Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing and remitting disease that includes ulcerative colitis (UC) and Crohn’s disease (CD). It affects the population in a bimodal distribution with the higher peak in the younger population. Approximately fifty percent of patients are less than 35 years of age at the time of diagnosis and twenty five percent conceive for the first time after their diagnosis of inflammatory bowel disease [1]. As medical therapy for IBD advances, more patients are in a position to consider pregnancy. Because ethical considerations generally preclude conducting randomized controlled trials in pregnant patients, the majority of the available information has been gathered from retrospective studies. Most of the drugs used to treat IBD are safe to use during pregnancy. Traces of drugs have been reported in breast milk in women on drug therapy, but no major fetal or neonatal complications have been reported. With the increasing early use of immunosuppressant and biological therapy to treat active IBD, more studies are focusing on these issues. A multidisciplinary team that considers the individual patient wishes and concerns, and that manages them accordingly should care for inflammatory bowel disease patients who are contemplating conception or who are already pregnant. The aim of this review article is to summarize the current literature on fertility, pregnancy and IBD management during and after gestation.

Fertility

Studies in male and female IBD patients have not demonstrated great differences in fertility when compared with the general population with the exception of notable sub-groups. Community-based and population-based studies suggest infertility rates in women with CD (5%–14%) similar to the general population [2]. Women with CD may have slightly decreased fertility when having active disease and after surgery [3]. This may partly be explained by the formation of adhesions resulting in tubal infertility. Women with UC who have undergone restorative proctocolectomy (RPC) with ileal pouch anal anastomosis (IPAA) also appear to have reduced fertility. A recent systematic review [4] showed that RPC for UC results in decreased fertility 40% of females have slightly decreased fertility when having active disease and after surgery [5]. This meta-analysis found no significant increase in small for gestational age or stillbirths in either UC or CD patients. In a prospective, case-control, European multicenter study [9] of 332 pregnant women with IBD, women with Crohn’s disease or ulcerative colitis had similar pregnancy outcomes (abortions, preterm deliveries, cesarean sections, congenital abnormalities, and birth weight) compared with non-IBD controls. The favorable outcomes may be attributed to the fact that 86 to 88 percent of patients in this study had quiescent disease at conception/first trimester. A Danish cohort study [10] in which the risk of preterm birth was increased when birth occurred after the mother’s first hospitalization (OR 1.4), particularly when the first hospitalization for ulcerative colitis took place during pregnancy (OR 3.4) indirectly suggests that the degree of disease activity accounts in part for the differences among studies. However, in the Kaiser population, [11] disease activity was not predictive of an adverse outcome in any category. The Northern California Kaiser population compared women with IBD (n=461) matched to controls (n=495) by age and hospital of delivery. Even when limited to the presence of moderate to severe disease activity, there was still no association with an adverse outcome. Most patients with both UC and CD, however, did have inactive or mild disease throughout pregnancy. Women with IBD were more likely to have a spontaneous abortion, OR=1.65 (95% CI=1.09-2.48); an adverse pregnancy outcome (stillbirth, preterm birth, or small for gestational age (SGA) infant), OR=1.54 (95% CI=1.00-2.38); or a complication of labor, OR=1.78 (95% CI=1.13-2.81). Independent predictors of an adverse outcome included a diagnosis of IBD, a history of surgery for IBD, and non-White ethnicity. Severity of disease and medical treatments were not associated with an adverse outcome suggesting that even women in remission with IBD were more likely to have complications of pregnancy than their general population counterparts.

A retrospective study [12] evaluated patient’s perceptions regarding the interaction between pregnancy and IBD management. Most female patients (84%) reported (unwarranted) concerns about the effect of IBD medications on pregnancy, free text responses indicating that this was of greater concern than any effect of IBD exacerbation. Many patients are concerned that IBD medications would harm their pregnancy, as reflected by medication taking behavior (stopping or decreasing medication). They and their partners should be educated about the possibility of disease exacerbation during pregnancy if treatment is stopped.

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Effect of Pregnancy on Inflammatory Bowel Disease

In general, women with IBD are as likely to flare during pregnancy, as they are to flare when not pregnant. The course of the ulcerative colitis during pregnancy appears to be determined in part by the activity of the disease at conception. Patients in remission at the time of conception are likely to remain in remission during pregnancy. Nielsen et al. [13] reported an exacerbation rate of 34% per year during pregnancy and 32% per year when not pregnant in women with UC. Pregnant women with CD also had similar rates of disease exacerbation [14]. In the Kaiser population, [11] most patients had inactive disease throughout their pregnancy with no sudden increase in the postpartum. When flares do occur, the data is unreliable in relation to the stage of pregnancy. It was initially believed that an increase of disease flare occurred in both the first trimester and post-partum, but timing of a flare appears to more related to disease activity at conception and at term [15]. Therefore it is recommended that women with IBD should be told to avoid conceiving during an acute phase of the disease. If the colitis recurs, it is likely to be mild and responsive to medical treatment.

Disease activity may even be slightly lower during pregnancy [15]. An interesting study by Kane et al. [16] has recently shown that improvement of IBD symptoms during pregnancy is associated with disparity in HLA class II antigens between mother and fetus. The authors studied 50 pregnancies in 38 women; 42 (84%) were disparate at the DRB1 locus, 34 (68%) at the DQ locus, and 31 (62%) at both loci. A significant difference was found in IBD activity between women mismatched at both loci versus only 1 or neither locus (OR=8.4 [1.5-14], p = 0.01). Logistic regression identified prepartum disease activity and disparity at both DRB1 and DQ as significant predictors of overall disease activity during pregnancy.

Evaluation During Pregnancy

Endoscopy

Indications for endoscopy during pregnancy include significant or continued gastrointestinal bleeding, dysphagia, severe or refractory nausea and vomiting or abdominal pain, and a strong suspicion of a colonic mass. Sigmodoscopy can be performed safely in pregnancy. Its use has not been associated with preterm labor or congenital malformations [17]. In most patients; this sole invasive investigation may suffice. The least extensive procedure possible should be employed. Colonoscopy should only be performed in carefully selected patients because of the need for sedation. It is best delayed until after delivery. Fetal monitoring is indicated in high-risk and third trimester pregnancies. Midazolam is recommended over diazepam for sedation (potential association between diazepam and oral clefts) [18]. Both are pregnancy category B drugs by the FDA. The aim should be to achieve calmness and relaxation but not somnolence. Another sedative for pregnancies. Midazolam is recommended over diazepam for sedation because of the need for sedation. It is best delayed until after delivery. Fetal monitoring is indicated in high-risk and third trimester pregnancies. Midazolam is recommended over diazepam for sedation (potential association between diazepam and oral clefts) [18]. Both are pregnancy category B drugs by the FDA. The aim should be to achieve calmness and relaxation but not somnolence. Another sedative for endoscopic procedures is propofol. It is a pregnancy category B drug. Propofol should preferably be avoided in the first trimester because of lack of data regarding its use during this period.

Radiological investigations

Radiological studies may be needed to rule out obstruction, perforation or toxic megacolon. It is preferred to use tests such as plain abdominal films or ultrasound as they use less radiation than CT or barium studies, and ultrasound can be used to assess for abscesses or bowel wall thickness. MRI is also safe, and can be used to diagnose terminal ileal CD during pregnancy [19].

<table>
<thead>
<tr>
<th>FDA Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Controlled studies in animals and women have shown no risk in the first trimester, and possible fetal harm remote.</td>
</tr>
<tr>
<td>B</td>
<td>Either animal studies have not demonstrated a fetal risk or there are no controlled studies in pregnant women, or animal studies have shown adverse effects but not confirmed in controlled studies in women in the first trimester.</td>
</tr>
<tr>
<td>C</td>
<td>No controlled studies in humans have been performed, and studies in animals have shown adverse effects, or studies in humans and animals are not available. Given the potential benefit of the weight of the mother, but the benefit may outweigh the risk of a fetal abnormality.</td>
</tr>
<tr>
<td>D</td>
<td>Positive evidence of fetal risk is available, but the potential benefit of the weight of the mother may outweigh the risk of a fetal abnormality.</td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or humans show fetal abnormalities; drug contraindicated</td>
</tr>
</tbody>
</table>

*Data from Food and Drug Administration. Regulations 1980; 44:37, 434-437, 467

Table 1: Food and drug administration categories for the use of medications in pregnancy

Treatment of Inflammatory Bowel Disease in Pregnancy

Most of the medications used to treat IBD are safe during gestation, except for Methotrexate and Thalidomide. The US FDA classification of drugs should be used to guide the use of medications during pregnancy. The FDA categories are listed in (Table 1). In general, pharmacological treatment for active disease during pregnancy is the same as for non-pregnant women (Table 2).

Aminosalicylates

All aminosalicylates (sulfasalazine, mesalamine, balsalazide) are pregnancy category B except olsalazine, which is pregnancy category C. Sulfasalazine is composed of 5-aminosalicylic acid azo-bonded to sulfapyridine. Given the concern over potential antifolate effects of the drug, it is recommended that women take folic acid 2 mg daily in the prenatal period and throughout pregnancy [19].

The safety of 5-ASA compounds during pregnancy has been demonstrated in a number of trials. A meta-analysis, including seven studies, suggested no association among 5-ASA drugs (mesalamine, olsalazine and sulfasalazine) and congenital abnormalities, stillbirths, spontaneous abortions, preterm deliveries and low birth weight [20].

Corticosteroids

Corticosteroids are pregnancy category C drugs. They are used to induce remission in CD and UC patients. The balance of risks in mothers with active IBD unresponsive to other treatments would favor treatment with steroids [19]. Corticosteroids are not effective in maintenance therapy and are associated with side effects in almost 100% of patients who use them long term. A meta-analysis showed a summary OR for case-control studies examining the risk of oral clefts (3.35 [95% CI, 1.97-5.69]) [21]. However, several large studies found no statistically increased rate of oral clefts and other congenital abnormalities, especially for exposure to corticosteroids during the first trimester, and a number of successful pregnancies have been reported among women exposed to these drugs during gestation [22]. Prolonged use of steroids has been associated with maternal adverse effects including hypertension, glucose intolerance, opportunistic infections and ocular and bone side effects.

Immunomodulators

Azathioprine and mercaptopurine: AZA/MP is classified as Pregnancy Category D drugs. The largest evidence on safety comes from transplantation studies where rates of anomalies ranged from 0.0% to 11.8% and no evidence of recurrent patterns of congenital anomalies emerged [23]. In IBD, multiple case series have not noted
an increase in congenital anomalies. The fetus lacks the enzyme inosinate phosphorylase that is necessary to convert AZA and MP to active metabolites, and therefore is protected from potential teratogenic effects of AZA and MP [24]. In a prospective, controlled, multicenter study Goldstein et al found no increase in congenital malformation, but there was more prematurity (21% vs. 5%, P < 0.001) and low birth weight (23% vs. 6%, P < 0.001) in the AZA treated women [25]. This most likely reflects their underlying disease state, which was not controlled for. A recent meta-analysis [26] of 8 studies showed that thiopurine exposure in women with IBD was not associated with LBW but there was more prematurity (21% vs. 5%, P < 0.001) and low birth weight (23% vs. 6%, P < 0.001) in the AZA treated women [25].

Based on the large experience in transplantation patients, AZA/MP are often continued during pregnancy. Furthermore, in IBD multiple studies have not demonstrated an increase in congenital anomalies. Thus, although thiopurines have FDA rating D, available data suggest that these drugs are safe and well tolerated during pregnancy. Therefore, in general, if a patient is established and well on AZA/MP and it is felt to be essential to continue this drug to retain remission (which will be the case in most patients), after full discussion with the patient and her partner it is reasonable to decide to continue treatment during pregnancy [27].

**Methotrexate:** Methotrexate is FDA category X, as it is clearly teratogenic, and therefore should not be used in women considering conception. Methotrexate is a folic acid antagonist and use during the critical period of organogenesis (6 to 8 weeks postconception) is associated with multiple congenital anomalies; craniofacial deformities, limb defects and severe central nervous system abnormalities [18,19]. Exposure in the second and third trimesters may be associated with fetal toxicity and mortality. It is imperative that women receiving methotrexate therapy for IBD be counseled on the importance of effective birth control. Methotrexate may persist in tissues for long periods and it is suggested that patients wait at least 3-6 months from discontinuation of the drug prior to attempting conception [19].

**Ciclosporin:** Ciclosporin (CsA) is FDA category C. Most available data regarding the use of CsA in pregnancy originates from transplant and rheumatology literature. A meta-analysis [28] of 15 studies of pregnancy in 410 transplant patients receiving CsA reported that the incidence of congenital malformations was 4.1%, which was similar to the general population. Pregnant transplant patients who are clinically stable on CsA have good pregnancy and fetal outcome. A recent series of eight patients with acute severe ulcerative colitis did not identify any congenital malformations [29].

### Biologic Therapy

Infliximab (IFX) is FDA category B. IFX is a chimeric monoclonal immunoglobulin G1 (IgG1) anti-TNF antibody, which does not cross the placenta in the first trimester, but very efficiently crosses in the second and third trimester. Although this protects the infant from exposure during the crucial period of organogenesis, IFX levels cross efficiently in the third trimester and are present in the infant for several months from birth. In the first large series of IFX use in 96 women with RA and CD, Katz et al. [30] queried the infliximab safety database and found that results of pregnancy outcomes in women exposed directly to IFX were similar to the general US population in terms of live births, miscarriages and therapeutic termination. Mahadevan et al. [31] studied a series of 10 CD patients who intentionally received IFX during pregnancy, the study showed good outcomes, with no congenital malformations, intrauterine growth retardation or small for gestational age infants. However, three infants were premature, and one had low birth weight. The TREAT Registry is a prospective registry of patients with CD. Of the 5807 patients enrolled, 66 pregnancies were reported, 36 of them with prior IFX exposure. The rates of spontaneous abortions and perinatal complications were not significantly different from women with CD not treated with IFX [32]. Of some concern is a 2009 analysis of the FDA database [33] documenting an increase in congenital abnormalities from the VACTERL spectrum in women taking IFX or etanercept.

Adalimumab (ADA) is, like infliximab, pregnancy category B. Limited human data about adalimumab use in pregnancy are available in literature but case reports of normal pregnancy outcome have been described. A recent observational study [34] assessed pregnancy outcomes in 212 women with IBD treated with anti-TNF treatments-42 pregnancies in women who received anti-TNF (35 IFX, 7 ADA), 23 pregnancies prior to IBD diagnosis, 78 pregnancies before start of IFX, 53 pregnancies with indirect exposure to IFX and 56 matched

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**Table 2:** Medications used in the treatment of inflammatory bowel disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Category</th>
<th>Recommendations for Pregnancy</th>
<th>Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>B</td>
<td>Limited human data: low risk if likely to cross placenta</td>
<td>No human data: probably compatible</td>
</tr>
<tr>
<td>Azathioprine/6-mercaptopurine</td>
<td>D</td>
<td>Data in IBD, transplant literature suggests some risk, but low</td>
<td>Limited transfer. Likely compatible</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>B</td>
<td>Low risk</td>
<td>No human data: potential diarrhea</td>
</tr>
<tr>
<td>Budesonide</td>
<td>C</td>
<td>Data withinhaled drug: low risk. Limited human data for oral drug</td>
<td>No human data</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>B</td>
<td>Limited human data: low risk. Limited transfer across placenta</td>
<td>No evidence of transfer. Likely compatible</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>C</td>
<td>Low risk: possible malformities of cleft palate, adrenal insufficiency, premature rupture of membranes</td>
<td>Compatible</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>C</td>
<td>Low risk</td>
<td>Limited human data: potential toxicity</td>
</tr>
<tr>
<td>Infliximab</td>
<td>B</td>
<td>Low risk: limited human data: crosses placenta and detectable in infant at birth</td>
<td>No evidence of transfer. Likely compatible</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>B</td>
<td>Low risk</td>
<td>Limited human data: potential diarrhea</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>X</td>
<td>Contraindicated: teratogenic</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>C</td>
<td>Low risk</td>
<td>Limited human data: potential diarrhea</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>B</td>
<td>Low risk. Give folate 2 mg daily</td>
<td>Limited human data: potential diarrhea</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>C</td>
<td>Low risk</td>
<td>Limited human data: potential toxicity</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>X</td>
<td>Contraindicated: teratogenic</td>
<td>No human data: potential toxicity</td>
</tr>
</tbody>
</table>

**Abbreviations:** FDA, Food and Drug Administration; IBD, inflammatory bowel disease.

*X-Low risk is defined as ‘the human pregnancy data do not suggest a significant risk of embryo or fetal harm.’ [18]*
pregnancies in healthy women. They found that pregnancy outcomes after exposure to anti-TNF treatments were no different than before anti-TNF treatment, but were worse than before IBD diagnosis. Certolizumab differs from IFX and adalimumab in that it is a Fab fragment of an anti-TNF-a monoclonal antibody rather than a whole human IgG1 antibody. As certolizumab is a relatively new agent, there are no published data regarding its use in pregnancy. Oussalah et al. [35] reported the case of a 22-year-old woman with a 4-year history of colonic CD who was successfully treated with certolizumab during the first and third trimesters, and she delivered a normal infant [35].

British Society Guidelines suggest that physicians should exercise caution when considering elective use of anti-TNF therapy in pregnant patients with IBD until further data become available. Conception should be discussed with women of childbearing age at the start of anti-TNF therapy. If treated patients present having become pregnant the treatment should be stopped after the second trimester [20]. Caution should be taken when considering vaccination for the infants who were exposed to IFX.

Delivery

Pregnant women with IBD may be up to 1.5–2 times more likely to undergo a caesarean section [6]. This may be an attempt to avoid risk of anal sphincter damage or to avoid the risk of development or worsening of perianal CD. Indications for caesarean section are active perianal disease and the presence of an ileoanal pouch, but there is no absolute contraindication to vaginal delivery in pregnant patients with inactive IBD. The patient, obstetrician, and surgeon should discuss the theoretical risk to long-term pouch function before making a decision on mode of delivery.

Breast Feeding

Breastfeeding while on aminosalicylates has been rarely associated with diarrhea in the infant [36]. Only a small amount of 5-ASA is excreted in breast milk. Sulphasalazine and sulphasalazine bind albumin and can displace bilirubin, but no increased risk of kernicterus in the full-term newborn has been shown with the doses used in IBD treatment.

The manufacturers of AZA/MP do not recommend breastfeeding. Traditionally, women receiving azathioprine have been discouraged from breast-feeding because of theoretical potential risks of neonatal bone marrow suppression, susceptibility to infection, and pancreatitis [18]. A case series [37] of 4 mothers who remained on AZA throughout lactation in which the mother's breast milk was analyzed and found undetectable levels of mercaptopurine in all samples. They also noted no adverse events in the infants, and therefore concluded that azathioprine likely poses no threat to the suckling infant. In another study [38] investigators measured the concentration of mercaptopurine in breast milk of 10 mothers receiving AZA and in the blood of their babies, and any immunosuppressive effects on the babies. Very low concentrations of mercaptopurine (compared with therapeutic immunosuppressant level achieved in serum) were detected in 2 breast milk samples obtained from 1 woman, while mercaptopurine was not detected in any of the other 29 samples. Mercaptopurine and 6-thioguanine nucleotides were undetectable in the neonatal blood. Furthermore, there were no clinical or hematological signs of immunosuppression in any of the 10 neonates. Based on the studies it seems that these drugs may be safe during breast-feeding.

Methotrexate is excreted in breast milk and may accumulate in neonatal tissues. Therefore, it is contraindicated in breast-feeding. Tacrolimus enters the breast milk and it is unknown what effects it might have on a suckling infant, thus it is currently not indicated during breast-feeding [18].

With respect to biologic therapies during breast-feeding, the implications are unknown and it has been recommended that it is probably best avoided while receiving IFX. However, theoretically, breast-feeding should be safe, as large protein molecules such as IFX are broken down or inactivated by digestive enzymes in the gastrointestinal tract [39]. Case reports of women who breastfed while on infliximab do not suggest adverse effects, [31] therefore the use of this drug is probably compatible with breast-feeding.

Summary

Management of a pregnant woman with IBD should include the family physician, the gastroenterologist and the obstetrician. Most women with IBD who are in remission will be able to conceive and have a normal pregnancy. Pregnancy should not be discouraged in women with IBD, because outcomes are generally good and maternal disease is not exacerbated by pregnancy. Because the risk of pregnancy-related complications and the disease behavior during pregnancy depends mainly on disease activity at the time of conception, before planning a pregnancy contraception advice seem reasonable and every medical effort useful to obtain clinical remission. If conception involuntary occurs in an active phase of disease, aggressive therapeutic strategy is justified.

Most drugs used to treat IBD are safe to use in pregnancy and breast-feeding. The risk of an adverse fetal event must be weighed against the benefit to the health of the mother from continuing her medication and controlling her underlying disease. The biological agents do cross the placenta, mainly in the third trimester, and should be held after 30 weeks of gestation and restarted after delivery. Pregnant IBD patients should be encouraged to continue their medications during the pregnancy and while breast-feeding, with the understanding of the current evidence of the risks and benefits of doing so. Breastfeeding should not be discouraged in IBD patients, except for women on immunosuppressive therapy.

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