SHORT REPORT

Therapeutic infliximab drug level in a child born to a woman with ulcerative colitis treated until gestation week 31

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Abstract
A 26 year old woman with ulcerative colitis was treated with regular infliximab (IFX) infusions until gestation week 31, and gave birth to a healthy child at gestation week 37. Maternal IFX trough level was relatively high during the course of pregnancy. In the infant, therapeutic level of IFX was detectable at week 16 after birth, but not at reassessment at week 28. Anti-IFX antibodies were consistently below the detection limit in the patient and in the child. This case illustrates that IFX is transferred through the placenta to the embryo, and may result in therapeutic drug levels in the newborn child despite IFX discontinuation in third trimester 6 weeks prior to delivery. The half life of IFX appeared markedly longer in infants as compared to adults. The safety of IFX beyond the first trimester is unknown, and this case highlights the need for further investigations of maternal transfer of IFX as well as the risks associated with IFX administrations in the second and third trimester.

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1. Introduction

The majority of patients with ulcerative colitis, a chronic inflammatory bowel disease (IBD), are managed well on conventional treatment with oral or topical 5-aminosalicylic acid (ASA), corticosteroids, and possibly a thiopurine immunosuppressant such as azathioprine. However, a subset of patients with chronic refractory or steroid-resistant severe disease may require additional immunosuppressive treatment with infliximab (IFX), a chimeric anti-TNF-alpha IgG1 antibody (Ab).1,2 IBD often affects younger females in the reproductive age...
and the benefits of immunosuppressive treatment must be carefully balanced against the potential risk for the fetus during pregnancy. Although IFX is useful in inducing and maintaining remission in moderate to severe IBD, little is known about the long term safety of this treatment in the offspring of IBD patients. IFX has been detected in cord blood in a higher concentration than in the periferal blood of the mothers. Detectable IFX blood levels have been reported up to 6 months after delivery in a case report on an infant of a mother with Crohn’s disease who had received regular IFX infusions of 10 mg/kg every 6–8 weeks throughout the pregnancy with last infusion only 2 weeks prior to delivery. Scarce data from five infants published in abstract form also indicate that IFX may be detected 2–6 months after delivery, but the time span between birth and last IFX infusion was highly variable among these patients. Due to the lack of widely available assays for assessment of IFX levels (and anti-IFX Ab), very limited data are available on fetal IFX blood levels in general. In this case we describe that IFX cross the placenta and is detectable in therapeutic concentrations in a newborn child up to at least 16 weeks after birth despite IFX discontinuation in third trimester 6 weeks prior to delivery.

2. Case report

A 26 year old woman with steroid dependent ulcerative colitis having received 5-ASA (4 g/day) and azathioprine (75 mg/day) for several years, was treated with an IFX induction series with infusions at week 0, 2, and 6 (5 mg/kg) at a disease flare resulting in complete clinical, biochemical, and endoscopic remission. Azathioprine was discontinued at time of IFX induced remission on the request of the patient. The patient remained well for 5 months but then relapsed. IFX was reinitiated with a new induction series (5 mg/kg), which resulted again in complete clinical and biochemical remission. The patient then realized that she was pregnant (unplanned) and in gestation week 10. 5-ASA was continued and IFX was paused as decided by the treating physician because the disease was now inactive, and because unnecessary IFX exposure was thought best to be avoided during the pregnancy. Only 9 weeks later, however, the disease flared with 15–20 liquid, bloody stools, moderate abdominal pain, and raised CRP value of 34 mg/l (normal range: <8 mg/ml). This resulted in administration of a further IFX infusion at gestation week 20, and a final infusion corresponding to gestation week 31 to which the patient responded well. The treating physician tried to avoid unnecessary IFX exposure of the fetus and therefore used an episodic strategy with administrations only at time of recurrence of symptoms.

Delivery was done by elective cesarean section at gestation week 37. The boy was healthy and without congenital malformations (weight 2925 g, length 51.5 cm, head circumference 35.4 cm). The patient continued IFX maintenance therapy after delivery with regular infusions every 8 to 12 weeks, and was in complete clinical remission at follow-up 13 months later. The child was breast fed until 14 weeks after delivery, and developed normally at time of follow-up corresponding to 13 months of age. The child received routine childhood vaccinations according to recommendations in Denmark, i.e. a combined vaccine for diphtheria, tetanus, pertussis, and polio; Haemophilus influenzae b; and pneumococcus at the ages of 3, 5, 12 months. Notably, the child had no abnormal reactions to the vaccinations, and furthermore had no signs of infectious or allergic diseases.

IFX trough levels during the patient’s second IFX series are displayed in Fig. 1. In the mother, IFX trough levels varied from 1.4 to 3.6 μg/ml before delivery, and 0.34 to 2.1 μg/ml after delivery; and anti-IFX Ab were negative at repeat assessments both before and after delivery (i.e. below the detection limit of 10 U/ml). In the child, IFX was detectable 16 weeks after birth at a concentration of 0.60 μg/ml, but IFX was undetectable at reassessment 28 weeks after birth (<0.05 μg/ml). Anti-IFX Ab were negative at both assessments.

3. Discussion

Active IBD at time of conception or flare of disease during pregnancy is associated with increased risk of adverse pregnancy outcomes in terms of preterm birth, low birth weight, and being small for gestational age. In order to prevent complications it is therefore generally recommended to aggressively treat active IBD during pregnancy. Most drugs conventionally used in IBD are considered to be of low risk during pregnancy, except methotrexate and thalidomide which are contraindicated. As regards IFX, this drug is probably also of low risk in pregnancy both for the early and late outcomes and does not seem to be teratogenic, but data are limited and only observational. IFX is classified as category B by the FDA, meaning that the drug is presumed to be safe based on animal studies. With respect to breast-feeding, several case reports have failed to detect IFX in the breast milk of women treated with IFX; and in addition, large protein molecules like IFX are in theory broken down in the gastrointestinal tract. Thus, IFX is not considered to be transferred through the breast milk in any significant amounts. Little is currently known about blood levels and clearance of IFX in the fetal circulation; however, IFX has been detected in cord blood, and detectable amounts of IFX extending up to several months after delivery have been reported in a few case reports. Based on these considerations it is generally recommended to...

![Image](https://academic.oup.com/ecco-jcc/article-abstract/6/3/358/474926/1)

**Figure 1** Infliximab (IFX) trough levels with respect to infu-

+26 weeks

+16 weeks

Infliximab (IFX) trough levels with respect to infusion number in the second IFX series and the time of delivery in a mother and her child.
avoid IFX therapy during pregnancy especially during the 3rd trimester.3,4,16

During pregnancy IgG-molecules are actively transported across the placenta via the FcRn-receptor to confer passive immunity on the fetus and infant.17,20 All other immunoglobulin classes (i.e. A, D, E, and M) are not transferred.17,20,21 The transfer mainly occurs during the 2nd and 3rd trimesters, and the rate increases exponentially up to delivery.17,20,21 There is a preference for transport of IgG1-molecules like IFX as compared to other IgG subtypes.17,20,21 In the present case we observed, that IFX administered up to gestation week 31 corresponding to 6 weeks prior to delivery, was detectable in an infant 16 weeks after birth, but not at reassessment at 28 weeks. The half life of IgG1 in adults is 21 days; and as expected, the half life of IFX is similar (20 days).22,23 In children the half life of IgG1 is longer being 48 days.22 Our case is consistent with these notions indicating that the half life of IFX in children is extended and considerably longer than in adults.6,7 Of note, the IFX concentration detected in the infant 16 weeks after delivery (0.6 μg/ml) was in the therapeutic range according to a recent receiver operating characteristic (ROC)-based calculation of cut-off levels associated with response types in IBD patients.1 Here we demonstrated that IFX >0.5 μg/ml is associated with maintained response to IFX in both Crohn’s disease and ulcerative colitis and thus represent a valid cut-off level for clinically relevant IFX concentrations. Taken together, our data highlight the potential risk of yet undefined adverse reactions due to the significant blood concentration of IFX persisting for a prolonged time period after delivery in newborn children of IBD patients receiving IFX up to the third trimester. Of particular concern is its effect on the child’s developing immune system in which TNF-alpha plays an important role.1,6 A recent report on a fatal case of a 3 month old child born to a woman treated with IFX during pregnancy due to disseminated mycobacterial infection after BCG vaccination further highlights this concern.24

We used clinically validated techniques for measuring IFX and anti-IFX Ab which are based on fluid-phase radioimmunoassays (RIA) (Biomonitor A/S, Copenhagen, DK).9–12 The RIA for detection of IFX measures the functional bioactive IFX concentration (TNF-binding capacity); i.e. the fraction of IFX which is not neutralized by anti-IFX Ab and is therefore capable of neutralizing TNF-alpha. The RIA for detection of anti-IFX Ab detects all isotypes of immunoglobulins and all IgG subclasses binding to IFX, and there is little or no interference from the presence of IFX.14

In conclusion IFX is transferred via the placenta to the fetus in considerable amounts in the third trimester and a significant concentration of IFX can be detected in the circulation of the newborn for several months after delivery. This highlights the need for studies on maternal transfer and potential adverse effects of IFX in the newborn. IFX treatment in the end of a pregnancy should carefully balance the potential risk of IFX exposure to the child with an adequate treatment of IBD in the mother.

Conflict of interest

Casper Steenholdt, Magid Al-Khalaf, Mark A. Ainsworth, and Jørn Brynskov have no conflicts of interest to declare.

Contributors

Study design and interpretation of data: All authors  
Collection of data: CS, MAK  
Analysis of data: CS, MAK  
Drafting the manuscript: CS  
Revising the manuscript and approval of final manuscript: All authors

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