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CLINICAL SCIENCE

Analysing cord blood levels of TNF inhibitors to validate the EULAR points to consider for TNF inhibitor use during pregnancy

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ABSTRACT

Background To minimise placental transfer of tumour necrosis factor inhibitors (TNFi), the European League Against Rheumatism (EULAR) created points to consider (PtC) for the use of TNFi during pregnancy. We are the first to validate the EULAR-PtC by analysing TNFi concentrations in cord blood.

Methods Patients were derived from the Preconceptional Counselling in Active Rheumatoid Arthritis Study. TNFi was stopped at the time points recommended by the EULAR. Maternal blood and cord blood were collected and analysed for the concentration of TNFi.

Results 111 patients were eligible for the analysis. Median stop time points were gestational age (GA) 37.0 weeks for certolizumab pegol, GA 25.0 weeks for etanercept, GA 19.0 weeks for adalimumab and GA 18.4 weeks for infliximab. Certolizumab pegol (n=68) was detectable in 5.9% of cord blood samples, with a median concentration of 0.3 µg/mL (IQR: 0.2–1.3) and a median cord/maternal concentration ratio of 0.010. Etanercept (n=30) was not detected in any cord blood samples. Adalimumab (n=25) was detectable in 48.0% of cord blood samples, with a median concentration of 0.5 µg/mL (IQR: 0.2–0.7) and a median concentration ratio of 0.062 (IQR: 0.018–0.15). Infliximab (n=14) was detectable in 57.1% of cord blood samples, with a median concentration of 0.4 µg/mL (IQR: 0.1–1.2) and a median concentration ratio of 0.012 (IQR: 0.006–0.081).

Conclusion Compliance with the EULAR-PtC results in absence or low levels of TNFi in cord blood.

Key messages

What is already known about this subject?

- Tumour necrosis factor (TNF) inhibitors can be actively transported across the placenta as early as week 20 of gestation, mediated by fetal Fc receptors and dependent on TNF inhibitor structure.
- European Alliance of Associations for Rheumatology (EULAR) points to consider (PtC) recommend to stop adalimumab and infliximab at gestational age (GA) 20 weeks, etanercept at GA 30–32 weeks and conditional continuation of certolizumab pegol.
- The EULAR-PtC are based on limited evidence; only for certolizumab pegol, it has been demonstrated that cord blood concentrations are minimal when treatment is continued throughout pregnancy.

What does this study add?

- This study demonstrates that stopping TNF inhibitor treatment according to the EULAR-PtC results in undetectable or low levels of TNF inhibitor in cord blood.

How might this impact on clinical practice or future developments?

- Compliance with the EULAR-PtC results in absence or low concentration of TNF inhibitors in cord blood, indicating that the children are most likely not immunologically compromised.

INTRODUCTION

Tumour necrosis factor inhibitors (TNFi) have become an important component of the treatment of rheumatic diseases during pregnancy.[1] A drawback of prescribing TNFi during pregnancy is active transport of these drugs across the placenta mediated by neonatal Fc receptors (FcRn).[2] Placental transfer starts around gestational week 20, and the rate of transfer increases throughout pregnancy.[2] The extend of placental transfer depends on the molecular structure of the drug. Adalimumab and infliximab are whole anti-TNF antibodies and have a strong affinity for the FcRn.[3] Etanercept is a fusion protein that comprises a TNF receptor and the Fc domain of human IgG1. Its affinity for the FcRn is lower than that of adalimumab and infliximab.[4] Certolizumab pegol is a PEGylated Fab fragment of an anti-TNF monoclonal antibody. Because certolizumab pegol lacks the Fc domain, it is not actively transported across the placenta.[5]

The European League Against Rheumatism (EULAR) created points to consider (PtC) for the use of TNFi during pregnancy.[6] These PtC recommend discontinuation of treatment at gestational age (GA) 20 weeks for adalimumab and infliximab, GA 30–32 weeks for etanercept and conditional continuation of certolizumab pegol throughout pregnancy. Until now, it is unknown whether stopping treatment at the advised GA results in the absence of TNFi in cord blood.[6]

The aim of this research is to validate the stop time points recommended by the EULAR-PtC. We hypothesise that no TNFi will be measured in cord blood when treatment was stopped at the recommended GA.

METHODS

Patients

Patients were derived from the Preconceptional Counselling in Active Rheumatoid Arthritis (PreCARA) cohort at Erasmus Medical Center in Rotterdam, the Netherlands (ClinicalTrials.gov registration: NCT01345071). The PreCARA cohort is an ongoing, prospective cohort study on inflammatory rheumatic diseases and pregnancy. Patients whose cord blood was collected at birth were used for the current analysis.

PreCARA treatment protocol

Patients in the PreCARA cohort were treated according to a modified treat-to-target approach. Details on the PreCARA treatment protocol have been previously described.[1] Patients were allowed to get pregnant on the TNFi used at enrolment. TNFi were discontinued at the GAs advised by the EULAR, and a switch to certolizumab pegol and/or prednisone was considered. Certolizumab pegol was discontinued at GA 38 weeks to prevent maternal infections during delivery, based on expert opinion.[1]

Data collection

Information on diagnosis and previous medication use was collected at the first visit. Maternal blood was collected in each trimester, at moments unrelated to the administration of TNFi. At birth, cord blood was collected by the patient's midwife or gynaecologist. Blood samples were clustered and subsequently sent to Sanquin Laboratory (Amsterdam) for analysis (online supplemental appendix).

Statistical analysis

Descriptive statistics on clinical characteristics and TNFi use are presented as mean (SD), median (IQR) or number (%). Differences in GA at stopping TNFi treatment between patients with and without measurable TNFi levels in cord blood were assessed with the two-sample Wilcoxon rank-sum test. P values <0.05 were considered significant. Stata software V.16.0 was used for all statistical analyses.

Table 1 Descriptive statistics of patients from PreCARA cohort that were included in the current analysis (n=111)

Variable	Value*
Age, years	31.2±3.9
Nulliparity	49 (44.1%)
Disease duration at inclusion, years	8.0±6.5
Disease activity in 3rd trimester (DAS28-CRP)	2.2±0.8
Diagnosis	
Rheumatoid arthritis	53 (47.7%)
Spondyloarthropathies	26 (23.4%)
Psoriatic arthritis	22 (19.8%)
Juvenile idiopathic arthritis	6 (5.4%)
Other rheumatic disorders	4 (3.6%)
Medication during pregnancy, any use†	
Sulfasalazine	63 (56.8%)
Hydroxychloroquine	54 (48.6%)
Prednisone	45 (40.5%)
Certolizumab pegol	68 (61.2%)
Etanercept	30 (27.0%)
Adalimumab	25 (22.5%)
Infliximab	14 (12.6%)

*Values are given as mean±SD or number (%).
†Either alone or in combination with other medication. The sum of TNFi exceeds 100%, because some patients switched from etanercept, adalimumab or infliximab to certolizumab pegol during pregnancy. DAS28-CRP, Disease Activity Score 28. CRP, C-reactive protein; PreCARA, preconceptional counselling in active rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

RESULTS

Data from 111 patients were used for the analysis (table 1). During some pregnancies, the use of etanercept, adalimumab or infliximab was switched to certolizumab pegol. Therefore, in the cord bloods of those pregnancies, the concentration of two TNFi was to be determined, resulting in a total of 137 cord blood measurements. Most patients stopped treatment before the recommended GA (table 2). Etanercept (n=30) was stopped before GA 30 weeks by 29 (96.7%) patients, adalimumab (n=25) was stopped before GA 20 weeks by 20 (80.0%) patients and infliximab (n=14) was stopped before GA 20 weeks by 10 (71.4%) patients. For certolizumab pegol, the median GA at stopping treatment was GA 37.0 weeks (IQR: 34.1–38.1 weeks), and the median time between last dose and delivery was 15 days (IQR: 2–34 days).

Certolizumab pegol (n=68) was detected in 5.9% of cord blood samples; the median level of certolizumab pegol was 0.3 µg/mL (IQR: 0.2–1.3). The maximum concentration (2.3 µg/mL) was measured in a patient that stopped treatment at 26 days before delivery and received 200 mg every other week. The concentration ratio of cord blood to maternal blood for certolizumab pegol was 0.010 (IQR: 0.007–0.066). Etanercept was not detected in any of the cord blood samples, including the sample of one patient who stopped after GA 30 weeks (GA 36.7 weeks).

Adalimumab and infliximab were detected in 12 (48.0%) and 8 (57.1%) cord blood samples, respectively. The median cord blood concentrations were 0.5 µg/mL (IQR: 0.2–0.7) for adalimumab and 0.4 µg/mL (IQR: 0.1–1.2) for infliximab. The median concentration ratios of cord blood to maternal blood were 0.062 (IQR: 0.018–0.15) for adalimumab and 0.012 (IQR: 0.006–0.081) for infliximab. The maximum concentration for adalimumab (2.1 µg/mL) was measured in a patient who stopped treatment at GA 19.4 weeks and received 40 mg every other week. For infliximab, the maximum concentration (4.5 µg/mL) was measured in a patient who stopped treatment at GA 21.1 weeks and received 400 mg every 5 weeks (online supplemental appendix).

Differences in GA at stopping adalimumab and infliximab between patients with and without detectable TNFi in the cord blood are shown in table 3.

DISCUSSION

In the current study, we show that stopping TNFi around the GA recommended by the EULAR-PtC results in no detectable or low levels of TNFi in the cord blood.

Most patients in our study used certolizumab pegol during pregnancy. We observed certolizumab pegol in 5.9% of the cord blood samples. In comparison, a study by Mariette *et al* observed certolizumab pegol in 20% of the umbilical cord samples.[5] The lower limit of quantification was higher in our study (0.1 µg/mL vs 0.032 µg/mL), which might explain the observed difference. Furthermore, there was one patient with a certolizumab pegol concentration of 2.3 µg/mL in our study; this was an outlier. In this particular case, placental blood sample contamination with mother's blood cannot be excluded.

The use of etanercept during pregnancy has not been investigated on a large scale before. Etanercept has a low affinity for the FcRn.[4] Our study shows that stopping treatment with etanercept before GA 30 weeks results in absence of etanercept in the cord blood. Interestingly, the patient that stopped after the recommended GA (at GA

Table 2 TNF inhibitor (TNFi) use during pregnancy and TNFi concentrations in maternal blood and cord blood. Values are expressed as median (IQR) unless indicated otherwise

	Certolizumab pegol (n=68)	Etanercept (n=30)	Adalimumab (n=25)	Infliximab (n=14)
Stop time point as recommended by EULAR-PtC, weeks	N/A	GA 30–32	GA 20	GA 20
Gestational age (GA) at time of stopping TNFi, weeks	37.0 (34.1–38.1)	25.0 (17.9–28.0)	19.0 (12.4–19.9)	18.4 (14.0–20.1)
Stopped before recommended GA, n (%)	N/A	29 (96.7%)	20 (80.0%)	10 (71.4%)
No measurable TNFi in cord blood, n (%)	64 (94.1%)	30 (100%)	13 (52.0%)	6 (42.8%)
Measurable TNFi in cord blood, n (%)	4 (5.9%)	0 (0%)	12 (48.0%)	8 (57.1%)
Maternal concentration of TNFi in the 1st trimester, µg/mL	24.6 (19.0–31.0)	2.1 (0.8–2.5)	8.2 (1.5–10.0)	14.0 (8.0–21.0)
Maternal concentration of TNFi in the 2nd trimester, µg/mL	22.5 (13.0–30.72)	1.4 (0.9–2.7)	6.0 (4.5–7.5)	6.4 (4.2–20.0)
Maternal concentration of TNFi in the 3rd trimester, µg/mL	20.5 (13.0–29.6)	0.2 (0.2–0.7)	0.9 (0.1–1.4)	1.4 (0.1–1.9)
Concentration of TNFi in the cord blood if measurable, µg/mL	0.3 (0.2–1.3)	–	0.5 (0.2–0.7)	0.4 (0.1–1.2)
Concentration ratio cord blood to maternal blood*	0.010 (0.007–0.066)	–	0.062 (0.018–0.15)	0.012 (0.006–0.081)

*Concentration ratios of cord blood to maternal blood were calculated with the maternal concentrations during active use of TNFi (trimester 3 for certolizumab pegol and trimester 1 for adalimumab and infliximab).
EULAR, European League Against Rheumatism; PtC, points to consider; TNF, tumour necrosis factor .

36.7 weeks or 7 days before delivery) also had no measurable levels. This is in line with a previous study by Eliesen *et al*, which reported a low cord to maternal concentration ratio of 0.04 in a patient who used etanercept until 4 days before delivery.[7] This might be explained by the shorter half-life of etanercept (circa 3 days) compared with other TNFi (8–10 days for infliximab and 14 days for certolizumab pegol and adalimumab). Both these observations might indicate that etanercept could be used beyond GA 30–32 weeks if necessary.

We detected adalimumab and infliximab in about half of the patients' cord blood samples, however in low concentrations. A study by Julsgaard *et al* reported median concentrations of 2.5 µg/mL for adalimumab and 10.0 µg/mL for infliximab in patients who continued treatment beyond GA 30 weeks,[3] considerably higher than the respective 0.5 µg/mL and 0.4 µg/mL in patients from our study, who stopped around GA 20 weeks. These discrepancies might be the result of different indication groups included in the study of Julsgaard *et al*, which were mainly patients with inflammatory bowel diseases and have continued infliximab and adalimumab until a higher GA period during pregnancy.

The effects of low TNFi concentrations in the fetal circulation are unknown. Previous research shows that a TNFi concentration as low as 0.1 µg/mL is sufficient to bind all circulating TNF.[8] Therefore, clinical relevance cannot be excluded. Nevertheless, the concentrations are only a few percent of those found in the mothers during active use. Intrauterine exposure to TNFi can have major consequences, as it may affect the infant's immune system. Immunological changes in infants exposed to high levels of TNFi have been observed, including neutropenia, decreased T_{reg} cells and B-cells with a more immature phenotype.[9] This can result in a different immune response to vaccines, resulting in reduced efficacy of vaccines in the first half year of the infant's life. In addition, the use of live attenuated vaccines in children with high serum levels of TNFi after intrauterine exposure to TNFi requires caution. These vaccines may be pathogenic in infants with a suppressed immune system. In one case, a Bacillus Calmette-Guérin (BCG) vaccination after intrauterine exposure to infliximab resulted in neonatal death after a disseminated BCG infection.[10] It can be concluded from the results of our study that, if PtC recommendations are followed, intrauterine exposure to certolizumab pegol or etanercept will not result in placental transfer and future recommendations for attenuated live vaccination could be less restrictive. If for adalimumab and infliximab minimal or absence of TNFi concentrations in cord blood are aimed, these should be withdrawn even earlier than week 20 of gestation (eg, week 15 of gestation) (online supplemental appendix). A possible consequence of TNFi in the infant's circulation is an increased risk for infections during the first months of life.[10] However, literature reports both increased and non-increased risk for infections and therefore remains inconclusive.[11 12]

Our study has several strengths. It is the first large study to evaluate the EULAR-PtC for the use of TNFi during pregnancy. All 111 patients included in the current analysis were treated at the same hospital, so differences between physicians were minimal. Patient data were retrieved directly from the patient; therefore, the risk for biases, like misclassification bias, was minimal.

A limitation of our study is that we did not measure trough and peak values of maternal TNFi concentrations. The concentration ratios we calculated are therefore less accurate than those calculated in a pharmacokinetic study. Another limitation is that the majority of patients using etanercept stopped or switched their TNFi quite earlier than the recommended stop time point of GA 32 weeks.

In conclusion, compliance with the EULAR-PtC results in undetectable levels or absence of TNFi in cord blood in most patients that use certolizumab pegol or etanercept. For adalimumab and infliximab, TNFi was detectable in cord blood in about half of the patients. The detected concentrations of TNFi in cord blood were far lower than the maternal levels during active use. The potential harmful effects of these low concentrations of TNFi in cord blood are unknown and require further investigation. If these concentrations of TNFi were

Table 3 Stop time points of TNFi for patients with and without detectable TNFi in the cord blood

	Stop time point if TNFi was detectable, GA, weeks	Stop time point if TNFi was undetectable, GA, weeks	P value for difference
Certolizumab pegol (n=68)	36.9 (34.8–38.6)	37.0 (34.1–38.1)	0.82
Etanercept* (n=30)	–	–	–
Adalimumab (n=25)	19.4 (18.7–20.1)	15.0 (4.4–18.8)	0.08
Infliximab (n=14)	19.1 (16.7–20.3)	13.6 (6.9–18.4)	0.06

*Etanercept was not detectable in any of the cord blood samples.
GA, gestational age; TNF, tumour necrosis factor.

to be clinically relevant, stopping infliximab and adalimumab at an earlier GA than the EULAR-PtC recommend may be appropriate.

Contributors All authors met the authorship criteria; they had a substantial contribution to the conception or design of the work (HTWS and RJEMD) or the acquisition (RJEMD), analysis (NG, EK, HTWS, RJEMD, GW and TR) or interpretation of data for the work (all authors) and were involved in revising a draft of this work, gave final approval of this version to be published and are accountable for all aspects of the work in ensuring accuracy and integrity.

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REFERENCES

1 Smeele HT, Röder E, Wintjes HM, *et al*. Modern treatment approach results in low disease activity in 90% of pregnant rheumatoid arthritis patients: the PreCARA study. *Ann Rheum Dis* 2021;80:859–64.
2 Simister NE, Story CM. Human placental fc receptors and the transmission of antibodies from mother to fetus. *J Reprod Immunol* 1997;37:1–23.
3 Julsgaard M, Christensen LA, Gibson PR, *et al*. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology* 2016;151:110–9.
4 Arora T, Padaki R, Liu L, *et al*. Differences in binding and effector functions between classes of TNF antagonists. *Cytokine* 2009;45:124–31.
5 Mariette X, Förger F, Abraham B, *et al*. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. *Ann Rheum Dis* 2018;77:228–33.
6 Götestam Skorpen C, Hoeltzenbein M, Tincani A, *et al*. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016;75:795–810.
7 Eliesen GAM, van Drongelen J, van Hove H, *et al*. Assessment of placental disposition of infliximab and etanercept in women with autoimmune diseases and in the ex vivo perfused placenta. *Clin Pharmacol Ther* 2020;108:99–106.
8 Berkhout LC, l'Ami MJ, Ruwaard J, *et al*. Dynamics of circulating TNF during adalimumab treatment using a drug-tolerant TNF assay. *Sci Transl Med* 2019;11:eaat3356.
9 Esteve-Solé A, Deyà-Martínez Àngela, Teixidó I, *et al*. Immunological changes in blood of newborns exposed to anti-TNF-α during pregnancy. *Front Immunol* 2017;8:1123.
10 Johansen CB, Jimenez-Solem E, Haerskjold A, *et al*. The use and safety of TNF inhibitors during pregnancy in women with psoriasis: a review. *Int J Mol Sci* 2018;19. doi:10.3390/ijms19051349. [Epub ahead of print: 03 May 2018].
11 Vinet Évelyne, De Moura C, Pineau CA, *et al*. Serious infections in rheumatoid arthritis offspring exposed to tumor necrosis factor inhibitors: a cohort study. *Arthritis Rheumatol* 2018;70:1565–71.
12 Bröms G, Kieler H, Ekbom A, *et al*. Paediatric infections in the first 3 years of life after maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther* 2020;52:843–54.