favorable safety profile

Surgery

- Non-emergent surgery should be performed in the second trimester

*ESR = erythrocyte sedimentation rate

that the dangers of active disease outweigh the risk of IBD therapies, and *preconception* counseling about the low risk of most medications may improve medication adherence during pregnancy. With the exception of methotrexate and thalidomide, most medications used to treat IBD are considered low risk and may be continued during pregnancy and breastfeeding. In accordance with recent FDA labeling revisions, the following discussion avoids the previously used pregnancy categories (A, B, C, D, X) in favor of a narrative risk summary, clinical considerations and a brief description of supporting data for the most commonly used IBD therapies.

Managing IBD Exacerbations in Pregnancy

In each trimester of pregnancy, patients (especially those with high-risk disease features) should be monitored for evidence of disease activity and poor nutrition using tools such as fecal calprotectin, serum inflammatory makers (though these may be unreliable in pregnancy) and gestational weight gain. Active disease during pregnancy commonly responds to standard medical therapy, and evaluation and treatment algorithms are the same as for the non-pregnant patient. There are, however, several considerations that are unique to pregnancy (Table 1).

Corticosteroids may be used to treat disease flares, though their use may be associated with an increased risk of pregnancy complications, including gestational diabetes, preterm birth, low birth weight and a possible increase in infant infections in the first four months of life.[7] Although the benefits of controlling active disease likely outweigh these risks, corticosteroid use during pregnancy should be limited to the lowest effective dose for the shortest duration. Further, steroids should not be used as planned maintenance therapy during pregnancy. Both prednisone and budesonide are compatible with breastfeeding, though avoiding breastfeeding for three to four hours after ingestion of prednisone may limit the amount received by the infant.

The two most commonly used antibiotics in IBD management are ciprofloxacin and metronidazole. While quinolones have been shown to have no association with an increased risk of adverse pregnancy outcomes and are considered compatible with breastfeeding, metronidazole use is more controversial. Metronidazole use in the first trimester has been associated with a possible increased risk of orofacial clefts, and it is incompatible with breastfeeding due to potential toxicities. Amoxicillin-clavulanic acid is the preferred antibiotic during pregnancy, with a favorable safety profile and breastfeeding compatibility.

Indications for surgery do not differ in the pregnant patient and include bowel obstruction, perforation, and medically refractory disease. Non-emergent surgery should preferentially be performed during the second trimester.

5-Aminosalicylates

The 5-aminosalicylates (balsalazide, mesalamine, olsalazine and sulfasalazine) are considered safe in pregnancy, though two points should be kept in mind. First, the coating of delayed release Asacol HD contains dibutyl phthalate (DBP), which has been associated with congenital anomalies in animals at doses much higher than the therapeutic human dose. Asacol HD should therefore be discontinued in favor of alterative mesalamines during pregnancy. Second, women taking sulfasalazine should receive supplemental folic acid 2 mg daily to prevent folate deficiency. Though aminosalicylates enter breast milk, they are considered compatible with use during breastfeeding.

Methotrexate

Methotrexate is an abortifacient, teratogenic inhibitor of DNA synthesis and is *contraindicated* during conception and pregnancy. It has been associated with a constellation of congenital limb and craniofacial anomalies as well as developmental delay. Given the long half-life of the drug, women should not attempt conception within 3-6 months of methotrexate use. Furthermore, methotrexate should only be given to those women of childbearing potential who are adherent with one to two methods of contraception and take supplemental folic acid. Despite low levels of excretion in breast milk, methotrexate is also contraindicated during breastfeeding as it may accumulate in neonatal tissue. Though less is known about the impact of methotrexate use among men, we recommend stopping therapy at least three months prior to attempts at conception.

Thiopurines

Like methotrexate, thiopurines (azathioprine and 6-mercaptopurine) inhibit DNA synthesis, and at high doses are teratogenic in animals. While previous meta-analyses have shown thiopurine treatment to be associated with preterm delivery and an increased risk of congenital anomalies compared to healthy women

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(though not to unexposed IBD controls), many of the included studies were confounded by unmeasured disease activity.[8-9] In studies that have attempted to account for disease activity, the results have been mixed. While one has shown an increased risk of preterm delivery irrespective of disease activity,[10] several have failed to detect an elevated risk of pregnancy complications or congenital anomalies.[11-14] However, infections at 9-12 months of age have been showed to be more common among infants exposed to thiopurine plus biologic therapy.[12] Given the overall body of evidence, we feel that it is reasonable to continue thiopurine monotherapy during pregnancy to maintain remission, as the risks associated with thiopurine use are likely outweighed by the risks of active disease. Due to the potential for delayed infant infections, women in deep remission with adequate trough biologic levels who are on combination thiopurine/biologic therapy may consider stopping the thiopurine before conception. Starting thiopurines for the first time during pregnancy should be discouraged due to their slow onset of action and unpredictable adverse events (bone marrow suppression and pancreatitis).

With regards to breastfeeding, clinically insignificant thiopurine concentrations have been found to peak in breast milk within 4 hours of maternal ingestion. Lactating mothers may consider avoiding breastfeeding during this interval.

Anti-tumor necrosis factor (TNF) Agents

The available data on the anti-TNF class suggest overall low risk for use during pregnancy, though the long term implications of intrauterine exposure remain unknown – particularly with regards to the development and function of the infant immune system.

Series of hundreds of women exposed to infliximab, adalimumab and certolizumab pegol have shown no adverse effect on pregnancy outcomes or congenital anomalies, and this has been confirmed in a systematic review including more than 1,500 anti-TNF exposed pregnancies.[15] A recent meta-analysis also showed a similar rate of unfavorable pregnancy outcomes between women taking anti-TNF therapy and unexposed controls, including preterm delivery, low birth weight, and congenital anomalies.[16] With the exception of certolizumab pegol, the anti-TNF agents are actively transported across the placenta (along with other maternal antibodies) beginning in the second trimester. With a majority of transfer occurring in the third trimester, cord blood infliximab and adalimumab concentrations at birth exceed maternal levels by up to fourfold and remain detectable in infants for over nine months.[17] This raises concern about potential adverse effects on neonatal immune system development. While the ongoing prospective, multicenter Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry of more than 1475 pregnant women with IBD has shown that third trimester anti-TNF exposure does not detrimentally affect infant growth rate, immune development, number of infections or achievement of developmental milestones, it is reasonable for women in sustained remission to consider third trimester dosing adjustments to reduce neonatal exposure (Table 2). Therapeutic drug monitoring with trough serum concentrations in the late second or early third trimester may help guide this pre-delivery dosing. Stopping anti-TNF therapy in the second trimester is *not* supported by the current data given the low risk of continuing therapy and potential risk of disease flare in the pregnancy and post-partum as well as the development of immunogenicity.

Infants exposed to anti-TNF agents should not receive live vaccines for at least the first nine months of life or until drug levels are undetectable. All other vaccinations may be given on schedule. This recommendation does not apply to certolizumab pegol, which is not actively transported across the placenta and does not reach significant levels in the infant. Pediatricians should be aware of intrauterine anti-TNF exposure so that vaccinations can be appropriately managed.

Combination therapy with an anti-TNF and thiopurine during pregnancy may be associated with a higher risk of preterm birth and any pregnancy complication, in addition to the risk of delayed infant infections (previously described).

There is clinically insignificant anti-TNF excretion into breast milk, with milk concentrations less than 1% of maternal plasma concentrations.

Non anti-TNF Therapies

The anti-integrin agents natalizumab and vedolizumab are both monoclonal antibodies that would be expected to actively cross the placenta. There has been no observed increased risk of preterm birth, low birth weight, or congenital anomalies among hundreds of women (most with multiple sclerosis) treated with

Table 2. Checklist for Managing the IBD Patient Before, During and After Pregnancy

Preconception	✓ Involve multidisciplinary team: primary care physician, gastroenterologist, obstetrician ✓ Ensure healthcare maintenance, vaccinations, and surveillance colonoscopy (as appropriate) are up to date ✓ Check baseline laboratories (complete blood count, iron studies, B12, folate, vitamin D) and correct nutrient deficiencies ✓ Assess disease activity - Consider baseline fecal calprotectin or colonoscopy (if appropriate) ✓ Optimize disease control - Adjust medications to achieve remission - Discontinue methotrexate ✓ Develop medication plan for pregnancy and postpartum period - Ensure patient understanding - Communicate with other providers
First Trimester	✓ Continue maintenance medications ✓ Establish care with a maternal-fetal medicine specialist
Second Trimester	✓ Continue maintenance medications ✓ Consider therapeutic drug monitoring of biologics
Third Trimester	✓ Continue maintenance medications ✓ Consider adjusting biologic medication dosing schedule to reduce placental transfer. Appropriate gestational week for last dose: - Infliximab – week 30-32 - Adalimumab – week 36-38 - Certolizumab pegol – no adjustment - Golimumab – week 34-36 - Natalizumab – week 36 - Vedolizumab – week 30-32 ✓ Obstetrics can consider serial ultrasounds to assess fetal growth (especially with active disease/inadequate maternal weight gain)
Delivery	✓ Mode of delivery determined by obstetric considerations - Active perianal disease is an indication for cesarean delivery
Postpartum	✓ Resume biologic therapy if interval appropriate and no infection - 24 hours after vaginal delivery - 48 hours after cesarean delivery ✓ Review safety of continuing most medications during lactation ✓ Inform pediatrician of *in utero* biologic medication exposures ✓ Avoid live vaccines for at least 9 months or until infant drug level becomes undetectable (applies to all biologic agents except certolizumab pegol)

natalizumab during pregnancy. Vedolizumab pregnancy safety data are extremely limited, though pregnant women treated with vedolizumab are being followed in several registries.

The newest FDA approved therapy for Crohn's disease is the anti-interleukin 12-23 agent ustekinumab. A series of 26 exposed pregnancies reported a spontaneous abortion rate similar to the general population.[18]

Lastly, tofacitinib (an oral janus kinase inhibitor) has showed efficacy in ulcerative colitis in phase II trials, but human pregnancy outcome data are sparse.

BREASTFEEDING

As discussed previously, most IBD medications are compatible with breastfeeding. Though women are commonly concerned about drug transfer to the infant via breast milk, the PIANO registry found no increased risk of infection or developmental delay among nursing infants whose mothers were being treated with thiopurines or anti-TNF agents. Furthermore, there may be a protective effect of breastfeeding for mothers, as studies have shown a decrease in disease flares in the first postpartum year among mothers who were breastfeeding.[19] LactMed is a free online database sponsored by the U.S. National Library of Medicine that provides reliable information on drugs and lactation.

SUMMARY

Women with IBD are at risk for pregnancy complications and adverse outcomes, and they should be managed as high-risk obstetric patients by a multidisciplinary team. Counseling about the importance of medication adherence to optimize and maintain disease control should begin in the preconception period. Disease activity is the strongest predictor of adverse pregnancy outcomes, and sustained remission maximizes the chance of a successful and healthy pregnancy. With the exception of methotrexate, most medications are low risk for continued use during pregnancy and lactation. On a case-by-case basis, medication adjustments to reduce fetal exposure can be considered. This includes thiopurine withdrawal from combination therapy and third trimester biologic dosing adjustments. ■

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