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Vedolizumab clearance in neonates, susceptibility to infections, and developmental milestones: a prospective multicenter population-based cohort study

Short title: vedolizumab and intrauterine exposure

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Contributors

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MJ was responsible for the study concept and design, obtaining funding, study supervision, acquisition of data, statistical analysis, interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. MMH was responsible for the performance of the vedolizumab analysis and critical revision of the manuscript for important intellectual content. BMB performed the neonatal clearance analysis, supervised the remaining statistical analysis, was responsible for figures, and critical revision of the manuscript for important intellectual content. JK was responsible for acquisition of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. DCB, SMDB, AG, NU, JKj, HGS, LL, SW, PW, KVH, IV, LS, JB, SL, TV, and CLH were responsible for acquisition of data, critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Declaration of personal interests

Mette Julsgaard has served on the advisory board of Tillotts, and has received speaker's fees from MSD, Ferring, and Takeda; Has received a research grant from Takeda for the present study (Takeda had no role in design, implementation or interpretation of the study). **Daniel C Baumgart** has served on scientific advisory boards with AbbVie, Gilead, Janssen, Merck, Amgen, Pfizer, and Takeda. All honoraria were collected by the University of Alberta. **Jens Kjeldsen** has received speaker's fees from Takeda, and Tillotts. **Signe Wildt** has served on the advisory boards of MSD, Takeda and Tillotts, and has received consultants fee from Tillotts and speaker's fees from Takeda. **Petra Weimers** has received consulting fees from Vifor Pharma Nordiska AB, grants from Ferring lægemidler and Tillotts Pharma AG, as well as non-financial support from Janssen-Cilag A/S, Calpro AS, Pharmacosmos A/S and Vifor Pharma Nordiska AB. **Kent V Haderslev** has received speaker's fees from MSD, Takeda, and Janssen. **Jørn Brynskov** has served on advisory boards of Abbvie, Janssen,

Pfizer, Gilead, MSD, and has received speaker's fee from Takeda and MSD. **Søren Lyhne** has received consulting fee from Takeda. **Christian L. Hvas** has received has received speaker's fees from Takeda, and Tillotts. **Jens Kelsen** has served on the advisory board of Gilead, Takeda and Janssen and has received speaker's fee from Pfizer. The remaining authors disclose no conflicts.

Summary

Background: Little is known about the consequences of intrauterine exposure to and the postnatal clearance of vedolizumab.

Aim: To investigate the levels of vedolizumab in umbilical cord blood of newborns and rates of clearance after birth, as well as how these correlated with maternal drug levels, risk of infection and developmental milestones during the first year of life.

Methods: Vedolizumab-treated pregnant women with inflammatory bowel disease were prospectively recruited from 12 hospitals in Denmark and Canada in 2016-2020. Demographics were collected from medical records. Infant developmental milestones were evaluated by the Ages and Stages Questionnaire (ASQ-3®). Vedolizumab levels were measured at delivery, and in infants every third month until clearance. Non-linear regression analysis was applied to estimate clearance.

Results: In 50 vedolizumab-exposed pregnancies, we observed 43(86%) live births, seven (14%) miscarriages, no congenital malformations, and low risk of adverse pregnancy outcomes. Median infant:mother vedolizumab ratio at birth was 0.44(95% confidence interval [CI], 0.32-0.56). The mean time to vedolizumab clearance in infants was 3.8 months (95% CI, 3.1-4.4). No infant had detectable levels of vedolizumab at 6 months of age. Developmental milestones at 12 months, were normal or above-average. Neither vedolizumab exposure in the 3rd trimester (RR 0.54, 95%CI, 0.28-1.03) nor combination therapy with thiopurines (RR 1.29, 95%CI, 0.60-2.77) seemed to increase the risk of infections in the offspring.

Conclusions: Neonatal vedolizumab clearance following intrauterine exposure is rapid. Infant vedolizumab level did not correlated to risk of infections during the first year of life. Continuation of vedolizumab throughout pregnancy is safe.

KEY WORDS: Pregnancy; inflammatory bowel disease; vedolizumab; pharmacokinetics; ASQ-3; vaccination; infant infections; disease activity, post-partum.

Introduction

Inflammatory bowel disease (IBD) often affects women during their reproductive years.[1-4] Therefore, safety of biological therapies during pregnancy is of great concern to patients and physicians. Active IBD prior to conception and during pregnancy correlates to adverse pregnancy outcomes, underscoring the need for continuation of medical treatment during pregnancy.[1-3]

Biologics such as adalimumab, infliximab, and vedolizumab are monoclonal immunoglobulin G1 proteins (IgG1). Infants with intrauterine exposure to one of the two TNFα inhibitors adalimumab and infliximab have levels at birth that exceed those of their mothers,[5,6] reflecting fetal accumulation as pregnancy progresses, in accordance with the general characteristics of placental transport of IgG1 molecules.[7] Further, neonatal anti-TNF clearance after intrauterine exposure is much longer than seen in adult non-pregnant patients.[5] Vedolizumab acts by blocking the $\alpha_4\beta_7$-integrin-mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) interaction in the gut vessels, inhibiting the trafficking of gut-homing lymphocytes,[8] but may also impact the innate immune system.[9] Surprisingly, cord blood vedolizumab levels were approximately half of the maternal levels in two studies with 22 and 17 vedolizumab-exposed pregnancies, respectively.[6,10] Clearance of vedolizumab in infants with intrauterine exposure is yet to be established.

An increased risk of infection during the first year of life has been reported among infants exposed to anti-TNF or combination therapy with anti-TNF and a thiopurine,[5,11-13] although this was not seen in other studies.[6,14,15] Risk of infant infections after intrauterine exposure to combination or monotherapy with vedolizumab has received little attention. Further, there is a paucity of data concerning the impact of intrauterine exposure to vedolizumab on child development and growth.

In order to address these issues, the current study aimed first to determine infant vedolizumab levels in umbilical cord blood and to measure vedolizumab levels every third month post-partum to estimate vedolizumab clearance rates in infants exposed *in utero*. Second, we aimed to correlate umbilical cord levels with maternal vedolizumab levels and other factors potentially influencing drug levels. Finally, we aimed to investigate child development, growth, and morbidity during the first year of life, following intrauterine vedolizumab exposure.

Methods

The "In utero exposure to vedolizumab" (NOVA) study prospectively recruited pregnant IBD women treated with vedolizumab (Entyvio®) from 12 IBD out-patient clinics at hospitals in Denmark and Canada from June 2016 to December 2020. Data regarding demographic, disease activity, medication, smoking, folic acid intake, and obstetric complications were prospectively collected throughout pregnancy and the first six months post-partum. Birth outcome, infant intensive care unit (ICU) admission, and infant hospitalization during the first year of life was obtained from the infant's electronic health record. All infant data were confirmed by the mother. Childhood infection requiring hospitalization was defined as a severe infection.

The duration of vedolizumab treatment in pregnancy for each patient was determined by the treating gastroenterologist based on history and disease activity. Disease activity was assessed prospectively by physician global assessment (PGA) as active or in remission at conception (6 months), in each trimester and post-partum (6 months).[16]

Preterm prelabor rupture of the membranes (pPROM) was defined as rupture of the fetal membranes prior to 37 weeks of completed gestation.[17] Small for gestational age (SGA) was defined as a child with a birth weight of more than 2 standard deviations (SD) below the mean for children of similar gestational age, according to the reference curve of estimated fetal growth.[5] Low birth weight (LBW) was defined as a child with a birth weight <2500g and preterm as birth at <37 weeks of gestation (GW).[5] Apgar scores at five minutes <7 were considered low, while scores ≥7 were considered normal.[5] Congenital malformations (CM) were defined as structural or functional anomalies, identified at the time of birth and at 1-year, according to World Health Organization (WHO) criteria.[5]

At birth, peripheral blood was taken from the mother and a blood sample was taken from the umbilical cord to determine the levels of vedolizumab. In the event of a measurable level, infant vedolizumab level were repeated three-monthly until undetectable. In four breastfed infants, three-monthly testing continued until 12 months of life. Clotted blood samples were spun, and serum frozen in aliquots at -80 °C. Serum vedolizumab levels were measured by ELISA (IDK-monitor®, Germany) according to the manufacturer's instructions. Samples were tested in duplicate and the average expressed as µg/ml serum. The coefficient of variation between assay wells was <10%. The lower limit of detection was 0.015 µg/ml.

Electronic 1-year questionnaire

One-year post-partum, the women completed a structured online questionnaire specifically developed for the study regarding infant growth, morbidity, CM, participation in the national immunization program, adverse reaction to vaccines, child-care, and breastfeeding. At 15 months, all Danish women received a phone-call from the first author asking if the MMR

(Measles, Mumps, Rubella) vaccine had been administered and, if so, if side-effects had occurred.

Ages and Stages Questionnaire – Third edition (ASQ-3®)

ASQ-3® is a parent-completed screening instrument for children age 1 to 66 months. It has 30 age-appropriate items that address five developmental domains: communication, gross motor, fine motor, problem-solving, and personal-social. Each item describes a skill, ability, or behaviour to which a parent responds “yes” (10 points), “sometimes” (5 points), or “not yet” (0 points). A score is calculated for each domain and categorized as: 1) above cut-off (typical development), 2) monitoring zone (score between one and two standard deviations below the mean), and 3) referral zone (score less than two standard deviations below the mean). Between 2% and 7% of children in the normative population of 18572 children scored in the referral zone.[18] All women were asked to fill in a postage prepaid 12 months ASQ-3® questionnaire.

Statistical analysis

Frequency tables of major study variables were constructed for the total population, and separately for women with Crohn’s disease and ulcerative colitis/IBD unclassified. Pearson's chi-squared test or Fisher’s exact were applied for the comparison of these groups. Vedolizumab levels were normalized by log transformation for all analyses except for the non-linear regressions. Two-sample t-tests were conducted to compare groups. Relative risks (RR) and risk differences (RD) with associated 95% confidence intervals (CI) were used to study the relationship between relapse at different time points and major study variables such as GW for last vedolizumab infusion. Further, RR with associated 95% CI was used to describe pPROM and caesarean section by relapse in pregnancy and infections in the offspring by continuation of maternal vedolizumab treatment in the 3rd trimester, maternal combination therapy with thiopurines and vedolizumab, and breastfeeding, respectively.

Simple linear regression analysis was used to determine factors influencing vedolizumab level at the time of birth. Variables used: type of IBD, gestational week for last vedolizumab infusion in pregnancy, disease activity in pregnancy, thiopurine use, gestational week of birth, and child weight. The relationship between vedolizumab cord level at birth and gestational week for last vedolizumab infusion in pregnancy was investigated using non-linear regression based on a three-parameter logistic curve. A non-linear mixed effects regression model was used to estimate the time to complete drug clearance. Vedolizumab levels below the detection limit was replaced by half of the limit of detection value (0.0075 µg/ml) for statistical analysis. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Aarhus University, Denmark.[19] A p-value <0.05 was regarded as statistically significant. All analyses

were performed using Stata version 13.0 and 16.1 (Stata Corporation LP, College Station, TX, USA 2013).

Ethics

Written informed consent was obtained from all participating women and the father of the infant. The study was approved by the Danish Data Protection Agency (reference1-16-02-645-16), by the Regional Ethical Review Board in Denmark (reference1-10-72-269-16), and by the University of Alberta Health Research Ethics Board, Alberta, Canada (reference Pro00083285_AME2).

Results

Mother-baby pairs

Of the 50 pregnant women recruited, seven (14%) miscarried at median gestational week 8 (range 6-9), leaving 43 (86%) (22 (51%) CD, 20 (47%) UC and one (2%) IBD-U) mother-baby pairs for analysis: 39 (91%) from Denmark and 4 (9%) from Canada. Demographic and clinical details are shown in Table 1.

Vedolizumab treatment

Three-quarters (n=32, 74%) received standard-dose treatment, vedolizumab 300 mg every 8th week during pregnancy. Eleven (26%) women received vedolizumab 300 mg at shorter intervals of 4-7 weeks. Most women (n=37, 86%) received vedolizumab prior to conception as well as during pregnancy, while only six women (14%) commenced treatment during the first (GW 0-8) or second trimester (GW 15 & 22). The last dose of vedolizumab given during pregnancy was administered at median GW 30 (range 5-40). Treatment was stopped prior to the 3rd trimester in 13 (30%) women. The median duration between last infusion and delivery was 8 weeks (range 1-35).

The majority of women (n=36, 84%) received vedolizumab 300 mg during the post-partum period. Most women received treatment every 8th week, and 12 women (28%) received treatment every 4-7th week and one (2%) every 10th week. The first treatment was given at median 3 (range 0-18) weeks after delivery.

Disease activity

Overall, 16 (37%) women experienced disease activity in the 1st, 2nd, or 3rd trimester of pregnancy, whereas 27 (63%) women were in complete remission throughout pregnancy (Table 1). Thirteen (81%) of the 16 women with disease activity during pregnancy had also experienced disease activity during the conception period. Disease activity during the conception period increased the risk of disease activity during pregnancy (RR 4.4; 95% CI 1.92-10.01; p=0.0001) and post-partum (RR 2.3; 95% CI 1.22-4.45; p=0.03). Disease activity during pregnancy also increased the risk of disease activity in the post-partum period with a RR of 2.8 (95% CI 1.42-5.64; p=0.01). None of the 13 (30%) women who received the last vedolizumab treatment in pregnancy prior to the 3rd trimester experienced disease activity during the remaining part of pregnancy. Women who stopped vedolizumab treatment prior to the 3rd trimester (n=13) were not at increased risk of relapse during the post-partum period (6 months) compared with women who continued treatment in the 3rd trimester (n=30), with a RR of 0.85; 95% CI, 0.23-3.14; p=0.80.

Pregnancy complications and outcomes

One in five (22%) women experienced PROM (table 2). However, only two (5%) had preterm PROM, which both occurred in gestational week 36. No significant association in respect to risk of PROM was found between women with disease activity in pregnancy compared with being in remission (RR 1.5, 95% CI, 0.68-3.29, p=0.34).

No infants were born with congenital malformations. The rates of preterm delivery, SGA, and LBW were low (Table 2). The risk of cesarean section was similar among women with disease activity (n=16) as in women who were in remission throughout pregnancy (n=27) (RR 0.84 (95% CI, 0.35-2.03)). The three (7%) children born preterm were all GW 33-36 at birth, and one was SGA. Infant median birthweight was alike in offspring of mothers who discontinued treatment prior to the 3rd trimester (n=13; 3320 gram; range 2600-3870), compared with those who continued in the 3rd trimester (n=30; 3330 gram; range 1535-4465) (p=0.98).

Vedolizumab levels

At the time of birth, median cord and maternal blood vedolizumab levels were 2.35 µg/ml (range 0.0-13.3) and 3.5 µg/ml (range 0.0-54.0), respectively. The ratio of infant to maternal vedolizumab level at birth was 0.44 (95% CI, 0.32-0.56).

There was a statistically significant correlation between gestational week for the last treatment in pregnancy and both cord blood level ($r = 0.63$, $p<0.0001$) (Figure 1) and maternal level at birth ($r = 0.65$, $p<0.0001$). Using simple linear regression analysis, only gestational week at last infusion in pregnancy was statistically significantly associated with the cord blood vedolizumab level. Maternal and cord blood levels were significantly correlated ($r=0.87$, $p<0.0001$). Maternal and cord blood levels were significantly lower at birth when vedolizumab was stopped prior to the 3rd trimester (Table 3).

The median vedolizumab level in maternal blood at the time of delivery was significantly lower in women with active disease at any time during pregnancy (1.4 µg/ml; 95% CI, 0.0-22.7) compared with women in remission throughout pregnancy (4.1 µg/ml; 95% CI, 0.0-36.1)(p=0.03), whereas the corresponding cord blood level did not significantly differ (infants of mothers with active disease, 1.7 µg/ml; 95% CI, 0.0-7.8, vs remission, 2.9 µg/ml; 95% CI, 0.0-11.4; p=0.09). The median cord blood vedolizumab level at the time of delivery did not differ between standardized exposure every 8th week during pregnancy (2.2 µg/ml; 95% CI, 1.6-3.9) and increased exposure (every 4, 6 or 7th week) (3.1 µg/ml; 95% CI, 0.0-7.7) (p=0.72).

Vedolizumab clearance in infants

In eight infants (20%), vedolizumab levels were undetectable at the time of birth. In all of these pregnancies, vedolizumab had been ceased prior to the 3rd trimester. At 3 months, only four (10%) infants had detectable vedolizumab levels, and these levels were very low

(median 0.31 µg/ml (range 0.17-0.42). The estimated mean time to infant clearance was 3.8 (95% CI, 3.3-4.2) months. Five (12%) infants did not have a 3-month test performed due to COVID-19 restrictions and/or parental choice. No infant had a detectable level at six months. We found no significant association between vedolizumab clearance and maternal breastfeeding (p=0.66). Further, four breastfed infants continued testing every third month up until 12 months of age. In all these, no detectable level was found at 3 months and onwards.

First year infant development

Overall, 37 (86%) infants had reached the age of 12 months at the time of data analysis. Thirty-four (92%) of the mothers answered the ASQ-3® questionnaire regarding infant development. Detailed results of the 12-month ASQ-3® are presented in Table 4. Only one (3%) infant, born preterm, did not achieve a minimum of 4 of the 5 areas. Vedolizumab exposed infants had a significant higher communication mean score than the reference mean score (p=0.001) (Table 4). No statistically significant variation in mean score was found in respect to gross motor, fine motor, problem solving and personal-social development.

First year infant growth and morbidity

Thirty-five (95%) of the women answered the electronic questionnaire regarding the course of the first year of life. Seven (20%) infants had not started day-care at 12 months follow-up. The median age for those who had started day-care was 10 (range 6-11) months.

Fourteen (40%) infants contracted a total of 20 viral or bacterial infections (Supplement 1). One in six infections (n=6, 17%) occurred after the infant had started day-care. The majority (n=16, 80%) were minor infections with no sequelae. Four (11%) infants had a severe infection resulting in hospitalization prior to starting day-care, but all infants responded to adequate treatment.

Median vedolizumab level at birth among infants who contracted an infection was 1.8 (95% CI, 0.0-11.4) µg/ml compared with 4.6 (95% CI, 0.0-13.3) µg/ml in infants without infections during the first year of life (p=0.24). No significant association between maternal breastfeeding and risk of infection in the offspring was found (RR 0.64, 95% CI, 0.32-1.31; p=0.29). Maternal vedolizumab treatment in the 3rd trimester did not increase the likelihood of infection in the offspring compared with discontinuation prior to 3rd trimester (RR 0.54, 95% CI, 0.28-1.03; p=0.09). No significant association in respect to risk of infection in the offspring within the first year of life was found between women on combination therapy with thiopurine compared with monotherapy in pregnancy (RR 1.29, 95% CI, 0.60-2.77, p=0.55).

No children were diagnosed with a CM, malignancy or growth failure at the age of 12 months. Three (9%) infants were diagnosed with asthmatic bronchitis at the age of 5-12 months, and two (6%) with atopic dermatitis at the age of 5 and 12 months, respectively.

Participation in the national immunization program and adverse reaction to vaccines

In all 35 (100%) infants with 12-months follow-up, the mothers stated that their child participated in the national immunization program. The three (9%) Canadian infants had not received the live rotavirus vaccine at 2, 4, and 6 months of life due to the intrauterine exposure to vedolizumab. The 32 (91%) Danish infants had received all vaccines, but no live vaccines are provided during the first year of life in the Danish immunization program. The live measles-mumps-rubella (MMR) vaccine was administered to all Canadian and Danish infants at 12 and 15 months of life, respectively. Overall, six (17%) experienced a minor side-effect to a vaccine: one (3%) localized post MMR vaccination granuloma, fever after MMR vaccination (n=3, 9%), and fever after diphtheria-tetanus-pertussis-polio vaccination (n=2, 6%).

In parallel with the immunization program, one infant received the seasonal influenza vaccine and two infants received the live BCG-vaccine at six months of age without experiencing side-effects.

Discussion

This international multicenter study comprehensively investigated clinical outcomes following intrauterine exposure to the IgG1 antibody, vedolizumab, in infants born of women with IBD. In a well characterized prospective cohort representative of clinical practice, we observed a rapid postnatal vedolizumab clearance and no increased risk of maternal or fetal adverse pregnancy outcomes following vedolizumab treatment throughout pregnancy.

In the PICCOLO study, six (60%) of 10 tested infants exposed to vedolizumab during pregnancy had a detectable vedolizumab level 6-9 weeks postpartum.[10] In the present study systematic vedolizumab measurements in the infants, using an ELISA with a low limit of detection, allowed for the first time, to our knowledge, the calculation of a pharmacokinetic profile for vedolizumab. Surprisingly, despite a longer half-life than anti-TNF in adult patients, vedolizumab was cleared more rapidly in infants exposed in utero than seen in neonates exposed to anti-TNF.[5] The rapid neonatal vedolizumab clearance legitimates the use of live vaccination from six months of life.[1]

Vedolizumab-exposed infants were born with an approximately 50% lower vedolizumab level than those in their respective mothers which is in line with the PIANO and the PICCOLO studies examining 22 and 17 mother-infant pairs, respectively.[6,10] It is in contrast to previous studies regarding other monoclonal IgG1 antibodies such as infliximab, adalimumab, golimumab, and ustekinumab where infant:mother drug level ratio is above 1.[5,6] This may result from a lower placental transport, possibly resulting from a reduced Fc receptor binding of vedolizumab. During the engineering of vedolizumab, point mutations were made to the Fc receptor-binding motif (ELLGGP), exchanging leucine[239] and glycine[241] with alanine to reduce vedolizumab binding to the Fc receptor.[20]

Breastfeeding did not affect vedolizumab clearance, adding evidence to the notion that there is no significant transfer of vedolizumab to the breast milk.[21,22] Also, breastfeeding did not influence the risk of disease activity. These results underpin the advise to continue breastfeeding while on vedolizumab.[1]

The placental transfer of IgG1 molecules increases exponentially during the 3rd trimester.[7] Due to concerns regarding long-term consequences after intrauterine exposure to biologics, the European Crohn's and Colitis guideline from 2015 recommend cessation of biological therapy prior to the 3rd trimester in women in sustained remission prior to and in pregnancy.[2] On the other hand, the recently published American Gastroenterological Association guideline recommends continuation of biologics throughout pregnancy.[1] More than one third of the women in the present study experienced disease activity during pregnancy, and most women continued treatment into the 3rd trimester, based on the clinical evaluation by the physician. Reassuringly, infant birthweight did not differ between women who discontinued and those who continued vedolizumab treatment in the 3rd trimester, which is in contrast to findings among anti-TNF exposed pregnancies.[23] Of note, in a subgroup of

women who stopped vedolizumab prior to the 3rd trimester, neonatal vedolizumab level were significantly lower, compared with offspring of women who continued treatment in the 3rd trimester. However, these results should be interpreted with caution due to the low number discontinuing vedolizumab of whom all were in remission. Disease activity is the greatest risk factor for adverse maternal and fetal pregnancy outcome.[6,24] Further, the body of long-term safety data with up to five years of follow-up after intrauterine exposure to biologics is increasing; no increased risk of infant infections including 3rd trimester exposure, normal developmental milestones, no increased risk of malignancy, and psychiatric diagnosis.[6,11,13-15]

Reassuringly, we found no congenital malformations and in general no increased risk of adverse pregnancy outcomes, which is in line with previous vedolizumab exposure studies.[6,10,25-28]

Concerning child development at 12 months of age based on ASQ-3®, all observed mean scores were similar or significantly above the reference mean scores. These findings are in line with results from the PIANO registry regarding child development in 411 infants at 12 months of age based on ASQ-3® after intrauterine exposure to primarily other types of biologics than vedolizumab and/or other kinds of medical IBD-treatments.[6]

Minor infections were common within the first year of life. Notably, no gastrointestinal infections occurred, and the risk of severe infections resulting in hospitalization was comparable with rates among infants exposed to anti-TNF or other types of medical IBD-treatments.[6,11,14,15] The vedolizumab level at birth did not differ significantly between infants with infections during the first year of life compared with those without infections. Further, we found no increased risk of infant infection after intrauterine exposure to vedolizumab therapy in combination with thiopurines compared with vedolizumab monotherapy. Of note, these results should be interpret with caution due to the small sample size.

All infants participated in the national immunization program, and all vaccines except the live rotavirus vaccine were administered during the first 15 months of life, which is in line with international guidelines.[1,2] Of note, no adverse reaction was seen in the two infants exposed to the live BCG-vaccine at 6 months of life.

The present study is the largest prospective vedolizumab study to date. Bias due to differential recruitment was limited by inclusion of patients from 12 hospitals in two countries, and loss of follow-up was negligible; only 6% did not answer the 12-month surveys.

We acknowledge limitations of the study. First, maternal self-reported data regarding minor infant infections, minor adverse reaction to vaccines and developmental milestones were used, while hospital records were reviewed in order to capture severe infections and adverse reactions to vaccines requiring hospitalization. However, self-report is the gold standard for ASQ-3® which has been found to have a high negative predictive value and accuracy in assessing developmental milestones.[29] Second, physician global assessment (PGA) was used to assess disease activity. Different indices have been developed to define

IBD disease activity but none have been validated in pregnant women. The definition of disease activity in pregnant IBD women is ambiguous as reflected by the different parameters that are affected throughout pregnancy, e.g. laboratory markers, nausea, stool frequency, and evaluation of an IBD-related abdominal mass. We believe that using the PGA to estimate disease activity was the most rational choice in this particular cohort.

In conclusion, in this prospective international multicentre cohort study, we provide a solid evidence-based rationale for the counselling and management of pregnant women and their offspring exposed to vedolizumab. No adverse maternal and fetal pregnancy outcomes were observed during vedolizumab therapy, and infants exposed *in utero* to vedolizumab demonstrated normal or above average achievement of developmental milestones at 12 months of age. Rapid neonatal clearance of vedolizumab occurred after intrauterine exposure and legitimates live vaccination at six months of age. Cord blood vedolizumab level and maternal combination therapy with thiopurines were not correlated with risk of infant infection during the first year of life. Continuation of vedolizumab throughout pregnancy is safe.

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Table 1. Characteristics of 43 women on vedolizumab in pregnancy who gave birth to a live-born singleton*

	n	(%)
Diagnosis		
Crohn's disease (CD)	22	(51)
Ulcerative colitis	20	(47)
IBD unclassified	1	(2)
Disease location CD (Montreal)		
Ileal only (L1)	3	(13)
Colon only (L2)	5	(23)
Ileocolonic (L3)	14	(64)
Isolated upper digestive (L4)	0	-
Disease behaviour CD (Montreal)		
B1 non-stricturing non-penetration	14	(67)
B2 stricturing	2	(9)
B3 Penetrating	5	(24)
Active perianal disease in pregnancy (CD)	3	(14)
Previous CD bowel resection	8	(19)
Previous perianal surgery (CD)	2	(5)
Disease extent UC/IBDU (Montreal)		
Proctitis (E1)	4	(19)
Left sided (E2)	4	(19)
Extensive (E3)	13	(62)
Medications		
Thiopurine (azathioprine or mercaptopurine)	8	(19)
Systemic 5-aminosalicylic acid	7	(16)
Topical 5-aminosalicylic acid	2	(5)
Systemic prednisolone	8	(19)
Topical prednisolone	2	(5)
Budesonide/budesonide MMX	6	(14)

Allopurinol (co-administered with thiopurine)	1	(2)
IVF treatment	2	(5)
Smoking		
Prior to pregnancy	4	(9)
During pregnancy	1	(2)
Post-partum period	2	(5)
Active disease defined by Physician Global Assessment		
Conception period (6 months)	18	(42)
1st Trimester	13	(30)
2nd Trimester	9	(21)
3rd Trimester	5	(12)
At delivery	3	(7)
Postpartum period (6 months)	8	(19)
Previous number of biologicals		
0	1	(2)
1	13	(30)
2	21	(49)
3	8	(19)
Primiparous	25	(58)
Folic acid intake	42	(98)
Breastfeeding commenced	36	(84)
	Median	**(Range)**
Maternal age at the date of birth (years)	30	(22 - 42)
Years since diagnosis	7.0	(1 - 21)
Height (m)	1.68	(1.52 - 1.82)
Body mass index prior to pregnancy (kg/m^2)	25.1	(17.0 - 40.1)
Weight gain during pregnancy (kg)	12	(0 - 27)
Breastfeeding, months	4.0	(0.5-19)

*There were no significant differences between CD and UC/IBDU except 5-ASA treatment was only administered to UC patients (p=0.003), only CD women had previously undergone bowel-resection (p=0.002), and more CD than UC women experienced postpartum flare (p=0.03).

Table 2. Maternal and pregnancy outcome in 43 vedolizumab exposed pregnancies[a]

	n	**(%)**
Maternal obstetric risk factors		
Obesity (BMI ≥ 30) prior to pregnancy	9	(21)
Hypertension	1	(2)
Gestational diabetes	4	(9)
Maternal complications during pregnancy		
Pre-eclampsia	2	(5)
Prelabor rupture of membranes (PROM)	10	(23)
Preterm PROM (< GW 37)	2	(5)
PROM (≥ GW 37)	8	(19)
Fever (> 38.2 Celsius) during delivery	3	(7)
Placental abruption	1	(2)
Maternal infection/complication resulting in hospitalisation[b]	5	(12)

Pregnancy outcome		
Caesarean section (CS)	15	(35)
Planned	9	(21)
Emergency	6	(14)
Preterm	3	(7)
Small for gestational age	2	(5)
Low birth weight (< 2500g)	2	(5)
Congenital malformation	0	-
Stillbirth	0	-
Apgar score < 7 (5 minutes after birth)	1	(2)
Sex:		
Girl	22	(51)
Boy	21	(49)
Infant admitted to intermediate/intensive care	8	(19)
Reason for intensive care		
Respiratory distress syndrome	2	(5)
Preterm delivery	2	(5)
Newborn jaundice	2	(5)
Asphyxia & cardiac arrest triggered by placental abruption[c]	1	(2)
Maternal insulin-dependent diabetes mellitus	1	(2)
	Median	**(Range)**
Gestational week at delivery	40	(33-42)
Weight, gram	3330	(1535-4465)
Length, cm	51	(41-57)

[a]There were no significant differences between CD and UC/IBDU

[b]1st trimester: Cervical cerclage at GW 14. 3rd trimester: Deep venous thrombosis, pulmonary embolism, polyhydramnios/intrauterine growth restriction, and intrahepatic cholestasis.

[c]No neonatal infections and normal development at 12 months.

Table 3. Vedolizumab levels at birth according to time of cessation in pregnancy[a]

	Last infusion prior to the 3rd trimester	**Last infusion during the 3rd trimester**	**P value**
Total number*	12 (30%)	28 (70%)	
Maternal blood**	0.0 µg/ml (95% CI, 0.0-0.5)	5.7 µg/ml (95% CI, 3.7-13.4)	< 0.0001
Cord blood**	0.0 µg/ml (95% CI, 0.0-1.0)	3.5 µg/ml (95% CI, 2.5-6.1)	< 0.0001

[a]There were no significant differences between CD and UC/IBDU

*Three failed blood collection at the time of delivery. GW = gestational week

**Medians are shown, with 95% confidence intervals in parentheses.

Table 4. Results of the 12-months ASQ-3® among 34 vedolizumab exposed infants

Areas	Reference values[a]		Results of the present study			Mean score comparison	Difference of mean
	Cut-off	Mean scores (SD)	On track (%)	Failed (%)[b]	Mean scores (SD)	P value	scores (95% CI)[c]
Communication	15.64	43.22 (13.79)	33 (97.1)	1 (2.9)	49.55 (10.18)	0.001	6.3 (1.7-11.0)
Gross motor	21.49	49.92 (14.22)	30 (88.2)	4 (11.8)	48.85 (16.96)	0.72	-1.1 (-5.9-3.7)
Fine motor	34.50	52.22 (8.86)	33 (97.1)	1 (2.9)	52.12 (9.85)	0.95	-1.0 (-3.1-2.9)
Problem solving	27.32	48.99 (10.84)	34 (100)	0 (-)	49.56 (7.68)	0.68	0.57 (-3.1-4.2)
Personal-social	21.73	45.73 (12.00)	34 (100)	0 (-)	47.19 (7.61)	0.29	1.5 (-2.6-5.5)

[a]The ASQ User's Guide for the Ages and Stages Questionnaires[22]

[b]An area was considered as failed when the score was below the reference cut-off. One preterm infant failed gross and fine motor.

[c]Study mean score – reference mean score.

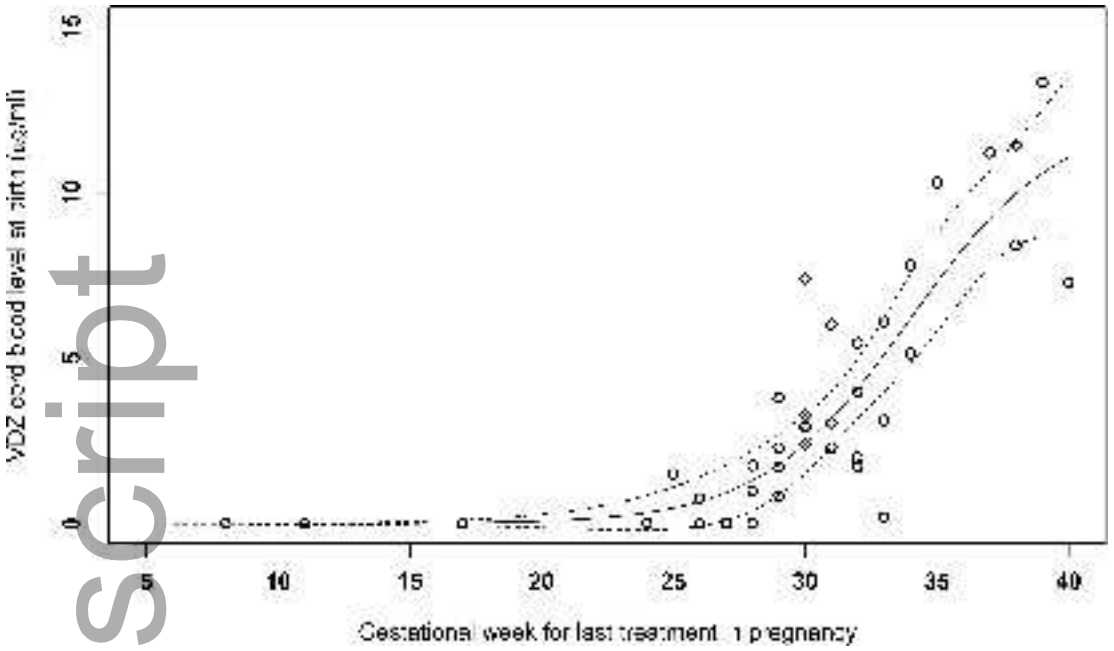
Figure legend

Figure 1. Non-linear regression model predicting vedolizumab cord blood level at birth from gestational week for the last intrauterine exposure using a three parameter logistic curve. The mean is represented by the continuous line, and the 95% confidence interval is represented by the dotted lines.

Appendices

Supplement 1. Types of infections in 35 vedolizumab exposed infants during the first year of life

Supplement 2. NOVA Study Group 2016



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