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TOPIC HIGHLIGHT

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Management of inflammatory bowel disease in the pregnant patient

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Abstract

Inflammatory bowel disease (IBD) is a chronic disorder affecting young adults in their reproductive years. Many young women with IBD express concern about the effect their disease will have on fertility, pregnancy course and fetal development. This article presents an approach to management of IBD in the pregnant patient, including counseling and investigation, and summarizes existing data on the safety of medications used to treat IBD in pregnancy and breastfeeding.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Fertility; Pregnancy; Breastfeeding

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disorder affecting young adults in their reproductive years. Voluntary childlessness in patients with IBD is greater than in the general population due to relationship difficulties, body image problems, fear of pregnancy and inappropriate medical advice that pregnancy might be dangerous[1-3]. Pregnancy planning should be discussed with the patient and her partner early on prior to conception. Education and open communication are important as patients may be reluctant to broach this topic on their own. Patient concerns often relate to fertility, impact of IBD on pregnancy and fetal development, and drug effects pre-conception, during pregnancy and while breastfeeding.

FERTILITY

Women with ulcerative colitis (UC) who have not undergone surgery or those with inactive Crohn's Disease (CD) have fertility rates comparable with the rest of the population. In comparison, women with UC who have had surgery[4] or those with active CD[5,6] have increased infertility. Fertility appears to revert to normal after induction of remission in women with CD. Women who have their first pregnancy after the onset of IBD have fewer pregnancies than population controls, whereas women who became pregnant prior to onset of IBD have similar reproductive history[5]. In addition, women with CD have a delayed age of first pregnancy after being diagnosed[7] and have been shown to have fewer children than might be expected after diagnosis with a higher rate of failure to conceive[8].

IMPACT OF IBD ON PREGNANCY AND FETAL DEVELOPMENT

The initial impression looking at multiple, small observational studies of pregnancy in women with IBD was that the outcome was normal[6,9]. Fetal mortality risk (spontaneous abortion, stillbirth or neonatal death) is not higher for IBD patients[3], but there is an increased risk of preterm delivery (< 37 wk) and low birth weight (< 2.5 kg) in mothers with IBD[10-14]. Still, the majority of women with IBD will have a normal outcome of pregnancy. Disease activity is the main adverse factor predisposing to prematurity and low birth weight babies[15].

DISEASE ACTIVITY

Approximately one-third of women with inactive IBD at conception will relapse during the pregnancy or puerperium.

This risk of a flare is no greater than any other year of the patient's life[3]. If conception occurs at a time when IBD is active, disease will settle only in about one-third of women with UC or CD[12,16]. One-quarter of patients with active IBD during pregnancy will experience chronically active disease and in about half of these patients, disease will worsen (45% UC, 33% CD)[15]. Active disease has been associated with miscarriage, stillbirth, prematurity and low birth weight[17]. Thus, conception is advised when IBD is in remission.

Maintenance therapy, if possible, should be continued throughout pregnancy and flare-ups of disease should be investigated and treated appropriately as in the non-pregnant patient. If conception occurs with active IBD, inducing remission with medical therapy carries less risk than continuing pregnancy without treatment.

TNF-α AND PREGNANCY LOSS

Tumour necrosis factor is a pivotal pro-inflammatory cytokine in IBD[18]. Active IBD, more so CD than UC, is associated with elevated TNF-α levels[19,20]. In the past, TNF-α has been thought to be primarily involved in triggering immunological pregnancy loss. Newer evidence suggests that the possible essential function of TNF-α is to boost death signaling to kill the embryo if damages triggered by detrimental stimuli will result in birth of offspring with structural anomalies[21]. This theory seems more plausible from a clinical perspective since risk of pregnancy loss is higher with active IBD.

COUNSELLING THE IBD PATIENT WITH POTENTIAL FOR PREGNANCY

Preconception counseling

As with all patient-physician interactions, the therapeutic alliance, education and communication are important components in assisting the patient with IBD to make decisions about conception and pregnancy. Early on in the patient-physician relationship, preferably prior to conception, the physician should address fertility, IBD impact on pregnancy outcomes, medication effects and importance of disease remission in minimizing fetal risk. Many women want to be drug free during pregnancy and should not feel guilty about making this choice as long as it is an informed decision. The patient, her partner and her physician should discuss the possibility of disease exacerbation during pregnancy while off treatment and the necessary courses of action in such an event. Treatment choices depend on individual preference, disease severity and potential for drug toxicity. Risks and benefits of maintenance therapies during pregnancy with the best available evidence should be addressed. In addition, breastfeeding should be presented as a favorable option since it confers numerous benefits to both mother and child. The likelihood of medication secretion in breast milk and impact on fetal wellbeing become essential topics.

Alcohol

Patients contemplating pregnancy should be educated about the adverse effects of alcohol on fetal development. Maternal consumption of alcohol during pregnancy can result in fetal alcohol syndrome (FAS), a permanent birth defect clinically defined by growth deficiency, central nervous system damage and dysfunction, and a unique cluster of facial abnormalities. Although FAS is the most extreme and recognizable expression of the adverse effects of alcohol on the fetus, prenatal alcohol exposure can also cause less pronounced mental, learning and behavioral disabilities in the child, commonly termed as Fetal Alcohol Spectrum Disorders (FASDs)[22].

Smoking

Tobacco smoking during pregnancy has been associated with placenta previa, placental abruption, premature rupture of membranes, preterm birth, intrauterine growth restriction and sudden infant death syndrome (SIDS)[22]. Smoking cessation should be encouraged in the patient prior to, during and after pregnancy.

Dietary supplementation and nutritional therapy

Folic acid, calcium and vitamin D: Folic acid supplementation is recommended for all pregnant women. Women with IBD may have folic acid deficiency or be taking medications that interfere with folic acid metabolism such as sulfasalazine[15]. Thus, pregnant women with IBD should be encouraged to take 5 mg of folic acid per day instead of 1 mg/d as recommended for the general population. Also, patients with IBD on steroid therapy should be encouraged to take calcium and vitamin D supplementation to prevent bone loss.

Nutritional therapy: The average weight gain during pregnancy is 11-16 kg. Early nutritional intervention is indicated in pregnant women with active IBD who may not be gaining weight. Enteral feeding has been anecdotally shown to be associated with normal pregnancy outcome[23] and total parenteral nutrition (TPN) may be required in very sick IBD patients.

Mode of delivery

In general, the decision to have a caesarean section should be made on purely obstetric grounds. Some surgeons advise elective caesarean section to avoid risk of anal sphincter damage[15]. Vaginal delivery and episiotomy may lead to development or worsening of perianal CD[24]. Current indications for caesarean section are active perianal disease and presence of an ileoanal pouch. There is no absolute contraindication to vaginal delivery in pregnant patients with inactive IBD.

RADIOLOGIC AND ENDOSCOPIC INVESTIGATION OF IBD EXACERBATIONS DURING PREGNANCY

Radiology

Radiographic imaging should be avoided unless obstruction, perforation or toxic megacolon are suspected. Investigations that expose the patient to less radiation are preferable - specifically plain abdominal films rather than CT or barium studies. Ultrasound is the safest form

Table 1 Food and drug administration (FDA) classes in pregnancy

Class	Definition
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in later trimesters) and the possibility of fetal harm appears remote
B	Either animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women OR animal reproduction studies have shown an adverse effect (other than decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters)
C	Either studies in animals have repeated adverse effects on the fetus (teratogenic, embryonic or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus
D	There is positive evidence of human fetal risk but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective)
X	Studies in animals or human beings have demonstrated fetal abnormalities OR there is evidence of fetal risk based on human experience OR both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant

Table 2 FDA classes of medications used to treat IBD

FDA class	Medications
B	5-Aminosalicylic acid preparations (sulfasalazine, mesalamine, balsalazide); metronidazole, amoxicillin/clavulanic acid; infliximab; adalimumab
C	5-Aminosalicylic acid preparations (Olsalazine); fluoroquinolones; corticosteroids; bisphosphonates; cyclosporin; tacrolimus
D	Azathioprine and 6-MP
X	Methotrexate; thalidomide

Table 3 Breastfeeding safety of medications used to treat IBD

Safe	Limited data, potential toxicity	Contraindicated
5-ASA preparations (sulfasalazine, mesalamine)	Metronidazole Fluoroquinolones Bisphosphonates	Thalidomide Methotrexate
Amoxicillin/clavulanic acid	Azathioprine	Cyclosporine (CsA)
Corticosteroids	6-mercaptopurine (6-MP) Adalimumab Infliximab	Tacrolimus (FK506)

of radiologic imaging - it can be used to assess abscess formation and can provide information on bowel wall thickness. MRI studies are also safe and have been used to diagnose terminal ileal CD during pregnancy[17]. Since active disease in the mother has an adverse effect on the fetus, investigation for diagnostic and therapeutic purposes is warranted and should not be delayed.

Endoscopy

Endoscopy does not increase risk of premature labor or fetal abnormalities. Colonoscopy and sigmoidoscopy are safe during pregnancy if indicated[25] and rigid sigmoidoscopy and rectal biopsy can be performed without fetal risk[16]. Fetal heart rate should be monitored closely during the procedure and if required, sedation for endoscopy is thought to be safe. Antispasmodics such as hyoscine butylbromide (Buscopan) are contraindicated[15].

MEDICAL/DRUG THERAPY

The most common medication classes used in treatment of IBD are presented below, along with US Food and Drug Administration (FDA) classifications for their use. Please refer to Table 1 for details of the FDA Drug Classification System and to Tables 2 and 3 for summaries of drug safety during pregnancy and breastfeeding respectively.

5-aminosalicylic acid preparations (FDA Class B)

This class of medications includes sulfasalazine, mesalamine, olsalazine and balsalazide. Aminosalicylates are used for maintenance therapy or induction of remission in IBD. All aminosalicylates are FDA category B except olsalazine which is FDA category C. Both sulfasalazine and mesalamine are safe in breastfeeding mothers.

Sulfasalazine: Sulfasalazine competitively inhibits the brush border enzyme folate conjugase[17]. It is a folic acid antagonist that theoretically can cause neural tube defects, cardiovascular and urinary tract abnormalities, and oral clefts[26]. Clinical studies show no increase in incidence of congenital anomalies with sulfasalazine treatment[27]. Given the effect of sulfasalazine on folic acid metabolism, extra folic acid supplementation is recommended for all pregnant women on this medication during the course of their pregnancy. Sulphasalazine and its metabolite sulphapyridine both cross the placenta and are secreted in breast milk at levels approaching that of maternal levels[15]. Initial concerns about sulphasalazine in the neonatal setting were raised because a related sulfonamide (sulphisoxazole) could cause kernicterus in neonates[28]. Several studies have shown that there is no increased incidence of neonatal jaundice with sulfasalazine[9,30]. It is safe in breastfeeding mothers unless the fetus suffers from pre-existing hemolysis or if a rhesus incompatibility between mother and fetus is suspected[17].

5-ASA (Mesalamine): Mesalamine is safe in pregnancy in conventional doses. Higher doses of greater than 3 g/d carry a potential risk of fetal nephrotoxicity, specifically interstitial nephritis[30]. There is no significant change in congenital abnormalities, abortions or fetal distress with conventional 5-aminosalicylic acid treatment[31-33]. Mesalamine is excreted in breast milk, but does not pose a significant risk to the baby[34].

Antibiotics

Metronidazole and the quinolones have limited benefit for long term treatment of IBD. Short courses of these medications in treatment of pouchitis and perianal disease are low risk in the pregnant patient.

Metronidazole (FDA Class B): Metronidazole is used for treatment of active CD as well as perianal disease. This medication does not increase risk of spontaneous abortion or congenital anomalies[35,36], although infants of women exposed to metronidazole in the second to third months of pregnancy have shown higher rates of cleft lip with or without cleft palate[37]. Potential toxicity exists for long-term metronidazole use while breastfeeding[38].

Fluoroquinolones (e.g. Ciprofloxacin) (FDA Class C): Human studies with fluroquinolones have not shown increase in spontaneous abortion or congenital abnormality incidence[39]. However, animal studies demonstrate musculoskeletal abnormalities induced by this medication class[40]. Fluroquinolones have a high affinity for bone tissue and cartilage, and may cause arthropathies in children. Although they are thought to have minimal risk overall, they should be avoided in the first trimester. Fluoroquinolones are likely compatible with breastfeeding, although data is limited.

Amoxicillin/clavulanic acid (FDA Class B): Amoxicillin/clavulanic acid is used as an alternative antibiotic for pouchitis. It does not confer increased teratogenic risk and is compatible with breastfeeding[41].

Corticosteroids (FDA Class C)

Corticosteroids come in parenteral, oral and topical formulations. They include prednisone, prednisolone, dexamethasone and budesonide, and are indicated in moderately to severely active disease[3]. Although corticosteroids cross the placenta, these agents pose a very small risk to the developing infant when used in the first trimester. This risk is often outweighed by the benefit of controlling the mother's IBD. Animal studies show increased frequency of cleft lip and cleft palate[42]. However, these findings do not correlate with human results. A prospective controlled study in 2004 did not demonstrate increased rate of congenital anomalies or oral cleft with corticosteroid treatment during pregnancy[43]. In addition, studies of corticosteroid use in pregnant patients with rheumatoid arthritis, antiphospholipid syndrome and SLE show no convincing evidence of teratogenesis[44-46] and steroid use in IBD patients is not associated with pregnancy complications[29].

Although adrenal suppression among neonates born to mothers taking corticosteroids is a theoretical concern, it has not been an issue in practice. Rectal preparations can be used until the third trimester unless there are specific concerns regarding miscarriage or premature delivery[15].

Corticosteroids are secreted into breast milk in low concentrations. The maternal: fetal ratio of steroid serum concentrations depends on which steroid the patient is taking. Fluorinated steroids, betamethasone and dexamethasone are less efficiently metabolized by the placenta compared to prednisolone, resulting in fetal levels 10%-12% of that in maternal serum[47]. While breastfeeding is safe with steroid use, mothers are encouraged to defer breastfeeding until 4 h after taking oral dosing of steroids to reduce neonatal exposure[48].

There is no data on the safety of oral budesonide in pregnancy. Inhaled or intranasal budesonide is not associated with adverse fetal outcomes. Budesonide effects on breastfeeding are unknown[38].

Bisphosphonates (FDA Class C)

IBD patients on long term corticosteroid treatment may be started on bisphosphonates to prevent bone loss or treat osteoporosis. Alendronate and risedronate are two common bisphosphonates used to this effect. Alendronate has been shown in animal studies to cross the placenta and incorporate into fetal bone[49]. Long-term effects of alendronate on human bone development are unknown and the half-life of alendronate is greater than 10 years. The concern with long-term bisphosphonate treatment is that the drug is slowly released from maternal bone and may result in continuous low-level exposure to the fetus during gestation. Thus, bisphosphonates should be used with caution in young women who have the potential for pregnancy.

Immunomodulators

Methotrexate (FDA Class X): Methotrexate is used as an alternative to azathioprine in treatment of steroid dependent or resistant CD. It is a teratogen that interferes with folic acid metabolism and purine synthesis. In obstetrics, it is used therapeutically to abort ectopic pregnancies[50]. Fetuses exposed to methotrexate develop congenital anomalies collectively known as methotrexate embryopathy or fetal aminopterin syndrome characterized by intrauterine growth retardation, decreased ossification of the calvarium, hypoplastic supraorbital ridges, small low-set ears, micrognathia, limb abnormalities and sometimes mental retardation. Methotrexate is contraindicated in pregnancy and breastfeeding. Female and male patients on methotrexate must be using a reliable form of contraception and should avoid conceiving for 6 mo after stopping the drug. A woman who conceives on methotrexate and refuses therapeutic abortion should stop the methotrexate and immediately start high dose folic acid replacement[51].

Azathioprine/6-mercaptopurine (6-MP) (FDA Class D): Azathioprine (a prodrug of 6-MP) and 6-MP are used in treatment of steroid-dependent or resistant IBD. Most evidence for safety of azathioprine in pregnancy comes from studies in transplantation. The fetus is protected from potential teratogenic effects of azathioprine and 6-MP since the fetal liver lacks the enzyme inosinate phosphorylase which is necessary to convert azathioprine and 6-MP to active metabolites. Both these medications when used in small doses in clinical practice do not affect human interstitial cell function or gametogenesis[52,53]. Renal transplant patients and SLE patients on treatment with azathioprine and 6-MP have had good outcomes[15]. Also, retrospective studies have also shown that these medications are safe in pregnant patients with IBD[54,55]. If a patient is established on azathioprine or 6-MP therapy and the drug is essential to maintain remission, the patient should continue treatment. Breastfeeding is not recommended by the manufacturers of azathioprine and 6-MP, but clinical experience of mothers shows no adverse side effects[15].

Cyclosporine (CsA) (FDA Class C): CsA is used to delay surgery in severe UC. It is a selective immunosuppressant with the ability to inhibit activation of T cells, preventing formation of IL-2. Although it is not teratogenic, it crosses the placenta and is secreted in breast milk at high concentrations. CsA is contraindicated with breastfeeding to avoid neonatal immunosuppression. It is most likely safe with no adverse fetal effects during pregnancy. Most of the data regarding the use of cyclosporine comes from transplant patients[48,56]. CsA is a highly toxic drug for the mother with risk of hypertension, nephrotoxicity and hepatotoxicity. CsA should not be used during pregnancy, except to prevent urgent colectomy in patients with fulminant UC[57].

Tacrolimus (FK506) (FDA Class C): Tacrolimus is a fungus-derived immunosuppressant with a mechanism of action similar to CsA. It has been associated with increased incidence of perinatal hyperkalemia and prematurity[58]. A single case report with favourable outcome for a pregnant patient with UC was published in 2005[59]. It is contraindicated in breastfeeding due to high concentrations in breast milk.

Thalidomide (FDA Class X): Thalidomide is used in treatment of refractory CD. It has extensive teratogenic sequelae including limb defects, central nervous system effects and abnormalities of the respiratory, cardiovascular, gastrointestinal and genitourinary systems. Thalidomide is contraindicated during pregnancy and breastfeeding. Women of childbearing age taking thalidomide should use two methods of contraception 1 mo prior to starting therapy, during therapy and for 1 mo after stopping therapy.

Biological therapy

Infliximab (FDA Class B): Infliximab is a chimeric monoclonal antibody that inhibits TNF-α, a pro-inflammatory cytokine. It is used in treatment of patients with severe active CD. One study and a patient series have provided data for safety of infliximab in pregnancy. The Infliximab Safety Database maintained by Centocor (Malvern, Pennsylvania, USA) presented outcome data on 96 women with direct exposure to infliximab. The outcomes for these women were not different from those of the general population[60]. A patient series of ten women on maintenance infliximab throughout pregnancy ended in live births with no congenital malformations for all women[61]. Still, long-term implications of in-utero exposure to infliximab remain unknown. Infliximab crosses the placenta but is not detectable in breast milk and case reports of women who breastfed while on infliximab do not suggest toxicity[62]. However, long-term effects on the developing infant's immune system while breastfeeding on infliximab are unknown.

Adalimumab (FDA Class B): Adalimumab has been recently demonstrated as a safe and efficacious therapy in induction of remission and maintenance therapy in CD[63]. There is one case report of a successful pregnancy in a woman with longstanding CD who began adalimumab 1 mo prior to conception[64]. There is no data on long-term effects of adalimumab on the developing fetus, or on its safety in breastfeeding.

Fish oil supplements (FDA Class-not applicable): Fish oil supplements are used by some patients with IBD as an adjunct to medical therapy. A randomized controlled trial of fish oil supplementation demonstrated prolongation of pregnancy without detrimental effects on growth of the fetus or course of labour[65]. Fish oil supplements are not rated by the FDA since they are not classified as a drug.

CONCLUSION

Mothers with IBD have an increased risk of preterm delivery (< 37 wk) and low birth weight (< 2.5 kg) babies. Active IBD has also been associated with miscarriage and stillbirth. Maintenance therapy for IBD, if possible, should be continued throughout pregnancy and flare-ups of disease should be investigated and treated appropriately as in the non-pregnant patient. If conception occurs with active IBD, inducing remission with medical therapy carries less risk than continuing pregnancy without treatment. Early on, the physician should address fertility, IBD impact on pregnancy outcomes, medication effects and importance of disease remission in minimizing fetal risk with female patients of child-bearing age. It is important to provide patients with careful counseling regarding potential teratogenicity or adverse outcomes of medication use during pregnancy and breastfeeding. Individual patient preference, disease severity and potential for drug toxicity should determine the best therapy choice for each patient.

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