Effects and treatment of inflammatory bowel disease during pregnancy

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ABSTRACT

QUESTION I have several patients with inflammatory bowel disease (IBD) who are pregnant or planning pregnancies. What information can I give them regarding the possible effects of IBD on pregnancy and the medications used to treat IBD during pregnancy?

ANSWER Women with IBD appear to be at increased risk of giving birth prematurely, having low-birth-weight infants, and having cesarean sections. Neither 5-aminosalicylic acid nor sulfasalazine has been found to increase the rate of major malformations, fetal mortality, or morbidity. There is conflicting evidence regarding the use of corticosteroids and azathioprine and 6-mercaptopurine. There are limited data on the use of infliximab during pregnancy, although no pattern of defects or complications has been reported to date.

RÉSUMÉ

QUESTION J'ai plusieurs patientes atteintes de maladie intestinale inflammatoire (MII) qui sont enceintes ou planifient une grossesse. Quels renseignements puis-je leur donner sur les effets possibles de la MII sur la grossesse et ceux des médicaments utilisés pour traiter la MII durant la grossesse?

RÉPONSE Les femmes atteintes d'une MII semblent être à risque plus élevé d'une naissance prématurée, d'un faible poids à la naissance et de césarienne. Il n'a pas été démontré que l'acide 5-aminosalicylique ou la sulfasalazine augmente le taux de malformations majeures, de mortalité ou de morbidité du fœtus. Les données scientifiques se contredisent quant à l'utilisation des corticostéroïdes, de l'azathioprine et de la mercaptopurine (6-MP). Les données sont limitées concernant l'utilisation de l'infliximab durant la grossesse, quoiqu'il n'y ait pas eu de rapports répétés de malformations ou de complications jusqu'à présent.

Inflammatory bowel disease (IBD) includes ulcerative colitis and Crohn disease (CD). Patients with ulcerative colitis have diffuse mucosal inflammation in the colon, and patients with CD have patchy inflammation in any part of the gastrointestinal tract.[1,2] Patients experience symptoms such as diarrhea, abdominal pain, and weight loss.[1] Symptoms of general malaise, anorexia, and fever can also occur, but are more commonly associated with CD.[1] In Canada it is estimated that 0.5% of the population has IBD, with the peak incidence occurring between the ages of 20 and 29 years.[2] As IBD is common in women during their childbearing years, it is important to understand its effects as well as the safety or risk of drugs used to treat this disease during pregnancy.

Several studies have examined the potential effects of IBD on pregnancy outcome. A recent meta-analysis pooled data from 12 studies published between 1980 and 2006 on pregnancy outcomes in women with IBD in comparison with women without IBD. The studies included a total of 3907 patients with IBD and 320 531 controls. The meta-analysis found a statistically significantly increased rate of premature births (<37 weeks) among women with IBD versus women in the control group (odds ratio [OR] 1.87, 95% confidence interval [CI] 1.52-2.3, $P<.001$) and an increased rate of low-birth-weight infants (<2500 g), with an OR of 2.1 (95% CI 1.38-3.79, $P<.001$). This meta-analysis also found an increased rate of cesarean section in women with IBD versus the control group, with an OR of 1.5 (95% CI 1.26-1.79, $P<.0001$). The study concluded that women with IBD are at increased risk of giving birth prematurely, having low-birth-weight infants, and having cesarean sections compared with women who do not have IBD. The main limitation of this meta-analysis was that it did not take into account disease severity.[3]

A Danish regional cohort study investigated the effects of disease activity on pregnancy outcomes for CD. The authors evaluated all births between 1977 and 2005 in patients with CD and classified them as having disease activity (N=71) or no disease activity (N=86). There was a statistically significant increase in preterm births (<37 weeks), with an adjusted odds ratio of 2.4 (95% CI 0.6-9.5). There was also an increase in low birth weight, but it was not statistically significant.[4]

Treatment options

Because women with IBD will need to be treated during pregnancy, it is important to evaluate whether or not the drugs used in IBD treatment have adverse effects on

pregnancy outcomes. There are several drugs commonly used to treat IBD and CD. There is good evidence regarding the use of some of these agents in pregnancy; however, there are agents that have limited or conflicting data.

5-Aminosalicylic acid (5-ASA). 5-Aminosalicylic acid has little systemic absorption and limited transplacental transfer.[5,6] A Motherisk study prospectively followed 165 women exposed to 5-ASA during pregnancy; 146 women were exposed in the first trimester. In comparison with a matched control group, there was no increase in the rate of major malformations. There was, however, an increase in the rate of preterm deliveries (13% vs 4.7%) and a decrease in mean birth weight (3253 g, SD 546 g, vs 3461 g, SD 542 g). This increased risk might be due to the severity of the disease, as increased disease activity also increases the risk of preterm delivery.[7]

Sulfasalazine. Sulfasalazine has been shown to cross the placenta.[8] Several studies have shown it does not increase the risk of fetal morbidity and is considered safe to use in pregnancy.[9-12] There are some case reports of congenital malformations in infants exposed to sulfasalazine; however, it is difficult to determine whether those malformations were due to the drug specifically, disease, or a combination of several factors.[13,14] There is 1 case report of fetal hemolytic anemia in the fetus of a woman who subsequently discontinued sulfasalazine. The fetus was treated with intrauterine blood transfusions and required extra care at birth.[15]

Sulfasalazine is a folic acid antagonist, and a recent case-control study examined the effect of folic acid supplementation on the risk of congenital defects. The authors found supplementation of folic acid reduced the teratogenic risk from sulfasalazine and similar folic acid antagonists.[16]

Corticosteroids. Corticosteroids can be used both orally and topically in the form of suppositories and enemas. Human teratology studies on the use of steroids have produced conflicting results. A meta-analysis of 5 studies of oral corticosteroid use found no substantial increase of major malformations in the exposed group (390 pregnancies) versus the control group (707 pregnancies); however, there was a significant increase in oral clefts, with an OR of 3.69 (95% CI 2.15-6.32).[17] Corticosteroids were also associated with an increase in the risk of preterm birth.[4]

Azathioprine and 6-mercaptopurine. Nørgård and colleagues found an increased relative risk of 18.5% for preterm birth and 9.7% for congenital anomalies (95% CI -4.3 to 23.6%) in patients exposed to azathioprine and 6-mercaptopurine during pregnancy.[4] A meta-analysis by Cornish and colleagues also found an increased risk of major congenital defects (6%) and premature birth (15%) in comparison with other agents commonly used to treat IBD.[3] This is in contrast to a study that examined exposure to 6-mercaptopurine before and during pregnancy and found no increased risk of premature births or congenital abnormalities.[18]

Infliximab. At present, there are limited data on the use of infliximab in pregnancy. Data from a post-marketing safety database were reported by Katz et al. Outcome data were available for 96 of 131 patients exposed directly to infliximab. In this group of 96 patients, 67% of the pregnancies resulted in live births, 15% in spontaneous abortions, and 19% in terminations. Among the live births there were 5 cases of varying fetal complications.[19] A case series of 10 women who received infliximab during their pregnancies has also been published. All 10 pregnancies resulted in live births. There were no malformations; however, 3 infants were premature and 1 had low birth weight.[20]

Conclusion

Inflammatory bowel disease is a common condition that can affect women during their childbearing years. Women with IBD appear to be at increased risk of giving birth prematurely, having low-birth-weight infants, and having cesarean sections. There are several drugs used to treat IBD. There is good evidence regarding the use of some of these agents in pregnancy; however, there are agents that have limited or conflicting data. Current evidence suggests neither 5-ASA nor sulfasalazine has been found to increase the rate of major malformations, fetal mortality, or morbidity; therefore, clinicians can initiate or continue these agents in pregnancy. There is conflicting evidence regarding the use of corticosteroids and azathioprine and 6-mercaptopurine; clinicians will have to assess the potential risks of the medications versus the potential risks of uncontrolled IBD. There are limited data on the use of infliximab during pregnancy, although no pattern of defects or complications has been reported to date.

Competing interests

None declared

MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Ms Brar** is a pharmacist. **Ms Einarson** is Assistant Director of the Motherisk Program.

Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at 416 813-7562; they will be addressed in future Motherisk Updates.

Published Motherisk Updates are available on the College of Family Physicians of Canada website (**www.cfpc.ca**) and also on the Motherisk website (**www.motherisk.org**).

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