Differences in the placental pharmacokinetics of vedolizumab and ustekinumab during pregnancy in women with inflammatory bowel disease: a prospective multicentre study

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Abstract

Background: Vedolizumab demonstrated different placental pharmacokinetics than other immunoglobulin G1 antibodies, leading to lower drug levels in cord blood in contrast to maternal blood at the time of delivery. The placental transfer of ustekinumab seems to have a pattern similar to anti-tumour necrosis factor agents. Current evidence on the placental pharmacokinetics of vedolizumab and ustekinumab is limited. We aimed to assess the placental transfer of ustekinumab and vedolizumab in pregnant patients with inflammatory bowel disease.

Methods: Consecutive women from a prospective observational study who were exposed to ustekinumab or vedolizumab within 2 months prior to conception or during pregnancy were included. Ustekinumab and vedolizumab levels were measured in maternal and cord blood at the time of delivery.

Results: Drug levels were available in 31 infant-mother pairs (15 exposed to ustekinumab and 16 to vedolizumab). The median maternal and newborn ustekinumab levels were 5.3 mg/l and 10.3 mg/l, respectively (the median infant-to-maternal ratio was 1.7), while the median maternal and cord vedolizumab levels were 7.3 mg/l and 4.5 mg/l (the median infant-to-maternal ratio was 0.66). The ustekinumab levels in cord blood positively correlated with the maternal levels at delivery ($\rho = 0.751$, $p = 0.001$). However, no correlation with the timing of the last drug administration was found. In contrast, the vedolizumab levels in cord blood demonstrated significant positive correlation with the maternal levels ($\rho = 0.831$, $p < 0.001$) along with the gestational week of the last infusion ($\rho = 0.736$, $p = 0.001$).

Conclusion: Vedolizumab demonstrated different placental pharmacokinetics, leading to lower drug levels in cord blood compared to maternal blood at delivery; in contrast, the placental transfer of ustekinumab seems to have a pattern similar to anti-tumour necrosis factor (TNF) agents.

Keywords: pregnancy, ustekinumab, vedolizumab

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Introduction

Inflammatory bowel diseases (IBDs) are mostly diagnosed in people of reproductive age; a significant portion of female patients become pregnant during the course of the disease. Current evidence clearly shows that the disease's activity is

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a major cause of complications during pregnancy. As a result, proper control of inflammatory activity through effective and safe medical therapy during pregnancy is crucial. The risk of foetal exposure to medication is widely discussed. The most commonly used biologics in IBD, the anti-tumour necrosis factor (TNF) antibodies, are considered safe during pregnancy and breastfeeding; in addition, evidence on the safety of new biologic agents such as vedolizumab and ustekinumab is increasing.[1–6] All the above-mentioned biological drugs (infliximab, adalimumab, vedolizumab and ustekinumab) are monoclonal immunoglobulin (Ig) G1 antibodies. In general, IgG1 antibodies are actively transmitted through the placenta to foetal circulation *via* the neonatal Fc receptor.[5,7] The transport capacity of the Fc receptor corresponds with the length of gestation, increases during the 2nd trimester and is the highest at the end of the third trimester. The timing of the last drug administration before delivery has to be considered when assessing the risk of exposure and the potential effect on the newborn.

Given the paucity of the data on the placental pharmacokinetics of the new biological agents, the aim of our study was to evaluate the placental transfer of ustekinumab and vedolizumab in a prospective cohort of women with IBD who were exposed to biological therapy during pregnancy.

Materials and methods

Study population

This is an ongoing, prospective, multicentre, observational study conducted in 13 centres in the Czech Republic with the aim of assessing the safety of using the new biologics ustekinumab and vedolizumab during pregnancy. Consecutive women with IBD who already delivered and were exposed to ustekinumab or vedolizumab within 2 months prior to conception or during pregnancy between March 2019 and December 2020, with the available pharmacokinetics data, were included in this study.

Data collection

The predefined form was used for data collection and was completed by the treating physician of each patient. The following data were recorded: the mother's demographics and disease-related characteristics prior to conception, the smoking status, details on biologic treatment and concomitant medication at the time of conception and during pregnancy, disease activity at the time of conception and during pregnancy, the date and mode of delivery, pregnancy and IBD-related complications and the new-borns outcome. The assessment of disease activity was based on the Physician Global Assessment (PGA). The treatment regimen of biological and non-biological therapy during pregnancy was at the discretion of the attending physician and depended on the patient's clinical condition and disease activity.

Measurement of ustekinumab and vedolizumab levels

Ustekinumab and vedolizumab levels were measured in all the women and new-borns at the time of delivery. Blood samples were obtained from the cubital vein of mothers, while cord blood samples were taken to measure the drug levels in new-borns. Clotted blood samples were centrifuged for 10 min at an ambient temperature and 1300 g and separated serum aliquots were frozen at −80C and placed in the IBD serum bank. All the samples were analysed in one certified laboratory.

Ustekinumab and vedolizumab serum levels were detected using an Ustekinumab ELISA monoclonal antibody (mAb) based assay (IG-AB121) and a Vedolizumab ELISA mAb based assay (IG-AB116), both manufactured by ImmunoGuide, AybayTech Biotechnology Ltd. These immunoassays are based on drug-specific mAbs (catcher Ab, ImmunoGuide clone IG-9C7 for ustekinumab and clone IG-19F3 for vedolizumab). For ustekinumab, the lowest detectable level that can be distinguished from the zero standard was 1.5 ng/ml, while the upper detection limit was 600 ng/ml. For vedolizumab, the analytical sensitivity was 5 ng/ml and the upper detection limit was 6000 ng/ml. Only diluted samples were used in both analyses.

Statistical analysis

Standard descriptive statistical analyses were performed, including frequency distributions for categorical data and the calculation of the median and range or the interquartile range for

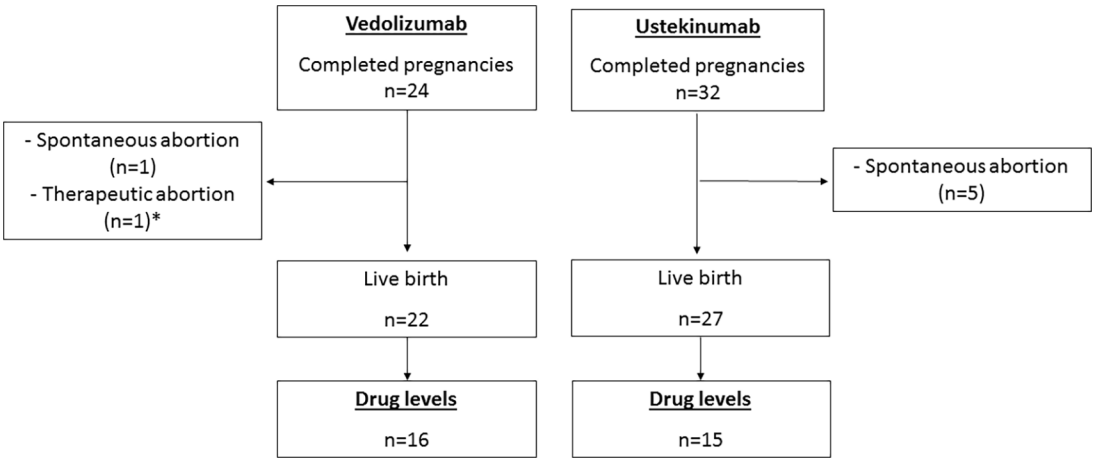

Figure 1. Study population.
*Therapeutic abortion due to down syndrome.

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continuous variables. Spearman's correlation (ρ) was used to analyse the relationship between the ustekinumab and vedolizumab levels in cord and maternal blood, alongside the gestational week of the last administration of the drug and the interval between the last dose and the time of delivery. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed with SPSS software (version 17.0, Chicago III, USA).

The data underlying this article are available in the article and its online supplemental material (Supplemental Tables 1, 2).

Ethical considerations

Ethical approval for the study was obtained from the Human Research Ethics Committee ISCARE a.s. in Prague (Reference number: 2019/IIa). The participants provided written informed consent before inclusion.

Results

Data on 32 pregnancies exposed to ustekinumab and 24 pregnancies exposed to vedolizumab were collected. Of them, 27 pregnancies on ustekinumab and 22 on vedolizumab resulted in live births. The drug levels in the cord and maternal blood were obtained in 15 and 16 infant-mother pairs on ustekinumab and vedolizumab, respectively (Figure 1). Five (15.6%) women on ustekinumab experienced a spontaneous abortion in the gestational weeks 7–16. Three of them (all in remission) had had at least 1 spontaneous abortion in the past while being on other IBD-related treatment. One woman had active Crohn's disease and was also treated with systemic corticosteroids. The last woman with quiescent Crohn's disease received concomitant treatment with azathioprine. Regarding vedolizumab, 2 (8.3%) women terminated their pregnancies without live birth. One woman had a therapeutic abortion at gestational week 19 due to Down syndrome of the foetus, while the other one, who was in remission on vedolizumab monotherapy, experienced a spontaneous abortion at gestational week 6. All the women continued ustekinumab or vedolizumab treatment after pregnancy termination.

Biologic treatment during pregnancy

The clinical and demographic characteristics of the women with the available pharmacokinetic data are presented in Table 1. Almost 60% of vedolizumab-exposed women and all but one treated with ustekinumab had Crohn's disease. Four (26.7%) women on ustekinumab and 2 (12.5%) on vedolizumab had an active disease at some time during pregnancy as assessed by the PGA. Concomitant thiopurines were administered to 4 (26.7%) and 7 (43.8%) women on ustekinumab and vedolizumab treatment, respectively. Intensified treatment regimens were reported for 5 patients on ustekinumab (every 4–6 weeks) and one woman on vedolizumab (every 6 weeks). All of them received treatment intensification before pregnancy and continued with this regime after conception.

Table 1. Clinical and demographic characteristics at the time of conception and during pregnancy.

	Vedolizumab *n* = 16	Ustekinumab *n* = 15
Age at conception*	31 (28–35)	28 (26–32)
Crohn's disease (%)	9 (56.3)	14 (93.3)
Ulcerative colitis (%)	7 (43.8)	1 (6.7)
Disease duration (years)*	11.9 (9.2–16.0)	11.0 (8.3–15.8)
Crohn's disease behaviour:		
Inflammatory (%)	8 (88.9)	9 (64.3)
Stricturing (%)	1 (11.1)	3 (21.4)
Penetrating (%)	–	2 (14.3)
Crohn's disease localization		
Ileal (%)	3 (33.3)	1 (7.1)
Colonic (%)	1 (11.1)	2 (14.3)
Ileocolonic (%)	5 (55.6)	11 (78.6)
Upper (%)	4 (44.4)	3 (21.4)
Perianal disease (%)	4 (44.4)	4 (28.6)
Ulcerative colitis – extension		
Extensive (%)	7 (100)	1 (100)
Previous bowel surgery** (%)	3 (18.8)	8 (53.3)
Smoking# (%)	2 (12.5)	1 (6.7)
Disease activity# (%)	2 (12.5)	4 (26.7)
Concomitant therapy#		
Thiopurines (%)	7 (43.8)	4 (26.7)
Systemic steroids (%)	1 (6.3)	–
Topical steroids (%)	–	2 (13.3)
Duration of biologic therapy (months)*	16.7 (5.4–28.1)	16.2 (6.2–19.8)
Intensification of biologic therapy during pregnancy (%)	1 (6.3)	5 (33.3)

*Median (interquartile range); **Surgery was performed only in patients with Crohn's disease; #At any time during pregnancy.

Pregnancy and newborn outcome

All children were born at term at a median gestational period of 39 weeks in both treatment groups (Table 2). One child exposed to both ustekinumab and vedolizumab had low birth weight. Perinatal complications occurred in 6 (40%) and 4 (25%) new-borns exposed to ustekinumab and vedolizumab, respectively. Most complications were not serious and mainly included mild jaundice. However, one newborn exposed to vedolizumab experienced right-sided pneumonia of streptococcal origin and prolonged hypoglycaemia, which was resolved after antibiotic treatment and glucose solution application. No major congenital malformation was observed (Table 2).

Ustekinumab levels in cord blood and maternal blood

All but one woman obtained their last ustekinumab dose during the 3rd trimester in median gestational week 33. Ustekinumab was detected in the cord blood of all the new-borns, although at a very low concentration in one case, where the mother interrupted her treatment during the 2nd trimester in week 22 (cord blood concentration 0.4 mg/l). Drug concentrations in the cord blood exceeded those in the maternal blood at the time of delivery in all but one infant-mother pair (cord *versus* maternal blood: 10.0 *versus* 15.4 mg/l). The median levels of ustekinumab were 10.3 mg/l in the cord blood and 5.3 mg/l in the maternal blood, resulting in a median infant-to-maternal ratio of 1.7 (Table 3).

The ustekinumab levels in the cord blood positively correlated with those in the maternal blood at the time of delivery ($\rho = 0.751$, $p = 0.001$) (Figure 2). However, there was no correlation between the ustekinumab levels in the cord blood and the gestational week of the last administration of the drug ($\rho = 0.299$, $p = 0.28$), nor between the cord drug levels and the interval between the last dose and delivery ($\rho = -0.157$, $p = 0.58$). Likewise, the maternal ustekinumab levels did not correlate with the interval between the last dose and delivery ($\rho = -0.447$, $p = 0.10$) and only a weak significant correlation with the gestational week of the last administration of ustekinumab was found ($\rho = 0.578$, $p = 0.02$).

Vedolizumab levels in cord blood and maternal blood

Vedolizumab was administered for the last time during pregnancy in a median gestational week of 32.5. Only 3 (18.8%) women interrupted their biological treatment before the 3rd trimester, while the majority of patients continued on

vedolizumab during the last trimester. The drug levels in the cord blood were detectable in all but one child whose mother obtained her last infusion in gestational week 19. In the majority of cases, the drug levels in the cord blood were lower than in the maternal blood, except for 3 (18.8%) infant-mother pairs. In the first case, the cord vedolizumab level was 4.3 mg/l while the maternal level was 4.2 mg/l; in the second case, the cord levels were 3.2 mg/l and the maternal levels 2.2 mg/l; in the third case, the cord and maternal levels were 4.7 mg/l and 3.0 mg/l, respectively. The median vedolizumab levels in the cord and maternal blood were 4.5 *versus* 7.3 mg/l, respectively, with a median infant-to-maternal ratio of 0.66 (Table 3).

The vedolizumab levels in the cord blood demonstrated a good positive correlation with the gestational week of the last administration of the drug ($\rho = 0.736$, $p = 0.001$) and a strong positive correlation with the maternal vedolizumab levels at the time of delivery ($\rho = 0.831$, $p < 0.001$) (Figure 3). Furthermore, a significant negative correlation was observed between the cord blood levels and the interval between the last drug exposure and delivery ($\rho = -0.795$, $p < 0.001$). A similar trend was also observed in the correlation of the maternal blood levels, the gestational week of the last vedolizumab administration ($\rho = 0.751$, $p = 0.001$) and the interval between the last infusion and delivery ($\rho = -0.917$, $p < 0.001$).

Discussion

In this study, we assessed the placental transfer of the new biologic agents ustekinumab and vedolizumab in pregnant women with IBD. Our results demonstrated the different placental pharmacokinetics of these two agents, with lower drug levels in the cord blood than the maternal blood in the majority of cases exposed to vedolizumab, while the opposite was found in infant-mother pairs treated with ustekinumab. The vedolizumab levels in the cord blood positively correlated with the maternal levels at the time of delivery. Furthermore, both the cord and maternal blood drug levels demonstrated a positive correlation with the gestational week of the last drug infusion and a negative correlation with the time interval to delivery. In contrast, we found no correlation between the ustekinumab levels in the cord blood with either the gestational week of the last drug administration or the interval between the last ustekinumab application and delivery. The only positive correlation was observed between the ustekinumab levels in the cord blood and the maternal blood at delivery.

Safety data on the use of ustekinumab in pregnancy, mostly from the experience of treating

Table 2. Pregnancy and newborn outcome.

	Vedolizumab *n* = 16	Ustekinumab *n* = 15
Preterm birth	0	0
Caesarean section (%)	9 (56.3)	8 (53.3)
Birth weight (g)*	3215 (2369–3780)	3300 (2480–3700)
Low birth weight (%)	1 (6.3)	1 (6.7)
Gestational age at birth	39 (38–41)	39 (37–41)
Apgar score <7	0	0
Perinatal complications (%)	4 (25.0)	6 (40.0)
Mild jaundice	2	6
Toxoalergic exanthema	1	–
Pneumonia and hypoglycaemia	1	–
Congenital malformation (%)	0	3 (20.0)
Hip dysplasia (mild)	–	2
Hydrocoele	–	1

*Median (range).

Table 3. Drug levels in cord blood and maternal blood.

	Vedolizumab *n* = 16	Ustekinumab *n* = 15
Gestational week of the last administration	32.5 (28–35.5)	33 (30–36)
Last administration <3rd trimester (%)	3 (18.8)#	1 (6.7)##
Cord blood levels*	4.5 (2.2–10.1)	10.3 (4.1–13.2)
Maternal levels at delivery*	7.3 (2.9–17.9)	5.3 (2.3–10.1)
Infant to maternal ratio (drug levels)	0.66 (0.54–0.77)	1.7 (1.5–2.1)

Values are expressed as median (interquartile range); *mg/l; #One patient at gestational week 19 and two patients at gestational week 25; ##Gestational week 22.

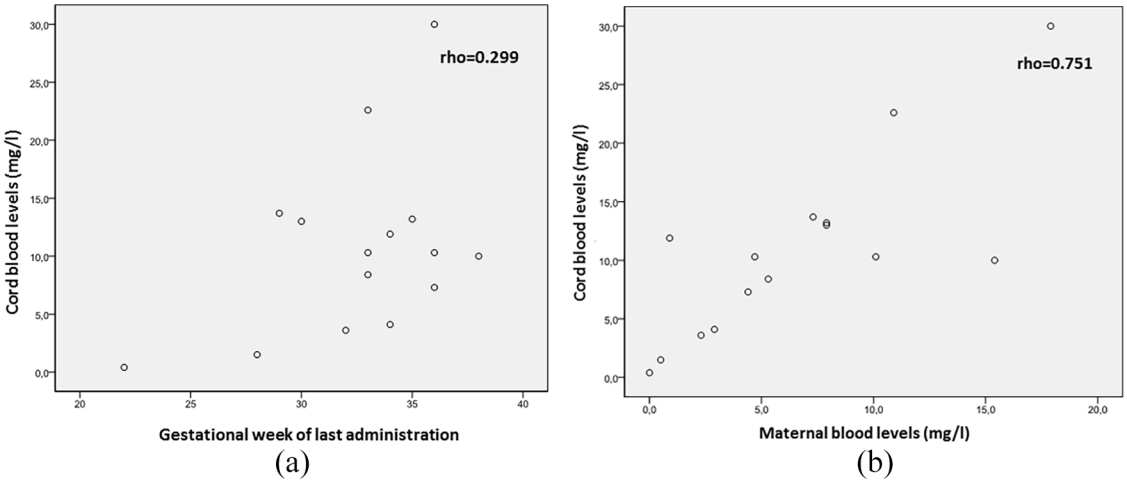

Figure 2. Correlation between ustekinumab levels in (a) cord blood and the gestational week of the last administration; (b) cord blood and maternal blood.

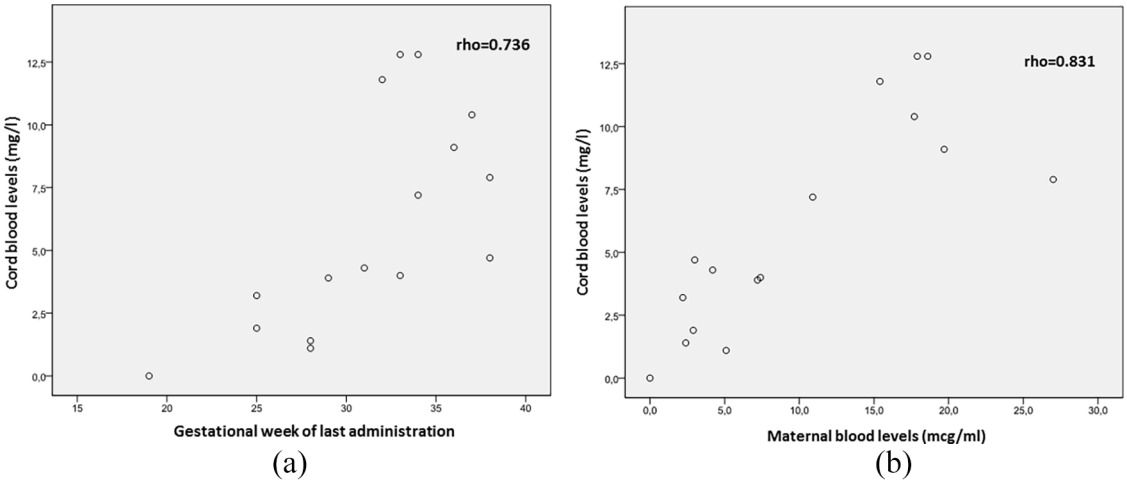

Figure 3. Correlation between vedolizumab levels in (a) cord blood and the gestational week of the last administration; (b) cord blood and maternal blood.

psoriasis, do not indicate any negative safety signals.[3,8–10] Similarly, increasing, although still limited, evidence on vedolizumab during pregnancy has not raised any safety concerns regarding maternal or newborn outcomes.[2,11] Our results, although in a small cohort of IBD patients, are in line with previously published evidence as well as with data from the background population in the Czech Republic and support a favourable safety profile of new biologic agents during pregnancy.[12] Although five (15.6%) women on ustekinumab experienced a spontaneous abortion, 4 of them had significant risk factors such as personal experience with abortion before or active Crohn's disease. In any case, these numbers still correspond with the background population.

The data on ustekinumab pharmacokinetics are very sparse as only two case reports and a small case series including a total of nine infant-mother pairs have been published so far.[13–15] To our knowledge, this prospective study represents the largest collection of ustekinumab levels from cord blood and maternal blood that assesses the placental pharmacokinetics of this agent used in IBD indication. As previously mentioned, ustekinumab is IgG1 antibody actively transported through the placenta by the neonatal Fc receptor, similar to

anti-TNF agents.[5,7] This transfer starts between week 14 and 16 of gestation and reaches its highest peak in the 3rd trimester. All but one woman in our cohort continued the medication throughout the 3rd trimester. As expected, the levels in the cord blood were detected in all cases and were higher than in the maternal blood. These results confirm the findings from previously published data and demonstrate the similar placental pharmacokinetics of ustekinumab as described in anti-TNF agents.[13–18] According to the recent PIANO study, which comprised the biggest collection on placental pharmacokinetic in ustekinumab so far (a total of 7 infant-mother pairs), the median infant/cord-maternal ratio was 1.4, which is very similar to our finding (a median infant to maternal ratio of 1.7).[15] However, we did not find any correlation between ustekinumab levels in new-borns and the time of the last drug administration. This correlation had previously been demonstrated for both anti-TNF agents: infliximab and adalimumab.[16,17] Our finding may thus suggest that ustekinumab levels in new-borns cannot be predicted based on the time of the last drug administration. Although our study population was relatively small, the absence of a correlation cannot just be explained by the sample size, as in a similarly sized cohort of women treated with vedolizumab such a correlation was confirmed. The other explanation might be a different mode of the administration of ustekinumab and vedolizumab (subcutaneous *versus* intravenous). However, with another subcutaneous agent, adalimumab, the correlation between the cord blood or the maternal blood levels and the timing of the last drug exposure had previously been demonstrated.[16] We assume that these findings might reflect the different pharmacokinetics of particular biologics as well as different dosing regimens. Differences in the pharmacodynamic patterns of biologic agents can also play a potential role in this phenomenon. Further studies should confirm or disprove our findings and can elucidate this hypothesis.

As mentioned above, due to the mechanism of the placental transfer of IgG1 antibodies, a similar pharmacokinetic pattern in pregnancy was seen in anti-TNF agents and ustekinumab. Since vedolizumab is an IgG1 monoclonal antibody against $\alpha 4\beta 7$ integrin, its placental transfer was expected to be similar to the other IgG1 antibodies. Accordingly, vedolizumab levels were detected in the cord blood of exposed new-borns. However, in the majority of infants, the drug concentrations were lower than those in the maternal blood. These results correspond with recently published data from the United States, Australia and Denmark, including 22, 17 and 30 infant-mother pairs, respectively.[15,19,20] All three studies found significantly lower vedolizumab levels in the new-borns than in the maternal blood, and the latter two also demonstrated a positive correlation between the gestational week of the last drug administration and both the cord and maternal blood levels. Our findings are in line with these results. The exact mechanism leading to lower newborn levels compared to maternal levels still remains unclear. Given the fact that vedolizumab is an IgG1 antibody like ustekinumab and anti-TNF agents, we hypothesize that there might be an 'uptake' of the vedolizumab by the placenta that causes the lower drug concentrations in the cord blood compared to the maternal blood. This mechanism has also been suggested by Flanagan *et al.*[19] Further studies are needed to elucidate this mechanism.

Our study has several limitations. Blood samples were not obtained from all the pregnancies since not all centres had the possibility to provide blood sampling. This resulted in a relatively small sample size which precluded making any further analyses, e.g. on the effect of concomitant thiopurines on drug levels, meaningful. Furthermore, most of the pregnancies with available drug levels were exposed to biologic therapy during the 3rd trimester, and we are missing relevant data on the placental pharmacokinetics of the new biologic agents in patients who only had earlier exposure. Finally, we did not evaluate the postnatal clearance of the drug in infants.

In conclusion, our study confirmed different placental pharmacokinetics of vedolizumab, leading to lower drug levels in the cord blood compared to the maternal blood at the time of delivery, while the placental transfer of ustekinumab seems to have a pattern similar to anti-TNF agents. Our findings of absent correlation between the ustekinumab drug levels at the time of delivery and the gestational week of the last exposure or the time to delivery need to be confirmed by further studies.

Abbreviations

IBD, inflammatory bowel disease; Ig, immunoglobulin; TNF, tumour necrosis factor; PGA, Physician Global Assessment

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Author contributions

K.M. and B.P.: The concept and study design; acquisition of data; interpretation of data, drafting and critical revision of the manuscript

M.B., L.B., J.B., T.D., T.D., P.D., P.F., P.K., V.L., A.N., P.S., J.S., J.U., M.V., B.Z., M.L.: Acquisition of data; critical revision of the manuscript

D.D.: The concept and study design; acquisition of data; interpretation of data, statistical analysis; drafting and critical revision of the manuscript.

Conflict of interest statement

Katarina Mitrova: Lectures/congress fees/consultancy (outside the submitted work): Abbvie, Takeda

Barbora Pipek: Pfizer

Martin Bortlik: Abbvie, Jansen, Pfizer, Takeda, Biogen, Egis

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Supplemental material

Supplemental material for this article is available online.

References

1. Mahadevan U, Robinson C, Bernasko N, *et al.* Inflammatory bowel disease in pregnancy clinical care pathway: a report from the American Gastroenterological Association IBD Parenthood Project Working Group. *Gastroenterology* 2019; 156: 1508–1524.

2. Moens A, van der Woude CJ, Julsgaard M, *et al.* Pregnancy outcomes in inflammatory bowel disease patients treated with vedolizumab, anti-TNF or conventional therapy: results of the European CONCEIVE study. *Aliment Pharmacol Ther* 2020; 51: 129–138.

3. Geldhof A, Volger S, Lin CB, *et al.* Pregnancy outcomes in women with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis treated with ustekinumab. *J Crohns Colitis* 2020; 14: S460.

4. Gisbert JP and Chaparro M. Safety of new biologics (vedolizumab and ustekinumab) and small molecules (tofacitinib) during pregnancy: a review. *Drugs* 2020; 80: 1085–1100.

5. Pham-Huy A, Sadarangani M, Huang V, *et al.* From mother to baby: antenatal exposure to monoclonal antibody biologics. *Expert Rev Clin Immunol* 2019; 15: 221–229.

6. Nielsen OH, Gubatan JM, Juhl CB, *et al.* Biologics for inflammatory bowel disease and their safety in pregnancy: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. Epub ahead of print 12 September 2020. DOI: 10.1016/j.cgh.2020.09.021.

7. Kane SV and Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. *Am J Gastroenterol* 2009; 104: 228–233.

8. Lund T and Thomsen SF. Use of TNF-inhibitors and ustekinumab for psoriasis during pregnancy: a patient series. *Dermatol Ther*. Epub ahead of print 10 January 2017. DOI: 10.1111/dth.12454.

9. Galluzzo M, D'Adamio S, Bianchi L, *et al.* Psoriasis in pregnancy: case series and literature review of data concerning exposure during pregnancy to ustekinumab. *J Dermatolog Treat* 2019; 30: 40–44.

10. Mahadevan U, Naureckas S, Sharma B, *et al.* Pregnancy outcomes in women exposed to ustekinumab. *Gastroenterology* 2018; 154: S-588–S-589.

11. Bar-Gil Shitrit A, Ben Ya'acov A, Livovsky DM, *et al.* Exposure to vedolizumab in IBD pregnant women appears of low risk for mother and neonate: a first prospective comparison study. *Am J Gastroenterol* 2019; 114: 1172–1175.
12. Institute of Health Information and Statistics of the Czech Republic. https://www.uzis.cz/sites/default/files/knihovna/potraty2016.pdf.
13. Klenske E, Osaba L, Nagore D, *et al.* Drug levels in the maternal serum, cord blood and breast milk of a ustekinumab-treated patient with Crohn's disease. *J Crohns Colitis* 2019; 13: 267–269.
14. Rowan CR, Cullen G, Mulcahy HE, *et al.* Ustekinumab drug levels in maternal and cord blood in a woman with Crohn's disease treated until 33 weeks of gestation. *J Crohns Colitis* 2018; 12: 376–378.
15. Mahadevan U, Long MD, Kane SV, *et al.* Pregnancy and neonatal outcomes after fetal exposure to biologics and thiopurines among women with inflammatory bowel disease. *Gastroenterology*. Epub ahead of print 21 November 2020. DOI: 10.1053/j.gastro.2020.11.038.
16. Julsgaard M, Christensen LA, Gibson PR, *et al.* Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology* 2016; 151: 110–119.
17. Bortlik M, Machkova N, Duricova D, *et al.* Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF-α therapy during pregnancy: three-center study. *Scand J Gastroenterol* 2013; 48: 951–958.
18. Mahadevan U, Wolf DC, Dubinsky M, *et al.* Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; 11: 286–292.
19. Flanagan E, Gibson PR, Wright EK, *et al.* Infliximab, adalimumab and vedolizumab concentrations across pregnancy and vedolizumab concentrations in infants following intrauterine exposure. *Aliment Pharmacol Ther* 2020; 52: 1551–1562.
20. Julsgaard M, Baumgart D, Jorgensen SMD, *et al.* Vedolizumab levels in mothers and newborns, clearance in neonates, susceptibility to infection, and achievement of developmental milestones. *United European Gastroenterol J* 2020; 8: 16.