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Infant Ustekinumab Clearance, Risk of Infection, and Development After Exposure During Pregnancy

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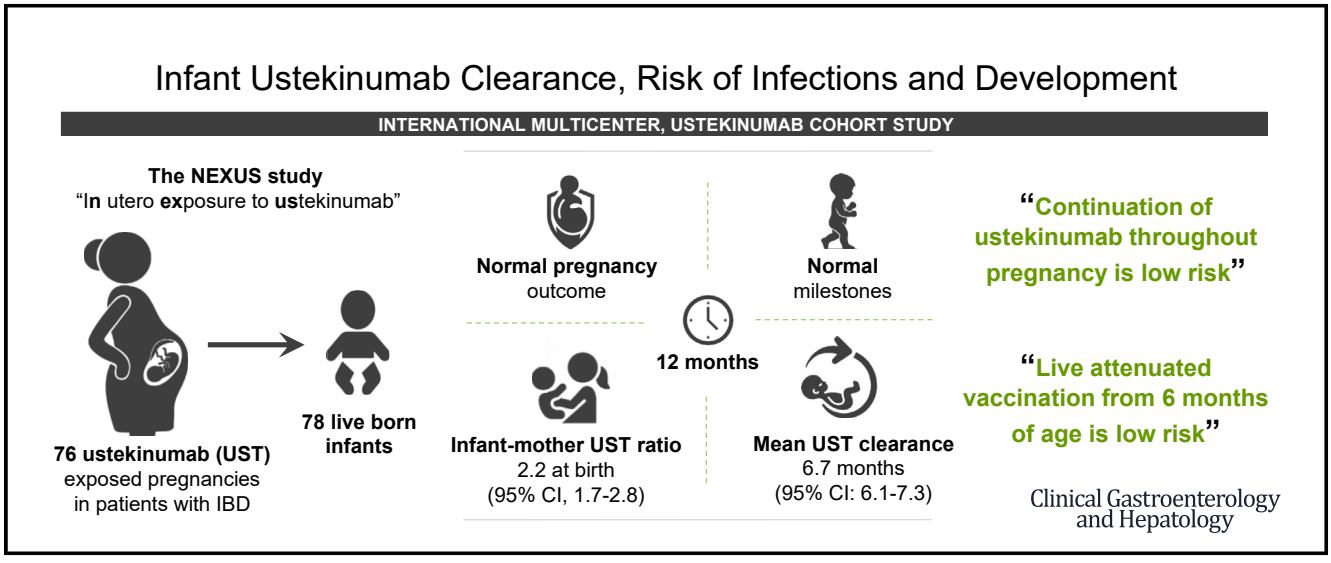

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Abbreviations used in this paper: anti-TNFα, anti-tumor necrosis factor α; ASQ-3, Ages and Stages Questionnaire 3; CD, Crohn's disease; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; GW, gestational week; IBD, inflammatory bowel disease; LLOQ, lower limit of quantification; RR, relative risk; SGA, small for gestational age; UC, ulcerative colitis.

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BACKGROUND: **Evidence on ustekinumab safety in pregnancy is gradually expanding, but its clearance in the postnatal period is unknown. The aim of this study was to investigate ustekinumab concentrations in umbilical cord blood and rates of clearance after birth, as well as how these correlate with maternal drug concentrations, risk of infection, and developmental milestones during the first year of life.**

METHODS: **Pregnant women with inflammatory bowel disease were prospectively recruited from 19 hospitals in Denmark and the Netherlands between 2018 and 2022. Infant infections leading to hospitalization/antibiotics and developmental milestones were assessed. Serum ustekinumab concentrations were measured at delivery and specific time points. Nonlinear regression analysis was applied to estimate clearance.**

RESULTS: **In 78 live-born infants from 76 pregnancies, we observed a low risk of adverse pregnancy outcomes and normal developmental milestones. At birth, the median infant-mother ustekinumab ratio was 2.18 (95% confidence interval, 1.69–2.81). Mean time to infant clearance was 6.7 months (95% confidence interval, 6.1–7.3 months). One in 4 infants at 6 months had an extremely low median concentration of 0.015 μg/mL (range 0.005–0.12 μg/mL). No variation in median ustekinumab concentration was noted between infants with (2.8 [range 0.4–6.9] μg/mL) and without (3.1 [range 0.7–11.0] μg/mL) infections during the first year of life ($P = .41$).**

CONCLUSIONS: **No adverse signals after intrauterine exposure to ustekinumab were observed with respect to pregnancy outcome, infections, or developmental milestones during the first year of life. Infant ustekinumab concentration was not associated with risk of infections. With the ustekinumab clearance profile, live attenuated vaccination from 6 months of age seems of low risk.**

Keywords: Pregnancy; Inflammatory Bowel Disease; Ustekinumab; Infant Infections.

Activity in inflammatory bowel disease (IBD) during pregnancy increases the risk of adverse pregnancy outcomes.[1,2] International guidelines recommend that pregnant women with active disease should be managed as nonpregnant patients with respect to the use of biologics, including the use of ustekinumab.[1,2]

Previous studies of ustekinumab exposure during pregnancy had relatively small sample sizes, though safety data were reassuring.[3–5] Due to the limited evidence, the European Crohn's and Colitis Organization recommends individualized decision on continuation of ustekinumab during pregnancy in women in remission.[2] The American Gastroenterological Association recommends timing the last ustekinumab treatment in pregnancy according to half-life to minimize fetal exposure.[1]

Biologic maternal-fetal transfer and infant clearance vary, and the latter has not been established for ustekinumab. In 3 studies with 26, 15, and 15 mother-infant pairs, respectively, the infants' ustekinumab concentration at birth exceeded that of their mothers,[3–5] which is in line with exposure to anti-tumor necrosis factor ; (anti-TNFα)[6–8] but is in contrast to vedolizumab.[4,9] Neonatal clearance of anti-TNFα after in utero exposure is substantially longer than what is observed in adult nonpregnant patients, whereas the opposite has been noted for vedolizumab.[6,9]

Providers and patients often worry about infection risks in infants exposed to biologics in utero. The risk is not increased following anti-TNFα monotherapy exposure,[7,10,11] but some studies found increased risk of infection following combination therapy with anti-TNFα and azathioprine.[6,12] There is a paucity of data on how intrauterine exposure to ustekinumab affects offspring development and infection risks.

The aims of this study were to estimate ustekinumab clearance rates in infants exposed in utero by collecting blood samples at specific time points during the first year of life, identify factors that could potentially influence offspring ustekinumab concentrations, and investigate offspring development and any risk of infections during the first year of life.

Materials and Methods

The NEXUS (In utero exposure to ustekinumab) study prospectively recruited pregnant women with IBD treated with ustekinumab (Stelara) from 19 IBD outpatient clinics in Denmark and the Netherlands (as a part of the Dutch PETIT cohort) from 2018 to 2022. Data regarding demographic features, disease activity, medications, and obstetric complications were prospectively collected throughout pregnancy. Data on birth outcomes and infant hospitalizations during the first year of life were obtained from the infants' health records and, in the Netherlands, through additional clinic visits. The mother confirmed all infant data. An infection requiring hospitalization was defined as a severe infection. The inclusion period overlapped with the COVID-19 pandemic, hence the mothers were asked to report if their infants tested positive for COVID-19. Prescription of antibiotics and breastfeeding

were registered after interview with the mother by survey, by telephone, or in person.

The duration of ustekinumab 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 as active or in remission in each trimester of pregnancy.[13]

Preterm prelabor rupture of the membranes was rupture of the fetal membranes prior to 37 weeks of completed gestation.[14] Small for gestational age (SGA) was a birth weight of more than 2 SDs below the mean weight for gestational age.[6] Low birth weight was a birth weight <2500 g and preterm as birth at <37 weeks of gestation (very preterm ≤ gestational week 32 [GW32]).[6] Apgar scores at 5 minutes <7 were considered low.[6] Congenital malformations were structural/functional anomalies, identified at birth and 1 year, according to World Health Organization criteria.[6]

At birth, blood was taken from the mother and the umbilical cord to determine ustekinumab concentrations. In the event of a detectable concentration, infant concentrations were repeated at 2 months (the Netherlands) or at 3 months (Denmark), then at 6 and at 12 months. Clotted blood samples were centrifuged and serum was frozen in aliquots at −80 °C. In Denmark, ustekinumab concentrations were measured by enzyme-linked immunosorbent assay (ELISA) (IDK-monitor Ustekinumab ELISA; Immundiagnostik AG) according to the manufacturer's instructions and additionally validated for wider dilution possibilities. In the Netherlands, ustekinumab concentrations were measured at Sanquin laboratory using in-house-developed ELISA.[15] The concentration was expressed as μg/mL. Samples were analyzed in duplicate with a coefficient of variation <10%. Both assays performed well at very low concentrations and had a very low lower limit of quantification (LLOQ) equivalent to 0.005 μg/mL. For data interpretation, we considered a median ustekinumab concentration <0.03 μg/mL to be extremely low, 0.03–0.8 μg/mL to be low, 0.8–10.0 μg/mL to be therapeutic, 10–20 μg/mL to be high, and >20 μg/mL to be very high.[7,16]

Offspring Developmental Milestones at 12 Months of Life

In Denmark, developmental milestones were assessed through the validated Ages and Stages Questionnaire 3 (ASQ-3).[9,17] In the Netherlands, developmental milestones were assessed by a pediatrician in the outpatient clinic. In both countries, specific categories of milestones evaluated included communication, gross motor skills, fine motor skills, personal-social development, and problem solving.

Statistical Analysis

Frequency tables of major study variables were constructed for the total population, and separately for women with Crohn's disease (CD) and ulcerative colitis (UC)/IBD unclassified. Pearson's chi-square test or Fisher's exact was applied to compare these groups. Ustekinumab concentrations were normalized by log transformation for all analyses except for the nonlinear regressions. Two-sample *t* tests were conducted to compare CD/UC+IBD unclassified, mother/infant (paired), disease activity in pregnancy (yes/no), and infant infection in the first year (yes/no) with regard to ustekinumab concentration. Relative risks (RRs) with associated 95% confidence intervals (CIs) were used to study the relationship between Physician Global Assessment of disease activity and major study variables. RR with associated 95% CI was used to describe infections in the offspring by major study variables.

Simple linear regression analysis was used to determine factors influencing ustekinumab concentration at the time of birth. The relationship between ustekinumab cord blood concentration at birth and number of weeks between final treatment in pregnancy and delivery was investigated using nonlinear regression based on a 3-parameter logistic curve. A nonlinear mixed-effects regression model based on an exponentially decreasing curve (corresponding to first order elimination in a one-compartment model) was used to estimate the time to complete drug clearance as well as the infant cord concentration corresponding to 6 month clearance. Ustekinumab concentrations below the LLOQ were replaced by half of the LLOQ value (0.0025 μg/mL) for statistical analysis. Twin deliveries were not taken into account in the statistical analyses due to the low number (n = 2). Study data were collected and managed using REDCap (Research Electronic Data Capture) hosted at Aarhus University, Denmark.[18] A *P* value <.05 was regarded as

What You Need To Know

Background

Active inflammatory bowel disease increases the risk of adverse pregnancy outcomes. Small cohort studies show no adverse outcomes in infants exposed in utero to the IgG1 antibody ustekinumab, but uncertainty remains.

Findings

Clearance of ustekinumab took around 6 months in 78 infants exposed in utero. Infant ustekinumab concentration at birth was not associated with risk of infections. There were no adverse signals regarding pregnancy outcomes and developmental milestones at 1 year.

Implications for patient care

Maternal ustekinumab treatment throughout pregnancy is of low risk for the offspring. Administering live-attenuated vaccines from 6 months of age to in utero ustekinumab–exposed infants seems of low risk.

statistically significant. All analyses were performed using Stata version 13.0 (StataCorp) and R version 4.3.1 (R Foundation for Statistical Computing).

Ethics

All participating women and parents of the infants provided written informed consent. The study was approved by the Danish Data Protection Agency (reference 1-16-02-670-16), by the Regional Ethical Review Board in Denmark (reference 1-10–72-303-18) and by the Dutch Medical Ethical Committee Leiden-Den Haag-Delft (METC LDD nr 18 –010, NL 63910.098.17).

Results

Mother-Baby Pairs

Of the 76 pregnant women recruited, 47 (62%) were from Denmark and 29 (38%) were from the Netherlands (Table 1). Overall, there were 74 singleton and 2 twin deliveries, resulting in 78 live-born infants.

Ustekinumab Treatment

The median interval between ustekinumab 90 mg injections was 8 (range 4–12) weeks. Most women (n = 61 of 76 [80%]) received ustekinumab prior to conception as well as in pregnancy. Intravenous induction treatment was initiated in 15 (20%) women at median GW 14 (range 4–29), and 7 of 15 received it in the first trimester (GW4–12), 7 in the second trimester (GW14–28), and 1 in the third trimester (GW29). The final dose of ustekinumab was administered at median GW31 (range 22–40). Most women (n = 66 of 76 [87%]) received treatment throughout pregnancy, but 10 (13%) of 76 women received the final dose prior to the third trimester. The median duration between last ustekinumab administration and delivery was 8 (range 0–17) weeks.

Disease Activity

Overall, 44 (58%) of 76 women experienced disease activity in pregnancy, whereas 32 (42%) of 76 were in remission throughout pregnancy. Women with UC showed higher risk of disease activity than women with CD (RR, 1.65; 95% CI, 1.17–2.32; $P = .01$) and were more likely to receive induction therapy in pregnancy (RR, 3.92; 95% CI, 1.59–9.69; $P = .002$). Few women (n = 10 of 76 [13%]) received the final dose of ustekinumab prior to the third trimester, of whom 2 (20%) of 10 experienced disease activity in the third trimester.

Pregnancy Complications and Outcomes

The risk of maternal pregnancy complications was low (Table 2). Six (8%) of 78 infants were born with different congenital malformations (Table 3). The 7 (9%) of 78 infants born preterm were all moderately preterm (GW33–36), including 5 singletons and 1 pair of twins. Two preterm singletons were also SGA. Infants exposed to ustekinumab induction treatment were not at substantially increased risk of adverse pregnancy outcome (preterm, low birth weight, SGA, and/or congenital malformations) compared with maintenance exposure (RR, 2.1; 95% CI, 0.84–5.24; $P = .12$).

Infant median birthweight was 515 g lower if ustekinumab was discontinued prior to the third trimester (stop cohort) (n = 10; 2797 g; 95% CI, 2302–3233 g), compared with those who continued in the third trimester (continue cohort) (n = 68; 3312 g; 95% CI, 3186–34,373 g) ($P = .007$). This finding remained highly significant when excluding the 2 twin deliveries ($P = .002$). No differences were found between the stop and continue cohorts concerning disease activity ($P = .66$), systemic corticosteroid exposure ($P = .61$), ustekinumab induction treatment ($P = .43$), or maternal body mass index >30 kg/m^2 ($P = .69$).

Ustekinumab Concentrations

At birth, median cord and maternal ustekinumab concentrations were 3.0 (range 0.26–26.1) μg/mL and 1.4 (range 0.0–17.1) μg/mL, respectively. The median ratio of infant to maternal ustekinumab concentration at birth was 2.18 (95% CI, 1.69–2.81).

Exceptional circumstances applied to the infant born with the very high concentration of 26.1 μg/mL. Due to severe UC activity, intravenous induction with 390 mg ustekinumab was administered in GW28 with effect on maternal disease activity, but another intravenous dose was needed and administered in GW34. The infant was born in GW38.

There was a significant negative correlation between number of weeks since last exposure and both cord blood concentration (r = –0.60, $P < .0001$) (Figure 1) and maternal concentration at birth (r = –0.55, $P < .0001$). Maternal and cord blood concentrations were correlated significantly (r = 0.78, $P < .0001$).

The median ustekinumab concentration in maternal blood at the time of delivery did not differ significantly in women with active disease in pregnancy (1.8 [range 0.0–17.1] μg/mL) compared with women in remission throughout pregnancy (1.2 [range 0.0–11.0] μg/mL) ($P = .49$).

Ustekinumab Clearance in Infants

All tested infants (n = 77) had detectable ustekinumab in cord blood at birth. At 2 or 3 months, 34 (44%) of 77 had undetectable concentrations and 43 (56%) of 77 had a low median concentration, 0.45 (range 0.05–3.00) μg/mL. At 6 months, 57 (74%) of 77 had undetectable concentrations and 20 (26%) of 77 had an extremely low

Table 1. Characteristics of 76 Women on Ustekinumab in Pregnancy Who Gave Birth to 78 Live-Born Infants

	n	%
Diagnosis		
CD	55	73
UC	20	26
IBDU	1	1
Disease location CD (Montreal)		
Ileal only (L1)	7	13
Colon only (L2)	11	20
Ileocolonic (L3)	36	65
Isolated upper digestive (L4)	1	2
Disease extent UC/IBDU (Montreal)		
Proctitis (E1)	4	19
Left sided (E2)	5	24
Extensive (E3)	12	57
Medications		
Thiopurine (azathioprine or mercaptopurine)	7	9
Systemic mesalamine	5	7
Topical mesalamine	7	9
Systemic prednisolone	12	16
Topical prednisolone	6	8
Budesonide/budesonide MMX	4	5
Discontinued another type of biologics in pregnancy due to disease activity		
Anti-TNFα (infliximab, adalimumab, or golimumab)	7	9
Vedolizumab	4	5
Smoking during pregnancy	6	8
Active disease defined by Physician Global Assessment		
First trimester	32	42
Second trimester	30	40
Third trimester	18	24
At delivery	16	21
Primiparous	41	54
Folic acid intake	70	92
Breastfeeding commenced	66	87

	Median	Range
Maternal age at the date of birth, y	30	23–42
Years since diagnosis	8.0	1–18
Height, m	1.68	1.52–1.83
Body mass index prior to pregnancy, kg/m^2	23.0	16.6–40.3
Breastfeeding, mo	6.0	0.2–12

There were no significant differences between CD and UC/IBDU in any of the variables except mesalamine treatment was only administered to UC patients ($P < .001$), and more UC than CD women experienced disease activity during pregnancy ($P = .01$).
anti-TNFα, tumor necrosis factor α; CD, Crohn's disease; IBDU, inflammatory bowel disease unclassified; UC, ulcerative colitis.

Table 2. Maternal Risk Factors and Complications in 76 Ustekinumab-Exposed Pregnancies

	n	%
Maternal obstetric risk factors		
Obesity (BMI $\geq$ 30 kg/m^2) prior to pregnancy	10	13
Hypertension	5	7
Maternal complications during pregnancy		
Gestational diabetes	3	4
Pre-eclampsia	4	5
PROM[a]	6	11
pPROM (<GW37)	3	5
PROM (≥GW37)	3	5
Maternal infection/complication resulting in hospitalization in pregnancy[b]	4	5

There were no significant differences between CD and UC/IBDU.
BMI, body mass index; GW, gestational week; PROM, prelabor rupture of membranes; pPROM, preterm prelabor rupture of the membranes.
[a]pPROM/PROM were only available for Danish women; hence, the percentage is based on 55 women.
[b]Cervical insufficiency, 2 cases of cholestasis of pregnancy, and pre-eclampsia.

median concentration, 0.015 (range 0.005–0.12) μg/mL. The infant with the highest concentration of 0.12 μg/mL at 6 months had cleared the drug at 7 months. Eleven infants were not tested until 12 months, all with undetectable concentrations. Four parents declined a 12-month test, and 4 infants await it. The mean time to infant clearance was 6.7 (95% CI, 6.1–7.3) months (Figure 2).

The estimated mean half-life of ustekinumab in infants was 23.2 (95% CI, 21.5–24.9) days. Of note, we found a significant association between drug half-life and cord blood concentration (n = 77; $P = .027$). Excluding the infant with the very high birth concentration of 26.1 μg/mL, the association remained significant (n = 76; $P = .029$). We found no significant association between ustekinumab half-life and infant birth weight (n = 77; $P = .91$) or breastfeeding (number of days breastfeeding) (n = 69; $P = .57$).

A cord serum concentration below 1.17 μg/mL (95% CI, 0.80–1.77) predicted clearance at 6 months of age.

Risk of Infant Infections

The type of infection resulting in hospitalization and/or antibiotic treatment is displayed in Table 4. Serious infections requiring hospitalization occurred in 9 (12%) of 78 infants, of whom 1 infant was born preterm (GW33). Hospitalization occurred at a median infant age of 2 (range 0–6) months. In total, 18 (23%) of 78 infants contracted a minimum of 1 infection requiring treatment with antibiotics during the first year of life.

Median ustekinumab concentration at birth among infants who contracted an infection requiring hospitalization and/or antibiotics was 2.8 (range 0.4–6.9) μg/mL compared with 3.1 (range 0.7–11.0) μg/mL in infants without infections during the first year of life ($P = .41$).

Table 3. Pregnancy Outcome Among 78 Ustekinumab-Exposed Infants

	n	%
Caesarean section	28	36
Preterm	7	9
Small for gestational age	5	6
Low birth weight (<2500 g)	7	9
Congenital malformation[a]	6	8
Stillbirth	0	—
Apgar score <7 (5 min after birth)	2	3
Sex		
Female	29	37
Male	49	63
Infant admitted to intermediate/intensive care	13	17
Reason for intensive care		
Respiratory distress syndrome	4	5
Preterm delivery	6	8
Newborn jaundice	3	4
Asphyxia and cardiac arrest triggered by placental abruption	1	1
Early-onset sepsis *Escherichia coli*/pneumonia	1	1
Twin-to-twin transfusion	1	1

	Median	Range
Gestational week at delivery	40	33–42
Weight, g	3312	1720–4495

There were no significant differences between Crohn's disease and ulcerative colitis/inflammatory bowel disease unclassified.
[a]Minor atrial septal defect (not requiring surgical intervention), clubfoot (diagnosed prior to ustekinumab induction therapy), congenital hydronephrosis, Stahl's ear deformity, mild ventriculomegaly/hydrocephalus (no surgical procedures needed, normal development at 1 year, and follow-up was no longer required), and mild pectus excavatum (also exposed to systemic corticosteroid).

Maternal ustekinumab treatment in the third trimester did not increase the likelihood of infection in the offspring compared with discontinuation prior to third trimester (RR, 0.92; 95% CI, 0.34–2.49; $P = .87$). Although the number of infants exposed to a combination of ustekinumab and azathioprine was low, the risk of an infection requiring hospitalization and/or antibiotic treatment was increased among infants exposed to combination treatment (n = 4 [67%]) compared with ustekinumab monotherapy (n = 18 [28%]) (RR, 2.41; 95% CI, 1.21–4.79; $P = .04$). When excluding the 7 infants who only received antibiotics for acute otitis media, no significant association was found (RR, 2.3; 95% CI, 0.77–6.88; $P = .20$). Neither intrauterine exposure to corticosteroids (n = 12; $P = .85$) nor preterm birth (n = 7; $P = .58$) increased the risk of infant infections. No significant association between breastfeeding and risk of infection in the offspring was found (RR, 0.54; 95% CI, 0.27–1.10; $P = .12$).

A total of 14 (18%) of 78 cases of COVID-19 were reported by the mothers occurring at a median infant age of 5 (range 1–11) months. All but 2 cleared the infection without antibiotics/hospitalization.

Overall, all but 1 infection was resolved without sequela. One full-term newborn infant, exposed in utero to ustekinumab and azathioprine, experienced a severe case of early-onset *Escherichia coli* sepsis and lobar pneumonia as recently described.[19]

First-Year Infant Development

Overall, 64 (82%) of 78 infants had reached the age of 12 months at the time of data analysis. All but 1 of the infants (n = 63 [98%]) were evaluated regarding development at 12 months of life either by ASQ-3 score or pediatric assessment. Overall, we found normal development in 57 (91%) of 63 after exposure in utero to ustekinumab with respect to communication, gross motor function, fine motor function, problem solving, and personal-social development.

Looking explicitly at the different categories, 1 (1.6%) of 63 experienced impaired communication due to unknown-origin hearing loss. Four (6%) of 63 showed impaired gross motor function, including 1 born preterm (GW33). One (1.6%) of 63 had impaired personal-social development. Fine motor function and problem solving were normal in all infants.

Discussion

This international multicenter cohort study comprehensively examined clinical outcomes in infants born to mothers with IBD exposed to the IgG1 antibody ustekinumab during pregnancy. In a thoroughly characterized cohort that mirrors clinical practice, we established postnatal clearance of ustekinumab, and no elevated risk of adverse pregnancy outcomes. The study is the largest of its kind to date and furnishes a robust evidence-based foundation for counseling and treating pregnant women who require ustekinumab induction/maintenance therapy during pregnancy.

All infants were born with detectable ustekinumab concentrations that surpassed those of their mothers. This aligns with the typical properties of IgG1 molecule transport across the placenta as pregnancy advances.[6] The ustekinumab concentration correlated with the duration since the last drug exposure in pregnancy in both mothers and infants, as reported earlier in smaller series.[3–5]

Reports of detectable ustekinumab concentrations in the postnatal period in a total of 11 infants exposed in utero have been noted.[4,5] However, no other studies have performed systematic drug measurements in infants to estimate clearance. Using ELISA assays with a very low LLOQ, allowed—for the first time to our knowledge—the calculation of a pharmacokinetic profile for ustekinumab.

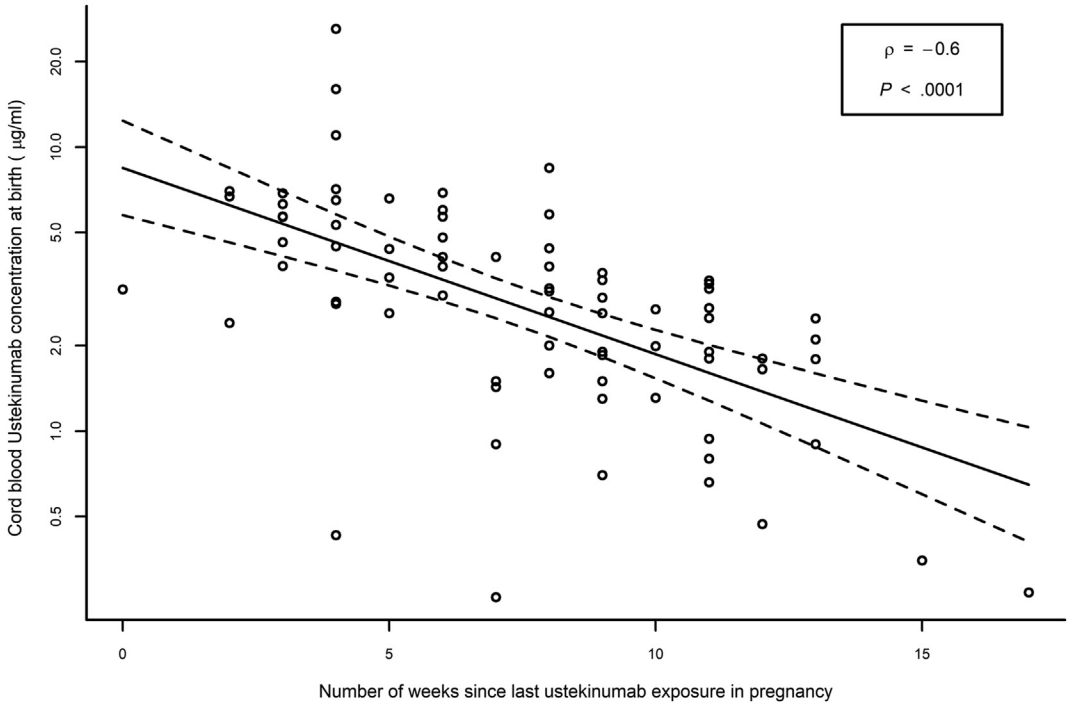

Figure 1. Simple linear regression model predicting ustekinumab cord serum concentration at birth from duration since last ustekinumab treatment in pregnancy in weeks in 77 infants. The mean is represented by the continuous line, and the 95% confidence interval is represented by the dotted lines.

The mean ustekinumab half-life in infants exposed in utero closely resembled that in adult nonpregnant patients,[20] and was, in contrast to anti-TNF and vedolizumab, significantly correlated with infant cord blood concentration.[6,9] It is unknown which ustekinumab concentration might cause an actual immunosuppressive state that could lead to adverse events from live-attenuated vaccinations. Based on the present extremely low ustekinumab concentrations at 6 months and the published safety data regarding live-attenuated vaccinations after exposure to biologics, and in particular rotavirus vaccination before 6 months of age after in utero exposure to ustekinumab,[21,22] the use of live-attenuated vaccines in general from 6 months of life seems of low risk in infants exposed in utero to ustekinumab.

Table 4. Type of Infection Resulting in Hospitalization and/or Treatment With Antibiotics

	Hospitalization		Antibiotics (No Hospitalization)[a]	
	n	%	n	%
None	69	88	60	77
Acute otitis media	0	—	9[b]	12
Upper respiratory infection	4[c]	5	5	6
Lower respiratory tract infection	2	3	2	3
Urinary infection	1	1	1	1
Gastrointestinal infection	1	1	0	—
Skin infection	0	—	3	4
Unknown location	1	1	1	1

[a]3 infants contracted different types of infections requiring antibiotics, hence the total sum of infections surpasses the total number of infants contracting an infection requiring antibiotics.
[b]2 infants with acute otitis media also contracted another type of infection requiring antibiotic at another time point.
[c]Due to COVID-19 in 2 cases, and 1 child with a bacterial infection received antibiotic prophylaxis from 9 months of age due to recurrent upper respiratory tract infections. Immunological tests were all normal (including normal blood cell count, T and B cell subsets, immunoglobulin concentration, and response to vaccination).

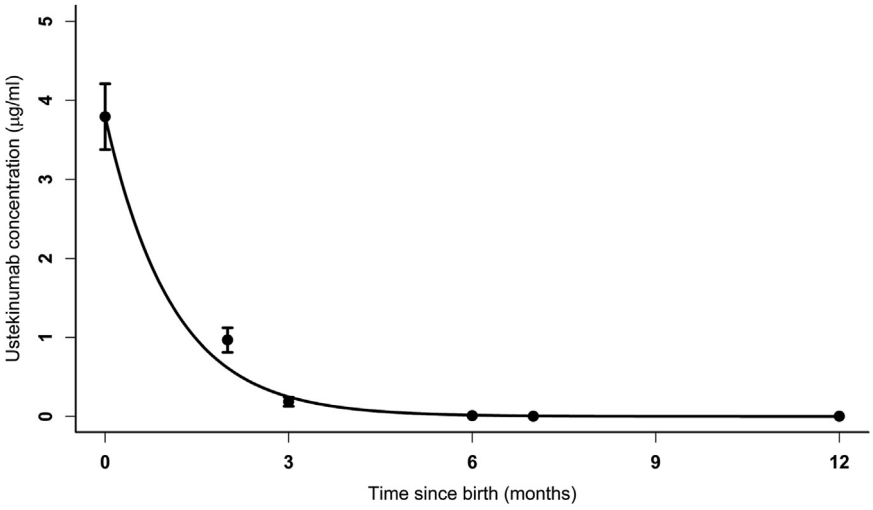

Figure 2. Mean ± SEM and fitted neonatal clearance of ustekinumab from the nonlinear mixed-effects model based on a decreasing exponential curve.

Breastfeeding did not affect ustekinumab clearance, and ongoing blood collection in an infant who had cleared the drug confirmed clearance during breastfeeding while the mother continued to receive treatment with ustekinumab. This supports that there is no significant ustekinumab transfer via breast milk.[2] These results imply that ustekinumab can be used with low risk during breastfeeding.[2,23]

Reassuringly, we found no significant increased risk of adverse pregnancy outcomes, which is consistent with previous studies.[3–5,24] However, while not statistically significant, we observed a 2-fold increased risk of adverse pregnancy outcomes in women exposed to induction compared with maintenance treatment during pregnancy. This finding is most likely driven by disease activity, not ustekinumab itself, as disease activity is the greatest risk factor for adverse pregnancy outcome.[7,25,26] Surprisingly, a 500 g lower median birth weight was seen in infants only exposed to ustekinumab up until the third trimester compared with infants exposed throughout pregnancy. This has no obvious explanation because disease activity, induction therapy, corticosteroid use, and maternal body mass index did not vary between the groups.

As an immune pathway inhibitor, ustekinumab could potentially affect an infant's developing immune system. However, the prevalence of severe infections leading to hospitalization in our study was similar to the prevalence observed in infants exposed to anti-TNFα or other immunomodulators in 2 studies among 1000 and 841 offspring of IBD-mothers, respectively.[10,11] Similar percentages were reported for serious/nonserious infections in relation to ustekinumab exposure among 47 infants in the Pregnancy in IBD And Neonatal Outcomes (PIANO) registry and among 20 infants from the Czech Republic.[3,4] Of note, the prevalence of infant infections requiring antibiotics was lower than that among the general population of 1-year-old infants in Denmark, which is equivalent to 44%.[27] Importantly, ustekinumab concentration at birth did not differ between infants with infections during the first year of life and those who had no infection. The present study revealed a significantly increased risk of infant infection after exposure to combination therapy (ustekinumab+azathiopurine). When the analysis was repeated excluding otitis media, no significant difference in risk was observed, as seen in the PIANO registry.[7] These results should be interpreted with caution due to the small sample size. In adults, in contrast to anti-TNFα treatment, there is no significant impact of azathioprine on ustekinumab concentrations and immunogenicity.[16] Considering this, clinicians should aim for ustekinumab monotherapy, particularly in women of reproductive age.

Normal developmental milestones were observed at 12 months of life in 91%, which is in line with exposure to other biologics.[4,6,7,9] Results from the PIANO registry also revealed normal developmental milestones at 12-months of life in 12 ustekinumab-exposed infants, and milestones were comparable with other groups of anti-TNFα, vedolizumab, immunomodulators, and unexposed.[4]

The strengths of the present study include its prospective design and the high number of mother-infant pairs. Bias due to differential recruitment was limited by the inclusion of patients on a national level in 2 countries, and loss of follow-up was negligible. Further, ELISA assays, which performed well at very low concentrations and with very low LLOQ, were chosen to investigate neonatal ustekinumab clearance in depth.

Important limitations apply. First, maternal self-reported information regarding infant infections requiring antibiotics was used, but hospital records were reviewed to capture/verify severe infections. Further, a high positive predictive value of self-reported medicine intake in pregnancy with data from the prescription database has been found; hence, we do not believe that recall bias significantly influenced the results.[28] Second, infant development was assessed using 2 different methods; however, both pediatric assessment and ASQ-3 have a high accuracy in assessing developmental milestones, hence we do not expect bias in assessment. Third, 2 different assays were used to analyze ustekinumab concentrations, but as

demonstrated, both performed very well at low concentrations. Finally, if infants had been tested monthly, an even more specific neonatal ustekinumab clearance could have been calculated. However, from an ethical point of view, monthly testing was not acceptable.

In conclusion, we provide a solid evidence-based foundation for counseling and managing pregnant women and their infants exposed to ustekinumab. No adverse maternal or fetal pregnancy outcomes were observed during ustekinumab therapy, and infants exposed in utero to ustekinumab demonstrated normal developmental milestones at 12 months of age. The risk of infant infection was not associated with ustekinumab concentration at birth. The neonatal clearance of ustekinumab indicates that live attenuated vaccination from 6 months of age seems of low risk. Continuation of ustekinumab throughout pregnancy is of low risk for pregnant women and their offspring.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2024.01.008.

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CRediT Authorship Contributions

Mette Julsgaard, MD, PhD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Funding acquisition: Lead; Investigation: Lead; Methodology: Lead; Project administration: Lead; Resources: Lead; Supervision: Lead; Validation: Lead; Visualization: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)

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