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Original Article

Safety of Ustekinumab and Vedolizumab During Pregnancy—Pregnancy, Neonatal, and Infant Outcome: A Prospective Multicentre Study

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Abstract

Background and Aims: Evidence on the safety of newer biologics during pregnancy is limited. We aimed to assess the safety of ustekinumab and vedolizumab treatment during gestation on pregnancy and infant outcome. Furthermore, we evaluated the placental transfer of these agents.

Methods: We performed a prospective, multicentre, observational study in consecutive women with inflammatory bowel disease exposed to ustekinumab or vedolizumab 2 months prior to conception or during pregnancy. Pregnancy, neonatal, and infant outcomes were evaluated and compared with the anti-tumour necrosis factor [TNF]-exposed control group. Drug levels were assessed in maternal and cord blood at delivery.

Results: We included 54 and 39 pregnancies exposed to ustekinumab and vedolizumab, respectively. In the ustekinumab group, 43 [79.9%] resulted in live births, and 11 [20.4%] led to spontaneous abortion. Thirty-five [89.7%] pregnancies on vedolizumab ended in a live birth, two [5.1%] in spontaneous, and two [5.1%] in therapeutic abortion. No significant difference in pregnancy outcome between either the vedolizumab or the ustekinumab group and controls was observed [$p > 0.05$]. Similarly, there was no negative safety signal in the postnatal outcome of exposed children regarding growth, psychomotor development, and risk of allergy/atopy or infectious complications. The median infant-to-maternal ratio of ustekinumab levels was 1.67 and it was 0.59 in vedolizumab.

Conclusions: Use of ustekinumab and vedolizumab in pregnancy seems to be safe, with favuorable pregnancy and postnatal infant outcomes. Placental transfer differed between these two drugs, with ustekinumab having similar and vedolizumab having inverse infant-to-maternal ratio of drug levels compared with anti-TNF preparations.

Key Words: Inflammatory bowel disease; ustekinumab; vedolizumab; pregnancy; placental transfer

1. Introduction

Inflammatory bowel disease [IBD] can be diagnosed at any age but is most commonly diagnosed in young adults during the childbearing period.[1] Therefore, patients are often concerned about fertility and pregnancy-related issues. When the diagnosis is made, the biggest effort is to get the disease under control to prevent complications and achieve optimal quality of life. Proper disease control is also the most important factor for favourable pregnancy outcomes. This control requires adequate anti-inflammatory treatment, including biologic therapy. As the long-term therapy can affect pregnancy and neonatal outcomes, strong evidence is needed to reassure patients about safety. Recent years have seen significant progress in research around anti-tumour necrosis factor [TNF] treatment in pregnancy, confirming its safe use, but the data on the new biologics are still limited.[2–4] Although the recently published safety data on vedolizumab and ustekinumab during pregnancy are promising, the biggest limitation is the small number of studied pregnancies, especially in users of ustekinumab.[5–9] Therefore, further studies are still needed to strengthen the evidence.

This study aimed to assess the safety of ustekinumab and vedolizumab during pregnancy and their impact on neonatal and infant outcomes. We also assessed the cord blood levels of both drugs.

2. Methods

We performed a prospective, multicentre, observational study in women with IBD receiving ustekinumab or vedolizumab during pregnancy. This study included consecutive women with IBD exposed to ustekinumab or vedolizumab within 2 months prior to conception or during pregnancy, between January 2017 and December 2021 in 15 centres across the Czech Republic. The control group was collected retrospectively and consisted of consecutive pregnant women with IBD exposed to anti-TNF treatment in two centres in the Czech Republic during 2013–2017 and 2017–2021 [86% of pregnancies], respectively. Only singleton pregnancies were included in the analyses due to the inherent increased risk of complications in multiple pregnancies.

The study was approved by the Human Research Ethics Committee of the Center for Reproductive Medicine [ISCARE a.s.] in Prague, and all participants signed informed consent.

2.1. Data collection

Two structured questionnaires were used for data collection for the study and control groups and were completed by the treating physician. The first questionnaire included data on the mother's demographics and disease-related characteristics prior to conception, 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 newborn outcome. Disease activity was assessed by Physician Global Assessment [PGA] per trimester. The type of treatment and biologic therapy regimen during pregnancy were adjusted according to the patient's clinical condition and disease activity. The second questionnaire was used to evaluate infant postnatal outcomes in children ≥6 months of age. We collected data on growth, psychomotor development, allergy/atopy occurrence, and infectious complications. Only infections requiring antibiotics and/or hospitalisation were recorded. The patient's gastroenterology reports and gynaecology/obstetric medical records, the child's medical records from mandatory postnatal check-ups which are standardised and obligatory in the Czech Republic, and direct questioning of the mothers were used as sources of information.

2.2. Measurement of ustekinumab and vedolizumab levels

Maternal venous blood and umbilical cord blood were collected on the day of delivery to determine the level of ustekinumab or vedolizumab. Serum levels were detected using Ustekinumab ELISA mAb-based assay [IG-AB121] or Vedolizumab ELISA mAb-based assay [IG-AB116], both manufactured by ImmunoGuide, AybayTech Biotechnology. The analytical sensitivity for ustekinumab was 1.5 ng/mL, and the upper detection limit was 600 ng/mL. The lower detection limit for vedolizumab was 5 ng/mL, and the upper limit was 6000 ng/mL.

2.3. Statistical analysis

Standard descriptive statistical analyses were done with frequency distributions for categorical variables and the calculation of the median and range or the interquartile range [IQR] for continuous data. When appropriate, the chi square test or Fisher´s exact test was used for comparison of categorical data, and the Mann–Whitney test was used for continuous variables. The relationship between the ustekinumab and vedolizumab levels in cord and maternal blood, alongside the gestational week of the latest administration of the drug and the interval between the latest dose and the time of delivery, were analysed by Spearman's correlation. A p-value of <0.05 was considered statistically significant. SPSS software [version 17.0, Chicago, Il., USA] was used for statistical analyses.

3. Results

3.1. Study population

The analysis included 54 pregnancies in 49 women exposed to ustekinumab and 39 pregnancies in 37 women exposed to vedolizumab. The median age at conception was 30 years and 29.5 years in the ustekinumab and vedolizumab groups, respectively. The majority of patients treated with ustekinumab [94%] had Crohn´s disease [CD], and the disease distribution was almost equal in patients on vedolizumab treatment. Active disease any time during pregnancy was reported in 17% of women on ustekinumab and in 23% of those on vedolizumab. Concomitant thiopurines were given to 28% and 31% of cases on ustekinumab and vedolizumab, respectively, and 11% and 15% of pregnancies were also exposed to corticosteroids. Baseline patients´ demographic and clinical characteristics per pregnancy are shown in Table 1.

The control group comprised 90 pregnancies in 81 women with IBD [78% with CD] exposed to anti-TNF therapy during pregnancy [26, 29% to adalimumab and 64, 71% to infliximab]. Compared with controls, women exposed either to ustekinumab or vedolizumab were younger at diagnosis and had longer disease duration and shorter duration of current biologic treatment. Moreover, women on ustekinumab had significantly more frequent diagnoses of CD and underwent more intestinal surgery than those exposed to anti-TNF [Table 1]. Regarding vedolizumab, there was a lower rate

Table 1 Patients' demographic and clinical characteristics at the time of conception and during pregnancy.

Number of pregnancies	Ustekinumab *n* = 54	Vedolizumab *n* = 39	Anti-TNFa *n* = 90	*p*-value UST vs anti-TNFα	*p*-value VDZ vs anti-TNFα
Age at conception[a]	30 [27–34]	29.5 [26–34]	29 [25–33]	0.439	0.587
Parity [%]				0.928	0.684
0	35 [64.8]	27 [69.2]	59 [65.6]		
≥1	19 [35.2]	12 [30.8]	21 [34.4]		
Smoking[b] [%]	5 [9.3]	3 [7.7]	6 [6.7]	0.747	1.00
CD [%]	51 [94.4]	19 [48.7]	70 [77.8]	0.008	0.001
UC [%]	3 [5.6]	20 [51.3]	20 [22.2]		
Age at diagnosis[a]	18 [14–21]	19 [15–22]	22 [18–25]	<0.001	0.018
Disease duration [years][a]	13 [8–18]	11 [8–15]	6.5 [4–11]	<0.001	0.001
CD behaviour [%]:				0.499	0.408
Inflammatory	33 [64.7]	14 [73.7]	43 [61.4]		
Stricturing	13 [25.5]	4 [21.1]	15 [21.4]		
Penetrating	5 [9.8]	1 [5.3]	12 [17.1]		
CD localisation [%]				0.222	0.708
Ileal	8 [15.7]	7 [36.8]	19 [27.1]		
Colonic	7 [13.7]	3 [15.8]	12 [17.1]		
Ileocolonic	36 [70.6]	9 [47.4]	39 [55.7]		
Upper	6 [11.8]	8 [42.1]	14 [20.0]	0.228	0.048
Perianal disease	20 [39.2]	7 [36.8]	33 [47.1]	0.385	0.423
UC—extension [%]				0.452	0.058
Proctitis	1 [33.3]	0	1 [5.0]		
Left-Sided	2 [66.7]	1 [5.0]	6 [30.0]		
Extensive	0	19 [95.0]	13 [65.0]		
Previous bowel surgery [%][a]	26 [48.1]	7 [17.9]	21 [23.3]	0.002	0.496
Disease activity [%][b]					
-PGA	9 [16.7]	9 [23.1]	9 [10.0]	0.242	0.049
-FC >250 µg/g	25/53 [47.2]	19/38 [50.0]	40/89 [44.9]	0.797	0.698
-FC >500 µg/g	14/53 [25.9]	10/38 [26.3]	29/89 [32.6]	0.439	0.483
-FC >1000 µg/g	11/53 [20.4]	7/38 [18.4]	22/89 [24.7]	0.589	0.439
Concomitant therapy[b] [%]					
Thiopurines	15 [27.8]	12 [30.8]	31 [34.4]	0.406	0.684
Systemic steroids	4 [7.4]	6 [15.4]	3 [3.3]	0.425	0.022
Topical steroids	2 [3.7]	0	2 [2.2]	0.631	1.00
Duration of biologic therapy [months][a]	12.5 [5–21]	10 [4–25]	30 [11–55]	<0.001	<0.001

CD, Crohn´s disease; UC, ulcerative colitis; TNF, tumour necrosis factor; VDZ, vedolizumab; UST, ustekinumab: PGA, Physician Global Assessment; FC, faecal calprotectin.
[a]Median [interquartile range].
[b]At any time during pregnancy.

of CD, more frequent upper gastrointestinal involvement in CD, a higher rate of active disease, and more frequent use of systemic steroids than in controls [Table 1].

3.2. Pregnancy outcome

In ustekinumab-exposed pregnancies, 43 [79.9%] resulted in live births and 11 [20.4%] led to spontaneous abortion. Of the abortions,three occurred in a single woman who was eventually diagnosed with hereditary thrombophilia, increasing the risk of miscarriages. There was no significant difference in pregnancy outcome [live birth vs non-live birth] according to steroid use or disease activity during pregnancy [data not shown].

Of pregnancies exposed to vedolizumab, 35 [89.7%] ended in a live birth, two [5.1%] in spontaneous abortion, and two [5.1%] in therapeutic abortion. One was in the 19th gestational week for Down syndrome of the fetus and the other in the 22nd gestational week for fetal brain malformation. The second woman was a very non-compliant patient who got pregnant during the active phase of ulcerative colitis [UC], did not attend regular prenatal obstetric screenings, and had persistent activity during the whole pregnancy. She was treated with vedolizumab every 4 weeks in combination with 4 g mesalazine daily and used analgesics with metamizole and paracetamol on demand. As in ustekinumab group, corticosteroid use or disease activity did not significantly affect

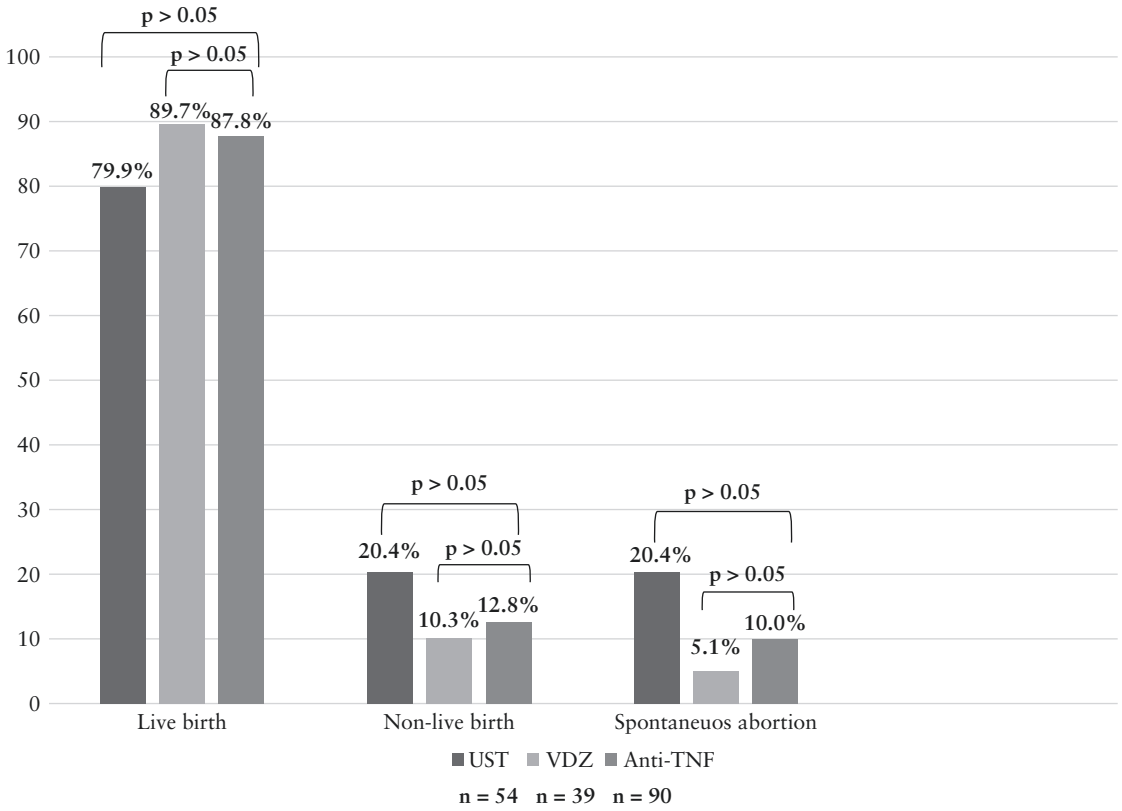

Figure 1. Pregnancy outcome. UST, ustekinumab; VDZ, vedolizumab; TNF, tumour necrosis factor.

pregnancy outcome [data not shown]. No significant difference in pregnancy outcome between either vedolizumab or ustekinumab group and controls was observed [Figure 1].

3.3. Biologic treatment in pregnancies with live births

Ustekinumab was administered for the last time during pregnancy at median gestational week 33 [range 18–38]. One patient with UC, who was being treated with ustekinumab in a clinical trial was terminated shortly after conception. Five [11.6%] women stopped the treatment during the second trimester [Week 18–24], and 37 [86.0%] continued ustekinumab during the third trimester. An intensified regime of ustekinumab [shortening the interval to 4–6 weeks] was given to 13 [30.2%] patients. There was no disease flare after stopping ustekinumab.

The last administration of vedolizumab during pregnancy was at median gestational week 32 [range 18–38]. One patient planning pregnancy stopped vedolizumab around conception due to fear of treatment-related adverse events, remained in remission during pregnancy without any treatment, and delivered at term. Seven [20%] women discontinued vedolizumab during the second trimester [Weeks 18–25], and the majority [27, 77%] continued the treatment in the third trimester. An intensified treatment regimen, shortening the application interval to 4–6 weeks, was used in six [17.1%] pregnancies. No disease relapse was observed after treatment discontinuation.

3.4. Newborn outcome

All but one child exposed to ustekinumab were born at term [median gestational age 39 weeks] with a median birthweight of 3250 g. One clinically relevant perinatal complication was observed in the form of congenital toxoplasmosis, which was successfully treated with anti-parasitic treatment. Congenital malformations were reported in three [7.0%] children, with one being considered major. This child was diagnosed with so-called Currarino syndrome, a genetic disorder leading to malformation of the sacral region and anus or rectum. Compared with the control group, no significant difference in newborns' outcomes was observed [Table 2].

In the vedolizumab-exposed group, the median gestational age at birth was Week 39, and the median birthweight was 3098 g. Three [8.6%] children were born preterm, with one being delivered very preterm at gestational week 26. This pregnancy ended by acute caesarean section due to the mother´s severe progressive preeclampsia and pathological placental blood flow. The mother also experienced symptomatic SARS-CoV-2 infection during the first trimester of pregnancy, followed by a flare of her CD and the need for systemic corticosteroids. Two clinically significant perinatal complications occurred: i] respiratory distress syndrome and sepsis caused by *E.coli* in a very preterm-delivered baby girl, both conditions completely resolving with intensive care and antibiotic treatment; and ii] bronchopneumonia treated successfully with antibiotics. Two congenital malformations were reported: mild cleft lip in a very preterm child and hypoplasia of the kidney in another newborn. No significant difference in newborns' outcomes was found between the vedolizumab and control group [Table 2].

3.5. Maternal pregnancy-related complications

Of the pregnancies which resulted in live births, maternal pregnancy-related complications occurred in six [14%]

women treated with ustekinumab and seven [20%] of those on vedolizumab. The most frequent complication was gestational diabetes mellitus, followed by arterial hypertension, preeclampsia, and intrapartum haemorrhage. The rate of complications was not significantly different from the control population in either biologic preparation [Table 3].

3.6. Placental transfer of ustekinumab and vedolizumab

Pharmacokinetic parameters were available in 26 and 23 infant-mother pairs exposed to ustekinumab and vedolizumab, respectively. In all but three cases, the levels of ustekinumab in cord blood were higher than in maternal blood at the time of delivery, with a median infant-to-maternal ratio of 1.67.

Table 2 Newborn outcome.

	Ustekinumab *n* = 43	Vedolizumab *n* = 35	Anti-TNF *n* = 79	*p*-value UST vs anti-TNF	*p*-value VDZ vs anti-TNF
Preterm birth [%]	1 [2.3]	3 [8.6]	5 [6.3]	0.423	0.699
Gestational age at birth[a]	39 [35–41]	39 [26–41]	39 [31–42]	0.246	0.249
Caesarean section [%]	25 [58.1]	19 [54.3]	38 [48.1]	0.289	0.685
Biologics, last application [g.w.][a]	33 [18–38][b]	33 [18–38][b]	30 [22–39]	0.008	0.090
Birthweight [g][a]	3250 [2240–4230]	3098 [650–3780]	3291 [1435–4170]	0.391	0.134
Low birthweight [%]	3 [7.0]	4 [11.4]	4 [5.1]		
Low birthweight [%] [Term deliveries only]	3 [7.0]	1 [3.1]	0		
Apgar score <7 [%]	1 [2.3]	1 [2.9]	2 [2.5]	1.00	1.00
Perinatal complications [%]	2 [4.7]	3 [8.6]	7 [8.9]	0.491	1.00
Icterus with phototherapy	1	1	5		
Bronchopneumonia	-	1	-		
RDS + sepsis [*E. coli*]	-	1	1		
Congenital toxoplasmosis	1	-	-		
Umbilical infection [*Staphylococcus* sp.]	-	-	1		
Congenital malformation [%]	3 [7.0]	2 [5.7]	2 [2.5]	0.344	0.585
-cleft lip	-	1	-		
-hypoplasia of kidney	-	1	-		
-asymmetric dilatation of brain ventricles	1	-	-		
-hydrocoele	1	-	1		
-Currarino syndrome	1	-	-		
-defect of heart ventricular septum#	-	-	1		

UST, ustekinumab; VDZ, vedolizumab; TNF, tumour necrosis factor; g.w., gestational week; RDS, respiratory distress syndrome.
[a]Median [range]; low-birth weight <2500.
[b]One woman stopped biologic treatment during/around conception.
p <0.05 statistically significant.

Table 3 Maternal pregnancy-related complications.

	Ustekinumab n = 43	Vedolizumab n = 35	Anti-TNF n = 79	p-value UST vs anti-TNF	p-value VDZ vs anti-TNF
Pregnancies with complications [%]	6 [14.0]	7 [20.0]	13 [16.5]	0.716	0.646
Type of complications[a]					
Gestational diabetes mellitus	4	4	7		
Arterial hypertension	1	1	2		
Preeclampsia/increased risk of preeclampsia	1	1	4		
Intrapartum haemorrhage	1	1	2		

Analysis on pregnancies with live birth only.
TNF, tumour necrosis factor; UST, ustekinumab; VDZ, vedolizumab.
[a]≥1 complication might have occurred in one pregnancy.

Table 4 Drug levels in cord blood and maternal blood.

	Ustekinumab *n* = 26	Vedolizumab *n* = 23
Gestational week of the last drug administration	33 [27.8–36]	32 [28–35]
Last administration < 3rd trimester [%]	4 [15.4]	4 [17.4]
Cord blood levels[a]	6.2 [1.7–10.9]	4.3 [3.2–9.1]
Maternal levels at delivery[a]	3.7 [0.6–7.9]	7.4 [2.9–18.6]
Infant to maternal ratio [drug levels]	1.67 [1.41–2.47]	0.59 [0.40–0.84]

Values are expressed as median [interquartile range].
[a]In mg/L.

In contrast, except for three cases, vedolizumab cord blood levels were lower than maternal ones, leading to a median infant-to-maternal ratio of 0.59 [Table 4]. Drug levels in cord blood of both preparations positively correlated with the gestational week of the last administration [ustekinumab: rho = 0.636, p <0.001; vedolizumab: rho = 0.717, p <0.001] and maternal levels at birth [ustekinumab: rho = 0.878, p <0.001; vedolizumab: rho = 0.735, p <0.001]. A negative correlation with time to delivery was observed [ustekinumab: rho = -0.552, p = 0.003; vedolizumab: rho = -0.721, p <0.001].

3.7. Infant outcome

Twenty ustekinumab-exposed and 16 vedolizumab-exposed children had follow-up at least 6 months after birth [median follow-up 18 and 21 months, respectively] and were compared with 49 control infants. Except for more males in the ustekinumab group, children were comparable regarding the frequency of preterm birth, birthweight, mother's smoking during pregnancy, and frequency or length of breastfeeding [Table 5]. All children had normal growth and normal psychomotor development. Compared with anti-TNF exposed children, infants exposed to either ustekinumab or vedolizumab *in utero* were not at increased risk of allergy/atopy development. Likewise, there was no significant difference in the rate of infectious complications requiring antibiotics and/or hospitalisation within the first year of life [Table 5].

All but one child exposed to ustekinumab and one to vedolizumab entered the mandatory vaccination programme [all non-live vaccines] without any serious or unexpected adverse events. Two children did not start vaccination due to mother's unsubstantiated concerns. Regarding the live vaccines within the first year of life, one child exposed to vedolizumab [the last drug administration at gestational week 38, cord blood level 7.9 mg/l] and three children exposed to ustekinumab [the last drug administration at gestational week 30–32, cord blood level 2.0 mg/l—available only in one patient] received rotavirus vaccination within 3 months after birth. No side effects were reported.

4. Discussion

We conducted a prospective, observational study to assess the safety of prenatal exposure to ustekinumab and vedolizumab in pregnant women with IBD. Our findings demonstrated a favourable safety profile of both drugs regarding pregnancy and newborn outcomes, maternal pregnancy-related complications, and postnatal infant development up to 1 year of life. Placental pharmacokinetics differed between the two biologics, with ustekinumab being similar to anti-TNF preparations, whereas an inverse infant-to-maternal ratio was observed in vedolizumab.

Anti-TNF therapy during pregnancy is generally considered safe for maternal and newborn outcomes.[1,2,10] There is also increasing evidence of a good safety profile of prenatal exposure to anti-TNF on long-term postnatal development of exposed children.[3,11,12] Regarding the newer biologics ustekinumab and vedolizumab, no negative safety signals on pregnancy outcomes have been reported so far.[5–8,13] However, the overall study population is still small to drive any firm conclusions, mainly that exposed to ustekinumab. Thus, there is a need for further evidence to support these findings.

The largest cohort of ustekinumab-exposed pregnancies to date, however not yet fully published [presented in abstract form only], included 478 pregnancies of patients with psoriasis [334], psoriatic arthritis [9], Crohn's disease [124], and ulcerative colitis,[11] with only 12% of pregnancies exposed to ustekinumab throughout the gestation. Live births occurred in 71.3% of the women in the cohort, of whom 20 [5.9%] were preterm and 18.4% had spontaneous abortions. The incidence of all congenital malformations was 3.8%. These rates were comparable to the general US population or the anti-TNF-treated pregnant women.[8] A recent French multicentre retrospective study presented a cohort of 29 IBD pregnancies treated with ustekinumab, but in the majority [69%], ustekinumab was stopped within 2 months before conception or during the first trimester[7]: 90% delivered a live baby; 7% of women had a spontaneous abortion; and 3% of pregnancies were terminated instrumentally. Compared with the anti-TNF-exposed control group, no significant difference in pregnancy outcome or congenital developmental defects was found. In our study, 80% of pregnancies ended in a live birth and 20% were miscarriages, which was not significantly different from the control group and is in line with the above-mentioned studies and the Czech background population.[9] In contrast to previous reports, the majority of our women [86%] also continued ustekinumab during the third trimester, with the rest of them [except one woman] stopping the treatment during the second trimester. None of our women experienced disease flare or worsening after stopping the treatment. According to recent guidelines, continuing with biologic therapy, including new biologics, is recommended throughout the pregnancy to prevent disease relapse, which is a strong risk factor of adverse pregnancy outcomes.[1]

In contrast to ustekinumab, the amount of evidence on vedolizumab safety during pregnancy is larger, although still limited. The largest cohort so far was published by A. Moens in 2020, who presented the results of the CONCEIVE study, a retrospective follow-up of 79 pregnancies in 73 women treated with vedolizumab compared with two control groups [pregnancies exposed to anti-TNF and pregnancies not exposed to biologic or immunosuppressive treatment].[5] The proportion of live births was significantly higher in the control group of women not treated with immunosuppressants or biologics compared with the vedolizumab-exposed group [89% control group vs 78% in patients treated with vedolizumab]. However, excluding patients with active disease, the numbers of live births were comparable. The CONCEIVE study

Table 5 Postnatal infant outcome.

	Ustekinumab *n* = 20	Vedolizumab *n* = 16	Anti-TNF *n* = 49	*p*-value UST vs anti-TNF	*p*-value VDZ vs anti-TNF
Age at last follow-up [months][a]	18.1 [6–38]	20.8 [6–42]	23.4 [6–61]	0.247	0.235
Females [%]	6 [30.0]	8 [50.0]	29 [59.2]	0.028	0.520
Pre-term birth [%][b]	1 [5.0]	1 [6.3]	4 [8.2]	1.00	1.00
Birthweight [g][a]	3283 [2460–4000]	3350 [650–3780]	3420 [1435–4170]	0.296	0.583
Low birthweight [%][c]	2 [10.0]	1 [6.3]	3 [6.1]	0.623	1.00
Mother smoking [%][d]	1 [5.0]	2 [12.5]	5 [10.2]	0.664	1.00
Nursing					
Any length [%]	18 [90.0]	12 [75.0]	41 [83.7]	0.712	0.470
Months[a]	7 [0.5–27]	11 [1–21]	7 [0.5–27]	0.824	0.572
Allergy/atopy					
Children	3 [15.0]	0	10 [20.4]	0.742	0.057
Children´s parents	7 [35.0]	6 [37.5]	23 [46.9]	0.364	0.510
Psychomotor development—abnormal	0	0	0	-	-
Follow-up ≥12 months	***n* = 17**	***n* = 12**	***n* = 41**		
Infections ≤1st year	3 [17.6]	3 [25.0]	5 [12.2]	0.681	0.361
Gastrointestinal	-	-	1		
Urinary	-	1	1		
Upper respiratory tract	3	1	1		
Lower respiratory tract	-	1	2		

UST, ustekinumab; VDZ, vedolizumab; TNF, tumour necrosis factor; g.w., gestational week.
[a]Median [range].
[b]Pre-term birth: gestational week <37.
[c]Low birthweight: weight <2500 g.
[d]Any time during pregnancy.
p <0.05 statistically significant.

thus reaffirmed that disease remission is a key factor for a safe pregnancy. A French study by the GETAID group recently reported 44 pregnancies on vedolizumab, 38 of which ended in live birth [86%].[7] Similar results were observed in a prospective study of 50 pregnancies by Julsgaard *et al*., with 86% live births.[6] We confirmed these findings in our patients, with almost 90% successfully completed pregnancies. More women in our cohort exposed to vedolizumab were reported to have active disease and higher use of steroids during pregnancy compared with controls. Although not statistically significant, there was a numerically higher rate of low birthweight and lower median birthweight in vedolizumab-exposed newborns than in controls, which might reflect the higher rate of disease activity in the exposed group.

The postnatal follow-up of exposed infants aged up to1 year revealed normal growth and psychomotor development in all our children. Furthermore, there was no increased risk of allergy/atopy development or occurrence of infectious complications compared with anti-TNF exposed controls. This may suggest favourable safety of ustekinumab and vedolizumab exposure *in utero* regarding the further postnatal outcome of infants. Nevertheless, the studied population was too small and the follow-up data were available in only less than 50% of our exposed children, which makes it difficult to draw any conclusion. Other relevant published data on long-term postnatal outcomes are very limited as well.[5,6] There were no unexpected or severe adverse events after vaccination, not even after live rotavirus vaccine [including three children exposed to ustekinumab and one to vedolizumab]. Likewise, data from the PIANO registry demonstrated safe administration of rotavirus vaccine after prenatal exposure to anti-TNF.[14] Although no serious side effects have been noticed so far, theoretical risk of potential infection induced by live vaccination requires individual risk-benefit assessment until more reassuring data are available.

Measurement of cord and maternal drug blood levels confirmed the different placental transfer between the vedolizumab and ustekinumab groups as described in our previous smaller study and recently published data from other centres.[6,9,13] Whereas vedolizumab levels were lower in cord blood than in maternal blood, the opposite was observed in the ustekinumab group [infant:maternal ratio 0.59 vs 1.67]. Drug levels in cord blood of both biologics correlated positively with the gestational week of the last drug administration and maternal levels at birth, whereas a negative correlation with time to delivery was observed. Flannagan *et al*. recently reported complete postnatal clearance of ustekinumab within 20 weeks in a small group of 20 infants exposed to ustekinumab prenatally.[13] Likewise in 2020, another study by Julsgaard reported postnatal vedolizumab clearance within a mean of 3.8 months.[6] These findings indicate faster postnatal clearance of new biologics compared with anti-TNF.[15]

The major strength of our study is that it is the largest prospective cohort of ustekinumab prenatal exposure to date. However, the study also has several limitations. The sample size of studied pregnancies was still small for strong conclusions about the safe use of new biologics in pregnancy. The limited sample size also precluded us from making any meaningful subgroup analyses. Another limitation is the low

number of offspring with postnatal follow-up and the absence of data on postnatal clearance due to mothers' refusal of venepuncture as invasive for their infants. Finally, we did not include a control group without exposure to biologics or immunosuppressant treatment because of the risk of reporting bias due to the lack of systematic recording of pregnancies in non-biologic treated women in the centres. Nevertheless, the already available solid evidence on the good safety profile of anti-TNF for both pregnancy and postnatal infant outcome makes it a reasonable control group.

In conclusion, based on our results, the use of the new biologics ustekinumab and vedolizumab seems to be safe, with favourable pregnancy and newborn outcomes. Also, there was no negative signal regarding postnatal infant development. The pharmacokinetic patterns of these two drugs differ, with ustekinumab similar to anti-TNF, in contrast to vedolizumab where the levels at the time of delivery are higher in maternal blood than in cord blood. More studies with larger cohorts are needed to confirm these findings.

The data underlying this article will be shared on reasonable request to the corresponding author.

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Conflict of Interest

Lectures/congress fees/consultancy [outside submitted work]: KM: Abbvie, Takeda; BP: Pfizer; MB: Abbvie, Takeda, Janssen, Pfizer, Biogen, Tillotts, Ferring, Alfasigma, PRO. MED.CS; TDo: Abbvie, Celltrion, Takeda, Janssen, Pfizer, Tillotts, Ferring; PKo: Takeda, Janssen, Abbvie; ML: Celltrion, Abbvie, Janssen, Takeda, Ferring; PM: Abbvie, Takeda; AN: Abbvie, Takeda, Pfizer, PRO.MED.CS; JU: Takeda, Janssen, Pfizer; DD: Takeda, Janssen, Pfizer.

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Author Contributions

The authors confirm contributions to the paper as follows: study concept and design: DD, KM, BP; data collection: KM, BP, DD, MB, LB, JB, TDo, TD, PK, PKo, VL, PM, AN, PS, JS, JU, MV, BZ, ML; analysis and interpretation of results: DD, KM; draft manuscript preparation: KM, DD. All authors reviewed the results and approved the final version of the manuscript.

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