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**Pregnancy and inflammatory bowel diseases: Current perspectives, risks and patient management**

Hosseini-Carroll P *et al*. Pregnancy and inflammatory bowel diseases

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**Abstract**

Inflammatory bowel diseases (IBD) are chronic idiopathic inflammatory conditions characterized by relapsing and remitting episodes of inflammation which can affect several different regions of the gastrointestinal tract, but also shows extra-intestinal manifestations. IBD is most frequently diagnosed during peak female reproductive years, with 25% of women with IBD conceiving after their diagnosis. While IBD therapy has improved dramatically with enhanced surveillance and more abundant and powerful treatment options, IBD disease can have important effects on pregnancy and presents several challenges for maintaining optimal outcomes for mothers with IBD and the developing fetus/neonate. Women with IBD, the medical team treating them (both gastroenterologists and obstetricians/gynecologists) must often make highly complicated choices regarding conception, pregnancy, and post-natal care (particularly breastfeeding) related to their choice of treatment options at different phases of pregnancy as well as post-partum. This current review discusses current concerns and recommendations for pregnancy during IBD and is intended for gastroenterologists, general practitioners and IBD patients intending to become, (or already) pregnant, and their families. We have address patterns of IBD inheritance, effects of IBD on fertility and conception (in both men and women), the effects of IBD disease activity on maintenance of pregnancy and outcomes, risks of diagnostic procedures during pregnancy and potential risks and complications associated with different classes of IBD therapeutics. We also have evaluated the clinical experience using ‘top-down’ care with biologics, which is currently the standard care at our institution. Post-partum care and breastfeeding recommendations are also addressed.

**Key words:** Inflammatory bowel diseases; Pregnancy; Biologics; Breast-feeding; Immunomodulators

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**Core tip:** Inflammatory bowel diseases (IBD) are chronic inflammatory conditions characterized by relapsing and remitting episodes of intestinal inflammation. IBD is most frequently diagnosed during peak female reproductive years, with 25% of women with IBD conceiving after their diagnosis. While therapies have improved dramatically, IBD have important effects on pregnancy and presents challenges for maintaining optimal outcomes for mothers and their developing fetus/neonate. Women with IBD and physicians must often make challenging decisions on conception, pregnancy, and breastfeeding. This review discusses concerns and recommendations for pregnancy during IBD and is intended for gastroenterologists, general practitioners and IBD patients and their families.

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**INTRODUCTION**

Inflammatory bowel diseases (IBD) are chronic idiopathic inflammatory conditions characterized by relapsing and remitting episodes of inflammation affecting several regions of the gastrointestinal (GI) tract[1,2]. In the United States, upwards of 1.4 million people have IBD[2], and there is a trend for increasing IBD incidence over the last decades[3]. The global incidence of Crohn’s disease (CD) varies between 0.1-16/100000 and that of ulcerative colitis (UC) varies between 0.5-24.5/100000, with an overall prevalence rate of IBD of 396/100000[4]. IBD is more common in women than in men[5], occurs more frequently in adolescents and young adults[6], and is most frequently diagnosed during peak reproductive years in women.

 IBD includes at least 3 different subtypes: CD, UC and indeterminate colitis[1]. UC and CD are distinguished by their affected locations and the histopathology of the disease at each affected site[6]. While UC primarily affects the colon and the rectum, with involvement of the submucosa and mucosa, CD can affect any region in the GI tract (often sparing the rectum) and is characterized by transmural inflammation[6]. When there is difficulty in discriminating between CD and UC, either based on colonoscopic evidence or excised colectomy specimens, the term “indeterminate” colitis (IC) is used[7].

Clinically, IBD symptoms reflect inflammatory changes within the GI tract. Hallmark GI symptoms of IBD include diarrhea, constipation, bloody stools, increased bowel movements, abdominal cramping, nausea, and vomiting[8]. In addition to GI symptomology, fever, weight loss, arthralgias, and malaise are other frequent systemic symptoms seen in IBD. Fistulizing disease, fat and vitamin malabsorption are long-standing complications that are associated with CD[6] and are less common in UC. These complications have serious consequences even in normal patients and can be devastating for pregnant women with IBD and their developing fetuses.

IBD therefore presents a unique and challenging set of conditions to effectively manage and control. Gastroenterologists are now at the helm of unique and dynamic treatment plans which can often be tailored to each patient’s individual needs. Pregnancy often presents several additional challenges in the management of IBD. Women with IBD, the physicians that care for them and their families must often face complex decisions on issues of conception, pregnancy and breastfeeding. As previously stated, at least 50% of patients are diagnosed by age 35[9], often10], which affects women during their peak reproductive years. Importantly, 25% of women with IBD will conceive after their diagnosis of IBD has been established[9]. This review will examine some of the important considerations for women with IBD and their families including heritability, fertility, risks unique to IBD in the setting of pregnancy and lactation.

**FERTILITY**

Women with active IBD experience reduced fertility for several reasons compared to the general population, with an overall “fertility rate” (lifetime births per woman) of 2.45 for healthy women, but only 2.06 for IBD patients (in the United States)[10]. Regional population studies show infertility rates in CD to be somewhere between 5% to 14%[11]. By comparison, UC has less of an effect on fertility rates, unless patients had undergone any IBD related surgery[12,13]. Several other factors associated with active IBD can also contribute to the overall reduced rate of conception in IBD including dyspareunia, low libido, and depression[14-16]. Dyspareunia (painful sexual congress) often occurs secondary to pelvic surgery, from IBD-associated inflammation, or psychological stress associated with IBD. Interestingly, the main cause of decreased rates of fertility in CD patients with history of previous surgeries was found to be conscious decisions against conception[17].

For women with inactive IBD and without history of pelvic surgery, fertility is comparable to their respective age-matched peers[18]. Pelvic surgery in IBD thus remains a major factor negatively affecting fertility, which varies with the extent and type of surgery[19]. Post-surgical adhesions also appear to play a key role in tubal infertility[20].

Proctocolectomy (PCL) and ileal-pouch anal anastomosis (IPAA) surgeries are associated with reduced fertility. Two studies showed approximately 50% of the women experienced fallopian tube obstruction (either unilaterally or bilaterally) following these procedures[21,22]. A meta-analysis evaluating IPAA in UC patients suggested that the risk of infertility increased 3-fold post-IPAA[23]. Proctocolectomy[24]. PCL with IPAA has a more pronounced effect on fertility compared to the laparoscopic approach, which produces fewer adhesions[18,19,23-26]. Studies involving laparoscopic IPAA indicate that women undergoing these procedures have significantly higher pregnancy rates as compared to open field IPAA[27]. Therefore, laparoscopic procedures are always preferable particularly when conception is a goal.

**INHERITANCE**

Questions on inheritance patterns in IBD remain concerns for patients and their families. If one parent has any form of IBD, their child will have between a 2 to 13 fold increased lifetime risk of developing IBD[28] and is empirically estimated as an approximately 5% heritable risk in CD and 1.6% in UC[29]. However when both parents have a form of IBD, this risk increases to ~33%-36% for their offspring to inherit a form of IBD[30,31]. Genomic studies have shown that at least 100 heritable loci influence IBD onset and penetrance[32]. Genomic studies have identified a vast heterogeneous distribution of genes linked with IBD, possibly suggesting different groupings that exhibit these conditions. Therefore, while in a population, the risk of IBD may be elevated by the presence of any particular gene variant, this does not necessarily hold true for individual patients bearing such alleles. The large number of genes creates several diverse patterns of IBD activity and inheritance involving different levels of penetrance and thereby requiring individualized therapy. Both UC and CD have been associated with excessive interleukin-23 (IL-23) pathway activation with the dysregulation of several transcription factors, including SMAD3, STAT3, c-REL, zinc-finger-MIZ-type containing 1 (ZMIZ1) and NK2[32]. Several genes specifically associated with UC include cytokines *e.g.,* IL-26, IL-22, structural proteins LAMB1 (encodes laminin β1), and hepatocyte nuclear factor (HNF) 4α. With respect to CD, CD pathogenesis has been linked with disturbances in nucleotide binding oligomerization domain protein 2 (NOD2) and genes that control autophagy (*e.g.,* ATGL)[32], as well as disturbances in IL-10, tumor necrosis factor superfamily (TNFSF) 8, TNFSF-15, ZMIZ-1, NK2 transcription factor (NKX2-3), SMAD-3, caspase recruitment domain family, member 9 (CARD-9), and CARD-15[32].

**DISEASE ACTIVITY DURING PREGNANCY**

The severity of IBD disease activity during pregnancy also significantly influences pregnancy outcomes. While pregnancy has not been shown to specifically increase the risks of IBD “flares”[19], approximately 30%-40% of women with IBD active at the time of conception will develop more intense disease or endure disease flares during pregnancy[33,34]. Some studies show that disease outcomes and flares in IBD outside of pregnancy are linked to environmental factors and lifestyle including hormone use, diet, mental health status, cigarette smoking, and vitamin D levels[35]. IBD activity at the time of conception apparently determines the clinical course IBD patients will experience during pregnancy. That is to say, 2/3 of women with IBD in remission at the time of conception are likely continue to remain in remission throughout their pregnancy[36-39]. Remarkably[37-40]. Because only 1/3 of those patients with active disease at time of conception will relapse during their pregnancy, the gravid state may suppress some disease processes in IBD[40]. Effective IBD control in prenatal planning is therefore essential for favorable pregnancy outcomes, (birth weight > 5.5 lbs, no spontaneous abortion, congenital malformations or antepartum hemorrhage)[41]. Women with inactive IBD at the time of conception have similar risks of adverse pregnancy outcomes as the general female population[12]. Women with active IBD have increased risks of preterm deliveries, intrauterine growth restriction, and low birth weight (LBW) babies (defined as live born infants < 2500 g regardless of total gestational age)[37,42-44]. This suggests that the IBD process itself produces the fetal risks during pregnancy. These complications are also more often seen in CD patients as compared to patients with UC.

The Crohn’s Disease Activity Index (CDAI) is used in CD patients to evaluate and quantify cumulative symptoms and assess the activity of the disease in affected individuals[45]. There are eight factors involved in determining CDAI, which are assessed daily for 7 d, including: (1) frequency of watery stools, (2) well-being; (3) abdominal pain; (4) presence of any complications; (5) presence of abdominal mass; (6) usage of opioids; (7) low hematocrit < 0.47 and < 0.42 in men and women respectively, and lastly; and (8) standard weight percentage deviation[45]. A CDAI below 150 is defined as remission, while a CDAI > 450 is termed severe disease[46]. Pregnant women with IBD should receive prenatal care similar to any other pregnant women including education regarding effects of drug usage, vaccinations and vitamin regimens. Ideally, gastroenterologists should confer with obstetricians in the care of females with IBD.

**COMPLICATIONS OF IBD DURING PREGNANCY**

Expectant mothers with IBD are at a greater risk for several complications including malnutrition, venous thromboembolism (VTE), antepartum hemorrhage, and cesarean delivery[19,47,48]. VTE is increased in women with UC, while antepartum hemorrhage risk is increased in women with CD[47]. There is nearly a 4-fold increase in the risk of VTE in women with UC; while CD affects women have a risk of VTE that was comparable with the general population[47]. The antepartum hemorrhage risk is shown to be doubled in women with CD[47]. Approximately 2% of women with CD and UC developed placental abruption in a study on obstetric hospitalizations[49]. The risk of cesarean delivery is also increased in females with either UC or CD[48]. According to Ng *et al*[19], women with perianal disease should opt for cesarean section, while those without perianal involvement can safely undergo a normal vaginal delivery.

As stated earlier, pregnant women with active IBD at conception suffer more complications compared to those with quiescent disease (at conception), with those with quiescent IBD having outcomes similar to the healthy pregnant population[40,50,51]. Complications associated with IBD activity at the time of conception include: abortion, low birth weight (LBW), and premature births[50,52-55]. These complications are seen more often in CD patients than UC patients. A 2007 study, which evaluated birth outcomes in CD, showed an increased risk of preterm births but did not report any other adverse birth outcomes[56]. Khosla *et al*[36] showed that individuals with active CD at the time of conception had a 35% higher rate of miscarriage than women with CD in remission. Moser *et al*[57] demonstrated ileal disease was a strong predictor for LBW. Relapse of UC in pregnant women was also associated with LBW and preterm births[58]. Fortunately, increased risks for congenital abnormalities have not been demonstrated in neonates whose mothers had IBD compared to the general population[57].

Women also suffer from diverse forms of inadequate nutrition during active IBD due to decreased appetite and/or history of multiple small bowel surgeries, both of which can negatively affect absorption of specific nutrients[59,60]; protein losing enteropathies can also exacerbate these nutritional deficits.

Overall, IBD disease activity at the time of conception will play some role in the outcome of the pregnancy. It is therefore advisable to optimally control disease prior to conceiving to diminish the likelihood of adverse outcomes from disease flares, the need to suppress symptoms and the need to medicate all of which can be harmful to both the mother and fetus. Monitoring maternal nutrition and providing proper prenatal care Giving heparin prophylactically to the gravid IBD patient, may help in prevention of VTE and malnutrition respectively.

**IBD DIAGNOSIS DURING PREGNANCY**

Imaging modalities used during evaluation of IBD during pregnancy can present risks to both mother and fetus and should be limited to ultrasound and MRI. Ultrasound avoids radiation exposure to the fetus and is always the preferred imaging compared to CT scan[19]. When more detailed imaging study is required, MRI without gadolinium contrast can be used to avoid teratogenicity, especially in the first trimester[19]. X-rays should be avoided throughout the pregnancy. Colonoscopy should be considered during pregnancy when life-threatening lower GI bleeds are present or when surgical interventions are the only available option[61]. However, flexible sigmoidoscopy is considered safe during pregnancy and is the endoscopic procedure of choice[61,62]. Generally according to the American Society for Gastrointestinal Endoscopy, procedural sedation is also safe during the 2nd trimester but is not recommended during the 1st and 3rd trimesters, except in emergent situations[63].

**MANAGEMENT**

Serious discussions and reflection need to be made regarding treatment modalities at different phases of pregnancy (see Figure 1). IBD therapy is still evolving and the focus of IBD management has now moved away from short-term control of symptoms to more long-term suppression of disease mechanism which alter the course and complications of IBD. Older drug classes such as 5-aminosalicylic acid (5-ASA) compounds (sulfasalazine, mesalamine, balsalazide), steroids, antibiotics and other immunomodulators (*i.e.,* 6-mercaptopurine (6-MP), azathioprine (AZA), cyclosporine and methotrexate) have given way to newer “biologic” agents. The biologics currently used for treatment of IBD are most often humanized monoclonal antibodies directed toward inflammatory cytokines such as tumor necrosis factor–alpha (TNF-α) or adhesive determinants on leukocytes (*e.g.,* integrin α4β7), which bind counter-ligands expressed on activated intestinal endothelial cells [like Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM-1)].

Traditional IBD therapy has been to “step up” or incrementally increase treatment in a stepwise fashion finally introducing more powerful medications for IBD. It involves gradual addition of relatively benign drugs early in the course of IBD like aminosalicylates and steroids. When these drugs eventually fail, they are substituted by more aggressive therapies like immunomodulators and lastly biologics. The ultimate escalation in the “step up therapy” approach was the use of biologic agents.

Over the last few years, clinical studies have suggested that aggressive medical therapies initiated earlier in the disease course helps to arrest the progressive nature of IBD (especially CD) leading to a “disease modifying effect”[64]. “Disease modifying” refers to the slowing or stabilization of IBD progression, which leads to a more benign clinical picture, often eliminating the need for multiple or complex surgeries and importantly, reducing the lifetime risk for colorectal malignancies. The most convincing IBD therapy data now seems to favor the use of biologics; either alone or in combination with immunomodulator therapy. The more aggressive combination therapy has gained widespread clinical acceptance of switching from the “step-up therapy” to the “top-down” approach (see Figure 2). The same principle of this treatment approach appears applicable during pregnancy, albeit with several safety considerations.

Currently, “top-down” therapy is the standard approach to IBD at Louisiana State University Health Sciences Center-Shreveport (LSUHSC-S), which provides state-sponsored free care to all patients despite the high annual cost of biologic drugs. LSUHSC–S has a ~500 patient population with IBD, and we have used the “top-down” approach for over 15 years since biologics were first introduced (1998), starting with infliximab (INF)[65]. We commonly initiate therapy with biologics and immunomodulators in new IBD patients to gain control of the disease early on and induce remission, rather than allowing the disease opportunities to develop an aggressive course before taking action. Other institutions in the surrounding region have followed suit and now also use “top-down” approach. “Top-down” therapy, while highly effective may be altered during pregnancy based on safety considerations and disease severity.

The FDA has established five distinguishing categories to designate the potential for a drug to cause birth defects if used during pregnancy[66] and reflect both documentation reliability and relative risk to benefit ratio considerations (Table 1).

**AMINOSALICYLATES**

There are several different formulations of aminosalicylates with differing risk stratifications in pregnancy. Sulfasalazine (SSZ), the first aminosalicylate used in treating IBD, is an FDA category ‘B’ drug. Since SSZ crosses the placenta, it presents several concerns in pregnancy[67]. SSZ is known to inhibit folate synthesis[68] and impairs folate absorption potentially causing fetal neural tube defects. This has raised some concerns about its safety during pregnancy, but these appear to have been refuted by several studies[36,56,68]. For example, Mogadam *et al*[69] performed a study on 181 pregnant women with IBD who were treated with SSZ. When matched with the overall population, these patients showed a lower incidence of having adverse outcomes. Nørgård *et al*[56] also conducted a regional retrospective cohort study, which showed no adverse outcomes in 17 CD patients who were treated with SSZ. Therefore, SSZ may be used in pregnancy with mandatory to folate supplements[68]. In fact, pregnant women taking SSZ are advised to increase their daily dose to 5 mg[70], compared to women not taking SSZ require between 0.4 mg and 1 mg of folate daily[70].

Men on SSZ therapy for IBD should switch to an alternate drug treatment 3-4 mo prior to conceiving given SSZ’s known deleterious effect on sperm[19]. One study compared the fertility of 10 men with IBD being treated with SSZ over 5 years to those of 19 control subjects. It showed that while SSZ treatment did reduce semen quality, this effect was reversed upon drug discontinuation[71].

Over the last two decades, preparations based on 5-aminosalicylic acid (5-ASA) have remained a mainstay of IBD therapy, avoiding the use of SSZ, which has been associated with several serious adverse effects[72,73]. Both topical 5-ASAs and non-enteric coated formulations of 5-ASA are understood to be safe in pregnancy. Bell *et al*[74] in a study of 19 pregnant patients with distal colitis on maintenance with topical 5-ASA therapies at the time of conception concluded that 5-ASA was safe and effective for managing distal colitis during pregnancy. Marteau *et al*[75] also conducted a study in which 123 pregnant IBD patients were monitored while taking between 1-4 g/d of mesalamine microgranules and found no serious complications during the course of pregnancy, nor were any adverse fetal outcomes observed.

Asacol (mesalamine) (Procter and Gamble Pharmaceuticals, OH, USA) and Asacol HD (mesalamine delayed-release tablet) (Procter and Gamble Pharmaceuticals, OH, USA) have been moved from pregnancy category ‘B’ to ‘C’ due to the use of dibutyl phthalate (DBP), which is used in the coating of these medications. DBP has adverse effects on the male reproductive system[76] and has been linked to precocious puberty[77]. However, it is important to note that the doses used in these animal models which have linked to skeletal deformities and reproductive system effect were approximately 190 times greater than the maximum doses used in humans. Precocious puberty was also caused by DBP doses that were 10 × the maximum recommended levels[77]. There have been no studies to date showing increased birth defects in patients taking mesalamine. All other formulations of mesalamine, as well as other aminosalicylates are classified as Category ‘B’ drugs. No statistically significant increases in congenital abnormalities, stillbirths, spontaneous abortions, preterm deliveries, or LBW have been observed with Asacol use[78].

Mesalamine is available as an enema or suppository in the United States. Since enemas can reach the left colon, rectal therapies are typically considered for patients with disease activity anywhere from the rectum to the left colon. UC often starts in the rectum with 1/3 of patients with UC having disease confined to the rectum, with another 1/3 having disease extending into the left colon, both of which can be reached by administration of drugs by enema[79]. CD affecting the rectum and sigmoid colon is also frequently treated by enema[80]. Enema is the treatment of choice for pregnant women suffering from distal UC because its therapeutic effect on the lining of the bowel is maximized while the systemic side effects are minimized.

Mesalamine can penetrate the placenta and also enters into breast milk. SSZ itself may be present in breast milk at 30% of the maternal plasma concentration, and sulfapyridine (SSZ metabolite) are found at 50% of the concentration in the maternal serum[81]. Therefore, SSZ should be avoided, if possible, for mothers of premature infants or those less than 1 mo of age. There is also a concern for kernicterus, a bilirubin-induced brain dysfunction, as sulfonamides can displace bilirubin from albumin, though there are no reported cases in the literature[82,83]. There is one case report of an infant with severe but reversible diarrhea after being breastfed by a mother using rectal 5-ASA[84]. Infant stool patterns should therefore be monitored if the mother is using mesalamine for IBD therapy and is breastfeeding[19]. There is a preference for a maximum dose of 2 grams mesalamine daily during pregnancy based on an association with neonatal renal insufficiency in a 1994 report[85]. This is in contrast to the normal non-pregnant patient maximum dose of 2.4 to 4.8 grams daily depending on the preparation being used.

Using 5-ASA for treating CD is controversial. Ford *et al*[86] performed a meta-analysis to determine the effectiveness 5-ASA in inducing and maintaining CD remission. That study suggested that 5-ASA based drugs were superior to placebo at inducing remission in patients with active CD, with a reported “number needed to treat” of 11. Approximately 68% of CD patients treated with 5-ASA failed to achieve remission versus 75% of patients who were receiving placebo. 5-ASA had no benefit in maintaining remission. A relapse rate of 56% was found in patients treated with 5-ASA compared with 57% for patients who received placebo. In a 2011 study, [mesalamine](http://www.uptodate.com/contents/mesalamine-mesalazine-drug-information?source=see_link) and [budesonide](http://www.uptodate.com/contents/budesonide-drug-information?source=see_link) were found to be equally efficacious in inducing remission in patients who had mild to moderate activity CD[87]. Remission rates were similar between those who are receiving budesonide and mesalamine (70 *vs* 62 percent). Therefore, 5-ASA, based on studies, is not as effective in the treatment of CD and its use in treating pregnant women is debatable.

5-ASA is however, an optimal drug for inducing and maintaining remission in mild to moderate UC[88]. Trallori *et al*[72] conducted a safety study on 5-ASA use in UC during pregnancy. All patients in the study were in clinical remission from UC at the beginning of pregnancy and were receiving regular maintenance therapy with 1.2 g/d 5-ASA. It was noted that 5-ASA usages during pregnancy did not affect the course or outcome of pregnancy, but it could prevent disease relapse of UC. Therefore, in general, aminosalicylates like 5-ASA can be used in pregnant women with IBD, but caution should be exercised.

**ANTIBIOTIC USE FOR IBD DURING PREGNANCY**

Metronidazole is an antimicrobial drug and a pregnancy category ‘B’ drug that works against anaerobic bacteria and is used for treating active colonic and perianal CD[89]. There have also been some benefits seen with the combined use of metronidazole and ciprofloxacin in treatment of pouchitis (inflammation of the ileal pouch), which is a long-term complication of IPAA surgery for UC[90,91]. Metronidazole should however be avoided in the 1st trimester as it has been linked to an increased rate of cleft lip/palate in a 1998 study of 17200 women exposed to the drug during the 1st trimester of pregnancy[92]. Metronidazole teratogenicity has also been demonstrated in animal models (when used in the equivalent of the 1st trimester) but there is less risk of teratogenicity in the 2nd and 3rd trimesters. A study of metronidazole in rats also demonstrated a depression of plasma gonadotropins (luteinizing hormone and follicle stimulating hormone), testosterone, testes weight, and spermatogenesis[93].

Metronidazole is also incompatible with breastfeeding as breastfed infants of mothers taking metronidazole experienced diarrhea, secondary lactose intolerance, and Candidiasis[94,95]. Women receiving a single dose of metronidazole may resume breastfeeding after 12-24 h[96].

Ciprofloxacin, another antibiotic used to control flares in IBD, carries a pregnancy category ‘C’ rating. There is increased uptake of ciprofloxacin in bone tissue which can cause arthropathy in children and therefore, its use is discouraged during pregnancy97]. Limited data exists on the safety of ciprofloxacin use during breastfeeding. It is recommended that women receiving a single dose of ciprofloxacin can resume breastfeeding after 48 h[98]. Conversely, there have been studies that indicate that short-term ciprofloxacin use is compatible with breastfeeding as it decreases in breast milk over time. One study involving 10 lactating women who were given ciprofloxacin in 3 doses every 12 h estimated that an exclusively breastfed infant would receive a maximum of 0.57 mg/kg daily dose of the drug. The dosage that an infant would receive is low compared to the levels used to treating newborn infants (10 to 40 mg/kg)[99-102]. Another study showed that an infant nursing from a woman being treated with ciprofloxacin for 10 days had no measurable ciprofloxacin in her serum (< 30 μg/L) 2.7 h after breastfeeding[103]. Therefore, modest or acute use of ciprofloxacin appears relatively safe for use in most pregnant women and even nursing mothers. Ciprofloxacin does not seem to affect sperm quality, however, the function of the accessory gland (consists of seminal vesicles, prostate gland, and bulbourethral glands) can be modified[104].

Rifaximin, a broad-spectrum antimicrobial, has shown to be useful in treating pouchitis and small bowel bacterial overgrowth in IBD. Rifaximin is used in IPAA, stricturing small bowel disease, or in patients with a history of multiple bowel surgeries, which can contribute to intestinal stasis. Rifaximin is relatively new to the clinic and market place and is a category class ‘C’ drug with respect to its use during pregnancy since its fetal effects and transfer in breastfeeding is still unclear. Studies have shown rifaximin-induced birth defects in animals, including partial ossification and cleft palate[105], however another study failed to show birth defects in rats[106]. The fertility of male rats was not affected the consumption of rifaximin[107]. Based on the limited data for rifaximin in pregnancy, it cannot be safely recommended to pregnant women with IBD. Amoxicillin/ clavulanic acid, are pregnancy class ‘B’ drugs, which are a safe alternative option for use in treating pouchitis. Unlike rifaximin, amoxicillin/ clavulanic acid failed to show birth defects in both a prospective controlled study[93] and a population-based case-control study[108].

**IMMUNOMODULATORS**

***6-MP/ AZA***

AZA is a prodrug that is metabolized to 6-MP, which is then further metabolized into several metabolites including the active metabolite 6-thioguanine (6-TG) and the inactive metabolite 6-methylmercaptopurine (6-MMP). Therapeutic efficacy is related to 6-TG levels, while high 6-MMP levels are correlated with liver and bone marrow toxicity. Several strategies have been utilized to try to optimize 6-TG levels while minimizing 6-MMP levels when administering thiopurines to patients that would not otherwise tolerate these drugs. 6–TG levels between 230 and 400 pmol/8 × 108 erythrocytes correlate with response and remission of IBD while levels over 400 pmol/8 × 108 erythrocytes correlate with bone marrow suppression. 6-MMP levels over 5700 pmol/8 × 108 erythrocytes have been linked with hepatotoxicity (measured by release of liver enzymes)[109,110].

AZA and 6-MP, both purine analogs, are pregnancy category ‘D’ drugs, since gestational animal studies demonstrate birth defects. Because of their cytotoxicity, and potential risk of birth defects, they should be used with caution during pregnancy[111]. Immunomodulators alter the activity of the immune system in order to decrease the body’s inflammatory response and cause an immunosuppressive effect. AZA and 6-MP both target rapidly dividing T lymphocytes, inducing lymphocyte apoptosis to depress inflammatory responses. These drugs effectively establish and maintain remission of IBD and are especially helpful in patients who have not responded to milder therapies (such as aminosalicylates), or are steroid-dependent[112]. There are variable and conflicting data on side effects of immunomodulators in humans. In a 2006 study, Cleary *et al* studied 476 women, the majority of which had IBD. This study found a 3 × increase in the frequency of cardiac defects in offspring of women who took immunomodulators early in their pregnancy. It was also noted increased preterm deliveries, LBW, and “small for gestational age” babies in AZA exposed pregnancies. A meta-analysis done in 2012 showed that men fathering children who were exposed to thiopurine around the time of conception did not increase rates of congenital birth defects and so did not recommend discontinuation of treatment in men[112]. However, if there is a medical history of unexplained infertility or miscarriages, men should stop taking thiopurines at least four months before conception to improve fertility[113].

Conversely, Goldstein *et al*. studied 189 women who took AZA for different indications and contacted a birth defects registry following delivery. That study failed to find a statistically significant increase in the rate of malformations (compared to 230 women who contacted the same service that were not on any teratogenic treatment). However, the Goldstein study did confirm a statistically significant difference in premature birth and LBW associated with AZA. Akbari *et al*[112] 2012 performed a meta-analysis and found that exposure to thiopurines during conception was not clearly associated with birth abnormalities and concluded that maternal use of thiopurine was not associated with low LBW, but confirmed an increase in the chance of preterm births due to thiopurine exposure. In fact, preterm birth had increased odds of 70% and was the only outcome found to be significantly affected by thiopurine use. Again, whether this is directly related to thiopurine use, or simply to a more severe disease state in which thiopurines are more often required is unclear[112]. For example, other studies have demonstrated a more severe disease course in IBD was also significantly associated with preterm births not related to drug loading[50,112]. Furthermore, data from the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry in 2012 found no increased frequency of gestational or fetal complications in Group A (6-MP/AZA) as compared to other groups. Data presented at Digestive Disease Week 2014 revealed improved milestone achievement in babies of mothers in Group A[114]. These were statistically significant for social interaction at 24 mo (50.75 *vs* 47.34, *P* = 0.04), problem solving 36 mo (mean 52.04 *vs* 48.66, *P* = 0.05), and problem solving 48 mo (mean 59.92 *vs* 57.66, *P* = 0.02).

CESAME, a prospective cohort population-based study included 11006 women that followed patients between 2004- 2007 in France, had a primary goal to determine the risk of malignancies in patients on thiopurines[115]. Coelho *et al*[116] ran a sub study that was added to the CESAME in 2005, which included 86 thiopurine-treated pregnancies compared to 129 IBD controlled pregnant patients. The key finding of the study demonstrated that there were no increases in congenital abnormalities in thiopurine-treated pregnancies[116].

Therefore we believe that benefits from maintenance on these immunomodulators during pregnancy outweigh potential fetal risks. AZA and 6-MP are also believed to be compatible with breastfeeding. So far studies have demonstrated only very low levels of the drugs transferred in breast milk and thus clinically insignificant concentrations accumulated in healthy breastfeeding infants. However, Mahadevan *et al*[117] suggests caution in infants with compromised immune systems. We agree with the comment since these drugs may intensify an already immunodeficient state due to their mechanism of action, which could be serious in the setting of perinatal pathogen exposures.

In conclusion, several different outcomes are proposed with the use of thiopurines and roles in congenital malformations. Thus, caution is warranted with the use of these drugs. Despite limitations of these studies *e.g.,* relatively small sample sizes, or failure to consider the disease activity of IBD, these data are consistent with moderate thiopurine use as being safe during pregnancy[56,57,116].

***Methotrexate***

The action of Methotrexate (MTX) in IBD involves several mechanisms. MTX inhibits DNA synthesis resulting in suppression of T-cell proliferation and induction of apoptosis. MTX also inhibits both lymphocyte and endothelial expression of intercellular adhesion molecule-1 (ICAM-1). MTX is a pregnancy category X drug, which is a folic acid antagonist that has been previously linked with several congenital abnormalities of fetal organogenesis. Although MTX has beneficial anti-inflammatory actions in IBD, the drug is considered to be so toxic that women should wait at least 6 mo after discontinuing MTX before resuming attempts to conceive. MTX also contraindicated during breastfeeding as it is passed into breast milk. For men on methotrexate, one study looked at 42 pregnancy outcomes involving paternal exposure to MTX around the time of or up to 3 mo prior to conception and concluded that this treatment did not enhance the risk of birth defects[118]. However, given the limited data available to date, some providers still recommend that men also wait at least 3 mo after discontinuing MTX before attempting to conceive based on the depressive effect of MTX on spermatogenesis leading to oligospermia[119].

**IMMUNOSUPPRESSANTS**

***Cyclosporine A/ Tacrolimus***

Cyclosporine A (CsA) and tacrolimus are immune suppressing drugs, which are listed as pregnancy category ‘C’ drugs. The majority of CsA information has been derived from transplant experiences. CsA blocks IL-2 formation by helper T-cells. Through binding to cyclophilin, CsA inhibits calcineurin, a cytoplasmic phosphatase enzyme participating T-cell activation. CsA also indirectly inhibits B-cell function by blocking T-helper cells. CsA has a more rapid onset of clinical action than either 6-MP or AZA, which can require 3-6 mo to show disease suppressing activity[120]. Patients with CD who respond to CsA show rapid improvements within 2-3 wk[120]. Improvement was also seen within 1-2 wk with the usage of CsA in severe UC[120].

Tacrolimus, a macrolide antibiotic, has immunomodulator properties like CsA but it is 100 times more potent than CsA. One advantage of tacrolimus is that it doesn’t depend on bile or mucosal integrity for its absorption. As a result, tacrolimus can be used in patients with small bowel involvement, including both CD and UC[121]. These drugs have not yet been linked to increased rates of congenital abnormalities. However, increased rates of maternal and perinatal complications have shown in kidney transplant recipients on different regimens of immunosuppressant medications, which included cyclosporine and tacrolimus[122]. These drugs are further contraindicated during breastfeeding as they develop high concentrations in breast milk, with the potential for perinatal immune suppression. However, according to Nielsen *et al*[97], tacrolimus is excreted into breast milk at 0.05% of the maternal dose and thus does not need to be discontinued while breastfeeding. Cyclosporine is also weakly transferred/passed into in breast milk and is likely safe while breastfeeding, although caution should be exercised based on its potential for immunosuppression[97]. At LSUHSC-S we routinely discuss the above risks with our patients before initiating therapy with either CsA or tacrolimus.

***Steroids***

As mentioned earlier, the biologic agents and immunomodulators remain key therapies in achieving remission of IBD. However, during acute flares many practitioners often resort to corticosteroids to provide patients with temporary relief from their symptoms. Due to side effects associated with their long term use, corticosteroids (prednisone and methylprednisolone) are used only short term and are not used for maintaining remission. Corticosteroids, specifically prednisone, are considered a pregnancy category ‘C’ drug. Prednisone use in pregnancy has been associated with orofacial clefts when used within a month of conception or during the first trimester[98]. However, no evidence currently links glucocorticoid use with major malformations[63,123,124]. Corticosteroids have also been linked to premature rupture of placental membranes and adrenal suppression (so far seen only in mothers in transplant studies)[19]. Corticosteroids are however usually thought to be compatible with breastfeeding since only very low levels of steroids are transferred into the breast milk and the risks to the neonate are considered to be very low clinically[125,126]. Consequently, no formal recommendations have yet been developed regarding timing of breastfeeding around administration of the corticosteroids[19].

***Biologics***

Biologics are now widely used for the treatment of IBD. However, since they function by targeting inflammatory cytokines or adhesive determinants, they may not be highly effective for treating acute flare-ups often requiring weeks to months to become effective. Biologics are broadly divided into TNF-α inhibitors and non TNF-α inhibitors. TNF-α inhibitors are often humanized recombinant IgG1 monoclonal antibodies that bind to TNF-α with high affinity. INF (Remicade, Janssen), adalimumab (ADA) (Humira, Abbvie) and certolizumab-pegol (CZP) (Cimzia, UCB) are currently the most commonly used drugs of this type in our practice, and are considered pregnancy category ‘B’ drugs.

The second class includes biologics like natalizumab, which is a class IgG4 monoclonal antibody IgG4 which has been ‘humanized’ to more closely resemble human IgG that inhibits leukocyte binding mediated by the integrin α4 adhesion molecule. IgG4 antibodies are not as readily transferred across the placenta as IgG1, however fetal levels of IgG4 still exceed those in the maternal circulation. The risk of congenital malformations has not been seen to be increased in a study of 164 pregnancies in patients with CD or Multiple Sclerosis (MS) during the first trimester[127]. Vedolizumab (Entyvio, Takeda) is the latest biologic (approved by FDA on May 2014) used for treating IBD. Vedolizumab is a humanized monoclonal antibody (IgG1) that binds to the human α4β7 integrin (expressed on the surface of T cells), thereby inhibiting T cells adhesion to MAdCAM-1[128]. Alpha-4 integrins have currently been labeled as a pregnancy category ‘B’ drug in terms of safety profile. Newer biologic therapies under development **are currently in different phases of clinical trials and** target other cytokines. For example, ABT-874 (Abbott) and CNTO 1275 (Ustekinumab, Centocor) are both **anti-IL-12/-23 antibodies and tocilizumab is anti-IL-6 antibody[129].**

Biologics like INF and ADA cross the placenta and do so at the greatest extent during the third trimester. Mahadevan *et al*[130] evaluated 31 pregnant women with IBD being treated with INF, ADA or CZP and compared concentrations of these biologics in infant and cord blood with concentrations in the mother. The levels of INF and ADA were elevated in infant and cord blood compared to their respective maternal levels with the median level of INF in cord blood 60% higher than that of the mother. Similarly the median concentration of ADA found in cord blood was seen to be 53% higher than that in the maternal circulation. The level of CZP was lower in neonatal circulation and in cord blood than in the mothers blood (median level of CZP in cord was only 3.9% that of the mother). CZP is, however, not actively transported across the placenta, as it does not have an Fc domain to bind to the FcR on the placenta[130]. In an independent clinical study on 10 pregnant women with IBD, CZP levels were measured in maternal, fetal, and cord blood *via* ELISA on the day of birth. CZP concentrations in fetal and cord blood were reduced by at least 75% as compared to concentrations in maternal blood thereby indicating low placental transfer[131].

While highly effective, there have been reported cases of infections following live vaccines in newborns following INF. For instance, there has been a case report of a fatal BCG infection in an infant who received the Rotavirus vaccine at 3 mo whose mother had been on INF as therapy for CD[132]. As such, significant caution is recommended with any live vaccines (specifically rotavirus vaccine) given during the first 6 neonatal months for any infants exposed to maternal biologics, since they cross the placenta. According to Nielsen *et al*[97], the vaccine schedule should be initiated 2-3 mo post-natally, as this should provide enough time for biologics to dissipate. In our practice, we typically wait until 6th month post-natally to give any live vaccines to infants potentially exposed to biologics in utero.

The PIANO study registry, a prospective analysis of 1315 currently enrolled pregnant women as of (March 2014) at 31 IBD centers around the country, will determine whether complication rates are significantly higher among women with IBD and their offspring who may be exposed to AZA, 6-MP or anti-TNF agents biologics during pregnancy, compared to women with IBD who do not take these medications. Pregnant women with IBD were registered for the study prospectively and evaluated at each trimester, at delivery and during for the first 4 years of the child’s life. Patients have been divided into groups based on their patterns of exposure from conception through delivery. The groups were wither ‘unexposed’ receiving neither thiopurines nor anti-TNF agents, those receiving 6MP/AZA, those receiving INF, ADA or CZP and the last group receiving combination therapy with thiopurines plus anti-TNF. Newborn complications during the first year of life, developmental milestones thereafter, maternal medications, disease activity and complications of pregnancy are all being recorded. Of the patients studied, those on biologics alone had a slightly increased rate of spontaneous abortions and C-section deliveries. These results may however be confounded by the fact that patients with more severe disease were given biologic therapies who already have clinical stress from advanced IBD. Of the patients studied, those on combination therapy (biologics and immunomodulators) had slightly elevated rates of preterm birth and infections at 12 mo. However, updated data from the registry later showed (as of April 2013) that relative risk (RR) at 1 year, adjusted for premature birth was 0.9 (95%CI: 0.7-1.1) for biologics alone, and 1.0 (95%CI: 0.7-1.3) for women using combination therapy[133]. The final results of the PIANO registry are pending. Thus far the data are reassuring for the application of immunomodulators and biologics in pregnant IBD patients.

The PIANO registry as of 2012 studied 291 patients exposed to biologic therapy alone and 75 patients exposed to biologics and immunomodulators[116], and found no increase in congenital abnormalities, infections, or developmental delays attributed to these drugs. Interestingly in the combination group, when CZP was excluded from the analysis and only INF and ADA were analyzed alone, there was an increase in infections in the combination therapy group[116]. This suggested that the presence of placentally transferred IgG1 antibodies in INF and ADA might have contributed to an increased infection risk. These antibodies can persist in the neonate for up to 6 mo. However, most of the infections occurred between months 9 and 12, a time when drug levels should be undetectable in the infants, and further research will be needed to determine if this reflects a chronically abnormal immune system development in these children[19]. CZP does not, however, actively cross the placenta and hence infection risk was not noted in CZP patients[131]. Data presented at the 2013 American Gastroenterological Association (AGA) Spring Postgraduate Course (Orlando, FL, USA) has suggested that of the 1232 women studied, there was no report of increased risk of serious infections seen in the progeny of mothers who were on TNF inhibitors.

Based on the information discussed, many experts would agree that continuing biologic therapy during pregnancy is likely to be safe with a favorable benefit/risk ratio. Despite a slightly higher infection risk in children of mothers treated with INF and ADA, if possible biologics should not be switched during pregnancy as the switch could precipitate disease flares with worse overall disease outcomes. Based on our knowledge of placental transfer, timing of biologic drug dosage can be manipulated to avoid transfer to the child while controlling disease in the mother. Ng *et al*[19] therefore suggest administering the final dose of INF at 32 wk and to continue CZP per usual dosing schedule. Since ADA requires biweekly dosing, the last dose would therefore be given at 36 weeks. According to Yiu *et al*[134] paternal exposure to anti-TNF-α therapy has not been shown to be teratogenic. Interestingly, anti-TNF-α therapy has actually been shown to increase fertility by increasing sperm count and motility.

More studies are needed regarding lactation while using biologic agents. The available data suggests that transfer of biologic agents into breast milk is low. Few data are available regarding the fetal absorption of biologics transferred into breast milk and further studies are needed to draw clinical conclusions. At present, it is thought that biologics, being very large proteins, would weakly transfer into breast milk. The small amount that does pass into breast milk is unlikely to enter the baby’s system as orally consumed biologics may ultimately be poorly absorbed by the gut. However, premature infants may absorb more drugs through breast milk due to having digestive tracts that have not fully developed[135]. Thus, the decision to breastfeed during biologic use in IBD should be made with some consideration for the health of the infant and the preferences of the mother.

**OUR EXPERIENCE WITH IBD THERAPY AND THE EVOLUTION OF BIOLOGICS AT LSU HEALTH**

In 1998, “step up therapy” for IBD was more a norm than a choice made by physicians treating IBD patients. At that time, Remicade had just been approved for use in IBD patients, but was not yet popular for this indication[65]. Physicians at LSUHSC-S were among the first in our state to use Remicade for the treatment of CD patients. The rationale behind the decision to use biologics in our patient class involved several stages. The prime objective was to rapidly decrease the inflammatory process and prevent ongoing accumulating damage to the bowel. This led to the concept of classifying our patients as ‘early’ or ‘late’ CD based on severity of disease, rather than simple and complex disease. We started by using biologics in our ‘late’ CD patients and the results were extremely encouraging. However, there were instances where patients who appeared to be in remission clinically had a contrasting picture of disease activity based on endoscopic visualization. This led us to include endoscopic evidence of remission in addition to symptomatic clinical improvement, to objectively describe success of biologic therapy in IBD patients.

The positive results noted with use of biologics in ‘late-phase’ CD patients encouraged us to incorporate biologic use in the early or recently diagnosed CD patients as well. The rationale for this approach was to halt the inflammatory process early enough in disease course so as to decrease or arrest disease progression into the severe morbidity and complications seen in late-phase disease.

Similarly, our goal for choosing appropriate treatment regimens for our pregnant IBD patients was disease control, as long as we were assured that medication regimens used to achieve therapeutic control would cause no harm to the fetus. With no evidence to suggest any adverse fetal outcomes and with biologics available and promising outcomes with their use in non-pregnant IBD patients, we decided to use biologics for uncontrolled disease in pregnant patients. We explained the potential risks and benefits to our patients who chose to be treated with these medications. Fortunately, we have not experienced any adverse outcomes to date in pregnant patients nor their fetuses as a result of treatment. Disease control with use of biologics has been excellent, and most patients have remained in remission throughout pregnancy. Therefore, we have continued to use the “top down” approach for initiation of therapy in our pregnant patients.

At LSUHSC-S, we encounter IBD patients in different phases of disease severity who may wish to conceive or already be pregnant. Our approach for management of pregnant IBD patients varies with respect to them being treatment naïve or already on some form of treatment for their disease.

As stated earlier, patients who have not been on IBD treatment are classified as per their disease activity. For patients well controlled on their regimens, we continue them on the same drug treatments. For patients with uncontrolled pathology we use “step up” approach, *i.e.,* maximizing their immunomodulator regimen if already on one. If this fails we prefer initiation of biologics. In an event of no response or suboptimal response to one biologic agent, we switch the patient to a different biologic, preferably within same class (anti-TNF or integrin). For instance, patients can be switched between INF, ADA and CZP. Similarly, for patients on a biologic prior to their pregnancy found to be with uncontrolled disease are switched from one biologic to another.

As of October 1, 2012 all CD patients at our institution were administratively directed to receive CZP for their biologic therapy needs. Another study at our institution done by Motlis *et al*, is currently evaluating both short and long-term outcomes of CD patients diagnosed with moderate to severe CD treated with INF or ADA as they undergo transition to CZP treatment. So far most patients exhibited a good clinical response to CZP and had stable disease at 1 year. This in addition to relative safety of CZP with no placental barrier transmission has made the use of CZP popular for our pregnant patients as well. Full results of this study will be submitted later this year.

The decision to initiate immunomodulator and/or biologic therapy should always be preceded by a thorough clinical workup in addition to extensive patient counseling regarding the risks and benefits of these medications these conversations should address each patient’s disease severity and underlying co-morbidities. IBD patients definitely need to be pre-screened for Hepatitis B and latent tuberculosis as per standard guidelines for all IBD immunomodulators. No guidelines exist for HCV screening in these patient populations. However, we also routinely screen for Hepatitis B, C and latent tuberculosis as a part of workup before initiation of therapy with these agents. A tuberculin skin test or IGRA (interferon gamma release assay) (Quantiferon® gold assay) is used to detect latent TB as there is a much higher incidence of reactivation of latent infection on initiation of biologic therapy and subsequent immune suppression. Contemplating use of immunomodulators like thiopurines also requires evaluation for TPMT (thiopurine methyl transferrase) activity. Phenotypic TPMT enzyme activity is measured in red blood cells and classified as - low, intermediate and normal reflecting 0.3% (homozygous for mutations of TPMT), 11% (heterozygous for mutations of TPMT), and 88.7% (wild type TPMT) of the population respectively. Patients with low to intermediate activity are at risk of decreased clearance of the drug and therefore more prone to its adverse effects. This testing helps gastroenterologists to make judicious decisions regarding the use of these medications in specific TPMT phenotype patient groups.

**CONCLUSION**

As IBD is characterized as a group of chronic and idiopathic inflammatory conditions of the gut with relapsing and remitting episodes, it has been estimated that as many as 1.4 million people in the United States have been diagnosed with a form of IBD[2]. IBD in pregnancy presents several important challenges for gastroenterologists, women with IBD, the unborn fetus, and family members. Physicians must often assist in making complicated and personal decisions on conception, pregnancy, and breastfeeding- postnatal considerations, which need to be weighed to optimize the course of pregnancy and long-term postnatal risk. At the same time, controlling disease and minimizing flares in IBD reduces disease severity and helps to maintain pregnancy but still carries risks to both mother and fetus. Future therapies that are more specific (*e.g.,* biologics) may improve outcomes with overall lower risks and may replace several currently used agents which have significant off-target effects.

Here at LSUHSC-S our approach for management of pregnant IBD patients depends on their treatment status (naïve vs being treated) and their response to the treatment (uncontrolled disease activity *vs* remission). Patients who have not been on treatment are classified based on their disease activity. For patients well controlled on their regimens, we maintain them on the same course of therapy. For patients with uncontrolled pathology we use a “top down” approach. By working closely with the patients, assessing benefits and risks of various treatment options, we are able to make judicious decisions in the management of IBD in pregnancy.

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**Figure 1 Inflammatory bowel disease drug metabolism considerations in pregnancy.**



**Figure 2 Treatment approach strategy.** IBD: Inflammatory bowel disease.

**Table 1 Food and Drug Administration pregnancy category definitions[66]**

|  |  |
| --- | --- |
| **Category** | **Definition** |
| A | Adequate and well-controlled (AWC) studies in humans have failed to demonstrate a risk to the fetus in the all trimesters of pregnancy. |
| B | 1. Studies in animals have failed to demonstrate a risk to the fetus and there are no AWC studies in humans and the drug usage benefits outweigh its potential risks, or, there were no studies performed either in animals nor in humans.
 |
| C | 1. There are no AWC studies in humans but studies in animals have shown a side effect on the fetus, and the drug usage benefits outweigh its potential risks, or, there were no studies performed either in animals nor in humans.
 |
| D | Investigational or marketing experience or studies in humans reported positive evidence of human fetus risk, but it can still be used in spite of its potential risks if there are extreme measures as in a life-threatening situation or serious disease in which safer drugs are ineffective or contraindicated. |
| X | Studies in animals or humans have demonstrated fetal abnormalities, or, there investigational or marketing experience, or both reported positive evidence of fetal risk, and, the potential risks of drug usage clearly outweigh any possible benefit (for example, other forms of therapy are available). |