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**Treatment of Crohn's disease in pregnant women: Drug and multidisciplinary approaches**

Cury DB *et al.* Treatment of Crohn’s disease in pregnancy

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**Abstract**

Inflammatory bowel disease (IBD) affects a substantial number of women in their reproductive years. Pregnancy presents a number of challenges for clinicians and patients; the health of the baby needs to be balanced with the need to maintain remission in the mother. Historically, treatments for Crohn’s disease (CD) were often discontinued during the pregnancy, or nursing period, due to concerns about teratogenicity. Fortunately, observational data has reported the relative safety of many agents used to treat CD, including 5-aminosalicylic acid, thiopurines, and tumor necrosis factor. Data on the long-term development outcomes of children exposed to these therapies in utero are still limited. It is most important that physicians educate the patient regarding the optimal time to conceive, discuss the possible risks, and together decide on the best management strategy.

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**Key words:** Pregnancy; Drugs; Inflammatory bowel disease; Crohn’s disease; Breastfeeding

**Core tip:** Patients should be encouraged to postpone conception until their Crohn’s disease (CD) is in remission. Monitoring of nutritional status remains important in patients with small bowel CD; folic acid, vitamin D and vitamin B12 may all need to be supplemented. Most drug treatments are safe in pregnancy, based on observational data, including 5-aminosalicylic acid, thiopurines, anti- tumor necrosis factor, and anti- integrins. Methotrexate should be avoided due to its teratogenicity. Cesarean section is only indicated from a CD perspective in women with active perianal disease at the time of delivery; all others can have a normal vaginal delivery.

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**INTRODUCTION**

In recent years, great advances have been made in the management of inflammatory bowel diseases (IBD)[1]. Nevertheless, many questions arise for physicians and patients when women considering pregnancy have IBD. In this situation, an understanding of the nutritional, pharmacological and diagnostic considerations is important for treating physicians to minimize harm to the fetus, while ensuring the mother’s disease remains in remission[2].

**FERTILITY IN CROHN'S DISEASE**

Fertility issues, risk of the disease in off-spring, and the impact of both the disease and medication on mother and child can all create fear in many patients wanting to have a child[2]. Some factors may influence the fertility rate in patients with Crohn's disease (CD); these include active disease and/or malnutrition, and drug-induced oligospermia in male partners[4]. Active CD with colonic location or in the terminal ileum or even surgeries such as proctocolectomy with ileoanal anastomosis (colitis) have been associated with lower fertility rates[4-6]. The psychological burden of disease may also play a role; in perianal CD, low fertility has been attributed to dyspareunia, decreased libido and depression in some women[7].

Sulfasalazine is a drug that is associated with infertility in men; in 80% of the cases sperm motility is reduced and morphology is changed. Such effects are not reversible with the administration of folic acid, but they may reverse two months after the end of the Sulfasalazine treatment[8,9]. In contrast to these data, mezalazine, which also is a 5-ASA, and immunosuppressants such as azathioprine, do not appear to affect spermiogenesis in patients[10].

**EFFECTS OF INFLAMMATORY DISEASE ON PREGNANCY AND PREGNANCY EFFECTS ON INFLAMMATORY DISEASE**

Even though most patients with inflammatory bowel disease may be classified as women with high-risk pregnancies, the course of the disease in this group usually does not present major complications. The rate of premature births in this specific group is frequently double of that without inflammatory disease[3].The risk of congenital malformation in the general population ranges from 1% to 4.8% and there is no current evidence of an increased risk for CD patients[11]. Conversely, miscarriage is more frequent in women with inflammatory bowel disease (above 35%), especially in those with active disease. The natural risk of fetal loss after 16 wk is approximately 1%, which is similar to the risk of healthy women[12]. Some studies have shown that women with active CD are more likely to bear children with low birth weight (less than 2500 g)[13].

The influence of pregnancy on the course of the disease is closely related to the disease status at the time of the delivery i.e., active or inactive. This status will determine the behavior of the disease itself, the clinical course, and the response to drug therapy[7]. Some studies show that women with active disease have worsening or persisting symptoms during pregnancy in 70% of the cases, whereas the risk of relapse in women who do not have active disease at conception is similar to women who are not pregnant[14-25]. A recent meta-analysis of these studies concluded that the risk of active disease during pregnancy is higher in women who conceive when their disease is active[26].

**THERAPEUTIC DRUGS AND THEIR SAFETY DURING PREGNANCY AND BREASTFEEDING**

Studies conducted in the last decades with women who underwent treatment during their pregnancy provides reassuring data for the specialist as well as for the patient both during the pregnancy and while breastfeeding. The FDA classification for drugs according to their known or potential teratogenicity is reviewed in Table 1. Table 2 presents the safety of medications commonly prescribed for IBD during pregnancy.

***Sulfasalazine and 5-ASA (Category B)***

5-aminosalicylic acid (5-ASA) is considered safe until doses of 3 mg/d. Above these doses, the risk has been considered uncertain[8-10]. Studies show that sulfasalazine and 5-ASA in doses below 3g a d do not increase the risk of congenital malformation, premature birth and miscarriage in patients with CD or UC with doses greater than 3g/d. A post-marketing study showed that of 55 pregnant women who used Mezalazine in doses of 1.6 to 4g a day, three had fetal malformation, but these data were not different from those found in the general population, which suggests that there is no greater risk of malformations with mesalamine use[9].

***Azathioprine and 6-mercaptopurine (Category D)***

Thiopurines (azathioprine and mercaptopurine) both cross the placental barrier and can be identified in the umbilical cord blood, but the serum level in the baby is not significant. Animal studies show the occurrence of cleft palate and skeletal and urogenital abnormalities in rats, and historical retrospective studies associated thiopurines with teratogenic effects in 5% of the cases and risk of preterm birth in 3%, in addition to the effects of low fetal weight and myelotoxicity[4].

More recent observational studies have not noted higher risk of these events in women with IBD. A recent prospective study of 30 children, developed by de Meij *et al*[15], to evaluate the effect of azathioprine on the uterus in relation to quality of life, psychosocial development and an increased risk of infection showed that this drug did not exert a direct influence on these factors when compared to children who had not undergone this therapy. The American Academy of Pediatrics does not recommend that mothers who are breastfeeding make use of immunosuppressants, due to the fact that these drugs induce immunosuppression in these children[16,22]. Most of the studies report that the most common adverse effect in pregnant women is related to low weight and miscarriage[4].

***Antibiotics***

Metronidazole and ciprofloxacin are often administered in the treatment of patients with IBD, especially perianal CD. Metronidazole is classified as Category B, and short-term use (7-10 d) is considered safe in pregnancy. In contrast, extended use in the third month of pregnancy has been associated with fetal cleft palate and cleft lip, and therefore prolonged use during pregnancy is contraindicated[4]. Ciprofloxacin is Category C, as quinolones act on the cartilage and in humans they can cause arthropathy and skeletal abnormalities of the fetus[27]. For this reason, they are not recommended for children under 18 or for pregnant women or for women who are breastfeeding.

***Corticosteroids (Category C)***

Corticosteroids (prednisolone) cross the placental barrier, but they represent a very small risk when used in the first trimester of pregnancy. Studies carried out in animals have shown that these drugs may increase the risk of cleft palate and cleft lip when administered in the first trimester[25]. The administration of glucocorticoids should always be careful and monitoring of blood pressure and blood glucose should take place due to their ability to induce gestational hypertension, diabetes, membrane rupture and preterm delivery.

***Cyclosporine / tacrolimus (Category C)***

Cyclosprine and Tacrolimus are both calcineurin inhibitors occasionally used in the management of CD. Both are category C, and can be employed in the treatment of fulminant colitis; their teratogenic action has not yet been proven. Doses above 25 mg/kg per day can induce renal damage in the fetus in animals and their use in humans requires serum monitoring of renal function and blood pressure because both drugs cross the human placenta but there are conflicting reports about this point[26].

***Thalidomide (Category X)***

Thalidomide is rated as category X (FDA) for pregnant women because of potential teratogenic effects. It is contraindicated in this population.

***Methotrexate (Category X)***

This drug has also been classified as category X. It is clearly teratogenic and should not be considered for use in pregnant women and in women who want to conceive. Patients who are using this medication should be instructed to delay conception attempts for three to six months after its cessation. It can cause growth retardation and even mental retardation, among other effects.

***Infliximab (Category B)***

Infliximab is a chimeric employed in the treatment of CD and UC. It is known to be able to cross the placental barrier after the second trimester, similar to all IgGs. Maternal and embryonic toxicity has not been observed, and neither has increased teratogenicity. The substance can be detected in high concentrations in the newborn up to 6 months after delivery, but the clinical significance of this finding is unknown[19]. Caution with any type of live vaccine in this group of infants during the first 6 months is required, particularly if the infant received anti-TNFs during gestation. There are no lethal cases of TB with three-month old children who received BCG[19].

***Adalimumab (Category B)***

Considered by the FDA as a category B drug, adalimumab has been approved for CD in induction, remission and maintenance phases. It exhibits a behavior similar to infliximab, also crossing the placental barrier in the third month of pregnancy. There are few data on its use by pregnant women, and so far related birth defects have been reported, but clear and further studies are needed. Jurgens *et al*[20] conducted a review study of 126 women who had been subjected to treatment with adalimumab and no increased risk of congenital malformation was observed. Recent studies have indicated dose adjustments during pregnancy to reduce maternal exposure. Specifically, it has been recommended that the last dose should be given between 34 and 36 weeks of gestation[16].

***Certolizumab pegol (Category B)***

Certolizumab is a Fab fragment of a monoclonal antibody linked to a polyethylene glycol chain. It is used during CD in remission and maintenance and it is known to cross the placental barrier throughout the pregnancy at a low level. In recent studies (PIANO), no increased risks in pregnant women who were subjected to certolizumab were noticed[21]. Besides, when breast milk was analyzed, it was noticed that from 3 to 6 days post-birth, serum levels of the drug could not be detected. Thus it seems that this drug is safe in this phase[21].

***Golimumab***

Golimumab is a completely human monoclonal antibody which aims to block anti-TNF. It is applied subcutaneously and was approved in May, 2013 by the FDA for the treatment of severe ulcerative colitis. There are no reports so far of the use of this drug in pregnant women[24].

***Natalizumab (Category C)***

Natalizumab was recently approved for induction and maintenance treatment of CD in patients who do not respond to therapy with anti-tumor necrosis factor alpha (anti-TNF-). Individual studies are necessary to prove that its use can be recommended for pregnant women. In a recent study with natalizumab, no increase in abnormalities was noticed in pregnant women who had received the drug. A similar result was found in the study carried out by PIANO[22]. However, most studies have not considered the drug to be safe enough to be used during pregnancy; thus, it is contraindicated[23].

**DRUGS AND THEIR SAFETY DURING PREGNANCY AND BREASTFEEDING**

It is important to bear in mind which drugs can be used during pregnancy and lactation. These drugs can be viewed in Table 3. In general, 5-ASA derivatives are considered safe (EL 3b, RGB) as well as corticosteroids (L4, RGC ). A low concentration of these steroids has been noted in breast milk. To minimize the effects of these it has been suggested that mothers can breastfeed 4 hours after their ingestion. The thiopurines are excreted in small amounts in milk, but they have also been considered safe. However, more studies are needed to fully confirm this security (EL 4, RGC). All anti- TNFs are also excreted in small amounts in the milk and once again there are few studies regarding the effects on these children who are being breastfed or who were breastfed and as a consequence received these medications (EL5, RGC). Metronidazole and ciprofloxacin are also excreted in breast milk and are not considered appropriate during this period and their safety is unknown and should, if possible, be avoided. Tacrolimus studies are very limited and perhaps it is safe. Drugs such as thalidomide, methotrexate and cyclosporine are contraindicated because they get into the milk and consequently, they are considered unsafe.

**ENDOSCOPIC METHODS DURING PREGNANCY**

Endoscopy, colonoscopy, retosygmoidoscopy and cholangiography have been considered safe during pregnancy according to ECCO Statement 7G (EL4, RGC). On the other hand, there should be great caution in relation to these procedures which must have a strong indication to be carried out in the second semester (EL5, RGD). Techniques of hemostasis are safe and should be done with precaution (EL3, RGC).

**RISK OF THROMBOEMBOLISM IN HOSPITALIZED PREGNANT WOMEN**

Many studies have considered the increased risk of venous thromboembolism in pregnant women. Such risk has been noticed in the first six weeks of the postnatal period; however, this risk is even higher in pregnant women with inflammatory bowel disease. The use of low- molecular-weight heparin is considered important to prevent this event and should be considered especially in women who have been or will be hospitalized (EL3 RGB).

**CONCLUSION**

Nowadays, due to great knowledge about inflammatory bowel disease, it may be stated that the majority of the drugs used during one’s pregnancy are safe for both the mother and the fetus. However, guidance to this group of patients (mothers-to-be) and control of the disease activity before conception is essential for the reduction of the risks of miscarriage or premature birth. Most drugs are also safe for breastfeeding.

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Table 1 Food and Drug Administration drug administration categories for the use of medications in pregnancy

|  |  |
| --- | --- |
| **Category** | **Observations** |
| A | Controlled studies both in humans and in animals have shown that there is no risk during the first trimester and the possibility of fetal harm is remote. |
| B | Studies in animals have shown no risk to the fetus. However, there are no controlled studies carried out in pregnant women. Besides, studies in animals have revealed adverse effects which were not confirmed in pregnant women in the first trimester. |
| C | There is no record of controlled studies in humans. Studies in animals have shown adverse effects. Moreover, studies in humans and animals showing that the benefit may outweigh the risk have not been validated. |
| D | Evidence of risk for the fetus. |
| X | Studies in animals and humans have shown fetal abnormalities, so these drugs are contraindicated. |

**Table 2** **Safety of medications prescribed for inflammatory bowel disease during pregnancy**

|  |  |  |
| --- | --- | --- |
| **Safe to Use When Indicated** | **Limited Data but Used When Clinically Indicated** | **Contraindicated** |
| Mesalamine | Olsalazine | Methotrexate |
| Sulfasalazine | AZA/6 MP | Thalidomine |
| Balsalazide | Ciprofloxacin |  |
| Corticosteroids | Metronidazole |  |
| TPN | Biologics |  |
| Loperamide | Cyclosporine |  |