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Treatment of the Pregnant IBD Patient with a Disease Flare

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Introduction

The incidence of inflammatory bowel disease (IBD) is increasing and the onset of Crohn’s disease (CD) and ulcerative colitis (UC) often coincide with the peak childbearing years. In North America, the prevalence of UC is 249 per 100,000 persons and the prevalence of CD is 319 per 100,000 persons; in Europe, prevalence of UC and CD has been reported to be as high as 505 per 100,000 persons and 322 per 100,000 persons, respectively [1]. Nørgård et. al. showed that mean incidence rates in Denmark, were highest among women ages 15-29 [2]. While research regarding fertility, medication safety during pregnancy, and pregnancy outcomes is increasing, there are still many knowledge gaps in these areas. Management of IBD is growing more complex and the stakes are especially high when dealing with a pregnant patient. For example, there are now seven different biologic therapies in use for IBD and they are not infrequently continued during conception and pregnancy. Many young patients who are contemplating or who have had surgery for IBD, especially an ileoanal pouch anastomosis (IPAA) or an ostomy, do not want to give up the opportunity to have children. When contemplating medical or surgical therapy, the most urgent questions patients often have are those regarding fertility and safety of a future pregnancy. Since this is a complex area with many knowledge gaps, the best way to manage women with IBD who are pregnant or contemplating pregnancy is a multidisciplinary approach. Team members often include a high-risk obstetrician,
especially for women on immunosuppressive medications, with severe and/or active disease or with a history of IBD surgery, an infertility specialist who can advise on assisted reproduction if needed, and a colorectal surgeon for patients with a history of IBD surgery or perianal fistulizing disease, in addition to the patient’s gastroenterologist. A pediatrician with experience in caring for children of mothers with IBD should also be part of the multidisciplinary team. By integrating expertise from these disciplines, women with even very complex IBD should be able to have a healthy pregnancy and delivery. This article will review the recent literature on the effects of fertility and pregnancy on IBD, the management of disease exacerbation during pregnancy and also discuss questions that remain unanswered regarding fertility and pregnancy in IBD.

**Fertility:** Are fertility rates decreased among women with IBD?

Fertility, or the ability to produce offspring, is often a concern among women with a diagnosis of IBD, and may affect decisions regarding medical management at the time a woman is trying to conceive. Fertility is not affected by IBD in general, although pelvic surgery may affect the ability to conceive [3]. It is not known whether disease activity can affect the ability to conceive. Studies have shown that there are no differences in fertility rates among women with and without IBD [4, 5]. Despite the lack of difference in fertility rates, women with IBD tend to have fewer children, a concept known as “voluntary childlessness.” Tavernier et. al. showed that women diagnosed with CD have half as many children as women without IBD [5]. Women with IBD often choose to have fewer children for a number of reasons, including fear of worsening disease during pregnancy, concern for passing IBD on to their offspring, concern of disease recurrence
because of pregnancy, concern regarding increased stress due to a child and fear of not being able to care for a child [4, 6].

While it was previously shown that there was no decreased fertility rate among women with IBD [7], the recent consensus statement published by the European Crohn’s and Colitis Organization (ECCO) states that although there is no evidence that UC or inactive CD disease has an impact on fertility, fertility may be reduced in active CD [8]. This statement is further supported by recent studies showing decreased levels of anti- Müllerian hormone (AMH) in women with active CD [9]. In addition, ECCO hypothesizes that inflammation in the fallopian tubes and ovaries and tubal adhesions associated with prior surgical interventions may impact fertility [8].

Accurate assessment of fertility can be difficult, especially if there is increased voluntary childlessness among women with IBD. AMH levels have recently been shown to be a good indicator of ovarian reserve and as a marker of fertility among women of reproductive age [9]. One study of 35 women with CD and 35 controls without CD showed significantly lower levels of serum AMH in the CD population [9]. Interestingly, among this same population, serum AMH levels were significantly lower among women with active CD than among those in remission, and a trend was seen showing lower serum AMH levels among women who had disease duration of CD for at least 5 years but this difference was not statistically significant [9]. This study raises the question of the effect of disease severity on fertility and also the long-term effects of CD on fertility.
Fertility rates among women who have undergone surgery for IBD have been shown to differ from rates of women who have not had surgical intervention. Specifically, a history of IPAA is associated with a 2-3 fold increased risk of infertility [3, 10, 11]. One meta-analysis showed a three-fold increased risk of infertility after IPAA, with infertility rates ranging from 14.6% among women before surgery to 48% among women after IPAA [3]. Another meta-analysis showed increased infertility rates from 12% to 26% before and after restorative proctocolectomy among women with UC [10]. A retrospective study of fertility rates among women who had undergone proctocolectomy and ileostomy for UC and CD reported a reduction in fertility to 37% from 72% after surgery [12]. Similarly, 17 percent of patients with familial adenomatous polyposis who underwent either ileorectal anastomosis, IPAA, and proctocolectomy with ileostomy reported difficulties with fertility after surgery, though type of surgery was not associated with fertility outcomes [13]. Women with UC who have undergone IPAA have been shown to have abnormal hysterosalpingography; a small study of 21 patients showed bilateral occlusion of the fallopian tubes in 2 of 21 patients after IPAA and unilateral occlusion in 9 [14]. Only 7 of the 21 women evaluated had a normal hysterosalpingography after IPAA [14].

Recent studies evaluating the effect of laparoscopic IPAA have shown lower rates of infertility after laparoscopic IPAA compared to open surgery, and Beyer-Berjot et. al. showed no difference in fertility rates among women who underwent surgery for laparoscopic IPAA and laparoscopic appendectomy, a procedure that has not been associated with decreased fertility [15]. Similarly, Bartels et. al. showed higher pregnancy rates among women who had undergone laparoscopic IPAA compared to those who had open procedures [16]. One study showed that women with UC who have undergone IPAA, however, have similar success with pregnancy via
in vitro fertilization (IVF) as women with UC without IPAA and women without IBD [17]. Although the cohort of women with UC who had undergone IPAA only included 22 women, the study suggests that among this population, conception via IVF likely is not impacted by prior surgical procedures. In addition, irrespective of medical or surgical treatment, initial research shows that IVF is just as successful among women with CD and UC as in women in the general infertile population [18]. This recent retrospective matched cohort study indicated that women with IBD who undergo IVF achieve rates of live births comparable to those of infertile women without IBD who undergo IVF [18] though additional studies are warranted to confirm these results.

**Fertility knowledge gaps:**

While it has not been shown that a diagnosis of IBD is associated with decreased fertility, data suggest that certain factors, such as surgical history, disease severity and duration of disease, may affect a woman’s ability to conceive naturally. Further studies are necessary to clarify the effects of surgical intervention, differences in laparoscopic versus open operations, and their effect on fertility as well as the possible impact of disease severity on fertility. In addition, further research is needed regarding on the role of AMH hormone and whether this can be used to predict which women to refer to a fertility specialist before 12 months of unsuccessful pregnancy. Due to the nature of studies using large databases or population-based studies, it is difficult to calculate the rate of pregnancy loss in women with IBD and to estimate the rate of ectopic pregnancy and whether it is increased from that in the general population. At this time, we recommend that post-surgical patients either with irregular menstrual cycles or with more than 3 months without success of conception should be referred to a fertility specialist. Data
suggest that laparoscopic surgery may be associated with lower rates of infertility, and the success of IVF in the IBD population is promising.

**Pregnancy:**

**What are the effects of pregnancy on IBD and the effects of IBD on birth outcomes?**

The majority of pregnant women with IBD will experience normal pregnancies; a meta-analysis from 1986 following over 1300 women with UC and 700 women with CD showed that 83-85% of women with IBD had normal pregnancies [19]. The status of disease at the time of conception can often help predict the course of disease activity during pregnancy. A woman who has active disease at the time of conception is more likely to have active disease throughout pregnancy than a woman who is in remission at the time of conception. A meta-analysis evaluating disease activity during pregnancy in relation to disease activity at conception showed that among women with UC, patients had a higher risk of active disease during pregnancy if they entered pregnancy with active disease [20]. Similar results were seen among women with CD [20]. The recommendation for women to be in remission at the time of conception is further supported by a recent retrospective study showing active disease at the time of conception is associated with increased adverse pregnancy outcomes among women with IBD [21]. One study has shown that disease activity probably has an impact on preterm birth, emphasizing the importance of disease management throughout pregnancy [22].

It has not been shown that pregnancy itself can predispose a woman to a flare of IBD. Pedersen et. al. followed pregnant and non-pregnant women with IBD and found no statistically significant difference in the disease course between these two groups [23]. However, it has been
suggested that IBD can affect birth outcomes. A recent meta-analysis showed increased odds of preterm birth (1.85; 95% CI 1.67-2.05), small for gestational age birth weight (1.36; 1.16-1.60), congenital anomalies (1.29; 1.05-1.58) and stillbirth (1.57; 1.03-2.38) for women with IBD compared to non-diseased controls [24]. Twenty-three studies including over 15,000 women with IBD were included in this meta-analysis, but the specific effects of flare on these birth outcomes are unknown. Boyd et. al. showed that women with IBD using systemic corticosteroids are at increased risk of severe pre-eclampsia, preterm premature rupture of membranes and medically induced preterm delivery (HR all >7), suggesting that either disease severity and/or the use of these medications may affect these outcomes [25]. There was also a modest increase in congenital abnormalities in women with Crohn’s disease only (RR 1.85; 95% CI 1.06-3.21). There was no evidence of an association between IBD and pregnancy loss. Additional studies have also shown increased rates of preterm delivery, small for gestational age, admission to the neonatal intensive care unit (NICU) and low 5-minute APGAR score [21].

**Knowledge gaps:**

There are currently many knowledge gaps regarding the effects of pregnancy on IBD making it difficult to advise women with IBD about pregnancy. In addition, we know that women with IBD have an increased risk of adverse birth outcomes, but there are insufficient data to be able to identify which women are more likely to have adverse outcomes. Data show that women who enter pregnancy in remission are less likely to have active disease during pregnancy than women who conceive during a flare; however, there are currently no data about how long a woman should be in remission before trying to conceive. There are also no data about differences between CD and UC regarding how remission or disease activity affects the disease during
pregnancy. In addition, some women decide to stop therapy prior to becoming pregnant. This further makes it difficult to determine if disease activity changes during pregnancy because of pregnancy alone or because of change, or discontinuation, of medications.

Regardless of disease activity during pregnancy, there is little information about the course of disease activity post-partum. Of 105 women with CD who completed a questionnaire regarding disease postpartum, 66.1% reported adherence to medical therapy, noting quiescent disease and fear of transmission of medication to breast milk as reasons for non-compliance [26]. In the postpartum period, 15 (14.3%) of the women reported relapse in CD, though five of these women reported non-adherence to medications; six reported mild disease activity and nine women reported moderate activity [26].

**What is the effect of pregnancy on the microbiome?**

While differences in the microbiome have been observed in patients with IBD compared to those without IBD, the exact role of the microbiome in the pathogenesis of IBD disease remains unclear. The gut microbiome is affected by many factors, including the immune system, environment, diet and genetics [27, 28].

There are limited data regarding the role of the microbiome and changes in the microbiome during pregnancy. One study including 91 pregnant women showed significant changes in the gut microbiota over the course of pregnancy [29]. Specifically, Koren et. al. observed an overall increase in Proteobacteria and Actinobacteria from the first to third trimester, a decrease in Faecalibacterium, and a decrease in the diversity of the microbiota [29]. Changes in diversity
over this time period were not related to the health of the pregnant woman. During pregnancy, a woman’s immune system must adapt to avoid rejection of the fetus. At this time, the relationship between the observed changes in the microbiome and the immune system and the role of the bacteria are not known [30]. It has been hypothesized that the changes in microbiome may promote weight gain or may stimulate the innate immune response, the latter of which may affect disease course during pregnancy [30]. In addition, the impairment of innate immunity that has previously been reported in IBD may improve during pregnancy with changes in the microbiome and hormones that affect this immune response [30]. The mechanism by which disease inflammation may be increased or decreased during pregnancy is not entirely understood. In pregnancy, the T helper 2 cell (Th2) responses are increased. CD is typically characterized by an exaggerated CD4 T helper 1 (Th1) cell response. The increased Th2 response in pregnancy may affect the Th1 response that is up-regulated in CD, resulting in decreased risk of flare [30].

As noted, changes in the microbiome have been observed over the course of three trimesters during pregnancy. However, very little change has been observed during the perinatal period. A small study evaluating the composition of the gut microbiota of 7 patients from 3-7 weeks prepartum to up to 30 days postpartum showed no significant changes in the gut microbiome composition nor in fecal short chain fatty acids, glucose, lactate or calprotectin [31]. Additional studies are warranted to further characterize changes over a longer time period including the first and second trimesters and also to correlate changes in the microbiome with disease activity.

**Knowledge gaps:**
There are no studies on changes in the microbiome in patients with IBD during pregnancy and there are very limited data on the microbiome and pregnancy in general. Further investigation is warranted to better understand the changes that occur in the microbiome during a normal pregnancy and how these changes may affect, or be impacted by, disease activity and severity. At this time, it is unknown if changes in the microbiome can predict flare or remission, how pregnancy may affect the microbiome, and how changes in the microbiome affect birth outcomes.

**How do we know if a pregnant woman is flaring?**

Assessment of flares and disease activity during pregnancy can be challenging. Current measures to evaluate disease activity of IBD include serum inflammatory markers, fecal calprotectin, colonoscopy, radiographic imaging and clinical indices including the Harvey-Bradshaw Index (HBI), Simple Clinical Colitis Activity Index (SCCAI) and the short or long form Inflammatory Bowel Disease Questionnaire (IBDQ) (Table 1). However, evaluating disease activity during pregnancy is very difficult, as the available methods are either not validated during pregnancy or often avoided due to possible risk to the fetus. During pregnancy, imaging studies and endoscopy are often avoided because of the risk of radiation to the fetus, possible toxicity of IV gadolinium (MRI contrast dye), and potential risks to the fetus from both an endoscopic procedure and administration of sedation. Inflammatory markers that are used to monitor disease activity in a non-pregnant patient increase during normal pregnancies in women without IBD. Disease activity questionnaires that have been validated in IBD, such as the Harvey-Bradshaw Index for CD, include questions both about the presence of an abdominal mass, which is difficult
to assess during pregnancy, and bowel habits, which may change because of pregnancy and not because of a change in disease activity.

Fecal calprotectin, a biomarker that recently has been studied to assess disease activity in non-pregnant IBD patients, is a validated marker of disease activity in non-pregnant IBD patients, but there are insufficient data of its role during pregnancy. Fecal calprotectin correlates with inflammation of the colon and increases with disease activity and flares [32, 33]. A recent study has also shown that fecal calprotectin levels correlate with ileal inflammation seen on MR enterography and with surgical inflammation [34]. However, a small study showed no statistically significant difference in fecal calprotectin levels among patients with and without endoscopic evidence of recurrence or remission of CD one year after ileocecal resection [35]. The impact of pregnancy on levels of fecal calprotectin is not known. One small study that followed seven pregnant women without IBD reported a mean fecal calprotectin of 18.8 ±6.1 µg g\(^{-1}\) feces using ELISA and no change in fecal calprotectin levels from stool collected at four time points between week 34 of gestation to 30 days postpartum [31].

Worsening of disease during pregnancy can have negative outcomes on the fetus, as fetal growth and development depend on the mother’s ability to provide nutrition [36]. Medical treatment should not be withheld when disease activity increases; however, medications that are used to treat IBD affect the immune system. While most are safe to give during pregnancy, administration of immune-modulating medications should only be given when essential, stressing the importance of the availability of reliable biomarkers and accurate means to assess disease severity during pregnancy in order to avoid administration of immune-modulating
medications that may not be necessary during pregnancy. Currently available methods, including serum inflammatory markers, hematocrit, physical examination, Harvey-Bradshaw Index or Simple Clinical Colitis Activity Index and a patient’s overall well being can be utilized by the treating physician to assess whether a patient is having a flare. MRI without contrast is safe during pregnancy, and can be ordered if there is uncertainty regarding disease status. Flexible sigmoidoscopy without sedation may also be pursued if results would change management. As with non-pregnant patients, a trial of enemas or suppositories may be appropriate if a patient has distal disease, and medications, including immunomodulators and anti-TNF medications, may be prescribed if necessary.

**Knowledge gaps:**

The currently available methods/modalities of measuring disease severity during pregnancy are suboptimal. Imaging options are limited due to physicians’ and patients’ worry regarding radiation to the fetus, serum inflammatory markers increase due to pregnancy alone and endoscopy is not preferred due to the possible risks of sedation for the fetus.

**What medical treatment options are available for pregnant women with IBD?**

There have been multiple studies regarding the safety of medications used to treat IBD and their use during pregnancy and there are currently ongoing studies evaluating the safety of medications during pregnancy and while breast-feeding. Since women with flares of disease are at increased risk for premature birth, medical management of IBD throughout pregnancy is extremely important to prevent flares or treat worsening of disease when it presents.
Despite recommendations to continue therapy and the safety of medications, studies have also shown that there is decreased adherence to medical therapy prior to and during pregnancy. Julsgaard et. al. showed that adherence to medical treatment among pregnant women with IBD was 60-75%. [37]. One predictor of non-adherence included fear of harming the fetus or negatively affecting fertility [37]. Medications that are commonly prescribed to patients with IBD, and that women often worry about continuing during pregnancy, include the biologic medications and also azathioprine/6-mercaptopurine. These two classes of medications will be reviewed.

**Biologics:**

Biologics are commonly prescribed medications for women with moderate to severe CD or UC, and recent data have shown that it is safe to administer these medications throughout pregnancy. Aside from small case reports, all studies regarding the use of anti-TNF medication during pregnancy reported in the IBD literature are detailed in Table 2. Although anti-TNF medications are considered to be safe during pregnancy, thalidomide, which has some anti-TNF effects, is pregnancy category X and should not be administered during pregnancy [38]. Teratogenic effects of thalidomide include defects in limb development and abnormalities in the cardiovascular, respiratory, gastrointestinal, genitourinary and central nervous systems. It is possible that initial hesitation to prescribe biologic therapy, including infliximab, adalimumab and certolizumab, derived from knowledge of the teratogenic effects of thalidomide and possible relation to effects of anti-TNF properties during pregnancy. However, data from the PIANO registry, a prospective study of the effects of medications during pregnancy among women with IBD, has shown the biologic medications to be safe during pregnancy [39].
The London Position Statement of the World Congress of Gastroenterology reported that infliximab, adalimumab and certolizumab were all considered low risk and could be continued during conception and at least the first two trimesters of pregnancy [40]. In a meta-analysis, no significant differences in unfavorable pregnancy outcomes, rates of abortion, preterm birth, low birth weight or congenital malformations were shown when comparing the pregnancies of women with IBD taking anti-TNF medications and those not taking anti-TNF medications [41]. Similar results showing no significant differences in pregnancy and neonatal outcomes were seen in a case-control study following 124 pregnant women over 133 pregnancies on anti-TNF therapy, including infliximab, adalimumab or certolizumab [42]. Smaller studies of 34 children born to mothers on infliximab or adalimumab showed no congenital malformations other than one case of hip dysplasia in a child [43] and another study of 28 children born to mothers on anti-TNF therapy reported one case of polydactyly but the mother had been on methotrexate prior to conception [44].

Previously, many clinicians discontinued biologic therapy prior to the third trimester. Discontinuation of anti-TNF medication prior to week 30 of pregnancy results in significantly lower levels of medication in cord blood, though levels are still detectable [44]. Both adalimumab and infliximab have been detected in cord blood, and certolizumab is detected only at very low levels [45]. The PIANO study, a prospective study of 1085 women with IBD on immunomodulators and/or biologic therapy, showed no increased risk of congenital anomalies, preterm birth, intrauterine growth retardation, cesarean section or neonatal intensive care unit stay on monotherapy or combination therapy. However, subgroup analysis did show increased
rates of preterm birth, low birth weights and NICU stay in infants born to mothers with UC on combination therapy [39]. Despite recent data showing that these medications are likely safe during pregnancy, the recent statement released by the European Crohn’s and Colitis Organization (ECCO) recommends discontinuing anti-TNF medication around gestational week 24-26 if possible, but that the decision to discontinue a medication should be determined individually based on maternal disease activity [8].

**Vedolizumab:**

There is currently very little data on pregnancy outcomes among women prescribed vedolizumab. One observational study followed pregnant women exposed to vedolizumab. Twenty-four women were exposed to vedolizumab prior to pregnancy and 27 pregnancies were reported (2 in healthy volunteers and 25 in women with a diagnosis of IBD) [46]. Eleven of the pregnancies resulted in a live birth, though two were premature. One congenital anomaly of agenesis of the corpus callosum in the child of a healthy volunteer was reported.

**6-MP/Azathioprine:**

There has not been shown to be increased risk of poor pregnancy outcomes in patients on immunosuppressant therapy. A meta-analysis showed increased risk of preterm birth to newborns of mothers taking thiopurines, but no increased risk of congenital anomalies or low birth weight [47]. The risk of preterm birth may have been affected by disease activity and the actual effect of thiopurines on preterm birth is not entirely clear. An analysis comparing use of thiopurines, anti-TNF with or without thiopurines, and no exposure to thiopurines showed that rate of pregnancy complications was lower in the thiopurine exposed group and that women
taking thiopurines had a more favorable global pregnancy outcome, with global pregnancy outcomes determined by rates of spontaneous or elective abortion, pregnancies that ended before 37 weeks, obstetric complications and newborn intensive care unit admission, low birth weight, congenital malformation or death [48]. However, a meta-analysis including 312 pregnant women with IBD who were taking thiopurines during pregnancy showed that women taking thiopurines had a 2.95 increased odds of congenital abnormalities in babies born to women taking thiopurines compared to women taking no medications for IBD (95% confidence interval 1.03-8.43) [49]; types of congenital abnormalities observed in the thiopurine group included Trisomy 21, congenital hyperplastic heart, bilateral cataract, cervical angioma, congenital cataract, occipital encephalocele, sternocleidomastoid muscle and unspecified malformations of the skin [49]. Of note, there was no difference in congenital malformations among children born to mothers on thiopurines alone and children born to women on other IBD medications [49].

Congenital malformations observed in children born to women not taking thiopurines included renal atrophy, congenital reflux nephropathy, partial syndactyly, Pierre Robin syndrome, complex cardiac malformation and omphalocele. No other differences in prematurity, low birth weight, spontaneous abortion or neonatal adverse outcomes, were seen [49]. One study raises concern over the use of thiopurine during pregnancy. Of thirty patients who were taking azathioprine or mercaptopurine, 60% of children were born with anemia [50]. This study showed that during pregnancy, median 6-thioguanine nucleotide (6-TGN) concentrations decreased while 6-methylmercaptopurine (6-MMP) increased, without evidence of hepatotoxicity or myelotoxicity. Fetal and maternal 6-TGN levels correlated positively, raising the question of whether newborns of mothers on thiopurines should be monitored for anemia [50]. All infants, even those with anemia, had normal APGAR scores and no congenital abnormalities were noted,
though one infant was born with pancytopenia [50]. Similarly, studies have shown that breastfeeding while taking thiopurines is generally safe. Christensen et. al. measured the levels of thiopurines in breast milk during 6 hours after administration of 6-MP or azathioprine. The highest concentrations of medication in breast milk were observed within 4 hours of medication administration; however, maximum exposures of the drug to the children was less than 1% of the dose of the drug administered to the mother [51]. A cohort of children born to mothers taking azathioprine during pregnancy showed no negative effects on the child’s development or increased rates of infection in children followed for an average of 3.8 years after delivery [52]. However, long-term follow-up of these children is not yet available.

Knowledge gaps
Biologic and combination immunomodulator and biologic medications used to treat IBD are relatively new. Thus, additional studies are warranted regarding the safety of biologics and combination therapies during pregnancy. Data show that there are no significant effects on childhood growth and development in the first few years of life, but long-term effects of these medications on offspring are unknown. In addition, long-term effects of children born to fathers treated with these medications at the time of conception is also unknown.

How do we manage women with stable disease during pregnancy?
Women who remain in remission during their pregnancy should continue their current therapy. As previously reviewed, most medications are safe to continue throughout pregnancy without increased risk of adverse events during pregnancy or adverse effects to the fetus. Additional considerations regarding management of the pregnant IBD patient include risk assessment for
venous thromboembolism (VTE) and monitoring for gestational diabetes. Women with UC are at risk of VTE, especially if they flare during pregnancy [53]. In addition, because women with IBD are at increased risk for VTE, prophylactic low molecular weight heparin should be considered in any woman who is hospitalized or flaring, or if they have additional risk factors for VTE [8]. Physicians should also be aware that women with CD are at higher risk of antepartum hemorrhage [53].

It has been shown that women with IBD are at increased risk for development of gestational diabetes, however subgroup analysis showed that only those women who received steroids during pregnancy were at increased risk [54]. There was no significant difference in risk of gestational diabetes between women with IBD who had not received steroids and controls [54]. The PIANO registry following over one thousand pregnant women with IBD has also shown an increased risk of gestational diabetes among women who received steroids during pregnancy [55].

**Knowledge gaps:** It is unclear if women should remain on combination therapy or de-escalate during pregnancy if in remission. At this time, we recommend that gastroenterologists continue biologics in the third trimester if the patient is flaring. However, further research is warranted to determine if biologic therapy can stopped during the third trimester if the patient is in remission. In addition, if medication is de-escalated during pregnancy, it is unclear if the therapeutic regimen used prior to pregnancy be re-started after delivery.

**How do we manage flares during pregnancy?**
As reviewed previously, administration of biologic and immunomodulator therapy is probably safe and these medications can be used to manage disease activity during pregnancy. Management of a flare during pregnancy is extremely important as the risk of preterm birth is increased in women with active disease. We know that disease severity is associated with worse pregnancy outcomes and therefore, aggressive therapy to control disease activity is recommended. Medications used to treat IBD in the non-pregnant patient have been shown to be safe during pregnancy and immunomodulators and anti-TNF medications should be prescribed if indicated. Medications that would be recommended in a non-pregnant patient should not be withheld from a pregnant patient if clinically indicated. A case-control study of pregnant IBD patients hospitalized with relapsing disease during pregnancy showed that women who had been hospitalized with a flare delivered three weeks earlier on average and had higher rates of preterm birth and lower birth weights [56]. However, there was no significant difference in APGAR scores of children born to mothers with and without flares, and no significant difference in the risk of complications [56].

In general, endoscopic evaluation during pregnancy is not favored by patients or practitioners. However, if necessary, esophagogastroduodenoscopy, sigmoidoscopy and colonoscopy are considered to be safe during pregnancy, and the recent ECCO statement recommends performing these procedures only when strongly indicated and preferably in the second trimester if possible [8]. Sigmoidoscopy without sedation can be helpful in evaluating a patient with an UC flare. Obstetricians and anesthesiologists should assist in management of the IBD pregnant patient undergoing an endoscopic procedure and presence of fetal heart sounds should be confirmed.
prior to and after completion of the procedure [8]. Small studies have shown that EGD and colonoscopy are safe during pregnancy and are not associated with pre-term labor [57-59].

There are little data on surgical outcomes during pregnancy, though case series of surgical intervention during pregnancy have been reported. In one study of three patients who underwent emergency colectomy within 2 days to 5 weeks postpartum, two of three infants died; one woman who had a colectomy twelve days antepartum also delivered a 1.4 kg newborn who survived [60]. All neonates were 33-40 weeks at the time of delivery. A second case series reported successful third trimester surgical intervention for fulminant colitis in two previously healthy women both diagnosed with IBD [61]. Both neonates survived although one was hospitalized for five weeks after birth for complications from respiratory distress syndrome.

Imaging as a tool for assessing disease severity during pregnancy should be considered. Both MRI and CT may be possible during pregnancy. MRI without intravenous (IV) contrast is preferred over CT in pregnant patients (American College of Radiology ACR Appropriateness Criteria: Crohn Disease, 2014). MRI should not be performed with IV contrast as gadolinium crosses the placenta and long-term effects of exposure are not known. In addition, contrast is not required for adequate imaging during pregnancy. A case series of ten MR enterographies (MRE) were performed on nine patients without IV gadolinium and image quality was satisfactory [62]. In seven patients, imaging features consistent with CD were identified and penetrating complications of CD were visualized in four patients [62].

Knowledge gaps:
There are very few studies regarding the safety and role of surgical intervention during pregnancy. However, with early effective medical therapy, there should be little need for surgical intervention for fulminant disease.

**What is the recommended mode of delivery?**

Data show that rates of Cesarean section (C-section) are increased among women with IBD. Specifically, women with UC have an almost two-fold risk of elective C-section and women with active CD also have higher rates of elective C-section [53]. While there may be certain instances, such as active perianal disease, in which a C-section is recommended, vaginal deliveries are not contra-indicated in CD or UC. In a cohort of over 2000 patients, there was no difference in IBD-related surgery, hospitalization or escalation of medical therapy among women who had vaginal deliveries versus C-section [63]. Recommendations by the European Crohn’s and Colitis Foundation include C-section for active perianal disease or active involvement of disease [8]. The statement also notes that presence of an ileoanal pouch or ileorectal anastomosis is a relative indication for a C-section but that decision regarding mode of delivery in these instances should be made on an individual basis [8]. While it is recommended to discuss mode of delivery on a case-by-case basis, there is wide variation both within and between groups of colorectal surgeons, gastroenterologists and obstetricians regarding vaginal delivery after IPAA [64].

Studies have shown no increased risk of development of a new perianal fistula after vaginal delivery compared to C-section among patients with CD [63], and thus vaginal delivery is not contra-indicated in CD. Women with UC have an almost double increased risk of elective C-
sections [53]. However, it has been recommended that mode of delivery be determined on an individual case basis as a history of UC or a history of IPAA does not exclude the possibility of a vaginal delivery. History of IPAA does not in itself warrant delivery via C-section. A study following women with UC before and after delivery showed an increase in occasional nighttime incontinence among women who had a vaginal delivery, but no other difference in pouch function among women who had vaginal deliveries compared to those who had C-sections [65]. Other studies have shown similar results lacking significant change in pouch function after vaginal delivery [66]. A study of 49 deliveries among women with IBD and pouches showed no adverse effects on pouch function after vaginal delivery and no correlation between short-term functional impairment or complications of the pouch and mode of delivery [67]. A small study of twenty pregnant women with IPAA showed a statistically significant increase in frequency of nocturnal bowel movements during pregnancy and in the first three month after delivery, but this increase did not differ based on mode of delivery [68]. Juhazs et. al. showed that among 43 women who became pregnant after undergoing IPAA, there was an increase in stool frequency, incontinence and pad use during pregnancy but that baseline pouch function was restored after pregnancy [69]. Pouch function was not compromised by vaginal delivery, multiple births, length of labor or birth weight and no permanent pouch function was observed among the women, who were followed for a mean of 2.4 years [69].

**Knowledge gaps:**

Larger studies and longer follow up are necessary to determine long-term effects of mode of delivery on patients with IBD, especially those who have had prior IBD-related surgeries. At this time, mode of delivery is recommended on a case-by-case basis, and delivery via C-section is
recommended in patients with active disease, in particular perianal disease. A discussion regarding C-section versus vaginal delivery can be had with the obstetrician and gastroenterologist in patients with an ileoanal pouch or anorectal anastomosis.

Summary: The majority of patients with Crohn’s disease and ulcerative colitis are diagnosed between the ages of 15 and 30, which coincides with the peak years of fertility and pregnancy. Patients have many questions regarding fertility and pregnancy, especially those with increased disease activity, those taking immunosuppressive medications and those with a history of surgery for inflammatory bowel disease. We know that surgery for IBD can decrease fertility, and it would be very helpful for patients contemplating surgery to know whether in vitro fertilization is an option after surgery. In addition, patients with increased disease activity and/or IBD surgery are often concerned about complications of a potential pregnancy. One of our most common questions from both male and female patients is whether the IBD medications they are taking are safe for conception and pregnancy. While there are an increasing number of studies on the impact of IBD medications on pregnancy, there are fewer studies on the impact of disease activity, IBD surgery and long-term follow-up of children born by women with IBD. In addition, our ability to measure disease activity during pregnancy is impaired, as we still do not have a reproducible and standardized measure of bowel inflammation during pregnancy in the clinic or in the lab. Prospective studies such as the PIANO study will help get us understand the affect of disease activity and immunosuppressive medications on pregnancy, birth and neonatal outcomes. However, studies on the effects of microbiome changes in pregnant IBD patients, the effects of combination immunomodulator + anti-TNF therapy versus monotherapy with anti-TNF, the course of disease activity post-partum, and, as mentioned above, assessing disease severity
during pregnancy, are needed. There are even more gaps of knowledge in the field of fertility. While we are beginning to understand the efficacy of IVF in patients with IBD and the effect of laparoscopic surgery on fertility, we still do not know the effect of disease activity and IBD medications on fertility, the rate of ectopic pregnancies and the rate of pregnancy loss. With the use of larger databases for pregnancy and fertility studies and large prospective studies in the near future, we will have meaningful information to enable our patients to make informed, evidence-based decisions.
<table>
<thead>
<tr>
<th>Method</th>
<th>Benefit</th>
<th>Potential Risk(s)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>-Gold standard for assessing disease activity in a patient with IBD</td>
<td>-Medications used for sedation -Procedure may be technically difficult in a woman with a gravid uterus</td>
<td>-Should preferentially be done in the 2nd trimester after discussion with GI, OB and anesthesia</td>
</tr>
<tr>
<td>Flexible Sigmoidoscopy</td>
<td>-Direct visualization and ability to take biopsies of the distal colon -May be done without sedation</td>
<td>-May not be beneficial in patients who do not have rectal, sigmoid colon or descending colon involvement</td>
<td></td>
</tr>
<tr>
<td>CT Enterography</td>
<td>-Ability to visualize inflammation of the small and large intestine</td>
<td>-Radiation risk to fetus</td>
<td></td>
</tr>
<tr>
<td>MR Enterography</td>
<td>-Satisfactory images to visualize radiographic changes consistent with Crohn’s flare</td>
<td>-IV contrast used for MRIs is contraindicated during pregnancy -Optimal imaging protocol includes administration of gadolinium</td>
<td>-MRI with gadolinium should not be performed during pregnancy due to risk of contrast to the fetus</td>
</tr>
<tr>
<td>Fecal Calprotectin</td>
<td>-May accurately reflect inflammation of the colon</td>
<td>-There is currently insufficient data regarding the use of fecal calprotectin during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Sedimentation Rate</td>
<td>-ESR is a nonspecific marker of inflammation and often increases with increase in disease severity</td>
<td>-ESR is affected by pregnancy alone and may not be an accurate reflection of disease activity</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>-CRP is a nonspecific marker of inflammation and often increases with worsening of disease</td>
<td>-CRP is affected by pregnancy and not only disease activity</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. The Safety of anti-TNF Medications During Pregnancy in Women with IBD

<table>
<thead>
<tr>
<th>Author</th>
<th>Anti-TNF</th>
<th>Publication Year</th>
<th>Number of pregnancies in exposed group</th>
<th>Number of pregnancies in control group</th>
<th>Control</th>
<th>Congenital Anomalies in anti-TNF group</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz et. al. [70]</td>
<td>IFX</td>
<td>2004</td>
<td>83</td>
<td>135</td>
<td>Pregnant CD women not on anti-TNF; Pregnant women in the general US population</td>
<td>Tetralogy of Fallot Intestinal malrotation</td>
<td>No increased risk in adverse pregnancy outcomes compared to controls</td>
</tr>
<tr>
<td>Mahadevan et. al. [71]</td>
<td>IFX</td>
<td>2005</td>
<td>10</td>
<td>n/a</td>
<td>None</td>
<td>None</td>
<td>3 pre-term, one low birth rate, no control group</td>
</tr>
<tr>
<td>Schnitzler et. al. [72]</td>
<td>IFX/ADA</td>
<td>2011</td>
<td>42</td>
<td>78</td>
<td>Pregnancies after IBD diagnosis but prior to anti-TNF treatment</td>
<td>1 trisomy 18</td>
<td>No increased risk in pregnancy or neonatal complications compared to controls</td>
</tr>
<tr>
<td>Zelnikova et. al. [73]</td>
<td>IFX</td>
<td>2011</td>
<td>4</td>
<td>n/a</td>
<td>None</td>
<td>1 polydactyly</td>
<td>None</td>
</tr>
<tr>
<td>Lichtenstein et. al. [74]</td>
<td>IFX</td>
<td>2011</td>
<td>142</td>
<td>75</td>
<td>Pregnant women with CD not on anti-TNF</td>
<td>Not reported</td>
<td>7.6% IFX, 14.7% controls, no specifics reported</td>
</tr>
<tr>
<td>Mahadevan et. al. [39]</td>
<td>IFX/ADA/CTZ</td>
<td>2012</td>
<td>458</td>
<td>356 (no AZA/6-MP/anti-TNF); 230 (+ ADA/6-MP/no anti-TNF)</td>
<td>Not increased from controls; No specifics reported</td>
<td>Cardiac malformation</td>
<td>Increased rates of preterm birth, NICU stay, low birth rates for UC women on combination AZA/6-MP + anti-TNF</td>
</tr>
<tr>
<td>Arguelles-Arias et. al. [75]</td>
<td>IFX</td>
<td>2012</td>
<td>12</td>
<td>n/a</td>
<td>None</td>
<td>None</td>
<td>No increased complications</td>
</tr>
<tr>
<td>Casanova et. al. [48]</td>
<td>IFX/ADA/CTZ</td>
<td>2013</td>
<td>66</td>
<td>318</td>
<td>Pregnant women with IBD not on thiopurines or anti-TNF</td>
<td>Cardiac malformation</td>
<td>No increased risk in pregnancy or neonatal complications compared to controls</td>
</tr>
<tr>
<td>Zelnikova et. al. [44]</td>
<td>IFX/ADA</td>
<td>2013</td>
<td>31</td>
<td>n/a</td>
<td>None</td>
<td>1 polydactyly</td>
<td>3 miscarriages</td>
</tr>
<tr>
<td>Mahadevan et. al. [45]</td>
<td>IFX/ADA/CTZ</td>
<td>2013</td>
<td>31</td>
<td>n/a</td>
<td>None</td>
<td>None</td>
<td>No serious complications</td>
</tr>
<tr>
<td>Bortlick et. al. [43]</td>
<td>IFX/ADA</td>
<td>2013</td>
<td>41</td>
<td>n/a</td>
<td>None</td>
<td>1 hip dysplasia</td>
<td>No serious complications</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Treatment</td>
<td>Year</td>
<td>N</td>
<td>Patients Characteristics</td>
<td>Outcomes</td>
<td>Remarks</td>
<td></td>
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<td>---------------------</td>
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</tr>
<tr>
<td>Seiráfi et. al.</td>
<td>IFX/ADA/CTZ</td>
<td>2014</td>
<td>133</td>
<td>99 Pregnant women with IBD not on anti-TNF</td>
<td>1 missing finger</td>
<td>No increased risk in pregnancy or neonatal complications compared to controls</td>
<td></td>
</tr>
<tr>
<td>Diav-Citrin et. al.</td>
<td>IFX/ADA/Etanercept</td>
<td>2014</td>
<td>83</td>
<td>86 +disease-matched and no anti-TNF. No autoimmune and no anti-TNF</td>
<td>1 VSD; 1 unilateral renal agenesis; 1 Kaposiform hemangioendothelioma; Kasabach-Merritt syndrome; bilateral hydronephrosis</td>
<td>No increased risk in pregnancy or neonatal complications compared to controls</td>
<td></td>
</tr>
<tr>
<td>Weber-Schoendorf et. al.</td>
<td>IFX/ADA/CTZ/Golumumab/Etanercept</td>
<td>2015</td>
<td>495</td>
<td>1532 Non anti-TNF-exposed pregnant women in the general population</td>
<td>12.3% major + minor anomalies versus control group; 6.2% controls (OR 1.64 (1.1, 2.6))</td>
<td>Increased preterm births, lower birth weight in anti-TNF group versus controls</td>
<td></td>
</tr>
<tr>
<td>de Lima et. al.</td>
<td>IFX/ADA</td>
<td>2015</td>
<td>106</td>
<td>804 No anti-TNF; No autoimmune disease</td>
<td>Cleft palate; VSD; Polydactyly</td>
<td>Lower birth weight, more C-section, shorter gestational term than controls</td>
<td></td>
</tr>
</tbody>
</table>
References


