Rev ACAD 2012; 28 (4): 170-173

THE SAFETY OF IMMUNOMODULATORS AND BIOLOGICS FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE DURING PREGNANCY AND BREAST-FEEDING

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INTRODUCTION

The majority of patients with inflammatory bowel disease (IBD) are affected during their peak reproductive years. Consequently, many female patients affected by Crohn's disease and ulcerative colitis are interested in bearing children. One of the most frequently asked questions during consultation with those affected by IBD is what are its effects on pregnancy, and how will the treatment impact upon conception and pregnancy outcomes. Discussion and education about pregnancy is an essential component of the management of young women with IBD. This should allow informed decisions to be made before conception.

In any woman with quiescent IBD at the time of conception, the likelihood of a flare-up of IBD during pregnancy or the puerperium is, in general, no greater than in any other year of her life. Although a diagnosis of either ulcerative colitis or Crohn's disease does not by itself pose a risk to pregnancy, it has been shown that active disease or disease flare, is associated with poor obstetrical outcomes, such as preterm delivery and low birth weight. Therefore, women with IBD can expect to have, in most cases, a normal pregnancy outcome provided they have inactive disease. They may have, perhaps, an increased risk of having a small or premature baby, but this is a small risk.

As a result, effective control of disease activity is vitally important during pregnancy. In fact, it has been shown that the most important factor in the success of a pregnancy in patients with IBD is the state of disease activity. A flare of disease during pregnancy may be more deleterious to neonatal outcome than any potential risk from the medication. Therefore, the goal prior to and during pregnancy is to best optimize control of the disease through medical therapy.

While initial concerns focus on attaining a durable remission and avoiding the side effects of medications, once in remission the focus often shifts to the effect of disease and the medications used to treat it on fertility and the ability to conceive a healthy child. The use of medications during the conception period and pregnancy is a cause of great concern for patients and the physicians caring for them. Most women's initial reaction is that they would not want to contemplate taking any sort of medication if they were planning conception or became pregnant. Therefore, an informed pre-pregnancy discussion, with the patient (and her partner if appropriate), facilitates a decision made in partnership with clinicians and the formulation of a management plan.

Overall, the majority of medications used for the treatment of IBD are not associated with significant adver-

TABLA I.-

FOOD AND DRUGS ADMINISTRATION (FDA) CATEGORIES FOR THE USE OF MEDICATIONS IN PREGNANCY.

FDA PREGNANCY CATEGORY	INTERPRETATION
A	Controlled studies in animals and women have shown no risk in the first trimester, and possible fetal harm is remote
B	Either animal studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester
C	No controlled studies in humans have been performed, and animal studies have shown adverse events, or studies in humans and animals are not available; give if potential benefit outweighs the risk
D	Positive evidence of fetal risk is available, but the benefits may outweigh the risk if lifethreatening or serious disease
X	Studies in animals or humans show fetal abnormalities; drug contraindicated

TABLA II.-

MEDICATIONS USED IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE (IBD).

DRUG	FDA PREGNANCY CATEGORY	RECOMMENDATIONS FOR PREGNANCY
Adalimumab	B	Limited human data: low risk
Azathioprine/ mercaptopurine	D	Data in IBD, transplant literature suggest low risk
Balsalazide	B	Low risk
Corticosteroids	C	Low risk; possible increased risk: cleft palate, adrenal insufficiency, premature rupture of membranes
Cyclosporine	C	Low risk
Infliximab	B	Low risk
Mesalamine	B	Low risk
Methotrexate	X	Contraindicated: teratogenic
Olsalazine	C	Low risk
Sulfasalazine	B	Considered low risk; give folate 2 mg daily
Tacrolimus	C	Use if mother's health mandates
Thalidomide	X	Contraindicated: teratogenic

se effects. The United States Food and Drug Administration (FDA) classification of drugs offers a guide to the use of medications during pregnancy (**Table I**). **Table II** summarises the safety of IBD medications for pregnancy.

On the other hand, breast-feeding is not associated with an increased risk of disease flare and may even provide a protective effect against disease flare in the postpartum year. Breast-feeding is known to provide significant health benefits to infants, including the transmission of protective antibodies through breast milk.

The commonly used drugs, in particular the aminosalicylates, appear to be safe and well tolerated in pregnancy. No evidence of teratogenicity has been demonstrated and the outcome of pregnancy has been shown to be similar to that in healthy women. Thus, all aminosalicylates (sulfasalazine, mesalamine, balsalazide) are pregnancy category B except olsalazine (which is pregnancy category C). Steroids are also probably safe and should be used for exacerbations of active disease. There has been no convincing evidence of teratogenesis despite reports of cleft lip and palate in the past. This small risk is often outweighed by the benefit of controlling the mother's IBD and, therefore, corticosteroids are considered pregnancy category C drugs.

However, the use of other agents for treating IBD during pregnancy is more controversial. In particular, the recommendation on the use of immunomodulators (mainly azathioprine or mercaptopurine) has been controversial and, although thiopurine drugs have FDA rating D, available data suggest that they may be safe and well tolerated during pregnancy. The safety of biological therapies (mainly infliximab and adalimumab) has been scarcely studied and, although they are considered pregnancy category B by the FDA, this classification and their presumed safety is based on limited data.

LIMITATIONS OF STUDIES DURING PREGNANCY

Unfortunately, the conclusions of most studies have to be considered with caution because of several reasons:

1) The lack of data in human trials. Although animal reproduction studies have been performed in some cases, animal studies are not always predictive of human response. In other words, safety in animal models does not ensure safety in humans because of species specificity. This variability in species sensitivity may be due to different metabolism of the drug, and reinforces the need to study the evidence in humans.

2) The lack of data specifically in IBD patients. Most of the studies reporting the use of immunosuppresive drugs in pregnancy have been performed in the transplantation population. Obviously the post-transplant setting has considerable differences in immunology and in polypharmacy to that of IBD, and the evidence suggests that this worrying picture may not translate to a different setting.

3) The observational and retrospective nature of data collection. For ethical reasons, randomized trials cannot

be designed to evaluate the safety of these drugs during pregnancy. Therefore, we have to base clinical decisions on evidence from observational studies that are often vulnerable to bias and confounding. As with any voluntary postmarketing adverse event reporting database, there is reporter bias: on one hand, to better assess the risk associated with anti-TNFα exposition during conception and pregnancies, all cases of new pregnancies occurring in women treated by anti-TNFα drugs should be declared and/or reported; on the other hand, adverse events are likely to be reported, whereas pregnant women exposed to TNFα antagonists without adverse events will probably not report this.

4) The small sample size. There are few controlled trials that include pregnant patients and even fewer that are specifically designed to study this patient population. Almost all controlled trials with new agents excluded pregnancy. Therefore, in most cases, the data must be obtained form post-marketing experience.

5) The lack of a truly normal (non-treated) control group. For example, it should be remembered that congenital anomalies are present in 3-5% of all live births in the general population. Furthermore, it has been estimated that in the general population 10% to 12% of pregnancies terminate in clinically recognized spontaneous abortions during the first trimester.

6) The lack of information regarding disease activity, comorbidities, and concomitant medications. In some cases, it is not clear whether the fetal effects are due to medication or the severity of the underlying illness. Furthermore, most studies looking at the effects of any one medication on pregnancy in IBD are confounded by the fact that most patients ?with comorbidities? are on multiple medications.

CONCLUSION

For patients with IBD, disease activity at the time of conception or during the course of pregnancy can be associated with a higher risk of low birth weight, premature infants and spontaneous abortions. A key principle of management is that active disease, not therapy, poses the greatest risk to pregnancy. Therefore, all women with IBD who become pregnant should be carefully monitored and aggressive control of disease activity prior to and during pregnancy is critical to optimize both maternal and fetal health. It is advisable that patients be in remission when considering pregnancy, and for the majority, this requires continuing their medications.

The management of IBD in pregnancy is a partnership between patient and clinician and as part of this, full discussion and planning before conception are required. Very few drugs are licensed for use in pregnancy, and the continuance of maintenance treatment needs to be discussed in full with the patient and possibly her partner before conception.

For a drug to clearly be associated with congenital anomalies, the same defect must be seen repeatedly, a phenomenon not demonstrated with any IBD medication except methotrexate and thalidomide, both of which are contraindicated during pregnancy (and breast-feeding). Therefore, most medications used for the therapy of IBD are compatible with pregnancy. Nevertheless, it is most prudent to err on the side of caution when dealing with pregnancy and potentially teratogenic drugs.

Although thiopurines have FDA rating D, available data (mainly based on the large experience in transplantation patients) suggest that these drugs are safe and well tolerated during pregnancy. Although traditionally women receiving azathioprine or mercaptopurine have been discouraged from breast-feeding because of theoretical potential risks, it seems that these drugs may be safe in this scenario.

Treatment with cyclosporine for steroid-refractory ulcerative colitis during pregnancy can be considered safe and effective, and the use of this drug should be considered in cases of severe ulcerative colitis as a means of avoiding urgent surgery. Breast-feeding is contraindicated for patients receiving cyclosporine.

The true short- and long-term implications of exposure to TNFα blockers during the newborn period are as yet unknown. However, biological therapies appear to be safe in pregnancy, as no increased risk of malformations has been demonstrated. Therefore, the limited clinical results available suggest that the benefits of infliximab and adalimumab in attaining response and maintaining remission in pregnant IBD patients might outweigh the theoretical risks of drug exposure to the fetus. The decision to use anti-TNFα therapy in pregnancy should be made on a case by case basis. In women with a complicated disease course, in whom biological therapies have been the only agents to induce and maintain remission, therapy should probably be continued during conception and pregnancy. On the other hand, stopping therapy in the third trimester may be considered, as we know that transplacental transfer of infliximab is low prior to this. This approach has the benefit of minimizing the break from treatment for the patient and therefore the risk of antibody development once treatment is recommenced postpartum. Certolizumab differs from infliximab and adalimumab in that it is a Fab fragment of an anti-TNFα monoclonal antibody, and therefore it may not be necessary to stop certolizumab in the third trimester, which could be an advantage over other biological therapies. In a patient on anti-TNFα therapy in combination with azathioprine/mercaptopurine, it may be considered stopping these last drugs to minimize risks of immunosuppression and adverse events to the fetus, given the limited benefit of combination therapy versus when a patient is maintained on anti-TNFα

therapy alone. Finally, the use of infliximab is probably compatible with breast-feeding, although more experience is necessary.

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