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TOPIC HIGHLIGHT

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

Didia Bismara Cury, Alan C Moss

Didia Bismara Cury, Center of Inflammatory Bowel Disease, Federal University of São Paulo, Sao Paulo, SP 040023-062, Brazil
Didia Bismara Cury, Center of Inflammatory Bowel Disease, Clinica Scope, Campo Grande, MS 79002212, Brazil
Didia Bismara Cury, Beth Israel Medical Center of Harvard Medical School, Sao Paulo, CEP 04023-062, Brazil
Alan C Moss, Beth Israel Deaconess Medical Center, Division of Gastroenterology, Boston, MA 02215, United States
Alan C Moss, Harvard Medical School, Boston, MA 02215, United States
Author contributions: Cury DB and Moss AC contributed to the manuscript.
Correspondence to: Didia Bismara Cury, Director, Center of Inflammatory Bowel Disease, Clinica Scope, Campo Grande, MS 79002212, Brazil. didia_cury@uol.com.br
Telephone: +55-673-3256040 Fax: +55-673-3256040
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Abstract

Inflammatory bowel disease 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.

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 with IBD consider pregnancy. 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[2,3].

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

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, no controlled studies have been carried out in pregnant women. In addition, 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

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 in the colon or the terminal ileum or even surgery 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 associated with infertility in men; in 80% of 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 is also 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 pregnant women with IBD may be classified as having 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 that in women 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 IBD (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 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 70% of women with active disease have worsening or persisting symptoms during pregnancy, 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 Food and Drug Administration (FDA) classification for drugs according to their known or potential teratogenicity is reviewed in Table 1. Table 2 shows the safety of medications commonly prescribed for IBD during pregnancy.

Sulfasalazine and 5-aminosalicylic acid (category B)

5-aminosalicylic acid (5-ASA) is considered safe up to doses of 3 mg/d. Above this dose, the risk is considered uncertain[8-10]. Studies show that sulfasalazine and 5-ASA in doses below 3 g/d do not increase the risk of congenital malformation, premature birth and miscarriage in patients with CD or ulcerative colitis (UC). A post-marketing study showed that of 55 pregnant women who used mezalazine in doses of 1.6 to 4 g/d, three had fetal malformations, however, these data were not different from those found in the general population, which suggests that there is no greater risk of malformations with mezalazine 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, however, serum level in the baby is not significant. Animal studies showed the occurrence of cleft palate and skeletal and urogenital abnormalities in rats, and historical retrospective studies associated thiopurines with teratogenic effects in 5% of cases and the risk of preterm birth in 3%, in addition to the effects of low fetal weight and myelotoxicity[4].

More recent observational studies did not observe a

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	Thalidomide
Balsalazide	Ciprofloxacin	
Corticosteroids	Metronidazole	
TPN	Biologics	
Loperamide	Cyclosporine	

TPN: Total parenteral nutrition; AZA: Azathioprine MP: Mercaptopurine.

higher risk of these events in women with IBD. A recent prospective study of 30 children, performed by de Meij *et al*[15], evaluated the effect of azathioprine on the uterus in relation to quality of life, psychosocial development and an increased risk of infection, and showed that this drug did not directly influence these factors when compared to children who had not undergone this therapy. The American Academy of Pediatrics recommends that breastfeeding mothers should not take immunosuppressants, as these drugs induce immunosuppression in children[16,22]. Most 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 or breastfeeding women.

Corticosteroids (category C)

Corticosteroids (prednisolone) cross the placental barrier, however, 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]. Glucocorticoids should be administered with care and both blood pressure and blood glucose should be monitored due to their ability to induce gestational hypertension, diabetes, membrane rupture and preterm delivery.

Cyclosporine/tacrolimus (category C)

Cyclosporine 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, however, there are conflicting reports on this point[26].

Thalidomide (category X)

Thalidomide is rated as category X (FDA) for pregnant women due to its 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 taking this medication should be instructed to delay conception 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 used in the treatment of CD and UC. It is known to cross the placental barrier after the second trimester, similar to all IgGs. Maternal and embryonic toxicity and increased teratogenicity have not been observed. Infliximab can be detected in high concentrations in the newborn up to 6 mo 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 mo is necessary, particularly if the infant received anti-tumor necrosis factors (TNFs) during gestation. There were no lethal cases of TB in three-month-old children who received BCG[19].

Adalimumab (category B)

Considered by the FDA to be a category B drug, adalimumab has been approved for CD in induction, remission and maintenance phases. It exhibits similar behavior to infliximab, also crossing the placental barrier in the third month of pregnancy. There are few data on its use by pregnant women, and related birth defects have been reported, however, further studies are needed. Waage *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. It has been specifically recommended that the last dose should be given between 34 and 36 wk 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 a recent study (PIANO), no increased risks in pregnant women administered certolizumab were ob-

Table 3 Classification of the drugs concerning the fetal risk according to Food and Drug Administration

Drugs	Recommendation
Adalimumab	Pregnancy (low risk)
Category B	Breastfeeding (probably compatible)
Azathioprine/6-mercaptopurina	Pregnancy (low risk) when used in low doses and as mono-therapy
Category D	Breastfeeding (it is recommended to breastfeed 4 h after taking the drug)
Balsalazide	Pregnancy (low risk)
Category B	Breastfeeding (probably compatible)
Certolizumab	Pregnancy (low risk)
Category B	Breastfeeding (probably compatible)
Ciprofloxacin	Pregnancy (not recommended due to skeletal muscular dysfunction)
Category C	Breastfeeding (compatible)
Corticosteroids	Pregnancy (risk of adrenal insufficiency, premature rupture of membrane, in the first trimester although there is little risk of cleft palate)
Category C	Breastfeeding (probably compatible)
Cyclosporine	Pregnancy (no congenital abnormalities have been noticed)
Category C	Breastfeeding (contraindicated)
Infliximab	Gestation (low risk when administered as mono-therapy) (increased risk of infection when used in combination with azathioprine)
Category B	Breastfeeding (probably compatible)
Mezalazine	Pregnancy (asacol showed low risk of teratogenicity in animal models)
Category B	Breastfeeding (both probably compatible)
Asacol (category C)	
Methotrexate	Contraindicated in both conditions
Category X	
Metronidazole	Pregnancy (used in the first trimester increases the risk of cleft palate)
Category B	Breastfeeding (toxic)
Olsalazine category (C)	Pregnancy (limited risk)
	Breastfeeding (probably compatible)
Rifaximin	Pregnancy (animal studies show teratogenicity)
Category C	Lactation (its safety is unknown)
Sulfasalazine	Pregnancy (low risk if administered in conjunction with folic acid)
Category B	Breastfeeding (probably compatible)
Tacrolimus	Pregnancy (no increased risk described)
Category C	Breastfeeding (contraindicated)
Thalidomide	Contraindicated in both conditions
Category X	

served[21]. In addition, when breast milk was analyzed, it was noted that from 3 to 6 d post-birth, serum levels of the drug were not 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 administered subcutaneously and was approved in May, 2013 by the FDA for the treatment of severe ulcerative colitis. To date, there are no reports on 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-TNF-α. 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 were noted in pregnant women who had received the drug. A similar result was found in the PIANO study[22]. However, most studies did not consider 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 are shown 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 drugs it has been suggested that mothers can breastfeed 4 h after their ingestion. The thiopurines are excreted in small amounts in milk, and are also considered safe. However, more studies are needed to fully confirm the safety of these drugs (EL 4, RGC). All anti-TNFs are also excreted in small amounts in the milk and there are few studies regarding the effects on children who are or were breastfed and consequently received these medications (EL5, RGC). Metronidazole and ciprofloxacin are also excreted in breast milk and are not considered appropriate during breastfeeding as their safety is unknown and these agents should, if possible, be avoided. Studies on tacrolimus

are limited and its safety is unconfirmed. Drugs such as thalidomide, methotrexate and cyclosporine are contraindicated as they have been found in breast milk and are consequently considered unsafe.

ENDOSCOPIC METHODS DURING PREGNANCY

Endoscopy, colonoscopy, retosigmoidoscopy and cholangiography are considered safe during pregnancy according to ECCO Statement 7G (EL4, RGC). However, caution is required in relation to these procedures and there must be a strong indication for these procedures to be carried out in the second trimester (EL5, RGD). Techniques for hemostasis are safe, but should be performed with caution (EL3, RGC).

RISK OF THROMBOEMBOLISM IN HOSPITALIZED PREGNANT WOMEN

Many studies have considered the increased risk of venous thromboembolism in pregnant women. This increased risk was noted in the first six weeks of the postnatal period, and 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

Due to the current knowledge on inflammatory bowel disease, it is thought that the majority of drugs administered during pregnancy are safe for both the mother and the fetus. However, guidance in this group of patients (mothers-to-be) and control of disease activity before conception are essential for the prevention of miscarriage or premature birth. Most drugs are also safe for breastfeeding.

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