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CONSENSUS STATEMENT

The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy

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BACKGROUND & AIMS: The management of inflammatory bowel disease (IBD) poses a particular challenge during pregnancy because the health of both the mother and the fetus must be considered. **METHODS:** A systematic literature search identified studies on the management of IBD during pregnancy. The quality of evidence and strength of recommendations were rated using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. **RESULTS:** Consensus was reached on 29 of the 30 recommendations considered. Preconception counseling and access to specialist care are paramount in optimizing disease management. In general, women on 5-ASA, thiopurine, or anti–tumor necrosis factor (TNF) monotherapy for maintenance should continue therapy throughout pregnancy. Discontinuation of anti-TNF therapy or switching from combination therapy to monotherapy may be considered in very select low-risk patients. Women who have a mild to moderate disease flare while on optimized 5-ASA or thiopurine therapy should be managed with systemic corticosteroid or anti-TNF therapy, and those with a corticosteroid-resistant flare should start anti-TNF therapy. Endoscopy or urgent surgery should not be delayed during pregnancy if indicated. Decisions regarding cesarean delivery should be based on obstetric considerations and not the diagnosis of IBD alone, with the exception of women with active perianal Crohn's disease. With the exception of methotrexate, the use of medications for IBD should not influence the decision to breast-feed and vice versa. Live vaccinations are not recommended within the first 6 months of life in the offspring of women who were on anti-TNF therapy during pregnancy. **CONCLUSIONS:** Optimal management of IBD before and during pregnancy is essential to achieving favorable maternal and neonatal outcomes.

Keywords: Ulcerative Colitis; Crohn's Disease; Inflammatory Bowel Disease; Pregnancy; Postpartum; Breast-feeding; Lactation; 5-Aminosalicylate; Corticosteroid; Thiopurine; Anti–Tumor Necrosis Factor.

The inflammatory bowel diseases (IBDs)—ulcerative colitis (UC) and Crohn's disease (CD)—are associated with a substantial burden of illness,[1] particularly in Western nations including Canada, the United States, and Europe.[2] IBD during pregnancy poses a challenging circumstance in which the health of both the mother and the fetus must be considered when selecting optimal therapy.

Optimal management of IBD during pregnancy is crucial because active disease, especially at the time of conception, is associated with higher risks of adverse pregnancy outcomes[3–7] as well as a greater likelihood of active disease and relapse during pregnancy and the postpartum period.[8,9] Because adverse pregnancy outcomes such as preterm delivery can lead to higher rates of infant mortality, appropriate and timely diagnostic and treatment interventions during the critical antenatal period can be considered lifesaving measures.[10,11]

The use of medications during pregnancy and lactation is a complicated, controversial topic. In recognition of this fact, the US Food and Drug Administration has abandoned the product letter categories (A, B, C, D, and X) because it was believed that they were being misinterpreted as a grading system and were providing an overly simplified view of the product risk.[12] In product regulatory labeling, the letter categories are being replaced with detailed subsections that describe the available information (human, animal, and pharmacological) about the potential benefits and risks for the mother, fetus, and breast-fed infant.[12] Although frequently cited around the world, the pregnancy letter categories were generally not used in product labeling in

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Abbreviations used in this paper: **CAG, Canadian Association of Gastroenterology; CD, Crohn's disease; CI, confidence interval; CT, computed tomography; DBP, dibutyl phthalate; ECCO, European Crohn's and Colitis Organisation; GRADE, Grading of Recommendation Assessment, Development and Evaluation; IBD, inflammatory bowel disease; Ig, immunoglobulin; IPAA, ileal pouch–anal anastomosis; LBW, low birth weight; MRI, magnetic resonance imaging; OR, odds ratio; RR, relative risk; TNF, tumor necrosis factor; UC, ulcerative colitis; US, ultrasonography; VTE, venous thromboembolism.**

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countries outside the United States, further reinforcing the limitations of that approach. These guidelines will help practitioners navigate the complex information, or lack thereof, on the use of medications during pregnancy and make informed decisions based on the current evidence.

Previous Canadian consensus guidelines addressed the management of severe UC in the hospitalized patient[13] and, more recently, the medical management of mild to severe active UC in the ambulatory patient.[14] There are no North American guidelines that comprehensively address the management of IBD during pregnancy and the postpartum period. The European Crohn's and Colitis Organisation (ECCO) recently published the second European consensus on reproduction and pregnancy in IBD, but it largely incorporated data published only to the end of 2013 and did not assess the evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[15] This consensus integrates more up-to-date evidence vetted by the GRADE approach and is tailored to North American clinical practices. The purpose of these consensus statements is to review the literature and develop specific recommendations relating to the management of IBD during the preconception period, pregnancy, and the postpartum period.

Methods

Scope and Purpose

On review of the literature on IBD, specific questions about the management of IBD during pregnancy were identified and discussed by the participants. The guideline development process was initiated in July 2014 with the first meeting of the steering committee, and it lasted approximately 1 year; the full meeting of the consensus group took place in March 2015, and the final manuscript was submitted for publication in September 2015.

Sources and Searches

The editorial office of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group at McMaster University conducted a systematic literature search of MEDLINE (1946 on) and EMBASE (1974 on) up to November 2014. Key search terms were ulcerative colitis, Crohn's disease, inflammatory bowel disease, pregnancy, postpartum, breast-feeding, lactation, 5-aminosalicylate, corticosteroid, thiopurine, and anti–tumor necrosis factor. The search was limited to human studies and the English language. The MEDLINE and EMBASE search strategies used are detailed further in Supplementary Appendix 1. Supplemental focused searches of these databases were performed up to June 2015.

Review and Grading of Evidence

Two nonvoting methodologists (Dr Grigorios I. Leontiadis and Dr Frances Tse) assessed the quality of evidence using the GRADE method.[16] The methodologists determined the risk of bias as well as the overall quality of evidence for each statement. GRADE assessments were then reviewed and agreed on by voting members of the consensus group at the meeting.

Evidence for each statement was graded in regard to its quality (high, moderate, low, very low) as described in GRADE[16,17] and prior Canadian Association of Gastroenterology (CAG) consensus documents.[14,18] In general, the quality of evidence was very low, largely due to "indirectness" related to extrapolation from nonpregnant populations for efficacy and observational and cohort data for safety in pregnant populations.

Approved product labeling from government regulatory agencies varies from country to country, and while not ignored, recommendations are based on evidence from the literature and consensus discussion and may not fully reflect the product labeling for a given country.

Consensus Process

The consensus group was composed of 12 voting participants (including gastroenterologists with expertise in IBD, obstetricians, maternofetal medicine specialists, and pharmacologists), with representation from the community, as well as nonvoting chairs, observers, and a meeting facilitator (Dr William Paterson).

Before the 2-day consensus meeting, which was held in Toronto, Ontario, Canada, in March 2015, the CAG facilitated the majority of the consensus process through the use of a web-based consensus platform (ECD Solutions, Atlanta, GA). The meeting cochairs (Dr Geoffrey C. Nguyen and Dr Cynthia H. Seow), along with members of the steering committee, developed the initial statements. The working group used the web-based platform to review the results of the literature search to "tag" (select and link) relevant references to a specific statement. This was followed by anonymous voting by the entire consensus group as to the level of agreement with each statement (via a modified Delphi process). Statements were revised through 2 iterations based on suggestions from the participants, followed by finalization of the statements at the consensus meeting. Electronic copies of all the "tagged" references pertaining to the statements were available to all members of the consensus group.

Over the course of the 2-day consensus meeting, data were presented, individual GRADE evaluations for each statement were provided, phrasing of the statements was discussed and finalized, and the participants voted on their level of agreement with each specific statement. A statement was accepted if >75% of participants voted 4 (agree) or 5 (strongly agree) on a scale of 1 to 5 (with 1, 2, and 3 indicating disagree strongly, disagree, and uncertain, respectively). One statement was rejected at the meeting, which is described in Appendix 2.

Once a statement was accepted, the participants then voted on the "strength" of the recommendation, which was accepted with a 51% vote. Per the GRADE system, the strength of each recommendation was assigned as strong ("we recommend...") or conditional ("we suggest..."). The strength of the recommendation considers risk/benefit balance, patients' values and preferences, cost and resource allocation, and quality of evidence. Therefore, it is possible for a recommendation to be classified as strong despite having low-quality evidence to support it or as conditional despite having high-quality evidence to support it.[19] Based on the GRADE approach, a strong recommendation indicates that the statement should be applied in most cases, whereas a conditional recommendation signifies that clinicians "…should recognize that different choices will be appropriate for different patients and that they must help each patient to arrive at a management decision consistent with her or his values and preferences."[19]

Drs Nguyen and Seow drafted the initial manuscript, which was then reviewed and revised by the steering committee, after which it was circulated to all members of the consensus group for final review and approval. Per CAG policy, all participants provided written disclosure of potential conflicts of interest for the 24 months before the consensus meeting, which were made available to the other members of the consensus group.

Role of the Funding Sources

Funding for the consensus meeting was provided by unrestricted grants to the CAG from Janssen Inc and Shire Canada. The CAG administered all aspects of the meeting, and the funding sources had no role in drafting or approving these guidelines.

Recommendation Statements

The individual recommendation statements are provided and include the "GRADE" of supporting evidence and the voting results, after which a discussion of the evidence considered for the specific statement is presented. A summary of the recommendation statements is provided in Table 1.

Impact of IBD During Pregnancy: Role of Disease Management

Statement 1. We recommend that women of reproductive age with IBD receive preconception counseling to improve pregnancy outcomes. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 83%; agree, 17%.*

Women with IBD overestimate the risk of infertility associated with their disease. A systematic review of 11 studies, however, found no increase in the rates of involuntary childlessness (eg, related to fecundability or fertility issues) in men or women with IBD who have not undergone surgery.[20] In contrast, women with IBD are significantly more likely to remain voluntarily childless (choosing to limit one's reproductive capacity) compared with the general population (14%–18% with IBD compared with 6%).[21] This has been attributed to women's fears of the effects of IBD on pregnancy outcomes, and conversely of pregnancy on the course of IBD, as well as specific concerns regarding infertility, hereditability of IBD, and the perceived negative impact of medications for IBD on the course of pregnancy and fetal development.[21–23] In fact, the evidence suggests that only those who have undergone resection surgery, especially ileoanal pouch procedures, are at increased risk for infertility. A meta-analysis of 6 studies found average infertility rates of 20% before ileal pouch–anal anastomosis (IPAA) and 63% after IPAA, for a relative risk (RR) of infertility after IPAA of 3.91 (95% confidence interval [CI], 2.06–7.44).[24] However, patients should be counseled that success rates for vitro fertilization in women with IBD who have undergone IPAA are comparable to those in women without IBD or with IBD but no history of IPAA.[25]

Fears of adverse effects of medication on pregnancy are highly prevalent in women with IBD, but there is poor awareness of the harmful effects of IBD flares during pregnancy.[22,26,27] A survey of 145 women with IBD found that one-fourth believed it is more important to tolerate symptoms than to expose the fetus to medications for IBD, one-third believed that all medications for IBD are harmful to unborn children, almost one-half were worried about infertility, and three-fourths expressed concern about passing IBD to their offspring.[22] Less knowledge was significantly associated with attitudes such as "medication should be stopped prior to conception," "pregnant women should avoid all IBD drugs," and "put up with symptoms."[22]

Preconception counseling is associated with healthier behaviors (eg, use of folic acid, alcohol and smoking cessation) among women in the general population[28,29] and those with IBD.[30] In women with chronic diseases, preconception counseling is associated with improved pregnancy outcomes.[31] Among women with IBD, preconception counseling predicts greater adherence to treatment of IBD, with prevalence odds ratios (ORs) for nonadherence showing statistical significance in patients with UC (0.2; 95% CI, 0.04–0.94)[32] but not in patients with CD (0.69; 95% CI, 0.2–2.9) compared with no counseling.[33] In a case-control study, improved adherence to treatment associated with preconception counseling led to a significantly lower risk of disease relapse.[30]

As a result of these findings, the consensus group recommended that all women of reproductive age receive preconception counseling as early as the time of diagnosis (Figure 1). Although patients may receive an overwhelming amount of information when they first receive their diagnosis, it is important to inform women that they should speak to a clinician when contemplating pregnancy. Pregnancy-specific information should be regularly discussed, because retention of information is better when it is temporally relevant. Issues of effective contraception should be discussed early in patient management, and patients should be counseled to strive toward a durable, sustained remission before conception (see statement 2). Counseling should address issues of IBD and fertility, the impact of IBD disease activity on pregnancy, and potential risks and benefits of medical treatment throughout pregnancy and the postpartum period.

Statement 2. In women with IBD who are contemplating pregnancy, we recommend objective disease evaluation before conception to optimize disease management. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 50%; disagree, 8%.*

A higher risk of adverse pregnancy outcomes, including increased risk of prematurity (<37 weeks' gestation), low birth weight (LBW) (<2500 g), congenital abnormalities, and cesarean delivery, was reported in women with IBD compared with the general population in a meta-analysis of 12 studies.[3] Other more recent observational and cohort studies also support a higher risk of adverse pregnancy outcomes, including prematurity,[7,34–40] LBW,[37,39–42] small for gestational age,[7,36,43] cesarean delivery,[7,35,36,38,43–45] spontaneous abortion,[45] and neonatal death,[7] in patients with IBD.

There have been several analyses of the impact of active versus quiescent disease on pregnancy outcomes.[4,5,7]

Table 1. Summary of Consensus Recommendations for the Management of IBD in Pregnancy

Impact of IBD During Pregnancy: Role of Disease Management

Statement 1. We recommend that women of reproductive age with IBD receive preconception counseling to improve pregnancy outcomes. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 2. In women with IBD who are contemplating pregnancy, we recommend objective disease evaluation before conception to optimize disease management. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 3. In women with UC who are contemplating pregnancy and taking a 5-ASA formulation containing dibutyl phthalate (DBP), we suggest switching to a 5-ASA drug without DBP. *GRADE: Conditional recommendation, very low-quality evidence.*

Statement 4A. In women with IBD who are taking methotrexate and contemplating pregnancy, we recommend stopping methotrexate at least 3 months before attempting to conceive to minimize the risk of teratogenicity. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 4B. If a woman becomes pregnant while taking methotrexate, we recommend immediate discontinuation of methotrexate and referral for obstetric counseling. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 5. In pregnant women with active or complicated IBD, we recommend consultation with an obstetrician, preferably one affiliated with a high-risk obstetrics program. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 6. In pregnant women with IBD, we recommend their IBD be managed by a gastroenterologist throughout pregnancy. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 7. In pregnant women who require hospitalization for IBD, we recommend transfer to a tertiary center with access to a gastro enterologist and an obstetrician, preferably one affiliated with a high-risk obstetrics program. *GRADE: Strong recommendation, very low-quality evidence.*

Medical Management of IBD During Pregnancy

Statement 8. In pregnant women with IBD on oral and/or rectal 5-ASA maintenance therapy, we recommend continuation of 5-ASA therapy throughout pregnancy. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 9. In pregnant women with IBD on thiopurine maintenance therapy, we recommend continuation of thiopurine therapy throughout pregnancy. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 10A. In pregnant women with IBD on anti–tumor necrosis factor (anti-TNF) maintenance therapy, we recommend continuation of anti-TNF therapy. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 10B. In select pregnant women at low risk for a relapse of IBD who have a compelling reason to discontinue anti-TNF therapy to minimize fetal exposure, we suggest administering the last dose at 22 to 24 weeks' gestation. *GRADE: Conditional recommendation, very low-quality evidence.*

Statement 11. In pregnant women with IBD on combination anti-TNF and thiopurine therapy, we suggest that the decision to switch to monotherapy should be individualized. *GRADE: Conditional recommendation, very low-quality evidence.*

Statement 12. In pregnant women with UC who have a mild to moderate disease flare while on 5-ASA maintenance therapy, we recommend that combination 5-ASA oral and rectal therapy be optimized to induce symptomatic remission. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 13. In pregnant women with CD who have perianal sepsis requiring antibiotic therapy, we suggest metronidazole and/or cipro floxacin therapy. *GRADE: Conditional recommendation, very low-quality evidence.*

Statement 14. In pregnant women with IBD who have a disease flare on optimal 5-ASA or thiopurine maintenance therapy, we recommend treatment with systemic corticosteroids or anti-TNF therapy to induce symptomatic remission. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 15. In pregnant women with IBD who have a corticosteroid-resistant flare, we recommend starting anti-TNF therapy to induce symptomatic remission. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 16. In pregnant women with IBD who are thiopurine naïve and starting anti-TNF therapy, we suggest anti-TNF monotherapy over combination therapy with anti-TNF and thiopurine therapy. *GRADE: Conditional recommendation, very low-quality evidence.*

Statement 17. In pregnant women hospitalized for IBD, we recommend anticoagulant thromboprophylaxis during hospitalization over no prophylaxis. *GRADE: Strong recommendation, very low-quality evidence.*

Imaging, Endoscopy, and Surgery for IBD During Pregnancy

Statement 18. In pregnant women with suspected IBD or IBD flare, we recommend use of flexible sigmoidoscopy or colonoscopy if the results will affect the antenatal management of IBD. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 19. In pregnant women with suspected IBD or IBD flare, we recommend limiting radiologic investigations to the use of sonography and magnetic resonance imaging where possible. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 20. In pregnant women with IBD, we recommend that urgent surgery to manage complications of IBD not be delayed solely due to pregnancy. *GRADE: Strong recommendation, very low-quality evidence.*

Issues Regarding Delivery for Pregnant Women With IBD

Statement 21. For pregnant women with IBD, we recommend basing the decision regarding cesarean delivery on obstetric considerations and not diagnosis of IBD alone. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 22. For pregnant women with IBD who have undergone IPAA, we suggest consideration of cesarean delivery to reduce the risk of anal sphincter injury, in consultation with an obstetrician and surgeon. *GRADE: Conditional recommendation, very low-quality evidence.*

Statement 23. For pregnant women with CD who have active perianal disease, we recommend cesarean delivery over vaginal delivery to reduce the risk of perianal injury. *GRADE: Strong recommendation, very low-quality evidence.*

Statement 24. For pregnant women with IBD who have undergone cesarean delivery, we recommend anticoagulant thromboprophylaxis during hospitalization over no prophylaxis. *GRADE: Strong recommendation, very low-quality evidence.*

Breast-feeding and Vaccination of Newborns of Women With IBD

Statement 25. In women with IBD, we suggest that use of 5-ASA, systemic corticosteroid, thiopurine, or anti-TNF therapy should not influence the decision to breast-feed, and breast-feeding should not influence the decision to use these medications. *GRADE: Conditional recommendation, very low-quality evidence.*

Table 1. Continued

Statement 26. In women with IBD who are breast-feeding, we suggest avoiding methotrexate therapy. *GRADE: Conditional recommendation, very low-quality evidence.*

Statement 27. For newborns of women who were on anti-TNF therapy during pregnancy, we recommend against administration of live vaccinations within the first 6 months of life. *GRADE: Strong recommendation, very low-quality evidence.*

Analysis of a large Swedish health registry cohort that included 470,110 births found an increased risk of preterm birth and LBW among women with IBD.[4] The risks were more pronounced in women with active disease during pregnancy. The adjusted ORs of preterm birth and LBW in women with flaring UC were 2.72 and 2.10, respectively, and in women with flaring CD were 2.66 and 3.3, respectively, compared with women without IBD. In addition, active CD during pregnancy was associated with an almost 5-fold increased risk of stillbirth (adjusted OR, 4.48; 95% CI, 1.67–11.90).[4] Another analysis reported a 4-fold increase in the incidence of miscarriage or abortion among women with active UC compared with those in remission at conception (95% CI, 1.2–13.9; $P = .02$).[5] Case-control studies report higher rates of adverse birth outcomes among patients with IBD who experience a relapse compared with those without[6] and among those with prior UC-related surgeries or hospitalizations.[7]

The risks posed by active disease at conception are greater for the mother as well. In a meta-analysis of 14 studies, there was a high risk of ongoing active disease during pregnancy in women with active disease at conception compared with the risk of relapse in women in remission at conception for both UC (55% vs 29%; RR, 2.0; 95% CI, 1.5–3; $P < .001$) and CD (46% vs 23%; RR, 2.0; 95% CI, 1.2–3.4; $P = .006$).[8] In the ECCO-EpiCom study, a longer duration of IBD was associated with a greater risk of relapse during pregnancy and the postpartum period.[9] IBD has also been associated with an increased risk of venous thromboembolism (VTE),[38,44] particularly among those with flaring UC.[44] Further supporting the benefits of optimizing the management of IBD before conception is a small retrospective study that found prepregnancy health-related quality of life scores to be predictive of subsequent health-related quality of life and disease activity over the course of the pregnancy.[46]

Although studies are lacking that directly assess whether optimal disease management before conception is superior to standard management in terms of pregnancy outcomes in women with IBD, the consensus group agreed that achieving corticosteroid-free remission for at least 3 months should be the goal before conception.

Disease activity should be objectively assessed according to recommendations for nonpregnant patients.[14] A growing body of evidence suggests that mucosal healing is an important predictor of clinical outcomes, including sustained disease remission.[47] Moreover, the correlation between clinical symptoms and endoscopic disease activity is weak, especially in CD.[48,49] Therefore, endoscopy and imaging are recommended when making important management decisions, and decisions around pregnancy would likely fall into this category. If the patient is not yet pregnant, special concerns about sedation and procedural risk for the mother and fetus would not yet be an issue. The utility of other objective measures of inflammation, such as fecal calprotectin or C-reactive protein levels, in pregnant women with IBD remains to be established.[14]

Statement 3. In women with UC who are contemplating pregnancy and taking a 5-ASA formulation containing dibutyl phthalate (DBP), we suggest switching to a 5-ASA drug without DBP. *GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 0%; agree, 75%; uncertain, 25%.*

Phthalates are used in some 5-ASA formulations because of their ability to localize the release of medication.[50] Data from animal studies have shown that phthalates, specifically dibutyl phthalate (DBP) and di-(2-ethyl-hexyl) phthalate, can inhibit in utero reproductive development and negatively affect neurodevelopment.[50,51] In addition, cohort and cross-sectional studies in humans have shown associations between phthalates and developmental problems.[51]

In a report of 6 cases, urinary concentrations of phthalate metabolites in patients treated with DBP-containing 5-ASA formulations were 50 times higher than in those not treated with these formulations,[52] and one case reported levels 200 times higher than in controls.[53] Although the quality of evidence is very low, particularly for the amount of phthalates contained in 5-ASA products, data suggest that there is at least uncertainty regarding the safety of phthalates in humans. Consequently, the US Food and Drug Administration has recommended against the use of phthalates in the delivery vehicles of drugs.[54] Phthalates are being phased out in some countries, but some 5-ASA formulations continue to contain these compounds. For example, in Canada, some mesalamine products ([Asacol; Actavis, Mississauga, Ontario]; [Mesasal, GlaxoSmithKline Inc, Mississauga, Ontario]) contain DBP.[50]

The consensus group concluded that given the theoretical potential for teratogenicity, switching to a non–DBP-containing 5-ASA formulation before conception may be prudent, particularly if patients express concerns regarding phthalates. For patients whose condition is well controlled with a DBP-containing 5-ASA formulation, switching to another formulation may pose a theoretical risk of precipitating a flare; therefore, switching should be performed with adequate time allowed to ensure sustained remission before conception. For women who are already pregnant and taking a DBP-containing 5-ASA formulation, the decision to switch to another formulation must be individualized and should take into consideration patient preference, gestational age (ie, if the patient is beyond the first trimester, then switching medications likely will not affect teratogenic risk), and disease characteristics.

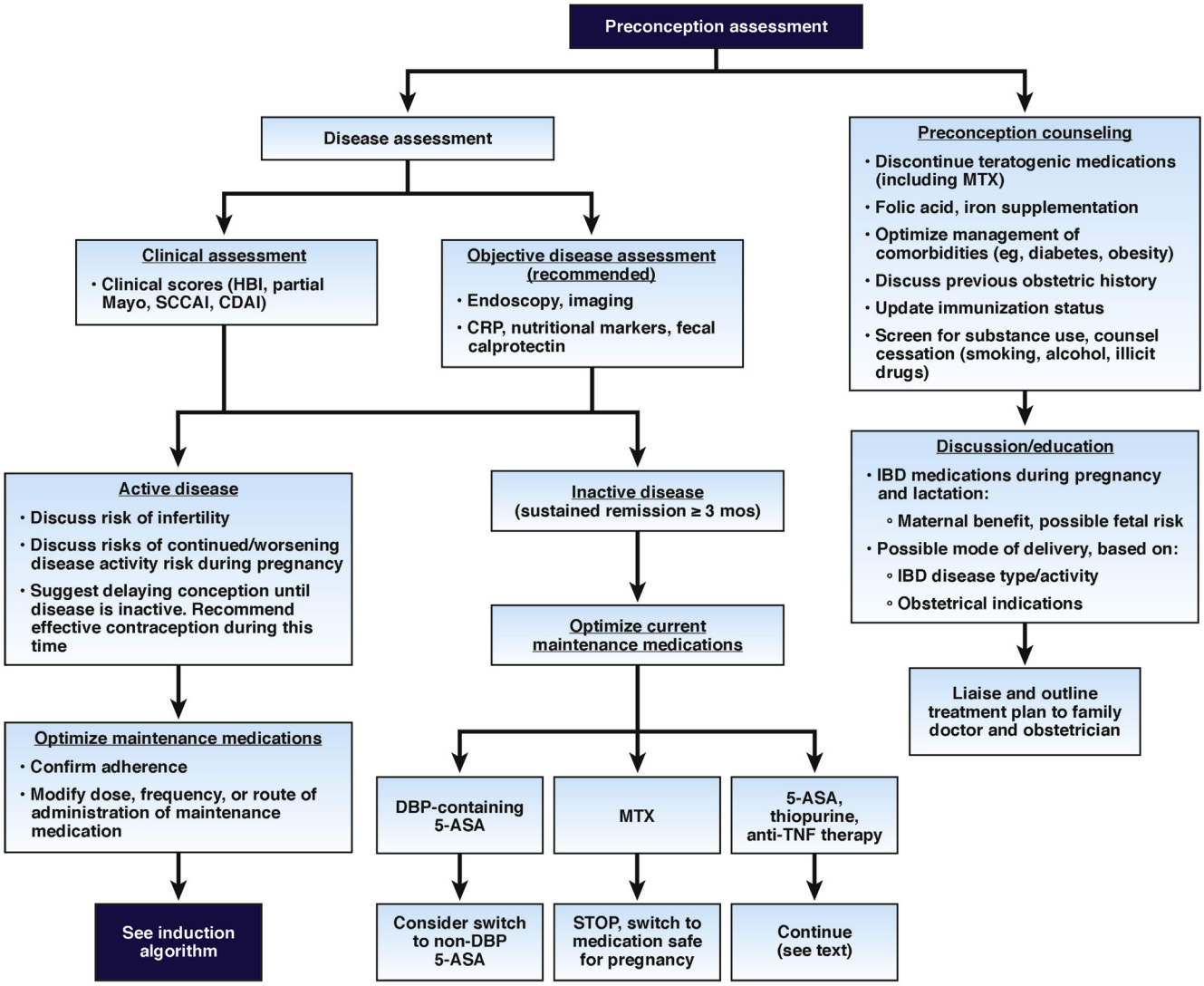

Figure 1. Algorithm for preconception counseling in women with IBD. HBI, Harvey–Bradshaw Index; SCCAI, Simple Clinical Colitis Activity Index; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; MTX, methotrexate DBP, dibutyl phthalate.

Statement 4A. In women with IBD who are taking methotrexate and contemplating pregnancy, we recommend stopping methotrexate at least 3 months before attempting to conceive to minimize the risk of teratogenicity. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 0%; agree, 75%; uncertain, 25%.*

Statement 4B. If a woman becomes pregnant while taking methotrexate, we recommend immediate discontinuation of methotrexate and referral for obstetric counseling. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 50%; agree, 50%.*

In a systematic review of studies evaluating 101 patients with rheumatoid arthritis exposed to methotrexate (5–25 mg/wk) from conception to the first trimester, 23% of pregnancies resulted in miscarriages, 5% in minor neonatal malformations, and 66% in live births (induced abortions were excluded from analysis).[55] Exposure to methotrexate was associated with a 3.4-fold increased risk of cardiovascular defects and a 2.6-fold increased risk of oral clefts compared with no exposure.[56]

In a prospective, observational cohort study in patients with rheumatic diseases, use of methotrexate after conception was associated with an increased risk of malformations but not those that were clearly consistent with methotrexate embryopathy. Malformations were not observed with use of methotrexate in the 3 months before conception.[57]

Product labeling suggests that women should discontinue methotrexate for 3 months to 1 year before conception.[58] Pharmacokinetic data have shown a median half-life for elimination of methotrexate polyglutamate from red blood cells of 1.2 to 4.3 weeks and a median time to undetectable levels of up to 10 weeks.[59]

Although there is little evidence for teratogenic effects of methotrexate in women with IBD, the consensus group recommended discontinuation of this agent before conception.

Although the quality of evidence was low, the group issued a strong recommendation based on the potential for catastrophic harm. The consensus group concluded that based on the pharmacokinetic data, 3 months is a sufficient washout period but the risk of relapse after discontinuation of methotrexate and the time needed to achieve a sustained remission with alternate therapy should also be considered. Although a longer duration of remission on alternate therapy is preferred, 3 months may be sufficient to achieve durable remission.

If conception occurs while taking methotrexate, the drug should be stopped immediately and folic acid supplementation should be initiated or continued. Folic acid supplementation has been associated with a reduced risk of methotrexate-related adverse effects.[56] In cases of methotrexate exposure, the consensus group concluded that termination of the pregnancy is not mandatory, and the patient should be referred to an obstetrician to discuss the risks of teratogenicity and further management of the pregnancy.

Statement 5. In pregnant women with active or complicated IBD, we recommend consultation with an obstetrician, preferably one affiliated with a high-risk obstetrics program. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 50%; uncertain, 8%.*

As described in statement 2, women with IBD have a higher risk of adverse pregnancy outcomes compared with control subjects,[3,7,34–45] including a higher risk of cesarean delivery,[7,35,36,38,43–45] reported at 1.5-fold in a meta-analysis (95% CI, 1.26–1.79; $P < .001$[3]). Risks are generally reported to be higher in women with active versus quiescent disease.[4–7] In addition, women with IBD are at greater risk for VTE[38,44] and are reportedly less likely to breast-feed.[35,42]

Although no data were found that show improved outcomes among patients with IBD managed by an obstetrician (regular or high-risk program) or nonobstetrician provider (eg, family physician or midwife), the consensus group determined that the increased risk of adverse pregnancy outcomes and cesarean delivery suggests the need for obstetric consultation. If, a nonobstetrician provider is following the pregnancy due to patient preference or barriers to access, then an initial consultation with an obstetrician is recommended, even in stable patients in clinical remission. This initial contact would help ensure access to an obstetrician in the event of complications during the pregnancy.

Particular situations that may warrant follow-up by an obstetrician affiliated with a high-risk obstetrics program might include patients with prior laparotomy, prior colectomy with IPAA, presentation suggesting the need for cesarean delivery (eg, breech positioning), prior cesarean delivery, treatment with biologics or combination therapy (suggesting a history of more complicated disease even among patients currently in remission), current active disease or recent hospitalization, perianal disease, or a history of adverse perinatal outcomes.

Statement 6. In pregnant women with IBD, we recommend that their IBD be managed by a gastroenterologist throughout pregnancy. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 58%; agree, 42%.*

As described in statements 2 and 5, women with IBD have a higher risk of adverse pregnancy outcomes, particularly those with active disease.[4–7] Women with active disease also have a higher risk of ongoing disease activity during pregnancy.[8,9] Women overestimate the harmful effects of medication and underestimate the harmful effects of IBD flares during pregnancy.[22,26,27]

Although there is no direct evidence to support an improvement in clinical outcomes among women with IBD who have regular visits with a gastroenterologist during pregnancy, the consensus group agreed that these consultations would allow for active monitoring of disease activity, provide an opportunity for ongoing patient education, and reinforce the importance of adherence to IBD therapy.

The interval of follow-up should be individualized based on the severity of IBD activity and other patient factors. However, the group determined that almost all women with IBD should be evaluated by a gastroenterologist at least once; as is the case for evaluation by an obstetrician, this will help ensure access to a gastroenterologist in the event that problems arise during the pregnancy and will also ensure that medications are continued or stopped as appropriate. Other gastroenterology health care providers with specialized training in IBD, such as nurse practitioners, may also play an important role in counseling and following women with IBD during pregnancy.

Statement 7. In pregnant women who require hospitalization for IBD, we recommend transfer to a tertiary center with access to a gastroenterologist and an obstetrician, preferably one affiliated with a high-risk obstetrics program. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 58%; agree, 42%.*

As described in statements 2, 5, and 6, risks of adverse pregnancy outcomes[4–7] and disease flares in women with IBD are higher in those with active disease.[8,9] Among a small group of women with IBD who required hospitalization for a disease flare, 83% had a clinical response to medical treatment, but 3 of 18 patients required colectomy.[6]

Although there is no direct evidence to suggest improved outcomes among women with IBD managed in a tertiary care center over those managed in a non–tertiary care setting, the consensus group agreed that a multidisciplinary team that includes a gastroenterologist, an obstetrician, and an experienced surgeon may be valuable in helping to optimize outcomes in pregnant women who are hospitalized for a disease flare.

Medical Management of IBD During Pregnancy

Statement 8. In pregnant women with IBD on oral and/or rectal 5-ASA maintenance therapy, we recommend continuation of 5-ASA therapy throughout pregnancy. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 58%; agree, 42%.*

As described in statement 2, women with active disease have a higher risk of adverse pregnancy outcomes. In

addition, women with UC are at higher risk for relapse during pregnancy and the postpartum period compared with nonpregnant women with IBD.[9] Among women with UC, the risk of relapse was highest in the first trimester (RR, 8.80; 95% CI, 2.05–79.3; $P < .0004$) and second trimester (RR, 2.84; 95% CI, 1.2–7.45; $P = .0098$).[9] Among patients treated with 5-ASA or sulfasalazine, the rate of flare was only 26.5% among women who continued to receive the same treatment during pregnancy compared with 56.3% among those who decreased the dose or discontinued therapy (OR, 3.6; 95% CI, 1.0–12.4; $P = .04$).[5]

Clinical practice guidelines for the management of UC in nonpregnant patients have recommended continued 5-ASA maintenance therapy in patients who achieved complete remission during induction therapy.[14] Meta-analyses have shown the efficacy of 5-ASA maintenance therapy in patients with UC compared with placebo, doubling the 12-month symptomatic remission rates (62% vs 30%; $P < .01$).[60,61] Although the studies were not conducted in pregnant women, there is no strong rationale to suggest that there would be differences in the efficacy of 5-ASA therapy in pregnant women versus nonpregnant women or men.

In terms of safety during pregnancy, a meta-analysis of 7 studies including 2200 women with IBD found that use of 5-ASA was not associated with a significantly increased risk of congenital abnormalities (OR, 1.16; 95% CI, 0.76–1.77; $P = .57$), stillbirth (OR, 2.38; 95% CI, 0.65–8.72; $P = .32$), spontaneous abortion (OR, 1.14; 95% CI, 0.65–2.01; $P = .74$), and preterm delivery (OR, 1.35; 95% CI, 0.85–2.13; $P = .26$).[62]

More recent cohort studies have shown varying results; one study showed an increased risk of major malformations (especially cardiovascular defects)[63] whereas other studies showed no increased risk[39,43,64,65] associated with use of 5-ASA compared with no use. The analysis showing an increased risk of major malformations speculated that the findings were influenced by concomitant use of systemic glucocorticosteroids or immunosuppressants.[63] Other studies have shown significant increases in the risk of cesarean delivery,[66] preterm delivery,[65,66] and stillbirth[65] associated with use of 5-ASA. An analysis that stratified use of 5-ASA by dose found that only the risk of preterm delivery was significantly increased with higher doses (≥3 g/day) compared with lower doses (<3 g/day).[67] It is difficult to assess the true impact of medication, because the majority of studies were confounded by disease activity.

The consensus group concluded that given the risks of active IBD on pregnancy and maternal outcomes and the low risk of adverse pregnancy outcomes associated with use of 5-ASA, maintenance therapy should be continued throughout pregnancy. No evidence was found to suggest that rectal treatments can lead to preterm labor or risks to the mother or fetus. From a practical perspective, some pregnant women may find it difficult to insert rectal therapy. Sulfasalazine may inhibit absorption and lower serum concentrations of folic acid; therefore, higher doses of folic acid may be required (2 mg/day of folate).

Statement 9. In pregnant women with IBD on thiopurine maintenance therapy, we recommend continuation of thiopurine therapy throughout pregnancy. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 58%; agree, 42%.*

As described in statements 2 and 8, women with active disease have a higher risk of adverse pregnancy outcomes and are at higher risk for continued active disease during pregnancy.

Clinical practice guidelines for the management of nonpregnant patients recommend thiopurines as an option for maintenance therapy in patients with UC[14] and CD[68–70] who have achieved symptomatic remission on oral corticosteroids. Meta-analyses support the benefit of azathioprine for maintenance of remission[71–73] in nonpregnant patients with UC, with rates of nonremission of 44% with azathioprine compared with 65% with placebo.[73] In CD, a meta-analysis of 7 trials showed the efficacy of azathioprine for maintenance of remission with an OR of 2.32 (95% CI, 1.55–3.49).[74]

In withdrawal studies, discontinuation of azathioprine compared with continued therapy was associated with an increased risk of relapse in both CD (relapse at 18 months of 21% vs 8%)[75] and UC (relapse at 12 months of 59% vs 36%).[76] However, it is unknown whether a shorter and temporary period of cessation of thiopurine therapy in pregnant patients may be associated with lower relapse rates.

Several meta-analyses have assessed the effects of thiopurine exposure on pregnancy outcomes in women with IBD.[77,78] A meta-analysis of 5 studies found an increased risk of preterm birth (OR, 1.67; 95% CI, 1.26–2.20) but not congenital abnormalities (OR, 1.45; 95% CI, 0.99–2.13) or LBW (OR, 1.01; 95% CI, 0.96–1.06).[77] Similarly, a meta-analysis of 9 studies found no increased risk of congenital malformations in women with IBD exposed to thiopurines compared with IBD controls (RR, 1.37; 95% CI, 0.92–2.05); however, the risk was increased compared with healthy women (RR, 1.45; 95% CI, 1.07–1.96).[78] More recent observational and cohort studies have shown varying results, with one study showing higher rates of preterm births[4] but other studies showing no increase[64,66] or lower risks[79] of adverse pregnancy outcomes associated with use of thiopurine compared with no use. Interestingly, the large Swedish health registry showing an increased risk of preterm birth associated with use of thiopurine found that while the risk was marginally increased in women with stable CD (adjusted OR, 2.41; 95% CI, 1.05–5.51), it was substantially increased in those with active disease (adjusted OR, 4.90; 95% CI, 2.76–8.69).[4] These data suggest that the risk may be associated with IBD itself rather than the medication. Finally, several small studies have suggested that exposure to thiopurine during pregnancy is not associated with negative effects on long-term development or immune function in the offspring.[80,81]

The consensus group decided that given the low risk of adverse pregnancy outcomes associated with use of thiopurine, maintenance therapy should be continued throughout

pregnancy. However, maternal metabolism of thiopurine is altered throughout pregnancy and then returns to preconception levels after delivery.[82] Thus, consideration should be given to measuring 6-thioguanine nucleotide and 6-methylmercaptopurine levels during pregnancy in women with active disease. In addition, a case report of 16 mothers who were treated with thiopurines during pregnancy showed that nearly two-thirds of their newborns had anemia at birth; however, there was no control group.[82] Although the anemia was mild, it has been suggested that complete blood cell counts be considered in these newborns.[82]

Statement 10A. In pregnant women with IBD on anti–tumor necrosis factor (TNF) maintenance therapy, we recommend continuation of anti-TNF therapy. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 50%; uncertain, 8%.*

As described in statements 2 and 8, women with IBD have an increased risk of adverse pregnancy outcomes and are at high risk for relapse or ongoing disease activity during pregnancy. Clinical practice guidelines for the management of UC[14] and CD[68–70,83] recommend the continued use of anti-TNF therapy to maintain clinical remission. In clinical trials of nonpregnant patients with UC, anti-TNF maintenance therapy was associated with approximately doubled remission rates compared with placebo (30%–35% vs 15%).[84–86] Similar results have been seen in patients with CD.[87,88]

Anti-TNF therapies are monoclonal antibodies. These molecules are large and require active transport across the placenta via a specific receptor-mediated mechanism. Transplacental transfer of these molecules generally does not occur during the first trimester but becomes more prominent in the second and particularly the third trimesters.[89] Both infliximab and adalimumab are immunoglobulin (Ig)G1 monoclonal antibodies, whereas certolizumab is a Fab fragment of IgG1. Because certolizumab does not contain the F_c portion of IgG1, there is significantly less placental transfer than with other anti-TNF agents.[89] Correspondingly, cord blood levels of certolizumab are very low.[90] In contrast, use of infliximab and adalimumab during pregnancy has been shown to result in fetal and cord blood levels that may be up to 4-fold higher than in the maternal peripheral blood,[90–94] and levels were detectable in infants for up to 6 months.[90] However, some studies fail to show measurable levels of anti-TNF agents in children born to mothers treated with these agents.[91,95]

In pregnant women with IBD in remission, discontinuation of anti-TNF therapy (before week 30) was associated with low relapse rates of 8% in a small case series (n = 25)[91] and 14% in a case-control study (n = 85).[96] However, an additional 32% of women (27/85) with stable disease who discontinued therapy experienced a relapse during the first 3 weeks postpartum. Among women who continued anti-TNF therapy throughout pregnancy because of active disease, the relapse rate was 26%.[96] In addition, one study reported better outcomes among women with IBD who continued anti-TNF therapy during all 3 trimesters compared with those who discontinued therapy during the first trimester, including a lower frequency of unfavorable pregnancy outcomes (25% vs. 69%; $P < .05$), a lower IBD activity rate (25% vs 39%; $P = .4$), and a lower frequency of spontaneous abortion (0% vs 46%; $P = .001$).[79] In contrast, a prospective study in women with IBD found no difference in relapse rates after week 22 among women in sustained remission who stopped anti-TNF therapy at week 25 compared with the remaining women who continued therapy beyond week 30 (9.8% vs 15.6%; $P = .14$).[97]

Data from a meta-analysis[98] and 2 systematic reviews[99,100] of cohort and observational studies suggest that use of anti-TNF therapy during pregnancy is not associated with an increased risk of unfavorable pregnancy outcomes, but data were not stratified by trimester of exposure. In a meta-analysis of 5 studies that included pregnant women with IBD who received anti-TNF therapy, there were no significant differences in rates of unfavorable pregnancy outcomes (OR, 1.00; 95% CI, 0.72–1.41), abortion (OR, 1.53; 95% CI, 0.97–2.41), preterm birth (OR, 1.00; 95% CI, 0.62–1.62), LBW (OR, 1.05; 95% CI, 0.62–1.78), or congenital malformations (OR, 1.10; 95% CI, 0.58–2.09) compared with women with IBD who were not exposed to anti-TNF therapy.[98] Similar results were reported in systematic reviews of more than 50 studies, showing no increased risk of congenital malformations, spontaneous abortions, or infections in the offspring.[99,100]

Several more recent case series or cohort studies have reported no increased risk of major congenital abnormalities[93,101] or other adverse pregnancy or neonatal outcomes.[93,96] One study reported an increased risk of pregnancy-related complications with exposure to anti-TNF therapy in the third trimester in a univariate analysis, but this was not significant in the multivariate analysis.[96]

A systematic review reported no increased risk of infections in the offspring.[99] A more recent case series suggested a high rate of infections in children exposed to anti-TNF therapy prenatally; however, there was no control group.[102] Anti-TNF therapy during pregnancy has also been associated with case reports of severe neutropenia in newborns.[103] However, an increased risk of perinatal bacterial infection in the offspring has also been associated with maternal UC not treated with biologic therapy.[40] No changes in growth or psychomotor development were reported in a case series of children exposed to anti-TNF therapy prenatally.[102]

As is the case for other studies reporting on the effects of medications, these studies are generally confounded by disease activity, concomitant medications (especially immunosuppressant therapies), comorbidities, and other maternal characteristics.

The consensus group concluded that given the low risk of adverse pregnancy outcomes associated with anti-TNF therapy and the importance of maintaining remission (especially in patients on anti-TNF therapy, which implies more moderate to severe disease), the short-term benefits of maintaining remission with continued anti-TNF therapy would likely outweigh the potential risks to the fetus.

Statement 10B. In select pregnant women at low risk for a relapse of IBD who have a compelling reason to discontinue anti-TNF therapy to minimize fetal exposure, we suggest administering the last dose at 22 to 24 weeks' gestation. *GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 8%; agree, 67%; uncertain, 8%; disagree, 8%; strongly disagree, 8%.*

Although women should generally continue anti-TNF therapy throughout pregnancy, there may be special situations in which early discontinuation of anti-TNF therapy is considered. A common scenario is one in which a pregnant woman may have a strong preference to stop anti-TNF therapy to minimize exposure to the fetus. However, there is substantial controversy around whether anti-TNF therapy should be discontinued and, if so, when during pregnancy. It is common practice to modify the dosing schedule during the third trimester (eg, providing an infusion of infliximab at weeks 30–32 and adalimumab at weeks 34–36 and then resuming therapy postpartum) to minimize the drug hiatus. However, although this helps minimize the impact of the disease state on the mother, there appears to be little evidence that this strategy minimizes transplacental drug transfer. The recent ECCO guidelines suggest stopping therapy at weeks 22 to 24 to minimize the risks of transplacental transfer and any hypothetical long-term effects on the newborn,[15] but there is little evidence of an increased risk of infection or developmental delay (at least in the short-term) with continued anti-TNF therapy.

There are a number of problems with a strategy of early discontinuation of anti-TNF therapy. First, there is no evidence that continuing anti-TNF therapy throughout pregnancy has a negative impact on the pregnancy or newborn outcomes. As noted in the preceding text, discontinuation of therapy may be associated with a risk of relapse during pregnancy and the postpartum period. In addition, resulting low trough levels may impact the development of anti-drug antibodies[104,105] and subsequent loss of response to therapy.

As discussed in statement 10A, the consensus group made a strong recommendation in favor of continuation of anti-TNF therapy. They concluded that there is no strong evidence to support the need for early discontinuation of anti-TNF therapy. If preferred, because of theoretical concerns or strong patient preference, this strategy of early discontinuation for the purpose of minimizing fetal exposure (conditional recommendation) should only be considered under special circumstances in which a patient is at low risk for relapse (eg, sustained symptomatic remission during the 12 months before conception, no active disease on endoscopy or imaging during the preconception period, no prior secondary loss of response to anti-TNF therapy or dose escalation, demonstrated therapeutic levels of anti-TNF therapy, no prior intestinal resections, and no hospitalizations in the past 36 months).[106]

Statement 11. In pregnant women with IBD on combination anti-TNF and thiopurine therapy, we suggest that the decision to switch to monotherapy should be individualized. *GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 8%; agree, 75%, disagree, 17%.*

Clinical practice guidelines for the management of UC[14] and CD[68,69] recommend the use of combination anti-TNF and thiopurine therapy for induction of remission but make no formal recommendations on continued use for maintenance treatment. The use of an immunosuppressant in combination with anti-TNF therapy may optimize induction and decrease the risk of developing anti-drug antibodies, thus decreasing the potential for a secondary loss of response to anti-TNF therapy.[14] Combination therapy has shown efficacy for induction of remission in patients with UC in the UC SUCCESS (NCT00537316, protocol number P04807) trial[107] and in patients with CD in the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC).[108]

In an observational study, the use of thiopurines was not associated with increased odds of maternal or fetal adverse events, either as monotherapy (OR, 2.55; 95% CI, 0.95–6.88) or in combination with anti-TNF therapy (OR, 0.97; 95% CI, 0.49–1.93).[109] Data from the large Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry reported that the use of combination therapy was not associated with an increase in adverse pregnancy outcomes or cesarean delivery.[110]

Observational studies suggest no relationship between maternal use of combination therapy and the rate of infection among offspring compared with anti-TNF therapy alone.[99,102,110] The PIANO registry reported a significant increase in infections at 12 months of age in the combination group relative to the unexposed group[110]; this continued to be significantly elevated with combination therapy, including infliximab and adalimumab, in an analysis of a more mature data set with certolizumab excluded from the analysis (RR, 1.35; 95% CI, 1.01–1.80) (Mahadevan, personal communication, September 2015).

There is little evidence of increased risk of adverse maternal or neonatal outcomes with thiopurines (see statement 9), anti-TNF therapies (see statement 10A), or the combination, at least in the short-term. However, as mentioned in the preceding text, although guidelines for nonpregnant patients make recommendations for the use of combination therapy for induction, they make no such recommendations in terms of continuation of both drugs for maintenance therapy. There is currently no evidence to guide the optimal duration of combination therapy. Therefore, the consensus group suggests that the decision to continue or switch to monotherapy should be individualized based on the patient's risk of relapse and preference. Again, patients considered at low risk for relapse include those with sustained symptomatic remission during the 12 months before conception, no active disease on endoscopy or imaging during the preconception period, no prior secondary loss of response to anti-TNF therapy or dose escalation, demonstrated therapeutic levels of anti-TNF therapy, no prior intestinal resections, and no hospitalizations in the past 36 months. If switching to monotherapy, it is preferable to continue anti-TNF therapy and discontinue the immunomodulator because there is more robust evidence for the role

of anti-TNF monotherapy in maintaining sustained remission.[106] Moreover, two de-escalation trials in patients with CD on combination anti-TNF and thiopurine therapy for at least 6 months showed that discontinuing the immunomodulator did not increase short-term relapse rates.[106,111,112] When possible, the transition to anti-TNF monotherapy should be performed with adequate time allowed to ensure sustained remission (ie, 3 months) before conception.

Statement 12. In pregnant women with UC who have a mild to moderate disease flare while on 5-ASA maintenance therapy, we recommend that combination 5-ASA oral and rectal therapy be optimized to induce symptomatic remission. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 33%; agree, 67%.*

Clinical practice guidelines for the management of UC in nonpregnant patients suggest the combination of a rectal and an oral 5-ASA preparation over oral 5-ASA alone for induction of remission and that the same therapy be continued for maintenance.[14] A meta-analysis reported that the combination of rectal and oral therapy was superior to oral 5-ASA alone for induction of remission (RR of no remission, 0.65; 95% CI, 0.47–0.91), with no significant difference in the rate of adverse events.[113] As described in statement 8, meta-analyses have shown the efficacy of 5-ASA maintenance therapy compared with placebo in patients with UC.[60,61]

The consensus group concluded that given the low risk of adverse pregnancy outcomes associated with 5-ASA therapy (see statement 8), pregnant women should be managed according to current guidelines for nonpregnant patients for induction, with the same maintenance throughout pregnancy (Figure 2).

Statement 13. In pregnant women with CD who have perianal sepsis requiring antibiotic therapy, we suggest metronidazole and/or ciprofloxacin therapy. *GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 17%; agree, 75%; uncertain, 8%.*

Pregnancy in women with CD is a significant risk factor for anorectal suppuration and intestinal-genitourinary fistulas.[114] Guidelines for nonpregnant patients with CD recommend metronidazole or ciprofloxacin as adjunctive treatments for fistulizing disease.[115,116] A meta-analysis of 3 randomized controlled trials reported a statistically significant effect of ciprofloxacin or metronidazole in reducing fistula drainage (RR, 0.8; 95% CI, 0.66–0.98).[117]

Meta-analyses[118,119] and a more recent cohort study[120] have shown no association between exposure to metronidazole during the first or later trimesters of pregnancy and preterm birth, LBW, or congenital anomalies. Cleft defects were reported with exposure to metronidazole in one case-control study.[121] A meta-analysis of studies in women exposed to quinolones during the first trimester of pregnancy

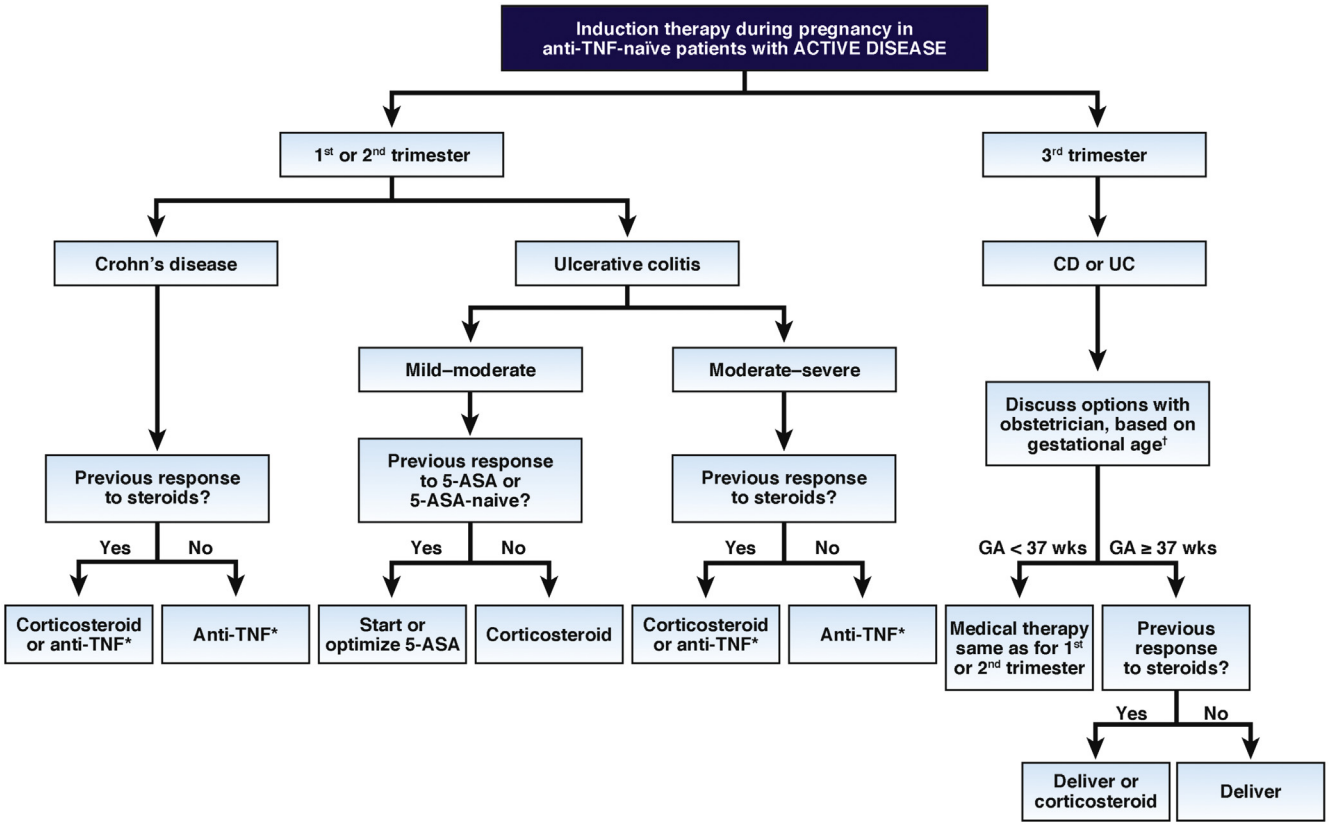

Figure 2. Algorithm for induction therapy in pregnant women with IBD. *Individualized per existing clinical practice guidelines and, in the case of UC, according to disease severity. †Generally, if GA is less than 37 weeks, the theoretical risk of induction therapy would be less than the risk of preterm delivery. GA, gestational age.

found no increased risk of malformations or musculoskeletal problems[122]; however, animal studies have reported musculoskeletal abnormalities.[123,124] In a small case series of women with IBD, neither metronidazole nor ciprofloxacin was associated with poor pregnancy outcomes.[125] Metronidazole[126,127] and ciprofloxacin[128] are excreted into breast milk. There are limited data on the use of other antibiotics, but data suggest no increased risk with amoxicillin-clavulanic acid,[129–131] so this may also be a safe choice.

In the absence of compelling evidence showing increased risks of adverse pregnancy outcomes, the consensus group suggested that perianal sepsis in pregnant women with CD generally be managed according to guidelines for nonpregnant patients.[115,116]

Statement 14. In pregnant women with IBD who have a disease flare on optimal 5-ASA or thiopurine maintenance therapy, we recommend treatment with systemic corticosteroids or anti-TNF therapy to induce symptomatic remission. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 33%; agree, 58%; disagree, 8%.*

Clinical practice guidelines for the management of UC[14] and CD[68–70] recommend the use of corticosteroids or anti-TNF therapy in nonpregnant patients who fail to respond to 5-ASA or thiopurine therapy. Anti-TNF therapy is also recommended for maintenance; however, corticosteroids are not. A meta-analysis showed that corticosteroids were effective in inducing remission in UC and may be of benefit in CD.[132] In a small series of pregnant women who were hospitalized with a relapse of IBD, 15 of 18 patients (83%) had a clinical response to intravenous corticosteroid or intravenous cyclosporine therapy and avoided colectomy.[6]

In the context of failure to respond to 5-ASA therapy, initiation of thiopurine therapy for maintenance after induction of a corticosteroid is not ideal because of the delayed onset of action[14] and the idiosyncratic risk of bone marrow suppression, pancreatitis, hepatotoxicity, allergic reactions, and opportunistic infections (see statement 9).[73,133,134]

In a small case-control study, there were significantly increased risks of preterm birth and LBW associated with exposure to corticosteroids; however, this was confounded by the fact that these patients were hospitalized for severe disease activity.[6]

Data on the risk of congenital malformations with exposure to corticosteroids are inconsistent.[135–138] A meta-analysis of cohort and case-control studies reported an increased risk of oral clefts associated with exposure to corticosteroids during pregnancy compared with no exposure.[136] Concerns about cleft palate are primarily associated with exposure during the first trimester, because this is the time of palate formation. However, a more recent systematic review[135] concluded that the evidence as a whole suggests that exposure to corticosteroids in early pregnancy does not appear to be associated with congenital malformations or oral clefts in offspring.[135] A cohort study in women with IBD found no increased risk of fetal complications in women exposed to corticosteroid therapy during pregnancy compared with nonexposed women or the general population.[139]

All corticosteroids can cross the placenta but are rapidly converted to less active metabolites, resulting in low fetal blood concentrations.[15] Short-acting prednisone, prednisolone, and methylprednisolone are more efficiently metabolized by the placenta and may result in lower fetal exposure than the longer-acting dexamethasone and betamethasone. In addition, budesonide is a systemic corticosteroid that has high first-pass metabolism. Its use has been reported in patients with CD during pregnancy and may be preferred for the treatment of mild to moderate disease because of low corticosteroid exposure to the fetus.[140] Evidence suggests a low risk of adverse pregnancy outcomes associated with anti-TNF therapy as discussed in statement 10A.

The consensus group concluded that, given the low risk of adverse pregnancy outcomes associated with corticosteroid or anti-TNF therapy and the increased risk of adverse outcomes associated with active disease, the benefits of achieving remission with these agents would likely outweigh the potential risks. The choice of either corticosteroid or anti-TNF therapy should be individualized and consider the severity of disease activity (Figure 2). Although the quality of evidence for the efficacy and safety of corticosteroids is weaker than that for anti-TNF therapy, in clinical practice, corticosteroid therapy may induce remission more rapidly than anti-TNF therapy. However, one advantage of anti-TNF therapy is that it may also be used for maintenance of remission.

Cyclosporine may be an alternative in pregnant women with acute severe relapses of UC[141,142]; however, guidelines for the management of UC concluded that there were insufficient data to support its routine use,[14] and cyclosporine is not recommended for the treatment of CD.[70] A meta-analysis of studies in transplant and rheumatology patients reported no increase in the rate of congenital malformations associated with exposure to cyclosporine during pregnancy.[143] In women with IBD, cases of adverse outcomes that include prematurity, LBW, and spontaneous abortion have been reported.[6,144,145] However, these reports are confounded by disease severity and the use of other medications. In addition, the narrow therapeutic index and adverse event profile (hypertension, paresthesia or tremor, headache, hypomagnesaemia, renal impairment, and gastrointestinal upset) tend to limit the acceptability of cyclosporine.[133]

Statement 15. In pregnant women with IBD who have a corticosteroid-resistant flare, we recommend starting anti-TNF therapy to induce symptomatic remission. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 33%; agree, 67%.*

Guidelines for the management of UC[14] and CD[68–70,83] recommend anti-TNF therapy in patients who have corticosteroid-dependent/resistant disease. Evidence for efficacy and the low risk of adverse pregnancy outcomes associated with anti-TNF therapy are discussed in statement 10A. Because of the low risk of transplacental transfer, certolizumab may be preferred in women who initiate anti-TNF therapy during pregnancy.[89,90] However, its availability in some countries, such as Canada, is limited.

The consensus group cautioned that in some pregnant women, depending on the severity and timing of the flare, initiating anti-TNF induction therapy may take too long and

hospitalization may be necessary. There are little data on the response of pregnant women to anti-TNF induction therapy, and studies are ongoing to assess whether the speed and magnitude of response would be affected by changes in maternal volume compartment (ie, volume of distribution) or immune responses (ie, immune tolerance) during pregnancy.

The consensus group recommended that for pregnant women with severe corticosteroid-resistant IBD, early delivery may be preferable before initiating anti-TNF therapy in those who are at least 37 weeks' gestation (Figure 2). Delivery before induction of anti-TNF therapy would reduce fetal exposure to anti-TNF therapy (see statement 10B). In these patients, concurrent colectomy, if clinically indicated, may also be an option.

As discussed in statement 14, cyclosporine may also be considered in corticosteroid-refractory patients with UC. Vedolizumab and ustekinumab may also be options, but there are few cases reporting exposure to these agents during pregnancy[146–151]; in regard to anti-TNF therapies, onset of action may be a concern (see Future Directions).

Statement 16. In pregnant women with IBD who are thiopurine naïve and starting anti-TNF therapy, we suggest anti-TNF monotherapy over combination therapy with anti-TNF and thiopurine therapy. *GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 0%; agree, 83%; uncertain, 17%.*

The evidence for the efficacy and safety of anti-TNF, thiopurine, and combination therapy is discussed in statements 8 to 10. As discussed in statement 11, guidelines for the management of UC[14] and CD[68,69] recommend the use of combination anti-TNF and thiopurine therapy for induction of remission. However, in pregnant women, despite the relative safety of combination therapy, the consensus group suggested that for thiopurine-naïve women, initiation of thiopurine therapy should probably be avoided mainly because of the risk of idiosyncratic adverse reactions (see statement 11 and Figure 2).[73,133,134] Careful consideration should be given to the risk of pancreatitis, which has serious implications for the mother (eg, preeclampsia) and fetus (eg, preterm delivery, small for gestational age, intrauterine growth restriction, and intrauterine death).[152] Conversely, women who have previously tolerated thiopurine therapy may benefit from the additional efficacy.

Statement 17. In pregnant women hospitalized for IBD, we recommend anticoagulant thromboprophylaxis during hospitalization over no prophylaxis. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 58%.*

The CAG guidelines on the prevention and management of VTE in patients with IBD suggest that pregnant women with IBD who have undergone cesarean delivery receive anticoagulant thromboprophylaxis during hospitalization.[18]

Patients with IBD are at higher risk for VTE compared with those without IBD,[153–157] particularly during a disease flare.[153,154] Similarly, there is a high risk of VTE in pregnant women with IBD,[38,44,158,159] particularly during a disease flare.[44] Anticoagulant thromboprophylaxis has been shown to be effective and safe in patients with IBD.[160,161] Guidelines recommend low-molecular-weight heparin over unfractionated heparin for pregnant women.[162]

Although the CAG VTE guideline mentioned in the preceding text only suggests VTE prophylaxis after cesarean delivery, this consensus group determined that given the higher risk of VTE in patients with disease flare, VTE prophylaxis should be recommended in women who are hospitalized with active IBD.

Imaging, Endoscopy, and Surgery for IBD During Pregnancy

Statement 18. In pregnant women with suspected IBD or IBD flare, we recommend use of flexible sigmoidoscopy or colonoscopy if the results will affect the antenatal management of IBD. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 75%; agree, 25%.*

The ECCO[15] and American Society for Gastrointestinal Endoscopy[163] guidelines for pregnant women recommend that gastrointestinal endoscopic procedures be performed during pregnancy when there is a strong indication, but they recommend deferral to the second trimester whenever possible.

Data on the safety and efficacy of endoscopy in pregnant women have been based on small and often uncontrolled retrospective studies. Concerns during gastrointestinal procedures in pregnant women include maternal and fetal hypoxia, the teratogenicity of medications given to the mother (eg, sedatives, antibiotics, colon-cleansing agents), and premature birth.[163]

A systematic review of controlled trials, cohort studies, and case series reported on the outcomes of 100 lower gastrointestinal endoscopies performed in all 3 trimesters of pregnancy.[164] Six adverse events were classified as related to the procedure: 3 with flexible sigmoidoscopy (incomplete spontaneous abortion, fetal death, and suspected perforation leading to emergency cesarean delivery) and 3 with colonoscopy (fetal death, pregnancy termination by physicians, and premature spontaneous labor). All but one of these events was classified as probably or possibly related to the procedure but could have been related to another intervention performed at the time or the underlying maternal disease. The suspected perforation was considered likely related to the flexible sigmoidoscopy. The investigators suggested that lower gastrointestinal endoscopy is likely safe to perform throughout all 3 trimesters of pregnancy.[164] This is further supported by a recent prospective cohort study in which 42 pregnant patients with IBD underwent lower gastrointestinal endoscopy, with no increased adverse outcomes for the mother or the newborn related to endoscopy.[165] Although 2 spontaneous abortions were temporally and probably related to endoscopy, the overall rate of spontaneous abortion was lower in cases than in controls (4.8% vs 23.8%; $P = .01$).

Regarding sedation, guidelines suggest that meperidine and fentanyl appear to be safe in humans during pregnancy.[15,163] A meta-analysis including more than 1 million pregnancies suggested that, in general, benzodiazepines do

not appear to be associated with an increased teratogenic risk, but case-control studies suggest a 2-fold increased risk of oral cleft.[166] Guidelines generally recommend that benzodiazepines be avoided, particularly in the first trimester; however, if meperidine or fentanyl sedation is inadequate, midazolam is preferred over other benzodiazepines.[163]

Positioning patients on their backs should be avoided because the pregnant uterus can compress the aorta or inferior vena cava, resulting in maternal hypotension and decreased placental perfusion. Most procedures should be performed with the patient in a left pelvic tilt or left lateral position to avoid vascular compression.[163]

The consensus group agreed that it is important to know the severity of the disease to direct management. Flexible sigmoidoscopy is preferred over pan-colonoscopy whenever possible, and there appear to be no compelling reasons to defer this procedure in pregnant patients. Colonoscopy may be warranted to make a new diagnosis in cases in which there is a strong suspicion of IBD (eg, rectal bleeding, anemia, poor fetal growth) and in cases in which it will affect the immediate management of IBD during pregnancy. In women with IBD who require conscious sedation for colonoscopy, the lowest effective dose should be used.[163] Because of the risk of fetal sedation or respiratory depression, the need for periprocedural fetal monitoring to ensure the viability of the pregnancy before and after the procedure should be discussed with an obstetrician.

Statement 19. In pregnant women with suspected IBD or IBD flare, we recommend limiting radiologic investigations to the use of sonography and magnetic resonance imaging where possible. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 50%; agree, 50%.*

Guidelines recommend that radiation exposure in pregnant women with IBD be kept to a minimum.[15,163] Guidelines from the Radiological Society of North America recommend contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) studies for pregnant women only when the risks of potential misdiagnosis due to withholding these procedures outweigh the potential risks to the fetus related to exposure to radiation, high magnetic fields, or contrast agents.[167]

A meta-analysis[168] and a systematic review[169] suggested that bowel ultrasonography (US), MRI, and CT have similar diagnostic accuracy for imaging IBD. US and MRI have an advantage over CT of not imparting ionizing radiation. US appears to be less accurate for difficult-to-assess anatomic regions (such as the lesser pelvis).[169,170] In practical terms, radiologists generally prefer not to perform US after approximately 28 to 30 weeks, because the presence of the fetus obscures the view of the bowel. In several case series, a modified MRI protocol, without gadolinium in the majority of cases, showed reliable diagnostic accuracy in pregnant women with IBD or other abdominal symptoms.[171,172] CT is likely acceptable if deemed necessary, because it has been determined that adverse effects to the fetus are unlikely to occur below a cumulative radiation exposure of 100 mGy, with a single procedure unlikely to result in exposure to more than 50 mGy.[167]

Although MRI has not been associated with adverse effects on the fetus, its safety has not been definitively established, including considerations about exposure to the static magnetic field, tissue heating effects from the radiofrequency pulses, and the high acoustic noise level.[167]

Concerns have also been raised about the use of gadolinium as contrast medium. Although animal studies have suggested adverse pregnancy outcomes, these have not been observed in reports of women exposed during pregnancy.[124] The consensus group concluded that gadolinium should be avoided during the first trimester, although some centers prefer not to administer gadolinium at any time during pregnancy.

Statement 20. In pregnant women with IBD, we recommend that urgent surgery to manage complications of IBD not be delayed solely due to pregnancy. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 50%; agree, 50%.*

Case series on outcomes of surgery for complicated UC have reported no increased risk of fetal or maternal morbidity or mortality; however, there are a small number of cases, and the majority were performed in tertiary centers under the care of specialized, multidisciplinary teams.[6,173–176] Although these reports do not include control groups, rates of adverse outcomes would be expected to be higher if surgeries were delayed. One cohort study reported higher incidences of cesarean delivery and LBW newborns among women with CD who underwent surgery for perianal lesions and bowel resection, which is likely explained by more severe disease.[45]

The consensus group concluded that the risks of active disease should be weighed against the risks of surgery and that urgent surgery should be performed if clinically indicated, regardless of trimester, such as when patients with severe colitis are nonresponsive to medical management. When possible, urgent surgery should be performed at a center with neonatal and pediatric services and take a multidisciplinary approach with input from an obstetrician who should be readily available.[177]

Issues Regarding Delivery for Pregnant Women With IBD

Statement 21. For pregnant women with IBD, we recommend basing the decision regarding cesarean delivery on obstetric considerations and not diagnosis of IBD alone. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 58%.*

Population-based cohort studies have shown that women with IBD are at high risk for cesarean delivery compared with the general population.[38,44,178,179] In one study, the risks were more than doubled for elective cesarean delivery and approximately 1.5-fold for emergency cesarean delivery.[44]

Some cohort studies have reported no difference in the rates of symptomatic perianal or luminal disease flares after delivery based on whether cesarean or vaginal delivery was performed.[180–182] Other studies have reported development of new perianal disease[183] or worsening in women with active perianal disease[179] after vaginal delivery. However,

several case series have suggested that cesarean delivery is not protective against flare in women with a history of perianal disease.[180,181,184] The impact of IPAA on choice of method of delivery is discussed in statement 22.

A large survey reported no association between fecal incontinence and vaginal delivery among women with IBD.[185] A smaller survey, however, found a higher rate of incontinence among women with IBD compared with those without IBD (33% vs 2%; $P < .01$).[186] Because the risk of fecal incontinence increases with age,[187] the effects of mode of delivery may not be apparent until years after delivery.

A meta-analysis of 7 observational studies found no increased risk of IBD in offspring delivered by cesarean section compared with those delivered vaginally.[188]

It appears that vaginal delivery is unlikely to result in exacerbation of disease during the postpartum period in women with inactive perianal CD.[180–182] The consensus group recommended that mode of delivery be discussed in consultation with the obstetrician and gastroenterologist and should be based primarily on obstetric considerations while also considering patient preference. Active perianal disease is an additional IBD-specific consideration when contemplating cesarean delivery, as are the factors of short perineal length and previous trauma to the area.

Statement 22. For pregnant women with IBD who have undergone IPAA, we suggest consideration of cesarean delivery to reduce the risk of anal sphincter injury, in consultation with an obstetrician and surgeon. *GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 8%; agree, 92%.*

Several studies of women who underwent IPAA found no increased rates of adverse pregnancy outcomes[189] and no change in pouch function after vaginal delivery.[189–194] One survey reported that 17% of women had some degree of permanent deterioration of pouch function after delivery, but this was not related to method of delivery.[195]

Although several studies of pregnancies after IPAA have shown vaginal delivery to be as safe as cesarean delivery in terms of pouch function,[193,194,196] physiological measurements and imaging studies suggest that there is a higher risk of sphincter injury with vaginal than cesarean delivery.[196] Data on the risk of fecal incontinence in pregnant women with IPAA are conflicting.[193,195,197] One study reported that women with IPAA had increased stool frequency and fecal incontinence during pregnancy,[195] whereas others found no association during[193] or after pregnancy.[197] A cohort study found that rates of incontinence were not significantly affected by mode of delivery.[193] These studies were small and many were not controlled; thus, the true rate of sphincter injury and the long-term risk of incontinence after vaginal delivery currently remain unclear. As is the case in women without IPAA, the risk of fecal incontinence increases with age, and the effects of mode of delivery may not be apparent in the short-term.

The consensus group concluded that given the physiological evidence of impaired sphincter quality and the lack of long-term follow-up data, it may be prudent to consider cesarean delivery in women with IPAA even if it is for a weak indication. If cesarean delivery is needed, a planned procedure is preferred over an emergency procedure.

Statement 23. For pregnant women with CD who have active perianal disease, we recommend cesarean delivery over vaginal delivery to reduce the risk of perianal injury. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 50%; agree, 50%.*

Perianal disease, a common manifestation of CD, may include anorectal fistula or abscess, rectovaginal fistula, anal fissure, and anal stenosis.[178] As discussed in statement 21, vaginal delivery has been associated with worsening of active perianal disease after delivery in some studies[179] but not in others.[180,181,184] However, active perianal disease, independent of the presence of CD, has been associated with a more than 10-fold increased risk of 4th-degree laceration.[178]

Based on the favorable benefit/harm profile, the consensus group recommended cesarean delivery in this group of patients to reduce the risk of perianal injury.

Statement 24. For pregnant women with IBD who have undergone cesarean delivery, we recommend anticoagulant thromboprophylaxis during hospitalization over no prophylaxis. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 67%; agree, 33%.*

As discussed in statement 17, there is a significant risk of VTE in pregnant women with IBD,[38,44,158,159] particularly during a disease flare.[44] Guidelines for VTE in patients without IBD recommend VTE prophylaxis in women who undergo cesarean delivery and have other risk factors.[162] The CAG guidelines on VTE in patients with IBD suggest that pregnant women with IBD who have undergone cesarean delivery receive anticoagulant thromboprophylaxis during hospitalization.[18] Although the CAG VTE guideline group made a weak/conditional recommendation for VTE prophylaxis after cesarean delivery,[18] the IBD pregnancy consensus group, which included obstetric representation, concluded that the recommendation should be strong given the life-threatening risk of VTE.

Breast-feeding and Vaccination of Newborns of Women With IBD

Statement 25. In women with IBD, we suggest that use of 5-ASA, systemic corticosteroid, thiopurine, or anti-TNF therapy should not influence the decision to breast-feed, and breast-feeding should not influence the decision to use these medications. *GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 58%.*

Breast-feeding has not been associated with an increased risk of disease flare, and some studies have suggested that it may in fact be protective against relapse.[198,199] Moreover, postpartum discontinuation of medication may lead to disease flare.[200] In addition, a meta-analysis[201] and more recent case-control studies[202,203] have suggested that breast-feeding may have a protective effect against the development of early-onset IBD in the offspring.

Data suggest that the amount of 5-ASA preparations and sulfasalazine metabolites excreted in breast milk is

low, and they are considered safe to use while breast-feeding.[15,204–207]

Corticosteroids are found in low concentrations in breast milk,[208,209] and although several guidelines suggest that women be advised to avoid breast-feeding within 4 hours of drug administration,[15,116] this consensus group did not.

Case reports suggest that exposure to thiopurines through breast milk is low,[210–213] and it is generally considered acceptable to continue throughout breast-feeding.[116] One study found that the majority of 6-mercaptopurine in breast milk was excreted within the first 4 hours after drug intake.[210] Studies have not detected azathioprine metabolites in the serum of breast-fed infants.[211,212] A small case-control study found age-appropriate mental and physical development and no increased risk of infections among offspring with and without exposure to azathioprine during breast-feeding.[81]

Few data are available on the use of anti-TNF therapy while breast-feeding. In case reports, no[95,214] or low levels of infliximab[215] have been reported in breast milk. One series of 3 cases reported no detectable levels of infliximab in the sera of breast-fed infants,[95] whereas another study reported that low levels were found 5 days after infusion.[216] In several case reports, low levels of adalimumab were reported in breast milk[216,217] but were undetectable in the sera of an infant 9 days after administration of adalimumab.[216] The PIANO registry reported no significant increase in infection in infants associated with drug exposure during breast-feeding.[110] There are theoretical concerns about whether the presence of Fc receptors in tissues of newborns may lead to absorption of anti-TNF therapy through the gut and whether this leads to any local, long-term negative effects in the gut.[89]

Based on evidence suggesting that the majority of medications used to manage IBD are not transferred into breast milk in substantial amounts, the consensus group concluded that there are no compelling reasons to discontinue these medications during breast-feeding. The decision to breast-feed should be made independent of therapy and consider the advantages to the newborn and the potential benefits to the patient as well as patient preference. There seemed to be little evidence to support the suggestions to discard breast milk or avoid breast-feeding within 4 hours of ingestion of thiopurines or corticosteroids.

Statement 26. In women with IBD who are breast-feeding, we suggest avoiding methotrexate therapy. *GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 17%; agree, 83%.*

In a report of one case, the use of oral methotrexate for treatment of cancer in a lactating woman was associated with low but detectable levels of methotrexate in milk.[218] The milk-to-plasma ratio was 0.08:1,[218] but it has been suggested that methotrexate may accumulate in neonatal tissues.[219]

Although higher doses are generally used for cancer therapy, and there are very few data on methotrexate during lactation, the consensus group determined that methotrexate would be the least preferred option in breast-feeding women. Methotrexate is contraindicated in pregnant patients (see statements 4A and 4B), and it is preferable not to initiate methotrexate therapy during breast-feeding.

Statement 27. For newborns of women who were on anti-TNF therapy during pregnancy, we recommend against administration of live vaccinations within the first 6 months of life. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 58%.*

Guidelines recommend that infants exposed to biologic therapies in utero not be given live vaccines (eg, rotavirus, oral polio, and bacille Calmette–Guérin [BCG]) for at least 6 months unless serum levels in the infant are undetectable.[15,220] One case has been reported in which a child exposed to anti-TNF therapy during pregnancy died of disseminated BCG infection after receiving the vaccination at 3 months of age,[221] suggesting the potential for catastrophic harm. Other vaccinations should be given according to standard schedules.

Data on 25 consecutive children exposed to anti-TNF therapy during pregnancy showed that 92% received vaccinations according to standard protocols, including 15 children who received tuberculosis vaccination within 1 week of birth without serious complications.[102] Most children (80%) had at least one infection during a median 34-month follow-up period; however, this analysis did not include a control group. The PIANO registry found no increased risk of infections at 4, 9, and 12 months of follow-up, including and excluding otitis media, in infants exposed to anti-TNF therapy during the third trimester of pregnancy compared with those not exposed.[222]

The consensus group agreed that, because there are very little data on immunosuppression in the infant related to prenatal exposure to anti-TNF therapy, live vaccinations should be deferred to after 6 months of age when possible. Despite low-quality evidence, the recommendation was strong, based on the potential for catastrophic harm associated with early use of live vaccines. If vaccinations are absolutely necessary because of childcare regulations, imminent travel, or exposure to a high-risk area, then it may be prudent to measure anti-TNF serum levels in the infant to help inform decisions. If anti-TNF therapy was stopped after the second trimester to limit transfer to the infant (see statement 10B), then live vaccination should still be deferred to 6 months of age when possible or blood levels in the infant should be assessed, because the impact of discontinuing therapy on drug levels in the infant has not been systematically assessed.

Future Directions

Vedolizumab and ustekinumab are 2 relatively new options for the management of IBD. In a report of 24 vedolizumab-treated women who became pregnant during clinical trials, outcomes were known in 20 cases and included 10 live births (2 preterm), 1 congenital anomaly, 4 spontaneous abortions, and 5 elective terminations.[146] Five case reports of pregnancy during ustekinumab treatment included one that resulted in miscarriage.[147–151]

Given the limited experience with vedolizumab and ustekinumab during pregnancy and the postpartum period, the consensus group determined that it would be premature

to provide guidance regarding their use in pregnant women at this time.

Summary

These guidelines present recommendations for women with IBD during pregnancy, during the postpartum period, and while breast-feeding. Consensus was reached on 29 statements, and one statement was rejected. The statements focused on the impact of IBD during pregnancy, including the role of optimal disease management; medical management and the use of imaging, endoscopy, and surgery during pregnancy; and issues regarding delivery, breast-feeding, and vaccination of newborns of women with IBD (Table 1).

The quality of evidence supporting these consensus statements was very low due to the absence of clinical trial data. Because of the nearly ubiquitous exclusion of pregnant women from IBD drug studies, higher-quality evidence is unlikely to become available in the near future.

Acknowledging the importance of quality of evidence, the consensus group also considered other determining factors in issuing 21 strong recommendations. The strength of these recommendations is driven by the life-threatening risks that active IBD poses to the fetus during pregnancy. Therefore, measures that optimize medical treatment of IBD (eg, patient counseling, involvement of specialists, and assessment of disease activity) are potentially lifesaving and reflect circumstances in which strong recommendations are warranted despite low-quality evidence.[223] Moreover, the strong recommendations for the use of specific IBD therapies were based on moderate/high-quality evidence from clinical trials in nonpregnant patients. Although the quality of evidence was downgraded to very low quality because it was extrapolated to pregnant women with IBD, there is no reason to believe that these therapies are any less efficacious in these patients.

Algorithms were developed to summarize the consensus-guided approach to preconception counseling (Figure 1) and induction therapy (Figure 2) with anti-TNF therapy and/or immunomodulators in pregnant women with IBD. These guidelines should help to optimize the management of IBD in women during the preconception, partum, and postpartum periods.

For a list of voting participants in the IBD in Pregnancy Consensus Group, see Appendix 1.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.12.003.

References

1. Rocchi A, Benchimol EI, Bernstein CN, et al. Inflammatory bowel disease: a Canadian burden of illness review. Can J Gastroenterol 2012;26:811–817.
2. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142:46–54.e42; quiz e30.
3. Cornish J, Tan E, Teare J, et al. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. Gut 2007;56:830–837.
4. Broms G, Granath F, Linder M, et al. Birth outcomes in women with inflammatory bowel disease: effects of disease activity and drug exposure. Inflamm Bowel Dis 2014;20:1091–1098.
5. Ujihara M, Ando T, Ishiguro K, et al. Importance of appropriate pharmaceutical management in pregnant women with ulcerative colitis. BMC Res Notes 2013;6:210.
6. Reddy D, Murphy SJ, Kane SV, et al. Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes. Am J Gastroenterol 2008;103:1203–1209.
7. Stephansson O, Larsson H, Pedersen L, et al. Congenital abnormalities and other birth outcomes in children born to women with ulcerative colitis in Denmark and Sweden. Inflamm Bowel Dis 2011;17:795–801.
8. Abhyankar A, Ham M, Moss AC. Meta-analysis: the impact of disease activity at conception on disease activity during pregnancy in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2013;38:460–466.
9. Pedersen N, Bortoli A, Duricova D, et al. The course of inflammatory bowel disease during pregnancy and postpartum: a prospective European ECCO-EpiCom Study of 209 pregnant women. Aliment Pharmacol Ther 2013;38:501–512.
10. Katz J, Lee AC, Kozuki N, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. Lancet 2013;382:417–425.
11. Kramer MS, Demissie K, Yang H, et al. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. JAMA 2000;284:843–849.
12. 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;79:72063–72103.
13. Bitton A, Buie D, Enns R, et al. Treatment of hospitalized adult patients with severe ulcerative colitis: Toronto consensus statements. Am J Gastroenterol 2012;107:179–194; author reply 195.
14. Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. Gastroenterology 2015;148:1035–1058.e3.
15. van der Woude CJ, Ardizzone S, Bengtson MB, et al. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. J Crohns Colitis 2015;9:107–124.
16. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–926.

17. Sultan S, Falck-Ytter Y, Inadomi JM. The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol 2013;11:329–332.
18. Nguyen GC, Bernstein CN, Bitton A, et al. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. Gastroenterology 2014;146:835–848.e6.
19. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. BMJ 2008;336:1049–1051.
20. Tavernier N, Fumery M, Peyrin-Biroulet L, et al. Systematic review: fertility in non-surgically treated inflammatory bowel disease. Aliment Pharmacol Ther 2013; 38:847–853.
21. Marri SR, Ahn C, Buchman AL. Voluntary childlessness is increased in women with inflammatory bowel disease. Inflamm Bowel Dis 2007;13:591–599.
22. Selinger CP, Eaden J, Selby W, et al. Inflammatory bowel disease and pregnancy: lack of knowledge is associated with negative views. J Crohns Colitis 2013;7:e206–e213.
23. Mountifield R, Bampton P, Prosser R, et al. Fear and fertility in inflammatory bowel disease: a mismatch of perception and reality affects family planning decisions. Inflamm Bowel Dis 2009;15:720–725.
24. Rajaratnam SG, Eglinton TW, Hider P, et al. Impact of ileal pouch-anal anastomosis on female fertility: meta-analysis and systematic review. Int J Colorectal Dis 2011;26:1365–1374.
25. Pabby V, Oza SS, Dodge LE, et al. In vitro fertilization is successful in women with ulcerative colitis and ileal pouch anal anastomosis. Am J Gastroenterol 2015; 110:792–797.
26. Mountifield RE, Prosser R, Bampton P, et al. Pregnancy and IBD treatment: this challenging interplay from a patients' perspective. J Crohns Colitis 2010;4:176–182.
27. Selinger CP, Leong RW, Lal S. Pregnancy related issues in inflammatory bowel disease: evidence base and patients' perspective. World J Gastroenterol 2012; 18:2600–2608.
28. Bixenstine PJ, Cheng TL, Cheng D, et al. Association between preconception counseling and folic acid supplementation before pregnancy and reasons for non-use. Matern Child Health J 2015;19:1974–1984.
29. Williams L, Zapata LB, D'Angelo DV, et al. Associations between preconception counseling and maternal behaviors before and during pregnancy. Matern Child Health J 2012;16:1854–1861.
30. de Lima A, Zelinkova Z, van der Ent C, et al. Preconception care in IBD women leads to less disease relapses during pregnancy (abstr Su1351). Gastroenterology 2014;146(suppl 1):S-444.
31. Lassi ZS, Imam AM, Dean SV, et al. Preconception care: screening and management of chronic disease and promoting psychological health. Reprod Health 2014; 11(suppl 3):S5.
32. Julsgaard M, Norgaard M, Hvas CL, et al. Self-reported adherence to medical treatment prior to and during pregnancy among women with ulcerative colitis. Inflamm Bowel Dis 2011;17:1573–1580.
33. Nielsen MJ, Norgaard M, Holland-Fisher P, et al. Self-reported antenatal adherence to medical treatment among pregnant women with Crohn's disease. Aliment Pharmacol Ther 2010;32:49–58.
34. Getahun D, Fassett MJ, Longstreth GF, et al. Association between maternal inflammatory bowel disease and adverse perinatal outcomes. J Perinatol 2014; 34:435–440.
35. Manosa M, Navarro-Llavat M, Marin L, et al. Fecundity, pregnancy outcomes, and breastfeeding in patients with inflammatory bowel disease: a large cohort survey. Scand J Gastroenterol 2013;48: 427–432.
36. Stephansson O, Larsson H, Pedersen L, et al. Crohn's disease is a risk factor for preterm birth. Clin Gastroenterol Hepatol 2010;8:509–515.
37. Lin HC, Chiu CC, Chen SF, et al. Ulcerative colitis and pregnancy outcomes in an Asian population. Am J Gastroenterol 2010;105:387–394.
38. Nguyen GC, Boudreau H, Harris ML, et al. Outcomes of obstetric hospitalizations among women with inflammatory bowel disease in the United States. Clin Gastroenterol Hepatol 2009;7:329–334.
39. Molnar T, Farkas K, Nagy F, et al. Pregnancy outcome in patients with inflammatory bowel disease according to the activity of the disease and the medical treatment: a case-control study. Scand J Gastroenterol 2010; 45:1302–1306.
40. Bengtson MB, Solberg IC, Aamodt G, et al. Relationships between inflammatory bowel disease and perinatal factors: both maternal and paternal disease are related to preterm birth of offspring. Inflamm Bowel Dis 2010; 16:847–855.
41. Raatikainen K, Mustonen J, Pajala MO, et al. The effects of pre- and post-pregnancy inflammatory bowel disease diagnosis on birth outcomes. Aliment Pharmacol Ther 2011;33:333–339.
42. Dotan I, Alper A, Rachmilewitz D, et al. Maternal inflammatory bowel disease has short and long-term effects on the health of their offspring: a multicenter study in Israel. J Crohns Colitis 2013;7:542–550.
43. Mahadevan U, Sandborn WJ, Li DK, et al. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. Gastroenterology 2007;133:1106–1112.
44. Broms G, Granath F, Linder M, et al. Complications from inflammatory bowel disease during pregnancy and delivery. Clin Gastroenterol Hepatol 2012; 10:1246–1252.
45. Naganuma M, Kunisaki R, Yoshimura N, et al. Conception and pregnancy outcome in women with inflammatory bowel disease: a multicentre study from Japan. J Crohns Colitis 2011;5:317–323.
46. Ananthakrishnan AN, Zadvornova Y, Naik AS, et al. Impact of pregnancy on health-related quality of life of patients with inflammatory bowel disease. J Dig Dis 2012;13:472–477.
47. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut 2012; 61:1619–1635.

48. Benitez JM, Meuwis MA, Reenaers C, et al. Role of endoscopy, cross-sectional imaging and biomarkers in Crohn's disease monitoring. Gut 2013;62:1806–1816.
49. Cellier C, Sahmoud T, Froguel E, et al. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. Gut 1994;35:231–235.
50. Kelley KE, Hernandez-Diaz S, Chaplin EL, et al. Identification of phthalates in medications and dietary supplement formulations in the United States and Canada. Environ Health Perspect 2012;120:379–384.
51. Gallinger ZR, Nguyen GC. Presence of phthalates in gastrointestinal medications: is there a hidden danger? World J Gastroenterol 2013;19:7042–7047.
52. Hernandez-Diaz S, Mitchell AA, Kelley KE, et al. Medications as a potential source of exposure to phthalates in the U.S. population. Environ Health Perspect 2009;117:185–189.
53. Hernandez-Diaz S, Su YC, Mitchell AA, et al. Medications as a potential source of exposure to phthalates among women of childbearing age. Reprod Toxicol 2013;37:1–5.
54. Food and Drug Administration. Limiting the use of certain phthalates as excipients in CDER-regulated products. Last update 2012. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm330792.htm. Accessed July 13, 2015.
55. Martinez Lopez JA, Loza E, Carmona L. Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy, and breastfeeding). Clin Exp Rheumatol 2009;27:678–684.
56. Hernandez-Diaz S, Werler MM, Walker AM, et al. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 2000;343:1608–1614.
57. Weber-Schoendorfer C, Chambers C, Wacker E, et al. Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy: a prospective multicenter cohort study. Arthritis Rheumatol 2014;66:1101–1110.
58. Methotrexate injection [product monograph]. Montreal, Quebec, Canada: Pharmascience, February 26, 2015.
59. Dalrymple JM, Stamp LK, O'Donnell JL, et al. Pharmacokinetics of oral methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2008;58:3299–3308.
60. Ford AC, Khan KJ, Sandborn WJ, et al. Efficacy of topical 5-aminosalicylates in preventing relapse of quiescent ulcerative colitis: a meta-analysis. Clin Gastroenterol Hepatol 2012;10:513–519.
61. Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2012;11:CD004118.
62. Rahimi R, Nikfar S, Rezaie A, et al. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. Reprod Toxicol 2008;25:271–275.
63. Kallen B. Maternal use of 5-aminosalicylates in early pregnancy and congenital malformation risk in the offspring. Scand J Gastroenterol 2014;49:442–448.
64. Ban L, Tata LJ, Fiaschi L, et al. Limited risks of major congenital anomalies in children of mothers with IBD and effects of medications. Gastroenterology 2014;146:76–84.
65. Norgard B, Fonager K, Pedersen L, et al. Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish cohort study. Gut 2003;52:243–247.
66. Bortoli A, Pedersen N, Duricova D, et al. Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003-2006. Aliment Pharmacol Ther 2011;34:724–734.
67. Marteau P, Tennenbaum R, Elefant E, et al. Foetal outcome in women with inflammatory bowel disease treated during pregnancy with oral mesalazine microgranules. Aliment Pharmacol Ther 1998;12:1101–1108.
68. Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology 2013;145:1459–1463.
69. Dassopoulos T, Sultan S, Falck-Ytter YT, et al. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology 2013;145:1464–1478.e1–5.
70. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis 2010;4:28–62.
71. Gisbert JP, Linares PM, McNicholl AG, et al. Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis. Aliment Pharmacol Ther 2009;30:126–137.
72. Khan KJ, Dubinsky MC, Ford AC, et al. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol 2011;106:630–642.
73. Timmer A, McDonald JW, Tsoulis DJ, et al. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2012;9:CD000478.
74. Prefontaine E, Sutherland LR, Macdonald JK, et al. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2009:CD000067.
75. Lemann M, Mary JY, Colombel JF, et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. Gastroenterology 2005;128:1812–1818.
76. Hawthorne AB, Logan RF, Hawkey CJ, et al. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. BMJ 1992;305:20–22.
77. Akbari M, Shah S, Velayos FS, et al. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. Inflamm Bowel Dis 2013;19:15–22.

78. Hutson JR, Matlow JN, Moretti ME, et al. The fetal safety of thiopurines for the treatment of inflammatory bowel disease in pregnancy. J Obstet Gynaecol 2013; 33:1–8.
79. Casanova MJ, Chaparro M, Domenech E, et al. Safety of thiopurines and anti-TNF-alpha drugs during pregnancy in patients with inflammatory bowel disease. Am J Gastroenterol 2013;108:433–440.
80. de Meij TG, Jharap B, Kneepkens CM, et al. Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. Aliment Pharmacol Ther 2013;38:38–43.
81. Angelberger S, Reinisch W, Messerschmidt A, et al. Long-term follow-up of babies exposed to azathioprine in utero and via breastfeeding. J Crohns Colitis 2011; 5:95–100.
82. Jharap B, de Boer NK, Stokkers P, et al. Intrauterine exposure and pharmacology of conventional thiopurine therapy in pregnant patients with inflammatory bowel disease. Gut 2014;63:451–457.
83. Sadowski DC, Bernstein CN, Bitton A, et al. Canadian Association of Gastroenterology clinical practice guidelines: the use of tumour necrosis factor-alpha antagonist therapy in Crohn's disease. Can J Gastroenterol 2009; 23:185–202.
84. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–2476.
85. Sandborn WJ, Colombel JF, D'Haens G, et al. One-year maintenance outcomes among patients with moderately-to-severely active ulcerative colitis who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 2. Aliment Pharmacol Ther 2013;37:204–213.
86. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:96–109.e1.
87. Peyrin-Biroulet L, Deltenre P, de Suray N, et al. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol 2008;6:644–653.
88. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2008:CD006893.
89. Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. Am J Gastroenterol 2013; 108:1426–1438.
90. Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11:286–292; quiz e24.
91. Zelinkova Z, van der Ent C, Bruin KF, et al. Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. Clin Gastroenterol Hepatol 2013; 11:318–321.
92. Zelinkova Z, de Haar C, de Ridder L, et al. High intrauterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. Aliment Pharmacol Ther 2011;33:1053–1058.
93. Bortlik M, Machkova N, Duricova D, et al. Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF-alpha therapy during pregnancy: three-center study. Scand J Gastroenterol 2013;48:951–958.
94. Steenholdt C, Al-Khalaf M, Ainsworth MA, et al. Therapeutic infliximab drug level in a child born to a woman with ulcerative colitis treated until gestation week 31. J Crohns Colitis 2012;6:358–361.
95. Kane S, Ford J, Cohen R, et al. Absence of infliximab in infants and breast milk from nursing mothers receiving therapy for Crohn's disease before and after delivery. J Clin Gastroenterol 2009;43:613–616.
96. Seirafi M, de Vroey B, Amiot A, et al. Factors associated with pregnancy outcome in anti-TNF treated women with inflammatory bowel disease. Aliment Pharmacol Ther 2014;40:363–373.
97. de Lima A, Zelinkova Z, van der Ent C, et al. Tailored anti-TNF therapy during pregnancy in patients with IBD: maternal and fetal safety. Gut 2015 May 12 [Epub ahead of print].
98. Narula N, Al-Dabbagh R, Dhillon A, et al. Anti-TNFalpha therapies are safe during pregnancy in women with inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis 2014;20:1862–1869.
99. Nielsen OH, Loftus EV Jr, Jess T. Safety of TNF-alpha inhibitors during IBD pregnancy: a systematic review. BMC Med 2013;11:174.
100. Marchioni RM, Lichtenstein GR. Tumor necrosis factor-alpha inhibitor therapy and fetal risk: a systematic literature review. World J Gastroenterol 2013;19: 2591–2602.
101. Diav-Citrin O, Otcheretianski-Volodarsky A, Shechtman S, et al. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. Reprod Toxicol 2014;43:78–84.
102. Bortlik M, Duricova D, Machkova N, et al. Impact of anti-tumor necrosis factor alpha antibodies administered to pregnant women with inflammatory bowel disease on long-term outcome of exposed children. Inflamm Bowel Dis 2014;20:495–501.
103. Guiddir T, Fremond ML, Triki TB, et al. Anti-TNF-alpha therapy may cause neonatal neutropenia. Pediatrics 2014;134:e1189–e1193.
104. Reinisch W, Sandborn WJ, Rutgeerts P, et al. Long-term infliximab maintenance therapy for ulcerative colitis: the ACT-1 and -2 extension studies. Inflamm Bowel Dis 2012;18:201–211.
105. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. Am J Gastroenterol 2013; 108:962–971.
106. Torres J, Boyapati RK, Kennedy NA, et al. Systematic review of effects of withdrawal of immunomodulators or biologic agents from patients with inflammatory bowel disease. Gastroenterology 2015;149:1716–1730.
107. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to

monotherapy with either agent in ulcerative colitis. Gastroenterology 2014;146:392–400.e3.
108. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383–1395.
109. Deepak P, Stobaugh DJ. Maternal and foetal adverse events with tumour necrosis factor-alpha inhibitors in inflammatory bowel disease. Aliment Pharmacol Ther 2014;40:1035–1043.
110. Mahadevan U, Martin C, Sandler R, et al. PIANO: A 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy (abstr 865). Gastroenterology 2012; 142(suppl 1):S-149.
111. Kierkus J, Iwanczak B, Wegner A, et al. Monotherapy with infliximab versus combination therapy in the maintenance of clinical remission in children with moderate to severe Crohn disease. J Pediatr Gastroenterol Nutr 2015; 60:580–585.
112. Van Assche G, Magdelaine-Beuzelin C, D'Haens G, et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. Gastroenterology 2008;134:1861–1868.
113. Ford AC, Khan KJ, Achkar JP, et al. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol 2012;107:167–176; author reply 177.
114. Hatch Q, Champagne BJ, Maykel JA, et al. The impact of pregnancy on surgical Crohn disease: an analysis of the Nationwide Inpatient Sample. J Surg Res 2014;190:41–46.
115. Gecse KB, Bemelman W, Kamm MA, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut 2014;63:1381–1392.
116. Van Assche G, Dignass A, Reinisch W, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: special situations. J Crohns Colitis 2010;4:63–101.
117. Khan KJ, Ullman TA, Ford AC, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol 2011;106:661–673.
118. Burtin P, Taddio A, Ariburnu O, et al. Safety of metronidazole in pregnancy: a meta-analysis. Am J Obstet Gynecol 1995;172:525–529.
119. Caro-Paton T, Carvajal A, Martin de Diego I, et al. Is metronidazole teratogenic? A meta-analysis. Br J Clin Pharmacol 1997;44:179–182.
120. Koss CA, Baras DC, Lane SD, et al. Investigation of metronidazole use during pregnancy and adverse birth outcomes. Antimicrob Agents Chemother 2012; 56:4800–4805.
121. Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. Br J Obstet Gynaecol 1998; 105:322–327.
122. Bar-Oz B, Moretti ME, Boskovic R, et al. The safety of quinolones—a meta-analysis of pregnancy outcomes. Eur J Obstet Gynecol Reprod Biol 2009;143:75–78.
123. Linseman DA, Hampton LA, Branstetter DG. Quinolone-induced arthropathy in the neonatal mouse. Morphological analysis of articular lesions produced by pipemidic acid and ciprofloxacin. Fundam Appl Toxicol 1995;28:59–64.
124. Schulze H, Esters P, Dignass A. Review article: the management of Crohn's disease and ulcerative colitis during pregnancy and lactation. Aliment Pharmacol Ther 2014;40:991–1008.
125. Moskovitz DN, Bodian C, Chapman ML, et al. The effect on the fetus of medications used to treat pregnant inflammatory bowel-disease patients. Am J Gastroenterol 2004;99:656–661.
126. Heisterberg L, Branebjerg PE. Blood and milk concentrations of metronidazole in mothers and infants. J Perinat Med 1983;11:114–120.
127. Passmore CM, McElnay JC, Rainey EA, et al. Metronidazole excretion in human milk and its effect on the suckling neonate. Br J Clin Pharmacol 1988;26:45–51.
128. Gardner DK, Gabbe SG, Harter C. Simultaneous concentrations of ciprofloxacin in breast milk and in serum in mother and breast-fed infant. Clin Pharm 1992; 11:352–354.
129. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. Obstet Gynecol 2006;107:1120–1138.
130. Pedler SJ, Bint AJ. Comparative study of amoxicillin-clavulanic acid and cephalexin in the treatment of bacteriuria during pregnancy. Antimicrob Agents Chemother 1985;27:508–510.
131. Czeizel AE, Rockenbauer M, Sorensen HT, et al. Augmentin treatment during pregnancy and the prevalence of congenital abnormalities: a population-based case-control teratologic study. Eur J Obstet Gynecol Reprod Biol 2001;97:188–192.
132. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011; 106:590–599; quiz 600.
133. Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012;6:991–1030.
134. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010;105:501–523; quiz 524.
135. Bay Bjorn AM, Ehrenstein V, Hundborg HH, et al. Use of corticosteroids in early pregnancy is not associated with risk of oral clefts and other congenital malformations in offspring. Am J Ther 2014;21:73–80.
136. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000;62:385–392.
137. Carmichael SL, Shaw GM, Ma C, et al. Maternal corticosteroid use and orofacial clefts. Am J Obstet Gynecol 2007;197:585.e1–585.e7; discussion 683–684.e1–7.
138. Skuladottir H, Wilcox AJ, Ma C, et al. Corticosteroid use and risk of orofacial clefts. Birth Defects Res A Clin Mol Teratol 2014;100:499–506.
139. Mogadam M, Dobbins WO 3rd, Korelitz BI, et al. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and

corticosteroids on fetal outcome. Gastroenterology 1981; 80:72–76.
140. Beaulieu DB, Ananthakrishnan AN, Issa M, et al. Budesonide induction and maintenance therapy for Crohn's disease during pregnancy. Inflamm Bowel Dis 2009; 15:25–28.
141. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330:1841–1845.
142. D'Haens G, Lemmens L, Geboes K, et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. Gastroenterology 2001;120:1323–1329.
143. Bar Oz B, Hackman R, Einarson T, et al. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. Transplantation 2001;71: 1051–1055.
144. Bertschinger P, Himmelmann A, Risti B, et al. Cyclosporine treatment of severe ulcerative colitis during pregnancy. Am J Gastroenterol 1995;90:330.
145. Branche J, Cortot A, Bourreille A, et al. Cyclosporine treatment of steroid-refractory ulcerative colitis during pregnancy. Inflamm Bowel Dis 2009;15:1044–1048.
146. Dubinsky M, Mahadevan U, Vermeire S, et al. Vedolizumab exposure in pregnancy: Outcomes from clinical studies in inflammatory bowel disease (abstr P563). J Crohns Colitis 2015;9(suppl 1):S361–S362.
147. Andrulonis R, Ferris LK. Treatment of severe psoriasis with ustekinumab during pregnancy. J Drugs Dermatol 2012;11:1240.
148. Fotiadou C, Lazaridou E, Sotiriou E, et al. Spontaneous abortion during ustekinumab therapy. J Dermatol Case Rep 2012;6:105–107.
149. Sheeran C, Nicolopoulos J. Pregnancy outcomes of two patients exposed to ustekinumab in the first trimester. Australas J Dermatol 2014;55:235–236.
150. Alsenaid A, Prinz JC. Inadvertent pregnancy during ustekinumab therapy in a patient with plaque psoriasis and impetigo herpetiformis. J Eur Acad Dermatol Venereol 2014 Nov 21 [Epub ahead of print].
151. Rocha K, Piccinin MC, Kalache LF, et al. Pregnancy during ustekinumab treatment for severe psoriasis. Dermatology 2015;231:103–104.
152. Hacker FM, Whalen PS, Lee VR, et al. Maternal and fetal outcomes of pancreatitis in pregnancy. Am J Obstet Gynecol 2015;213:568.e1–e5.
153. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. Lancet 2010;375:657–663.
154. Nguyen GC, Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. Am J Gastroenterol 2008;103:2272–2280.
155. Saleh T, Matta F, Yaekoub AY, et al. Risk of venous thromboembolism with inflammatory bowel disease. Clin Appl Thromb Hemost 2011;17:254–258.
156. Wang JY, Terdiman JP, Vittinghoff E, et al. Hospitalized ulcerative colitis patients have an elevated risk of thromboembolic events. World J Gastroenterol 2009; 15:927–935.
157. 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;37:953–962.
158. Sultan AA, Tata LJ, West J, et al. Risk factors for first venous thromboembolism around pregnancy: a population-based cohort study from the United Kingdom. Blood 2013;121:3953–3961.
159. Bleau N, Patenaude V, Abenhaim HA. Risk of venous thromboembolic events in pregnant patients with autoimmune diseases: a population-based study. Clin Appl Thromb Hemost 2014 Oct 7 [Epub ahead of print].
160. Ra G, Thanabalan R, Ratneswaran S, et al. Predictors and safety of venous thromboembolism prophylaxis among hospitalized inflammatory bowel disease patients. J Crohns Colitis 2013;7:e479–e485.
161. Shen J, Ran ZH, Tong JL, et al. Meta-analysis: the utility and safety of heparin in the treatment of active ulcerative colitis. Aliment Pharmacol Ther 2007;26:653–663.
162. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141: e691S–e736S.
163. Shergill AK, Ben-Menachem T, Chandrasekhara V, et al. Guidelines for endoscopy in pregnant and lactating women. Gastrointest Endosc 2012;76:18–24.
164. De Lima A, Galjart B, Wisse PH, et al. Does lower gastrointestinal endoscopy during pregnancy pose a risk for mother and child? A systematic review. BMC Gastroenterol 2015;15:15.
165. de Lima A, Zelinkova Z, van der Woude CJ. A prospective study of the safety of lower gastrointestinal endoscopy during pregnancy in patients with inflammatory bowel disease. J Crohns Colitis 2015;9: 519–524.
166. Enato E, Moretti M, Koren G. The fetal safety of benzodiazepines: an updated meta-analysis. J Obstet Gynaecol Can 2011;33:46–48.
167. Tremblay E, Therasse E, Thomassin-Naggara I, et al. Quality initiatives: guidelines for use of medical imaging during pregnancy and lactation. Radiographics 2012; 32:897–911.
168. Horsthuis K, Bipat S, Bennink RJ, et al. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. Radiology 2008;247:64–79.
169. Panes J, Bouzas R, Chaparro M, et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment Pharmacol Ther 2011; 34:125–145.
170. Schreyer AG, Menzel C, Friedrich C, et al. Comparison of high-resolution ultrasound and MR-enterography in patients with inflammatory bowel disease. World J Gastroenterol 2011;17:1018–1025.
171. Stern MD, Kopylov U, Ben-Horin S, et al. Magnetic resonance enterography in pregnant women with

Crohn's disease: case series and literature review. BMC Gastroenterol 2014;14:146.
172. Birchard KR, Brown MA, Hyslop WB, et al. MRI of acute abdominal and pelvic pain in pregnant patients. AJR Am J Roentgenol 2005;184:452–458.
173. Aytac E, Ozuner G, Isik O, et al. Surgical management of patients with ulcerative colitis during pregnancy: maternal and fetal outcomes. J Crohns Colitis 2015;9:82–85.
174. Dozois EJ, Wolff BG, Tremaine WJ, et al. Maternal and fetal outcome after colectomy for fulminant ulcerative colitis during pregnancy: case series and literature review. Dis Colon Rectum 2006;49:64–73.
175. Haq AI, Sahai A, Hallwoth S, et al. Synchronous colectomy and caesarean section for fulminant ulcerative colitis: case report and review of the literature. Int J Colorectal Dis 2006;21:465–469.
176. Overbey D, Govekar H, Gajdos C. Surgical management of colonic perforation due to ulcerative colitis during pregnancy: report of a case. World J Gastrointest Surg 2014;6:201–203.
177. ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 474: nonobstetric surgery during pregnancy. Obstet Gynecol 2011;117:420–421.
178. Hatch Q, Champagne BJ, Maykel JA, et al. Crohn's disease and pregnancy: the impact of perianal disease on delivery methods and complications. Dis Colon Rectum 2014;57:174–178.
179. Ilnyckyji A, Blanchard JF, Rawsthorne P, et al. Perianal Crohn's disease and pregnancy: role of the mode of delivery. Am J Gastroenterol 1999;94:3274–3278.
180. Cheng AG, Oxford EC, Sauk J, et al. Impact of mode of delivery on outcomes in patients with perianal Crohn's disease. Inflamm Bowel Dis 2014;20:1391–1398.
181. Smink M, Lotgering FK, Albers L, et al. Effect of childbirth on the course of Crohn's disease; results from a retrospective cohort study in the Netherlands. BMC Gastroenterol 2011;11:6.
182. Grouin A, Brochard C, Siproudhis L, et al. Perianal Crohn's disease results in fewer pregnancies but is not exacerbated by vaginal delivery. Dig Liver Dis 2015; 47:1021–1026.
183. Brandt LJ, Estabrook SG, Reinus JF. Results of a survey to evaluate whether vaginal delivery and episiotomy lead to perineal involvement in women with Crohn's disease. Am J Gastroenterol 1995;90:1918–1922.
184. Rogers RG, Katz VL. Course of Crohn's disease during pregnancy and its effect on pregnancy outcome: a retrospective review. Am J Perinatol 1995;12:262–264.
185. Norton C, Dibley LB, Bassett P. Faecal incontinence in inflammatory bowel disease: associations and effect on quality of life. J Crohns Colitis 2013;7:e302–e311.
186. Ong JP, Edwards GJ, Allison MC. Mode of delivery and risk of fecal incontinence in women with or without inflammatory bowel disease: questionnaire survey. Inflamm Bowel Dis 2007;13:1391–1394.
187. Whitehead WE, Borrud L, Goode PS, et al. Fecal incontinence in US adults: epidemiology and risk factors. Gastroenterology 2009;137:512–7.e1–2.
188. Bruce A, Black M, Bhattacharya S. Mode of delivery and risk of inflammatory bowel disease in the offspring: systematic review and meta-analysis of observational studies. Inflamm Bowel Dis 2014;20:1217–1226.
189. Hahnloser D, Pemberton JH, Wolff BG, et al. Pregnancy and delivery before and after ileal pouch-anal anastomosis for inflammatory bowel disease: immediate and long-term consequences and outcomes. Dis Colon Rectum 2004;47:1127–1135.
190. Juhasz ES, Fozard B, Dozois RR, et al. Ileal pouch-anal anastomosis function following childbirth. An extended evaluation. Dis Colon Rectum 1995;38:159–165.
191. Kitayama T, Funayama Y, Fukushima K, et al. Anal function during pregnancy and postpartum after ileal pouch anal anastomosis for ulcerative colitis. Surg Today 2005;35:211–215.
192. Farouk R, Pemberton JH, Wolff BG, et al. Functional outcomes after ileal pouch-anal anastomosis for chronic ulcerative colitis. Ann Surg 2000;231:919–926.
193. Seligman NS, Sbar W, Berghella V. Pouch function and gastrointestinal complications during pregnancy after ileal pouch-anal anastomosis. J Matern Fetal Neonatal Med 2011;24:525–530.
194. Scott HJ, McLeod RS, Blair J, et al. Ileal pouch-anal anastomosis: pregnancy, delivery and pouch function. Int J Colorectal Dis 1996;11:84–87.
195. Ravid A, Richard CS, Spencer LM, et al. Pregnancy, delivery, and pouch function after ileal pouch-anal anastomosis for ulcerative colitis. Dis Colon Rectum 2002;45:1283–1288.
196. Remzi FH, Gorgun E, Bast J, et al. Vaginal delivery after ileal pouch-anal anastomosis: a word of caution. Dis Colon Rectum 2005;48:1691–1699.
197. Lepisto A, Sarna S, Tiitinen A, et al. Female fertility and childbirth after ileal pouch-anal anastomosis for ulcerative colitis. Br J Surg 2007;94:478–482.
198. Julsgaard M, Norgaard M, Hvas CL, et al. Self-reported adherence to medical treatment, breastfeeding behaviour, and disease activity during the postpartum period in women with Crohn's disease. Scand J Gastroenterol 2014;49:958–966.
199. Moffatt DC, Ilnyckyj A, Bernstein CN. A population-based study of breastfeeding in inflammatory bowel disease: initiation, duration, and effect on disease in the postpartum period. Am J Gastroenterol 2009;104:2517–2523.
200. Kane S, Lemieux N. The role of breastfeeding in postpartum disease activity in women with inflammatory bowel disease. Am J Gastroenterol 2005;100:102–105.
201. Barclay AR, Russell RK, Wilson ML, et al. Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. J Pediatr 2009; 155:421–426.
202. Hansen TS, Jess T, Vind I, et al. Environmental factors in inflammatory bowel disease: a case-control study based on a Danish inception cohort. J Crohns Colitis 2011; 5:577–584.
203. Gearry RB, Richardson AK, Frampton CM, et al. Population-based cases control study of inflammatory bowel disease risk factors. J Gastroenterol Hepatol 2010; 25:325–333.
204. Christensen LA, Rasmussen SN, Hansen SH. Disposition of 5-aminosalicylic acid and N-acetyl-5-aminosalicylic

acid in fetal and maternal body fluids during treatment with different 5-aminosalicylic acid preparations. Acta Obstet Gynecol Scand 1994;73:399–402.
205. Esbjorner E, Jarnerot G, Wranne L. Sulphasalazine and sulphapyridine serum levels in children to mothers treated with sulphasalazine during pregnancy and lactation. Acta Paediatr Scand 1987;76:137–142.
206. Silverman DA, Ford J, Shaw I, et al. Is mesalazine really safe for use in breastfeeding mothers? Gut 2005; 54:170–171.
207. Klotz U, Harings-Kaim A. Negligible excretion of 5-aminosalicylic acid in breast milk. Lancet 1993;342:618–619.
208. Ost L, Wettrell G, Bjorkhem I, et al. Prednisolone excretion in human milk. J Pediatr 1985;106:1008–1011.
209. Greenberger PA, Odeh YK, Frederiksen MC, et al. Pharmacokinetics of prednisolone transfer to breast milk. Clin Pharmacol Ther 1993;53:324–328.
210. Christensen LA, Dahlerup JF, Nielsen MJ, et al. Azathioprine treatment during lactation. Aliment Pharmacol Ther 2008;28:1209–1213.
211. Gardiner SJ, Gearry RB, Roberts RL, et al. Exposure to thiopurine drugs through breast milk is low based on metabolite concentrations in mother-infant pairs. Br J Clin Pharmacol 2006;62:453–456.
212. Sau A, Clarke S, Bass J, et al. Azathioprine and breastfeeding: is it safe? BJOG 2007;114:498–501.
213. Moretti ME, Verjee Z, Ito S, et al. Breast-feeding during maternal use of azathioprine. Ann Pharmacother 2006; 40:2269–2272.
214. Stengel JZ, Arnold HL. Is infliximab safe to use while breastfeeding? World J Gastroenterol 2008; 14:3085–3087.
215. Ben-Horin S, Yavzori M, Kopylov U, et al. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. J Crohns Colitis 2011;5:555–558.
216. Fritzsche J, Pilch A, Mury D, et al. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol 2012;46:718–719.
217. Ben-Horin S, Yavzori M, Katz L, et al. Adalimumab level in breast milk of a nursing mother. Clin Gastroenterol Hepatol 2010;8:475–476.
218. Johns DG, Rutherford LD, Leighton PC, et al. Secretion of methotrexate into human milk. Am J Obstet Gynecol 1972;112:978–980.
219. Gisbert JP. Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding. Inflamm Bowel Dis 2010; 16:881–895.
220. Mahadevan U, Cucchiara S, Hyams JS, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. Am J Gastroenterol 2011;106:214–223; quiz 224.
221. Cheent K, Nolan J, Shariq S, et al. Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. J Crohns Colitis 2010;4:603–605.
222. Mahadevan U, Martin CF, Dubinsky M, et al. Exposure to anti-TNFα therapy in the third trimester of pregnancy is not associated with increased adverse outcomes: results from the PIANO registry (abstr 960). Gastroenterology 2014;146(suppl 1):S-170.
223. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66: 726–735.
224. McLaughlin KJ, Crowther CA, Walker N, et al. Effects of a single course of corticosteroids given more than 7 days before birth: a systematic review. Aust N Z J Obstet Gynaecol 2003;43:101–106.

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CAG Statement

This clinical practice guideline on the management of IBD in pregnancy has been developed under the direction of Drs Geoffrey C. Nguyen and Cynthia H. Seow, in accordance with the policies and procedures of the CAG and under the direction of CAG Clinical Affairs. It has been reviewed by the CAG Practice Affairs and Clinical Affairs Committees and the CAG Board of Directors. The clinical practice guideline was developed after a thorough consideration of the medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian and international panel composed of experts on this topic. The clinical practice guideline aims to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The clinical practice guideline is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available, and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

Conflicts of interest
The authors disclose the following: Advisory Board: AbbVie (AB, CHS, GCN, JKM, CJV, LT, SF), AstraZeneca (JKM), Celltrion (JKM), Cubist (JKM), Ferring (AB, BB, JKM), Forest (JKM), Hospira (JKM), Janssen (AB, CHS, GCN, JKM, LT, SF), MSD (CJV), Procter & Gamble (JKM), Shire (AB, BB, CHS, JKM), Takeda (AB, CHS, JKM, LT).

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Speaker's Bureau: AbbVie (AB, BB, JJ, JKM, SF, YL), Aptalis (JKM), Falk Benelux (CJV), Ferring (BB, JJ, JKM), Forest (JKM), Janssen (BB, CHS, JJ, JKM, SF, YL), Pfizer (CHS, LT), Proctor & Gamble (JKM), Shire (BB, JJ, JKM, SF), Takeda (BB, JJ, JKM), Warner Chilcott (BB, CHS, JKM).

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Appendix 1

Inflammatory Bowel Disease in Pregnancy Consensus Group

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Appendix 2

Rejected Statement

For pregnant women with IBD who are currently on or have recently received systemic corticosteroids, we suggest/recommend stress-dose intravenous corticosteroids peripartum. *GRADE: Rejected recommendation, evidence level could not be determined. Vote: strongly agree, 0%; agree, 67%; uncertain, 33%.*

Although administration of stress-dosed systemic corticosteroids around the time of delivery is common in clinical practice, there appears to be no evidence for this strategy. A meta-analysis of a single course of corticosteroids more than 7 days before delivery found no reduction in the risk of infant respiratory distress syndrome but an increased risk of perinatal mortality.[224]

It has been suggested that women who have recently received a course of systemic corticosteroids may have infants experiencing hypothalamic–pituitary–adrenal axis suppression. However, in the absence of any studies assessing whether intravenous administration of corticosteroids during the peripartum period affects short-term or long-term outcomes in the infants born to mothers within 3 weeks of corticosteroid taper, the consensus group rejected this statement.