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*World J Gastroenterol* 2008 May 21; 14(19): 3085-3087
***World Journal of Gastroenterology*** ISSN 1007-9327


*CASE REPORT*

# Is infliximab safe to use while breastfeeding?

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Received: February 8, 2008 Revised: April 20, 2008

## Abstract

Inflammatory bowel disease (IBD) often affects women around the age of conception and pregnancy. Most drugs used to treat IBD are safe in pregnancy, but physicians must consider the clinical implications of certain treatment regimens in young, fertile females. We report an informative case of a pregnant patient with IBD who underwent treatment with infliximab during her pregnancy and while nursing her infant. Serum and breast milk infliximab levels were monitored throughout this time period. This case report suggests that targeted monoclonal antibodies and other biologic agents can be used with caution in pregnant and breastfeeding patients.



**Key words:** Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Pregnancy; Breast-feeding; Monoclonal antibodies

**Peer reviewer:** Akira Andoh, MD, Department of Internal Medicine, Shiga University of Medical Science, Seta Tukinowa, Otsu 520-2192, Japan

Stengel JZ, Arnold HL. Is infliximab safe to use while breastfeeding? *World J Gastroenterol* 2008; 14(19): 3085-3087 Available from: URL: http://www.wjgnet.com/1007-9327/14/3085.asp DOI: http://dx.doi.org/10.3748/wjg.14.3085

## INTRODUCTION

In recent years, targeted monoclonal antibodies and other biologic agents have been at the forefront of the numerous therapeutic options available to treat many immune-mediated disorders. A large number of young and fertile patients are afflicted with disorders like inflammatory bowel disease (IBD), rheumatologic diseases, asthma, and multiple sclerosis. These circumstances force patients and physicians to consider the safety of biologic agents during the peripartum time period.

## CASE REPORT

A 22-year-old female ($G_1P_1$) was referred to the Gastroenterology Clinic for treatment of fistulizing ileocolonic Crohn's disease (CD). The patient was initially treated with high dose corticosteroids, 6-mercaptopurine, metronidazole, and mesalamine with only mild improvement in her symptoms. The patient was eventually treated with infliximab and had a positive clinical response allowing her to be weaned off corticosteroids. Unfortunately, her 6-mercaptopurine was discontinued because of high thiopurine methyltransferase (TMPT) activity resulting in excessive production of the hepatoxic 6-methylmercaptopurine metabolite. The patient's CD continued to respond modestly to 3.6 mg/d mesalamine (1200 mg tid) and 5 mg/kg infliximab (500 mg) Ⅳ infusions every 8 wk. The patient responded well to the medications but continued to have progressive symptoms requiring a stepwise increase in the maintenance dose of infliximab to 10 mg/kg (1000 mg) Ⅳ infusions every 4 wk.

Three years after her diagnosis with CD, the patient was discovered to be pregnant with her second child. The patient was successfully treated with mesalamine and infliximab when she was discovered to be 12 wk pregnant. The patient was informed that her disease could potentially worsen, nutritional deficiencies could develop, and that her medications could be potentially harmful to the fetus. The patient understood the risks and decided to proceed with the pregnancy after multiple discussions regarding the side effects and potential teratogencity of her medications. She continued to take daily mesalamine and received a total of six doses of infliximab during her pregnancy with the last infusion occurring approximately 2 wk before delivery.

A healthy male infant weighing 7 pounds 6 ounces was born at thirty-nine weeks' gestation by an uncomplicated caesarian birth. The patient desired to breastfeed the infant while continuing to receive her mesalamine and infliximab. Again, the potential dangers of her medications were discussed with particular emphasis on their impact on breastfeeding. After taking the discussion under advisement, the patient decided to attempt to begin breastfeeding and to continue treatment with infliximab.

In an effort to determine if the infliximab was actually excreted into the breast milk, the patient's breast milk was collected and sent to the laboratory for analysis

**Table 1 IBD medications during pregnancy**

| Low risk | Limited data | Not recommended | Contraindicated |
|---|---|---|---|
| Oral mesalamine | Olsalazine | Tetracycline | Methotrexate |
| Topical mesalamine | Azathioprine | Sulfonamides | |
| Sulfasalazine | 6-Mercaptopurine | | |
| Ampicillin | Metronidazole | | |
| Cephalosporins | Ciprofloxacin | | |
| Corticosteroids | Infliximab | | |
| Cyclosporine | Adalimumab | | |
| Loperamide | | | |

**Table 2 IBD medications during nursing**

| Low risk | Limited data | Not recommended | Contraindicated |
|---|---|---|---|
| Oral mesalamine | Olsalazine | Tetracycline | Methotrexate |
| Topical mesalamine | Infliximab | Sulfonamides | Cyclosporine |
| Sulfasalazine | Adalimumab | Azathioprine | |
| Corticosteroids | | 6-Mercaptopurine | |
| | | Loperamide | |
| | | Metronidazole | |
| | | Ciprofloxacin | |

(Prometheus Laboratories, San Diego, CA) with an enzyme-linked immunosorbent assay. A spike and recovery study was performed to investigate whether any non-specific binding by breast milk components was interfering with the assay. A sample of breast milk was spiked with 40 ng/mL solution of infliximab, a concentration comparable to the mother's serum concentration. A dilutional analysis (1:2, 1:4, and 1:8) was also performed and the infliximab was detected by the laboratory in all the spiked breast milk samples, but was not identified in her regular breast milk. The patient then received her regularly scheduled infliximab infusion (10 mg/kg) and her breast milk was collected daily for 30 d. No infliximab was identified in any of the breast milk samples, even with dilutional analysis. At 27 mo, no developmental abnormalities were noted in the child.

## DISCUSSION

New medications and aggressive treatment approaches to medical management have put more women with IBD in the position of being healthy enough to consider pregnancy. In women with IBD, the key to a healthy pregnancy is adequate control of disease activity throughout pregnancy[1]. Biologic agents are increasingly becoming a mainstay in the treatment regimens of both CD and ulcerative colitis (UC). Unfortunately, little information is available about the short-term and the long-term consequences of treatment with target monoclonal antibodies on the maturing fetus[2,3]. The safety of IBD medications during pregnancy and nursing are summarized in Tables 1 and 2.

Infliximab (Remicade; Centocor Inc, Malvern, PA) is a chimeric monoclonal antibody to tumor necrosis factor-alpha (TNF-α)[4]. It is indicated for inducing and maintaining clinical remission in moderately to severely active CD and UC patients that have had an inadequate response to conventional therapy and maintenance of remission[5]. Infliximab is increasingly used to treat pregnant women and data on its safety during pregnancy are scarce. Infliximab is listed as a pregnancy category B medication and the product label states that "It is not known whether infliximab can cause fetal harm when administered to a pregnant woman[4]". Most clinicians believe that the chimeric structure of the infliximab molecule containing a human IgG1 constant region, limits placental transfer during the first trimester[6]. However, the safety of infliximab beyond the first trimester is unknown because IgG subclasses are readily passed into the fetus during the second and third trimesters[7]. Until recently, the medical literature contained no evidence that engineered therapeutic antibodies could cross the placenta when administered to expectant mothers. A recent case report documents clinically significant fetal exposure to infliximab *via* placental transfer and a prolonged half-life of the medication in newborns[2]. The presumed mechanism of fetal exposure to infliximab is transplacental maternal IgG antibody transfer beginning in the second trimester and peaking at term. No fetal abnormalities were apparent in this case, but the long-term implications of infliximab exposure during early childhood development are unknown. These findings suggest that pregnant patients should avoid therapeutic antibody treatments after thirty weeks' gestation and if necessary, the expectant mother can be bridged with steroids to control the disease activity until delivery[2,8].

Limited clinical data are available on the safety of infliximab in pregnancy, because no controlled study is available in pregnant women. The manufacturer's safety database contains information on the outcomes of 131 pregnant women who received infliximab for rheumatoid arthritis or IBD[9]. An analysis performed on this safety database suggests no significant difference in pregnancy outcomes in women with infliximab exposure[7]. A published retrospective review of 10 pregnancies in CD patients in which infliximab was continued throughout the course of the pregnancy reported favorable fetal and maternal outcomes[7]. The limited clinical results available suggest that the benefits of infliximab in attaining response and maintaining remission in pregnant IBD patients might outweigh the risks of drug exposure to the fetus[10].

The primary concern of the case we report is the safety of infliximab while breastfeeding, because many drugs and immunoglobulins are excreted in human milk. The infliximab product label states that "It is not known whether infliximab is excreted in human milk or absorbed systemically after ingestion[4]". A commercially available infliximab assay was used to measure drug levels in breast milk taken daily from our patient over a 30 d time period. No infliximab was detected in our patient's breast milk. Other published reports only tested breast-feeding mothers for one or two days but the results were consistent with our data[2]. We believe the daily testing performed on our patient's breast milk before and immediately after receiving an infliximab infusion clearly demonstrates that infliximab is not excreted in breast milk in any clinically significant amount.

Several case reports have recently emerged describing

the off-label usage of other biologics during pregnancy. A pregnant woman with treatment-refractory CD who failed treatment with infliximab was successfully treated with adalimumab (Humira; Abbott Laboratories, Chicago, IL), a recombinant human IgG1 monoclonal anti-TNF antibody[11,12]. The pregnancy was uncomplicated and at 6 mo, the infant showed normal growth and development[13]. Another case reported the use of etanercept (Enbrel; Amgen, Thousand Oaks, CA), a soluble TNF receptor fusion protein that binds to and inactivates TNF, in an uneventful pregnancy of a patient with refractory rheumatoid arthritis[14]. Etanercept has been shown to be excreted in breast milk, but it is not known whether the drug can be absorbed orally because it is such a large protein[15].

In conclusion, therapeutic monoclonal antibodies and other biologic agents are used to a greater extent to treat immune-mediated disorders in pregnant patients. The limited clinical data currently available show no significant difference in pregnancy outcomes of patients exposed to infliximab during pregnancy compared to a healthy population. Physicians should be aware that the fetus may be exposed to therapeutic monoclonal antibodies when administered to pregnant patients and the long term implications on the child's developing immune system are unknown at this time. While physicians must remain cautious about maternofetal exposure to medications like therapeutic monoclonal antibodies, additions to the literature from reports like this one will hopefully assuage some of the fears faced by gastroenterologists, obstetricians, and patients, alike.

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