SYSTEMATIC REVIEW

Pharmacokinetics of Monoclonal Antibodies Throughout Pregnancy: A Systematic Literature Review

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Abstract

Background and Objective Although little information is available on the pharmacokinetics (PK) of monoclonal antibodies (mAbs) during pregnancy, multiple mAbs are being used during pregnancy for various indications. The aim of this systematic literature review was to characterize the PK of mAbs throughout pregnancy.

Methods A systematic literature search was carried out in PubMed and Embase on 21 April 2023. Articles were included when information on PK or exposure parameters of mAbs in pregnant women was available.

Results A total of 42 relevant articles were included, of which eight discussed adalimumab, three certolizumab pegol, five eculizumab, one golimumab, 12 infliximab (IFX), two natalizumab, one canakinumab, one omalizumab, five tocilizumab, eight ustekinumab, and five vedolizumab. One of the 42 studies reported information on clearance (CL) and volume of distribution (VD) of IFX; all other studies only reported on serum concentrations in the pre-pregnancy state, different trimesters, and the postpartum period. For all of the assessed mAbs except IFX, serum concentrations were similar to concentrations in the pre-pregnancy state or modestly decreased. In contrast, IFX trough concentrations generally increased in the second and third trimesters in comparison to the non-pregnant state.

Conclusion Available information suggests that the anatomical and physiological changes throughout pregnancy may have meaningful effects on the PK of mAbs. For most mAbs (not IFX), modestly higher dosing (per mg) maybe needed during pregnancy to sustain a similar serum exposure compared to pre-pregnancy.

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Key Points

This systematic literature review aims to describe the pharmacokinetics (PK) of monoclonal antibodies (mAbs) throughout pregnancy. The anatomical and physiological changes throughout pregnancy may have meaningful effects on the PK of mAbs.

For all of the assessed mAbs except infliximab (IFX), serum concentrations were similar to concentrations in the pre-pregnancy state or modestly decreased. In contrast, IFX trough concentrations generally increased in the second and third trimesters in comparison to the non-pregnant state.

For most mAbs (not IFX), modestly higher dosing (per mg) may be needed during pregnancy to sustain a similar serum exposure compared to pre-pregnancy.

△ Adis

1 Introduction

Monoclonal antibodies (mAbs) are an important therapeutic modality for conditions that commonly affect women of child-bearing potential, such as autoimmune disorders [1]. Although relatively little information is available on the pharmacokinetics (PK) and safety of mAbs during pregnancy, they are frequently used. Benefit is often presumed to outweigh risk in these scenarios; for example, failure to maintain clinical and biochemical remission of an autoimmune disorder throughout pregnancy is associated with adverse health outcomes for both the mother and fetus, and comparable immunosuppressants or therapeutic alternatives are well-established teratogens [1]. Recommendations from the manufacturer or the regulator are sparse [2–10]. mAbs are well-known to cross the placenta [11–14] and fetal exposures may be clinically relevant [15]. Most mAbs are rated as pregnancy risk category 'B' or 'C' based on the results of reproductive toxicity studies in pre-clinical species, but there are no adequate and well-controlled studies in pregnant women for any mAb at this time [16–18].

The PK properties of mAbs are much different from those of conventional small molecule drugs. As they are therapeutic proteins and large molecules (approximately 150 kDa), distribution is predominantly confined to the extracellular fluid. Extravasation from the plasma to the interstitial fluid in tissues is slow, governed by restrictive flow through vascular pores. Most elimination is by catabolism following cellular uptake. Many endothelial and hematopoietic cells express the neonatal Fc receptor (FcRn), which can salvage mAbs from acidic endosomes and recycle them to the extracellular fluid. As a result, the plasma half-life of mAbs ranges from days to weeks, and is correlated with their binding affinity for FcRn [19, 20].

During pregnancy, several anatomical and physiological changes in the body occur [21] that may be relevant to the disposition and PK of mAbs [22]. Total body weight, total blood volume, and blood flow all progressively increase with pregnancy [21]. As a result, concentrations of plasma proteins such as IgG and albumin tend to decline as the volume of distribution is diluted by the increase in plasma volume [23]. Most of the increase in total body weight is driven by the growth of the placenta and fetal tissue. Compared to the other body organs (excluding the brain), the placenta is relatively impermeable to plasma proteins since it does not draw maternal blood supply – placental transfer occurs only through transcytosis [24, 25]. Therefore, the influences of increased pregnant weight on mAb volume of distribution are expected to be low, as lean body weight is only modestly increased [21]. Clearance is also expected to modestly increase along with the increased size of eliminating organs, such as the liver, muscle, and skin, but in a way that is less than proportional to the increase in total body weight [26, 27]. Therefore, if administering a dose that is independent of body weight (mg rather than mg/kg), serum concentrations in pregnancy would be expected to be similar to or lower than those observed in the non-pregnant state. On the other hand, dosing in proportion to total body weight (mg/kg) would cause increased exposures compared to the non-pregnant state.

Considering the above hypotheses, dosage regimen changes may be indicated to optimize disease control in pregnancy [28]. A special case is infliximab (IFX); while it is normally dosed on a mg/kg basis, common clinical practice is not to deviate from the absolute pre-pregnancy dose (mg), despite the increases in total body weight throughout pregnancy [29]. Gaining knowledge regarding alterations of PK and exposure parameters during pregnancy is the first step in designing evidence-based dosing regimens of mAbs for pregnant women.
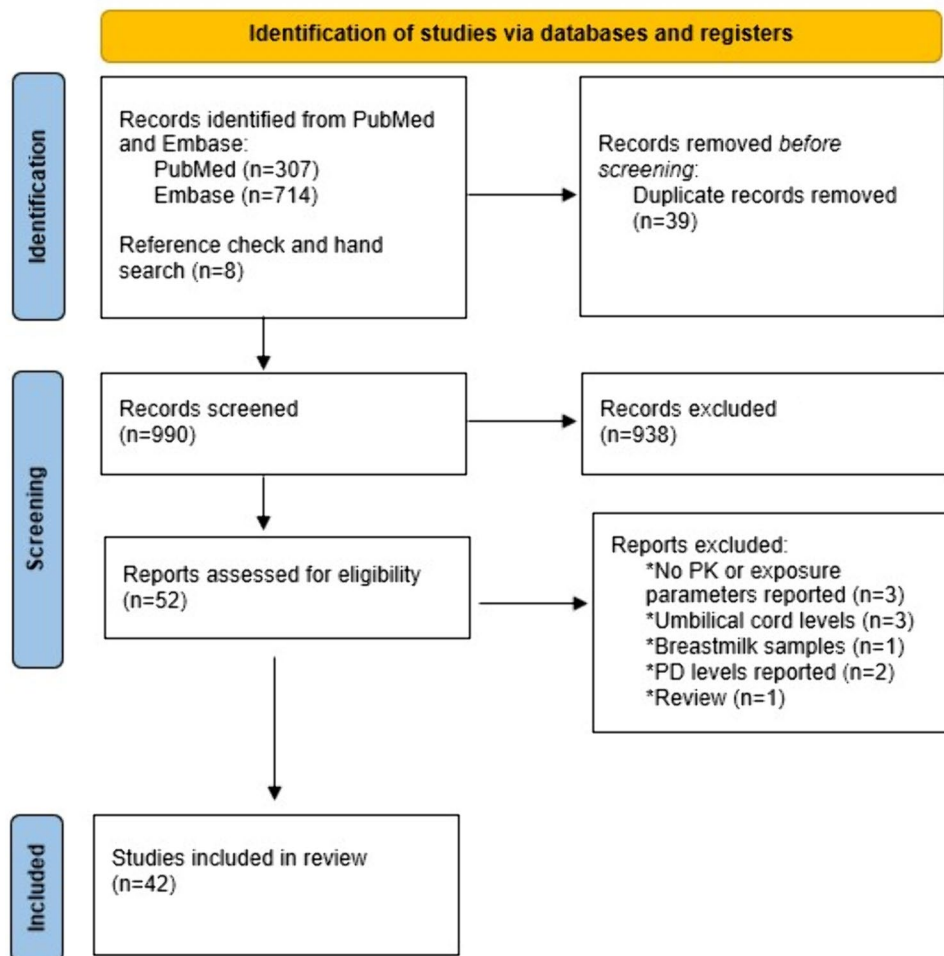
Therefore, this study aims to systematically review available literature on the PK of mAbs in pregnant women in relation to the stated hypotheses. Following the identification of trends throughout the trimesters, important considerations and key questions are presented that may help to lay the groundwork for evidence-based dosing regimens in the future. The effects of mAbs on the placenta (drug transfer) and fetus (safety) are outside the scope of this review.

2 Methods

2.1 Search Strategy

A systematic literature review was performed in accordance with the PRISMA guidelines of 2020 [30]. For the PRISMA flow diagram, see Fig. 1. All mAbs registered in the Netherlands were included in this study [31] and can be found in Electronic Supplemental File 1 in the electronic supplemental material. A search using PubMed and Embase was performed on April 21, 2023 for every individual mAb with a combination of the following terms: 'selected drug name,' 'pregnancy,' and 'pharmacokinetic.' For the specific keywords and field codes per topic, see Table 1. The detailed search strategy per mAb is outlined in Electronic Supplemental File 2. While certolizumab pegol (CZP) is a pegylated Fab fragment that does not bind FcRn, it is included in this systematic review as a mAb according to the classification and terminology of the European Medicines Agency (EMA) [3, 32].

Fig. 1 PRISMA 2020 flow diagram for mAbs. *mAb* monoclonal antibody, *PK* pharmacokinetics, *PRISMA* preferred reporting items for systematic reviews and meta-analyses

Identification of studies via databases and registers

Identification

Records identified from PubMed and Embase:
   PubMed (n=307)
   Embase (n=714)

Reference check and hand search (n=8)

Records removed *before screening*:
   Duplicate records removed (n=39)

Screening

Records screened (n=990)

Records excluded (n=938)

Reports assessed for eligibility (n=52)

Reports excluded:
   *No PK or exposure parameters reported (n=3)
   *Umbilical cord levels (n=3)
   *Breastmilk samples (n=1)
   *PD levels reported (n=2)
   *Review (n=1)

Included

Studies included in review (n=42)

2.2 Inclusion Criteria

Studies were included if they reported at least one PK concentration or exposure parameter for a mAb in one or more pregnant women. Serum concentrations, PK, or exposure parameters were extracted. Percent changes during pregnancy (i.e., pregnancy vs. pre-pregnancy or postpartum) were calculated, and trimester-specific changes were reported when available. Both intravenous and subcutaneous dosage forms were included in this study. The following studies were included when available: randomized controlled trial, non-randomized controlled trial, cohort study, case–control study, case-series study, or case report. Reviews, guidelines, editorials, consensus papers, animal studies, ex vivo studies, and non-English studies were excluded for this systematic review. There was no year of publication restriction. This review focuses only on the influence of pregnancy on maternal PK, not on other aspects of mAbs during pregnancy, e.g., effects or safety in the mother, placenta, or fetus/infant.

2.3 Study Selection

For first selection, title and abstract were screened for relevance. Full texts of these articles were obtained, whereafter studies not meeting the criteria were excluded. Two investigators (RE and PMi) conducted the search strategy and study selection for mAb number 1–42 (Supplemental File 1 in the electronic supplemental material), separately from each other. For the others, mAb number 43–80, two investigators (JvG and PMi) separately conducted the search strategy and study selection. The obtained results were discussed, and in the case of disagreement, a third author (DT) was consulted.

2.4 Data Extraction

Data extraction from all eligible studies on mAb number 1–42 was performed by an investigator (RE), while data extraction from all eligible studies on mAb number 43–80 was performed by another investigator (JvG). All data were checked by a third author (PMi). The extracted study

Table 1 Key terms with the corresponding field used in the PubMed search strategy

Pregnancy	Pharmacokinetics	Monoclonal antibody
("Pregnancy"[Mesh] OR pregnanc*[tiab] OR gestation*[tiab] OR caesarean*[tiab] OR cesarean*[tiab] OR "abdominal deliver*"[tiab] OR "C-section*"[tiab] OR "Delivery, Obstetric"[Mesh] OR "obstetric deliver*"[tiab] OR "Labor, Obstetric"[Mesh] OR "obstetric labor"[tiab] OR labor [tiab] OR labour [tiab])	("Pharmacokinetics"[Mesh] OR pharmacokinetic*[tiab] OR "drug kinetic*"[tiab] OR ADME*[tiab] OR LADMER[tiab] OR (absorption[tiab] AND distribution[tiab] AND metabolism[tiab] AND elimination[tiab]) OR "pharmacokinetics" [Subheading])	"selected drug name" [Mesh] For further specifications per drug, see Supplemental File 2 in the electronic supplementary material

characteristics were: study design, population (number of participants), and type of medication (with indication, dosage, and dosage interval). Other patient characteristics were condition, weight, age, and gestational age. Serum concentrations and exposure parameters were collected along with the post-dose sampling times. When serum concentrations were not reported in the text and only available in figures, the serum concentrations were digitized from the figures in duplicate (RE, JvG) using web plot digitizer (WPD). In Table 2, data extracted using WPD are marked with a #. Furthermore, disease activity (individual or group level) as measured by clinical scales was reported when available (Table 2). Additional extracted information was summarized: medication and population, inclusion criteria, dose advice (different than the standard dose based on potential PK/PD changes and target attainment), paper conclusions, and analytical methods (with lower limit of quantification [LLOQ] or lower limit of detection [LLOD] (Table 3). Data visualization was performed using GraphPad Prism 9.1.0.

3 Results

3.1 Study Selection and Data Extraction

In total, 42 studies reporting on the PK of mAbs during pregnancy were included in this systematic review, of which nine studies reported data on two or three different mAbs. A total of eight studies for adalimumab (ADL), three for CZP, five for eculizumab (ECU), one for golimumab (GOL), 12 for IFX, two for natalizumab (NAT), one for canakinumab (CAN), one for omalizumab (OMA), five for tocilizumab (TCZ), eight for ustekinumab (UST), and five for vedolizumab (VDZ) were included. An overview of the patient populations and study characteristics is presented in Table 2, and an overview of results and dosing guidance is presented in Table 3.

3.2 Tumor Necrosis Factor (TNF)-α Inhibitors

3.2.1 Adalimumab

Eight studies were included reporting serum concentrations of ADL in pregnant women [11, 29, 33–38]. Most PK information was available from two studies [29, 36] (Tables 2, 3, Fig. 2). Dosing was generally consistent between pre-pregnancy, pregnancy, and postpartum periods, and most participants received 40 mg subcutaneously every 2 weeks. Median steady-state concentrations measured during pregnancy were consistently lower when compared to those measured in the non-pregnant states (either pre-pregnancy or postpartum) [29, 36] (Fig. 2).

Table 2 Patient and study characteristics of the included studies in this systematic literature search

Authors (year) [reference] Study design	Population	Medication Dose and interval	Condition	Age (years) and weight (kg)	GA (weeks)	Sample information	Serum concentration	Disease activity
Bortlik et al. (2013) [33] Prospective cohort study	5	ADL 40 mg q2w	27 CD 14 UC*	Age: 29 (19–43) years*	T4: GA 39 (34–42)*	GA at last dose (mean): 29.0 (24–35)	µg/mL (mean + range) T4: 0.8 [0.0–2.5]	Disease activity during pregnancy (n): T0: 10, T1: 11, T2: 6, T3: 5*
Flanagan et al. (2020) [36] Prospective cohort study	15	ADL 40 mg q2w N: 13; 40 mg q1w N: 2	14 CD 1 UC	Age: 34.0 (32.0–36.7) years Weight: 70.0 (65.0–86.0) kg	T4: GA 39 (38–39)*	Obtained at steady state GA at last dose: 37 (31–38)	µg/mL T0: 10.4 (10.0–10.8) N_{OBS}: 2; T1: 5.7 (4.8–10.2) N_{OBS}: 9; T2: 5.2 (4.0–6.8) N_{OBS}: 12; T3: 5.8 (4.8–8.0) N_{OBS}: 14; T4: 6.7 (5.1–8.0) N_{OBS}: 8; T5: 7.2 (4.3–9.7) N_{OBS}: 8	No activity during pregnancy according to PGA
Julsgaard et al. (2013) [34] Case report	1	ADL 40 mg q2w Stopped therapy at GW 16, reintroduced 24 days postpartum (= day 0)	CD	Age: 36 years	T4: GA 37.5	GA at last dose: 16	µg/mL T4: 0.3 T5: Day 0: 0, Day 3: 2.2, Day 13: 1.0	–
Julsgaard et al. (2016) [35] Prospective cohort study	36	ADL 40 mg q2w ($n = 30$) Increased dose ($n = 6$)	66 CD 14 UC*	Age at T4: 31 (24–39) years* Weight at T0: 67.5 [48.0–115.0] kg*	T4: GA 39 [33.0–42.0]*	GA at last dose: 35 (14–41)	µg/mL T4 (last dose < GW 30): 0.3 [0.0–0.7] N_{OBS}: 7; T4 (last dose ≥ GW 30): 2.1 [0.0–10.0] N_{OBS}: 29; T4 (total): 1.5 [0.0–10.0]	38 women (48%), using either ADL or IFX, experienced a disease relapse in the first, second, or third trimester of pregnancy

Table 2 (continued)

Authors (year) [reference] Study design	Population	Medication Dose and interval	Condition	Age (years) and weight (kg)	GA (weeks)	Sample information	Serum concentration	Disease activity
Kanis et al. (2018) [38] Prospective cohort study	58	ADL 40 mg q2w $N = 47$ Increased frequency $N = 11$	51 CD 6 UC 1 unclassified (IBD)	Age during conception: 30 (28–33) years BMI at T0: 23 (21–27) kg/m²	T4: GA 39 (38–40)	GA at last dose: 23 (22–37)	µg/mL T4: 0.6 (0.3–3.6) N_{OBS}: 42	Total disease activity during pregnancy (n): 19
Labetoulle et al. (2019) [37] Case report	1	ADL Variating dose, up to 40 mg q1w	1 CD	Age: 34 years	T4: GA 39	Two samples, one during the first trimester and one during an unknown period	µg/mL T1: 3.5 Unknown: 10	Flare in first trimester
Mahadevan et al. (2013) [11] Prospective cohort study	10	ADL 40 mg q2w N: 9 40 mg q1w N: 1	8 CD 2 UC	Age: 32.5 (25–40) years	T4: GA 39 (38–41)	Time between last dose and delivery: 5.5 [0.14–8] weeks	µg/mL T4: 3.3 [0.0–16.1]	Flare of disease (n): T3: 3 T5: 5 Active disease in T3 (n): 3
Seow et al. (2017) [29] Prospective cohort study	10 (11 pregnancies)	ADL 40 mg q2w N: 9 40 mg q1w N: 2	8 CD 7 UC	Age: 31.9 (28.2–35.0) years	T4: GA 38.4 (37.2–39.6)	Obtained at steady state GA at last dose: 34 (31.5–35.2)	µg/mL T0: 17.63# (14.7–22.5) N_{OBS}: 4 T1: 8.6# (0.0–16.3) N_{OBS}: 5 T2: 12.18# (6.7–17.0) N_{OBS}: 11 T3: 9.26# (0.4–14.5) N_{OBS}: 8 T5: 7.4# (0.0–15.2) N_{OBS}: 9	Disease activity HBI index (CD patients): 9–14 (n = 1)
Mahadevan et al. (2013) [11] Prospective cohort study	10	CZP	10 CD	Age: 28 (22–42) years	T4: GA 37.8 (36–40)	Time between last dose and T4: 19 (5–42) days	µg/mL T4: 19.5 [1.9–59.6]	–
Mariette et al. (2018) [76] Prospective cohort study	14	CZP 200 mg q2w N: 15 200 mg q4w N: 1	11 RA 3 CD 1 PA 1 axSpA/AS	Age: 31 (18–40) years	T4: GA 39.9 [37.7–41.7]	Obtained within 24 h before or after T4 Time between last dose and delivery: 11 (1–27) days	µg/mL 24.4 [5.0–49.4]	–

Table 2 (continued)

Authors (year) [reference] Study design	Population	Medication Dose and interval	Condition	Age (years) and weight (kg)	GA (weeks)	Sample information	Serum concentration	Disease activity
Morita et al. (2018) [40] Case report	1	CZP q4w	1 RA	Age: 30 years	T4: GA 40 weeks	Time between dose and sampling: T3: 2, 24, 48 h; T5: 7, 14 days	µg/mL T3: 40, 35, 22; T5: 26, 35	Disease activity according to DAS28-ESR: T1: 3.86; T3: 5.71
Burwick et al. (2022) [48] Case series	3	ECU Day 1: 1200 mg; Day 4: 1200 mg	3 COVID-19	Age (mean): 32 (SD ± 6) years*; BMI (mean): 28 (SD ± 4) kg/m²*	T4: GA 39.5 (36–41)*	Measurement 1: day 1, 1 h after first dose N: 3; Measurement 2: day 4, before second dose N: 2	µg/mL Measurement 1 (mean + SD): 321 (±13); Measurement 2: 150 and 160	–
Duineveld et al. (2019) [49] Case report	1	ECU 1200 mg q2w	Atypical hemolytic uremic syndrome	–	T4: GA 36^{+2}	GA at last dose: 36^{+1} Through concentration	µg/mL T3: 262	–
Gustavsen et al. (2017) [50] Case report	1	ECU Day 0: 600 mg; Day 7: 600 mg	1 APS	Age: 22 years	T4: GA 32	–	µg/mL # Day 0 (T3): 67; Day 2 (T3): 47; Day 8 (T4): 98	–
Servais et al. (2016) [52] Case series	1	ECU 1200 mg q1w/q2w/q3w	aHUS	Age: 29 years	T4: GA 30^{+1}	An additional dose of 1500 mg was administered the day before T4	µg/mL T3#: 39, 29, 91; T4: 1598; T5#: 607, 162, 825	–
Sharma et al. (2015) [51] Case report	1	ECU GA 0–29: 900 mg q2w; GA 30–34: 900 mg q1w; GA 35–36: 1200 mg q2w	1 PNH	Age: 30 years	T4: GA 36	–	µg/mL GA 30 (T3): < 11; GA 35 (T3): 100	–
Benoit et al. (2019) [42] Case report	1	GOL 100 mg q2w	1 UC	Age: 28 years	T4: GA 43	Time between last dose and T4: 3 days	µg/mL T4: 6.6	–
Bortlik et al. (2013) [33] Prospective cohort study	8	IFX 5 mg/kg q8w N: 32	27 CD 14 UC*	Age: 29 (19–43) years	T4: GA 39 (34–42)	Obtained on the day of delivery GA at last dose: 28 (24–35)	µg/mL (mean) T4: 4.1 [0.0–18.0] N_{OBS}: 8	Active disease activity (n): T0: 10; T1: 11; T2: 6; T3: 5

Table 2 (continued)

Authors (year) [reference] Study design	Population	Medication Dose and interval	Condition	Age (years) and weight (kg)	GA (weeks)	Sample information	Serum concentration	Disease activity
Eliesen et al. (2020) [12] Prospective cohort study	3	IFX 5 mg/kg q8w (400 mg) N: 3	2 CD 1 RA	Patient 1: Age: 27 years Weight: 22.3 kg/m² Patient 2: Age: 25 years Weight: 24.7 kg/m² Patient 3: Age: 37 years Weight: 21.5 kg/m²	Patient 1: T4: GA 40⁺¹ Patient 2: T4: GA 41⁺⁶ Patient 3: T4: GA 38⁺⁶	Obtained on the day of delivery Time from last dose to delivery (days) Patient 1: 23 Patient 2: 57 Patient 3: 31	µg/mL Patient 1, T4: 12.0 Patient 2, T4: 17.0 Patient 3, T4: 25.3	–
Flanagan et al. (2020) [36] Prospective cohort study	23	IFX 5 mg/kg q8w N: 21 q4w N: 1 10 mg/kg N: 1	17 CD 4 UC Unclassified IBD (n): 2	Age: 32.3 (28.8–35.2) years Weight: 65.0 (58.0–73.0) kg	–	Obtained at steady state GA at last dose: 31 (29–33)	µg/mL T0: 7.9 (6.3–11.0) N_{OBS}: 6 T1: 8.8 (5.5–12.4) N_{OBS}: 15 T2: 10.0 (7.1–13.7) N_{OBS}: 30 T3: 11.0 (7.1–16.8) N_{OBS}: 20 T4: 11.2 (8.4–15.7) N_{OBS}: 8 T5: 10.3 (4.3–13.8) N_{OBS}: 12	Disease activity during pregnancy according to PGA (n): 2
Grišić et al. (2020) [44] Retrospective cohort study	19 (23 pregnancies)	IFX 5 mg/kg q8w N: 17 5 mg/kg q6w N: 4 5 mg/kg q10w N: 1 10 mg/kg q8w N: 1	14 CD 5 UC	Age: 31 (27–34) years	–	All trough levels, expressed as dose-normalized IFX	mg/mL/kg T0: 7.3 (2.0–11.6) N_{OBS}: 119 T1: 8.5 (1.4–11.5) N_{OBS}: 16 T2: 15.0 (9.8–20.5) N_{OBS}: 18 T3: 13.0 (6.5–35.8) N_{OBS}: 7 T5: 5.9 (3.3–11.1) N_{OBS}: 12 CL: 0.608 L/d V_d: 18.2 L	Disease activity HBI index (CD patients): 3 (2–5) Disease activity SCCAI (UC patients): 2.5 (0.0–5.5)

Table 2 (continued)

Authors (year) [reference] Study design	Population	Condition	Medication Dose and interval	Age (years) and weight (kg)	GA (weeks)	Sample information	Serum concentration	Disease activity
Julsgaard et al. (2016) [35] Prospective cohort study	44	66 CD 14 UC*	IFX 5 mg/kg q8w N: 42 Increased dose N: 2	Age at T4: 31 (24–39) years* Weight at T0: 67.5 [48.0–115.0] kg*	T4: GA 39 [33.0–42.0]*	GA at last dose: 30 (8–37)	µg/mL T4 (last infusion < GA 30): 0.6 [0.0–3.3] N_{OBS}: 18 T4 (last infusion ≥ GA 30): 4.0 [0.0–22.2] N_{OBS}: 26 T4 (total): 2.0 [0.0–22.2]	38 women (48%), using either ADL or IFX, experienced a disease relapse in the first, second, or third trimester of pregnancy
Kane et al. (2009) [43] Prospective cohort study	3	3 CD	IFX 5 mg/kg q8w N: 3	Patient 1: Age: 29 years Patient 2: Age: 32 years Patient 3: Age: 24 years	Patient 1: T4: GA 38 Patient 2: T4: GA 39 Patient 3: T4: GA 36	GA at last dose: Patient 1: GA 31 Patient 2: GA 32 Patient 3: GA 25 IFX treatment; sample collected (days postpartum) Patient 1: 3; 9 Patient 2: 10; 15 Patient 3: 14; 57	µg/mL Patient 1, T5: 74.27 Patient 2, T5: 62.62 Patient 3, T5: 59.97	–
Kanis et al. (2018) [38] Prospective cohort study	73	54 CD 18 UC 1 unclassified IBD	IFX 5 mg/kg q8w (standard)	Age: 30 (27–33) years Weight: 25 (22–27) kg/m²	T4: GA 39 (38–40)	GA at last dose: 25 (21–32)	T4: 1.7 (0.4–6.9) N_{OBS}: 52	Disease activity at some point during pregnancy (n): 15
Mahadevan et al. (2013) [11] Prospective cohort study	11	7 CD 4 UC	IFX 5 mg/kg q8w N: 4 10 mg/kg q6w N: 1 10 mg/kg q8w N: 1 5 mg/kg q6w N: 5	Age: 36 (29–40) years	T4: GA 40 (38–41)	Obtained on the day of delivery Time from last dose to delivery (days): 35 (14–74)	µg/mL T4: 5.0 [1.4–19.2]	Flare of disease (n): T3: 2 T5: 3

Table 2 (continued)

Authors (year) [reference] Study design	Population	Medication Dose and interval	Condition	Age (years) and weight (kg)	GA (weeks)	Sample information	Serum concentration	Disease activity
Seow et al. (2017) [29] Prospective cohort study	15	IFX 5.29 (4.87–5.96) mg/kg q7w (6.0–8.0)	8 CD 7 UC	CD Age: 28.4 (26.87–30.0) years Weight: 25.7 (21.4–27.1) kg/m² UC Age: 29.3 (27.1–29.9) years Weight: 27.0 (25.9–28.8) kg/m²	T4: GA 39.2 (38.1–40.2)	Obtained at steady state GA at last dose: 30.3 (26.5–31.1)	µg/mL T0: 6.9 N_{OBS}: 1 T1: 8.5 (7.23–10.7) N_{OBS}: 5 T2: 10.31 (7.66–15.63) N_{OBS}: 15 T3: 21.02 (16.01–26.70) N_{OBS}: 13 T5: 10.17# (6.4–17.4) N_{OBS}: 11	Disease activity HBI index (CD patients): 9–14 (n = 1) Disease activity SCCAI (UC patients): 5 (n = 1)
Steenholdt et al. (2011) [47] Case report	1	IFX 5 mg/kg Interval T5: q8w–q12w Paused GA: 10–19	1 UC	Age: 26 years	T4: GA 37	GA at last dose: 31	µg/mL# T2: 3.6 T3: 1.4 T5: 1.3, 0.6, 0.34, 2.1	Flare of disease at GA 19
Vasilauskas et al. (2006) [14] Case report	1	IFX 10 mg/kg q6w–q8w	1 CD	Age: 35 years	T4: GA 41	GA at last dose: 39 IFX treatment; (weeks postpartum) 2 and 10	µg/mL T5: 40 (w6), 9.6 (w10), 84 (w13)	Flare of disease T5: w10
Vestergaard et al. (2017) [45] Case report	1	IFX q7w	1 CD	Age: 35 years	T4: GA 37.0	GA at last dose: 25	µg/mL T4: 1.41	No disease activity during pregnancy

Table 2 (continued)

Authors (year) [reference] Study design	Population	Medication Dose and interval	Condition	Age (years) and weight (kg)	GA (weeks)	Sample information	Serum concentration	Disease activity
Proschmann et al. (2021) [54] Prospective cohort study	11	NAT 300 mg q4w T0–T5 N: 9 300 mg q4w–q6w T0–T5 N: 1 300 mg q4w T2–T5 N: 1	11 MS	Age: 29.4 (2.7) years Weight: 72 (10) kg	–	Obtained immediately before and 20 min after NAT infusion	μg/mL [#] T0: 27.8 (24.5–48.0) N_{OBS}: 10 T1: 25.8 (16.5–50.9) N_{OBS}: 8 T2: 23.6 (17.5–41.4) N_{OBS}: 7 T3: 13.3 (9.8–29.1) N_{OBS}: 8 T4: 12.9 (6.3–29.9) N_{OBS}: 5 T5: 18.2 (12.6–26.9) N_{OBS}: 20	Disease activity according to EDSS: 1.7 (1.3)
Toorop et al. (2022) [53] Case series	3	NAT 300 mg q4w 300 mg q4w 300 mg q6w/q7w/ q5w	MS	Age at T1: 32 years, 31 years 31 years Weight at T5: 81 kg 73 kg 82 kg	GA at T4: 37 40 41	All trough levels	μg/mL [#] T0: 19.0 (17.0–32.0) N_{OBS}: 5 T1: 18.1 (13.1–31.1) N_{OBS}: 3 T2: 11.6 (4.3–23.2) N_{OBS}: 4 T3: 7.3 (2.8–12.5) N_{OBS}: 4 T5: 18.0 (15.5–29.0) N_{OBS}: 6	All patients remained clinically stable
Weber and Millet (2022) [60] Case series	7	CAN 150 mg q4w	3 CAPS 2 SJIA (N = 1 sample is from) 1 FMF 1 MKD	Age: 25 years [17–32]	GA at T4: [35–41]	–	μg/mL T4: 35 N_{OBS}: 1	Three women had a disease flare and required treatment escalation
Saito et al. (2020) [61] Case report	1	OMA 150 mg q4w	Urticaria	Age: 38 years	T4: 38^{+4}	GA at last dose: 28	ng/mL T3: 4378.8 T4: 3239.9	The patient's urticaria worsened after discontinuing OMA at week 28 of gestation

Table 2 (continued)

Authors (year) [reference] Study design	Population	Medication Dose and interval	Condition	Age (years) and weight (kg)	GA (weeks)	Sample information	Serum concentration	Disease activity
Moriyama et al. (2020) [39] Case report	1	TCZ 162 mg q2w sc	RA	Age: 32 years	T4: GA 39^{+4}	–	µg/mL T4: 13.3	No disease activity during pregnancy
Saito et al. (2018) [62] Case report	2	TCZ 8 mg/kg once a month iv Patient 1: Discontinued at GA 5. Continued 5 weeks postpartum Patient 2: Discontinued at GA 1^{+2}. Continued 9 days postpartum	2 RA	Patient 1: Age: 43 years Patient 2: Age: 35 years	Patient 1: T4: GA 37 Patient 2: T4: GA 36	Obtained at steady state	µg/mL$^{\#}$ T5: 9.8 (3.6–21.3) N_{OBS}: 6	CDAI during pregnancy Patient 1: persistent remission Flare of disease during pregnancy Patient 2: low score
Saito et al. (2019) [63] Case report	1	TCZ Dose unknown	AOSD	Age: 31 years	T4: GA 40^{+5}	Sample 1 (T3): immediately after last administration Sample 2 (T4): approximately 4 weeks after administration Sample 3, 4, and 5 (T5): 32, 23, and 0 days after last administration	µg/mL Sample 1: 57.65 Sample 2: 4.90 Sample 3: 3.24 Sample 4: 3.72 Sample 5: 43.00	–
Saito et al. (2020) [64] Case report	1	TCZ Dose unknown	RA and autoimmune hepatitis	Age: 43 years	T4: GA 39	Therapy was started 7 days after delivery	µg/mL T5: 35.5, 3.3, 3.9	RA symptoms were well controlled without any treatment from 14 weeks of gestation until delivery
Tada et al. (2019) [13] Case report	1	TCZ 8 mg/kg q4w iv Switch during pregnancy 162 mg q2w sc	1 RA	Age: 39 years	T4: GA 38	Time from last dose to delivery (days): 24	µg/mL T3 (GA 36^{+6}): 16.20 T3 (GA 37^{+6}): 6.17	CDAI during pregnancy: 2.7–8.8

Table 2 (continued)

Authors (year) [reference] Study design	Population	Medication Dose and interval	Condition	Age (years) and weight (kg)	GA (weeks)	Sample information	Serum concentration	Disease activity
Flanagan et al. (2021) [67] Observational study	19	UST 90 mg q8w N: 11 90 mg q6w N: 1 90 mg q4w N: 4	19 CD	Age: 31 (27–33) years	T4: GA 39 (38–39.43)	GA at last dose: 32.2 [24.86–35.71]	µg/mL T1: 2.2 [1.3–2.4] N_{OBS}: 4 T2: 2.1 [1.0–4.5] N_{OBS}: 14 T3: 1.9 [1.6–4.6] N_{OBS}: 9 T4: 1.6 [0.67–4.4] N_{OBS}: 15	Disease activity at some point during pregnancy (n): 4
Klenske et al. (2019) [68] Case report	1	UST 90 mg q8w	CD	Age: 24 years	T4: GA 38	All trough levels GA at last dose: 30	µg/mL T1: 3.6 T2: 2.7 T3: 2.1 T4: 0.3 T5: 4.6	–
Mitrova et al. (2021) [58] Prospective multi-center study	32	UST Dose unknown	14 CD 1 UC	Age: 28 (26–32) years	T4: GA 39 (37–41)	GA at last dose: 33 (30–36)	mg/L T4: 5.3 (2.3–10.1) N_{OBS}: 15	Disease activity at some point during pregnancy (n): 4
Mitrova et al. (2022) [59] Prospective multi-center study	49 (54 pregnancies)	UST Dose unknown	51 CD 3 UC	Age: 30 (27–34) years	T4: GA 39 (35–41)	GA at last dose: 33 (18–38)	mg/L T4: 3.7 (0.6–7.9) N_{OBS}: 26	Disease activity in 17% of all patients
Prentice et al. (2023) [56] Congress abstract	97*	UST Dose unknown	IBD	Age: 31 (29–34)*	T4: GA 38^{+6} $(37–40^{+4})$	GA at last dose: 31^{+3} $(29–33^{+3})$	µg/mL T0: 5.25 (3.9–5.6) N_{OBS}: 5 T1: 2.4 (1.9–7.7) N_{OBS}: 5 T2: 2.2 (1.4–3.1) N_{OBS}: 38 T3: 2.6 (1.7–4.6) N_{OBS}: 27 T4: 2.1 (0.7–4.8) N_{OBS}: 35 T5: 3.1 (2.3–3.3) N_{OBS}: 7	Clinical and bio-chemical disease remission was maintained in the majority of patients

Table 2 (continued)

Authors (year) [reference] Study design	Population	Medication Dose and interval	Condition	Age (years) and weight (kg)	GA (weeks)	Sample information	Serum concentration	Disease activity
Rowan et al. (2018) [69] Case report	1	UST 90 mg q4w	CD	Age: 35 years	T4: GA 37	All trough levels GA at last dose: 33	µg/mL T0: 2.5 T1: 3.3 [1–3.8] T2: 5 [4.7–5.2] T3: 5.1 [4.3–5.9] T4: 4.3 N_{OBS}: -	The pregnancy was uneventful
Saito et al. (2022) [66] Case report	1	UST 90 mg q8–12w	1 UC	Age: 36 years	T4: GA 38^{+3}	GA at last dose: 29	µg/mL T3: 7.97 and 1.36 T5: 0.34 [0.11–2.83]	No disease activity during pregnancy
Sako et al. (2021) [65] Prospective cohort study	1	UST 90 mg q8w	1 CD	Age: 35 years	T4: GA 38	GA at last dose: 23^{+3}	µg/mL T4: 0.2677	No disease activity during pregnancy
Flanagan et al. (2018) [57] Case series	5	VDZ 300 mg q8w	2 CD 3 UC	Age (mean): 32 (24–40) years	T4: GA 38–39	Time from last dose to delivery (days) (mean): 57.4 [25–98]	µg/mL T4: 9.90 [1.10–14.40]	Disease activity at some point during pregnancy (n): 2
Flanagan et al. (2020) [36] Prospective cohort study	17	VDZ 300 mg q8w N: 14 300 mg q4w N: 3	5 CD 12 UC	Age: 30.7 (27.8–33.5) years Weight: 67.0 (58.0–81.0) kg	T4: GA 38.5 (38–39)	Obtained at steady state GA at last dose: median 30	µg/mL T1: 19.0 (13.0–23.0) N_{OBS}: 5 T2: 15.1 (8.6–21.7) N_{OBS}: 16 T3: 9.5 (3.7–20.0) N_{OBS}: 9 T4: 5.5 (1.1–9.9) N_{OBS}: 2	Disease activity during pregnancy according to PGA (n): 6
Julsgaard et al. (2018) [55] Case report	2	VDZ Patient 1: 300 mg q8w Patient 2: 300 mg q4w/q8w	Patient 1: UC Patient 2: CD	–	Patient 1: T4: GA 38 Patient 2: T4: GA 39	GA at last dose Patient 1: 28 Patient 2: 34	µg/mL Patient 1, T4: 1.94 Patient 2, T4: 7.37	No disease activity during pregnancy
Mitrova et al. (2021) [58] Prospective observational study	24	VDZ	9 CD 7 UC	Age: 31 (28–35) years	T4: GA 39 (38–41)	GA at last dose: 32.5 (28–35.5)	µg/mL T4: 7.3 (2.9–17.8) N_{OBS}: 16	Disease activity at some point during pregnancy (n): 2

Table 2 (continued)

Authors (year) [reference] Study design	Population	Medication Dose and interval	Condition	Age (years) and weight (kg)	GA (weeks)	Sample information	Serum concentration	Disease activity
Mitrova et al. (2022) [59] Prospective multicenter study	37 (39 pregnancies)	VDZ Dose unknown	19 CD 20 UC	Age: 29.5 (26–34) years	T4: median GA 39 (18–38)	GA at last dose: 32 (18–38)	μg/mL T4: 7.4 (2.9–18.6) N_{OBS}: 23	Disease activity in 23% of all patients
Prentice et al. (2023) [56] Congress abstract	97*	VDZ	IBD	Age: 31 (29–34)*	T4: GA 39 $(34–41^{+1})$	GA at last dose: 31^{+2} $(29–33^{+2})$	μg/mL T0: 20.5 (8.8–25.7) N_{OBS}: 6 T1: 17 (9.2–24) N_{OBS}: 27 T2: 13.5 (9.1–18.2) N_{OBS}: 50 T3: 9.8 (6.5–17) N_{OBS}: 36 T4: 8.5 (3.0–14.0) N_{OBS}: 45 T5: 13.7 (12.5–14.3) N_{OBS}: 4	Clinical and biochemical disease remission was maintained in the majority of patients

The data are presented as mean (SD), median (IQR), or median [range]. Data are ordered by alphabetical order of the pharmaceutical, followed by alphabetical order of author

Trimesters of pregnancy are defined as follows: T1, week 1–12; T2, week 13–26; T3, week 27–end of pregnancy. Other periods are defined as follows: T0, up to 1 year before pregnancy; T4, during delivery; T5, up to 6 months after delivery.

*– Not reported, ADL adalimumab, aHUS atypical hemolytic uremic syndrome, AOSD adult-onset Still's disease, APS antiphospholipid syndrome, axSpA/AS axial spondyloarthritis/ankylosing spondylitis, BMI body mass index, CAN canakinumab, CAPS cryopyrin-associated periodic syndrome, CD Crohn's disease, CDAI clinical disease activity index, CL clearance, COVID-19 coronavirus disease 2019, CZP certolizumab pegol, DAS28-ESR Disease Activity Score 28-erythrocyte sedimentation rate, ECU eculizumab, EDSS expanded disability status scale, FMF familial mediterranean fever, GA gestational age, GOL golimumab, GW gestational week, HBI Harvey-Bradshaw Index, IBD inflammatory bowel disease, IFX infliximab, IQR intra-quartile range, iv intravenous, MKD mevalonate kinase deficiency, MS multiple sclerosis, NAT natalizumab, OBS observations, OMA omalizumab, PA psoriatic arthritis, PGA Physician Global Assessment, PNH paroxysmal nocturnal hemoglobinuria, qxw (i.e. q1w/q2w/etc.) (dose) once a week / once every two weeks / etc., RA rheumatoid arthritis, sc subcutaneous, SCCAI Simple Clinical Colitis Activity Index, SD standard deviation, SJIA systemic juvenile idiopathic arthritis, T0 pre-pregnancy, T1 trimester 1, T2 trimester 2, T3 trimester 3, T4 during delivery, T5 postpartum, TCZ tocilizumab, UC ulcerative colitis, UST ustekinumab, Vd volume of distribution, VDZ vedolizumab, wx (i.e. w6, w10, etc.) week number

*Data represent a larger population than the patients of interest for this review. This is because of the lack of individual patient information. For the study of Bortlik et al. [33], indication, disease activity per trimester, and maternal age were based on all participants in the study (using either ADL or IFX [n = 41]), and the GA at T4 is based on all newborns in the study (n = 41). For the study of Julsgaard et al. [35], the condition, maternal age, weight, and GA of the patients were only reported over all patients (using either ADL or IFX) in the study. For the study of Flanagan et al. [36] on ADL, the median GA at T4 was calculated over patients using either ADL or IFX (n = 38). For the study of Burwick et al. [48], the maternal age and BMI are based on all participants in the study (n = 8), and the GA at T4 are based on all participants in the study that were included during pregnancy (n = 6). For the study of Prentice et al. [56], the patient population and maternal age are based on all participants in the study, using either UST or VDZ

#Indicates that concentration–time data points were extracted from graphs from the original paper

Table 3 Summary of the study design with dose advice and conclusions

Authors (year) [reference] Study design	Medication Population	Inclusion criteria	Dose advice	Paper conclusions	Analytical methods (detection limit)	Remarks
Bortlik et al. (2013) [33] Prospective cohort study	ADL N_{total}: 5	IBD patients treated with IFX or ADL during pregnancy	NR	Use of anti-TNFα agents during pregnancy is considered safe and effective	ELISA (LLOQ: 30 ng/mL)	Three of five patients had undetectable ADL levels
Flanagan et al. (2020) [36] Prospective cohort study	ADL N_{total}: 15	Women with a confirmed diagnosis of IBD who were either planning a pregnancy or were pregnant and on IFX, ADL or VDZ	NR	Altered clearance profiles of biologicals used during pregnancy, differ per drug. ADL levels remain stable in pregnancy	ELISA (LLOQ: 30 ng/mL)	T0: up to 12 months T5: up to 6 months
Julsgaard et al. (2013) [34] Case report	ADL N_{total}: 1	NR	Treatment with ADL should be discontinued, if possible, later in the second or early in the third trimester to reduce maternal–fetal transfer	ADL crosses the placenta and is detectable in umbilical cord serum at time of birth, despite discontinuation of ADL therapy 21.5 weeks prior to delivery	ELISA	NR
Julsgaard et al. (2016) [35] Prospective cohort study	ADL N_{total}: 36	Patients with IBD that used ADL or IFX during pregnancy. Only singleton pregnancies were included	NR	Clearance of IFX in infants that were exposed during pregnancy was slower than previously reported, whereas clearance of ADL was more rapid	ELISA (LLOQ: 0.03 µg/mL)	There was a statistically significant inverse correlation between the duration since last exposure and maternal serum concentrations
Kanis et al. (2018) [38] Prospective cohort study	ADL N_{total}: 58	IBD patients treated with ADL or IFX during pregnancy	NR	NR	ELISA (LLOQ 0.04 µg/mL*)	79% of the patients had the standard ADL dose
Labetoulle et al. (2019) [37] Case report	ADL N_{total}: 1	NR	NR	NR	NR	Flare in first trimester whereafter first serum level is measured, after dosage increase until clinical stable second serum level measurement
Mahadevan et al. (2013) [11] Prospective cohort study	ADL N_{total}: 10	IBD patients treated with IFX, ADL, or CZP during pregnancy	The authors advise minimizing or avoiding ADL use within 4–8 weeks of delivery	ADL can be safely used through conception, T1, and T2 on schedule. Slow clearance of ADL during T5, however, raises concerns about its use during T3	ELISA (LLOQ: 3.13 ng/mL)	NR

Table 3 (continued)

Authors (year) [reference] Study design	Medication Population	Inclusion criteria	Dose advice	Paper conclusions	Analytical methods (detection limit)	Remarks
Seow et al. (2017) [29] Prospective cohort study	ADL N_{total}: 10 (11 pregnancies)	Patients attending the IBD pregnancy clinic who were treated with IFX or ADL were prospectively enrolled if they became pregnant in the study period	Anti-TNF drug levels may be targeted to the lower end of the therapeutic range in the T0 period in patients who are in stable remission, to be rechecked at T2, and then a decision to provide a T3 dose to be made accordingly, with resumption of scheduled dosing in T5	ADL levels remained stable during pregnancy after accounting for changes in albumin, BMI, and CRP	ELISA (LLOQ: 1.6 µg/mL)	IQR values of all periods were extracted via WPD T0: up to 12 months T5: up to 6 months
Mahadevan et al. (2013) [11] Prospective cohort study	CZP N_{total}: 10	IBD patients treated with IFX, ADL, or CZP during pregnancy	NR	CZP can be safely used through conception, T1 and T2 on schedule. It has the lowest level of placental transfer, compared to ADL and IFX	ELISA (LLOQ: 0.41 µg/mL)	NR
Mariette et al. (2018) [76] Prospective cohort study	CZP N_{total}: 16	Women ≥ 30 weeks pregnant, under treatment of commercial CZP for a locally approved indication. Patients were required to receive a CZP dose within 35 days prior to delivery	NR	No to minimal placental transfer of CZP from mothers to infants occurs during T3	ELISA (LLOQ: 0.032 µg/mL)	NR
Morita et al. (2018) [40] Prospective cohort study	CZP N_{total}: 1	NR	NR	The unique structure of CZP limits its transfer to the fetus and breast milk	ELISA (LLOQ: 1 µg/mL)	Patient only started CZP in week 28 in pregnancy

Table 3 (continued)

Authors (year) [reference] Study design	Medication Population	Inclusion criteria	Dose advice	Paper conclusions	Analytical methods (detection limit)	Remarks
Burwick et al. (2022) [48] Case series	ECU N_{total}: 3	Hospitalized adults were eligible if they were ≥ 18 years of age and had confirmed SARS-CoV-2 infection presenting as severe COVID-19, as evidenced by symptomatic bilateral pulmonary infiltrates on chest imaging and supplemental oxygen requirement due to severe pneumonia, acute lung injury or acute respiratory distress syndrome	NR	The authors describe use of ECU to treat severe COVID-19 in a small series of pregnant adults	LC with MS/MS (LLOQ: 5.00 μg/mL)	Severe comorbidity
Duineveld et al. (2019) [49] Case report	ECU N_{total}: 1	NR	NR	Higher levels can be expected with increasing GA and higher drug levels in the mother	NR	NR
Gustavsen et al. (2017) [50] Case report	ECU N_{total}: 1	NR	NR	The authors suggest complement inhibition as a treatment option to safely prolong pregnancy without affecting the infant. In addition, they stress the importance of monitoring treatment effects of ECU	ELISA (LLOQ: NR)	All data were extracted via WPD
Servais et al. (2016) [52] Case series	ECU N_{total}: 1	aHUS patients treated with ECU (serum levels were reported in only 1 patient)	NR	ECU therapy displayed no overt safety issues but did not appear to prevent adverse outcomes in the observed pregnancies	NR	Data at T3 and T5 were extracted via WPD

Table 3 (continued)

Authors (year) [reference] Study design	Medication Population	Inclusion criteria	Dose advice	Paper conclusions	Analytical methods (detection limit)	Remarks
Sharma et al. (2015) [51] Case report	ECU N_{total}: 1	NR	NR	The authors highlight that breakthrough hemolysis can occur early in gestation, that pregnant patients with PNH require close monitoring and that ECU can be safely used throughout pregnancy	ELISA (NR)	NR
Benoit et al. (2019) [42] Case report	GOL N_{total}: 1	NR	NR	The reporters demonstrated that GOL was detectable in the fetal circulation after prolonged exposure, with a significant accumulation	NR	NR
Bortlik et al. (2013) [33] Prospective cohort study	IFX N_{total}: 41	Women with IBD exposed to ADL or IFX during pregnancy	The authors recommend discontinuing treatment at the end of T2 or early T3 to minimize the exposure of IFX and ADL to the child	NR	ELISA (LLOD: 0.3 ng/mL)	One patient switch interval from q8w to q6w from GA 18 until 30
Eliesen et al. (2020) [12] Prospective cohort study	IFX N_{total}: 3	Women with autoimmune diseases exposed to IFX during pregnancy	NR	NR	ELISA (NR)	NR
Flanagan et al. (2020) [36] Prospective cohort study	IFX N_{total}: 17	Women with IBD exposed to IFX during pregnancy	Intrapartum dosing adjustments are not indicated	A small significant increase in IFX levels per gestational week of 0.16 (95% CI 0.08–0.24) µg/mL was observed ($p < 0.001$)	ELISA (LLOD: 100 ng/mL) [77]	Via Endnote retrieved T0: up to 12 months T5: up to 6 months
Grišić et al. (2020) [44] Retrospective cohort study	IFX N_{total}: 19	Women with IBD exposed to IFX during pregnancy	If desired, it is necessary to continue the IFX therapy in late T2 or early T3 to maintain a constant maternal IFX concentration until the end of the pregnancy	A significant increase in IFX maternal levels was shown in T2 compared to T0 ($p = 0.003$) and T1 ($p = 0.04$)	TRFIA (LLOD: 0.1 µg/mL)	NR

Table 3 (continued)

Authors (year) [reference] Study design	Medication Population	Inclusion criteria	Dose advice	Paper conclusions	Analytical methods (detection limit)	Remarks
Julsgaard et al. (2016) [35] Prospective cohort study	IFX N_{total}: 44	Patients with IBD that used ADL or IFX during pregnancy. Only singleton pregnancies were included	NR	Clearance of IFX in infants that were exposed during pregnancy was slower than previously reported, whereas clearance of ADL was more rapid	ELISA (LLOQ: 0.02 µg/mL)	There was a statistically significant inverse correlation between the duration since last exposure and maternal serum concentrations
Kane et al. (2009) [43] Prospective cohort study	IFX N_{total}: 3	NR	NR	NR	ELISA (LLOD: 0.10 µg/mL)	Patient 1 received GA: 0, 2, and 6 a dose IFX, after that continued q8w T5: NR
Kanis et al. (2018) [38] Prospective cohort study	IFX N_{total}: 73	IBD patients treated with ADL or IFX during pregnancy	NR	NR	ELISA (LLOQ 0.04 µg/mL)	67% of the patients had the standard IFX dose
Mahadevan et al. (2013) [11] Prospective cohort study	IFX N_{total}: 11	Women with CD exposed to IFX during pregnancy	Considerations to avoid IFX use 4–8 weeks before delivery to keep the placental transfer rate as low as possible. This advice is only applicable if the mother is in stable remission	NR	ELISA (LLOQ: 1.41 µg/mL)	NR
Seow et al. (2017) [29] Prospective cohort study	IFX N_{total}: 15	Patients attending the IBD pregnancy clinic who were treated with IFX or ADL were prospectively enrolled if they became pregnant in the study period	The authors suggest that anti-TNF levels can be targeted to the lower end of the therapeutic range during T0 in clinical stable patients. The regimen used in T0 should be continued in T5	There was an inverse relationship between IFX levels and CRP in CD ($p = 0.03$) After adjusting for albumin, BMI, and CRP, gestational age had a significant effect on the IFX concentrations with multivariate mixed modeling ($p = 0.02$)	Mobility shift assay (LLOD: 0.0074 µg/mL) [78]	The IQR of T5 were extracted via WPD
Steenholdt et al. (2011) [47] Retrospective case report	IFX N_{total}: 1	NR	IFX > 0.5 µg/mL is associated with maintained response in both CD and UC. They suggest this as a valid cut-off level for clinically relevant IFX concentrations	NR	Fluid-phase RIA (LLOD: 10 U/mL)	All data were extracted via WPD T5: 16 and 28 weeks after T4

Table 3 (continued)

Authors (year) [reference] Study design	Medication Population	Inclusion criteria	Dose advice	Paper conclusions	Analytical methods (detection limit)	Remarks
Vasilauskas et al. (2006) [14] Retrospective case report	IFX N_{total}: 1	NR	NR	NR	ELISA (NR)	NR
Vestergaard et al. (2017) [45] Case report	IFX N_{total}: 1	NR	NR	NR	ELISA (NR)	NR
Proschmann et al. (2021) [54] Prospective cohort study	NAT N_{total}: 11	Women diagnosed with remitted relapse multiple sclerosis with highly active disease course	NR	Authors confirm that NAT is transferred into human breastmilk in reassuringly low amounts. The observed alteration of drug levels during pregnancy are small and unlikely to be of clinically significance regarding efficacy.	FACS assay (LLOD: 14 ng/mL) [79]	All data were extracted via WPD T0: up to 6 months T5: up to 6 months
Toorop et al. (2022) [53] Case series	NAT N_{total}: 3	Patients with multiple sclerosis that used NAT during the entire pregnancy	NR	NAT concentrations can decrease during pregnancy; therefore, neurologists should be aware	Cross-linking essay	All data were extracted via WPD
Weber and Millet (2022) [60] Case series	CAN N_{total}: 7 (1 sample measurement)	NR	NR	Further studies needed to confirm safety of CAN during pregnancy	LC with MS (LLOQ 1 µg/mL)	NR
Saito et al. (2020) [61] Case report	OMA N_{total}: 1	NR	NR	Further study is encouraged to clarify mother-to-child transmission of OMA and the safety profile of the drug	NR	T3: 2 days before delivery
Tada et al. (2019) [13] Case report	TCZ N_{total}: 1	NR	NR	NR	ELISA (LLOD: 6 ng/mL)	NR
Moriyama et al. (2020) [39] Case report	TCZ N_{total}: 1	NR	NR	NR	ELISA (LLOD: 5 ng/mL) [80]	NR
Saito et al. (2018) [62] Case report	TCZ N_{total}: 2	NR	NR	NR	NR	All data were extracted via WPD T5: 13, 18, 22, 35, 44, and 49 weeks after delivery

Table 3 (continued)

Authors (year) [reference] Study design	Medication Population	Inclusion criteria	Dose advice	Paper conclusions	Analytical methods (detection limit)	Remarks
Saito et al. (2019) [63] Case report	TCZ N_{total}: 1	NR	NR	TCZ proved to be safe in a mother and her child during both pregnancy and breastfeeding	NR	NR
Saito et al. (2020) [64] Case report	TCZ N_{total}: 1	NR	NR	NR	ELISA (LLOD: 0.002 μg/mL)	An undetectable level of TCZ was measured at delivery (37 weeks of gestation); however, this measurement was not included in this study as the patient stopped TCZ therapy at 14 weeks of gestation T5: 3, 33, and 23 days after injection
Flanagan et al. (2021) [67] Observational study	UST N_{total}: 19	IBD patients treated with UST during pregnancy	NR	UST levels appear stable during pregnancy, suggesting that monitoring of levels in stable patients is not warranted. No new safety signals were reported	ELISA (LLOD: 0.04 μg/mL)	3 patients started in 2nd or 3rd trimester with first 390 mg iv and after that q8w
Klenske et al. (2019) [68] Case report	UST N_{total}: 1	NR	NR	Consistent with previous reports, the authors report elevated UST cord blood levels in comparison with the maternal drug level, as well as breast milk levels and serum trough levels in similar range	NR	NR
Mitrova et al. (2021) [58] Prospective observational study	UST N_{total}: 15	Women with IBD exposed to UST 2 months prior to conception or during pregnancy	NR	Between maternal UST levels and GA of last administration, there was a significant correlation ($\rho = 0.578$, $p = 0.02$)	ELISA (LLOQ: 0.4 μg/mL) [81]	NR

Table 3 (continued)

Authors (year) [reference] Study design	Medication Population	Inclusion criteria	Dose advice	Paper conclusions	Analytical methods (detection limit)	Remarks
Mitrova et al. (2022) [59] Prospective multicenter study	UST N_{total}: 37 (39 pregnancies)	IBD patients treated with UST or VDZ during pregnancy. Only singleton pregnancies were included	NR	The use of the new biologic UST seems to be safe. The pharmacokinetic pattern of UST seems similar to anti-TNF	ELISA (detection limits: 1.5–600 ng/mL)	Pharmacokinetic parameters were available in 26 infant–mother pairs exposed to UST
Prentice et al. (2023) [56] Congress abstract	UST N_{total}: 97	IBD patients treated with UST or VDZ during pregnancy	Proactive dose adjustment and level monitoring during pregnancy is not necessary	UST levels are stable over the course of pregnancy, while VDZ levels fall but without parallel increase of biochemical disease activity	ELISA (LLOQ: 0.4 μg/mL)	This study is published as a congress abstract
Rowan et al. (2018) [69] Case report	UST N_{total}: 1	NR	NR	UST levels remained stable throughout pregnancy, cord levels were nearly 2-fold higher than maternal serum levels	ELISA (detection limits: NR)	NR
Saito et al. (2022) [66] Case report	UST N_{total}: 1	NR	NR	NR	ELISA (LLOD: 1.0 ng/mL)	Treatment at GA: 5, 17, and 29. Continued again at 48 days postpartum
Sako et al. (2021) [65] Prospective cohort study	UST N_{total}: 1	Women diagnosed with CD, dosed with UST during and/or after 2nd trimester	NR	NR	ELISA (LLOD: 0.747 ng/mL)	NR
Flanagan et al. (2018) [57] Case report	VDZ N_{total}: 5	IBD patients treated with VDZ during pregnancy	NR	Placental transfer of VDZ may potentially be less than those documented with anti-TNFα agents	ELISA (LLOD: 2 μg/mL)	NR
Flanagan et al. (2020) [36] Prospective cohort study	VDZ N_{total}: 17	Women with IBD exposed to VDZ during pregnancy	Intrapartum dosing adjustments are not indicated	A small significant decrease in VDZ levels per gestational week of -0.18 (95% CI -0.33 to -0.02) μg/mL was observed ($p = 0.03$)	ELISA (LLOD: 2 and 0.25 μg/mL)	Pre-term < 37 weeks (n): 2 T0: up to 12 months T5: up to 6 months
Julsgaard et al. (2018) [55] Case report	VDZ N_{total}: 2	IBD patients treated with VDZ during pregnancy	NR	NR	ELISA (LLOD: 2 μg/mL)	NR

Table 3 (continued)

Authors (year) [reference] Study design	Medication Population	Inclusion criteria	Dose advice	Paper conclusions	Analytical methods (detection limit)	Remarks
Mitrova et al. (2021) [58] Prospective observational study	VDZ N_{total}: 16	Women with IBD exposed to VDZ 2 months prior to conception or during pregnancy	NR	Between maternal VDZ levels and GA of last administration, there was a significant correlation ($\rho = 0.751$, $p = 0.001$) Between maternal drug level and the interval between the last infusion and delivery, there was a significant correlation ($\rho = -0.917$, $p < 0.001$).	ELISA (LLOQ: 2 µg/mL) [81]	NR
Mitrova et al. (2022) [59] Prospective multicenter study	VDZ N_{total}: 49 (54 pregnancies)	IBD patients treated with UST or VDZ during pregnancy. Only singleton pregnancies were included	NR	The use of the new biologic VDZ seems to be safe. The pharmacokinetic pattern of VDZ differs from anti-TNF, as the levels at the time of delivery are higher in maternal blood than in cord blood	ELISA (detection limits: 5–600 ng/mL)	Pharmacokinetic parameters were available in 23 infant–mother pairs exposed to VDZ
Prentice et al. (2023) [56] Congress abstract	VDZ N_{total}: 97	IBD patients treated with UST or VDZ during pregnancy	Proactive dose adjustment and level monitoring during pregnancy is not necessary	UST levels are stable over the course of pregnancy, while VDZ levels fall but without parallel increase of biochemical disease activity	ELISA (LLOQ: 0.25 µg/mL)	This study is published as a congress abstract

ADL adalimumab, *aHUS* atypical hemolytic uremic syndrome, *BMI* body mass index, *CAN* canakinumab, *CD* Crohn's disease, *CI* confidence intervals, *COVID-19* coronavirus disease 2019, *CZP* certolizumab pegol, *ECU* eculizumab, *ELISA* enzyme-linked immunosorbent assay, *FACS* fluorescence-activated cell sorting, *GA* gestational age, *GOL* golimumab, *IBD* inflammatory bowel disease, *IFX* infliximab, *IQR* intra-quartile range, *iv* intravenous, *LC* liquid chromatography, *LLOD* lower limit of detection, *LLOQ* lower limit of quantification, *MS/MS* tandem mass spectrometry, *NAT* natalizumab, *NR* not reported, *OMA* omalizumab, *PNH* paroxysmal nocturnal hemoglobinuria, *qxw (i.e. q1w/q2w/etc.)* (dose) once every two weeks / etc., *RIA* radioimmunoassay, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *T0* pre-pregnancy, *T1* trimester 1, *T2* trimester 2, *T3* trimester 3, *T4* during delivery, *T5* postpartum, *TCZ* tocilizumab, *TNF* tumor necrosis factor, *TRFIA* time-resolved fluorescent immunoassay, *UC* ulcerative colitis, *UST* ustekinumab, *VDZ* vedolizumab, *WPD* web plot digitizer

ADL Concentration Over Time
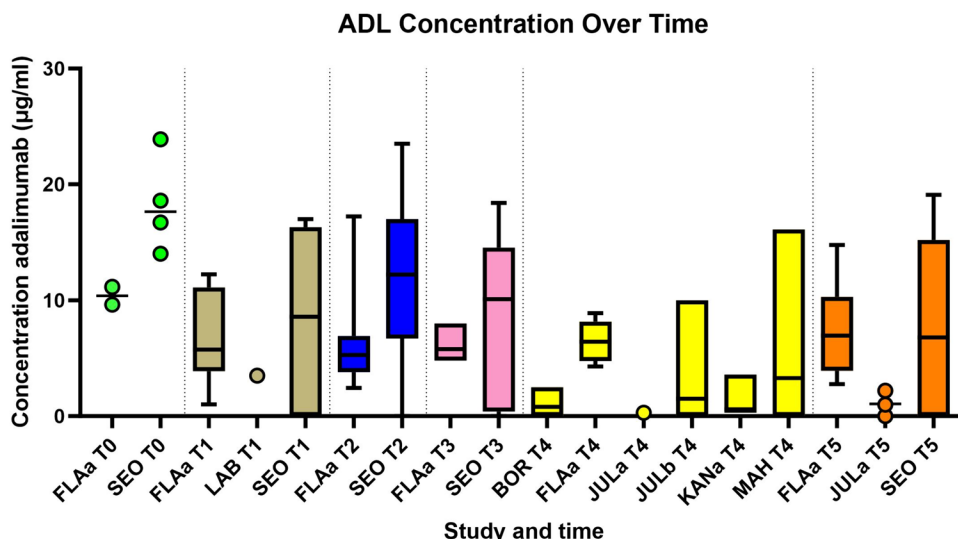
Fig. 2 The concentration of adalimumab (ADL) during different states of pregnancy. The concentration of ADL is expressed in μg/mL on the y-axis (median with corresponding IQR and range). The different states of pregnancy per study are shown on the x-axis. The different states of pregnancy are expressed as pre-pregnancy (T0), first trimester (T1), second trimester (T2), third trimester (T3), dur-ing delivery (T4), and postpartum (T5). *FLAa* stands for the study of Flanagan et al. (2020); *SEO* for Seow et al. (2017); *LAB* for Labetoulle et al. (2019); *BOR* for Bortlik et al. (2013); *JULa* for Julsgaard et al. (2013); *JULb* for Julsgaard et al. (2016); *KANa* for Kanis et al. (2018); and *MAH* for Mahadevan et al. (2013) [11, 29, 33–38]. *IQR* interquartile range

The first study found non-significant decreases of median ADL concentrations, as compared to the pre-pregnancy values, in all trimesters, at delivery, and postpartum of 45.2%, 50.0%, 44.2%, 35.6%, and 33.7%, respectively [36]. The second study also showed a non-significant decrease in median ADL concentrations in comparison with pre-pregnancy concentrations; first, second, third trimester, and postpartum concentrations showed decreases of 51.2%, 30.9%, 47.5%, and 58.0%, respectively [29]. Both studies used mixed effect modelling to conclude that, after accounting for covariates such as maternal body mass index (BMI), albumin, and C-reactive protein (CRP), ADL concentrations may remain consistent between trimesters one to three, but comparisons were not made to the non-pregnant states [29, 36]. Overall, median concentrations were not meaningfully different between the trimesters, and these authors agree with the assertion of consistency throughout pregnancy following a visual inspection of the individual plots and based on limited sample sizes to otherwise detect minor differences. The other six studies [11, 33–35, 37, 38] reported ADL concentrations at the first trimester, delivery, and/or non-pregnancy state (postpartum). When considering adapted dosing regimens based on the measured PK data, Flanagan et al. stated that routine therapeutic drug monitoring (TDM) or intrapartum dosing

CZP Concentration Over Time
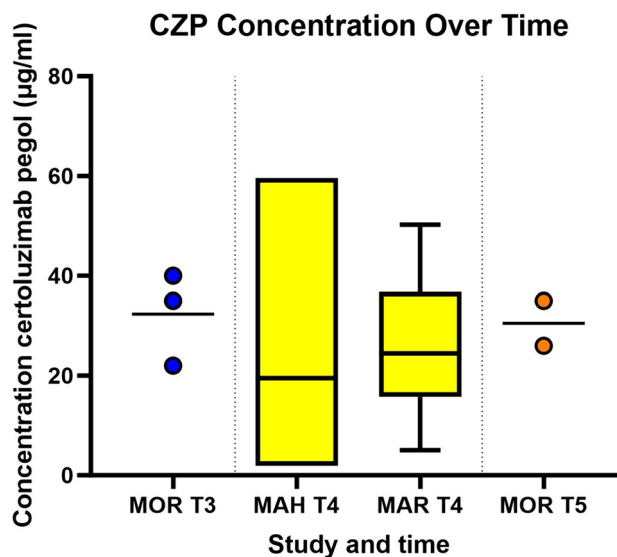
Fig. 3 The concentration of certolizumab pegol (CZP) during different states of pregnancy. The concentration of CZP is expressed in μg/mL on the y-axis (median with corresponding IQR and range). The different states of pregnancy per study are shown on the x-axis. The different states of pregnancy are expressed as third trimester (T3), during delivery (T4), and postpartum (T5). *MOR* stands for the study of Morita et al. (2018); *MAH* for Mahadevan et al. (2013); and *MAR* for Mariette et al. (2018) [11, 40, 76]. *IQR* interquartile range

adjustment are not indicated [36]. Seow et al. advised that TDM in the second trimester may be useful in guiding dosing in the third trimester [29]. None of the other studies reported PK-based dosing guidance for ADL during pregnancy.

In summary, available evidence suggests that ADL serum concentrations may be unaffected or modestly decreased during pregnancy, and may remain relatively stable throughout the three trimesters.

3.2.2 Certolizumab Pegol

Three studies were included reporting serum concentrations of CZP in pregnant women [11, 39, 40] (Tables 2, 3, Fig. 3). Concentrations at delivery were within the range of concentrations observed from a previous population PK analysis [41] in non-pregnant individuals based on the reported number of days since the last dose, and were mostly within the proposed therapeutic range [41] when the sample was collected up to 28 days after the last dose [41]. Within-individual comparisons to the non-pregnant state were not possible except for one study in a single Japanese patient [40], where concentrations were similar (albeit slightly slower) in the third trimester compared to postpartum.

In summary, there is not sufficient evidence to indicate that CZP serum concentrations may be meaningfully impacted by pregnancy.

3.2.3 Golimumab

One case report of Benoit et al. [42] reported that GOL was detectable in maternal plasma in one patient immediately after delivery (Tables 2, 3). The time since last dose was not reported to enable further interpretation.

3.2.4 Infliximab

In total, twelve studies were included in this systematic literature review reporting PK or exposure parameters of IFX in pregnant women [12, 14, 29, 33, 35, 36, 38, 43–47] (Tables 2, 3, Fig. 4). While IFX is typically dosed on an mg/kg basis, most studies specified a practice where the dose during pregnancy was not increased from the pre-pregnancy dose despite an increase in body weight.

In all studies reporting IFX serum concentrations in all six periods (pre-pregnancy, first, second, third trimester, at delivery and postpartum) [29, 36, 44], IFX serum concentrations generally increased during pregnancy compared to pre-pregnancy serum concentrations (Fig. 4). One of the studies [44] showed increases of 16.4% in the first trimester, 105.5% in the second trimester, and 78.1% in the third trimester. In another study [36], the serum concentrations increased by 11.4%, 26.6%, and 39.2% in the first, second, and third trimesters. The third study [29] showed the highest rise in concentration, with increases of 23.0%, 49.2%,
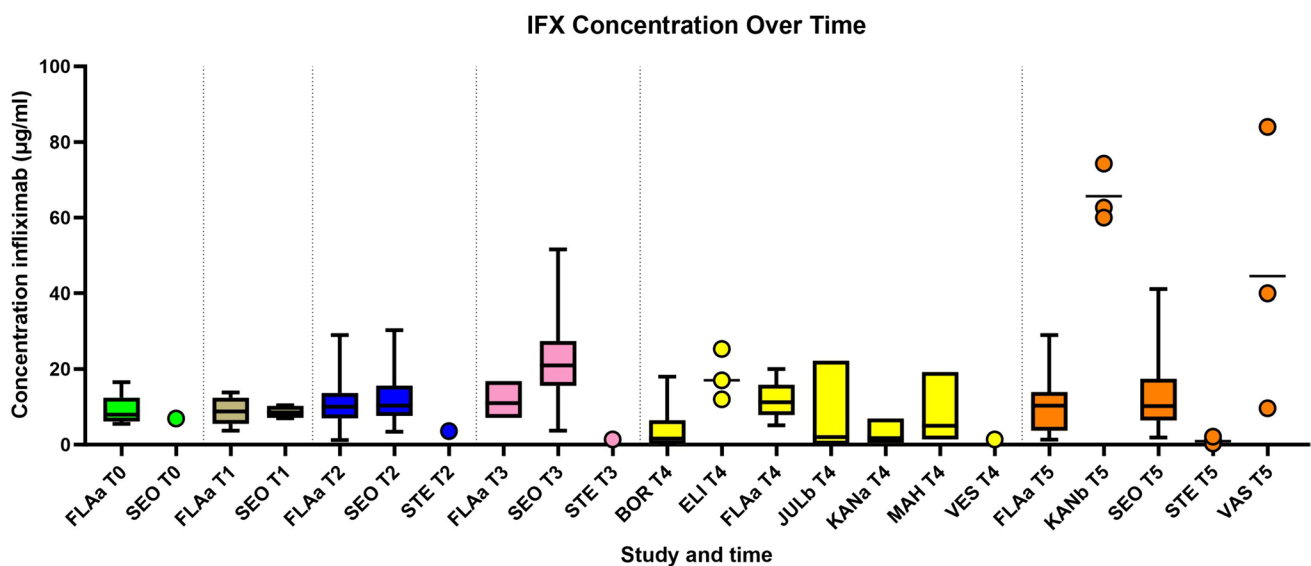
Fig. 4 The concentration of infliximab (IFX) during different states of pregnancy. The concentration of IFX is expressed in µg/mL on the *y*-axis (median with corresponding IQR and range). The different states of pregnancy per study are shown on the *x*-axis. The different states of pregnancy are expressed as pre-pregnancy (T0), first trimester (T1), second trimester (T2), third trimester (T3), during delivery (T4), and postpartum (T5). The different *colors* indicate the stages of pregnancy. *FLAa* stands for the study of Flanagan et al. (2020); *SEO* for Seow et al. (2017); *STE* for Steenholdt et al. (2011); *BOR* for Bortlik et al. (2013); *ELI* for Eliesen et al. (2020); *JULb for Julsgaard et al. (2016); KANa for Kanis et al. (2018); MAH* for Mahadevan et al. (2013); *VES for Vestergaard et al. (2017); KANb* for Kane et al. (2009); and *VAS* for Vasilauskas et al. (2006) [11, 12, 14, 29, 33, 35, 36, 38, 43, 45, 47]. *IQR* interquartile range

and 204.2% in the first, second, and third trimesters. In two studies, only postpartum concentrations were described and could not be compared to concentrations in other periods [14, 43]. In three studies, IFX concentrations at postpartum were compared to pre-conceptional concentration, showing a decrease of 19.2% [44] or increases of 30.4% and 50.1% [29, 36]. Other studies are case reports [14, 45, 47].

Only one study reported exposure parameters; Grišić et al. [44] used a population PK model to determine clearance (CL) (0.608 L/d) and volume of distribution (V_d) (18.2 L) of IFX, and reported an effect of −0.121 of second and third trimester state on CL [44]. However, the population PK model was constructed on only trough concentrations and only tested covariates (including possible effects of pregnancy) on CL; possible effects of pregnancy on V_d were not evaluated.

In light of a small significant increase in IFX serum concentrations during the second and third trimesters [36, 44], some commentaries on the use of TDM or the need for dosing adjustments have emerged. One study stated that antenatal dosing adjustments are not needed [36]. Another study adds that TDM can assist in regulating constant maternal IFX concentrations during pregnancy, in the hopes of minimizing IFX exposure for the fetus [44]. Other studies suggest discontinuation of treatments around the third trimester to minimize placental transfer [11, 33]. One study advised that IFX serum concentrations could be targeted to the lower end of the therapeutic range (e.g., 3 μg/mL) during the pre-pregnancy phase and postpartum phase, and measuring serum concentrations in the second trimester may help to decide whether to give a dose in the third trimester [29].

Overall, available evidence shows that IFX serum concentrations generally increase throughout pregnancy. Considerations for the use of TDM to maintain constant exposures throughout pregnancy are emerging.

3.3 Complement Inhibitor

3.3.1 Eculizumab

Five studies were included reporting serum concentrations of ECU in pregnant women [48–52] (Tables 2, 3).

In women with coronavirus disease 2019 (COVID-19) (ranging from 25 weeks gestation until day 1 of the postpartum period), mean ± standard deviation ECU concentrations at 1 h following an intravenous dose of 1200 mg were 321 ± 13 μg/mL, and trough concentrations approximately 3 days after dosing were not below the proposed therapeutic range (> 116 μg/mL) (150 μg/mL and 160 μg/mL) [48]. Substantial concentrations were reported in one mother who received eculizumab 1200 mg intravenously for treatment of atypical hemolytic uremic syndrome 26

h prior to delivery [49]. In another mother receiving 1200 mg of ECU in different dosing regimens (every week up to every 3 weeks), substantially higher levels were measured after pregnancy when compared to during pregnancy [52]. At delivery, 1 day after an additional dose of 1500 mg, a level of 1589 μg/mL was measured. One woman continuously treated with ECU 900 mg every 2 weeks for paroxysmal nocturnal hemoglobinuria experienced breakthrough hemolysis at approximately week 30 of her pregnancy, and required re-induction and an increased maintenance dose (up to 1200 mg every 2 weeks) [51]. Concentrations before dose adjustment were < 11 μg/mL, and therapeutic concentrations were restored following the dose increase [51]. After her pregnancy, the dose was returned to 900 mg every 2 weeks and the condition was reported as stable. Another study reported complexed ECU-C5 concentrations following 600-mg doses for treatment of antiphospholipid syndrome as detectable and well-tolerated [50]. Interpretation of complexed concentrations is limited. None of the studies report any evidence-based dosing advice or PK-related conclusions.

In summary, very limited evidence from case reports suggests that ECU serum concentrations may be unaffected or modestly decreased during pregnancy. One case of breakthrough hemolysis requiring dose adjustment is of interest [51].

3.4 Anti-integrin

3.4.1 Natalizumab

Two studies were included reporting serum concentrations of NAT in pregnant women [53, 54] (Tables 2, 3, Fig. 5).

The first study, reviewing 11 patients, reported a nonsignificant trend for decreases of 14.6%, 30.9%, 50%, and 55.3% in the first, second, and third trimesters and at delivery, respectively, compared to the pre-pregnancy state [54]. The second study reviewing three patients reported similar progressive decreases of 4.7%, 39.0%, and 61.6% in the first, second, and third trimesters, respectively, when compared to the pre-pregnancy state. Concentrations returned to normal pre-pregnancy levels in the postpartum period (approximately 3–6 months after delivery). Despite reductions in trough concentrations during pregnancy, multiple sclerosis disease activity remained stable for these patients with no dose adjustment. Proschmann et al. [54] suggest that there may be pregnancy-related changes that marginally increase NAT clearance and that measurements of serum concentration across pregnancy are not required. Toorop et al. [53] stated that professionals should be aware of the possibility of NAT concentrations decreasing during pregnancy. None of the women who received

Fig. 5 The concentration of natalizumab (NAT) during different stages of pregnancy. The concentration of NAT is expressed in μg/mL on the *y*-axis (median with corresponding IQR and range). The different states of pregnancy per study are shown on the *x*-axis. The different states of pregnancy are expressed as pre-pregnancy (T0), first trimester (T1), second trimester (T2), third trimester (T3), during delivery (T4), and postpartum (T5). *PRO* stands for the study of Proschmann et al. (2021) and *TOO* for Toorop et al. (2022) [53, 54]. *IQR* interquartile range
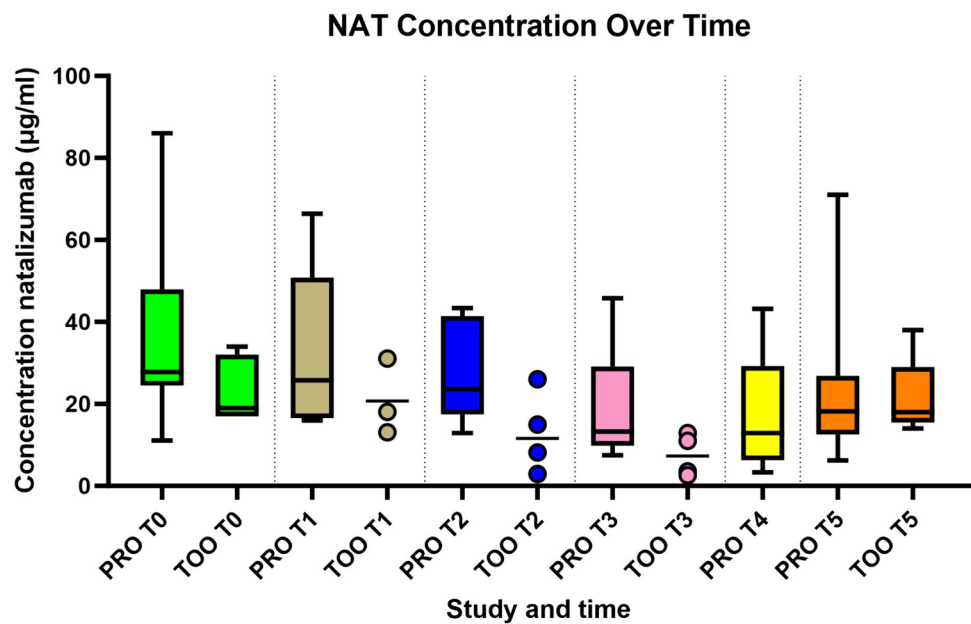
Fig. 6 The concentration of vedolizumab (VDZ) during different stages of pregnancy. The concentration of VDZ is expressed in μg/mL on the *y*-axis (median with corresponding IQR and range). The different states of pregnancy per study are shown on the *x*-axis. The different states of pregnancy are expressed as pre-pregnancy (T0), first trimester (T1), second trimester (T2), third trimester (T3), during delivery (T4), and postpartum (T5). *FLAa* stands for the study of Flanagan et al. (2020); *FLAc* for Flanagan et al. (2018); *JULc* for Julsgaard et al. (2018); *MITa* for Mitrova et al. (2021); *MITb* for Mitrova et al. (2022); and *PRE* for Prentice et al. (2023) [36, 55–59]. *IQR* interquartile range
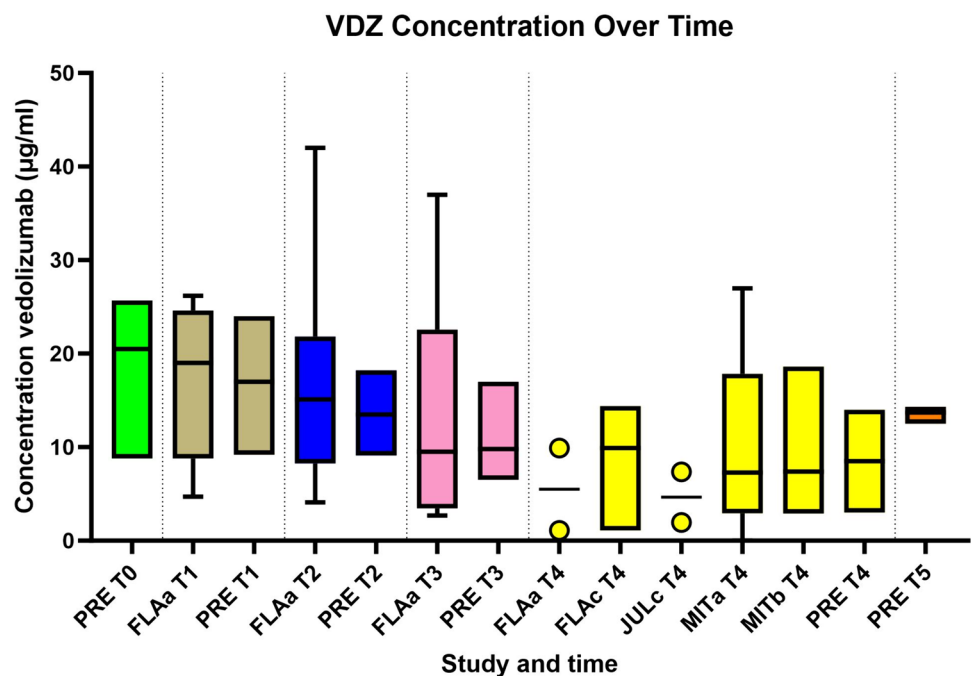
NAT suffered from relapse during gestation, indicating that the disease remained stable during pregnancy.

In summary, NAT concentration may modestly decrease during pregnancy, with return to pre-pregnancy concentrations in the postpartum period.

3.4.2 Vedolizumab

Six studies reporting serum concentrations of VDZ in pregnant women were included [36, 55–59] (Tables 2, 3, Fig. 6).

Most PK information was available from Prentice et al. [56] and Flanagan et al. [36]. Data on the non-pregnancy state for comparison with the pregnancy period were exclusively available from Prentice et al. [56], reporting 20.5 μg/mL and 13.7 μg/mL for the pre-pregnancy and postpartum periods, respectively. For Prentice et al. [56], the concentrations during pregnancy progressively decreased as compared with the pre-pregnancy state, with reductions up to 58.5% at delivery. For Flanagan et al. [36], similar results were reported with reductions up to 71.1% at delivery. The

concentration of VDZ at time of delivery was similar in most studies, with medians ranging from 4.7 to 9.9 µg/mL. When focusing on evidence-based dosing regimens, Flanagan et al. [36] stated that, while a small significant decrease in VDZ serum concentrations per period was observed, no antenatal dosing adjustments were indicated.

In summary, serum concentrations of VDZ seem to progressively decrease during pregnancy. However, one study suggested that no dose adjustments were indicated [36].

3.5 Interleukin-1 Inhibitor

3.5.1 Canakinumab

One case series of Weber and Millet [60] reported that CAN was detectable in maternal plasma in one patient immediately after delivery (Tables 2, 3). The time since last dose was not reported to enable further interpretation.

3.6 Interleukin-5 Inhibitor

3.6.1 Omalizumab

One case report of Saito et al. [61] reported two OMA concentrations, obtained during the third trimester and at delivery, with a 2-day interval between samplings. Both measurements were acquired 10 weeks subsequent to the last administration of a 150-mg subcutaneous monthly dose. Considering PK behavior of OMA [61], the authors considered the observed maternal serum concentration at delivery (3239.9 ng/mL) to be within an acceptable range.

3.7 Interleukin-6 Inhibitor

3.7.1 Tocilizumab

Five studies reporting serum concentrations of TCZ in pregnant women were included [13, 39, 62–64] (Tables 2, 3).

In the paper of Tada et al. [13], the TCZ concentration was documented twice during the third trimester 1 week apart (16.20 and 6.17 µg/mL). Moriyama et al. [39] reported a TCZ concentration of 13.30 µg/mL at delivery. Saito et al. published three case reports, of which two reported TCZ concentrations exclusively during the postpartum period [62, 64], with medians of 9.8 µg/mL and 3.9 µg/mL. The third case report of Saito et al. [63] reported five TCZ concentrations observed during various periods, ranging from 3.24 to 57.65 µg/mL.

Overall, little information is available to form a conclusion about the possible effects of pregnancy on the PK of TCZ.

UST Concentration Over Time
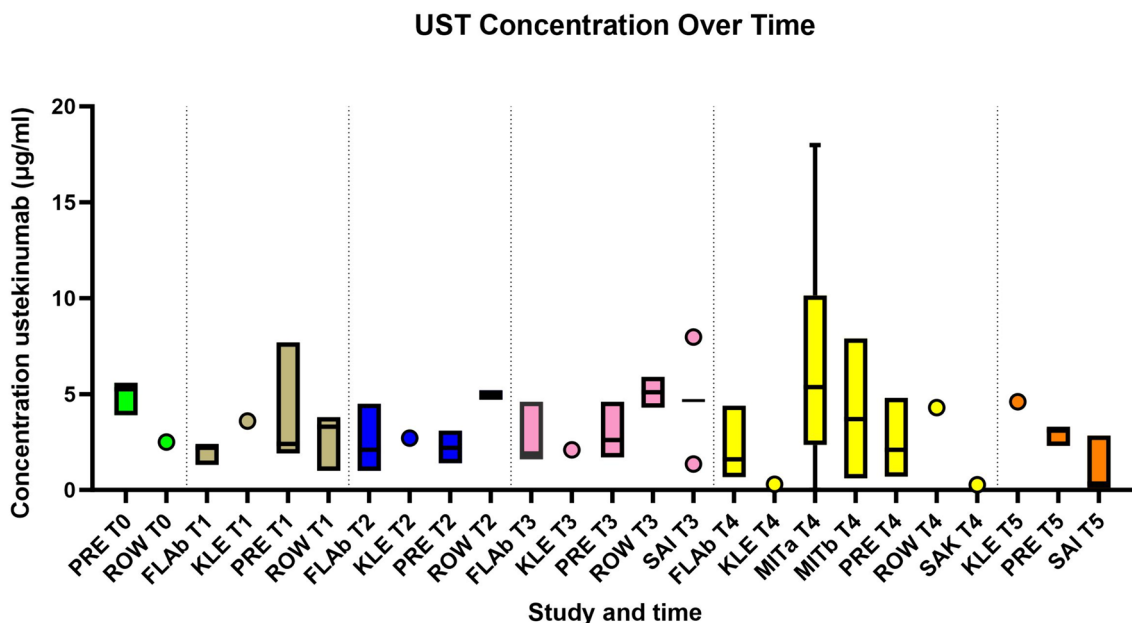
Fig. 7 The concentration of ustekinumab (UST) during different stages of pregnancy. The concentration of UST is expressed in µg/mL on the *y*-axis (median with corresponding IQR and range). The different states of pregnancy per study are shown on the *x*-axis. The different states of pregnancy are expressed as pre-pregnancy (T0), first trimester (T1), second trimester (T2), third trimester (T3), during delivery (T4), and postpartum (T5). *FLAb* stands for the study of Flanagan et al. (2021); *KLE* for Klenske et al. (2019); *MITa* for Mitrova et al. (2021); *MITb* for Mitrova et al. (2022); *PRE* for Prentice et al. (2023); *ROW* for Rowan et al. (2018); *SAI* for Saito et al. (2022); and *SAK* for Sako et al. (2021) [56, 58, 59, 65–69]. *IQR* interquartile range

3.8 Interleukin-23 Inhibitor

3.8.1 Ustekinumab

In total, eight studies reported on serum concentrations of UST in pregnant women [56, 58, 59, 65–69] (Tables 2, 3, Fig. 7). Two studies [56, 67] reported concentration of UST during first, second, and third trimesters, demonstrating that UST concentrations remained relatively stable during pregnancy. Klenske et al. [68] and Rowan et al. [69] also reported sparse measurements of UST concentrations during pregnancy, with variable results. Three other studies reported median UST concentrations exclusively at delivery [58, 59, 65]. Over all studies, the median UST concentration at delivery ranged from 0.27 to 5.3 μg/mL. Interpretation of concentrations at delivery is difficult because the dosage regimens are variable or not clearly reported, but the concentrations would generally fall within a proposed therapeutic range (> 1.1 μg/mL) [70].

In summary, evidence largely formed from two studies [56, 67] suggests that UST concentrations remain relatively stable during pregnancy.

4 Discussion

Overall, available information suggests that the anatomical and physiological changes throughout pregnancy may have meaningful effects on the PK of mAbs. For all of the assessed mAbs, except IFX, serum concentrations were similar or decreased during pregnancy. For only IFX, serum concentrations generally increased throughout pregnancy. Therefore, for most mAbs (except IFX), modestly higher dosing (per mg) may be needed during pregnancy to sustain a similar serum exposure compared to pre-pregnancy. Cases of poor disease control during pregnancy with undetectable mAb concentration have been documented in the literature [48]. While these general trends are observed, any risk–benefit considerations to modestly increase a flat dose in pregnant women should consider the unique properties, pharmacology, and the safety profile of the mAb, as well as the individual patient characteristics.

The findings of decreased concentrations in pregnancy for most mAbs are consistent with the general understanding of the anatomical and physiological changes that occur in pregnancy. Blood volume increases by 40%, potentially diluting serum concentrations [21]. Total volume of distribution (L) may also increase along with increasing pregnant body weight. However, mAbs have relatively restricted distribution into the placenta and any additional increase in volume of distribution would be less than proportional to the increase in total body weight. Sizes of major eliminating organs (such as the liver, skin, and muscle) of the maternal body are increased [23, 26]. Maternal muscle that increases in pregnancy includes uterine smooth muscle, placental smooth muscle, abdominal muscle, and other muscle groups in arms and legs that increase in mass slightly along with increased pregnant weight [27]. There is no evidence that systemic FcRn increases or decreases throughout pregnancy. Indeed, any meaningful effects of altered expression or availability of FcRn would be expected to affect endogenous plasma proteins that bind to FcRn (e.g., IgG, albumin) in the same way – dramatic changes in which are not observed in pregnancy [42].

IFX is the mAb with the greatest amount of PK data available from pregnant women [11, 12, 14, 29, 33, 35, 36, 38, 43–45, 47], yet is an apparent anomaly among all other mAbs with available data. Twelve PK studies have been performed during pregnancy showing a general increase in serum concentrations. Reduced target-mediated drug disposition (TMDD) clearance of IFX has been proposed as the physiological driver of this observation; however, a dissimilar finding for ADL almost rules out this proposed impact of target or disease characteristics [23, 36].

It has to be noted that when deciding to study the PK of drugs in pregnant women it is difficult to recruit pregnant women and that there are many ethical issues around their inclusion in clinical trials. Therefore, all studies currently performed are with limited samples, both in terms of the number of patients and the inconsistent post-dose sampling times. To obtain formal PK parameters, dense blood sampling is often required or a large population for population-PK modelling. Physiologically based pharmacokinetic (PBPK) modelling can be an attractive tool to make use of existing PK data from sparse or variable sources. Limited data collected could be confirmatory to the mechanistic hypotheses, rather than purely exploratory. One PBPK modeling paper for three mAbs (IFX, ADL, and golimumab) in pregnant women was identified following submission of this manuscript [71]. The drug-specific rates of cellular uptake in pregnancy were optimized to observed PK data from the third trimester (kup, kupp). As such, the models are not considered to have mechanistically captured the changes in mAb PK that occur throughout pregnancy because any unexplained differences after updating the structural compartments were attributed to these optimized constants. The optimized models were used to estimate the optimal timing of the last dose prior to delivery to ensure that mAb concentrations did not fall below therapeutic levels [71].

A limitation when using the serum/plasma PK concentrations of mAbs in pregnant women for dose adjustment or TDM is that they may not be appropriately representative of tissue concentrations or PD effects. Future evidence-based dosing recommendations should also consider maternal PD information and disease control when available.

Finally, this systematic literature review is limited to PK in pregnant women, without including additional PK or safety data on the fetus. It is known that all tumor necrosis factor (TNF)-α mAbs, except CZP, cross the placenta by the Fc receptor [1, 72]. Large studies showed a low risk, no increase in the rate of congenital abnormalities, adverse pregnancy outcomes, or neonatal infections out to 1 year of life of anti-TNF use in pregnancy [46]. Also, for other non-TNFα mAbs used in autoimmune diseases, such as NAT, VDZ, UST, GOL, ECU, and TCZ, which all crossed the placenta, no increased risk of adverse events in both mother and infant is reported [1, 73–75]. Second, maternal clinical endpoints (PD parameters) are not addressed within our systematic literature review.

5 Conclusions

We performed a systematic literature review on the PK of mAbs in pregnant women receiving therapy for various indications. In general, no PK parameters except serum concentrations were reported. Pregnancy-related physiological and anatomical changes could influence the PK of mAbs. Overall, we conclude that a modest increase in the flat dose, expressed in mg, may be needed to obtain the same serum concentrations compared to the pre-pregnancy state and thereby to achieve target concentrations. Our study clearly shows the knowledge gap with regard to PK of mAbs during pregnancy and encourages future researchers to collect PK data from mAbs in pregnant women, so that evidence-based dosing regimens may be generated.

Declarations

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