



**Disclaimer:** This newsletter, provided by ITIS, is funded by a grant from the Illinois Department of Public Health and supported by Northwestern Memorial Hospital and Northwestern University Medical School. It is for educational purposes only and is meant to summarize the information available at the time of its creation. It should be construed neither as medical advice nor opinion on any specific clinical situation. For more information on a specific clinical situation, or updated information, please consult your health care provider.

## **Crohn's Disease in Pregnancy**

Volume 10, Issue 2

Crohn's disease, an inflammatory bowel disease is a serious, chronic condition of the gastrointestinal tract with unknown cause. However, it does appear have a strong genetic component in some families (CCFA 1999). Crohn's disease causes diarrhea, abdominal cramps, pain, fever, and occasionally rectal bleeding. Subsequently, an individual with Crohn's disease suffers from a loss of appetite and weight loss. The symptoms of the disease usually manifest themselves between the ages of fifteen and thirty (Moser et al., 2000, CCFA 1999). Unlike ulcerative colitis, which affects the mucosal layer of the bowel, Crohn's disease affects all layers (CCFA 1999).

There is consensus that patients with active disease should avoid pregnancy (Moser et al., 2000, Connell and Miller, 1999). The effects of active inflammation are believed to be more harmful to a fetus than the effects of treatment; subsequently disease activity plays a more important role in determining fetal outcome than drug treatment. In order to maintain remission, treatment during pregnancy is justified (Connell and Miller, 1999).

Connell and Sandborn (1999) suggest fertility is relatively normal in patients that are treating their Crohn's disease. However, some data suggest that even in remission, regardless of the type of treatment, Crohn's disease may cause pregnancy complications (Kornfeld et al., 1997). For example, an association between Crohn's disease and poor maternal weight gain, vaginal bleeding, premature rupture of the membrane, miscarriage and low birth weight independent of medication use has been raised (Moser et al., 2000). In fact, the severity of the disease is related to the severity of the complications experienced in pregnancy (Mogadam et al., 1981).

Corticosteroids, aminosalicylic acids, immunosuppressives, methotrexate, and antibacterial medications are used in the treatment of Crohn's disease. These medications are also used to maintain remission. This newsletter will review these medications.

### **Corticosteroids**

Corticosteroids are frequently used in the treatment of Crohn's disease, with prednisolone being the most common choice. Prednisolone in doses of 40mg or more resulted in an overall remission in 67% of patients whereas doses of 60mg yielded remission in 83% of patients. This medication, however, can aggravate pregnancy complications, such as glucose intolerance, hypertension, sodium retention and peripheral oedema. Abrupt cessation of high dose, or prolonged use of prednisolone may induce maternal adrenal insufficiency and supplemental treatment may be needed during labor (Connell and Miller, 1999).

In humans, the concentration of prednisolone in the fetus has been found to be approximately 10% of that in maternal circulation. This is comparatively different from other corticosteroids; for example,

dexamethasone crosses the placenta freely and is used in the treatment of congenital adrenal hyperplasia. This small amount of prednisolone is unlikely to cause fetal adrenal suppression (Connell and Miller, 1999). However, there are case reports of neonatal adrenal insufficiency. Thus, it is recommended that prednisolone be used with caution in pregnancy.

The Motherisk Teratogen Information Service documented a slight increased risk of cleft palate in association with prednisolone (Park-Wyllie L, et al., 2000). In most studies, prednisolone was not found to be associated with an increase in congenital anomalies (Reprotox #1359). However, early studies found that it may be associated with fetal growth retardation, stillbirth, placental insufficiency, reduced neonatal birth weight and fetal distress. It is unclear if these complications are due to the medication or to the underlying condition, and subsequent studies have not confirmed these findings (Connell and Miller, 1999 and Illinois Teratogen Information Service, 2000). The Crohn's and Colitis Foundation of America has stated that prednisolone is appropriate to use as treatment in pregnant women (Connell and Sandborn, 1999).

### **Aminosalicylates**

#### **Sulfasalazine**

Sulfasalazine (Azulfidine®) is used in the induction and maintenance of remission of mild to moderate inflammatory bowel disease. Sulfasalazine is a 5-aminosalicylic acid conjugated to a sulfapyridine. Sulfapyridine is thought to be responsible for the drug's adverse side effects, which include nausea, vomiting and hepatitis (Connell and Miller, 1999 and Connell and Sandborn 1999).

Most studies on animals do not show an increase in congenital malformations associated with sulfasalazine (Reprotox #1253). There are case reports of human pregnancies with maternal sulfasalazine use resulting in various isolated anomalies (Connell and Miller 1999). However, this medication has been used extensively in pregnancy with no apparent increase in the risk of miscarriage, congenital anomalies or prematurity (Connell and Miller 1999 and Mogadam et al., 1981). The concentration of sulfasalazine in cord blood is approximately equal to that of the maternal concentration. Sulfasalazine inhibits both metabolism and transportation of folic acid. Norgard et al., (2001) studied sulfasalazine use in pregnancy because of its effect on folate metabolism. This study did not find an increase in any congenital malformations, including neural tube defects, with use of this medication. However, supplementation of 1mg twice daily of folic acid is recommended for pregnant women taking this drug (Connell and Miller 1999 and Connell and Sandborn 1999).

#### **5-Aminosalicylic acid**

5-Aminosalicylic acid (5-ASA) was developed as an alternative to sulfasalazine. Asacol®, Pentosa®, Dipentum®, and Rowasa® are brand names for 5-ASA (Connell and Sandborn 1999). Because it lacks the sulfapyridine, it does not produce the same side effects as sulfasalazine. 5-ASA is most often used to treat acute episodes of Crohn's disease, but also to maintain remission. It is usually well tolerated, but there are reports of occasional myocarditis, pancreatitis or renal toxicity (Connell and Miller 1999 and Connell and Sandborn 1999).

Human data has shown that 5-ASA is found in very low concentrations in the fetus. Overall, at therapeutic doses, 5-ASA is unlikely to produce any adverse pregnancy effects, nor does it appear to be associated with an increased risk of congenital malformations (Connell and Miller 1999 and Connell and Sandborn 1999).

### **Immunosuppressives**

Azathioprine (Imuran®) and Mercaptopurine (Purinethol®) are purine antimetabolites used in the treatment of active Crohn's disease. After absorption, azathioprine is metabolized to 6-mercaptopurine.

These drugs are used for severely ill Crohn's patients when other drug treatments fail (Korelitz 1990). Patients taking these medications may experience such complications as reversible pancreatitis, myelotoxicity, hepatotoxicity, hypersensitivity reactions and opportunistic infections (Connell and Miller 1999 and Korelitz 1990).

### **Current Research Studies**

ITIS is currently enrolling and following up on pregnancies as part of the following studies. If you have a patient who would like to participate in one of the studies, please contact ITIS at (800) 252-4847.

Asthma Medications in Pregnancy Project

Rheumatoid Arthritis in Pregnancy Study

Ondansetron in Pregnancy Study

While azathioprine has been found to cross the placenta, low amounts of the active metabolite are found in fetal blood. In humans, azathioprine circulates in the fetus primarily as the inactive metabolite, thiouric acid. It appears that the fetus may be protected from adverse effects of the medication because the fetal liver lacks the enzyme, inosinate pyrophosphorylase, which converts azathioprine to its active metabolites. Most studies on the effects of azathioprine in pregnancy involve pregnant renal transplant patients rather than patients with Crohn's disease. Many studies found an increased risk of fetal growth retardation, lymphopenia, decreased thymus size and prematurity (Bermas and Hill, 1995, Connell and Miller, 1999 and Witter et al., 1981). This risk was increased above the risk for renal transplant patients who did not take azathioprine. Still, the malformation rate was 3.9%, which is close to the general population rate. The association between azathioprine and IUGR appears to be the highest when used in combination with a corticosteroid such as prednisone. Thus the direct role of azathioprine in infants with IUGR is difficult to determine as other medications (corticosteroids have been associated with IUGR), maternal hypertension, maternal vascular disease, and maternal renal impairment may also have a role.

Connell and Miller (1999) stated that because there have been isolated cases of neonatal myelotoxicity and immunosuppression, a dose of 2mg/kg/day or less should be used in pregnancy. However, this dose may not be high enough to produce a therapeutic effect. Another alternative is to reduce maternal dose in the third trimester.

A potential risk for chromosome anomalies has been raised following a case report of a woman with lupus who took the drug during two different pregnancies. She delivered two infants with separate de novo translocations. Due to these being isolated cases it is unlikely a true association. However, further investigation is required to determine if this is a true risk from gestational exposure to azathioprine (Bermas and Hill, 1995, Connell and Miller 1999, Reprotax #1459, 1980 and Witter et al., 1981).

There is one study of azathioprine use in pregnant patients with inflammatory bowel disease. This study did not find an increased risk for congenital abnormalities or subsequent health problems (Connell and Miller, 1999 and Connell and Sandborn 1999). Still, due to the potential risks, azathioprine and mercaptopurine are usually not prescribed in pregnancy unless the disease is severe (Connell and Sandborn 1999).

azathioprine or mercaptopurine (Rampton 20001). It is also used in nonsurgical treatment of ectopic pregnancy due to its abortifacient properties (Bermas and Hill 1995 and Reprotax #1036)). Patients who take this medication may experience: hypersensitive pneumonitis, hepatic fibrosis, myelotoxicity, nausea, increased hepatic enzyme activity, skin rash and reversible oligospermia (Connell and Miller 1999). Methotrexate does not appear to have any long term effects on fertility (Bermas and Hill 1995).

Methotrexate is contraindicated in pregnancy for many reasons. It is a folic acid antagonist which

crosses the placenta, and therefore poses a potential increased risk for neural tube defects. Additionally, methotrexate is embryotoxic and teratogenic in animals and humans (Bermas and Hill 1995, Connell and Sandborn 1999, Connell and Miller 1999 and Rampton 2001). Many abnormalities such as large fontanelles, craniosynostosis, abnormal head shape, hypertelorism, and skeletal deformities have all been reported with use of methotrexate in human pregnancy (Connell and Miller 1999). These abnormalities were primarily noted in children born to mothers given 10mg of methotrexate. Studies on this population of women also revealed a miscarriage rate of approximately 44%. The average dose used in these women was from 7.5mg-10mg (Bermas and Hill 1995). There appears to be a critical time period for exposure of 6-8 weeks postconception. There are cases of first trimester exposure to methotrexate in which no teratogenic effect was detected. Four cases of exposure to methotrexate during the early first trimester (0 -6 weeks post conception) all resulted in healthy newborns. An additional study identified eight pregnancies for which methotrexate was given to treat rheumatoid arthritis early in pregnancy. There were five healthy newborns and three spontaneous abortions.

Methotrexate has also been associated with fetal growth retardation resulting from bone marrow suppression. Finally, there are case reports of an association between maternal methotrexate use and fetal chromosome abnormalities (Connell and Miller 1999). Rampton (2001) recommends that use of this medication in either partner be discontinued six months prior to conception.

### **Antibacterials**

#### **Metronidazole**

Metronidazole (Flagyl®) is mostly used for treatment of perianal Crohn's disease. Mothers taking metronidazole may experience nausea, anorexia, metallic taste, glossitis, and peripheral neuropathy. Sporadic cases of midline facial defects in humans, as well as rare reports of bone disorders, have been reported (Connell and Sandborn 1999). Therefore, it has been suggested that the use of this medication should be limited to the second and third trimesters of pregnancy (Connell and Miller 1999). However, two large meta-analysis showed no increased risk for congenital malformations, miscarriage, intrauterine growth retardation or prematurity with maternal metronidazole use (Connell and Miller 1999, Reprotox #1129). A recent prospective cohort study followed 132 first trimester exposed pregnancies and did not find an increased incidence of congenital malformations (Diav-Citrin et al 2001). Often metronidazole is used to treat bacterial vaginosis during pregnancy.

#### **Ciprofloxacin**

Ciprofloxacin is a quinolone. It can be used as an alternative to metronidazole to treat Crohn's disease (Connell and Sandborn 1999). Quinolones as a class have a high affinity for bone tissue, and juvenile animals may develop arthropathy following exposure in pregnancy (Reprotox #1965). However, other animal studies did not find an increased risk of congenital malformations associated with maternal ciprofloxacin use. Additionally, a prospective study on thirty-eight pregnant women receiving ciprofloxacin during pregnancy did not associate this medication with an increased risk of malformations, including musculoskeletal problems. It should be noted, however, that there are no studies of ciprofloxacin use during pregnancy as the primary treatment for inflammatory bowel disease (Connell and Miller 1999 and Reprotox #1965).

### **New Therapies**

There are no reproductive data available regarding newer treatments for Crohn's disease in pregnancy. These therapies may include: Tissue necrosis factor-A, mycophenolate mofetil, interleukin-10, short chain fatty acids and Tacrolimus. Due to the lack of data, use of these medications in pregnancy is not recommended.

### **Summary**

Pregnancy should be avoided when a patient has active Crohn's disease. The complications of active disease regardless of medication use are poor maternal weight gain, vaginal bleeding, premature rupture of the membranes, low birth weight, and miscarriage. It is recommended that pregnancy be undertaken only when the disease is in remission. Treatment during pregnancy is recommended to control maternal disease and decrease the risk for disease related complications. Any alterations to dosage should be done prior to pregnancy and it is not recommended that dosage be decreased during pregnancy. The majority of studies have found that decreasing dosage during pregnancy increases the rate of relapse and complications due to active or uncontrolled disease.

### **References:**

Bernas BL and Hill JA (1995) Review: Effects of Immunosuppressive Drugs During Pregnancy. *Arthritis and Rheumatism* 3 (12):1722-1732

Connell and Miller (1999) Treating Inflammatory Bowel Disease During Pregnancy *Drug Safety* 4:311-323

Connell WR and Sandborn WJ (1999) Drug Therapy for IBD During Pregnancy. <http://www.ccfa.org/medcentral/library/family/drugpreg.htm>

Crohn's and Colitis Foundation of America (1999) Questions & Answers about Crohn's Disease. <http://www.ccfa.org/Physician/crohnsb.html>

Diav-Citrin O et al (2001). Pregnancy outcome after gestational exposure to metronidazole: a prospective controlled cohort study. *Teratology* 63:186-192.

Korelitz BI (1990) Antimetabolites in Inflammatory Bowel Disease: Long Term Experience. *Mount Sinai J of Medicine* 57(5):297-304

Kornfeld D, Cnattingius S, Ekblom A (1997) Pregnancy outcomes in women with Inflammatory bowel disease - A population-based cohort study. *Am J Obstet Gynecol* 177(4):942-946

Mogadam M, Dobbins WO, Korelitz BI, Ahmed SW (1981) Pregnancy in Inflammatory Bowel Disease: Effect of Sulfasalazine and Corticosteroids on Fetal Outcome. *Gastroent* 80:72-76

Moore AJ, Okun NB, Mayes DC, Bailey RJ (2000) Crohn's Pregnancy and Birth Weight. *Am J of Gastroent* 95(4):1019-1026

Norgard B, Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT (2001) Population-based Case control study of the safety of sulfasalazine use during pregnancy. *Alimentary Pharmacology & Therapeutics* 15(4):483-486

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 (2000) Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 62(6):385-92

Rampton DS (2001) Methotrexate in Crohn's disease. *Gut* 48(6):790-791

Reprotox, [www.reprotox.org](http://www.reprotox.org) #1359, 1253, 1459, 1980, 1129, 1036, 1965

Witter FR, King TM, Blake DA (1981) The Effects of Chronic Gastrointestinal Medication on the Fetus and Neonate. *Obstet & Gynec* 58(5):79S-84S