INHERITANCE

BD has a genetic predisposition, but not in true Mendelian fashion. The child of an affected parent has 5%–7.5% risk of developing Crohn’s disease and 1.6% of ulcerative colitis (1). If both parents have the disease, the risk of developing IBD is up to 37% (2). The risk of inheriting IBD is higher in Jewish families (7.8%) than non-Jewish families (5.7%) (2). Ten percent of patients with IBD have an affected first degree relative usually with disease concordance in families.

FERTILITY

The infertility rate, failure to become pregnant after 12 months of unprotected intercourse, is 15% in the general population (3). Voluntary childlessness is higher in IBD patients (4). This results from disease impact on interpersonal relationships, body image problems, fear of pregnancy and inappropriate medical advice (5). In addition, physician views of medications and IBD effects on the fetus contribute to fear of pregnancy. Drugs to treat IBD do not affect female fertility.

Patients with quiescent ulcerative colitis (UC) have the same fertility rates as the general population (4,6). In Crohn’s disease, women with active inflammation have reduced fertility by several mechanisms depending on site of inflammation. Active inflammation and previous surgical intervention, especially in terminal ileum, causes scarring of fallopian tubes and ovaries (7,8). Patients with perianal disease have secondary dyspareunia and decreased libido contributing to decreased fertility (4,7,9,10).

UC is frequently treated with proctocolectomy with ileal pouch anal anastomosis (IPAA). IPAA does not affect pregnancy and childbirth, but does affect fertility. It is thought that the extent and location right to the pelvic floor of the IPAA surgery as well as adhesions and blockage of the fallopian tubes causes severe reductions in fecundity (6,11,12). The risk of male impotence after total proctocolectomy is very rare and should not dissuade patients to undergo the surgery.

Men with IBD have normal reproductive capacity. However, medications can affect fertility. The sulfapyridine moiety of sulfasalazine causes transient reversible sperm count and motility in up to 60% of men (13–15). Taking folate does not reverse this effect nor does dose reduction. Men should be off this medication for a few months before attempting conception. The 5-ASA compounds and azathioprine/6-mercaptopurine have no effect on male fertility. Methotrexate causes reversible oligospermia in men (16).
Infliximab therapy in men may decrease sperm motility and the number of normal oval forms (17). Semen quality of 10 male patients receiving infliximab infusions (seven for maintenance and three for induction) were studied. Significant differences in sperm progression were noted (17).

**EFFECTS OF IBD ON PREGNANCY**

The question of whether IBD in the mother entails an increased risk for pregnancy complications is of great concern to many patients. Discussions between the patient and physician should help to facilitate a successful pregnancy. Women with quiescent disease will more likely have an uncomplicated pregnancy. If disease is active at the time of conception and throughout the pregnancy, it will increase the risk of complications (18). Though no formal guidelines exist, it is recommended that patients be in remission for at least three months prior to planned conception (19).

Pregnant women with quiescent inflammatory bowel disease do not have increased incidence of congenital abnormalities, spontaneous abortion or stillbirth. Studies from Sweden, Denmark and Washington state report women with IBD, independent of disease activity, have higher rates of low-birth-weight infants, preterm births, and small-for-gestational-age infants (20–22). The proposed theories include infectious agents, aberrant prostaglandin production or impaired smooth muscle neurological control.

**EFFECTS OF PREGNANCY ON IBD**

The activity of disease at the time of conception determines the course of disease during pregnancy. For women with quiescent UC and Crohn’s disease at conception, the rate of relapse is approximately the same in pregnant and nonpregnant women; approximately one-third of patients will relapse (22). If conception occurs during active disease, many will experience active disease throughout the pregnancy. In UC 24% get no better, 45% worsen (18). In Crohn’s disease, one-third of women with active disease will have worsened activity, one-third will continue at the same level of severity, and one-third will improve (9,23).

Possible explanations for why one-third of patients improve are the role of maternal-fetal disparity resulting in down-regulation of the maternal immune system (24) and cessation of tobacco during pregnancy. However, UC patients who stop smoking may cause the disease to flare. Older literature suggests that patients with Crohn’s disease tended to flare more during the first trimester and post partum; this did not account for the fact that many patients stopped maintenance medications when they found out they were pregnant and when breastfeeding.

For the health of both mother and baby, it is important to attempt to induce remission before conception or to wait for a period of remission of three months before attempting to conceive. The activity of IBD at conception is the primary predictor of the course of pregnancy. It is important to emphasize to your patients, that conception should be planned when disease is quiescent.

**MANAGEMENT OF IBD DURING PREGNANCY**

**Medications (Table 1)**

The key principle of management of IBD in pregnancy is that active disease, not therapy, poses the greatest risk to pregnancy. Disease activity, not medication use, most strongly affects pregnancy outcome.

Sulfasalazine crosses the placenta, but no evidence of harmful effects to the fetus exists, so it is considered low-risk for use by pregnant women (25). Sulfasalazine interferes with folic acid metabolism; therefore, folate supplementation (2 mg daily) is recommended to prevent neural tube malformations such as spina bifida (26).

Mesalamine is a commonly used 5-aminosalicylic acid (5-ASA). Several prospective studies of mesalamine use during pregnancy as well as large pharmacy databases show no increase in the incidence of major malformations compared with controls (27–29). Women with IBD should not discontinue treatment during pregnancy because they will experience relapses that are associated with a higher incidence of perinatal risk. There has been a single case report of renal interstitial damage in a child born to a woman taking mesalamine, but this finding has not been confirmed in other studies (30).

Metronidazole and ciprofloxacin are currently the most frequently used antibiotics for extended periods in IBD. Metronidazole is a known carcinogen in rodents,
but not in humans (31). Although a few cases of cleft lip have been reported, a meta-analysis failed to show any relationship between metronidazole exposure and birth defects (31). A prospective study of 226 women exposed to metronidazole during pregnancy showed 86% of whom were exposed during the first trimester, malformation rate was 1.6% in exposed group versus 1.4% in control group (31,32). Metronidazole use is considered low-risk for use during pregnancy.

Ciprofloxacin, a pregnancy category C drug, is not teratogenic, but musculoskeletal abnormalities have been noted in animals which led to restricted use of ciprofloxacin during pregnancy (33,34). A large prospective controlled trial of 200 women did not reveal increase risk of congenital malformations. This information is comforting, but applies to short term use which is not the case in IBD (35). Since safer alternatives such as amoxicillin/clavulanic acid (category B) exist, the use of ciprofloxacin and other quinolones are not recommended during pregnancy.

Rifaximin, a non-absorable antibiotic currently approved for traveler’s diarrhea, is also used to treat IBD. It is a pregnancy class C drug. Animal studies show no effect on fertility or teratogenicity but not enough human data exist (36).

Corticosteroids are used often to treat acute flares in IBD. It is a pregnancy category C drug. Corticosteroids cross the placenta, but are rapidly metabolized. Prednisolone and prednisone are more efficiently metabolized than dexamethasone resulting in fetal concentrations approximately 10% of maternal levels (37). Women exposed to steroids during pregnancy show no increased incidence of prematurity, spontaneous abortion, still-birth or developmental defects (25). Although there is a theoretic risk of adrenal insufficiency in the neonate born to mothers taking corticosteroids, this is rarely seen in practice (38). Corticosteroids may exacerbate gestational diabetes and pregnancy induced hypertension, so close monitoring must be conducted.

There are no studies of the use of budesonide during pregnancy in humans with IBD. Studies from the asthma literature of inhaled budesonide suggests that it is safe during pregnancy (39,40).

Azathioprine and 6-mercaptopurine (6MP) are category D medications. Teratogenicity in mice and rabbits, but not rats exist possibly due to drug metabolism differences by species (41). Like corticosteroids, azathioprine crosses the placenta but the fetal liver lacks inosinate pyrophosphorylase, necessary to convert azathioprine to its active metabolite. The largest experience of AZA and 6MP in pregnancy comes from the transplant literature recommending its use safe during pregnancy (42,43). Most of the IBD literature on this topic is retrospective, but concludes that these drugs are safe and well tolerated during pregnancy (41,44,45). The Mount Sinai group conducted a retrospective review of 485 patients who received 6MP for IBD (44). Pregnancies were analyzed as to whether the patient had taken 6-MP before, or at the time of, conception. There was no statistical difference in conception failures (defined as a spontaneous abortion), abortion secondary to a birth defect, major congenital malformations, childhood neoplasia, or increased infections among male or female patients taking 6-MP compared with controls (44).

Methotrexate is a pregnancy category X drug, associated with fetal loss with a spontaneous abortion rate as high as 40% and with congenital anomalies, including neural tube defects and craniofacial defects. In humans, methotrexate is an abortifacent and contraindicated before and during pregnancy. Methotrexate causes reversible oligospermia in men (16). It is recommended

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that both men and women discontinue methotrexate three to six months prior to attempting conception.

Infliximab, a chimeric monoclonal antibody active against tumor necrosis factor alpha, has a class B safety rating. The Infliximab Safety Database, a retrospective database maintained by Centocor, identified 96 women with exposure to infliximab during pregnancy (47). Data from the TREAT registry, a prospective registry of patients with CD receiving infliximab as well as a control group receiving conventional therapy, as of 2004 identified 66 pregnancies, 36 which had prior infliximab exposures. The miscarriage rate was 11.1% vs 7.1% and neonatal complications were 8.3% vs 7.1%. No fetal malformations occurred in any of these pregnancies. There was not a significant difference in terms of neonatal complications, fetal malformations and miscarriage rates between infliximab treated or naïve patients (48). A retrospective review of intentional infliximab use in ten pregnant patients resulted in live births. Three infants were premature and one had low birth weight, but no congenital malformations or intrauterine growth retardation were noted (49). The long term effects of exposure of infliximab to a newborn are not known. Timing infusions to minimize antibody transfer to the fetus is important to counsel while using this medication during pregnancy.

Adalimumab is another biologic agent currently used off-label for Crohn’s disease patients intolerant to infliximab. Like infliximab, it is a category B medication. There are two case reports of successful use of adalimumab during pregnancy (50,51).

Loperamide is considered safe during pregnancy. Its use should be monitored because increased stool frequency may indicate increased disease activity.

Diphenoxylate with atropine is teratogenic in animals and infants exposed during first trimester have developed fetal malformations. Antispasmodics and anticholinergics have been associated with fetal malformations so should be avoided during pregnancy. Codeine has been used safely in pregnancy for years without fetal teratogenicity. Drug dependence and withdrawal in the newborn can occur, but is very rare.

**Disease Assessment**

A range of modalities may be used to assess disease activity in pregnant patients with IBD. Hemoglobin decreases from hemodilution occur in pregnancy, making it a less useful marker of disease activity. Ultrasound, used to monitor the development of the fetus, is safe. MRI is a safe modality that can be used to assess colonic wall thickening or detection of intra-abdominal abscess (52). Low-dose X-rays (less than 5 rads) pose a minimal risk to the fetus (53).

Flexible sigmoidoscopy is a valuable tool to assess the severity of disease and anatomic extent of disease. It is considered a safe procedure to perform during pregnancy when indicated (54). Full colonoscopy is rarely indicated. Polyethylene glycol solution has not been studied in pregnancy, thus fetal outcomes are unknown. Generally oral preps are not recommended, and if a full colonoscopy is necessary tap water enemas are recommended for bowel preparation (55).

**Surgery for IBD During Pregnancy**

The indications for surgery in the pregnant IBD patient are the same as for the non-pregnant IBD patient. These include toxic megacolon, perforation, medically refractory severe colitis, obstruction, abscess and intractable bleeding (56). Surgery for an acute indication in the setting of pregnancy carries a high-risk of fetal loss and is considered when other options are not available (57,58). Continued severe illness poses a greater risk to the fetus than the operation. Case reports of deliveries of healthy infants following colectomy for fulminant colitis are reported (59). There is no evidence that therapeutic abortion improves outcome of fulminant colitis so it is not indicated. Surgery in the setting of pregnancy carries a high-risk of fetal loss (57). A team approach with early management and continuous assessment by the OB, surgeon, and gastroenterologist is vital for the patient.

**Mode of Delivery**

The mode of delivery should be dictated by obstetric indication and necessity, but the decision should be made with the gastroenterologist to avoid complications. Caesarean section should be performed for active perianal disease and considered for inactive perianal disease. Higher rates of caesarean section in IPAA have been reported, and may reflect physicians (continued from page 19)
The Pregnant IBD Patient

**INFLAMMATORY BOWEL DISEASE: A PRACTICAL APPROACH, SERIES #28**

(continued from page 22)

**Table 2**

<table>
<thead>
<tr>
<th>Safe to Use When Warranted</th>
<th>Limited Data Available</th>
<th>Contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral mesalamine</td>
<td>Azathioprine</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Topical mesalamine</td>
<td>6-Mercaptopurine</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Infliximab</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Tacrolimus</td>
<td>Metronidazole</td>
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<tr>
<td></td>
<td>Budesonide</td>
<td>Ciprofloxacin</td>
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<tr>
<td></td>
<td>Olsalazine</td>
<td>Diphenoxylate</td>
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<td></td>
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<td>Loperamide</td>
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concern about extensive pelvic scarring or damage to the pouch during vaginal delivery and the theoretical risk of damage to the anal sphincter (60,61). Ileostomy or colostomy does not preclude vaginal delivery, but if obstetric risk is present, a caesarean section should be performed (62). Episiotomy should be avoided if possible, because of the possibility of disease extension, rectovaginal fistulas, and nonhealing perineal wounds, but is better than a spontaneous laceration (63).

Pouch function does not appear to be greatly affected during pregnancy or by route of delivery (64,65). Mean number of bowel movements per day was 8.1 during pregnancy compared with 6.5 in the postpartum period (64). Based on these results, we conclude that pregnancy is safe for women who have undergone IPAA and that the method of delivery does not affect pouch function (62,65).

**Breastfeeding (Table 2)**

Historical literature indicated that breastfeeding caused flare of disease, but did not account for the cessation of maintenance medication. A retrospective questionnaire of 122 patients with IBD identified 54 patients who breast fed, 71% UC and 29% CD. The primary reason indicated for not breastfeeding included fear of medication interactions (52%), physician recommendation (30%) and personal choice in 18% (66). The majority of women who breastfed 40/54 (74%) stopped taking their medications prior to breastfeeding. Thirty percent of patients had post partum flare of which 64% breastfed for at least one month prior to onset of their flare. An odds ratio of 2.2 for post partum disease activity was found for those who breastfed, but this effect disappeared when adjusted for medication cessation. A true association between breastfeeding and disease activity may be more a consequence of discontinuation of medications to control disease.

**Other Issues During Pregnancy**

Heartburn, constipation, hepatitis, cholelithiasis occur increasingly during pregnancy in IBD and non-IBD patients.

**SUMMARY**

- Fertility is affected in UC after IPAA and in active CD.
- Adverse fetal outcomes are not increased when IBD is quiescent.
- Most medications for IBD are safe during pregnancy and breastfeeding.
- Active disease is more harmful than medications needed for maintenance.
- Active disease is a risk for preterm delivery and low birth weight. It is important to be in clinical remission prior to conception and treat flares aggressively.

**References**


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