Clinical Considerations for Contraception, Sexual Health, and Pregnancy in Patients With Inflammatory Bowel Disease

These materials were created in conjunction with Pfizer Inc.

Management of Pregnancy in IBD

- Optimal management of IBD before and during pregnancy is crucial[1]
  - Active disease increases the likelihood of adverse pregnancy outcomes
- Pregnant women with IBD are more likely to have complications, including spontaneous abortion and preterm birth, compared with the general population[1]
- Data and information on medication use during pregnancy and lactation are limited, making continuing medication use to maintain remission during conception, pregnancy, and lactation challenging[1,2]

IBD=inflammatory bowel disease.

1. Nguyen GC, et al. *Gastroenterology.* 2016;150(3):734-757.e1. **2.** Mahadevan U, et al. *Gastroenterology*. 2017;152(2):451-462.e2.

Development of the AGA Pregnancy Clinical Care Pathway for IBD

- The American Gastroenterological Association (AGA) IBD Parenthood Project Working Group published clinical guidelines on IBD in pregnancy in 2019
  - The IBD in Pregnancy Clinical Care Pathway was created by representatives from fields of gastroenterology, maternal- fetal medicine, teratology, and lactation, as well as patient stakeholders, and was backed by a multisociety team
- Goal was to provide guidance on continuum of care and best practices for managing patients with IBD who either are pregnant or have a desire to become pregnant
- Provided recommendations outline the care process—from preconception counseling through the postpartum phase for patients with IBD

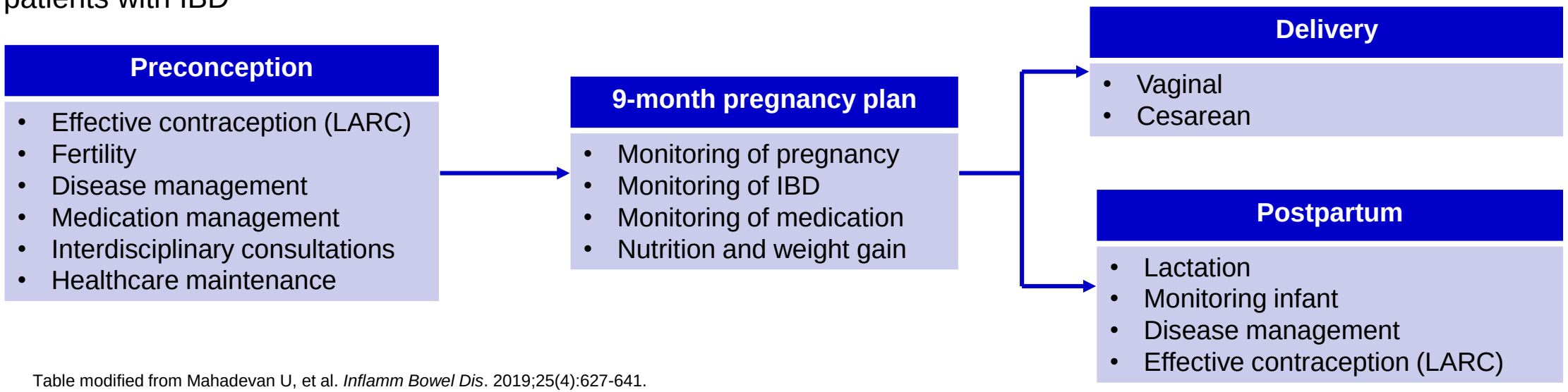


Table modified from Mahadevan U, et al. *Inflamm Bowel Dis*. 2019;25(4):627-641.
IBD=inflammatory bowel disease; LARC=long-acting, reversible contraception.
Mahadevan U, et al. *Inflamm Bowel Dis*. 2019;25(4):627-641.

Clinical Considerations for the Gastroenterologist in the Management of Pregnancy in IBD[1,2]

- Publications from 2017 and 2019 highlight US recommendations for managing IBD in pregnancy[1,2]

Planned pregnancy	• Gastroenterologist should coordinate IBD care and see patient once in first or second trimester as appropriate for her disease severity and pregnancy status • Discuss active disease and the fact that certain medications may be harmful
Healthcare maintenance and monitoring	• Ensure up-to-date vaccinations, cancer surveillance, and health status screening (anemia and vitamin deficiency) • Recommend that patients be closely monitored by a maternal-fetal medicine specialist during pregnancy to decrease risks for adverse outcomes
Multidisciplinary team	• Cross-specialty communication is important and should be encouraged • Gastroenterologist should coordinate with patient's obstetric provider who will lead pregnancy-related care

IBD=inflammatory bowel disease.

1. Mahadevan U, et al. *Inflamm Bowel Dis*. 2019;25(4):627-641. **2.** Mahadevan U, et al. *Gastroenterology*. 2017;152(2):451-462.e2.

IBD Patients and Menstruation

- Gastrointestinal symptoms can vary during the menstrual cycle in patients with IBD
- Patients may confuse symptoms with a disease flare
- Important to obtain history of menstrual cycle to determine if hormonal changes may be contributing to current symptoms
- Helpful for patients to track symptoms in relation to their menstrual cycle to differentiate if symptoms are secondary to a flare versus hormonal fluctuations

Symptoms and changes in menstrual cycle in patients with IBD	
Age at menarche	Can be delayed until early 20s (CD more than UC)
Premenstrual symptoms	Increase in symptoms of nausea, flatulence, abdominal pain, and diarrhea
Changes in cycle interval	
Increased	8.3%
Decreased	5.8%
Irregular	9.1%
Change in duration of flow	
Increased	4.1%
Decreased	9.1%
Irregular	5.8%
Change in intensity of menstrual pain	
Increased	13.2%
Decreased	2.5%

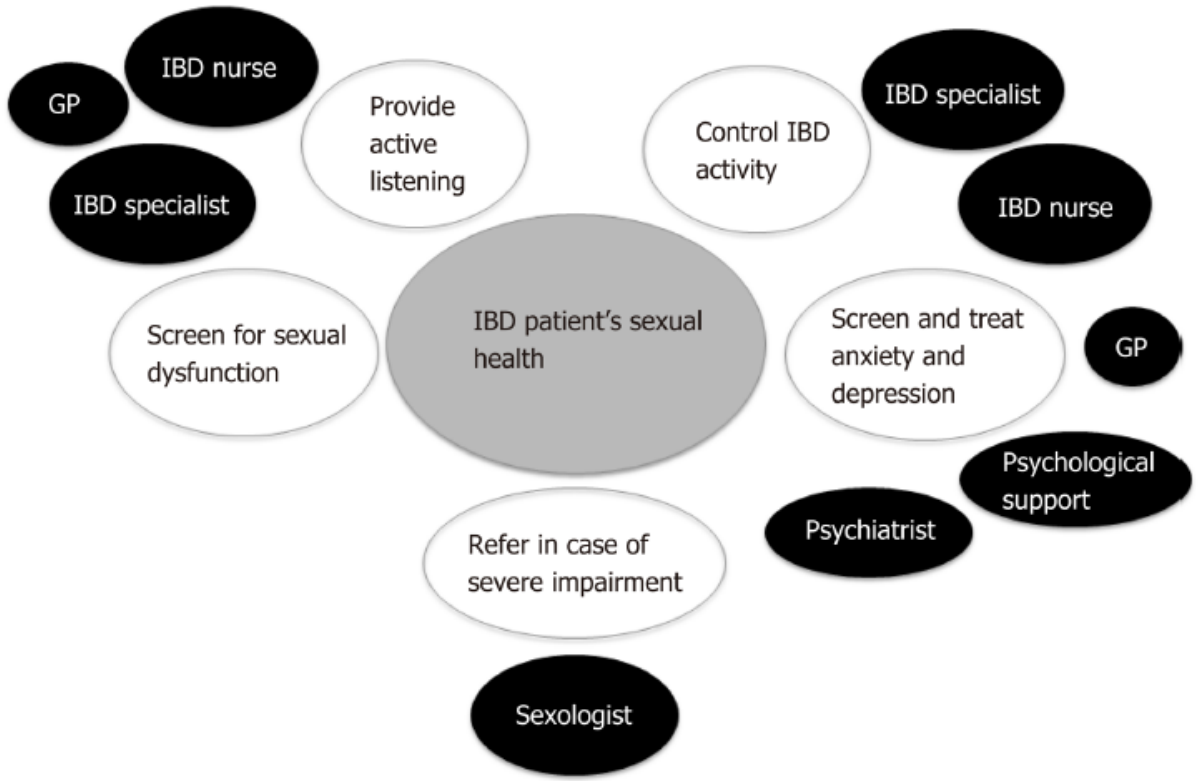
CD=Crohn's disease; IBD=inflammatory bowel disease; UC=ulcerative colitis.

Chowdhury R, Kane SV. In: Beniwal-Patel P, Shaker R, eds. *Gastrointestinal and Liver Disorders in Women's Health*. Springer Nature Switzerland AG; 2019:187-203.

Managing Concerns of Sexual Dysfunction in Patients With IBD

- Management of sexual dysfunction is a complex bio-psycho-social process for both men and women
- Patients with IBD may expect their gastroenterologist to provide information about the impact of IBD on their sexual health
- Screening patients for impaired sexual function can be a first step
- Psychoeducational sessions, medications, and referral to sexologist could be considered

Proposals for the Management of Sexual Dysfunction



GP=general practitioner; IBD=inflammatory bowel disease.

Leenhardt R, et al. *World J Gastroenterol*. 2019;25(36):5423-5433.

Contraception Counseling for Women of Reproductive Age With IBD

- Contraception should be discussed early in IBD patient management with women who are of reproductive age and wish to delay conception until sustained remission is achieved[1]
- An internet-based prevalence study of female patients with IBD in the US (N=1340) found that ~46% of women aged 18 to 34 years with IBD use hormonal contraception[2]

  Note: The findings of this survey may be limited by selection bias (as with any survey). This cohort likely represents a better educated, English speaking, younger population of Internet users as compared with the general population.
- Selection of contraceptive methods may be based on clinical and personal concerns discussed between patients and their physicians[3]
  - In a meta-analysis of English-language studies published on or after January 1, 1995, an increased risk of approximately 3-fold for VTE was associated with use of oral contraceptive pills (OR: 2.97; 95% CI: 2.46-3.59)[4,a]

    Note: The major limitation is the lack of randomized trials available to assess possible causal relationship between use of oral contraceptive pills and increased risk of VTE
  - In a meta-analysis of English-language studies published from 1961 through December 31, 2012, patients with IBD had an approximately 2-fold increased risk for VTE compared with individuals without IBD (RR: 2.20; 95% CI: 1.83-2.65)[5,b]

    Note: All studies included are observational studies and thus subject to bias

Note: There are limitations of applicability of ex-US data to patients with IBD in the US.

[a]Meta-analysis included 14 studies evaluating effect of current compared with noncurrent use of oral contraceptive pills on VTE incidence. [b]Meta-analysis included 11 studies evaluating association of IBD with VTE risk.

CDC=Centers for Disease Control and Prevention; CI=confidence interval; IBD=inflammatory bowel disease; OR=odds ratio; RR=relative risk; VTE=venous thromboembolism.

1. Nguyen GC, et al. *Gastroenterology.* 2016;150(3):734-757.e1. **2.** Cotton C, et al. *Inflamm Bowel Dis*. 2016;22(7):1631-1638. **3.** Martin J, et al. *Gastroenterol Hepatol (N Y).* 2016;12(2):101-109. **4.** Peragallo Urrutia R, et al. *Obstet Gynecol.* 2013;122(2 pt 1):380-389. **5.** Yuhara H, et al. *Aliment Pharmacol Ther.* 2013;37(10):953-962.

Contraceptive Considerations in Patients With IBD

For patients with IBD[1]:

- Intrauterine devices and implants are preferred forms of contraception
- CDC states that the benefits outweigh the risk of low bone density with depot medroxyprogesterone acetate and progestin only pills
- However, use of combined oral contraceptives is associated with risks such as VTE
- There is not sufficient evidence to suggest that using contraception causes a relapse of IBD[2,3]

Advantages	Considerations in IBD patients	Pregnancy rate in first year of use	Types
Intrauterine devices and implants			
Long-term reversible	Recommended first line	<1%	Copper IUD Levonorgestrel-releasing IUD Etonogestrel implant
Depot medroxyprogesterone acetate injection (DMPA)			
Injection every 3 months	Association with decrease in bone density, caution in patients with osteopenia or osteoporosis	6%	Progestin
Combined hormonal contraceptives			
May improve cyclical gastrointestinal symptoms during menstrual cycle	Avoid in IBD patients with prior history of VTE or high risk for VTE (active disease, steroid use, recent surgery, immobilization)	9%	OCP Contraceptive patch Vaginal ring
Behavioral and barrier methods			
Protection against STIs	Least effective	12%-24%	

Table modified from Chowdhury R, Kane SV. In: Beniwal-Patel P, Shaker R, eds. *Gastrointestinal and Liver Disorders in Women's Health*. Springer Nature Switzerland AG; 2019:187-203.
Please see the respective Prescribing Information for each product for information on use during pregnancy.
CDC=Centers for Disease Control and Prevention; DVT=deep vein thrombosis; IBD=inflammatory bowel disease; IUD=intrauterine device; OCP=oral contraceptive pills; STI=sexually transmitted illness; VTE=venous thromboembolism. **1.** Chowdhury R, Kane SV. In: Beniwal-Patel P, Shaker R, eds. *Gastrointestinal and Liver Disorders in Women's Health*. Springer Nature Switzerland AG; 2019:187-203. **2.** Martin J, et al. *Gastroenterol Hepatol (N Y).* 2016;12(2):101-109. **3.** Zapata LB, et al. *Contraception*. 2010;82(1):72-85.

Fertility Considerations in Patients With IBD

- Fertility in women with IBD, whose disease is in remission and who have never had surgery is comparable to women in the general population[1]
- Treatment for IBD,[a] including biologic therapies, steroids, thiopurines, methotrexate,[b] and mesalamine, does not decrease fertility[1,2]
- Risk of infertility is increased in those who have undergone surgery[1]
- Patients with IBD who have tried unsuccessfully to conceive for 6 months should be referred for infertility evaluation[1]

Please see the respective Prescribing Information for each product for information on use during pregnancy.

[a]Limited human data for JAK inhibitors.

[b]Contraindicated in patients trying to conceive.

IBD=inflammatory bowel disease; JAK=Janus kinase.

1. Mahadevan U, et al. *Inflamm Bowel Dis*. 2019;25(4):627-641. **2.** Martin J, et al. *Gastroenterol Hepatol (N Y).* 2016;12(2):101-109.

Increased Risk for Infertility in Women With IBD After Surgery

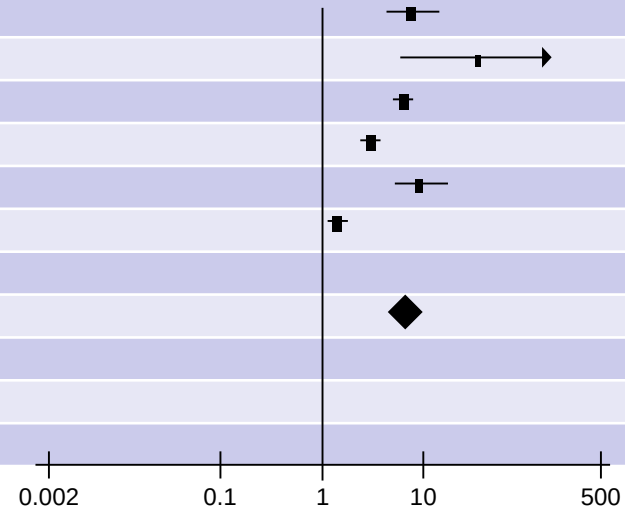
- A systematic review of 11 studies published between 1984 and 2009 from Europe, the United States, and Australia showed comparable fertility rates in patients with IBD who have not undergone surgery compared with the general population[1]

  Note: Limitations to this study were mainly linked to their heterogeneity. The studies were conducted during different time periods when therapeutic strategies and medical beliefs were different from current practice; in addition, different outcome measures reflecting fertility were used.

- However, increased risk for infertility was observed in patients with IBD who had undergone resection surgery, particularly ileoanal pouch procedures (IPAA)[2,3]
  - Meta-analysis of 6 English-language studies published between 1986 and 2010 found a significant increase in risk of infertility post-IPAA (RR: 3.91; 95% CI: 2.06-7.44)[3]

    Note: This study was limited by using the same population of women pre-IPAA as their own control group for post-IPAA patients. As fertility decreases with increasing maternal age, some reduction in fertility after IPAA could be expected for that reason alone.

Study or subgroup	Weight	Risk ratio M-H, random, 95% CI	Year	Risk ratio M-H, random, 95% CI
Counihan et al	15.9%	6.03 [2.44, 14.89]	1994	
Oresland et al	4.4%	51.21 [3.25, 807.18]	1994	
Olsen et al	21.3%	3.62 [2.42, 5.41]	2002	
Olsen et al	21.2%	2.49 [1.65, 3.75]	2003	
Johnson et al	14.9%	10.44 [3.85, 28.28]	2004	
Gorgun et al	22.3%	1.49 [1.14, 1.95]	2004	
Total (95% CI)	**100.0%**	**3.91 [2.06, 7.44]**		
Total events				
Heterogeneity: Tau^2=0.46; Chi^2=38.61, df=5 (*P*<0.00001); I^2=87%				
Test for overall effect: Z=4.16 (*P*<0.0001)				

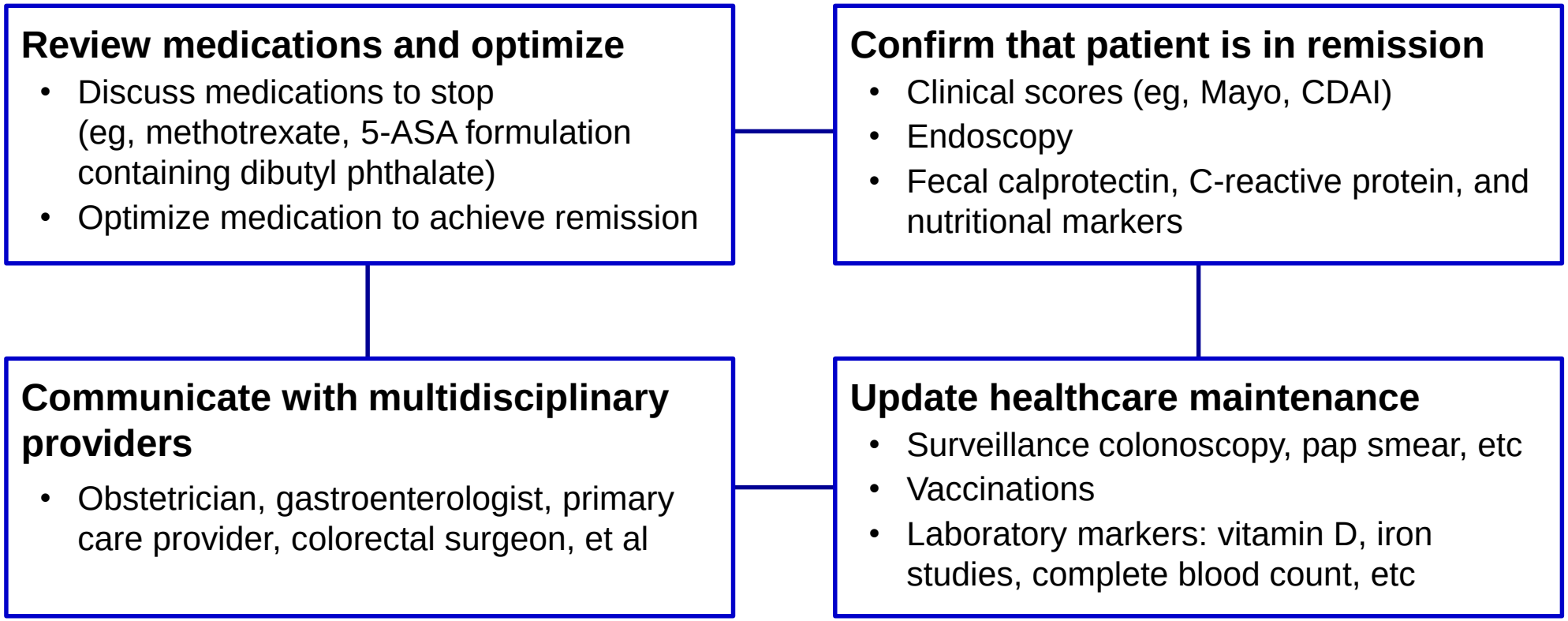


Note: There are limitations of applicability of ex-US data to patients with IBD in the US.

CI=confidence interval; df=degrees of freedom; IBD=inflammatory bowel disease; IPAA=ileal pouch–anal anastomosis; M-H=Mantel-Haenszel; RR=risk ratio.

1. Tavernier N, et al. *Aliment Pharmacol Ther.* 2013;38(8):847-853. **2.** Nguyen GC, et al. *Gastroenterology.* 2016;150(3):734-757.e1. **3.** Rajaratnam SG, et al. *Int J Colorectal Dis.* 2011;26(11):1365-1374.

Preparation for Pregnancy[1,2]



5-ASA=5-aminosalicylic acid; CDAI=Crohn's disease activity index.

1. Nguyen GC, et al. *Gastroenterology.* 2016;150(3):734-757.e1. **2.** Mahadevan U, et al. *Gastroenterology*. 2017;152(2):451-462.e2.

9-Month Plan From AGA's Pregnancy Clinical Care Pathway

9-month plan

IBD remission

IBD monitoring

- GI visit in first or second trimester and then as needed
- Labs at least every trimester: complete blood count, liver enzymes, albumin (combine with obstetric labs)

Maternal/fetal monitoring

- Routine antepartum care
- Third trimester fetal growth ultrasound
- Examine perineum for evidence of active disease
- Counseling on mode of delivery

Medication

- Stool softeners as needed
- Appropriate antimicrobials as needed
- Aminosalicylates and thiopurine monotherapy can continue throughout
- Corticosteroids are not maintenance therapy
  - Use as indicated for flares
- Biologics should continue throughout pregnancy without interruption
  - Can time last dose in third trimester to deliver infant at presumed drug trough

Nutrition and weight gain

- Prenatal vitamin
  - Iron may worsen abdominal pain
- First trimester: check iron/B_{12} levels
- Adequate folate supplementation
- Monitor gestational weight gain, which can be low in IBD
- Nutrition consult if needed
  - Postsurgical changes (short bowel, ostomy)
  - Inadequate weight gain
  - Active disease

IBD flare

IBD monitoring

- GI follow-up every 2 weeks (patient portal, live, video)
- Adjust medication
- Monitor labs, calprotectin
- Management of flares

Maternal/fetal monitoring

- Consider fetal growth surveillance every 4 weeks after 24 weeks
- Recommend antepartum surveillance for patients with active disease in third trimester
- Recommend ultrasound cervical length screening at 18-22 weeks' gestation with follow-up if indicated by short cervix (<25 mm) per usual obstetric indications
- Nutrition counseling
- NST/BPP for usual indications
- Patients receiving steroids should have early glucose screen
- Counseling on mode of delivery

AGA=American Gastroenterological Association; BPP=biophysical profile; GI=gastrointestinal; IBD=inflammatory bowel disease; NST=nonstress test.

Mahadevan U, et al. *Inflamm Bowel Dis*. 2019;25(4):627-641.

Preconception Counseling Leads to Healthier Behaviors and Reduced Disease Relapse During Pregnancy

- In a European prospective study conducted from 2008 to 2014, patients who received preconception counseling had
  - Healthier behaviors (adequate folate intake and smoking cessation)
  - Increased adherence to IBD medication during pregnancy as directed by prescribing physician
  - Reduced disease relapse during pregnancy

Note: The study was limited by its nonrandomized design because different types of biases were experienced by the study and the control groups

	Preconception counseling			
	Yes (n=155)	No (n=162)	*P* value	Adjusted OR (95% CI)
Adequate folate intake, n (%)	118 (76.1)	90 (55.6)	0.0001	5.26 (2.70-10.26)[a]
Smoking cessation, n (%)	17 (70.8)	7 (29.2)	0.009	4.63 (1.22-17.55)[a]
Adherence to IBD medications, n (%)	151 (97.4)	140 (86.4)	0.002	5.69 (1.88-17.27)[b]
Periconceptional disease activity, n (%)	19 (12.3)	29 (17.9)	0.53	1.02 (0.50-2.09)[c]
Disease activity during pregnancy, n (%)	28 (18.1)	55 (34.0)	0.05	0.51 (0.28-0.95)[d]

Note: There are limitations of applicability of ex-US data to patients with IBD in the US.
Table modified from de Lima A, et al. *Clin Gastroenterol Hepatol.* 2016;14(9):1285-1292.
[a]Adjusted for education level. [b]Adjusted for parity. [c]Adjusted for parity, disease duration, and number of relapses in year preceding pregnancy. [d]Adjusted for parity, disease duration, and periconceptional disease activity.
CI=confidence interval; IBD=inflammatory bowel disease; OR=odds ratio.
de Lima A, et al. *Clin Gastroenterol Hepatol.* 2016;14(9):1285-1292.

Maternal-Fetal Medicine Specialist (High-Risk Pregnancies)

- Because the risks of IBD to a pregnancy are significant and manifold, the AGA guidelines recommend consultation with a maternal-fetal medicine specialist, if available, for every pregnant patient with IBD. This is especially relevant for patients with[1]
  - Prior laparotomy, ostomy, or ileal pouch-anal anastomosis surgery
  - Prior or current presentation suggesting cesarean delivery
  - Treatment with biologic or combination therapy
  - Current active disease or recent hospitalization
  - Perianal disease
  - A history of adverse pregnancy outcomes
- The maternal-fetal medicine specialist can determine the type of monitoring needed, as well as the frequency and depth of monitoring based on maternal risk and pregnancy progression[1,2]
- Types of monitoring include, but are not limited to[2]
  - Inadequate gestational weight gain for the mother
  - Potential preterm labor
  - Maternal medical issues
  - Fetal growth and testing

AGA=American Gastroenterological Association; IBD=inflammatory bowel disease.

1. Mahadevan U, et al. *Inflamm Bowel Dis*. 2019;25(4):627-641. **2.** Mahadevan U, et al. *Gastroenterology*. 2017;152(2):451-462.e2.

Method of Delivery in Pregnant Women With IBD

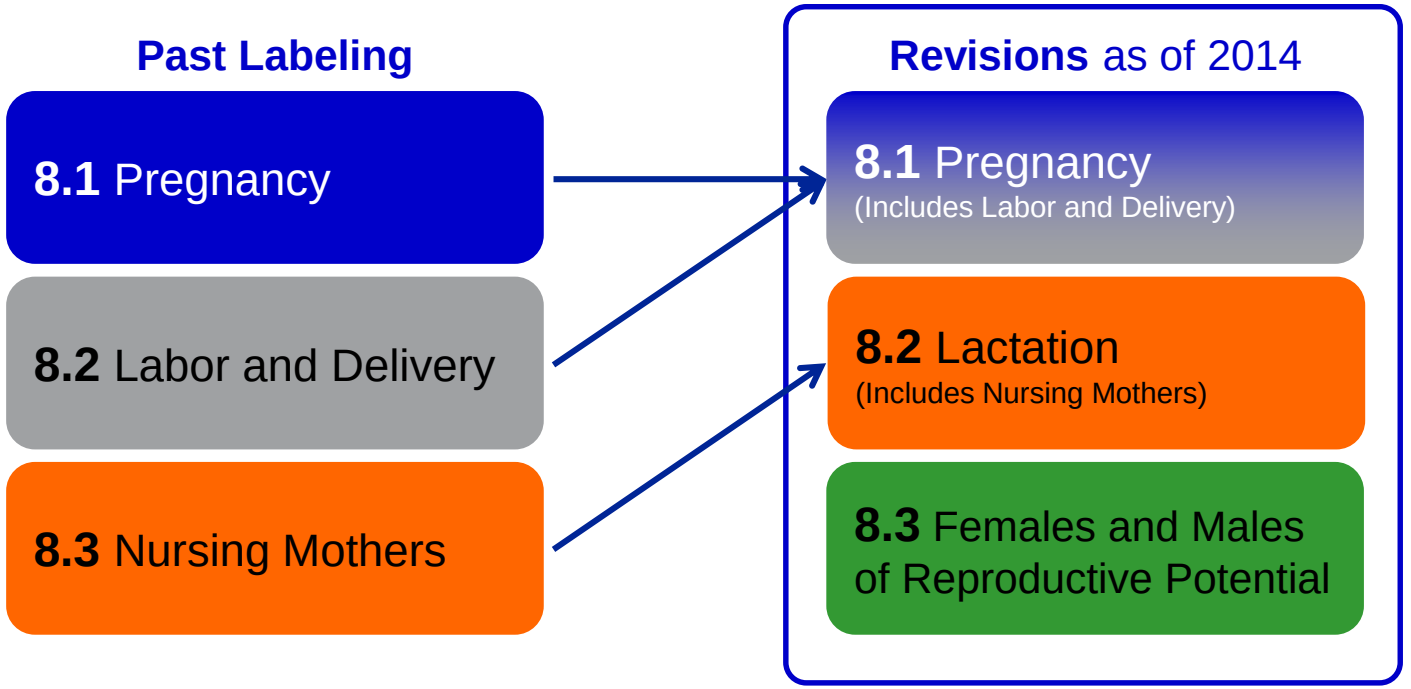
- Method of delivery should be discussed during preconception counseling[1]
- Method of delivery should be at discretion of obstetrician and not based on diagnosis of IBD alone[2,3]
- A healthy mother with IBD should be able to have a successful vaginal delivery[3]
- Exceptions[2,3]
  - Cesarean section is recommended in women with active perianal disease
  - Cesarean section may be considered in women who have undergone IPAA to preserve sphincter function

IBD=inflammatory bowel disease; IPAA=ileal pouch–anal anastomosis.

1. Mahadevan U, et al. *Gastroenterology*. 2017;152(2):451-462.e2. **2.** Nguyen GC, et al. *Gastroenterology*. 2016;150(3):734-757.e1. **3.** Mahadevan U, et al. *Inflamm Bowel Dis*. 2019;25(4):627-641.

FDA Drug Labeling for Pregnancy

Pregnancy and Lactation Labeling Rule[1,2]



Pregnancy letter categories A, B, C, D, and X eliminated and replaced with narrative descriptions of data (updated when new data available)

FDA=US Food and Drug Administration.

1. US Food and Drug Administration. *Fed Regist*. 2014;79(233):72063-72103.

2. US Food and Drug Administration. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/labeling/ucm093307.htm. Accessed December 1, 2020.

Summary

- Comparable fertility in women with and without IBD; however, risk of subfertility is increased in those who have undergone surgery[1]
- Active disease increases likelihood of adverse pregnancy outcomes; thus, optimal management of IBD before and during pregnancy is crucial[1,2]
- Preconception counseling is strongly recommended for women of reproductive age with IBD[1]
- Potential risks and benefits of continuing IBD medications should be discussed with patients[1,2]

IBD=inflammatory bowel disease.

1. Nguyen GC, et al. *Gastroenterology.* 2016;150(3):734-757.e1. **2.** Mahadevan U, et al. *Gastroenterology*. 2017;152(2):451-462.e2.

Resources and References

Available Resources

US Department of Health and Human Services

- Centers for Disease Control and Prevention (CDC)
  - Treating for Two
- US National Library of Medicine
  - DailyMed
  - LactMed

Other Resources

- MotherToBaby
- Society for Maternal-Fetal Medicine
- IBD Parenthood Project

References

- Chowdhury R, Kane SV. Inflammatory bowel disease: fertility, menses, and contraception. In: Beniwal-Patel P, Shaker R, eds. *Gastrointestinal and Liver Disorders in Women's Health*. Springer Nature Switzerland AG; 2019:187-203.
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- Martin J, Kane SV, Feagins LA. Fertility and contraception in women with inflammatory bowel disease. *Gastroenterol Hepatol (N Y).* 2016;12(2):101-109.
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- US Food and Drug Administration. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling: final rule. *Fed Regist*. 2014;79(233):72063-72103. https://www.ncbi.nlm.nih.gov/pubmed/25509060
- US Food and Drug Administration. Pregnancy and lactation labeling (drugs) final rule. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/labeling/ucm093307.htm. Accessed December 1, 2020.
- Yuhara H, Steinmaus C, Corley D, et al. Meta-analysis: the risk of venous thromboembolism in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2013;37(10):953-962.
- Zapata LB, Paulen ME, Cansino C, et al. Contraceptive use among women with inflammatory bowel disease: a systematic review. *Contraception*. 2010;82(1):72-85.

Thank You