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CLINICAL AT

Concentrations of Adalimumab and Infliximab in Mothers and Newborns, and Effects on Infection

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BACKGROUND & AIMS: Little is known about in utero exposure to and postnatal clearance of anti–tumor necrosis factor (anti-TNF) agents in neonates. We investigated the concentrations of adalimumab and infliximab in umbilical cord blood of newborns and rates of clearance after birth, and how these correlated with drug concentrations in mothers at birth and risk of infection during the first year of life. **METHODS:** We performed a prospective study of 80 pregnant women with inflammatory bowel diseases at tertiary hospitals in Denmark, Australia, and New Zealand from March 2012 through November 2014: 36 received adalimumab and 44 received infliximab; 39 received concomitant thiopurines during pregnancy. Data were collected from medical records on disease activity and treatment before, during, and after pregnancy. Concentrations of anti-TNF agents were measured in blood samples from women at delivery and in umbilical cords, and in infants for every 3 months until the drug was no longer detected. **RESULTS:** The time from last exposure to anti-TNF agent during pregnancy correlated inversely with the concentration of the drugs in the umbilical cord (adalimumab: r = -0.64, $P = .0003$; infliximab: r = -0.77, $P < .0001$) and in mothers at time of birth (adalimumab, r = -0.80; infliximab, r = -0.80; $P < .0001$ for both). The median ratio of infant:mother drug concentration at birth was 1.21 for adalimumab (95% confidence interval [CI], 0.94–1.49) and 1.97 for infliximab (95% CI, 1.50–2.43). The mean time to drug clearance in infants was 4.0 months for adalimumab (95% CI, 2.9–5.0) and 7.3 months for infliximab (95% CI, 6.2–8.3; $P < .0001$). Drugs were not detected in infants after 12 months of age. Bacterial infections developed in 4 infants (5%) and viral infections developed in 16 (20%), all with benign courses. The relative risk for infection was 2.7 in infants whose mothers received the combination of an anti-TNF agent and thiopurine, compared with anti-TNF monotherapy (95% CI, 1.09–6.78; $P = .02$). **CONCLUSIONS:** In a prospective study of infants born to mothers who received anti-TNF agents during pregnancy, we detected the drugs until 12 months of age. There was an inverse correlation between the time from last exposure during pregnancy and drug concentration in the umbilical cord. Infliximab was cleared more slowly than adalimumab from the infants. The combination of an anti-TNF agent and thiopurine therapy during pregnancy increased the relative risk for infant infections almost 3-fold compared with anti-TNF monotherapy. Live vaccines therefore should be avoided for up to 1 year unless drug clearance is documented, and pregnant women should be educated on the risks of anti-TNF use.

Keywords: ERA Study; Inflammatory Bowel Diseases; Safety; Vaccination.

Anti–tumor necrosis factor α antibodies (anti-TNF) are used to treat an increasing number of patients with inflammatory bowel disease (IBD). Global sales for the 2 anti-TNF drugs adalimumab and infliximab for treating

Abbreviations used in this paper: **anti-TNF, anti–tumor necrosis factor α antibodies; BCG, Bacille Calmette-Guerin; CD, Crohn's disease; CI, confidence interval; CM, congenital malformation; GW, gestational week; IBD, inflammatory bowel disease; LBW, low birth weight; PIANO, pregnancy IBD and neonatal outcomes; RR, relative risk; SGA, small for gestational age; UC, ulcerative colitis.**

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autoimmune diseases in the areas of gastroenterology, rheumatology, and dermatology exceeded 20 billion US dollars in 2013.[1]

In IBD patients, the use of anti-TNF therapy improves clinical outcomes, reduces serious disease-related complications, decreases the need for surgery, and decreases hospitalizations.[2] A recent European population-based study of 1367 IBD patients found that 18% of Crohn's disease (CD) and 5% of ulcerative colitis (UC) patients received anti-TNF within the first 12 months of being diagnosed, and 23% of CD and 6% of UC patients received anti-TNF by 7 years after diagnosis.[3,4] Because the IBD incidence peaks in the second and third decades, anti-TNF exposure is common during the reproductive years.[5] IBD has no particular gender predilection, and women with IBD commonly wish to bear children, regardless of anti-TNF treatment. Knowledge of its safety therefore remains a key issue.

Maternal clinical remission in IBD is desirable to optimize pregnancy outcome because active IBD increases the risk of prematurity, low birth weight (LBW), small for gestational age (SGA), and low Apgar scores.[6,7] To control disease activity, medical treatment often is needed during pregnancy.[6,7] Studies of antenatal exposure to anti-TNF drugs have been reassuring; a 2013 systematic review of 21 case series and 4 prospective studies (including 1533 women) concluded that anti-TNF drugs was not associated with adverse neonatal outcomes, including congenital malformations.[8] However, studies to date have focused on the period of pregnancy itself, and there is a paucity of data concerning clearance in infants and childhood development.

Adalimumab and infliximab are monoclonal IgG1 proteins with limited transport across the placenta during the first trimester.[9] Between gestational weeks (GWs) 17 and 22, the fetal IgG level is 5%–10% of the maternal level, and by term it exceeds the maternal level by 3-fold.[10] In view of the placental transport kinetics, neonatal exposure to anti-TNF would be expected to be higher in infants of mothers exposed later in pregnancy. It seems intuitive that the greater the exposure of anti-TNF to the infant, the greater the risk of adverse effects such as infections or developmental disturbances. However, data are lacking. The clearance of anti-TNF in infants has received little attention. Clearance in adalimumab-exposed infants has not been investigated, but clearance in 10 infliximab-exposed infants took up to 7 months.[11] This raised concerns about the safety of live vaccines, and was highlighted by the death from disseminated Bacille Calmette-Guerin (BCG) of a 4.5-month-old infliximab-exposed infant after vaccination.[11,12]

To address these issues, the current study aimed first to determine infant drug concentrations of adalimumab and infliximab in umbilical cord blood and the rate of clearance by infant drug measurements every 3 months post-partum. Second, we aimed to determine maternal drug concentrations at birth and correlate these with the umbilical cord concentration and other factors potentially influencing the drug concentration. Finally, we aimed to investigate child development and the risk of infections during the first year of life, after in utero anti-TNF exposure.

Materials and Methods

Pregnant women with IBD who received treatment with adalimumab (Humira, AbbVie, North Chicago, IL) or infliximab (Remicade, MSD, Kenilworth, NJ) were recruited prospectively from 14 tertiary hospitals in Denmark, Australia, and New Zealand from March 2012 to November 2014. Multiple pregnancies were excluded because they were associated with an increased risk of adverse outcomes.[13] If a woman gave birth more than once during the study period (n = 2), both pregnancies were included.

All eligible women were interviewed in the outpatient clinic or by videoconferencing, and completed a structured online questionnaire after birth. The questionnaire covered demographics, disease, treatment, birth, and neonatal details. All data were confirmed with the treating physician. One year post-partum, the women completed a second online questionnaire regarding medical treatment, disease activity, breastfeeding, child development, and infections.

The duration of anti-TNF treatment in pregnancy for each patient was determined by the treating gastroenterologist based on history and disease activity. Disease activity was assessed prospectively by a physician global assessment as active or in remission at conception, in each trimester, and post-partum. SGA was defined as a child with a birth weight of more than 2 SDs below the mean for children of similar gestational age, according to the reference curve of estimated fetal growth.[14] LBW was defined as a child with a birth weight less than 2500 g, and preterm was defined as birth before 37 GWs.[6,7] Apgar scores less than 7 were considered low, and scores of 7 or higher were considered normal.[15] Congenital malformations (CMs) were defined as structural or functional anomalies, present at the time of birth, according to World Health Organization criteria.[16]

At birth, peripheral blood was taken from the mother and a blood sample was taken from the umbilical cord to determine the concentrations of anti-TNF. In the event of a measurable concentration, infant drug concentrations were repeated every 3 months until undetectable. Clotted blood samples were spun and serum was frozen in aliquots at -80°C. Serum adalimumab and infliximab concentrations were measured by enzyme-linked immunosorbent assay (QS-INFLIXI and Q-ADA; Matriks Biotek, Ankara, Turkey) according to the manufacturer's instructions. Samples were tested in duplicate and the average was expressed as micrograms per milliliter of serum. The coefficient of variation between assay wells was less than 10%. In case of very low or very high concentrations, the sample was retested in different dilutions. In case of variation between the 2 results, a third analysis was performed. The lower limit of detection was 0.03 μg/mL for adalimumab and 0.02 μg/mL for infliximab, and, in control experiments, false-positive results for blank sera were not seen. The presence of antibodies to infliximab or adalimumab were not assessed.

Statistical Analysis

Frequency tables of major study variables were constructed for the total population, separately for adalimumab- and infliximab-treated women, and for the Danish and Australian/New Zealand cohorts, respectively. The Pearson chi-squared test was used for the comparison of these groups. Two-sample t tests of major study variables were constructed by type of anti-TNF drug. Biochemical data were normalized by

log transformation. The relative risk (RR) with associated 95% confidence intervals (CIs) was used to describe relapse in the third trimester by time of anti-TNF discontinuation, for infections in the offspring by continuation of maternal anti-TNF treatment after GW 30, and infections in the offspring by maternal combination therapy with thiopurine and anti-TNF. The Wilcoxon rank-sum test was performed to compare anti-TNF concentrations by infections in the infants during the first year of life. Simple linear regression analysis was used to determine factors influencing drug concentration at the time of birth. The following variables were used: weeks since last anti-TNF dose, duration of anti-TNF, mesalamine use, thiopurine use, maternal weight before pregnancy, child weight, gestational week of birth, type of IBD, and use of a second anti-TNF. A nonlinear, mixed-effects regression model was used to analyze the clearance data. More specifically, for each of the 2 parameters describing the exponentially decreasing drug concentration (ie, the concentration at birth and the elimination rate constant), a fixed drug (adalimumab/infliximab) effect and a random infant effect were included. Model validation was performed by comparing individual observed and fitted values and by inspecting residuals. The time to complete drug clearance was estimated directly from the nonlinear mixed-effects regression. A P value less than .05 was regarded as statistically significant. Neonatal clearance analysis was performed using R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria). All other analyses were performed using Stata version 13.0 (Stata Corporation LP, College Station, TX).

Ethics Committee Approval

Written informed consent was obtained from all participating women. The study was approved by the Danish Data Protection Agency (reference 116-02-174-13), by the Regional Ethical Review Board in Denmark (reference 1-10-72-471-12), by the St Vincent's Hospital Ethics Committee in Australia (reference 105/12), and by the Southern Ethics Committee in New Zealand (reference 12/NTB/14).

Results

Mother–Baby Pairs

Of the 89 pregnant women recruited, 5 (6%) miscarried before GW 10 and 4 (4%) failed blood collection (samples were not correctly prepared or transported), leaving 80 mother–baby pairs for analysis: 42 from Denmark, 29 from Australia, and 9 from New Zealand. Demographic and clinical details are shown in Table 1.

Medical Therapy During Pregnancy

Thirty-six (45%) women received adalimumab and 44 (55%) received infliximab. The majority (90%) received standard-dose treatment (ie, adalimumab 40 mg every other week or infliximab 5 mg/kg every 8 weeks). Six (7.5%) adalimumab- and 2 (2.5%) infliximab-treated women received anti-TNF at an increased dose or frequency. Most women (88%) received anti-TNF in the 6 months before conception as well as during pregnancy, with only 10 women (12%) commencing treatment in the first trimester or early in the second trimester. The median duration of anti-TNF therapy before pregnancy was 2.5 years (range, 0–11 y). The last dose of anti-TNF given during pregnancy was administered at a median of GW 35 (range, 14–41 GWs) for

Table 1. Characteristics of 80 Women on Biological Therapy in Pregnancy

	n	%
Inflammatory bowel disease	80	100
Crohn's disease	66	83
Ileal only (L1)	14	18
Colon only (L2)	26	33
Ileocolonic (L3)	25	31
Isolated upper digestive (L4)	1	1
Perianal disease	33	41
Ulcerative colitis	14	17
Proctitis (E1)	0	0
Left-sided (E2)	6	8
Extensive (E3)	8	10
Medications		
Adalimumab	36	45
Infliximab	44	55
Thiopurine	39	49
Mesalamine	14	18
Prednisolone	13	16
Budesonide	1	1
Allopurinol (co-administered with thiopurine)	1	1
Combination therapy		
Adalimumab and thiopurine	16	44
Infliximab and thiopurine	23	52
Smoking		
Before pregnancy	13	16
During pregnancy	6	8
Post-partum period	6	8
Previous CD bowel resection	24	30
ADA or IFX before pregnancy (6 months)	70	88
Active disease defined by Physician Global Assessment		
Conception (6 months)	25	31
1st trimester	19	24
2nd trimester	25	31
3rd trimester	27	34
Postpartum (6 months)	29	36
Primiparous	31	39
Obstetric risk factors	20	25
Obesity (BMI $\geq$ 30)	15	19
Hypertension	3	4
Gestational diabetes	2	3
Breastfeeding commenced	65	80
	Median	Range
Maternal age at birth, *y*	31	24–39
Years since diagnosis	8	0.8–32
Height, *m*	1.68	1.55–1.82
Weight, *kg*	67.5	48.0–115.0
Body mass index, kg/m^2	23.6	17.0–42.5
Gestational week at delivery	39.0	33.0–42.0
Breastfeeding, *mo*	6.0	0.25–15

NOTE. There were no significant differences between adalimumab (ADA)- and infliximab (IFX)-treated women or between women from Denmark and Australia/New Zealand except that the Danish cohort had a lower rate of perianal disease ($P = .007$).
BMI, body mass index.

adalimumab and GW 30 (range, 8–37 GWs) for infliximab ($P < .001$). Treatment was ceased before GW 30 in 25 (31%) women. More infliximab-treated women (n = 18; 72%) than adalimumab-treated women (n = 7; 28%) ceased treatment before GW 30 ($P = .03$).

Disease Activity

Overall, 38 (48%) women experienced a disease relapse in the first, second, or third trimester of pregnancy, whereas 42 (52%) women were in complete remission throughout pregnancy (Table 1). Women who had active disease (n = 25) in the 6 months before pregnancy were more likely to have active disease during pregnancy (n = 19) than women in remission (n = 55) before pregnancy; 19 women had active disease during pregnancy ($P = .001$). There were no significant differences in physician global assessment–defined disease activity between the pregnancy trimesters (Table 1). Women who stopped anti-TNF treatment before GW 30 (n = 25) did not seem to have an increased risk of relapse in the third trimester after stopping treatment compared with women who continued treatment after GW 30 (n = 55), with an RR of 0.64 (95% CI, 0.18–2.20) for adalimumab and 0.72 (95% CI, 0.26–2.04) for infliximab.

Pregnancy Outcomes

The rates of preterm delivery, SGA, LBW, and CM were low (Table 2). Women with perianal disease had a higher rate of caesarean section (n = 26; 79%) than vaginal delivery (n = 7; 21%) ($P = .004$). The 3 (4%) children born preterm were all GWs 33–36 at birth, but none were SGA. There were 3 CMs (4%): 1 cleft palate (adalimumab-exposed), 1 duplex kidney (infliximab-exposed), and 1 aberrant subclavian artery (infliximab-exposed).

Table 2. Pregnancy Outcome in 80 Children Exposed In Utero to Adalimumab or Infliximab

	n	%
Caesarean section	45	56.3
Planned	38	47.5
Emergency	7	8.8
Preterm	3	3.8
Small for gestational age	3	3.8
Low birth weight, <2500 g	6	7.5
Congenital malformation	3	3.8
Stillbirth	0	0.0
Apgar score <7		
1 minute after birth	6	7.5
5 minutes after birth	1	1.3
Sex		
Girl	38	47.5
Boy	42	52.5
	Median	Range
Weight, *g*	3318	2105–5070
Length, *cm*	51	41–56

NOTE. There were no significant differences between women from Denmark vs Australia/New Zealand and adalimumab vs infliximab, respectively.

Drug Concentrations

At the time of birth, the median maternal and cord blood drug concentrations were 1.5 μg/mL (range, 0.0–10.0 μg/mL) and 2.0 μg/mL (range, 0.0–12.1 μg/mL) for adalimumab, respectively, and 2.0 μg/mL (range, 0.0–22.2 μg/mL) and 5.9 μg/mL (range, 0.12–28.7 μg/mL) for infliximab, respectively. The median ratio of infant to maternal drug concentration at birth was 1.21 (95% CI, 0.94–1.49) for adalimumab and 1.97 (95% CI, 1.50–2.43) for infliximab.

There was a statistically significant inverse correlation between the duration since last exposure and both cord blood drug concentrations (adalimumab: r = -0.64, $P = .0003$; infliximab: r = -0.77, $P < .0001$) (Figure 1) and maternal concentrations at birth (adalimumab, r = -0.80; infliximab, r = -0.80; both $P < .0001$) (Figure 2). By using simple linear regression analysis, only the time since last anti-TNF dose was associated significantly with the maternal and cord blood anti-TNF concentration. Maternal and cord blood concentrations were correlated significantly (adalimumab, r = 0.80; infliximab, r = 0.82; both $P < .0001$) (Figure 3). Maternal and umbilical cord blood anti-TNF concentrations were significantly lower at birth when the drug was stopped before GW 30 (Table 3).

The median infliximab concentrations in maternal blood at the time of delivery did not differ between women with active disease at any time during pregnancy (2.1 μg/mL) and women who were in remission throughout pregnancy (1.5 μg/mL) ($P = .63$), neither did the corresponding cord blood infliximab concentrations differ (infants of mothers with active disease, 5.5 μg/mL, vs remission, 6.3 μg/mL; $P = .96$). Similar findings were observed for adalimumab. The median maternal adalimumab blood concentrations for women with active disease were 1.2 μg/mL vs in remission 2.6 μg/mL ($P = .26$), and cord blood concentrations in active disease were 1.2 μg/mL vs in remission 2.4 μg/mL ($P = .42$).

Time to Clearance in Infants

Of adalimumab-exposed infants, 8 (22%) had an undetectable concentration of adalimumab at the time of birth and, in these cases, maternal treatment had been discontinued at a median of GW 32 (range, 14–36 GWs). All infliximab-exposed infants had detectable infliximab in cord blood at birth. The mean time to clearance for adalimumab-exposed infants was 4.0 months (95% CI, 2.9–5.0 mo), and for infliximab-exposed infants was 7.3 months (95% CI, 6.2–8.3 mo), showing a 46% slower clearance of anti-TNF in infliximab-exposed infants compared with adalimumab-exposed infants ($P < .0001$) (Figure 4). Although no adalimumab-exposed infant had a detectable concentration at 9 months, 5 (11%) infliximab-exposed infants had a detectable concentration at 9 months. Of these, 1 had a concentration of 10.9 μg/mL at birth and a detectable concentration of 0.03 μg/mL at the age of 12 months. At 15 months, the infliximab concentration was undetectable. The estimated mean half-life of adalimumab was 26 days (95% CI, 23–29 days), and was 33 days (95% CI, 30–37 days) for infliximab ($P = .003$). We found no statistically significant associations between drug half-life and birth weight (adalimumab, $P = .72$; infliximab, $P = .10$), cord blood concentration

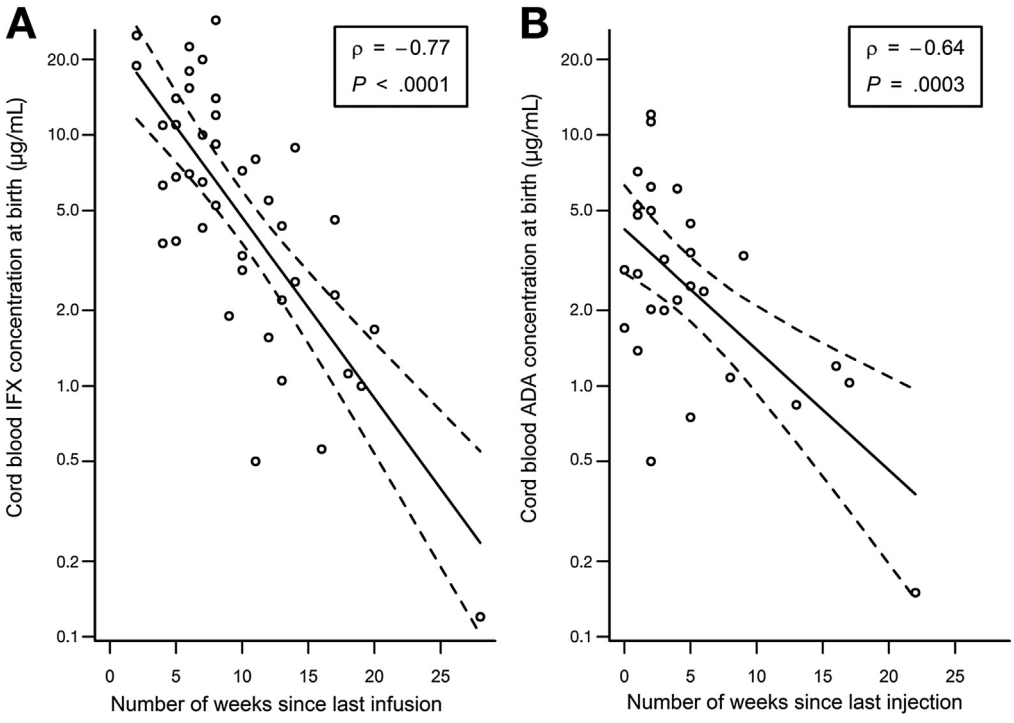

Figure 1. (*A*) Infliximab and (*B*) adalimumab cord blood concentration and duration since last dose in pregnancy.

(adalimumab, $P = .40$; infliximab, $P = .39$), or maternal breastfeeding (adalimumab, $P = .95$; infliximab, $P = .43$).

Infant Development and Risk of Infections

Seventy-two (90%) of the mothers answered the questionnaire regarding infant development, infections, and childhood diseases during the first year post-partum. In all but 1 infant, development with respect to gross and fine-motor development, vision, language, speech, hearing, communication, and social behavior was normal. Four (5%) cases of infant bacterial infections were observed, and all resolved with antibiotics (cellulitis, 2 weeks old; pneumonia, 7 weeks old; acute otitis media, 6 months old; and

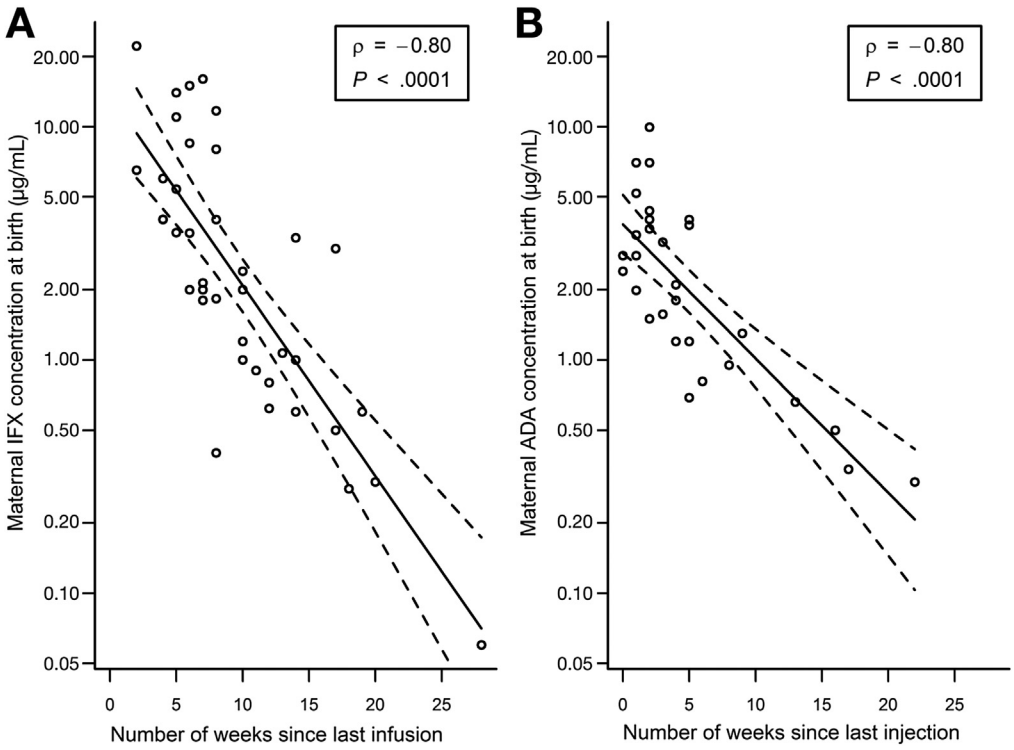

Figure 2. (*A*) Infliximab and (*B*) adalimumab maternal concentration at birth and duration since last dose in pregnancy.

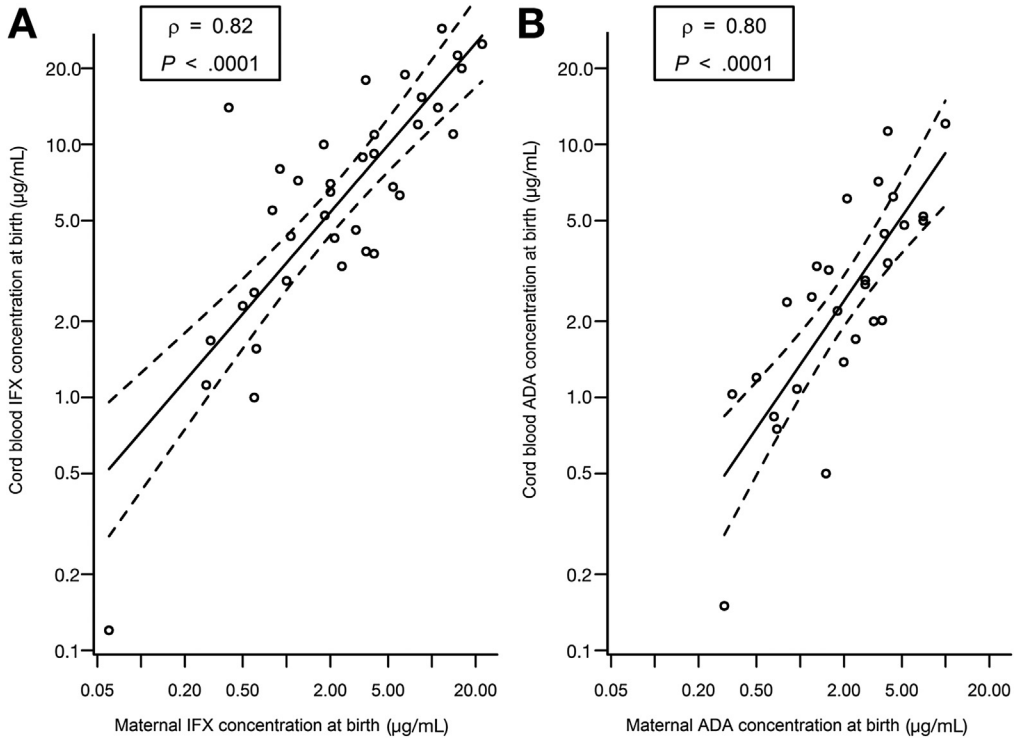

Figure 3. Correlations between cord blood and maternal concentrations of (*A*) infliximab and (*B*) adalimumab at birth.

upper respiratory tract infection, 10 months old). Three of the 4 infants were exposed in utero to combination therapy with thiopurine and anti-TNF, and 1 infant was born preterm.

Sixteen (20%) infants, of whom 12 (75%) were exposed in utero to combination therapy with thiopurine and anti-TNF, suffered from at least 1 viral infection during the first year of life, but all had a benign course. None of the infants were born with adverse outcomes. Chicken pox, confirmed clinically in all but 1 case, affected 8 Danish infants (19%) between the ages of 3 and 12 months. All infants were breastfed and all mothers previously had chicken pox. Hand-foot-and-mouth disease and roseola infantum were seen in 3 (4%) and 5 (6%) infants, respectively.

The median anti-TNF concentration at birth among infants who contracted an infection was 2.8 μg/mL (range, 0.0–28.7 μg/mL), compared with 3.3 μg/mL (range, 0.0–24.9 μg/mL) in infants without infections during the first year of life ($P = .41$). Continuing maternal anti-TNF treatment after GW 30 did not increase the likelihood of infection in the offspring compared with discontinuation before GW 30 (RR, 0.54; 95% CI, 0.26–1.16; $P = .12$). The risk of any infection in the offspring within the first year of life was more than twice as great among women on combination therapy compared with monotherapy (RR, 2.7; 95% CI, 1.09–6.78; $P = .02$).

Discussion

This international multicenter study comprehensively examined the outcomes of fetal exposure to the 2 complete IgG1 antibodies, adalimumab and infliximab, in infants born of women with IBD. It provides novel data in a well-characterized prospective cohort representative of clinical practice, showing that postnatal clearance of anti-TNF is prolonged, particularly of infliximab. The study provides a solid evidence-based rationale for the counseling and

Table 3. Drug Concentrations at Birth According to Time of Cessation of Adalimumab and Infliximab

	IFX concentration, μg/mL			ADA concentration, μg/mL		
	Last infusion < GW 30	Last infusion ≥ GW 30	*P* value	Last injection < GW 30	Last injection ≥ GW 30	*P* value
Total number	18 (41%)	26 (59%)		7 (19%)	29 (81%)	
Maternal blood	0.6 (0.0–3.3)	4.0 (0.0–22.2)	<.0001	0.3 (0.0–0.7)	2.1 (0.0–10.0)	.0006
Cord blood	2.2 (0.1–8.9)	10.0 (1.9–28.7)	<.0001	0.2 (0.0–1.2)	2.5 (0.0–12.1)	.0047

NOTE. Medians are shown, with ranges in parentheses.

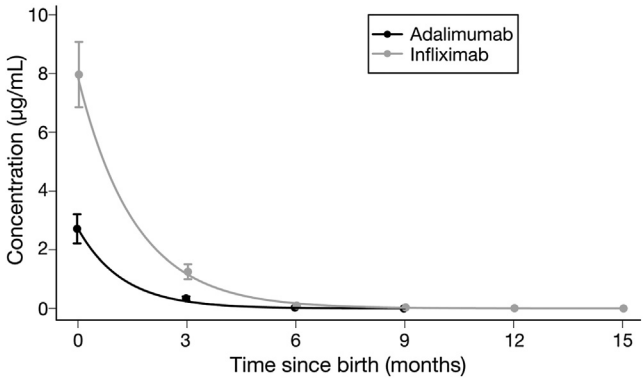

Figure 4. Mean (±SEM) and fitted neonatal clearance of adalimumab and infliximab.

management of pregnant women and infants exposed to these drugs.

The majority of exposed infants were born with detectable drug concentrations that exceeded those of their respective mothers, reflecting fetal accumulation as pregnancy progresses, in accordance with the general properties of placental transport of IgG1 molecules.[10] The drug concentration correlated with the duration since last drug exposure in pregnancy in both mothers and infants, as found by other investigators in smaller series.[11,17] It was not possible to identify a gestational week to stop maternal anti-TNF treatment that reliably would predict undetectable drug concentrations at birth. This indicates that other factors may influence clearance, such as individual pharmacokinetic differences in exposed pregnant women.

Systematic drug measurements in the infants allowed the calculation of a pharmacokinetic profile for both drugs. A novel finding was that the mean infliximab half-life was 3.7 times longer in infants than in adult nonpregnant patients.[18] Detectable drug concentrations were present up to 12 months of age, showing that the time to drug clearance is longer than previously found among 10 infliximab-exposed infants.[11] Clearance data for adalimumab have not, to our knowledge, been reported previously. Here, the average adalimumab half-life was 2-fold longer in infants than in adult nonpregnant patients, and drug concentrations were detectable up to 6 months of age.[19]

The prolonged clearance of adalimumab and infliximab may have significant clinical impact, in particular when planning live vaccines (eg, measles-mumps-rubella, rotavirus, oral polio, smallpox, varicella, BCG, and yellow fever) to infants exposed in utero to anti-TNF. A death was reported after administration of the BCG vaccine in a 4.5-month-old infant exposed in utero to infliximab.[12] In contrast, Bortlik et al[20] reported large local skin reactions in a minority of, but no serious adverse outcome in, 15 infants exposed in utero to infliximab who received BCG vaccination within 1 week of birth. International guidelines recommend that live vaccines should be given only to anti-TNF exposed infants in the second half of the first year.[6,7,21] Because it is not possible to predict the necessary anti-TNF concentration associated with an adverse immune reaction to a live vaccine, the present data suggest that live vaccinations should be postponed until either 12 months of age, or after documented clearance of the drug in the child. At 12 months of age, infants exposed to anti-TNF in utero can receive live vaccines such as measles-mumps-rubella and varicella to protect the infant from potentially severe illnesses.

Breastfeeding did not affect anti-TNF clearance, adding evidence to the lack of any significant transfer of drug to the breast milk.[22–24] Because the proportion of lactating women has increased during the past 2 decades, these results underpin the advice to women to continue breastfeeding on anti-TNF treatment.[25,26]

Most women continued treatment into the third trimester, based on the clinical evaluation by the physician and reflecting the severe phenotype of the cohort. However, in those women whose IBD was in remission and who stopped anti-TNF treatment before GW 30, neonatal drug concentrations were significantly lower for both drugs, compared with women who continued treatment after GW 30. Although our data indicate that treatment suspension did not seem to be associated with an increased frequency of relapse in the third trimester, this result should be interpreted with caution. First, the number of observations was small, and confidence intervals were wide. Second, we cannot completely rule out selection bias because only women in remission throughout pregnancy were eligible to discontinue treatment before GW 30. The finding, however, is in accordance with those of de Lima et al,[27] who found that, in case of sustained remission in IBD, discontinuation of anti-TNF before GW 25 ($n = 51$) did not increase the risk of relapse during the remaining part of the pregnancy compared with women who continued anti-TNF beyond GW 30 ($n = 30$).

Reassuringly, we found no increased risk of adverse pregnancy outcomes, which is consistent with previous studies.[7,28,29] In particular, we found a lower risk of preterm birth than previously reported in all 3 countries,[30] despite a complex cohort with a long median disease duration, moderately severe phenotype, and a high rate of concomitant immunosuppression. This observation supports the current European Crohn & Colitis Organization guideline, which states that remission in IBD is important for normal pregnancy outcome and that this may require aggressive medical treatment.[7] Furthermore, a high percentage of caesarean sections was found, especially in women with perianal disease. This finding is in line with several previous studies.[6,7,27,31]

Infections were seen in one fifth of the neonates in the cohort during the first year, with most being common childhood infections, with no sequelae. All cases of chicken pox occurred in Danish children. In contrast to the Australian immunization program, varicella-zoster virus vaccination is not a part of the immunization program in Denmark and New Zealand. It is estimated that 98% of the adult Danish population has had chicken pox, which is equivalent to the rate in The Netherlands.[32,33] At 3 years of age, almost 70% of children in The Netherlands are varicella-zoster virus seropositive.[32] Therefore, we do not find the observed frequency of chicken pox among Danish

children during the first year of life in the present study alarming. The drug concentration at birth did not differ significantly between infants with infections during the first year of life compared with those without infections. Data regarding anti-TNF and thiopurine combination therapy compared with anti-TNF monotherapy in pregnancy and infection risk in offspring are sparse and conflicting. In keeping with preliminary results from a large prospective American registry (pregnancy IBD and neonatal outcomes [PIANO]) (RR, 1.50; 95% CI, 1.08–2.09), we found that maternal combination therapy increased the risk of infections in the infants during the first year of life,[34] whereas de Lima et al[27] found no increased risk (monotherapy, n = 16 [38%] vs combination-therapy, n = 2 [20%]; $P = .29$). It is yet to be determined whether maternal combination therapy may result in dysfunctional immune development in the offspring. A recent study by Sheibani et al[35] found that 12 infants exposed to anti-TNF in utero, of whom 33% were exposed to combination therapy, showed appropriate response to the 2 neonatal inactive vaccines tetanus toxoid and *Haemophilus influenza*, and showed adequate immunoglobulin levels, except for IgM. However, combination therapy in pregnant patients should be counterbalanced carefully between risk of relapse in pregnancy in case of switch to anti-TNF monotherapy and an increased risk of infection in the offspring if combination therapy is continued in pregnancy.

Normal developmental milestones were observed at 12 months in all but 1 of the infants irrespective of in utero exposure to anti-TNF monotherapy or combination therapy with thiopurines. These findings are in line with preliminary results from the American PIANO registry, which found that infants exposed to monotherapy or combination therapy had equivalent or better achievement of milestones than unexposed infants of women with IBD.[36] We found no increased risk of infections during the first year of life in offspring of mothers who continued anti-TNF after GW 30, which is in accordance with preliminary results from the American PIANO registry (odds ratio, 1.1; 95% CI, 0.5–1.6).[37] No increased risk of maternal relapse in the third trimester was found if anti-TNF was discontinued before GW 30. However, the present study was not powered adequately and did not have a long enough duration to answer these questions.

In conclusion, this prospective observational study showed that infant clearance of infliximab after exposure during pregnancy was slower than previously reported. More rapid clearance was seen with adalimumab. Based on these results, we suggest that no live virus vaccine should be given during the first year of life in offspring of women treated with anti-TNF during pregnancy. The umbilical cord blood drug concentration is not correlated with the risk of infant infection during the first year of life. Combination therapy increases the risk of infections in the offspring but all were benign. Pregnant women treated with combination therapy should receive counseling regarding the potential increased risk of postnatal infections in their infant, which should be assessed promptly. Further studies are warranted to investigate any associations between anti-TNF exposure and long-term risk of infection or developmental disturbances in the infants.

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Conflicts of interest
These authors disclose the following: Lisbet Christensen has served on the advisory boards of AbbVie and MSD, and has received speaker's fee from MSD, Ferring, UCB, Takeda, Tillotts, and AbbVie; Peter Gibson has served on the advisory boards of AbbVie, Ferring, Janssen, Merck, Nestle Health Science, Danone, Allergan, and Takeda, has received consultation fees from AbbVie, Ferring, Janssen, Merck, Nestle Health Science, Danone, Allergan, and Takeda, has received research grants for other investigator-driven studies/clinical trial funding from AbbVie, Janssen, Falk Pharma, Danone, and A2 Milk Company, and has received speaker's fees from Ferring, Takeda, AbbVie, Janssen, Fresenius Kabi, and Pfizer; Richard Gearry has served on the advisory boards of AbbVie, MSD, Janssen, and Baxter, has received research grants for other investigator-driven studies/clinical trial funding from AbbVie and Ferring, and has received speaker's fees from MSD, Ferring, Takeda, AbbVie, and Janssen; Alissa Walsh has served on the advisory boards of AbbVie, Ferring, Janssen, Takeda, and Hospira, and has received speaker's fees from Ferring, Takeda, AbbVie, Janssen, and Hospira; Susan Connor has served on the advisory boards of AbbVie, Janssen, Hospira, and Vifor, and has received speaker's fees from Ferring, AbbVie, Janssen, and Shire; Ian Lawrance has served on the advisory boards of AbbVie, MSD, Ferring, Janssen, Takeda, and Hospira, has received speaker's fees from Ferring, Takeda, AbbVie, Janssen, Hospira, and Shire; Jane Andrews has served on the advisory boards of AbbVie, Ferring, Janssen, Takeda, Hospira, Abbott, Shire, and Pfizer, and has received research grants for other investigator-driven studies/clinical trial funding from AbbVie, Janssen, Ferring, Abbott, Takeda, Shire, Hospira, and Pfizer; Signe Wildt has served on the advisory boards of MSD and Tillotts, and has

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