World Journal of Gastrointestinal Pharmacology and Therapeutics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4292/wjgpt.v6.i4.156

World J Gastrointest Pharmacol Ther 2015 November 6; 6(4): 156-171
ISSN 2150-5349 (online)

REVIEW

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

Pegah Hosseini-Carroll, Monica Mutyala, Abhishek Seth, Shaheen Nageeb, Demiana Soliman, Moheb Boktor, Ankur Sheth, Jonathon Chapman, James Morris, Paul Jordan, Kenneth Manas, Felix Becker, Jonathan Steven Alexander

Pegah Hosseini-Carroll, Abhishek Seth, Moheb Boktor, Ankur Sheth, James Morris, Paul Jordan, Kenneth Manas, Department of Medicine, Section of Gastroenterology and Hepatology, Louisiana State University Health Sciences Center, Shreveport, LA 71130, United States

Monica Mutyala, Shaheen Nageeb, Demiana Soliman, Felix Becker, Jonathan Steven Alexander, Department of Molecular and Cellular Physiology, Louisiana State University Health Sciences Center, Shreveport, LA 71130, United States

Jonathon Chapman, Digestive Health Center of Louisiana, Baton Rouge, LA 70809, United States

Felix Becker, Department of General and Visceral Surgery, Muenster, 48149 Muenster, Germany

Author contributions: Hosseini-Carroll P and Alexander JS planned and supervised the study; Hosseini-Carroll P, Mutyala M, Nageeb S, Soliman D, Becker F and Alexander JS wrote the manuscript; Seth A, Boktor M, Sheth A, Chapman J, Morris J, Jordan P and Manas K made critical revisions of the manuscript; Becker F and Alexander JS contributed equally as senior authors.

Conflict-of-interest statement: There are no known conflicts of interest. The authors (Pegah Hosseini-Carroll, Monica Mutyala, Abhishek Seth, Shaheen Nageeb, Demiana Soliman, Moheb Boktor, Ankur Sheth, Jonathon Chapman, James Morris, Paul Jordan, Kenneth Manas, Felix Becker, and J Steven Alexander) have no relevant financial considerations related to this proposal, and the study was not supported by any corporate entity. There is no known intellectual property associated with this report.

Correspondence to: Jonathan Steven Alexander, PhD, Department of Molecular and Cellular Physiology, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, LA 71130, United States. jalexa@lsuhsc.edu
Telephone: +1-318-6754151
Fax: +1-318-6754156

Received: April 27, 2015
Peer-review started: April 29, 2015
First decision: June 19, 2015
Revised: June 30, 2015
Accepted: August 29, 2015
Article in press: September 7, 2015
Published online: November 6, 2015

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 addressed 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; Immunomodulatorsi

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, IBDs have important effects on pregnancy and present 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.

Hosseini-Carroll P, Mutyala M, Seth A, Nageeb S, Soliman D, Boktor M, Sheth A, Chapman J, Morris J, Jordan P, Manas K, Becker F, Alexander JS. Pregnancy and inflammatory bowel diseases: Current perspectives, risks and patient management. *World J Gastrointest Pharmacol Ther* 2015; 6(4): 156-171 Available from: URL: http://www.wjgnet.com/2150-5349/full/v6/i4/156.htm DOI: http://dx.doi.org/10.4292/wjgpt.v6.i4.156

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 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 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] but 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 creates a unique and challenging set of conditions to effectively manage and control. Gastroenterologists can now provide specific and targeted treatment plans which can often be managed according to each patient's individual needs. 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], more frequently[10], affecting 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 and IBD therapy 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]. 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, unless patients had undergone any IBD related surgery[12,13]. Several other factors associated with active IBD can also contribute to the overall lower 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 a conscious and concerted decision against conception[17].

For women with inactive IBD and without history of pelvic surgery, fertility is however comparable to their respective age-matched peers[18]. Pelvic surgery in IBD thus remains a major factor negatively impacting 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]. PCL[24] 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 approximately 33%-36% for their offspring to inherit a form of IBD[30,31]. Genomic studies have shown that at least 100 heritable loci may influence IBD onset and penetrance[32]. Genomic studies have identified a vast heterogeneous distribution of genes linked with IBD, possibly suggesting different populations clusters that exhibit these conditions. Consequently, 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 any individual IBD patient bearing such alleles. The large number of genes creates several diverse patterns of IBD activity and inheritance involving different levels of disease activity and thereby necessitate 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 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 4α. With respect to CD, its pathogenesis has been linked with disturbances in nucleotide binding oligomerization domain protein 2 and genes that control autophagy (*e.g.,* ATG)[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, Editor, 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 only similar risks of adverse pregnancy outcomes as the general female population[12]. Women with active IBD however 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 greater 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 baseline disease severity quantify cumulative symptoms and assess the changes of the disease in response to therapies in afflicted 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 "in remission", while a CDAI > 450 is termed severe disease[46]. Pregnant women with IBD should seek early prenatal care similar to other pregnant women but need additional education

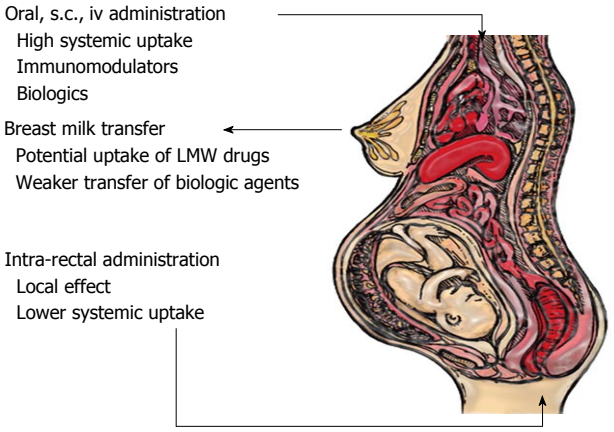

Figure 1 Inflammatory bowel disease drug metabolism considerations in pregnancy. LMW: Low molecular weight.

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 more prevalent 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 were seen to develop placental abruption in a study on obstetric hospitalizations[49]. The risk of cesarean delivery is also increased in the setting of 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 opt for a normal vaginal delivery.

As stated earlier, pregnant women with active IBD at conception suffer more frequent complications compared to those with quiescent disease (at conception), with those with low levels of disease activity for 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 again, are usually 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 particularly reliable index predicting 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 observed 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]. Recommendations by the American Society for Gastrointestinal Endoscopy, state that procedure associated 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 consideration need to be made regarding treatment modalities at different phases of pregnancy (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 mechanisms 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),

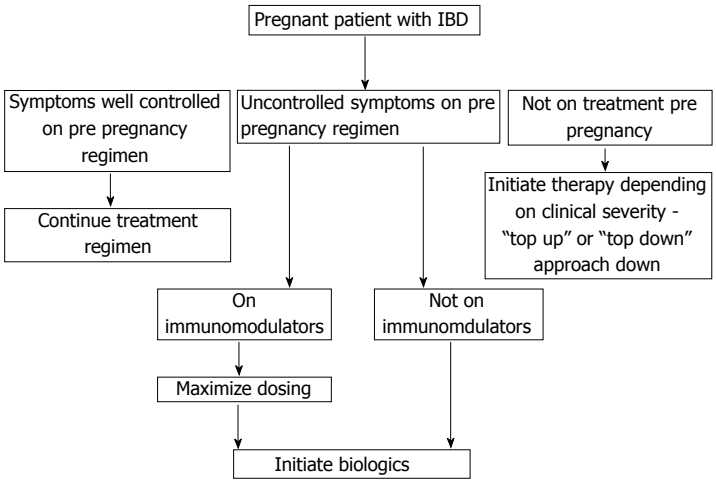

Figure 2 Treatment approach strategy. IBD: Inflammatory bowel disease.

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 $\alpha4\beta7$), which bind counter-ligands expressed on inflammation-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 final step for escalation in the "step up therapy" approach was the introduction 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" describes 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 overall 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 intensive combination therapy has gained widespread clinical acceptance of switching from the "step-up therapy" to the "top-down" approach (Figure 2). The same principle of this treatment approach also appears applicable during pregnancy, albeit with several safety considerations.

Currently, "top-down" therapy is our 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 approximately 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 obtain control of the disease early on and achieve 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 Food and Drug Administration (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 levels of risk in the setting of pregnancy. Sulfasalazine (SSZ), the first aminosalicylate used in treating IBD, is an FDA category "B" drug. Since SSZ crosses the placenta, there are several concerns in pregnancy[67]. SSZ is known to inhibit folate synthesis[68] and impairs folate absorption potentially leading to fetal neural tube defects. This has raised some concerns about its safe use during pregnancy, but these appear to have been alleviated 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 net lower incidence of having adverse outcomes. Nørgård *et al*[56] also conducted a regional retrospective cohort study, which also showed no adverse outcomes in 17 CD patients who were treated with SSZ. Therefore, SSZ may be used in pregnancy with the requirement of patients taking folate supplements[68]. In fact, pregnant women taking SSZ are advised to increase

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

Category	Definition
A	AWC studies in humans have failed to demonstrate a risk to the fetus in the all trimesters of pregnancy
B	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	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)

AWC: Adequate and well-controlled.

their daily dose of folate to 5 mg[70], compared to women not taking SSZ who only 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 suppressive 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-ASA have remained a standard 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 accepted 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 found 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 did they find any adverse fetal outcomes.

Asacol (mesalamine) (Procter and Gamble Pharmaceuticals, OH, United States of America) and Asacol HD (mesalamine delayed-release tablet) (Procter and Gamble) 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 disturbances 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 reported in association 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 found in locations from the rectum to the left colon. UC often starts in the rectum with 1/3 of patients with UC having disease restricted 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 very commonly treated by enema[80]. Enemas are 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 compartmentalized.

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 (an SSZ metabolite metabolite) is found at 50% of the concentration in the maternal circulation[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 however 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 general preference for clinicians in limiting limiting the maximum dose to 2 g mesalamine daily during pregnancy based on an association with neonatal renal insufficiency in a 1994 report[85]. This dose is low compared to the normal non-pregnant patient maximum dose of 2.4 to 4.8 g 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 of 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 *vs* 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 on placebo treatments. In a 2011 study, mesalamine and budesonide 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 were receiving budesonide and mesalamine (70% *vs* 62%). Therefore, 5-ASA, based on studies, is not as effective in the treatment of CD and its use in treating pregnant women is unclear.

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 for treating 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 of 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 still advised regarding dosing.

ANTIBIOTIC USE FOR IBD DURING PREGNANCY

Metronidazole is an antimicrobial drug and a pregnancy category "B" drug that works to limit proliferation of 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[92]. Metronidazole teratogenicity has also been demonstrated in animal models (when used in the same developmental stage equivalent of the 1st trimester) but there is apparently 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 have exhibited 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 pregnancy[97]. 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 considered whether short-term ciprofloxacin use is acceptable during 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 infant fed only by breast 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 d had no measurable ciprofloxacin in the infant's 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. In men, ciprofloxacin does not seem to affect sperm quality, however, the function of the accessory glands (including the seminal vesicles, prostate gland, and bulbourethral glands) can in some cases 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, and in patients with a history of multiple bowel surgeries, which can contribute to intestinal stasis. Rifaximin is relatively new to both the clinic and market place and is listed as a category class "C" drug during pregnancy since its fetal effects and transfer in breastfeeding is still unclear. Studies have shown rifaximin-induced birth defects in animals, including abnormalities in bone maturation and cleft palate[105], however another study failed to demonstrate as strong evidence for 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, this drug cannot yet 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 later metabolized into several metabolites including the active metabolite 6-thioguanine (6-TG) and the inactive metabolite 6-methylmercaptopurine (6-MMP). Therapeutic efficacy in IBD 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 × 10^8 red cells correlate with response and remission of IBD but levels which exceed 400 pmol/8 × 10^8 red cells correlate with bone marrow suppression. 6-MMP levels over 5700 pmol/8 × 10^8 red blood cells 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 show a defined association with birth defects. Because of their cytotoxicity, and potential risk of birth defects, they should be used with great care during pregnancy[111]. Immunomodulators alter the activity of the immune system in order to decrease the body's inflammatory response and cause an overall immunosuppressive effect. AZA and 6-MP both target the expansion of T lymphocytes, and suppress lymphocyte survival to depress inflammatory responses in IBD. These drugs effectively establish and maintain remission of IBD and are especially helpful in patients who have do not respond strongly 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*[113] studied 476 women, the majority of which had IBD. This study found a 3 × increase in the frequency of cardiac defects in children of women who took these immunomodulators early in their pregnancy. It was also found that there was a risk for increased preterm deliveries, LBW, and "small for gestational age" babies in AZA treatment associated pregnancies. A meta-analysis performed 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 discontinue taking thiopurines at least four months before conception to improve fertility[114].

Conversely, Goldstein *et al*[111] studied 189 women who took AZA for different indications and later 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 potentially 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 risk of preterm births associated with thiopurine exposure. In fact, preterm birth had an 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 the result of the more 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 evidence for an 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[115]. These milestones 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, $P = 0.02$).

Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France (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[116]. Coelho *et al*[117] 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. One of the main findings of the study was that there were no increases in congenital abnormalities in thiopurine-treated pregnancies[117].

Therefore we believe that benefits from maintenance on these immunomodulators during pregnancy may in some cases outweigh potential fetal risks. AZA and 6-MP are also believed to be generally 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*[118] suggests caution in infants with weaker than normal immune systems. We agree with this comment since these drugs may intensify an already immunodeficient state due to their mechanism of action, which could become more serious in the setting of perinatal pathogen exposures.

In conclusion, several different outcomes are possible with the use of thiopurines with the worst being a potential increase in congenital malformations. Consequently some, 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 very moderate thiopurine use as potentially safe during pregnancy[56,57,117].

Methotrexate

The action of Methotrexate (MTX) in IBD involves several mechanisms. MTX interferes with DNA synthesis producing a suppression of T-cell expansion and also diminished immune cell persistence. MTX also inhibits both lymphocyte and endothelial cell expression of intercellular adhesion molecule-1 (ICAM-1) to

lower leukocyte extravasation and its accompanying inflammation. MTX is a pregnancy category X drug, and acts as a folic acid antagonist that has been previously linked with several forms of birth defects affecting fetal organ development. Although MTX has beneficial anti-inflammatory actions in IBD, this particular drug is considered to be so dangerous in the setting of pregnancy that women should be advised to wait at least 6 mo after discontinuing MTX before resuming any attempts to conceive. MTX is also not to be used during breastfeeding as it is passed into breast milk. For men on methotrexate, one study which considered 42 pregnancy outcomes involving paternal exposure to MTX around the time of or up to 3 mo prior to conception concluded that this treatment did not enhance the risk of birth defects[119]. However, given the limited data available to date, some health 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[120].

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 recommendations have been derived from transplant experiences. CsA blocks IL-2 formation by helper T-cells. Binding of CsA to cyclophilin, inhibits calcineurin, a cytoplasmic phosphatase which participates in the control of T-cell activation. CsA also indirectly inhibits the function of B-cells by suppression of T-helper cells. CsA has a more rapid onset of clinical action than either 6-MP or AZA, which can require 3-6 mo before showing detectable disease suppressing activity[121]. Patients with CD who respond to CsA show rapid improvements within 2-3 wk[121]. Clinical improvements have also been seen within 1-2 wk following the initiation of therapy with CsA in severe UC[121].

Tacrolimus, a macrolide antibiotic, has immunomodulator properties like CsA but two orders of magnitude more potent than CsA. One advantage of tacrolimus is that it doesn't require 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[122]. So far these drugs have not yet been linked to increased rates of congenital abnormalities. However, increased rates of maternal and perinatal complications have been reported in kidney transplant recipients on different regimens of immunosuppressant medications, including those using either cyclosporine and tacrolimus[123]. These drugs are further restricted 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 only 0.05% of the maternal dose suggesting that it does not need to be discontinued while breastfeeding. Cyclosporine is also weakly transferred/passed into in breast milk and is possibly safe while breastfeeding, although caution should be recommended and exercised based on its potential for immunosuppression[97]. At LSUHSC-S we routinely discuss the such risks with our patients before initiating therapy with either CsA or tacrolimus.

Steroids

As mentioned earlier, biologic agents and immunomodulators remain key therapies in achieving remission of IBD. However, during acute flares many practitioners often fall back upon the use of 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 sporadically 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 development of when used within the first month after conception or during the first trimester[98]. However, no evidence currently links glucocorticoid use with major malformations[63,124,125]. Corticosteroids have also further been linked to premature rupture of placental membranes and adrenal suppression (so far seen only in mothers observed 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 appear to be considered to be very low clinically[126,127]. Consequently, no absolute guidelines/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 because they frequently can often 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 neutralize 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 Tysabri (natalizumab, Biogen), 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 efficiently transported 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 pregnant patients with CD or multiple sclerosis who were treated with Tysabri during their first trimester[128]. 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 $\alpha4\beta7$ integrin (expressed on the surface of T cells), thereby inhibiting T cell adhesion presumably to MAdCAM-1[129]. However vedolizumab and natalizumab are not equivalent. Although vedolizumab is listed as a category B agent, natalizumab is listed as a class C agent and therefore carries an unknown level of and is not recommended for use during pregnancy. Newer biologic therapies under development are currently in different phases of clinical trials and target other cytokines. For example, ABT-874 (Briakinumab, Abbott) and CNTO 1275 (Ustekinumab, Centocor) are both anti-IL-12/-23 antibodies and tocilizumab is anti-IL-6 antibody[130]. Briakinumab has no preganancy category assigment yet, while Ustekinumab is listed a category B agent. Tocilizumab is listed as a category C drug based on abortifacient potential of this agent; its use should be terminated prior to and during pregnancy.

Biologics like INF and ADA cross the placenta and do so at the greatest extent during the third trimester. Mahadevan *et al*[131] 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 mothers circulation. 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 being 60% higher than that of the mother. Similarly the median concentration of ADA found in cord blood was found 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 by comparison only 3.9% of that within the mother). This may reflect the fact that CZP is, not actively transported across the placenta, because it lacks an Fc domain to bind to the FcR and is confined to the maternal compartment[131]. 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 seen to be low, reduced in concentration by 75% as compared to levels in maternal blood thereby indicating low placental transfer[132].

While highly effective, there have been reported cases of infections following live vaccines in newborns following INF. For instance, there has been one 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[133]. As such, great caution is recommended with the use of any live vaccines (particularly rotavirus vaccine) given during the first 6 neonatal months for any infants potentially exposed in utero to maternal biologics, since some biologics can 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 become sufficiently cleared to accomodate immunization. In our practice, we typically wait until the 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, is intended to 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 either "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, alterations in developmental milestones, maternal medications, disease activity and complications encountered during pregnancy are all being recorded. Of the patients studied so far, those on biologics alone had a slightly increased rate of spontaneous abortions and C-section deliveries. These observations may however be confounded by the fact that patients with more severe disease were given biologic therapies and may 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 at 1 year, adjusted for premature birth was 0.9 for biologics alone, and 1.0 for women using combination therapy[134]. 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[117], and found no increase in congenital abnormalities, infections, or developmental delays which could be clearly attributed to these drugs. Interestingly in the combination group, when CZP was left out of the analysis and only INF and ADA were analyzed individually, there was an increase in infections in the combination therapy group[117]. This suggested that the presence of placentally transferred IgG1 antibodies in INF and ADA treatment groups 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 have

been undetectable in the infants, and further research will be needed to determine if these infections chronic immune system development in these children[19]. CZP does not, however, actively cross the placenta and infection risk was not noted in CZP patients[132]. Data presented at the 2013 American Gastroenterological Association (AGA) Spring Postgraduate Course (Orlando, FL, United States of America) has suggested that among the women studied, there has been no report of increased risk of serious infections seen in the newborns of mothers with IBD who had been treated with TNF inhibitors.

Based on the information discussed, many clinical experts in this field 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 wk. According to Yiu *et al*[135] paternal exposure to anti-TNF-α therapy has not been shown to be teratogenic. Interestingly, anti-TNF-α therapy has actually however been shown to improve male fertility by increasing sperm count and motility.

More studies are also needed regarding breastfeeding while using biologic agents. The available data suggests that transfer of biologic agents into breast milk may be low. Few data are available regarding the fetal absorption of biologics transferred into breast milk and more studies are needed to draw meaningful 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 substantively penetrate the baby's circulatory 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 potentially having digestive tracts that are more permeant to large molecules like biologics[136]. Thus, the decision to breastfeed during biologic use in IBD is still unclear and 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 anti-

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 in progress at our institution done by Motlis *et al*[137], 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 the 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 family and 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 according to 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 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 upon or following initiation of biologic therapy and subsequent immune suppression. Consideration of use of immunomodulators like thiopurines also requires evaluation for thiopurine methyl transferrase (TPMT) 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) in the population respectively. Patients found to have either low to intermediate activity are at risk of decreased clearance of the drug and therefore are more prone to its adverse effects. TPMT testing helps gastroenterologists to make more judicious decisions regarding the use of these medications in specific TPMT phenotype patient groups.

CONCLUSION

IBD remains characterized as a group of chronic and idiopathic inflammatory conditions of the gut exhibiting relapsing and remitting episodes. At present it is 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 particularly gastroenterologists, 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 mechanism-specific (*e.g.,* biologics) may improve clinical outcomes with overall lower to both the mother and fetus 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 generally try to 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, patient and physicians can together make prudent decisions in the management of IBD in pregnancy.

REFERENCES

1 **Baumgart DC**, Carding SR. Inflammatory bowel disease: cause and immunobiology. *Lancet* 2007; **369**: 1627-1640 [PMID: 17499605 DOI: 10.1016/S0140-6736(07)60750-8]

2 **Guidi L**, Pugliese D, Armuzzi A. Update on the management of inflammatory bowel disease: specific role of adalimumab. *Clin Exp Gastroenterol* 2011; **4**: 163-172 [PMID: 21904462 DOI: 10.2147/CEG.S14558]

3 **Langholz E**. Current trends in inflammatory bowel disease: the natural history. *Therap Adv Gastroenterol* 2010; **3**: 77-86 [PMID: 21180592 DOI: 10.1177/1756283X10361304]

4 **Lakatos PL**. Recent trends in the epidemiology of inflammatory bowel diseases: up or down? *World J Gastroenterol* 2006; **12**: 6102-6108 [PMID: 17036379 DOI: 10.3748/wjg.v12.i38.6102]

5 **Betteridge JD**, Armbruster SP, Maydonovitch C, Veerappan GR. Inflammatory bowel disease prevalence by age, gender, race, and geographic location in the U.S. military health care population. *Inflamm Bowel Dis* 2013; **19**: 1421-1427 [PMID: 23518811 DOI: 10.1097/MIB.0b013e318281334d]

6 **Assadsangabi A**, Lobo AJ. Diagnosing and managing inflammatory bowel disease. *Practitioner* 2013; **257**:13-18

7 **Price AB**. Overlap in the spectrum of non-specific inflammatory bowel disease--'colitis indeterminate'. *J Clin Pathol* 1978; **31**: 567-577 [PMID: 670413 DOI: 10.1136/jcp.31.6.567]

8 **World Gastroenterology Organisation (WGO)**. World Gastroenterology Organisation Global Guideline. Inflammatory bowel disease: a global perspective. Munich, Germany: World Gastroenterology Organisation (WGO), 2009

9 **Elbaz G**, Fich A, Levy A, Holcberg G, Sheiner E. Inflammatory bowel disease and preterm delivery. *Int J Gynaecol Obstet* 2005; **90**: 193-197 [PMID: 16043179 DOI: 10.1016/j.ijgo.2005.06.003]

10 Total Fertility Rate (Children Born Per Woman). Accessed July 23, 2014. Available from: URL: http://kff.org/global-indicator/total-fertility-rate/

11 **Hudson M**, Flett G, Sinclair TS, Brunt PW, Templeton A, Mowat NA. Fertility and pregnancy in inflammatory bowel disease. *Int J Gynaecol Obstet* 1997; **58**: 229-237 [PMID: 9252260]

12 **Dubinsky M**, Abraham B, Mahadevan U. Management of the

pregnant IBD patient. *Inflamm Bowel Dis* 2008; **14**: 1736-1750 [PMID: 18626967 DOI: 10.1002/ibd.20532]
13 **Olsen KO**, Joelsson M, Laurberg S, Oresland T. Fertility after ileal pouch-anal anastomosis in women with ulcerative colitis. *Br J Surg* 1999; **86**: 493-495 [PMID: 10215821 DOI: 10.1046/j.1365-2168.1999.01076.x]
14 **Baiocco PJ**, Korelitz BI. The influence of inflammatory bowel disease and its treatment on pregnancy and fetal outcome. *J Clin Gastroenterol* 1984; **6**: 211-216 [PMID: 6144706]
15 **Fielding JF**, Cooke WT. Pregnancy and Crohn's disease. *Br Med J* 1970; **2**: 76-77 [PMID: 5420236]
16 **Timmer A**, Bauer A, Dignass A, Rogler G. Sexual function in persons with inflammatory bowel disease: a survey with matched controls. *Clin Gastroenterol Hepatol* 2007; **5**: 87-94 [PMID: 17234557 DOI: 10.1016/j.cgh.2006.10.018]
17 **Mountifield R**, Bampton P, Prosser R, Muller K, Andrews JM. Fear and fertility in inflammatory bowel disease: a mismatch of perception and reality affects family planning decisions. *Inflamm Bowel Dis* 2009; **15**: 720-725 [PMID: 19067431 DOI: 10.1002/ibd.20839]
18 **Ørding Olsen K**, Juul S, Berndtsson I, Oresland T, Laurberg S. Ulcerative colitis: female fecundity before diagnosis, during disease, and after surgery compared with a population sample. *Gastroenterology* 2002; **122**: 15-19 [PMID: 11781275 DOI: 10.1053/gast.2002.30345]
19 **Ng SW**, Mahadevan U. Management of inflammatory bowel disease in pregnancy. *Expert Rev Clin Immunol* 2013; **9**: 161-174 [DOI: 10.1586/eci.12.103]
20 **Arkuran C**, McComb P. Crohn's disease and tubal infertility: the effect of adhesion formation. *Clin Exp Obstet Gynecol* 2000; **27**: 12-13 [PMID: 10758789]
21 **Oresland T**, Palmblad S, Ellström M, Berndtsson I, Crona N, Hultén L. Gynaecological and sexual function related to anatomical changes in the female pelvis after restorative proctocolectomy. *Int J Colorectal Dis* 1994; **9**: 77-81 [PMID: 8064194]
22 **Asztély M**, Palmblad S, Wikland M, Hultén L. Radiological study of changes in the pelvis in women following proctocolectomy. *Int J Colorect Dis* 1991; **6**: 103-107 [DOI: 10.1007/BF00300204]
23 **Waljee A**, Waljee J, Morris AM, Higgins PD. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. *Gut* 2006; **55**: 1575-1580 [PMID: 16772310 DOI: 10.1136/gut.2005.090316]
24 **Johnson P**, Richard C, Ravid A, Spencer L, Pinto E, Hanna M, Cohen Z, McLeod R. Female infertility after ileal pouch-anal anastomosis for ulcerative colitis. *Dis Colon Rectum* 2004; **47**: 1119-1126 [PMID: 15164254 DOI: 10.1007/s10350-004-0570-7]
25 **Rajaratnam SG**, Eglinton TW, Hider P, Fearnhead NS. Impact of ileal pouch-anal anastomosis on female fertility: meta-analysis and systematic review. *Int J Colorectal Dis* 2011; **26**: 1365-1374 [PMID: 21766164 DOI: 10.1007/s00384-011-1274-9]
26 **Mortier PE**, Gambiez L, Karoui M, Cortot A, Paris JC, Quandalle P, Colombel JF. Colectomy with ileorectal anastomosis preserves female fertility in ulcerative colitis. *Gastroenterol Clin Biol* 2006; **30**: 594-597 [PMID: 16733384]
27 **Bartels SA**, Vlug MS, Henneman D, Ponsioen CY, Tanis PJ, Bemelman WA. Less adhesiolysis and hernia repair during completion proctocolectomy after laparoscopic emergency colectomy for ulcerative colitis. *Surg Endosc* 2012; **26**: 368-373 [PMID: 21993930 DOI: 10.1007/s00464-011-1880-1]
28 **Orholm M**, Fonager K, Sørensen HT. Risk of ulcerative colitis and Crohn's disease among offspring of patients with chronic inflammatory bowel disease. *Am J Gastroenterol* 1999; **94**: 3236-3238 [PMID: 10566721 DOI: 10.1111/j.1572-0241.1999.01526.x]
29 **Yang H**, McElree C, Roth MP, Shanahan F, Targan SR, Rotter JI. Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews. *Gut* 1993; **34**: 517-524 [PMID: 8491401 DOI: 10.1136/gut.34.4.517]
30 **Bennett RA**, Rubin PH, Present DH. Frequency of inflammatory bowel disease in offspring of couples both presenting with inflammatory bowel disease. *Gastroenterology* 1991; **100**: 1638-1643 [PMID: 2019369]
31 **Laharie D**, Debeugny S, Peeters M, Van Gossum A, Gower-Rousseau C, Bélaïche J, Fiasse R, Dupas JL, Lerebours E, Piotte S, Cortot A, Vermeire S, Grandbastien B, Colombel JF. Inflammatory bowel disease in spouses and their offspring. *Gastroenterology* 2001; **120**: 816-819 [PMID: 11231934 DOI: 10.1053/gast.2001.22574]
32 **Cho JH**, Brant SR. Recent insights into the genetics of inflammatory bowel disease. *Gastroenterology* 2011; **140**: 1704-1712 [PMID: 21530736 DOI: 10.1053/j.gastro.2011.02.046]
33 **Andres PG**, Friedman LS. Epidemiology and the natural course of inflammatory bowel disease. *Gastroenterol Clin North Am* 1999; **28**: 255-281, vii [PMID: 10372268]
34 **Ferguson CB**, Mahsud-Dornan S, Patterson RN. Inflammatory bowel disease in pregnancy. *BMJ* 2008; **337**: a427 [PMID: 18599468 DOI: 10.1136/bmj.39566.681458.BE]
35 **Ananthakrishnan AN**. Environmental risk factors for inflammatory bowel disease. *Gastroenterol Hepatol* (N Y) 2013; **9**: 367-374 [PMID: 23935543]
36 **Khosla R**, Willoughby CP, Jewell DP. Crohn's disease and pregnancy. *Gut* 1984; **25**: 52-56 [PMID: 6140209 DOI: 10.1136/gut.25.1.52]
37 **Willoughby CP**, Truelove SC. Ulcerative colitis and pregnancy. *Gut* 1980; **21**: 469-474 [PMID: 6107262 DOI: 10.1136/gut.21.6.469]
38 **Friedman S**. Medical therapy and birth outcomes in women with Crohn's disease: what should we tell our patients? *Am J Gastroenterol* 2007; **102**: 1414-1416 [PMID: 17593158 DOI: 10.1111/j.1572-0241.2007.01214.x]
39 **Katz JA**, Pore G. Inflammatory bowel disease and pregnancy. *Inflamm Bowel Dis* 2001; **7**: 146-157 [PMID: 11383588 DOI: 10.1097/00054725-200105000-00011]
40 **Miller JP**. Inflammatory bowel disease in pregnancy: a review. *J R Soc Med* 1986; **79**: 221-225 [PMID: 2871190]
41 **Casanova MJ**, Chaparro M, Domènech E, Barreiro-de Acosta M, Bermejo F, Iglesias E, Gomollón F, Rodrigo L, Calvet X, Esteve M, García-Planella E, García-López S, Taxonera C, Calvo M, López M, Ginard D, Gómez-García M, Garrido E, Pérez-Calle JL, Beltrán B, Piqueras M, Saro C, Botella B, Dueñas C, Ponferrada A, Mañosa M, García-Sánchez V, Maté J, Gisbert JP. Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease. *Am J Gastroenterol* 2013; **108**: 433-440 [PMID: 23318480 DOI: 10.1038/ajg.2012.430]
42 **Kwan LY**, Mahadevan U. Inflammatory bowel disease and pregnancy: an update. *Expert Rev Clin Immunol* 2010; **6**: 643-657 [PMID: 20594137 DOI: 10.1586/eci.10.35]
43 **Kornfeld D**, Cnattingius S, Ekbom A. Pregnancy outcomes in women with inflammatory bowel disease--a population-based cohort study. *Am J Obstet Gynecol* 1997; **177**: 942-946 [PMID: 9369849]
44 **Fonager K**, Sørensen HT, Olsen J, Dahlerup JF, Rasmussen SN. Pregnancy outcome for women with Crohn's disease: a follow-up study based on linkage between national registries. *Am J Gastroenterol* 1998; **93**: 2426-2430 [PMID: 9860403 DOI: 10.1016/S0002-9270(98)00579-6]
45 **Freeman HJ**. Use of the Crohn's disease activity index in clinical trials of biological agents. *World J Gastroenterol* 2008; **14**: 4127-4130 [PMID: 18636655 DOI: 10.3748/wjg.14.4127]
46 **Best WR**, Becktel JM, Singleton JW, Kern F. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; **70**: 439-444 [PMID: 1248701]
47 **Bröms G**, Granath F, Linder M, Stephansson O, Elmberg M, Kieler H. Complications from inflammatory bowel disease during pregnancy and delivery. *Clin Gastroenterol Hepatol* 2012; **10**: 1246-1252 [PMID: 22922307 DOI: 10.1016/j.cgh.2012.08.018]
48 **Cornish J**, Tan E, Teare J, Teoh TG, Rai R, Clark SK, Tekkis PP. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007; **56**: 830-837 [PMID: 17185356 DOI: 10.1136/gut.2006.108324]
49 **Nguyen GC**, Boudreau H, Harris ML, Maxwell CV. Outcomes of obstetric hospitalizations among women with inflammatory bowel disease in the United States. *Clin Gastroenterol Hepatol* 2009; **7**: 329-334 [PMID: 19027089 DOI: 10.1016/j.cgh.2008.10.022]
50 **Bush MC**, Patel S, Lapinski RH, Stone JL. Perinatal outcomes in

inflammatory bowel disease. *J Matern Fetal Neonatal Med* 2004; **15**: 237-241 [PMID: 15280131 DOI: 10.1080/14767050410001668662]
51 **Calderwood AH**, Kane SV. IBD and Pregnancy. *MedGenMed* 2004; **6**: 14 [PMID: 15775841]
52 **Morales M**, Berney T, Jenny A, Morel P, Extermann P. Crohn's disease as a risk factor for the outcome of pregnancy. *Hepatogastroenterology* 2000; **47**: 1595-1598 [PMID: 11149010]
53 **Nielsen OH**, Andreasson B, Bondesen S, Jarnum S. Pregnancy in ulcerative colitis. *Scand J Gastroenterol* 1983; **18**: 735-742 [PMID: 6669937]
54 **Fedorkow DM**, Persaud D, Nimrod CA. Inflammatory bowel disease: a controlled study of late pregnancy outcome. *Am J Obstet Gynecol* 1989; **160**: 998-1001 [PMID: 2712128]
55 **Nielsen OH**, Andreasson B, Bondesen S, Jacobsen O, Jarnum S. Pregnancy in Crohn's disease. *Scand J Gastroenterol* 1984; **19**: 724-732 [PMID: 6515312]
56 **Nørgård B**, Hundborg HH, Jacobsen BA, Nielsen GL, Fonager K. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. *Am J Gastroenterol* 2007; **102**: 1947-1954 [PMID: 17573787 DOI: 10.1111/j.1572-0241.2007.01355.x]
57 **Moser MA**, Okun NB, Mayes DC, Bailey RJ. Crohn's disease, pregnancy, and birth weight. *Am J Gastroenterol* 2000; **95**: 1021-1026 [PMID: 10763954 DOI: 10.1111/j.1572-0241.2000.01852.x]
58 **Reddy D**, Murphy SJ, Kane SV, Present DH, Kornbluth AA. Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes. *Am J Gastroenterol* 2008; **103**: 1203-1209 [PMID: 18422816 DOI: 10.1111/j.1572-0241.2007.01756.x]
59 **Husain A**, Korzenik JR. Nutritional issues and therapy in inflammatory bowel disease. *Semin Gastrointest Dis* 1998; **9**: 21-30 [PMID: 9547853]
60 **Mijac DD**, Janković GL, Jorga J, Krstić MN. Nutritional status in patients with active inflammatory bowel disease: prevalence of malnutrition and methods for routine nutritional assessment. *Eur J Intern Med* 2010; **21**: 315-319 [PMID: 20603043 DOI: 10.1016/j.ejim.2010.04.012]
61 **Cappell MS**, Colon VJ, Sidhom OA. A study at 10 medical centers of the safety and efficacy of 48 flexible sigmoidoscopies and 8 colonoscopies during pregnancy with follow-up of fetal outcome and with comparison to control groups. *Dig Dis Sci* 1996; **41**: 2353-2361 [PMID: 9011442]
62 **Cappell MS**, Sidhom O. Multicenter, multiyear study of safety and efficacy of flexible sigmoidoscopy during pregnancy in 24 females with follow-up of fetal outcome. *Dig Dis Sci* 1995; **40**: 472-479 [PMID: 7851214]
63 **Shergill AK**, Ben-Menachem T, Chandrasekhara V, Chathadi K, Decker GA, Evans JA, Early DS, Fanelli RD, Fisher DA, Foley KQ, Fukami N, Hwang JH, Jain R, Jue TL, Khan KM, Lightdale J, Pasha SF, Sharaf RN, Dominitz JA, Cash BD. Guidelines for endoscopy in pregnant and lactating women. *Gastrointest Endosc* 2012; **76**: 18-24 [PMID: 22579258 DOI: 10.1016/j.gie.2012.02.029]
64 **Oldenburg B**, Hommes D. Biological therapies in inflammatory bowel disease: top-down or bottom-up? *Curr Opin Gastroenterol* 2007; **23**: 395-399 [PMID: 17545775 DOI: 10.1097/MOG.0b013e32815b601b]
65 **Bayless TM**, Hanauer SB. Advanced Therapy of Inflammatory Bowel Disease, Volume 2: IBD and Crohn's Disease. PMPH-USA, 2014
66 **Sachdeva P**, Patel BG, Patel BK. Drug use in pregnancy; a point to ponder! *Indian J Pharm Sci* 2009; **71**: 1-7 [PMID: 20177448 DOI: 10.4103/0250-474X.51941]
67 **Baggott JE**, Morgan SL, Ha T, Vaughn WH, Hine RJ. Inhibition of folate-dependent enzymes by non-steroidal anti-inflammatory drugs. *Biochem J* 1992; **282** (Pt 1): 197-202 [PMID: 1540135]
68 **Van Assche G**, Dignass A, Reinisch W, van der Woude CJ, Sturm A, De Vos M, Guslandi M, Oldenburg B, Dotan I, Marteau P, Ardizzone A, Baumgart DC, D'Haens G, Gionchetti P, Portela F, Vucelic B, Söderholm J, Escher J, Koletzko S, Kolho KL, Lukas M, Mottet C, Tilg H, Vermeire S, Carbonnel F, Cole A, Novacek G, Reinshagen M, Tsianos E, Herrlinger K, Oldenburg B, Bouhnik Y, Kiesslich R, Stange E, Travis S, Lindsay J. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. *J Crohns Colitis* 2010; **4**: 63-101 [PMID: 21122490 DOI: 10.1016/j.crohns.2009.09.009]
69 **Mogadam M**, Dobbins WO, Korelitz BI, Ahmed SW. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. *Gastroenterology* 1981; **80**: 72-76 [PMID: 6108894]
70 **Wilson RD**, Johnson JA, Wyatt P, Allen V, Gagnon A, Langlois S, Blight C, Audibert F, Désilets V, Brock JA, Koren G, Goh YI, Nguyen P, Kapur B. Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. *J Obstet Gynaecol Can* 2007; **29**: 1003-1026 [PMID: 18053387]
71 **Cosentino MJ**, Chey WY, Takihara H, Cockett AT. The effects of sulfasalazine on human male fertility potential and seminal prostaglandins. *J Urol* 1984; **132**: 682-686 [PMID: 6147421]
72 **Trallori G**, d'Albasio G, Bardazzi G, Bonanomi AG, Amorosi A, Del Carlo P, Palli D, Galli M, Pacini F. 5-Aminosalicylic acid in pregnancy: clinical report. *Ital J Gastroenterol* 1994; **26**: 75-78 [PMID: 8032081]
73 **De Broe ME**, Stolear JC, Nouwen EJ, Elseviers MM. 5-Aminosalicylic acid (5-ASA) and chronic tubulointerstitial nephritis in patients with chronic inflammatory bowel disease: is there a link? *Nephrol Dial Transplant* 1997; **12**: 1839-1841 [PMID: 9306332]
74 **Bell CM**, Habal FM. Safety of topical 5-aminosalicylic acid in pregnancy. *Am J Gastroenterol* 1997; **92**: 2201-2202 [PMID: 9399752]
75 **Marteau P**, Tennenbaum R, Elefant E, Lémann M, Cosnes J. Foetal outcome in women with inflammatory bowel disease treated during pregnancy with oral mesalazine microgranules. *Aliment Pharmacol Ther* 1998; **12**: 1101-1108 [PMID: 9845399]
76 Asacol (mesalamine), package insert. Warner Chilcott Pharmaceuticals Inc., OH, USA, 2010
77 **Hernández-Díaz S**, Mitchell AA, Kelley KE, Calafat AM, Hauser R. Medications as a potential source of exposure to phthalates in the U.S. population. *Environ Health Perspect* 2009; **117**: 185-189 [PMID: 19270786 DOI: 10.1289/ehp.11766]
78 **Rahimi R**, Nikfar S, Rezaie A, Abdollahi M. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. *Reprod Toxicol* 2008; **25**: 271-275 [PMID: 18242053 DOI: 10.1016/j.reprotox.2007.11.010]
79 Advantages in IBD: Current Developments in the Treatment of Inflammatory Bowel Diseases. *Gastroenterol Hepatol* (N Y) 2010; **6**: 309-316 [PMID: 20567586]
80 **Williams C**, Panaccione R, Ghosh S, Rioux K. Optimizing clinical use of mesalazine (5-aminosalicylic acid) in inflammatory bowel disease. *Therap Adv Gastroenterol* 2011; **4**: 237-248 [PMID: 21765868 DOI: 10.1177/1756283X11405250]
81 **Khan AK**, Truelove SC. Placental and mammary transfer of sulphasalazine. *Br Med J* 1979; **2**: 1553 [PMID: 43760]
82 **Nielsen OH**, Munck LK. Drug insight: aminosalicylates for the treatment of IBD. *Nat Clin Pract Gastroenterol Hepatol* 2007; **4**: 160-170 [PMID: 17339853 DOI: 10.1038/ncpgasthep0696]
83 **Järnerot G**, Into-Malmberg MB, Esbjörner E. Placental transfer of sulphasalazine and sulphapyridine and some of its metabolites. *Scand J Gastroenterol* 1981; **16**: 693-697 [PMID: 6119765]
84 **Nelis GF**. Diarrhoea due to 5-aminosalicylic acid in breast milk. *Lancet* 1989; **1**: 383 [PMID: 2563532]
85 **Colombel JF**, Brabant G, Gubler MC, Locquet A, Comes MC, Dehennault M, Delcroix M. Renal insufficiency in infant: side-effect of prenatal exposure to mesalazine? *Lancet* 1994; **344**: 620-621 [PMID: 7914992]
86 **Ford AC**, Kane SV, Khan KJ, Achkar JP, Talley NJ, Marshall JK, Moayyedi P. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 617-629 [PMID: 21407190 DOI: 10.1038/ajg.2011.71]
87 **Tromm A**, Bunganič I, Tomsová E, Tulassay Z, Lukáš M, Kykal J, Bátovský M, Fixa B, Gabalec L, Safadi R, Kramm HJ, Altorjay I, Löhr H, Koutroubakis I, Bar-Meir S, Stimac D, Schäffeler E,

Glasmacher C, Dilger K, Mohrbacher R, Greinwald R. Budesonide 9 mg is at least as effective as mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease. *Gastroenterology* 2011; **140**: 425-434.e1; quiz e13-14 [PMID: 21070781 DOI: 10.1053/j.gastro.2010.11.004]

88 **Cottone M**, Renna S, Modesto I, Orlando A. Is 5-ASA still the treatment of choice for ulcerative colitis? *Curr Drug Targets* 2011; **12**: 1396-1405 [PMID: 21466493]

89 **Sack DM**, Peppercorn MA. Drug Therapy of Inflammatory Bowel Disease. *Pharmacotherapy* 1983; **3**: 158-176 [DOI: 10.1002/j.1875-9114.1983.tb03245.x]

90 **Wolf JM**, Lashner BA. Inflammatory bowel disease: sorting out the treatment options. *Cleve Clin J Med* 2002; **69**: 621-626, 629-631 [PMID: 12184470 DOI: 10.3949/ccjm.69.8.621]

91 **Mahadevan U**, Sandborn WJ. Diagnosis and management of pouchitis. *Gastroenterology* 2003; **124**: 1636-1650 [PMID: 12761722 DOI: 10.1016/S0016-5085(03)00325-1]

92 **Czeizel AE**, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. *Br J Obstet Gynaecol* 1998; **105**: 322-327 [PMID: 9532994]

93 **Sohrabi D**, Alipour M, AwsatMellati A. Effect of Metronidazole on Spermatogenesis, Plasma Gonadotrophins and Testosterone in Male Rats. *IJPR* 2010; **10**: 279-283

94 **Passmore CM**, McElnay JC, Rainey EA, D'Arcy PF. Metronidazole excretion in human milk and its effect on the suckling neonate. *Br J Clin Pharmacol* 1988; **26**: 45-51 [PMID: 3203060]

95 **Clements CJ**. Metronidazole and breast feeding. *N Z Med J* 1980; **92**: 329 [PMID: 6934434]

96 **Niebyl JR**. Antibiotics and other anti-infective agents in pregnancy and lactation. *Am J Perinatol* 2003; **20**: 405-414 [PMID: 14703588 DOI: 10.1055/s-2003-45391]

97 **Nielsen OH**, Maxwell C, Hendel J. IBD medications during pregnancy and lactation. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 116-127 [PMID: 23897285 DOI: 10.1038/nrgastro.2013.135]

98 **Carmichael SL**, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. *Am J Med Genet* 1999; **86**: 242-244 [PMID: 10482873 DOI: 10.1002/(SICI)1096-8628(19990917)86:3<242::AID-AJMG9>3.0.CO; 2-U]

99 **Gürpinar AN**, Balkan E, Kiliç N, Kiriştioğlu I, Doğruyol H. The effects of a fluoroquinolone on the growth and development of infants. *J Int Med Res* 1997; **25**: 302-306 [PMID: 9364293]

100 **van den Oever HL**, Versteegh FG, Thewessen EA, van den Anker JN, Mouton JW, Neijens HJ. Ciprofloxacin in preterm neonates: case report and review of the literature. *Eur J Pediatr* 1998; **157**: 843-845 [PMID: 9809826]

101 **Belet N**, Haciömeroğlu P, Küçüködük S. Ciprofloxacin treatment in newborns with multi-drug-resistant nosocomial Pseudomonas infections. *Biol Neonate* 2004; **85**: 263-268 [PMID: 14739554 DOI: 10.1159/000076364]

102 **Drossou-Agakidou V**, Roilides E, Papakyriakidou-Koliouska P, Agakidis C, Nikolaides N, Sarafidis K, Kremenopoulos G. Use of ciprofloxacin in neonatal sepsis: lack of adverse effects up to one year. *Pediatr Infect Dis J* 2004; **23**: 346-349 [PMID: 15071291]

103 **Gardner DK**, Gabbe SG, Harter C. Simultaneous concentrations of ciprofloxacin in breast milk and in serum in mother and breast-fed infant. *Clin Pharm* 1992; **11**: 352-354 [PMID: 1563233]

104 **Merino G**, Carranza-Lira S. Infection and male infertility: effect of different antibiotic regimens on semen quality. *Arch Androl* 1995; **35**: 209-212 [PMID: 8585775]

105 **Bertoli D**, Borelli G. [Teratogenic action of Rifaximin in the rat and rabbit and its effect on perinatal development in the rat]. *Boll Soc Ital Biol Sper* 1984; **60**: 1079-1085 [PMID: 6466468]

106 **Adams CA**, Anderson LS, Juanengo JC. Effect of medications on semen analysis and sperm chromatin structure assay (SCSA) parameters. Presented at the American Association of Bioanalysts, Las Vegas, 2004

107 **Bertoli D**, Borelli G. Fertility study of rifaximin (L/105) in rats. *Chemioterapia* 1986; **5**: 204-207 [PMID: 3719854]

108 **Berkovitch M**, Diav-Citrin O, Greenberg R, Cohen M, Bulkowstein M, Shechtman S, Bortnik O, Arnon J, Ornoy A. First-trimester exposure to amoxycillin/clavulanic acid: a prospective, controlled study. *Br J Clin Pharmacol* 2004; **58**: 298-302 [PMID: 15327589 DOI: 10.1111/j.1365-2125.2004.02138.x]

109 6-Mercaptopurine (6-MP) Metabolite Monitoring and TPMT Testing in the Treatment of Inflammatory Bowel Disease with 6-MP or Azathioprine. Accessed August 13, 2014. Available from: URL: http://www.uptodate.com/contents/6-mercaptopurine-6-mp-metabolite-monitoring-and-tpmt-testing-in-the-treatment-of-inflammatory-bowel-disease-with-6-mp-or-azathioprine

110 **Bradford K**, Shih DQ. Optimizing 6-mercaptopurine and azathioprine therapy in the management of inflammatory bowel disease. *World J Gastroenterol* 2011; **17**: 4166-4173 [PMID: 22072847 DOI: 10.3748/wjg.v17.i37.4166]

111 **Goldstein LH**, Dolinsky G, Greenberg R, Schaefer C, Cohen-Kerem R, Diav-Citrin O, Malm H, Reuvers-Lodewijks ME, Rost van Tonningen-van Driel MM, Arnon J, Ornoy A, Clementi M, Di Gianantonio E, Koren G, Braunstein R, Berkovitch M. Pregnancy outcome of women exposed to azathioprine during pregnancy. *Birth Defects Res A Clin Mol Teratol* 2007; **79**: 696-701 [PMID: 17847119 DOI: 10.1002/bdra.20399]

112 **Akbari M**, Shah S, Velayos FS, Mahadevan U, Cheifetz AS. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 15-22 [PMID: 22434610 DOI: 10.1002/ibd.22948]

113 **Cleary BJ**, Källén B. Early pregnancy azathioprine use and pregnancy outcomes. *Birth Defects Res. Part A Clin. Mol. Teratol* 2009; **85**: 647-654

114 **Fertility**, Pregnancy, and Nursing in Inflammatory Bowel Disease. Accessed September 10, 2014. Available from: URL: http://www.uptodate.com/contents/fertility-pregnancy-and-nursing-in-inflammatory-bowel-disease

115 A SPECIAL MEETING REVIEW EDITION: Highlights in Crohn's Disease and Ulcerative Colitis: Digestive Disease Week 2012 May 19-22, 2012 • San Diego, CaliforniaSpecial Reporting on: • Safety and Efficacy of Subcutaneous Golimumab Induction Therapy in Patients with Moderately to Severely Active UC: PURSUIT-SC• The Future of IBD Therapy: Individualized and Optimized Therapy and Novel Mechanisms• Infliximab Concentration and Clinical Outcome in Patients with UC• Vedolizumab Induction Therapy for UC: Results of GEMINI I, A Randomized, Placebo-Controlled, Double-Blind, Multicenter, Phase III Trial• Novel Infliximab and Antibody-to-Infliximab Assays Are Predictive of Disease Activity in Patients with CD• Accelerated Step-Care Therapy with Early Azathioprine Versus Conventional Step-Care Therapy in CD• PIANO: A 1,000-Patient Prospective Registry of Pregnancy Outcomes in Women with IBD Exposed to Immunomodulators and Biologic TherapyPLUS Meeting Abstract Summaries With Expert Commentary by: William J. Sandborn, MDChief of the Division of Gastroenterology Director of the UCSD IBD Center UC San Diego Health System La Jolla, California. *Gastroenterol Hepatol* (N Y) 2012; **8**: 1-24 [PMID: 24847182]

116 **Beaugerie L**, Brousse N, Bouvier AM, Colombel JF, Lémann M, Cosnes J, Hébuterne X, Cortot A, Bouhnik Y, Gendre JP, Simon T, Maynadié M, Hermine O, Faivre J, Carrat F. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009; **374**: 1617-1625 [PMID: 19837455 DOI: 10.1016/S0140-6736(09)61302-7]

117 **Coelho J**, Beaugerie L, Colombel JF, Hébuterne X, Lerebours E, Lémann M, Baumer P, Cosnes J, Bourreille A, Gendre JP, Seksik P, Blain A, Metman EH, Nisard A, Cadiot G, Veyrac M, Coffin B, Dray X, Carrat F, Marteau P. Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines: cohort from the CESAME Study. *Gut* 2011; **60**: 198-203 [PMID: 21115547 DOI: 10.1136/gut.2010.222893]

118 **Mahadevan U**, Sandborn WJ, Li DK, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. *Gastroenterology* 2007; **133**: 1106-1112 [PMID: 17764676 DOI: 10.1053/j.gastro.2007.07.019]

119 **Beghin D**, Cournot MP, Vauzelle C, Elefant E. Paternal exposure to methotrexate and pregnancy outcomes. *J Rheumatol* 2011; **38**: 628-632 [PMID: 21239747 DOI: 10.3899/jrheum.100600]

120 **French AE**, Koren G. Effect of methotrexate on male fertility. *Can Fam Physician* 2003; **49**: 577-578 [PMID: 12790266]

121 **Sandborn WJ**. A critical review of cyclosporine therapy in inflammatory bowel disease. *Inflammatory Bowel Diseases* 1995; **1**: 48-63 [DOI: 10.1002/ibd.3780010107]

122 **Longo D**, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill Medical Publishing Division, 2011: 2490-2491

123 **Deshpande NA**, Coscia LA, Gomez-Lobo V, Moritz MJ, Armenti VT. Pregnancy after solid organ transplantation: a guide for obstetric management. *Rev Obstet Gynecol* 2013; **6**: 116-125 [PMID: 24826201]

124 **Nørgård B**, Pedersen L, Christensen LA, Sørensen HT. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish nationwide cohort study. *Am J Gastroenterol* 2007; **102**: 1406-1413 [PMID: 17437503 DOI: 10.1111/j.1572-0241.2007.01216.x]

125 **Park-Wyllie L**, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, Friesen MH, Jacobson S, Kasapinovic S, Chang D, Diav-Citrin O, Chitayat D, Nulman I, Einarson TR, Koren G. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000; **62**: 385-392 [PMID: 11091360 DOI: 10.1002/1096-9926(200012)62: 6<385::AID-TERA5>3.0.CO; 2-Z]

126 **McKenzie SA**, Selley JA, Agnew JE. Secretion of prednisolone into breast milk. *Arch Dis Child* 1975; **50**: 894-896 [PMID: 1211963 DOI: 10.1136/adc.50.11.894]

127 **Greenberger PA**, Odeh YK, Frederiksen MC, Atkinson AJ. Pharmacokinetics of prednisolone transfer to breast milk. *Clin Pharmacol Ther* 1993; **53**: 324-328 [PMID: 8453851 DOI: 10.1038/clpt.1993.28]

128 **Nazareth M**, Cristiano L, Kooijmans M. Natalizumab use during pregnancy. *Am J Gastroenterol*, 2008; **104**: S114

129 **McLean LP**, Shea-Donohue T, Cross RK. Vedolizumab for the treatment of ulcerative colitis and Crohn's disease. *Immunotherapy* 2012; **4**: 883-898 [PMID: 23046232 DOI: 10.2217/imt.12.85]

130 **Reenaers C**, Louis E, Belaiche J. Current directions of biologic therapies in inflammatory bowel disease. *Therap Adv Gastroenterol* 2010; **3**: 99-106 [PMID: 21180594 DOI: 10.1177/1756283X09356872]

131 **Mahadevan U**, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, Ullman T, Glover S, Valentine JF, Rubin DT, Miller J, Abreu MT. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; **11**: 286-292; quiz e24 [PMID: 23200982 DOI: 10.1016/j.cgh.2012.11.011]

132 **Wolf D**, Mahadevan U. Certolizumab Pegol Use in Pregnancy: Low Levels Detected in Cord Blood. *Arthritis Rheum* 2010; **62** Suppl 10: 718 [DOI: 10.1002/art.28486]

133 **Cheent K**, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case Report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J Crohns Colitis* 2010; **4**: 603-605 [PMID: 21122568 DOI: 10.1016/j.crohns.2010.05.001]

134 CRA_Newsletter_MAY-2014-1.pdf. Accessed July 17, 2014. Available from: URL: http://ccfacra.org/wp-content/uploads/2014/06/CRA_Newsletter_MAY-2014-1.pdf

135 **Yiu ZZ**, Griffiths CE, Warren RB. Safety of biological therapies for psoriasis: effects on reproductive potential and outcomes in male and female patients. *Br J Dermatol* 2014; **171**: 485-491 [PMID: 24749725 DOI: 10.1111/bjd.13060]

136 Specific Treatments - Autoimmune Studies - Adalimumab (Humira®) and Pregnancy. Accessed September 9, 2014. Available from: URL: http://www.pregnancystudies.org/ongoing-pregnancy-studies/autoimmune-studies/specific-treatments-autoimmune/specific-treatments-autoimmune-studies-adalimumab-humira-and-pregnancy/

137 **Motlis A**, Aravantagi A, Boktor M, Sheth A, Manas K, Morris J, Jordan P, Becker F, Alexander JS. Substitution With Alternative Anti-TNF-alpha Therapy (SaVANT): Outcomes of a Crohn's Disease Cohort Undergoing Substitution Therapy With Certolizumab. *Am. J. Gastro.* 109, S522

P-Reviewer: Wegrzyn G **S- Editor**: Yu J
L- Editor: A **E- Editor**: Li D

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com