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High Intra-Uterine Exposure to Infliximab Following Maternal Anti-Tnf Treatment During Pregnancy

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Key word: pregnancy, infliximab

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Summary

Background: Typically, inflammatory bowel disease (IBD) patients are in their reproductive years, raising questions about safely using anti-tumor necrosis factor antibodies like infliximab (IFX) during pregnancy. IgG antibodies naturally cross the placenta, especially during the last trimester. To prevent fetal intra-uterine exposure, stopping IFX treatment at gestational week 30 is recommended. However, whether this limits intra-uterine and early post-natal IFX exposure is unestablished.

Aim: To determine the intra-uterine exposure to IFX following maternal treatment with IFX.

Methods: Four pregnant IBD patients intentionally continued IFX during pregnancy. IFX levels were assessed in newborns' cord blood and the mothers' peripheral blood at delivery. The children's development during the first 3–6 months, infections, vaccine reactions and antibody responses to vaccinations against *Haemophilus influenzae* type b and *Pneumococcus* were assessed.

Results: The patients stopped IFX therapy at gestational week 21, 26, 26, and 30, respectively. In three infants, therapeutic IFX levels were present in cord blood at levels of 5.5–13.7 µg/mL and were two- to three-fold higher than in the peripheral blood of their mothers. During the 3–6-month follow-up, the children developed normally without signs of infections or allergic reactions, and had normal antibody titers after routine childhood vaccinations.

Conclusion: The use of IFX until gestational week 30 leads to fetal intra-uterine exposure to IFX at levels that exceed those in the mothers' peripheral blood. Although no short-term complications were detected, the high IFX levels observed in newborns raise concerns about unknown effects of IFX on the developing immune system.

Introduction

Anti-tumor necrosis factor (anti-TNF) agents are frequently-used powerful immunomodulatory agents available to clinicians to treat several autoimmune conditions including inflammatory bowel disease (IBD). Potential candidate patients for anti-TNF treatment are often young and in their reproductive years, which is also reflected in the observation that 20% of IBD patients with active reproductive wishes require treatment with anti-TNF agents.¹ Therefore, the safety of anti-TNF use during conception and pregnancy has become a major concern for patients and their clinicians.

Of the various anti-TNF agents, infliximab (IFX), a chimeric monoclonal antibody against TNF, is the best characterised with respect to safety during human reproduction. Short-term data from two safety registries found no important teratogenicity issues^{2,3}. However, intra-uterine exposure to IFX resulting from placental antibody transfer was previously reported in children born to mothers treated with IFX during pregnancy^{4,5}. Like all IgG antibodies, IFX crosses the placenta beginning in the second trimester, probably reaching its maximal transport capacity during the third trimester⁶. To limit this placental transfer stopping IFX treatment prior to gestational week 30 was proposed^{7,8}. Nevertheless, in view of the strong immunomodulatory properties of IFX and the lack of long-term outcome data, the safety of terminating IFX therapy at gestational week 30 is difficult to take for granted without data showing that this is sufficient to prevent transfer of significant amounts of anti-TNF to the unborn child.

Concern about the unpredictable outcomes of early exposure of the developing immune system to powerful TNF-alpha neutralization and the immunomodulatory potential of anti-TNF molecules is, at least on a theoretical basis, substantial. This concern, together with an absence of data in which the level of IFX transfer to the unborn child is actually assessed following termination of anti-TNF therapy during different gestational weeks, prompted us to

1
2
3 determine the exposure of the newborn to IFX in this case series of four IBD patients
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5 intentionally treated with IFX until gestational week 30. We found that this approach is not
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7 sufficient to limit the placental transfer of IFX, resulting in IFX levels in the cord blood that
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9 exceed the therapeutic level for adults.
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For Peer Review

Patients and Methods

Four patients (three with Crohn`s disease and one with ulcerative colitis, aged 19, 29, 29, and 31 years, respectively) were intentionally treated with IFX during pregnancy. All patients continued the remission-maintaining preconception dose regimen. In one patient, methotrexate was advised to be discontinued following her expressed wish to reproduce. Three patients were receiving IFX at a stable dose of 5 mg/kg every eight weeks, and one patient received 10 mg/kg every eight weeks. Two patients had periconceptional IFX monotherapy, one patient was using azathioprine. The patient using methotrexate conceived within two months after stopping methotrexate and continuing IFX monotherapy. The other three patients had stable medication during the six months prior to conception. One patient stopped IFX at gestational week 21, two patients at week 26, and one patient at week 30. The respective gestational weeks at delivery are shown in Table 1. The decision of discontinuation of IFX was at the discretion of treating gastroenterologist who discussed all pros and cons of the treatment continuation with the patients at an early stage of their pregnancy. The timing of discontinuation was motivated by the current approach advising not to extend the use of IFX beyond 30 weeks of pregnancy. The exact date of the last infusion was based on the 8-weeks schedule with which patients entered the pregnancy so that the last infusion would be given prior or at the week 30 at the latest. At delivery, cord blood was collected from the newborns, and peripheral blood serum was obtained within two days after delivery from the patients.

All children received routine childhood vaccinations according to recommendations in the Netherlands, i.e. a combined vaccine for diphtheria, tetanus, pertussis, and polio; *Haemophilus influenzae* b; and *pneumococcus* at the ages of 2, 3, and 4 months. The response to bacterial vaccines was assessed at month 6 of life in two of the three children born with significant IFX levels.

The IFX serum levels were measured by ELISA, the assay has been adapted and validated in our laboratory based on the previously reported and validated assay⁹. High binding

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3 capacity 96-well ELISA plates (Nunc-Immuno™ Plates) were coated overnight at 4°C with
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5 50µl of 2µg/mL recombinant human TNF-alpha (Invitrogen) diluted in phosphate buffered
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7 saline (PBS). The plates were washed twice with PBS 0.05% Tween 20 (PBST). The
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9 remaining protein-binding sites were blocked during two hours at room temperature with
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11 250µl of 3% non-fat dry milk (Elk Campina, Eindhoven, The Netherlands) diluted in PBST.
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13 The plates were washed five times with PBST and 100µl of serum, standard and control
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15 samples were added. For the negative control, a pooled human serum, obtained from
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17 random 40 different healthy individuals was used. To generate standard curve, serial
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19 concentrations of infliximab (Remicade®, Merck Sharp&Dohme) were used. The serum
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21 samples were serially diluted at concentrations of 1:1000 to 1: 32000. All samples were
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23 diluted in PBST containing 1% bovine serum albumine (BSA). The samples were incubated
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25 during one hour at room temperature and subsequently washed four times with 0.05% PBST.
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27 The reaction was revealed using 100µl of 3,3',5,5'tetramethylbenzidine (eBioscience)
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29 solution at room temperature and stopped with 100µl of 1M H₂SO₄. Reading was performed
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31 at two wave lengths; 450 and 620 nm using Biorad 680 plate reader. The samples were run in
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33 different concentrations as mentioned above and the final infliximab serum concentrations
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35 were interpolated from the standard curve. The results were rejected if difference between
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37 the calculated concentration of the serial dilution was higher the 20%, and the accepted
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39 measurements were considered as triplicates to calculate the mean.
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44 The assay was tested and validated using serum samples from patients receiving IFX and
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46 those who were naïve to this drug. For the average inter-assay coefficient of variation
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48 calculation, 10 samples were run on different days and the standard deviation per patients
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50 sample was expressed as a percentage of the mean. The average inter-assay coefficient
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52 was 4%. The inter-assay coefficient was calculated using the serial dilutions of samples that
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54 were used instead of triplicates. For this calculation 3 dilutions of 10 samples were measured
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56 with the intra-assay variability coefficient of 4.4%.
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59 Since the treatment protocol is considered a standard care, no approval of ethical committee
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has been solicited.

Results

Pregnancy outcomes

Patients gave birth at gestational weeks 37, 36, 41, and 38, respectively (Table 1). Three children were healthy without congenital malformations. One baby girl, born to a 19 year old mother (patient Nr 3), experienced respiratory depression after birth owing to anesthetics used during delivery, and which resolved spontaneously. This child was also diagnosed with polydactyly of her left hand. Apart from infliximab, the mother had used methotrexate till two months prior to conception and had omitted to use the recommended folic acid supplementation during the first weeks of the pregnancy. Other risk factors for congenital malformations, such as alcohol consumption, smoking or consanguinity were not revealed.

During the follow-up of 4 to 11 months, all children developed normally, there were no signs of infections, and no abnormal reactions to vaccinations were observed. The antibody response to vaccinations against *pneumococcus* and *Haemophilus influenzae* b were assessed in two of the three children born with detectable IFX levels. Both children had protective levels of vaccine antibodies when checked at month 6.

IFX levels

Only one patient (patient 1) had undetectable levels of IFX in her peripheral blood at delivery and undetectable levels in her infant's cord blood. This patient received her last IFX infusion at gestational week 21. In three other patients, therapeutic levels of IFX were found in the cord blood at levels of 13, 5.5 and 13.7 $\mu\text{g/mL}$, respectively. The levels in cord blood were higher than the levels measured in peripheral blood of mothers ($p=0.032$ with one-tailed paired t-test), which were 4.9, 2.4, and 5 $\mu\text{g/mL}$ respectively.

Patient follow-up

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3 All four IBD patients remained in remission throughout their pregnancy and resumed IFX
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5 treatment within 4 weeks after delivery. The re-treatment with IFX did not result in allergic
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7 reactions and all patients remained in remission during the 4 to 11 months of follow-up after
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9 delivery.
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For Peer Review

Discussion

In this case series, we show that the currently advocated approach of stopping IFX at gestational week 30 does not prevent the intra-uterine exposure of the fetus to significant levels of IFX. This finding is important in clinical practice because of the potential short-term as well as long-term complications of early exposure to anti-TNF.

Data from the safety registries^{2,3}, as well as a recently published first prospective cohort on the outcomes of pregnancies exposed to infliximab¹⁰ did not reveal significant teratogenicity issues. In one out of the four patients presented in our study, polydactyly of the hand was diagnosed in a child born to a mother using IFX at conception and during the first two trimesters of the pregnancy. However, this patient also conceived only two months after stopping methotrexate. Digital malformations have been reported with the use of methotrexate but almost exclusively in combination with other birth defects¹¹ which were not present in this child. To our knowledge, no isolated polydactyly has been reported in the case of the pre-natal exposure to infliximab. In addition, polydactyly is a very common birth defect in general population¹². Thus, no clear association with the medication can be concluded, however, the role of the pre-conceptional use of methotrexate remains a subject of discussion in this patient.

Intra-uterine exposure to IFX of children born to mothers receiving IFX treatment was first suggested by Vasiliauskas et al. in 2006⁴. In this case report, the mother used IFX during the entire pregnancy, and clinically significant levels of IFX were detected in the child's serum sample. The hypothesis of placental transfer of IFX was further supported by a study by Mahadevan et al.⁵ where authors reported clinically significant levels in the cord blood of the infant and serum samples taken directly postpartum from five children born to mothers treated with IFX. In this case series, the mean time between birth and last IFX infusion was 30 days. Kane et al.¹³ measured the levels of IFX in two children born to mothers treated with IFX until gestational week 32 and 24, respectively. In both children, IFX was undetectable;

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3 however, the samples were taken postpartum on days 15 and 57, respectively, which makes
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5 the assumption of a lack of intra-uterine and early postnatal exposure to IFX uncertain.
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7 The kinetics of IgG antibodies in general are governed by the neonatal Fc receptor (FcRn)¹⁴.
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9 Antibodies are passively taken up by endothelial cells among other cell types and
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11 subsequently sequestered through binding to intracellularly expressed FcRn then shuttled
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13 back to the extracellular milieu. This recycling helps to increase the life time of the antibodies
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15 by protecting them from catabolism¹⁵. The same mechanism is used by maternal IgG
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17 antibodies that cross the placenta beginning in the second trimester¹⁶. IFX, being an IgG1
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19 class antibody with a functional Fc, very probably crosses the placenta in the same way¹⁷
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21 and is subject to the efficient FcRn-mediated protection from break down in the newborn.
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23 The biological half time of IFX in the newborn is also expected to be longer than in adults
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25 because of the high expression of the FcRn during the first months of life. Indeed, the series
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27 of 5 children born with detectable IFX levels showed the persistence of IFX in the peripheral
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29 blood of the children for as long as 6 months⁵. Thus, the placental transfer of IFX not only
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31 raises the issue of intra-uterine exposure but, most importantly, the concern about
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33 consequences for immune system functioning and development during the first weeks of life.
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35 Children born with detectable levels of IFX do not seem to have an increased risk of
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37 infections in their first year of life and have normal responses to vaccinations with bacterial
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39 non-live vaccines. This was documented in the eight-patient series reported by Mahadevan
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41 et al.¹⁸ and is also supported by the findings in the current study. However, a fatal case of
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43 disseminated mycobacterial infection after BCG administered at month 3 to a child born to a
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45 mother treated with IFX during the entire pregnancy was recently reported¹⁹. In this case, the
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47 likely mechanism of insufficient immune control of the live attenuated vaccine would be the
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49 neutralization of TNF-alpha by IFX, although no measurements of IFX levels in the child were
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51 performed. The specific infectious complications resulting from the use of anti-TNF agents
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53 are well known and, therefore, vaccinations with live antigens are also prohibited in patients
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55 on anti-TNF treatment. Because significant levels of IFX may persist for several months in
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3 children born to mothers treated with IFX, vaccinations with attenuated vaccines should be
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5 postponed until IFX levels are undetectable.
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8 Early exposure of the immune system to powerful TNF-alpha blockade also raises concerns
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10 about the long-term consequences for the maturation of the immune system. In the context
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12 of the increasing number of reports of hepatosplenic T-cell lymphoma in young adolescents
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14 treated with combined immunosuppressive therapy containing, in most cases, anti-TNF²⁰,
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16 and keeping in mind the lack of long-term outcome data, we believe the actual approach
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18 should be to try to limit the intra-uterine and postnatal exposure of children to anti-TNF in
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20 general.
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23 The decision to stop treatment with a drug that keeps the mother's underlying disease in
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25 remission during pregnancy is a difficult decision for the treating physician. A disease flare
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27 may represent a substantial risk not only for the patient, but also for the unborn child. **On the**
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29 **other hand, in the absence of convincing long-term safety data of the perinatal exposure to**
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31 **IFX, the continuation of the treatment remains a subject of discussion. Simultaneously, the**
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33 **decision to stop IFX is difficult in the current absence of predictors for the disease course**
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35 **during pregnancy in this specific setting. In addition, in case of treatment with anti-TNF,**
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37 **allergic reactions during retreatment which had been postponed for more than 12 weeks**
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39 **represent another concern.** In this limited series of patients, we did not observe any of these
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41 problems; all patients remained in remission after stopping IFX and no allergic reactions
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43 occurred during retreatment after delivery. **Our observation is also supported by the results of**
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45 **the first prospective cohort of 35 IBD patients treated with IFX during first two trimesters of**
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47 **the pregnancy that did not show negative impact of this approach nor on the disease course**
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49 **neither on the pregnancy outcomes¹⁰.** Interestingly, in three patients with detectable levels of
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51 IFX at delivery, the interval between the last IFX infusion was 10, 15, and 9 weeks,
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53 respectively. **The elimination half-time of IFX for women being 18 days²¹, one would expect**
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55 **no detectable levels in these patients at delivery.** That these patients still had detectable
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57 levels of IFX may indicate changes in the pharmacokinetics of IFX during pregnancy that
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3 would lead to a longer biological half-life of IFX and, therefore, possibly may provide a safe
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5 way to stop treatment earlier in the pregnancy.
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8 In conclusion, the use of IFX at the end of the second trimester of pregnancy leads to intra-
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10 uterine exposure of the fetus to IFX. This exposure does not seem to have a negative impact
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12 on the child in terms of increased infection rate and vaccination failure, but in specific
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14 situations, such as vaccinations with attenuated live antigens, the presence of IFX may have
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16 fatal consequences. Therefore, we propose that the levels of IFX be assessed in every child
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18 born to mothers treated with IFX during pregnancy, and to administer attenuated live
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20 vaccines only to children with undetectable IFX levels. Additionally, the long-term effects of
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22 this early exposure of the immune system to IFX are hard to predict. **Therefore, for patients**
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24 **in whom the quiescent disease during pregnancy allows interruption of treatment, intra-**
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26 **uterine and postnatal exposure of newborns to IFX may probably be avoided by stopping IFX**
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28 **at the beginning of the second trimester. In order to determine the exact timing of the**
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30 **discontinuation of IFX during pregnancy, further studies on the pharmacokinetics in this**
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32 **setting need to be conducted.**
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Statement of Interests

L. De Ridder had support from MSD for consultancy

C. van der Woude had support from Abbott, Shering-Plough and Shire for consultancy and received payment for lectures including service on speakers bureaus from Falk and Abbott

For Peer Review

Table 1. Pregnancy outcomes and medication during pregnancy

<i>Patient Number</i>	<i>Infliximab dose</i>	<i>Co-medication</i>	<i>Infliximab stopped (gestational week)</i>	<i>Gestational week delivery</i>	<i>Birth weight (g)</i>	<i>Congenital malformations</i>
1	5 mg/kg, every 8 weeks	None	21	37	2650	none
2	5 mg/kg, every 8 weeks	None	26	36	4030	none
3	5 mg/kg, every 8 weeks	None*	26	41	3030	Polydactyly left hand
4	10 mg/kg, every 8 week	Azathioprine 2 mg/kg	30	39	3185	none

*Methotrexate two months prior to conception

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2
3 **Figure 1.** Infliximab levels in cord blood of newborns (black bars) and in the peripheral blood of the mothers (grey bars) at delivery. In the three patients with
4 detectable IFX levels, the levels in newborn were higher than the levels at the peripheral blood of the mothers (one-sided paired t-test, $p=0.032$)
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7 * Levels undetectable
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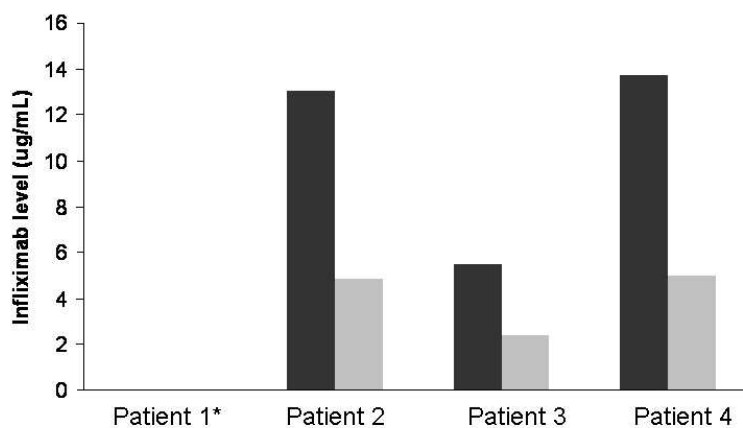


Figure 1. Infliximab levels in cord blood of newborns (black bars) and in the peripheral blood of the mothers (grey bars) at delivery. In the three patients with detectable IFX levels, the levels in newborn were higher than the levels at the peripheral blood of the mothers (one-sided paired t-test, $p=0.032$)

* Levels undetectable

254x190mm (96 x 96 DPI)