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Review Article

Inflammatory Bowel Disease and its Impact on Fertility and Pregnancy

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ABSTRACT

The peak age of onset of inflammatory bowel disease (IBD) is simultaneous with the peak reproductive years. Patients have many concerns about the impact of IBD on fertility and pregnancy outcomes. The most important reason for voluntary childlessness is the fear of side effects from medications for IBD. Decision making for medical therapy is a complex equation. It is important to summarize available information about the management of IBD during pregnancy and its interactions.

Among IBD patients, those undergoing surgery are at risk for reductions in fertility. Patients with ileal pouches–anal anastomosis (IPAA) experience higher rates of infertility. Disease activity at the time of conception is the main determinant of the impact of IBD on adverse pregnancy outcomes. In different nations, disease activity and relapse depend on many factors and may even be slightly lower during pregnancy. The recommended mode of delivery in IBD is still controversial. However, there is an increased rate of cesarean sections in women with IBD. Choosing the appropriate method of delivery should be based on the obstetrician's opinion, however active perianal disease and the presence of an ileoanal pouch are two major exceptions. If women remain on their maintenance therapy, there would be no increased risk of a flare-up during the postpartum period. In most patients, maintaining remission with medication outweighs the risks of their adverse effects. However, the pros and cons must be discussed with the patient and decisions should be made on an individual basis. Among all drugs used in IBD treatment, only methotrexate (MTX) and thalidomide are contraindicated in pregnancy.

Keywords: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Pregnancy; Fertility

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases that have an increasing incidence and prevalence. The etiology of inflammatory bowel disease (IBD) is precisely unknown, but there are complex interactions of genetic, immunological, and environmental factors (1). IBD is characterized by a peak age of onset during the peak reproductive years (2). Approximately 55% of patients are less than 35 years of age at the time of diagnosis. Of these, 25% will conceive for the first time following diagnosis (3). Parenthood is one of the

most important events in an individual's life. Thus, these patients and their partners have many concerns about the impact of IBD on fertility, pregnancy outcomes, and the developing child (4,5).

Previously, female IBD patients were prompted to avoid pregnancy (6). A recent study has revealed that concerns about the adverse reproductive outcome are the main reason IBD patients refrain from pregnancy (7). Medical advice given by physicians, the fear of medication side effects and its impact on the child are the most important reasons for voluntary childlessness (8).

Many published studies have investigated the correlation between IBD, pregnancy outcome, and fetal safety, with debatable results (2-5). While some, mainly older retrospective studies, have suggested no significant impact of IBD on pregnancy outcome, (9,10) others have found IBD to be associated with an increased risk of preterm delivery and low birth weight (LBW) in women with either CD or UC (11,12). A recent large community-based study has reported disease activity to be related to an increased risk of preterm birth rate in female CD patients (5). In another study, women with UC have increased rates of congenital abnormalities (13). Active CD, especially at the time of conception, has been reported to be associated with a higher risk of premature delivery, often combined with LBW, spontaneous abortion, stillbirth, and neonatal defects (2).

Medical therapy during pregnancy in IBD is complex. Decision making, considering the protectiveness of parents towards their children, the gastroenterologist's desire to keep the mother healthy, and obstetrician's goal of avoiding adverse events during pregnancy, is challenging (14). Additionally, counseling these women on fertility, conception, medication safety, pregnancy, delivery, and breastfeeding has been hampered by the paucity of detailed population-based data (6). Fortunately, nowadays successful pregnancy outcomes are attainable for women (15). Decision making regarding the management of pregnant IBD patients requires a comprehensive review of available data and careful clinical judgment, such that the clinician shall be familiar with current information (16).This review summarizes available information about the management of IBD during pregnancy and their interactions. Also covered are the points on the impact of IBD on fertility in both sexes, indicating that the average patient with IBD has a good chance to have a healthy baby.

FERTILITY

Female fecundability

Currently, the current infertility rate in the general population has been estimated to be approximately 10%, including 11.8% of women ages 15 to 44 years (15). Women with IBD have similar fertility rates as the general population (14). Naganuma et al. (4) have indicated that the history of treatment for infertility was more common in CD patients (20.2%) than UC patients (9.0%) after disease onset. Active CD disease reduces fertility by various mechanisms such as abdominal adhesions and inflammation in the ovaries and ovarian tubes (17,18). Patients undergoing surgery experience the risk of impaired tubal function, which results in fecundity reduction (17). Conclusively, fertility in non-penetrating type CD patients could be higher than penetrating type as pelvic dissections, adhesions and potential scarring are reduced in non-stricturing or penetrating CD patients(4). Besides, infertility is increased in those who have ileal pouches–anal anastomosis (IPAA). A systematic review based on seven studies (945 patients) has reported an infertility rate of 12% before proctocolectomy and 26% after restorative proctocolectomy (19). This represents a significant reduction in the ability to conceive after IPAA, which is thought to be the result of pelvic dissection while creating the pouch, which leads to adhesions and tubal obstruction (14). Age is the only pre-operative independent risk factor affecting IBD fertility. Voluntary childlessness in IBD women is probably more highlighted than in the general population, due to a case-control study of 216 patients which has revealed that the decrease in the mean number of children born to IBD women was according to their choice, not their inability to conceive. In 2002, Ording Olsen and colleagues (20) found that women's fecundability ratios, before and after the diagnosis of UC (5:1.01), were equal to that of the general population (5:1.01), but after IPAA the the ratio decreased to 0.20 ($p<0.001$). A meta-analysis has demonstrated a three-fold increased risk for infertility in patients that have an IPAA, with infertility increasing from 15% to 48% in women post-IPAA (15).

Male fecundability

The true rate of male IBD infertility is unknown and is difficult to measure. In a study of 106 CD men, 62 UC men, and 140 controls, a similar fecundability between IBD patients and controls was noted, which suggested that the high rate of infertility in CD men

was voluntary (21). There are no definitive studies, but the consensus is that IBD does not affect male fertility. In those men who have undergone an IPAA, there has been a small incidence of retrograde ejaculation and erectile dysfunction but overall IPAA may preserve or improve sexual function outcome (22).

Men on sulfasalazine have reversible impairment of sperm motility and sperm counts in up to 60% of patients (15). A small, single-center survey suggests that sperm motility and oval forms are decreased by infliximab (INF) therapy, but this has yet to be translated into a clinical decrease in male fertility rates on INF (23).

In conclusion, the risk of infertility and sexual dysfunction should be discussed individually with the patient before surgery, as part of the potential risks of the operation. It is unclear whether techniques (laparoscopic IPAA or a subtotal colectomy with rectal stump and ileostomy) during the childbearing years are beneficial in reducing rates of infertility and sexual dysfunction. Cervical dysplasia has been found to be increased among female IBD patients, particularly in those who use immuno-suppressants or infliximab. Thus, regardless of medication status it is recommended that women with IBD have annual papanicolau smears and young women should receive the human papilloma virus vaccine (24).

Effect of IBD on pregnancy

Disease activity at the time of conception is mostly agreed to adversely influence IBD pregnancy outcomes. In previous surveys, it has been suggested that quiescent disease during pregnancy leads to similar risks compared to the general population with regards to spontaneous abortion, pregnancy-related complications, and adverse perinatal outcomes (15). Disease activity at conception has been reported to be associated with a higher rate of fetal loss, preterm birth, and LBW (25,26). Ileal CD and prior bowel resection are other potential predictors of adverse outcomes (24). Active disease during pregnancy has been shown the greatest risk of adverse perinatal outcomes. This risk seems to be higher in CD than UC. Reddy and colleagues (27) have found a higher risk of preterm births among their study group, with the mean gestational age of 35 weeks versus 38.7 weeks in the control group (without disease relapse). In a cohort study that consisted of 54 pregnant CD patients, those with active disease at conception had 35% higher rates of miscarriage than those in remission (15). Khosla et al. (3) have conducted a cohort of 54 pregnant CD patients and demonstrated that those with active disease at the time of conception had rates of miscarriage up to 35% higher when compared with patients in remission (3). In a study by Dominitz and colleagues, (11) a greater risk of congenital abnormalities was seen in UC women when compared with controls (7.9% vs 1.7%, $p<0.001$). The largest study, a meta-analysis by Cornish and colleagues, (13) has evaluated 12 studies concerning the impact of IBD on pregnancy. This study comprised 3907 patients with IBD and 320,531 controls. Based on this analysis, female IBDs were more likely to have adverse pregnancy outcomes, such as premature birth and LBW. The risk of premature delivery was almost twice when compared with the general population. Women with IBD were also 1.5 times more likely to undergo cesarean section.

Mahadevan and colleagues (28), in the largest US study to date, compared pregnancy outcomes between 461 pregnant IBD patients and those unaffected. They found IBD patients had more adverse pregnancy complications (stillbirth, preterm birth, or small for gestational age) with an odds ratio of 1.54 (95% CI 1.00-2.38), spontaneous abortion (OR: 1.65, 95%CI: 1.09-2.48), or labor complication (OR: 1.78, 95%CI: 1.13-2.81) compared to those without IBD. There were no differences in congenital abnormalities or adverse newborn outcomes. IBD medications were not predictive of adverse outcome. There was no statistically significant difference found in newborn outcomes between the IBD and control pregnancies. In addition, medical treatment and severity of disease were not associated with adverse outcomes (15).

However, in the Kaiser population, (28) IBD activity was not shown to be predictive of any adverse outcomes. Similarly, a population-based study from Denmark (29) reported the same results. Overall, these two population-based studies have suggested that IBD patients have higher rates of adverse pregnancy outcomes regardless of disease activity, (24) thus the debate remains.

Effect of pregnancy on IBD

In many nations, disease activity and relapse depend on many factors and may even be slightly lower during pregnancy (24,30). One study has found that the rate of relapse may decrease in the three years following pregnancy(31). Similarly, a ten-year study of a European cohort follow up of patients (580 pregnancies) was performed (24). In 2008, Dubinsky et al. (15,24) demonstrated that women with IBD

were as likely to have a flare-up during pregnancy, as when not pregnant (15,24). Exacerbation rates of 34% per year in pregnant UC women and 32% per year in non-pregnant UC women were reported by Nielsen and colleagues (9). Pregnant women with CD also had similar rates of disease exacerbation (10). In addition, the Kaiser cohort as discussed previously, included women with inactive disease throughout their pregnancy with no sudden increase in activity postpartum (24).

When conception occurs during a quiescent state, 70%-80% of UC patients will remain in remission, (32) thus the rate of relapse remains similar to non-pregnant UC patients. Nowadays, it is believed that the timing of a flare-up appears to be more related to disease activity at conception and at term. Furthermore, disease flare-up during the first trimester is often due to discontinuation of medical therapy and post-partum flare-up is related to resumption of smoking after delivery (33). Active disease at conception can be associated with worse prognosis. In a cohort of UC patients, Willoughby et al.(34) have noted that active disease during these times was more resistant to treatment. Patients who have undergone an ileoanal anastomosis procedure present a unique situation. In 38 UC women with IPAA that had 67 pregnancies, pregnancy was found to be safe with some alterations in pouch function, exclusively during the third trimester (35). For most women, pouch function ultimately returned to its prepregnancy state. There was a minority of women who suffered from long-term disturbances in pouch function. This long-term effect was not related to the method of delivery (15).

CD during pregnancy is similar to patients with UC. In patients with UC, good outcome is guaranteed by the disease status at the time of conception and delivery. As with quiescent CD, 70% of pregnant CD patients will maintain remission compared to non-pregnant CD patients (3). When disease is active at the time of conception, the rule of thirds is followed by the authors. One-third of the women get better, one-third remain the same and the remainder worsen. Several studies have suggested that immune disparity in HLA class II antigens between the fetus and mother may play a role in immune regulation, thereby altering immune function and pathology, but its biologic mechanism has yet to be fully explained (15).

Delivery

The suggested delivery mode in CD patients is still debatable. Cesarean sections in women with IBD hold an increased risk ratio (36). In comparison with the general population, CD patients undergo cesarean sections more frequently, with the rate of cesarean sections increasing after the first delivery. By taking the 2005 Nationwide Inpatient Sample, Nguyen and colleagues (37) have investigated 1368 UC and 2372 CD deliveries. This population-based study indicated that the adjusted ORs of cesarean sections were higher in CD (adjusted OR 1.72) and UC women (adjusted OR 1.29) than in non-IBD controls.

Generally, the decision to have a cesarean section should be made on purely obstetric grounds. The two exceptions are active perianal disease and the presence of an ileoanal pouch. However, if a patient has inactive perianal disease or no history of perianal disease, she is not at increased risk for perianal disease if vaginal delivery is chosen. If the patient has active perianal disease, she can be at higher risk for aggravating the injury by vaginal delivery (24). Ileorectal anastomosis or an ileoanal pouch are regarded as relative indications for caesarean section (8). Patients who have an IPAA can have a normal vaginal delivery without the fear of damaging the pouch. However, damage to the anal sphincter remains a main concern with vaginal delivery. Although pouch function may deteriorate during pregnancy, after pregnancy it returns to its pre-pregnancy state. The patient, obstetrician, and surgeon should discuss the risk to long-term pouch function before making a decision on mode of delivery (24).

The risk of relapse after delivery

There will be no increased risk of disease flare in the postpartum period if patients remain on maintenance therapy. About one third of IBD mothers experience a flare-up after delivery considering the low risk compared to the risk of having a flare-up while not being pregnant. Pregnant patients who have an IPAA suffer from a 20%–30% chance of developing pouch dysfunction, particularly during the third trimester because of increased bowel frequency and decreased continence. These changes often resolve completely during the puerperium (8,38).

Breastfeeding

Patient concerns surrounding breastfeeding are related to secretion of medication into the breast milk, causing exposure to the baby (15). IBD activity is not independently affected by lactation. Kane and Lemieux have demonstrated that lactation is associated with an increase in disease activity, (39)

however medication cessation was a confounding factor. More recent reports have demonstrated no association between lactation and increased risk of flare-up in CD or UC patients (8).
Medications known to be safe for breastfeeding include sulfasalazine, mesalamine, and steroids with only a minimal amount secreted into the milk. Metronidazole is excreted in breast milk and breastfeeding should be suspended for 12 to 24 hours after dosing. Data on thiopurines suggest they are minimally secreted into the breast milk. Previously, breastfeeding has been discouraged with azathioprine (AZA)/6-mercaptopurine (6-MP) use but current data is more positive. The most recent study by Christensen and colleagues (40) in 2008 has revealed that most of 6-MP was excreted in breast milk during the first 4 hours after drug intake. Therefore, waiting 4 hours after dosing to breastfeed is warranted. One strategy is night-time dosing and pumping breast milk 4 hours later. In all, AZA/6-MP is not a contraindication to breastfeeding. Biologics have not been detected in breast milk and are usually continued postpartum (15). All anti-TNFs are possibly secreted in the breast milk in very small amounts. However, no adverse effects have been reported. Based on such scant data, their use in the breastfeeding mother needs to be carefully discussed. Drug and antibody monitoring in milk and infants should be considered, if available (8). Table 1(8) shows the safety aspects of frequent IBD medications according to ECCO recommendation categories.

IBD MEDICATIONS

In an often referenced paper published by Miller (41) in 1986, it has been shown that IBD patients who undergo flare-ups at the time of conception have higher risks for spontaneous abortion, still births, and premature deliveries. Therefore two-thirds of the patients have to live with active disease during pregnancy. Preferably, conversations between patient and physician should occur before conception. Continued monitoring and aggressive control of the disease prior to conception and throughout pregnancy plays a key role for achieving optimal outcomes for both mother and baby (3).
In most patients, maintaining remission with medical treatment outweighs the potential risks of adverse drug effects. However, the pros and cons must be discussed with the patient and individual decisions should be made (8). Active disease is the greatest risk to IBD pregnancy compared to active therapy; the main reason for discontinuation of all medications is the fear of their effects on the fetus. Pregnancy data on outcomes and disease course are complicated by the cessation of drugs, but the risk of complications during pregnancy seems primarily related to disease activity and not medication effects. Zelinkova and colleagues (42) have addressed voluntary childlessness and found that the two most important reasons, which prompted mothers to not have a child, were fear of medication side effects on the baby and advice given by physicians (15).

Aminosalicylates, sulfasalazine

In several trials, 5-aminosalicylate compounds (mesalamine, balsalazide, and sulfasalazine) have been demonstrated to be safe. However, mesalamine and its metabolite, acetyl-5-aminosalicylic acid, have been found in cord plasma (15). Case series, population-based cohort studies, and two meta-analyses did not show increased risks for early adverse outcomes such as miscarriages and ectopic pregnancies. Some trials have shown that premature births, stillbirths, and LBW were higher than other studies. A meta-analysis by Cornish et al. has revealed a small increase in congenital malformations, which could have been the direct result of the disease (8). In two separate studies, either UC or CD women who took 2 to 3 g of 5-aminosalicylates per day had no higher incidence of fetal abnormalities than normal controls (15). An Iranian meta-analysis has suggested no more than a 1.16-fold increase in congenital malformations, a 2.38-fold increase in stillbirths, a 1.14-fold increase in spontaneous abortions, a 1.35-

Table 1: Safety of IBD drugs during lactation (ECCO rating).

Safe	Probably safe	Unknown safety	Contraindicated
Oral 5-aminosalicylates	Infliximab	Metronidazole	Methotrexate
Topical 5-aminosalicylates	Adalimumab	Ciprofloxacin	Thalidomide
Sulfasalazine	Certolizumab	Budesonide	Cyclosporin
Corticosteroids (4 hour delay)	Azathioprine		
	6-Mercaptopurine		
	Tacrolimus		

fold increase in preterm deliveries, and a 0.93-fold increase in LBW (43). Recently, the Food and Drug Administration (FDA) has changed the pregnancy rating on Asacol because of dibutyl phthalate, a compound found in its coating. Dibutyl phthalate has been associated with urogenital defects in male offspring of exposed female rats. The given dose to rats is significantly higher than prescribed to humans, therefore the clinical consequences are unclear (3,15). As a result, asacol has been classified as a category "C" medication based on the presence of dibutyl phthalate in its coating. However, there has been no documented increase in the risk of birth defects with asacol in the doses used to treat IBD (44).

Corticosteroids

Corticosteroids are not teratogenic in humans and can be used as much as is necessary to control active disease (15). All forms of corticosteroids (systemic, oral and topical) can cross the placenta but are rapidly converted to less active metabolites, which provide low concentrations in fetal blood circulation. Short-acting prednisone, prednisolone and methylprednisolone are more efficiently metabolized in the placenta when compared to longer-acting dexamethasone and betamethasone, thus the former molecules are preferred for treatment. Adverse effects on pregnancy outcome as shown in animal studies have not been confirmed in humans (28,45). The overall risk of major malformations was reported to be low (15). Beaulieu and colleagues (46) described a case series of eight CD patients treated with budesonide, which were not in an increased risk for adverse pregnancy outcomes. Furthermore, inhaled or intranasal budesonide has not been associated with adverse outcomes (15). There are case reports of corticosteroid-induced neonatal adrenal suppression during late IBD pregnancy (8).

Azathioprine (AZA) and 6-mercaptopurine (6-MP)

Exposure of the fetus to AZA and 6-MP has been reported in several cases. Most studies have demonstrated their safety with no increased risk of malformations in the newborn (45). The most commonly cited pregnancy adverse outcomes are increased rate of spontaneous abortions, preterm delivery and LBW. Immunological and hematological abnormalities, as well as chromosomal aberrations caused by immunosuppression have been described in a few cases of newborns and infants (8).

The thiopurines carry a pregnancy category D rating. Francella and colleagues (47) have retrospectively reviewed records of 79 women with 325 pregnancies. Patients who consumed 6-MP during conception, those that stopped prior to conception, and those who were never exposed to 6-MP were compared. Although they did not consider prematurity or LBW, there were no statistically significant differences in spontaneous abortions, major congenital abnormalities, neoplasia, or increased infections (8). Moskovitz et al. (48) have investigated 6-MP and AZA during pregnancy. This age-controlled multivariate analysis of 113 patients with 207 conceptions revealed no evidence of medications' effects on pregnancy outcomes (abortions, premature birth, healthy full-term birth, ectopic pregnancy, congenital abnormalities, birth weight, or type of delivery) (3). Two large national data registries with a national prescription database were combined by Norgard and colleagues (29) to search for therapeutic drug use in CD women and birth outcomes. Among the women exposed to AZA/6-MP throughout their pregnancies, the risks of preterm birth were 4.2 (95% CI: 1.4-12.5) and congenital abnormalities were 2.9 (95% CI: 0.9-8.9). Preterm births were more prevalent among steroid and AZA/6-MP–exposed women when compared to the reference group. Data have suggested that continuing AZA/6-MP during pregnancy holds low risk. One strategy when using AZA/6-MP and a biologic agent is cessation of the immunomodulator during conception and pregnancy to lessen the possibility of any potential risks (15). Angelberger et al. have suggested that there is no increased risk of infections in babies born to mothers who have exposed their babies to AZA in utero and via breastfeeding. They have supported a current recommendation from the evidence based consensus of ECCO that breastfeeding under maintenance AZA treatment could be advised to women who wish to nurse their infants. However, mothers should be counseled to use a breast pump 4 hours after medication intake and to discard the first portion of milk produced after taking the medication (49).

Another recent study by Shim and colleagues has shown no increased risk with preterm birth, LBW at term, neonatal adverse outcomes, and congenital anomaly in women with IBD whose babies were exposed to AZA/6-MP. Therefore, consideration should be made for continuation of these medications during pregnancy as disease flare-ups can result in adverse birth outcomes (50).

Cyclosporin and tacrolimus

Cyclosporine is used in patients with severe UC and has not been found to be teratogenic (15). A meta-analysis of 15 studies (410 patients) did not find an increased rate of congenital malformations (8). Cyclosporine is excreted into breast milk and is contraindicated during breastfeeding (15).

Similar data exist for tacrolimus. However, evidence is limited to a small series of women with severe relapses during pregnancy (8). With tacrolimus there is just a single published case report of one UC patient (8).

Methotrexate (MTX) and thalidomide

Both are considered teratogenic and contraindicated in pregnancy. However, normal pregnancy outcomes have been reported. Methotrexate (MTX) exposure, particularly in the first trimester, may result in abortions, growth retardation, fetal loss, and congenital malformations that include craniofacial anomalies, limb defects and CNS abnormalities (51). If conception should accidentally occur, therapeutic abortion should be discussed, but not necessarily performed. Mothers should be advised to stop MTX immediately and begin high dose folate replacement. Both males and females should stop MTX for at least 3–6 months before trying to conceive (8). Since it can be excreted in breast milk it is contraindicated in breastfeeding (15). Thalidomide, with a neonatal mortality rate of 40%, has been associated with major fetal malformations of the limbs, ears, eyes, and neural tube defects (8).

Biologic therapy

Nowadays, biologics are used for more aggressive disease, and usually are used as a first line in the "top-down" therapeutic approach (52). There is cumulative evidence for infliximab as a low risk drug, which is compatible with use during conception and the first two trimesters of pregnancy. Infliximab crosses the placenta in the third trimester and may be present in the infant for several months after birth, which raises concerns about risks of infection and response to vaccines. Infliximab can be resumed immediately after delivery. Live virus vaccines should not be given to infants exposed to infliximab in utero in the first 6 months of life (53). A single case report has described fatal BCGitis from the live attenuated vaccination of a 3-month old infant born to a mother treated with infliximab, demonstrating the potential grave consequences of its trans-placental transfer. Hence, although labeled as FDA class B and generally considered safe during pregnancy in terms of mutagenesis, many authorities advocate the cessation of infliximab before the third trimester of pregnancy to reduce the potential for immune suppression of the newborn from the circulating drug (54).

Mahadevan and colleagues (55) looked at the outcomes of intentional INF in 10 women with active CD during pregnancy. All pregnancies ended in live births and without any congenital malformations. There were 3 preterm births and 1 LBW infant reported but these were not unexpected in a population of women with CD significant enough to require biologic therapy (15).

Concerning adalimumab, there is no commercially available test to detect its levels at this time. A prospective study by the Organization for the Teratology Information Specialists registry has reported 27 women on ADA and 47 ADA-exposed pregnant women with no increases in stillbirths or

Table 2: FDA classifications regarding IBD drug safety during pregnancy (54).

FDA Category	Definition	IBD drug
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester; possibility of fetal harm appears remote.	
B	Either animal studies do not indicate a risk to the fetus, and there are no controlled studies in women or animal studies have shown an adverse effect, but controlled studies in women failed to demonstrate a risk.	Adalimumab, Amoxicillin/Clavulanic acid, Balsalazide, Certolizumab pegol, Infliximab, Mesalamine, Metronidazole, Sulfasalazine
C	Either animal studies indicate a fetal risk, and there are no controlled studies in women, or studies in women and animals are not available.	Budesonide, Corticosteroids, Cyclosporine, Natalizumab, Olsalazine, Quinolones, Rifaximin, Tacrolimus
D	There is positive evidence of fetal risk, but the benefits may be acceptable despite the risk.	Azathioprine 6-mercaptopurine
X	There is definite fetal risk based on studies in animals or humans or based on human experience, and the risk clearly outweighs any possible benefit.	Methotrexate Thalidomide

spontaneous abortions in comparison with the general population. The rates of congenital malformations and preterm delivery were within the expected range. The successful use of ADA was reported in a patient with severely active disease at conception (15). Three ADA case reports were published on 3 pregnancies in CD patients. No complications occurred in any of these pregnancies and all babies were developing normally at 6 months (56). ADA at 40 mg every other week or weekly was administered in 14 women with previous recurrent spontaneous abortions to prevent miscarriages. There were 4 miscarriages and 10 normal pregnancies (57). Biologics have been considered compatible with breastfeeding but there are no published human data on ADA and breastfeeding at this time.

There has been a single case report on certolizumab pegol, where a successful pregnancy in CD and in 2 UC patients were reported by Mahadevan and colleagues (24). A study of pregnant rats that received a murinized IgG1 antibody of TNFα and a PEGylated Fab′ fragment of this antibody has shown much lower drug concentrations in their infants and breast milk with the Fab′ fragment when compared to the full antibody. Certolizumab pegol studies are limited, but experimental data in animals and first clinical data do not reveal an increased teratogenic risk in humans (8). Recent data on natalizumab has reported on 101 patients exposed to natalizumab during pregnancy with a spontaneous abortion rate comparable to that expected in the general population (58). The number of exposed patients, however, is too low to draw any definitive conclusions.

Metronidazole, ciprofloxacin

Both drugs have limited benefit for long-term IBD treatment. Short courses may be beneficial in pouchitis and perianal disease therapy, holding a low risk during pregnancy. Metronidazole does not increase the risk of spontaneous abortion or congenital anomalies, although infants of women exposed to metronidazole in the second to third months of pregnancy have shown higher rates of cleft lip with or without cleft palate (8,15). Table 2 lists the classification of IBD drugs used during pregnancy.

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