

# 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.

Western nations including Canada, the United States, and Europe.<sup>2</sup> 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<sup>3–7</sup> as well as a greater likelihood of active disease and relapse during pregnancy and the postpartum period.<sup>8,9</sup> 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.<sup>10,11</sup>

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.<sup>12</sup> 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.<sup>12</sup> 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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The inflammatory bowel diseases (IBDs)—ulcerative colitis (UC) and Crohn's disease (CD)—are associated with a substantial burden of illness,<sup>1</sup> particularly in

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<sup>13</sup> and, more recently, the medical management of mild to severe active UC in the ambulatory patient.<sup>14</sup> 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.<sup>15</sup> 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.<sup>16</sup> 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<sup>16,17</sup>

and prior Canadian Association of Gastroenterology (CAG) consensus documents.<sup>14,18</sup> 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.<sup>19</sup> 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."<sup>19</sup>

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.<sup>20</sup> 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%).<sup>21</sup> 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, heritability of IBD, and the perceived negative impact of medications for IBD on the course of pregnancy and fetal development.<sup>21–23</sup> 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).<sup>24</sup> 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.<sup>25</sup>

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.<sup>22,26,27</sup> 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.<sup>22</sup> 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."<sup>22</sup>

Preconception counseling is associated with healthier behaviors (eg, use of folic acid, alcohol and smoking cessation) among women in the general population<sup>28,29</sup> and those with IBD.<sup>30</sup> In women with chronic diseases, preconception counseling is associated with improved pregnancy outcomes.<sup>31</sup> 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)<sup>32</sup> but not in patients with CD (0.69; 95% CI, 0.2–2.9) compared with no counseling.<sup>33</sup> In a case-control study, improved adherence to treatment associated with preconception counseling led to a significantly lower risk of disease relapse.<sup>30</sup>

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.<sup>3</sup> Other more recent observational and cohort studies also support a higher risk of adverse pregnancy outcomes, including prematurity,<sup>7,34–40</sup> LBW,<sup>37,39–42</sup> small for gestational age,<sup>7,36,43</sup> cesarean delivery,<sup>7,35,36,38,43–45</sup> spontaneous abortion,<sup>45</sup> and neonatal death,<sup>7</sup> in patients with IBD.

There have been several analyses of the impact of active versus quiescent disease on pregnancy outcomes.<sup>4,5,7</sup>

**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 gastroenterologist 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 ciprofloxacin 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.<sup>4</sup> 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).<sup>4</sup> 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;  $P = .02$ ).<sup>5</sup> Case-control studies report higher rates of adverse birth outcomes among patients with IBD who experience a relapse compared with those without<sup>6</sup> and among those with prior UC-related surgeries or hospitalizations.<sup>7</sup>

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;  $P = .006$ ).<sup>8</sup> In the ECCO-EpiCom study, a longer duration of IBD was associated with a greater risk of relapse during pregnancy and the postpartum period.<sup>9</sup> IBD has also been associated with an increased risk of venous thromboembolism (VTE),<sup>38,44</sup> particularly among those with flaring UC.<sup>44</sup> 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.<sup>46</sup>

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.<sup>14</sup> A growing body of evidence suggests that mucosal healing is an important predictor of clinical outcomes, including sustained disease remission.<sup>47</sup> Moreover, the correlation between clinical symptoms and endoscopic disease activity is weak, especially in CD.<sup>48,49</sup> 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

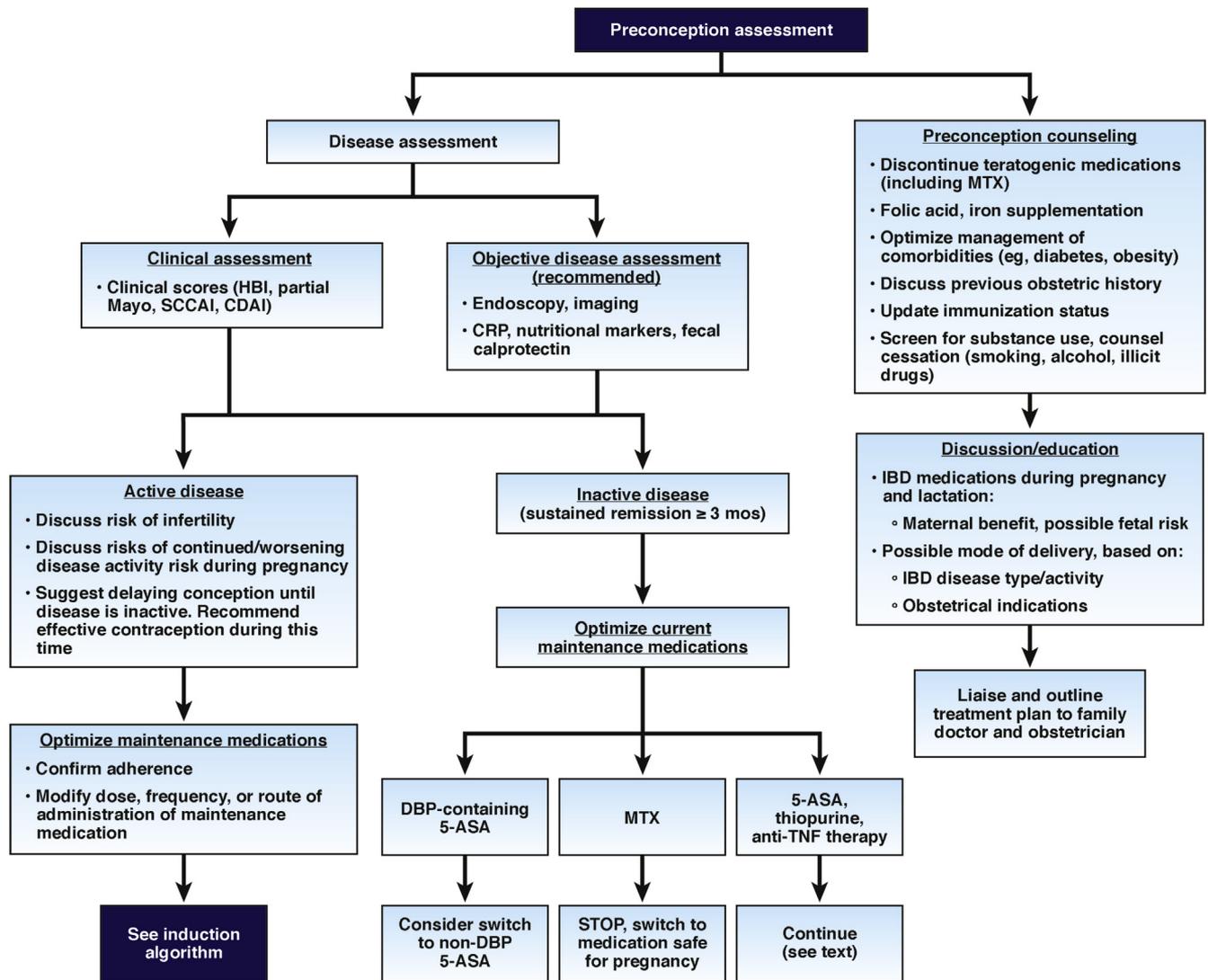
pregnant, special concerns about sedation and procedural risk for the mother and fetus would not yet be an issue. The utility of other objective measures of inflammation, such as fecal calprotectin or C-reactive protein levels, in pregnant women with IBD remains to be established.<sup>14</sup>

**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.<sup>50</sup> 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.<sup>50,51</sup> In addition, cohort and cross-sectional studies in humans have shown associations between phthalates and developmental problems.<sup>51</sup>

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,<sup>52</sup> and one case reported levels 200 times higher than in controls.<sup>53</sup> 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.<sup>54</sup> 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.<sup>50</sup>

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).<sup>55</sup> 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.<sup>56</sup>

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.<sup>57</sup>

Product labeling suggests that women should discontinue methotrexate for 3 months to 1 year before conception.<sup>58</sup> 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.<sup>59</sup>

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.<sup>56</sup> 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,<sup>3,7,34–45</sup> including a higher risk of cesarean delivery,<sup>7,35,36,38,43–45</sup> reported at 1.5-fold in a meta-analysis (95% CI, 1.26–1.79;  $P < .001$ <sup>3</sup>). Risks are generally reported to be higher in women with active versus quiescent disease.<sup>4–7</sup> In addition, women with IBD are at greater risk for VTE<sup>38,44</sup> and are reportedly less likely to breast-feed.<sup>35,42</sup>

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.<sup>4–7</sup> Women with active disease also have a higher risk of ongoing disease activity during pregnancy.<sup>8,9</sup> Women overestimate the harmful effects of medication and underestimate the harmful effects of IBD flares during pregnancy.<sup>22,26,27</sup>

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<sup>4–7</sup> and disease flares in women with IBD are higher in those with active disease.<sup>8,9</sup> 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.<sup>6</sup>

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.<sup>9</sup> 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;  $P = .0098$ ).<sup>9</sup> 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;  $P = .04$ ).<sup>5</sup>

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.<sup>14</sup> 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%;  $P < .01$ ).<sup>60,61</sup> 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;  $P = .26$ ).<sup>62</sup>

More recent cohort studies have shown varying results; one study showed an increased risk of major malformations (especially cardiovascular defects)<sup>63</sup> whereas other studies showed no increased risk<sup>39,43,64,65</sup> 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.<sup>63</sup> Other studies have shown significant increases in the risk of cesarean delivery,<sup>66</sup> preterm delivery,<sup>65,66</sup> and stillbirth<sup>65</sup> 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 ( $\geq 3$  g/day) compared with lower doses ( $< 3$  g/day).<sup>67</sup> 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<sup>14</sup> and CD<sup>68–70</sup> who have achieved symptomatic remission on oral corticosteroids. Meta-analyses support the benefit of azathioprine for maintenance of remission<sup>71–73</sup> in nonpregnant patients with UC, with rates of nonremission of 44% with azathioprine compared with 65% with placebo.<sup>73</sup> 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).<sup>74</sup>

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%)<sup>75</sup> and UC (relapse at 12 months of 59% vs 36%).<sup>76</sup> 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.<sup>77,78</sup> 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).<sup>77</sup> 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).<sup>78</sup> More recent observational and cohort studies have shown varying results, with one study showing higher rates of preterm births<sup>4</sup> but other studies showing no increase<sup>64,66</sup> or lower risks<sup>79</sup> 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).<sup>4</sup> 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.<sup>80,81</sup>

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.<sup>82</sup> 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.<sup>82</sup> Although the anemia was mild, it has been suggested that complete blood cell counts be considered in these newborns.<sup>82</sup>

**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<sup>14</sup> and CD<sup>68-70,83</sup> 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%).<sup>84-86</sup> Similar results have been seen in patients with CD.<sup>87,88</sup>

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.<sup>89</sup> Both infliximab and adalimumab are immunoglobulin (Ig)G1 monoclonal antibodies, whereas certolizumab is a Fab fragment of IgG1. Because certolizumab does not contain the Fc portion of IgG1, there is significantly less placental transfer than with other anti-TNF agents.<sup>89</sup> Correspondingly, cord blood levels of certolizumab are very low.<sup>90</sup> 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,<sup>90-94</sup> and levels were detectable in infants for up to 6 months.<sup>90</sup> However, some studies fail to show measurable levels of anti-TNF agents in children born to mothers treated with these agents.<sup>91,95</sup>

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)<sup>91</sup> and 14% in a case-control study (n = 85).<sup>96</sup> 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%.<sup>96</sup> 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%;  $P = .001$ ).<sup>79</sup> 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%;  $P = .14$ ).<sup>97</sup>

Data from a meta-analysis<sup>98</sup> and 2 systematic reviews<sup>99,100</sup> 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.<sup>98</sup> 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.<sup>99,100</sup>

Several more recent case series or cohort studies have reported no increased risk of major congenital abnormalities<sup>93,101</sup> or other adverse pregnancy or neonatal outcomes.<sup>93,96</sup> 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.<sup>96</sup>

A systematic review reported no increased risk of infections in the offspring.<sup>99</sup> 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.<sup>102</sup> Anti-TNF therapy during pregnancy has also been associated with case reports of severe neutropenia in newborns.<sup>103</sup> However, an increased risk of perinatal bacterial infection in the offspring has also been associated with maternal UC not treated with biologic therapy.<sup>40</sup> No changes in growth or psychomotor development were reported in a case series of children exposed to anti-TNF therapy prenatally.<sup>102</sup>

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,<sup>15</sup> 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<sup>104,105</sup> 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).<sup>106</sup>

**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<sup>14</sup> and CD<sup>68,69</sup> 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.<sup>14</sup> Combination therapy has shown efficacy for induction of remission in patients with UC in the UC SUCCESS (NCT00537316, protocol number P04807) trial<sup>107</sup> and in patients with CD in the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC).<sup>108</sup>

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).<sup>109</sup> 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.<sup>110</sup>

Observational studies suggest no relationship between maternal use of combination therapy and the rate of infection among offspring compared with anti-TNF therapy alone.<sup>99,102,110</sup> The PIANO registry reported a significant increase in infections at 12 months of age in the combination group relative to the unexposed group<sup>110</sup>; 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.<sup>106</sup> 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.<sup>106,111,112</sup> 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%.*

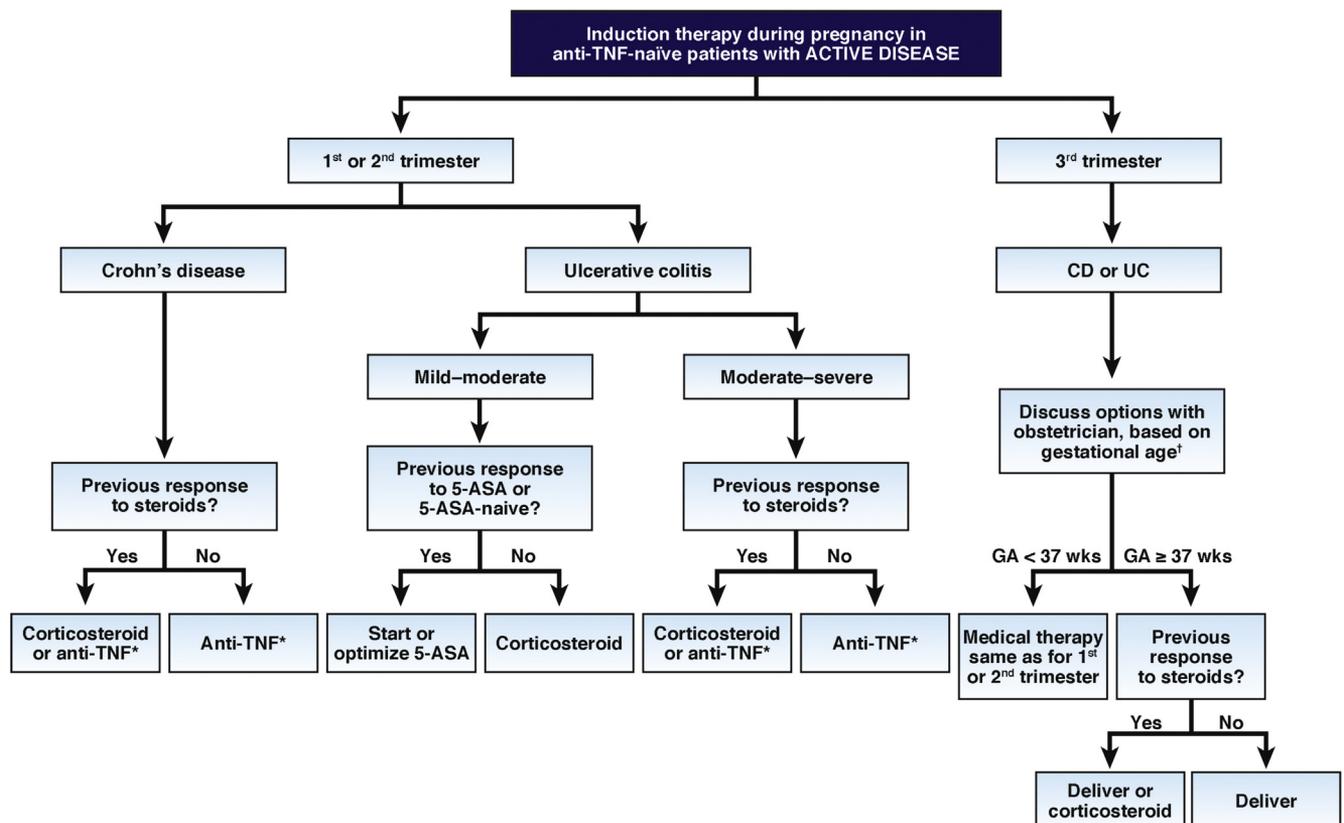
Clinical practice guidelines for the management of UC in nonpregnant patients suggest the combination of a rectal and an oral 5-ASA preparation over oral 5-ASA alone for induction of remission and that the same therapy be continued for maintenance.<sup>14</sup> A meta-analysis reported that the combination 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.<sup>113</sup> As described in statement 8, meta-analyses have shown the efficacy of 5-ASA maintenance therapy compared with placebo in patients with UC.<sup>60,61</sup>

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.<sup>114</sup> Guidelines for nonpregnant patients with CD recommend metronidazole or ciprofloxacin as adjunctive treatments for fistulizing disease.<sup>115,116</sup> 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).<sup>117</sup>

Meta-analyses<sup>118,119</sup> and a more recent cohort study<sup>120</sup> 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.<sup>121</sup> 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<sup>122</sup>; however, animal studies have reported musculoskeletal abnormalities.<sup>123,124</sup> In a small case series of women with IBD, neither metronidazole nor ciprofloxacin was associated with poor pregnancy outcomes.<sup>125</sup> Metronidazole<sup>126,127</sup> and ciprofloxacin<sup>128</sup> 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,<sup>129-131</sup> 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.<sup>115,116</sup>

**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<sup>14</sup> and CD<sup>68-70</sup> 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.<sup>132</sup> 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.<sup>6</sup>

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<sup>14</sup> and the idiosyncratic risk of bone marrow suppression, pancreatitis, hepatotoxicity, allergic reactions, and opportunistic infections (see statement 9).<sup>73,133,134</sup>

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.<sup>6</sup>

Data on the risk of congenital malformations with exposure to corticosteroids are inconsistent.<sup>135-138</sup> 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.<sup>136</sup> 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<sup>135</sup> 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.<sup>135</sup> 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.<sup>139</sup>

All corticosteroids can cross the placenta but are rapidly converted to less active metabolites, resulting in low fetal blood concentrations.<sup>15</sup> 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.<sup>140</sup> 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<sup>141,142</sup>; however, guidelines for the management of UC concluded that there were insufficient data to support its routine use,<sup>14</sup> and cyclosporine is not recommended for the treatment of CD.<sup>70</sup> 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.<sup>143</sup> In women with IBD, cases of adverse outcomes that include prematurity, LBW, and spontaneous abortion have been reported.<sup>6,144,145</sup> 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.<sup>133</sup>

**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<sup>14</sup> and CD<sup>68-70,83</sup> 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.<sup>89,90</sup> 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<sup>146-151</sup>; 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<sup>14</sup> and CD<sup>68,69</sup> 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).<sup>73,133,134</sup> 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).<sup>152</sup> 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.<sup>18</sup>

Patients with IBD are at higher risk for VTE compared with those without IBD,<sup>153-157</sup> particularly during a disease flare.<sup>153,154</sup> Similarly, there is a high risk of VTE in pregnant women with IBD,<sup>38,44,158,159</sup> particularly during a disease flare.<sup>44</sup> Anticoagulant thromboprophylaxis has been shown to be effective and safe in patients with IBD.<sup>160,161</sup>

Guidelines recommend low-molecular-weight heparin over unfractionated heparin for pregnant women.<sup>162</sup>

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<sup>15</sup> and American Society for Gastrointestinal Endoscopy<sup>163</sup> 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.<sup>163</sup>

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.<sup>164</sup> 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.<sup>164</sup> 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.<sup>165</sup> 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.<sup>15,163</sup> 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.<sup>166</sup> 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.<sup>163</sup>

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.<sup>163</sup>

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.<sup>163</sup> 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.<sup>15,163</sup> 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.<sup>167</sup>

A meta-analysis<sup>168</sup> and a systematic review<sup>169</sup> 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).<sup>169,170</sup> 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.<sup>171,172</sup> 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.<sup>167</sup>

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 radio-frequency pulses, and the high acoustic noise level.<sup>167</sup>

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.<sup>124</sup> 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.<sup>6,173-176</sup> 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.<sup>45</sup>

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.<sup>177</sup>

### 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.<sup>38,44,178,179</sup> In one study, the risks were more than doubled for elective cesarean delivery and approximately 1.5-fold for emergency cesarean delivery.<sup>44</sup>

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.<sup>180-182</sup> Other studies have reported development of new perianal disease<sup>183</sup> or worsening in women with active perianal disease<sup>179</sup> 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.<sup>180,181,184</sup> 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.<sup>185</sup> A smaller survey, however, found a higher rate of incontinence among women with IBD compared with those without IBD (33% vs 2%;  $P < .01$ ).<sup>186</sup> Because the risk of fecal incontinence increases with age,<sup>187</sup> 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.<sup>188</sup>

It appears that vaginal delivery is unlikely to result in exacerbation of disease during the postpartum period in women with inactive perianal CD.<sup>180-182</sup> 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<sup>189</sup> and no change in pouch function after vaginal delivery.<sup>189-194</sup> 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.<sup>195</sup>

Although several studies of pregnancies after IPAA have shown vaginal delivery to be as safe as cesarean delivery in terms of pouch function,<sup>193,194,196</sup> physiological measurements and imaging studies suggest that there is a higher risk of sphincter injury with vaginal than cesarean delivery.<sup>196</sup> Data on the risk of fecal incontinence in pregnant women with IPAA are conflicting.<sup>193,195,197</sup> One study reported that women with IPAA had increased stool frequency and fecal incontinence during pregnancy,<sup>195</sup> whereas others found no association during<sup>193</sup> or after pregnancy.<sup>197</sup> A cohort study found that rates of incontinence were not significantly affected by mode of delivery.<sup>193</sup> 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.<sup>178</sup> As discussed in statement 21, vaginal delivery has been associated with worsening of active perianal disease after delivery in some studies<sup>179</sup> but not in others.<sup>180,181,184</sup> 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.<sup>178</sup>

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,<sup>38,44,158,159</sup> particularly during a disease flare.<sup>44</sup> Guidelines for VTE in patients without IBD recommend VTE prophylaxis in women who undergo cesarean delivery and have other risk factors.<sup>162</sup> 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.<sup>18</sup> Although the CAG VTE guideline group made a weak/conditional recommendation for VTE prophylaxis after cesarean delivery,<sup>18</sup> 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.<sup>198,199</sup> Moreover, postpartum discontinuation of medication may lead to disease flare.<sup>200</sup> In addition, a meta-analysis<sup>201</sup> and more recent case-control studies<sup>202,203</sup> 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.<sup>15,204–207</sup>

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

Case reports suggest that exposure to thiopurines through breast milk is low,<sup>210–213</sup> and it is generally considered acceptable to continue throughout breast-feeding.<sup>116</sup> One study found that the majority of 6-mercaptopurine in breast milk was excreted within the first 4 hours after drug intake.<sup>210</sup> Studies have not detected azathioprine metabolites in the serum of breast-fed infants.<sup>211,212</sup> 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.<sup>81</sup>

Few data are available on the use of anti-TNF therapy while breast-feeding. In case reports, no<sup>95,214</sup> or low levels of infliximab<sup>215</sup> have been reported in breast milk. One series of 3 cases reported no detectable levels of infliximab in the sera of breast-fed infants,<sup>95</sup> whereas another study reported that low levels were found 5 days after infusion.<sup>216</sup> In several case reports, low levels of adalimumab were reported in breast milk<sup>216,217</sup> but were undetectable in the sera of an infant 9 days after administration of adalimumab.<sup>216</sup> The PIANO registry reported no significant increase in infection in infants associated with drug exposure during breast-feeding.<sup>110</sup> 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.<sup>89</sup>

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.<sup>218</sup> The milk-to-plasma ratio was 0.08:1,<sup>218</sup> but it has been suggested that methotrexate may accumulate in neonatal tissues.<sup>219</sup>

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.<sup>15,220</sup> 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,<sup>221</sup> 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.<sup>102</sup> 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.<sup>222</sup>

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.<sup>146</sup> Five case reports of pregnancy during ustekinumab treatment included one that resulted in miscarriage.<sup>147–151</sup>

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.<sup>223</sup> 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](http://www.gastrojournal.org), and at <http://dx.doi.org/10.1053/j.gastro.2015.12.003>.

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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).

Consultation Fees: AbbVie (BB, JJ, JKM, UM, YL), AstraZeneca (JKM), Celgene (UM), Celltrion (BB, JKM), Cubist (JKM), Ferring (JJ, JKM), Forest (JKM), Genentech (BB), Hospira (JKM), Janssen (AB, BB, CHS, JJ, JKM, UM, YL), Procter & Gamble (JKM), Prometheus (UM), Shire (AB, JJ, JKM, YL), Takeda (BB, JJ, JKM, UM, YL), UCB (UM).

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## Appendix 1

### *Inflammatory Bowel Disease in Pregnancy Consensus Group*

Alain Bitton (Department of Medicine, McGill University Health Centre, Montreal, Quebec), Brian Bressler (Department of Medicine, Division of Gastroenterology, St Paul's Hospital, Vancouver, British Columbia), Sharyle Fowler (Department of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan), John K. Marshall (Hamilton Health Sciences Centre, Hamilton, Ontario), Carrie Palatnick (Department of Obstetrics and Gynecology, University of Manitoba, Winnipeg, Manitoba), Anna Pupco (Motherisk, SickKids Hospital, Toronto, Ontario), Joel Ray (Department of Medicine, University of Toronto, Toronto, Ontario), Laura Targownik (Department of Gastroenterology, University of Manitoba, Winnipeg, Manitoba), Janneke van der Woude (Department of Gastroenterology and Hepatology, Erasmus University MC, Rotterdam, The Netherlands), William Paterson (nonvoting participant) (Department of Medicine, Queen's University, Kingston, Ontario).

## 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.<sup>224</sup>

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.