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Review

Evaluation of Patients with Inflammatory Bowel Disease of Childbearing Age

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Abstract

This comprehensive review examines the challenges faced by women of reproductive age who have inflammatory bowel disease (IBD). It focuses on the management of IBD during the periconceptional, gestational, and postpartum periods, as well as its effects on fertility and pregnancy outcomes. The review emphasizes the impact of disease activity, surgical interventions, and medications on fertility and pregnancy, underscoring the importance of achieving disease remission prior to conception to improve outcomes. Preconception counseling is identified as essential in reducing disease flares and complications during pregnancy. Most IBD medications-excluding methotrexate, thalidomide, JAK inhibitors, and S1P modulators-are deemed safe for use during pregnancy and lactation. The article also stresses the need for the timely resumption of treatment after delivery and highlights the increased risk of postpartum disease flare, particularly in cases of ulcerative colitis. Additionally, it offers guidance for male IBD patients, emphasizing the importance of medication adjustments to address fertility concerns. A multidisciplinary approach, involving gastroenterologists, obstetricians, and surgeons, is recommended to ensure optimal care and favorable outcomes for both mother and child.

Keywords: Fertility, inflammatory bowel disease, lactation, medication safety, preconception counseling, pregnancy management

INTRODUCTION

Inflammatory bowel disease (IBD) primarily affects adults between the ages of 20 and 40, coinciding with their reproductive years.[1] In patients of reproductive age, both fertility and sexual health may be impacted by the disease itself or by the medications used in its treatment.[2] These factors can also influence pregnancy and lactation. Since not all pregnancies are planned, it is recommended that all women of reproductive age with IBD receive preconception counseling. This counseling aims to address parental concerns-such as the risk of disease inheritance, potential medication side effects, and the importance of continued treatment-while achieving disease remission, correcting anemia and vitamin deficiencies, optimizing nutritional status, and discontinuing teratogenic medications.[3]

FERTILITY AND SEXUALITY

Fertility and sexual function in women with IBD during their reproductive years can be significantly affected by various factors. Fertility may be impacted by disease activity, medications, and surgical treatments. Both men and women with active disease often experience reduced fertility. Although most IBD medications are considered safe, sulfasalazine has been linked to oligospermia and asthenospermia, which can lead to infertility. In women, fertility and fecundity may decline, particularly after pelvic surgeries.[4-6] Elective childlessness is also common among IBD patients, particularly those with Crohn's disease, with prevalence rates ranging from 17% to 44%. The primary reasons for this include fears of transmitting the disease to the child, concerns about disease exacerbation during pregnancy, and anxiety regarding the potential teratogenic effects of medications.[7,8]

Sexual dysfunction is another concern and can be influenced by several factors, including active disease (e.g., inflammation, fatigue, discomfort, perianal disease, and body image issues), depression, medication side effects (e.g., corticosteroid-induced weight gain, acne, hirsutism; erectile dysfunction associated with methotrexate or sulfasalazine), and surgical complications (e.g., erectile dysfunction due to autonomic nerve damage).[9-12] Research shows that sexual dysfunction is more prevalent among individuals with IBD than in the general population, affecting 45–60% of women and 15–25% of men, compared to 30% of women and 5% of men in the general population.[13]

PRECONCEPTIONAL COUNSELING

The key components of preconceptional counseling for women with IBD include the following:[14]

- Providing information about the inheritance risk of IBD
- Discontinuing smoking, alcohol, and, if applicable, narcotic drug use
- Completing cervical cancer screening and ensuring vaccinations are up to date
- Screening for anemia and vitamin deficiencies; providing folic acid supplementation

- Reviewing the safety of medications used in treatment
- Assessing disease activity and achieving remission before conception
- Monitoring the disease and developing an individualized treatment plan during pregnancy
- Evaluating the benefits and risks of continuing medication therapy during pregnancy and lactation, as well as discussing delivery method options

Research indicates that preconceptional counseling improves pregnancy outcomes. It reduces patient anxiety, enhances medication adherence, encourages the cessation of harmful substances, and lowers the risk of disease flares and complications during pregnancy.[15-17]

Information on Disease Inheritance

Patients should be informed about the genetic risks associated with IBD. For example, Crohn's disease occurs in approximately 12% of first-degree relatives, while ulcerative colitis is observed in about 9%. If a first-degree relative is affected, the risk of developing Crohn's disease increases eightfold and ulcerative colitis fourfold.[18] This risk can rise up to 57 times if more than two first-degree relatives are affected.[19] Additionally, studies suggest that if both parents have IBD, their child has a 30% risk of developing the condition.[20]

Smoking, Alcohol, and Drug Cessation

Patients should be advised to stop the use of tobacco, alcohol, and narcotics.[14]

Cervical Cancer Screening and Vaccinations

Preconceptional counseling should include cervical cancer screening through a Pap smear and ensuring that vaccinations are up to date. In patients undergoing immunosuppressive therapy, inactivated vaccines are safe to administer, while live vaccines are contraindicated. Pregnant women should be current on hepatitis B and pneumococcal vaccinations. It is essential to confirm rubella immunity in patients receiving small-molecule immunomodulators and biological agents, as live vaccines such as MMR (measles, mumps, rubella) and varicella cannot be administered during immunosuppressive treatment. Women who are pregnant or planning pregnancy should receive the inactivated influenza vaccine during flu season. Additionally, the COVID-19 vaccine is strongly recommended during both pregnancy and lactation.[14,21]

Screening and Management of Anemia and Vitamin Deficiencies:

Screening for and treating anemia and vitamin deficiencies is crucial. Malnutrition is common in IBD patients and, if left untreated, can lead to infertility. Annual monitoring of micronutrient status is recommended, with preconceptional optimization beginning 3–6 months prior to conception. Folate supplementation should start four weeks before conception and continue through the first 12 weeks of pregnancy, with a recommended dose of 1 mg/day, increasing to 2 mg/day for patients on sulfasalazine. Additionally, supplementation with iron (if deficiency persists, continue 30–60 mg/day during pregnancy), B12, calcium (800–1000 mg/day with 800 IU/day of vitamin D if on corticosteroids), vitamin D (2000 IU/day if deficient; otherwise, 400 IU/day), and energy and protein support (+70 kcal/day in the first trimester, +260 kcal/day in the second trimester, +500 kcal/day in the third trimester, and +500 kcal/day during lactation) is recommended.[22]

Assessment of Disease Activity Before Conception:

The presence of active disease before conception correlates with an increased risk of pregnancy complications, such as preterm birth, low birth weight, and newborns classified as small-for-gestational-age. In contrast, women who conceive during remission have pregnancy outcomes comparable to those without IBD. Therefore, a remission period of at least 3–6 months before conception is recommended. Clinical assessment, biomarker monitoring, endoscopic evaluation, and, if necessary, cross-sectional imaging should be performed prior to conception.[23]

Medication Management Before Conception:

Methotrexate should be discontinued at least three months before conception. Small-molecule drugs, including tofacitinib, upadacitinib, and filgotinib (four weeks prior), and ozanimod (three months prior) should also be discontinued. Corticosteroids should be tapered and discontinued if possible. Other medications may be continued, but thiopurines and biological agents should be optimized before conception, with drug levels monitored to ensure appropriate dosing.[14,21,23]

MAIN POINTS

- Preconception Counseling: All women of reproductive age with IBD should receive preconception counseling. This counseling increases the likelihood of successful conception, improves pregnancy outcomes, and reduces the risk of postpartum disease flares. The primary goals include achieving disease remission (for a minimum of 3–6 months) before conception, discontinuing teratogenic medications (e.g., methotrexate-three months prior, JAK kinase inhibitors-three months prior, S1P modulators-one month prior), optimizing nutritional status, and eliminating harmful substances (e.g., smoking, narcotics).
- Medication Safety: Most medications used to manage IBD are considered safe during pregnancy and lactation, with the exception of methotrexate, thalidomide, JAK kinase inhibitors, and S1P modulators. If no contraindications exist, these medications should be continued throughout pregnancy.
- Diagnostic Considerations: Certain parameters, such as hemoglobin, albumin, sedimentation rate, and CRP levels, may change during pregnancy, while fecal calprotectin levels typically remain stable. Endoscopic evaluation should only be performed if strongly indicated and preferably during the second trimester. Ultrasound and MRI, which do not involve radiation, should be prioritized as imaging modalities.
- Delivery Planning: Although the mode of delivery is generally determined by the obstetrician, cesarean sections may be recommended in cases of active perianal disease, a history of rectovaginal fistula, or restorative proctocolectomy. Delivery decisions should follow a multidisciplinary evaluation.
- Postpartum Treatment: IBD treatment should be resumed as soon as possible after delivery to prevent disease flare-ups.
- Guidance for Male IBD Patients: In male patients, mesalazine should be prioritized over sulfasalazine, and 5-ASA formulations containing phthalates should be avoided. Methotrexate must be discontinued three months prior to conception to minimize risks of paternal teratogenicity and infertility.

MANAGEMENT AND RECOMMENDATIONS FOR WOMEN WITH IBD

Medication Use During Pregnancy

- **5-Aminosalicylates (5-ASA):** The use of sulfasalazine during pregnancy is considered safe. However, because its sulfapyridine component can interfere with folate metabolism (inhibiting folate synthesis), concurrent folate supplementation of 2 mg/day is recommended. Mesalazine is also regarded as low-risk and safe for use during pregnancy. However, 5-ASA preparations with dibutyl phthalate coatings should be avoided due to the potential risk of urogenital malformations in the fetus. In Türkiye, mesalazine products do not contain dibutyl phthalate and can be used safely.[24]

- **Corticosteroids:** These are typically used to induce remission during disease flares. Short-term use is considered low-risk. Although earlier studies suggested a correlation between first-trimester use and orofacial deformities, extensive research has not confirmed this risk.[25] Maternal complications include hypertension, diabetes, and preeclampsia.[26] Additionally, there is an increased risk of preterm birth, low birth weight, and intrauterine growth restriction. Corticosteroid use during the second and third trimesters may also increase the risk of serious infections in infants at 9 and 12 months of age.[27]

- **Thiopurines:** These drugs are considered low-risk and safe during pregnancy.[28,29] If a patient becomes pregnant while on thiopurine monotherapy, it is recommended to continue the medication. In cases of dual therapy with a biological agent, discontinuation of thiopurines may be considered if the disease is in long-term remission and the patient can be managed with biological monotherapy. However, if dual therapy is necessary for disease control, it should be continued. Initiating thiopurines de novo during pregnancy is not advised due to their delayed onset of action and the risk of idiosyncratic adverse effects, including pancreatitis.[21]

- **Methotrexate, Thalidomide:** These drugs are teratogenic and strictly prohibited during pregnancy.[30]

- **JAK (Janus Kinase) Inhibitors (tofacitinib, upadacitinib, filgotinib) and S1P (Sphingosine 1-Phosphate) Modulators (ozanimod):** Due to insufficient human data, these drugs should not be used during pregnancy.[21]

- **Calcineurin Inhibitors (Cyclosporine, Tacrolimus):** Although studies with low evidence levels suggest that these medications pose minimal risk, their use during pregnancy should be undertaken with caution due to insufficient data. They carry risks of hypertension, preeclampsia, and gestational diabetes in pregnant women. In neonates, hyperkalemia and renal dysfunction should be monitored.[31,32]

- **Biological Agents (Anti-TNF Agents, Vedolizumab, Ustekinumab):** Biological agents, which are monoclonal antibodies of the IgG1 class, cross the placenta in minimal amounts during early pregnancy through passive diffusion. However, from the 13th to 17th weeks of gestation, the development of neonatal Fc receptors in the placenta increases the transfer of these agents. In some cases, their concentrations in the infant's umbilical cord can be up to four times higher than maternal levels. The transfer level depends on the specific biological agent, with maternal/fetal ratios of 2.6 for infliximab and 1.5 for adalimumab, as well as the duration of exposure. These agents can remain detectable in newborns for up to 12 months after birth. Certolizumab pegol, which contains polyethylene glycol, does not cross the placenta and is an exception.

  It is recommended to continue anti-TNF agents, vedolizumab, and ustekinumab during pregnancy in cases of active disease or when disease control was difficult prior to conception. The timing of the final anti-TNF dose in the third trimester should be adjusted to reduce fetal exposure. For agents administered every eight weeks, the last dose should be given between 31 and 33 weeks; for those given every four weeks, the last dose should be administered between 35 and 37 weeks; and for agents administered every one to two weeks, the last dose should be given between 37 and 39 weeks.

  It is not advisable to discontinue anti-TNF agents before the third trimester due to the risk of disease exacerbations and poor pregnancy outcomes. If a patient requests discontinuation before the third trimester, it is crucial to ensure that the disease is in long-term remission, with treatment restarted soon after delivery. Discontinuation of vedolizumab and ustekinumab in patients in remission should be evaluated on a case-by-case basis, considering the limited data on fetal outcomes and the risk of relapse.[21,33,34]

- **Antibiotics:** Antibiotics commonly used in IBD include metronidazole and ciprofloxacin, primarily for the treatment of conditions such as perianal disease, abdominal sepsis, and pouchitis.[35] Both are considered safe during pregnancy. However, fluoroquinolones, due to their affinity for bones and cartilage, should be avoided during the first trimester if possible to reduce the risk of arthropathy in children.[36]

  A summary of the medications that can be used or are contraindicated during pregnancy and lactation for patients with IBD is provided in Table 1.

Table 1. Medication recommendations for IBD patients during pregnancy and lactation (adapted from [21] and [34])

Medication	During Pregnancy	During Lactation
Mesalazine	Low risk	Low risk
Sulfasalazine	Low risk	Low risk
Corticosteroids	Low risk	Low risk
Thiopurines	Low risk	Low risk
Anti-TNF	Low risk	Low risk
Vedolizumab	Low risk, limited information	Low risk, limited information
Ustekinumab	Low risk, limited information	Low risk, limited information
Cyclosporine	Low risk, limited information	Limited information
Tacrolimus	Low risk, limited information	Limited information
Methotrexate	Contraindicated	Contraindicated
Thalidomide	Contraindicated	Contraindicated
JAK inhibitors	Contraindicated	No data available, do not use
S1P modulators	Contraindicated	No data available, do not use
Metronidazole	Low risk	Do not use
Ciprofloxasin	Avoid in 1st trimester	Low risk *

Anti-TNF: anti-tumor necrosis factor; **JAK inhibitors:** Janus kinase inhibitors; **S1P modulator:** Sphingosine 1-phosphate ***:** May be preferred for short-term use in perianal disease; if possible, it is advisable to choose a different agent**.**

Medication Choices During Disease Flares in Pregnancy

Managing disease flares during pregnancy requires a multidisciplinary approach involving a gastroenterologist, obstetrician, and general surgeon. Treatment decisions should be based on the severity of the flare and the gestational age. The treatment regimen should follow guidelines for non-pregnant patients, including the use of 5-ASA preparations, corticosteroids, anti-TNF agents, cyclosporine, vedolizumab, and ustekinumab as needed. JAK inhibitors and S1P modulators should be avoided. Thiopurines are not recommended due to their potential adverse effects and delayed onset of action. Emergency surgery should be performed when indicated, regardless of gestational age, after a thorough evaluation of the associated risks and benefits. For pregnancies extending beyond 37 weeks, delivery may be considered before initiating medical treatment.[34]

Monitoring During Pregnancy

Laboratory tests, endoscopy, and imaging studies can be used to monitor disease activity during pregnancy. Some IBD-related parameters may change physiologically during pregnancy, such as increased sedimentation rate, elevated CRP levels, and decreased hemoglobin and albumin levels, which may not accurately reflect disease activity.[37] Therefore, it is more useful to monitor trends in these parameters to assess disease activation. Studies have shown that fecal calprotectin remains a reliable marker for active disease during pregnancy.[38,39] Shmidt E and Dubinsky MC recommend assessing fecal calprotectin prior to conception, during each trimester, and in the postpartum phase.[21]

Endoscopy during pregnancy is generally considered safe, except in certain situations (e.g., placental abruption, imminent delivery, ruptured membranes, uncontrolled eclampsia). However, due to potential complications, it should only be performed when strongly indicated. Flexible sigmoidoscopy without sedation is preferred, but if necessary, full colonoscopy can be performed. The second trimester is considered the safest time for the procedure. It must be conducted with brevity, utilizing the lowest effective dose of sedation if required. Although anesthetic and sedative agents are generally considered safe for the infant, diazepam should be avoided. Midazolam is a safer alternative, though it should be avoided during the first trimester. Propofol, ketamine, and naloxone are classified as pregnancy category B. During the procedure, the patient should be positioned in a left lateral or left pelvic tilt to prevent compression of the inferior vena cava and aorta. Oral polyethylene glycol solution and water-based enemas are considered safe as laxatives.[21,40,41]

Ultrasound and magnetic resonance imaging (MRI) are preferred imaging modalities because they do not involve radiation exposure. Ultrasound can visualize the colonic loops until the beginning of the third trimester and the terminal ileum until approximately the 20th week of gestation. However, as the uterus enlarges, it becomes increasingly difficult to visualize the terminal ileum.[42] Gadolinium contrast should be avoided during MRI, particularly in the first trimester.

Although computed tomography (CT) is not recommended, it can be performed with a low radiation dose (<50 mGy) in cases of serious medical indications.[43,44]

Thromboembolic Monitoring and Management

The incidence of venous thromboembolism (VTE) is higher in pregnant women with IBD. Compared to pregnant women without IBD, those with the disease are four times more likely to experience VTE, particularly in the postpartum period, with the highest risk occurring during the first six weeks after delivery. Consequently, low molecular weight heparin (LMWH) prophylaxis is recommended during the peripartum period, especially for patients at elevated risk of VTE due to moderate to severe disease activity or hospitalization for other reasons.[45] For patients with a history of VTE, LMWH prophylaxis should be continued for up to six weeks postpartum.[46]

Recommendations for Mode of Delivery

The choice of delivery method should be determined primarily by obstetricians based on their clinical evaluation. Research has shown that there is no significant difference in the risk of anal sphincter injury or the development and progression of perianal disease between vaginal delivery and cesarean section. However, in cases of active perianal disease, previous rectovaginal fistula, or a history of restorative proctocolectomy, a multidisciplinary evaluation involving a gastroenterologist, obstetrician, and IBD surgeon is recommended. For these patients, a cesarean section may be considered based on individual case assessment.[47]

POSTPARTUM AND LACTATION PERIOD RECOMMENDATIONS

Postpartum Disease Flare Risk and Medication Management

The risk of postpartum disease flare is more pronounced in ulcerative colitis than in Crohn's disease. Risk factors for flare include active disease before conception and during pregnancy, de-escalation of therapy during pregnancy, discontinuation of biological therapy in the third trimester, long disease duration, and complicated Crohn's disease (e.g., with stricturing or penetrating behavior). Biological agents adminis-

Table 2. Childhood vaccination schedule in Turkey (48)

	Birth	1^{sh} month	2nd month	4th month	6th month	12th month	18th month	24th month	48th month	13 yers old
Hep B	I	II			III					
BCG			I							
PCV			I	II		R				
DTaP-İPV-Hib			I	II	II		R			
OPV					I		R			
Varicella Vaccine						I				
MMR						I			II	
Hep A							I	II		
DTaP-IPV									R	
Td										R

(Obtained from the official website of the Ministry of Health of the Republic of Turkey); **Hep B:** Hepatitis B; **BCG:** Tuberculosis vaccine (Bacillus Calmette-Guérin); **PCV:** Pneumococcal conjugate vaccine; **DTaP-IPV-Hib:** Diphtheria, acellular Pertussis, Tetanus, Inactivated Polio, Haemophilus influenzae type b; **OPV:** Oral Polio vaccine; **MMR:** Measles, Mumps, Rubella; **Hep A:** Hepatitis A; **Td:** Adult-type diphtheria, Tetanus; **R:** Booster; **Yellow cells:** Live vaccines

tered throughout pregnancy should be continued postpartum unless contraindicated (e.g., due to active infection or adverse events). If therapy was discontinued during pregnancy (e.g., in well-controlled disease), it should be restarted as soon as possible postpartum. Decisions regarding re-induction and continuation of the same biological agent should be made based on clinical factors, such as the duration of the drug holiday, disease activity, concomitant immunomodulator use, and the type of biological agent.[21,34]

Neonatal Vaccination Recommendations

In accordance with national guidelines, inactivated vaccines can be safely administered to newborns during the neonatal period. However, in cases where the mother received biological therapy during the third trimester (after 27 weeks of gestation), live vaccines are contraindicated for the newborn during the first six months of life. This includes the oral live rotavirus vaccine, which is typically given at two months.[3] In Türkiye, live vaccines administered within the first 12 months post-birth include the BCG (tuberculosis) vaccine at two months, the oral polio vaccine at the end of the sixth month, the combined MMR (measles, mumps, rubella) vaccine at the end of the 12th month, and the varicella vaccine at the end of the 12th month. Among these, the BCG vaccine is considered the riskiest and should be postponed in infants born to mothers who received biological therapy during pregnancy.[48] The childhood vaccination schedule in Türkiye is summarized in Table 2.

Breastfeeding Period Recommendations

Medications deemed low-risk during pregnancy are generally also considered low-risk during lactation. Aminosalicylates are regarded as safe, though they may occasionally cause diarrhea in newborns. In such cases, dose adjustment or temporary cessation of the drug is recommended. Corticosteroids are detected in breast milk at low levels; when high doses are required, breastfeeding can be delayed for four hours after administration to reduce infant exposure. Azathioprine and mercaptopurine are excreted in breast milk in very small amounts and are classified as low-risk. Since most immunoglobulins in breast milk are of the IgA type, IgG-type biological agents are expelled in breast milk in minimal amounts. The peak concentration of biological agents in breast milk is less than 1% of maternal serum levels, well below the recommended 10% threshold for drug transfer into breast milk, which classifies them as safe and low-risk. Methotrexate is contraindicated during lactation. Due to insufficient data on tofacitinib, filgotinib, and ozanimod, breastfeeding should be avoided while on these medications.[34,47,49]

The use of IBD medications during breastfeeding is summarized in Table 1.

MANAGEMENT OF MALE IBD PATIENTS

In male patients, it is essential to ensure that the disease is in remission and that there is no malnutrition, as both can affect fertility. Most medications used in treatment are generally safe. However, sulfasalazine should be replaced with mesalazine due to its potential to cause sperm abnormalities, such as low sperm count and motility (oligospermia). Additionally, mesalazine preparations containing phthalates should be avoided because of their negative impact on sperm quality. Recent studies indicate that methotrexate use in men does not lead to significant side effects; however, discontinuation of the drug three months before conception is recommended due to concerns about potential infertility (sperm damage) and paternal teratogenicity. For patients undergoing surgery, particularly restorative proctocolectomy, laparoscopic techniques should be preferred to minimize the risk of erectile dysfunction and retrograde ejaculation.[34,50-53]

CONCLUSION

The management of IBD in women of reproductive age presents unique challenges that require careful consideration and a multidisciplinary approach. Preconceptional counseling is essential to optimize fertility, reduce pregnancy-related complications, and ensure better maternal and fetal outcomes. Achieving disease remission before conception is a critical goal, as active disease during pregnancy is associated with an increased risk of adverse outcomes. Most IBD medications-excluding methotrexate, thalidomide, JAK inhibitors, and S1P modulators-are safe for use during pregnancy and lactation, allowing for continued disease management without compromising maternal or fetal health. The postpartum period, particularly for women with ulcerative colitis, requires vigilant monitoring due to the heightened risk of disease flares. Prompt resumption of IBD therapy after delivery is crucial to maintain disease control and minimize long-term complications. For male IBD patients, preserving fertility through careful medication management is important, especially for those planning to conceive.

Overall, this review emphasizes the importance of individualized care plans that address the specific needs and risks associated with IBD during the reproductive years. Ongoing collaboration between gastroenterologists, obstetricians, and surgeons is essential to provide comprehensive care that supports both the short- and long-term health of patients and their offspring.

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