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SYSTEMATIC REVIEW

The Pharmacokinetics and Target Attainment of Antimicrobial Drugs Throughout Pregnancy: Part III Non-penicillin and Non-cephalosporin Drugs

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Abstract

Introduction Understanding the pharmacokinetics (PK) of antimicrobial drugs in pregnant women is crucial to provide effective and safe treatment. This study is part of a series that systematically reviews literature on the PK and analyzes if, based on the changed PK, evidence-based dosing regimens have been developed for adequate target attainment in pregnant women. This part focusses on antimicrobials other than penicillins and cephalosporins.

Methods A literature search was conducted in PubMed according to the PRISMA guidelines. Search strategy, study selection, and data extraction were independently performed by two investigators. Studies were labeled as relevant when information on the PK of antimicrobial drugs in pregnant women was available. Extracted parameters included bioavailability for oral drugs, volume of distribution (Vd) and clearance (CL), trough and peak drug concentrations, time of maximum concentration, area under the curve and half-life, probability of target attainment, and minimal inhibitory concentration (MIC). In addition, if developed, evidence-based dosing regimens were also extracted.

Results Of the 62 antimicrobials included in the search strategy, concentrations or PK data during pregnancy of 18 drugs were reported. Twenty-nine studies were included, of which three discussed aminoglycosides, one carbapenem, six quinolones, four glycopeptides, two rifamycines, one sulfonamide, five tuberculostatic drugs, and six others. Eleven out of 29 studies included information on both Vd and CL. For linezolid, gentamicin, tobramycin, and moxifloxacin, altered PK throughout pregnancy, especially in second and third trimester, has been reported. However, no target attainment was studied and no evidence-based dosing developed. On the other hand, the ability to reach adequate targets was assessed for vancomycin, clindamycin, rifampicin, rifapentine, ethambutol, pyrazinamide, and isoniazid. For the first six mentioned drugs, no dosage adaptations during pregnancy seem to be needed. Studies on isoniazid provide contradictory results.

Conclusion This systematic literature review shows that a very limited number of studies have been performed on the PK of antimicrobials drugs—other than cephalosporins and penicillins—in pregnant women.

1 Introduction

Because of several mechanistic and pathophysiological changes (e.g., decrease in respiratory volumes and urinary stasis due to an enlarging uterus), pregnant women could be more severely affected by bacterial infections than non-pregnant women [1]. Immunologic alterations during pregnancy may help to explain the altered severity of and susceptibility to infectious diseases during pregnancy. As pregnancy progresses, hormone levels change dramatically. Estradiol can enhance several aspects of the innate immunity and both cell-mediated and humoral adaptive immune response. Progesterone can suppress the maternal immune response and alter the balance between T-helper (Th)1 and Th2 cell response [2]. It is estimated that during pregnancy, one third of pregnant women receive an anti-microbial drug [3]. Because of risk for the fetus, it is important that infections are adequately treated at an early stage to prevent complications [1].

The anatomical and physiological changes that occur during pregnancy comprise a decrease in intestinal motility, an increase in total body water and an increase in glomerular filtration rate [4]. These changes can directly influence volume of distribution (Vd) and clearance (CL) of drugs. It is therefore likely that the pharmacokinetics (PK) of antimicrobial

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Key Points

During pregnancy, several mechanistic and pathophysiological changes occur. Immunologic alterations occurring in pregnancy may help to explain the altered severity of and susceptibility to infectious diseases during pregnancy.

This systematic review provides a complete and comprehensive overview of all studies regarding pharmacokinetics (PK), target attainment, and evidence-based dosing regimens of antimicrobial drugs—other than penicillin and cephalosporins—throughout pregnancy.

This systematic literature review shows that current knowledge gaps include almost all antimicrobial drugs, other than penicillins and cephalosporins, that lack data altogether in this patient population.

With this literature review we hope to stimulate other researchers to fill in the missing gaps by providing both PK data as well as dosing guidance for clinical implementation. Optimization of antibiotic treatment is vital for this vulnerable population.

drugs change during pregnancy [5]. The above-mentioned physiological changes may lead to either subtherapeutic or toxic drug concentrations in the mother. The latter, especially, could potentially lead to toxic drug concentrations in the fetus. As a result, dosage adaptations are often necessary [4]. Currently, pregnant women are often administered the same dose as non-pregnant women [5]. Understanding the PK and how to reach the pharmacodynamic (PD) targets of antimicrobial drugs in pregnant women is essential to obtain evidence-based dosing regimens and to provide the most effective and safe treatment. While the PK for antimicrobial drugs have been extensively studied in non-pregnant adult populations, knowledge of PK and the ability to reach adequate target attainment of antimicrobial drugs in pregnant women is limited.

In separate contributions, we have reviewed the effect of pregnancy on the PK of penicillins [6] and cephalosporins (in preparation). This systematic literature review aims to describe PK and exposure as well as target attainment of antimicrobial drugs other than penicillins and cephalosporins throughout pregnancy (and when possible, compared with non-pregnant women). The effect of the antimicrobial drug on the fetus is outside the scope of this review. Furthermore, in this study it will be analysed if, based on the changed PK, evidence-based dosing regimens have already been developed for adequate target attainment in pregnant women.

2 Methods

2.1 Search Strategy

This systematic literature review is performed in accordance with the PRISMA guidelines of 2020 [7]. A search was conducted using PubMed on 1 September 2021 and updated on 28 August 2022 for a selection of antimicrobials. The following antimicrobial drugs were included in the search: *aminoglycosides* (amikacin, framycetin, gentamicin, neomycin, paromomycin, streptomycin, tobramycin); *carbapenems* (ertapenem, imipenem, and meropenem); *quinolones* (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin); *glycopeptides* (dalbavancin, oritavancin, teicoplanin, vancomycin); macrolides (azithromycin, clarithromycin, erythromycin); *polypeptides* (bacitracin, colistin, gramicidin, polymyxin B); rifamycines (rifabutin, rifampicin, rifaximin); *sulfonamides* (sulfadiazine, sulfamethoxazole, sulphametrole, sulphapyridine); *tetracyclines* (demeclocycline, doxycycline, eravacycline, minocycline, oxytetracycline, tetracycline, tigecycline); *tuberculostatic drugs* (bedaquiline, cycloserine, delamanid, ethambutol, isoniazid, para-aminosalicylic acid, prothionamide, pyrazinamide); and *others* (including dapsone, clofazimine, aztreonam, chloramphenicol, daptomycin, fidaxomicin, fosfomycin, fusidic acid, linezolid, methenamine, mupirocin, nitrofurantoin, tedizolid, trimethoprim). Three domains, referring to the PICO elements of the research question ('pharmacokinetics', 'pregnancy' and 'antimicrobial drugs') were used in the search (Table 1).

For each antimicrobial drug we performed a separate search, indicating that overall 62 unique searches were conducted. Keywords were allocated to these domains and as many relevant synonyms for each keyword as possible were included in the search. Whenever possible, keywords were converted to corresponding MeSH terms and/or title/abstract terms. In the final search, both MeSH terms and keywords searched for in the title and abstract were included The MeSH and title/abstract terms used for each search are shown in Supplementary Data File Table 2 (see electronic supplementary material [ESM]). Additionally, studies were identified through reference checks of the included studies. Search results were stored in Microsoft Excel (version 16.59).

2.2 Inclusion Criteria

We included studies comparing PK of the drug of interest in pregnant women with that of non-pregnant or postpartum women, to accurately determine the potential influence of pregnancy. However, a full separate search on PK data for antimicrobial drugs in non-pregnant and postpartum women

Table 1 Overview of final search strategy in PubMed

Pharmacokinetics	Pregnancy	Antimicrobial drugs
MeSH and title/abstract terms	*MeSH and title/abstract terms*	*MeSH and title/abstract terms*
("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])	("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 labor [tiab])	A selection of antimicrobials within the following classes: aminoglycosides, carbapenems, quinolones, glycopeptides, macrolides, polypeptides, rifamycines, sulfonamides, tuberculostatic drugs and other antibiotics. See supplementary file 2 in the ESM for the complete search strategy

was not performed, as differences in PK results could be caused by different study methodologies. Thus, only non-pregnant and/or postpartum women data, if reported within the context of a study with pregnant women, were found eligible for this literature review. Comparison of PK parameters between non-pregnant/postpartum and pregnant women were made as follows: the percentage changes were calculated between those two groups and reported in the results section. When multiple studies reported PK data, the lowest and highest percentage changes between non-pregnant and pregnant women within all those studies were reported in the results section. The following types of studies were included in this literature review: prospective or retrospective cohort studies, randomized control studies, case-control studies, and case-series. We did not include reviews and physiological-based PK studies. Only studies performed in humans were included and studies written in the English language. All dosage forms (intravenous, intramuscular, and oral) were included in this study, as locally acting drugs can be reabsorbed to some extent (e.g., miconazole) [8]. If at least one PK parameter was investigated in pregnant women, the study was included. This literature review only focusses on PK-related endpoints and does not include efficacy studies. However, for antimicrobial drugs other than penicillins and cephalosporins it is known that efficacy is supported by reaching the PK/PD free-drug concentrations above the minimal inhibitory concentration (MIC) at the site of infection ($fT > MIC$), peak concentration over MIC (fC_{max}/MIC) or area under the curve (AUC) over MIC (fAUC/MIC) [9]. Furthermore, this literature review is limited to pregnant women, without including additional PK data from literature on the fetus.

2.3 Study Selection

During the initial selection, duplicate articles were excluded and titles and abstracts were screened for relevance to the study. Full texts of articles were obtained. Studies not meeting the study aim and inclusion criteria were excluded. The search strategy and study selection were separately performed by two investigators (FG and PM). Obtained results were discussed. In case of disagreement, a third author (DT) was consulted.

2.4 Data Extraction

Data extraction from all studies included was performed by two separate investigators (FG and PM).

In case of disagreement, a third author (DT) was consulted. Study and population characteristics such as study design, population number, age, weight (and BMI if reported), height, conditions, gestational age (GA), dosage form, and dose were identified and collected. The collected PK parameters of interest were bioavailability (F) for oral drugs, volume of distribution (Vd), and clearance (CL). Furthermore, exposure parameters such as trough (C_{min}) and peak (C_{max}) drug concentrations, time of maximum concentration (t_{max}), area under the curve (AUC), and half-life ($t_{½}$) were collected. Collected PD parameters included probability of target attainment (PTA) and MIC. Finally, it was investigated if, based on the potentially changed PK/PD, adapted dosages were advised by the studies for adequate target attainment. Data was, when possible, stratified over six different pregnancy-related conditions of the patient populations: non-pregnant; first, second, third trimester of pregnancy, intrapartum and postpartum. All data extracted from the included studies was stored in Microsoft Excel (version 16.59).

3 Results

3.1 Study Selection and Data Extraction

A detailed overview of the study selection is presented in the PRISMA flow diagram in Fig. 1. Twenty-nine studies were included in this systematic literature review, providing data for 8 of the 11 originally selected antimicrobial drug

classes. The PK and exposure of the antimicrobial drugs are presented in alphabetical order of antimicrobial class and drugs within this class. Subsequently, the antimicrobial drugs are presented in the result section according to the ADME (absorption [if applicable], distribution, metabolism, elimination) sequence, followed by the obtained target, PTA, and evidence-based dosages if provided.

3.2 Aminoglycosides

No PK or exposure studies could be found for amikacin, framycetin, neomycin, paromomycin, and streptomycin in pregnant women.

3.2.1 Gentamicin

One prospective cohort study of 18 third trimester pregnant women and four non-pregnant women reported on gentamicin PK and exposure [10]. All women were scheduled for a caesarean section or a gynecological surgery under general anesthesia and received gentamicin 4 mg/kg intravenously over 2–3 minutes, 10 minutes prior to surgical incision [10]. The study characteristics including the PK parameters of pregnant women (if possible, in comparison with non-pregnant women) from the included studies are reported in Table 2. When focusing on the distribution, a 39% higher C_{max} was reached in pregnant compared with non-pregnant women. Furthermore, Vd was decreased by 24% in pregnant women. The CL was minimally increased by 5% during pregnancy. No p values were reported, except for the change in the elimination constant. This parameter was significantly increased in pregnant women compared with non-pregnant women (0.4127 ± 0.0736/h vs 0.3198 ± 0.0943/h; $p < 0.05$) [10].

In summary, it is plausible that the PK and exposure of gentamicin changed during pregnancy based on the limited data; however, more robust studies are needed. Regardless of the change in PK and exposure parameters during pregnancy, no statements on target attainment or suggestions for the starting dose were reported.

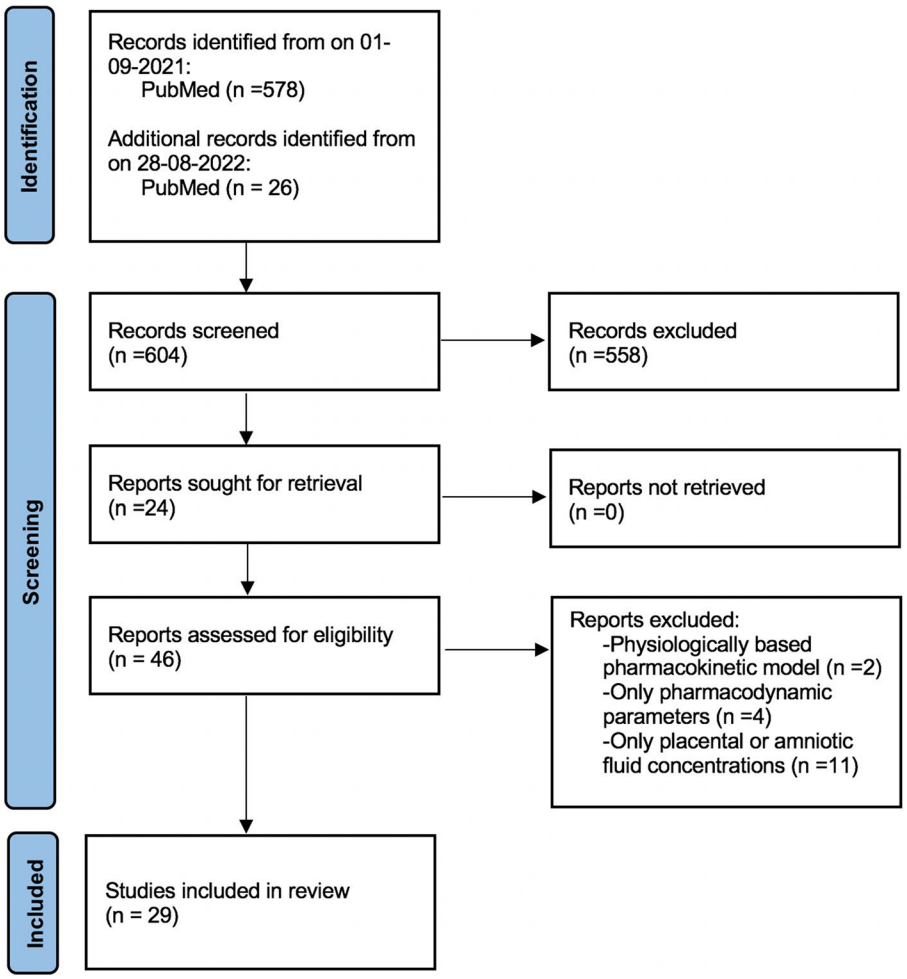

Fig. 1 PRISMA flow diagram

Table 2 Study, patient characteristics, PK and exposure parameters, probability of target attainment and dose advice of the included studies of aminoglycosides, in alphabetical order by antimicrobial drug followed by author

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (y)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Popovíc et al. (2007) [10]	Gentamicin	4 mg/kg IV over 2–3 min, 10 min before surgical incision	Prospective cohort study	P3/D: 18 NP: 4	19–40	P3: 81 (10) NP: 66 (16)	All: scheduled for caesarean section or gynecological surgery under general anesthesia. Received (ceftriaxone, cefazolin or) gentamicin prophylactic doses. No pre-eclampsia, eclampsia, life-threatening conditions to the fetus. No history of DM, hypertension or other serious disorders (CV, neurological, metabolic, immunological, infectious or oncologic) and no other drugs were taken		C_{mean}: 6 h after administration P3/D: 3.44 mg/L (2.22) NP: 3.42 mg/L (1.09) C_{max}: P3: 25.82 mg/L (4.99) NP: 15.72 mg/L (5.82) *Vd:* P3/D: 9.05 L (2.49) NP: 12.05 L (6.32) $t_{½}$: P3/D: 1.78 h (0.58) NP: 2.33 h (0.72) *CL:* P3/D: 216 L/h (60.6) NP: 204.6 L/h (52.8)	–	–

Table 2 (continued)

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (y)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Bourget et al. (1991) [11]	Tobramycin	2.5 mg/kg IV over 15 min daily for 7 ± 1 days	Prospective cohort study	18 P2: 9 P3: 9	P2: 30.1 (4.60) P3: 29.5 (6.10)	P2: 71.7 (24.8) P3: 81.5 (16.7)	12 patients hospitalized for fetal problems with indicated termination of pregnancy, 3 patients for chorioamnionitis due to Streptococcus, 3 patients for Gram-negative pyelonephritis	P2: 21.07 (2.06) weeks' GA P3: 37.5 (3.00) weeks' GA	C_{max}: At sixth dose: P2: 13.98 mg/L (5.21) P3: 15.0 mg/L (3.15) *AUC:* P2: 21.51 mg•h/L (4.16) P3: 27.63 mg•h/L (5.95) *Vd:* P2: 0.24 L/kg (0.05) P3: 0.27 L/kg (1.10) $t_{½}$: P2: 1.60 h (0.19) P3: 2.39 h (0.66) *CL:* P2: 2.00 mL/min/kg (0.37) P3: 1.58 mL/min/kg (0.41)	–	–
Fernandez et al. (1990) [12]	Tobramycin	2 mg/kg IV over 10 min 5.6 hours before caesarean	Case report	1	29		All: woman with heterotopic pregnancy with both intrauterine and ovarian gestations and two living fetuses. Surgical termination of ovarian pregnancy	P3/D	*Vd:* 0.29 L/kg $t_{½}$: 2.03 h *CL:* 1.73 mL/min/kg	–	–

Values given as mean (standard deviation) or median [range] unless otherwise specified

AUC area under the concentration–time curve, C_{max} maximum concentration of drug, C_{mean} mean concentration of drug, *CL* clearance, *D* at delivery, *GA* gestational age, *IV* intravenously, *N* total number of study participants, *NP* non-pregnant, *P* pregnant, *P2* pregnancy at second trimester, *P3* pregnancy at third trimester, *PK* pharmacokinetic, *PTA* probability of target attainment, $t_{½}$ half-life, t_{max} time to reach maximal concentration, *Vd* volume of distribution

3.2.2 Tobramycin

Two papers investigated the PK and exposure of tobramycin during pregnancy, one being a prospective cohort study and one a case report with 18 pregnant women in their second or third trimester. All pregnant women were admitted to the hospital for an underlying disease demanding tobramycin treatment. In the cohort study, the women received tobramycin 2.5 mg/kg once daily intravenously over 15 minutes for 7 ± 1 days, while in the case report tobramycin 2 mg/kg was administered intravenously once over 10 minutes, 5.6 hours before caesarean (Table 2) [11, 12]. PK parameters were reported in the cohort study, in contrast with the case report. Maximum concentrations (C_{max}) were slightly higher (7%) in third-trimester pregnant women than in second-trimester pregnant women. In addition, it was observed that Vd was comparable between second-and third-trimester pregnant women [11]. This result was also supported by the case report [12]. As for the elimination, AUC was increased by 22% during the third trimester compared with the second trimester. CL was significantly higher with 21% (no *p*-value reported) in the second trimester compared with the third trimester [11, 12], explaining the difference in AUC.

In summary, the PK and exposure of tobramycin seem to change throughout pregnancy. No PTA was reported. The authors recommended accurate therapeutic drug monitoring during pregnancy [11, 12], but did not provide evidence-based starting dose advice.

3.3 Carbapenems

No studies were found that investigated the PK or exposure for ertapenem and meropenem in pregnant women.

3.3.1 Imipenem

Only one paper investigated the PK and exposure of imipenem during pregnancy. This prospective cohort study included a total of 20 subjects, of whom seven were in their first trimester, seven in their third trimester and six were not pregnant. Imipenem was given in a single intravenous dose of 500 mg (imipenem-cilastatin 1:1) as infusion over 20 minutes (Table 3) [13]. When focusing on the distribution, C_{max}, measured immediately after infusion, and plasma concentrations 2 hours after administration, were significantly decreased by 65% ($p < 0.05$) in first and third trimester pregnant women in comparison with non-pregnant women. Vd was significantly increased by 60% and 65% for first ($p < 0.005$) and third trimester ($p < 0.05$) compared with non-pregnant women, respectively. Furthermore, the AUC was also significantly decreased ($p < 0.05$) during pregnancy by 44% and 58% for first and third trimester compared with non-pregnant women, respectively. The total CL was significantly increased ($p < 0.05$) in the pregnant patients (52% and 65% during first and third trimester compared with non-pregnant women) [13].

In summary, although only one study has been performed, there are indications that the PK or exposure of imipenem significantly changes during pregnancy. PTA was not reported and no recommendation for evidence-based dosing was provided.

3.4 Quinolones

No studies were found that investigated the PK or exposure for norfloxacin in pregnant women.

3.4.1 Ciprofloxacin, Levofloxacin, and Ofloxacin

One prospective cohort study reported on the PK and exposure of ciprofloxacin and one on the PK and exposure of ofloxacin during the second trimester of pregnancy [14]. In each study, 20 pregnant women were included with fetuses affected by beta-thalassemia major undergoing termination of gestation. Both ciprofloxacin (200 mg) and ofloxacin (400 mg) were administered every 12 hours intravenously (Table 4). In addition, only one prospective cohort study studied the PK and exposure during pregnancy for levofloxacin [15]. Levofloxacin 500 mg was given intravenously over 60 minutes to 12 pregnant women scheduled to undergo caesarean section for obstetric indications. Only maternal concentrations were reported in the above-mentioned studies (Table 4).

In summary, no conclusion can be made about PK or exposure changes for ciprofloxacin, ofloxacin, and levofloxacin in pregnant women.

3.4.2 Moxifloxacin

Three studies, two prospective cohort studies and one case report, reported on the PK and exposure of moxifloxacin during pregnancy [15–17]. The prospective cohort study by Nemutlu et al. [17] included nine non-pregnant women and six pregnant women scheduled for caesarean section. Both groups received moxifloxacin 400 mg in a single dose intravenously over 20 minutes, with completion of infusion 30 minutes prior to surgical incision. Ten pregnant women scheduled for caesarean section were included in the prospective study by Ozyuncu et al. [15] receiving moxifloxacin 400 mg in a single dose intravenously over 60 minutes, with completion of infusion 20–25 minutes before surgical incision. The case report by van Kampenhout et al. [16]

Table 3 Study, patient characteristics, PK and exposure parameters, probability of target attainment and dose advice of the included studies of carbapenems

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Heikkila et al. (1992) [13]	Imipenem	Single 500-mg dose of (imipenem-cilastatin 1:1) as IV infusion over 20 min	Prospective cohort study	20 P1: 7 P3: 7 NP: 6	P1: 30.7 [16–36] P3: 30.3 [26–3] NP: 37.5 [27–42]	P1: 61.8 (6.4) P3: 78.3 (9.7) NP: 59.2 (10.7)	P1: artificial termination of the pregnancy for social reasons P3: parturient women who delivered by caesarean section because of secondary arrest of labor or premature rupture of the membranes NP: gynaecological operation for benign disease	P1: 8.6 ± 1.5 $(7–11)^2$ weeks' GA P3: 38.7 ± 1.4 $(37–41)^2$ weeks' GA	*Maternal serum levels:* P1: 0.52 mg/L (0.32) P3: 5.13 mg/L (2.81) C_{mean}*:* P1: 14.7 mg/L (4.9) P3: 14.9 mg/L (5.2) NP: 43 mg/L (28.3) C_{max}*:* P1: 14.7 mg/L (4.9) P3: 14.9 mg/L (5.2) NP: 43.0 mg/L (28.3) $p < 0.05$ *AUC:* P1: 862 mg•min/L (346) P3: 643 mg•min/L (326) NP: 1548 mg•min/L (339) $p < 0.05$ *Vd:* P1: 54.7 L (23.7) P3: 47.1 L (14.8) NP: 18.9 L (5.8) P1: 0.98 L/kg (0.45) P3: 0.59 L/kg (0.19) NP: 0.33 L/kg (0.10) $p < 0.05$ $t_{½}$*:* P1: 48 min (21) P3: 36 min (8) NP: 41 min (16) *CL/F:* P1: 703 mL/min (365) P3: 973 mL/min (47) NP: 338 mL/min (85) $p < 0.05$ P1: 13 $mL•min^{-1}kg^{-1}$ (8) P3: 11 $mL•min^{-1}kg^{-1}$ (5) NP: 6 $mL•min^{-1}kg^{-1}$ (1) $p < 0.05$ CL_R*:* P1: 12.7 $mL•min^{-1}kg^{-1}$ (7.8) P3: 10.7 $mL•min^{-1}kg^{-1}$ (4.6) NP: 5.77 $mL•min^{-1}kg^{-1}$ (1.19) $p > 0.05$ P1: 270 mL/min (187) P3: 301 mL/min (69) NP: 110 mL/min (43) $p < 0.05$	–	–

Values given as mean (standard deviation) or median [range] unless otherwise specified

AUC area under the concentration–time curve, C_{max} maximum concentration of drug, C_{mean} mean concentration of drug, *CL* clearance, CL_R renal clearance, *F* bioavailability, *GA* gestational age, *IV* intravenous, *N* total number of study participants, *NP* non-pregnant, *P1* pregnancy at first trimester, *P3* pregnancy at third trimester, *PK* pharmacokinetic, *PTA* probability of target attainment, $t_{½}$ half-life, *Vd* volume of distribution

Table 4 Study, patient characteristics, PK and exposure parameters, probability of target attainment and dose advice of the included studies of quinolones, in alphabetical order by antimicrobial drug followed by author

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Giamarellou et al. (1989) [14]	Ciprofloxacin	2× 200-mg IV doses every 12 h	Prospective cohort study	20	26.40 (6.05)		All: pregnant women, with gestational age 19–25 weeks, with fetuses affected by beta-thalassemia major undergoing termination of gestation induced by amniocentesis and intrauterine instillation of prostaglandin F2α	P2: 21.16 (1.89) weeks' GA	Maternal serum levels: 0.01–0.28 mg/L	–	–
Ozyuncu et al. (2010) [15]	Levofloxacin	1× 500-mg IV dose over 60 min, with completion 20–25 min before surgical incision	Prospective cohort study	12	31.08 (4.94)	70.70 (8.93)	All: pregnant women scheduled to undergo caesarean section for obstetric indications	D: 38.28 (0.26) weeks' GA	Maternal serum levels: 8.18 (1.68) mg/L	–	–
Van Kampenhout et al. (2017) [16]	Moxifloxacin	400 mg once daily orally	Case report	1	25		Pregnant woman with tuberculosis	P2: 25+5 weeks' GA, P3: 35+5 weeks' GA (1 mo before delivery) PP: 18 weeks postpartum	$AUC_{0\text{-}24h}$: P2: 31.6 mg*h/L P3: 32 mg*h/L PP: 34.9 mg*h/L	–	–
Nemutlu et al. (2010) [17]	Moxifloxacin	1× 400-mg IV dose over 20 min, with completion of infusion 30 min prior to surgical incision	Prospective cohort study	NP: 9 D: 6			D: caesarean-sectioned women		C_{max}: NP: 4.95 mg/L (0.5) D: 1.56 mg/L (0.16) *AUC:* NP: 0.4995 mg*h/L (0.00630) D: 0.01053 mg*h/L (0.00066) *Vd:* NP:65.58 L (6.30) D: 215.85 L (24.87) $t_{½}$: NP: 5.54 h (0.73) D: 3.50 h (0.37)	–	–
Ozyuncu et al. (2010) [15]	Moxifloxacin	1× 400-mg IV dose over 60 min, with completion 20–25 min before surgical incision	Prospective cohort study	10	27.60 (5.42)	75.30 (8.81)	All: women who were scheduled to undergo caesarean section for obstetric indications were selected	D: 38.6 (0.36) weeks' GA	Maternal serum levels: 4.96 mg/L (1.36)	–	–

Table 4 (continued)

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Giamarellou et al. (1989) [14]	Ofloxacin	400 mg IV every 12 h	Prospective cohort study	20	26.1 (5.53)		All: pregnant women, with gestational age 19–25 weeks, with fetuses affected by beta-thalassemia major underwent termination of gestation induced by amniocentesis and intrauterine instillation of prostaglandin F2α	P2: 21.07 (1.89) weeks' GA	Maternal serum levels: 0.07 • 10^{-6}–0.68 • 10^{-6} mg/L	–	–

Values given as mean (standard deviation) or median [range] unless otherwise specified

AUC area under the concentration–time curve, $AUC_{0\text{-}24h}$ area under the concentration–time curve from administration to 24 hours after administration C_{max} maximum concentration of drug, *CL* clearance, *D* at delivery, *GA* gestational age, *IV* intravenous, *N* total number of study participants, *NP* non-pregnant, *P* pregnant, *P2* pregnancy at second trimester, *P3* pregnancy at third trimester, *PK* pharmacokinetic, *PP* postpartum, *PTA* probability of target attainment, $t_{½}$ half-life, *Vd* volume of distribution

followed a pregnant woman with tuberculosis from the second trimester to 18 weeks postpartum. She received moxifloxacin 400 mg orally once a day (Table 4). The study of Ozyuncu et al. [15] only reported maternal concentrations and the case report by van Kampenhout et al. [16] only reported the AUC. As for the distribution-related parameters, Nemutlu et al. [17] reported a 65% decrease in C_{max} during pregnancy. The Vd seemed to be increased during pregnancy by 70%. Furthermore, the AUC was decreased at delivery by 80% compared with non-pregnant women. No *p*-values were reported by Nemutlu et al. [17]. Contradictory results on AUC were reported in the case report [16], in which overall AUC did not change throughout pregnancy. The $t_{½}$ seemed to be decreased by 37% at delivery compared with non-pregnant women (*p*-value not reported) [17].

In summary, based on the limited results, it seems that the PK and exposure of moxifloxacin changed during pregnancy compared with non-pregnant women. However, PTA and dose adjustments were not reported.

3.5 Glycopeptides

No PK or exposure studies could be found for dalbavancin, oritavancin, or teicoplanin throughout pregnancy.

3.5.1 Vancomycin

Four papers were found on PK and exposure of vancomycin during pregnancy [18–21]. Three were prospective cohort studies and one study was a case report (Table 5) [18]. In total, 86 pregnant women in labor were included [18–21]. Dosages and dosing intervals varied for these studies. Bourget et al. [18] administered vancomycin 15 mg/kg intravenously every 12 hours for 13 days. Laiprasert et al. [19] used a single dose of 1 g intravenously 6 hours before delivery. The study by Onwuchuruba et al. [20] included three dosing regimens; 1 g intravenously every 12 hours, 15 mg/kg intravenously every 12 hours, and 20 mg/kg intravenously every 8 hours. Towers and Weit [21] also administered vancomycin 20 mg/kg intravenously every 8 hours. Only the case report by Bourget et al. reported PK parameters [18]. No comparison with non-pregnant women was made. The other studies [19–21] only reported maternal serum levels.

In summary, based on these papers, the changes in PK or exposure of vancomycin during pregnancy cannot be determined. However, the studies from Onwuchuruba et al. [20] and Towers and Weit [21] both showed that a dosing regimen of 20 mg/kg intravenously every 8 hours (with a maximum individual dose not exceeding 2 g) before delivery resulted in therapeutic serum vancomycin levels in more than 80% of the mothers.

Table 5 Study, patient characteristics, PK and exposure parameters, probability of target attainment and dose advice of the included studies of glycopeptides, in alphabetical order by antimicrobial drug followed by author

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Bourget et al. (1991) [18]	Vancomycin	15 mg/kg IV every 12 h for 13 days	Case report	1	33	–	All: pregnant women with chorioamnionitis due to *Streptococcus agalactiae* with allergy to β-lactam antibiotics	P2: 26+3	C_{max}: 28.30–41.55 mg/L $AUC_{0-\infty}$: 66.29 mg•h/L *Vd:* 1.48 L/kg $t_{½}$: 4.55 h	–	Treatment should begin with a test dose of 15–20 mg/kg. Adjustment of the dose based on blood levels will ensure that therapeutic levels are maintained
Laiprasert et al. (2007) [19]	Vancomycin	Single dose of 1 g IV 1, 4 or 6 h before delivery	Prospective cohort study	13	29.9 ± 5.2 (21–41)[a]	93 ± 24.2 (65–163)[a]	All: uncomplicated, clinically uninfected, nonlaboring pregnant women undergoing scheduled caesarean delivery	D: 38–42 weeks	Maternal serum: 2.6–19.8 mg/L	–	–

Table 5 (continued)

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Onwuchuruba et al. (2014) [20]	Vancomycin	Initial phase: 1 g every 12 h IV Second phase: 15 mg/kg every 12 h Third phase: 20 mg/kg every 8 h	Prospective cohort study	55 Ph1: 31 Ph2: 12 Ph3: 12	–	–	All: pregnant women who entered labor with a positive group B streptococcal culture and a high-risk penicillin allergy with resistance to clindamycin or unknown sensitivity, or pregnant women <37 GA and unknown group B streptococcal status and high-risk penicillin allergy	–	–	Ph1: 10 (32%) therapeutic maternal levels Ph2: 6 (50%) therapeutic maternal levels Ph3: 10 (83%) therapeutic maternal Ph3 maximum maternal serum level: 35.5 mg/L	20 mg/kg IV every 8 h achieves higher percentage of women (80%) obtaining therapeutic levels with a maximal individual dose not exceeding 2 g rather than 1 g every 12 h

Table 5 (continued)

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Towers and Weit (2018) [21]	Vancomycin	20 mg/kg every 8 h IV	Prospective cohort study	30	–	–	All: pregnant women that entered labor with a high-risk penicillin allergy and a positive Group B streptococcus culture that was resistant to clindamycin or erythromycin or had unknown sensitivity, or pregnant women <37 GA and unknown group B streptococcal status and high-risk penicillin allergy	–		– 23/30 (77%) therapeutic maternal levels 8 patients with sub-therapeutic maternal blood levels of which 6 patients violated the dosing regimen by receiving the wrong dose or the correct dose at the wrong time Of 24 patients with correct dosing regimen, 22 (92%) obtained therapeutic maternal blood levels Maximum maternal serum level: 44.4 mg/L	20 mg/kg IV every 8 h (maximum individual dose of 2 g)

Values given as mean (standard deviation) or median [range] unless otherwise specified

$AUC_{0-\infty}$ area under the concentration–time curve from administration to infinity, C_{max} maximum concentration of drug, *D* at delivery, *GA* gestational age, *IV* intravenously, *N* total number of study participants, *P2* pregnancy at second trimester, *Ph1* initial phase, *Ph2* second phase, *Ph3* phase 3, *PK* pharmacokinetic, *PTA* probability of target attainment, $t_{½}$ half-life, *Vd* volume of distribution

[a]Value given as mean ± standard deviation (range)

3.6 Macrolides

No studies were found that investigated the PK or exposure of the macrolides (azithromycin, clarithromycin, erythromycin) in pregnant women.

3.7 Polypeptides

No studies were found that investigated the PK or exposure of the polypeptides (bacitracin, colistin, gramicidin, polymyxin B) throughout pregnancy.

3.8 Rifamycines

No studies were found that investigated the PK or exposure of rifabutin and rifaximin in pregnancy.

3.8.1 Rifampicin

For the PK and exposure of rifampicin during pregnancy, one prospective cohort study with 33 HIV-infected pregnant women was conducted. Rifampin was given once daily orally in a fixed-dose combination tablet (Rifafour® or Rifinah®) at a dose of ~10 mg/kg. Most participants received 600 mg daily. Twenty samples were collected during the third trimester, four during delivery and 24 postpartum (Table 6) [22]. As for the distribution, Vd was used for weight-based allometric scaling of the PK model. No differences between pregnant and non-pregnant women were reported. The elimination of rifampicin seemed to be affected by pregnancy. CL/F was significantly decreased by 14% during pregnancy compared with postpartum ($p = 0.026$). However, the model-estimated C_{max} was similar during pregnancy and postpartum. Furthermore, the observed proportion of women achieving the target C_{max} (≥ 8 mg/L) was very similar during pregnancy (54%) versus postpartum (58%). The model-estimated AUC increased slightly in pregnant women [22].

In summary, this study suggests that although CL/*F* of rifampicin is decreased in pregnant HIV-infected women, this appears to only modestly increase the rifampicin concentration and thus the rifampicin exposure. Therefore, no dose adjustment of rifampicin for HIV-infected women seems necessary during pregnancy.

3.8.2 Rifapentine

One study reported on the PK and exposure of rifapentine during pregnancy. This was a phase I/II trial including 50 pregnant women with indications for tuberculosis prophylaxis. Twenty-five women received rifapentine in the second trimester, of which ten were HIV positive and 25 women received the drug in the third trimester, of which ten were also HIV positive. In this paper, isoniazid was also administered and studied for PK (see tuberculostatic drugs). Rifapentine was given at a dose of 900 mg/week orally in combination with isoniazid in a combination preparation named 3HP for 12 weeks (Table 6) [23]. The AUC for HIV-positive pregnant women was increased by 14% compared with postpartum women and this was 21–50% higher than for HIV-positive pregnant women. No *p*-value was reported for this increase in AUC. As for the CL/F of rifapentine, no significant difference was observed between second and third trimester. However, a 30% increase ($p < 0.001$) in CL/F of rifapentine was seen for HIV-positive women compared with HIV-negative women. Additionally, it was found that HIV-negative women had a 28% decrease in CL during pregnancy compared with postpartum ($P < 0.001$). Based solely on these results, it cannot be concluded whether the change in AUC and CL in HIV-positive pregnant women was caused by the effect of HIV or by the efavirenz-based antiretroviral regimen [23].

In summary, although CL/F is decreased in HIV-negative pregnant women compared with postpartum women, no dose adjustments are needed for pregnant women as all women achieved the same rifapentine exposure as postpartum women.

3.9 Sulfonamides

No studies were found that investigated the PK or exposure of sulfadiazines, sulfametrole, and sulfapyridine throughout pregnancy.

3.9.1 Sulfamethoxazole (With and Without Trimethoprim)

One prospective study was found that investigated PK and exposure of sulfamethoxazole, including 20 pregnant women in total, of which 13 received sulfamethoxazole and seven received sulfamethoxazole in combination with trimethoprim. Both drugs were administered orally; sulfamethoxazole 480 mg every 12 hours for 13 women in combination with trimethoprim 960 mg every 12 hours. All women were in the first or second trimester of pregnancy and were admitted for abortion or tubal ligation. Maternal serum levels of sulfamethoxazole and trimethoprim were measured (Table 7) [24].

In summary, it is not known if the PK or exposure of sulfamethoxazole and trimethoprim changed during pregnancy as there was no comparison for PK and exposure during different trimesters of pregnancy or with non-pregnant women. PTA and dose adjustments were not reported.

3.10 Tetracyclines

No studies were found that investigated the PK or exposure of tetracyclines (demeclocycline, doxycycline, eravacycline

Table 6 Study, patient characteristics, PK and exposure parameters, probability of target attainment and dose advice of the included studies of rifamycines, in alphabetical order by antimicrobial drug

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dosing advice
Denti et al. (2015) [22]	Rifampicin	~10 mg/kg daily of fixed-dose combination tablet (Rifafour® or Rifanah®) orally. Most patients received 600 mg daily	Prospective cohort study Population-PK model	48, of which 33 for PK P3: 20 D: 4 PP: 24	28 (25–31)[a] PK group: 28 (26–30)[a]	67 (60–76)[a] PK group: 66 (60–77)[a]	All: pregnant HIV-infected women aged ≥18 y with GA of >13 weeks with or without tuberculosis receiving rifampicin for ≥10 days during pregnancy or postpartum. Sampling at 37 weeks' GA or at delivery and then 6 weeks PP	P3/D GA at D: 38 (37–40)[a] weeks' GA	*C_{max} :* P3/D: 8.4 mg/L (95% CI: 7.1–10.0) PP: 9.0 mg/L (95% CI; 6.6–11.9) *$AUC_{0\text{-}24h}$:* P3/D: 40.8 mg•h/L (95% CI: 27.1–54.2) PP: 37.4 mg•h/L (95% CI: 26.8–50) *Vd:* P3/D/PP: 43.3 L (95% CI: 35.6–48.5) *CL:* P3/D/PP:16.2 L/h (95% CI: 13.8–19.1) *Pregnancy effect on CL with 14%*	C_{max} of ≥8 mg/L P3/D: 54% PP: 58%	No dose adjustment during pregnancy

Table 6 (continued)

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dosing advice
Mathad et al. (2022) [23]	Rifapentine	900 mg/week orally in combination with isoniazid in combination preparation with the name 3HP for 12 weeks	Phase I/II trial Population-PK model	50 P2: 25 (10 HIV+) P3: 25 (10 HIV+)	27 (20–32)[a] P2: 26 (22–33)[a] P3: 27 (20–31)[a]	61 (56–67)[a] P2: 59 (55–66)[a] P3: 61 (58–67)[a]	All: pregnant women with indications for tuberculosis preventative therapy in Haiti, Kenya, Malawi, Thailand, and Zimbabwe with or without HIV	26 (20–30)[a] weeks' GA P2: 20 (16–24)[a] weeks' GA P3: 30 (28–31)[a] weeks' GA	C_{max} : 27.4 mg/L (24.7–34.6)[a] *AUC:* At steady-state: HIV+: P2/P3: 522 mg•h/L (359–803)[a] PP: 554 mg•h/L (434–751) HIV−: P2/P3: 786 mg•h/L (549–1171)[a] PP: 673 mg•h/L (471–847)[a] *CL:* HIV+: P2/P3: 1.60 L/h PP: 1.56 L/h HIV−: P2/P3: 1.53 L/h PP: 1.20 L/h	–	No dose adjustment during pregnancy

Values given as mean (standard deviation) or median [range] unless otherwise specified

AUC area under the concentration–time curve, $AUC_{0\text{-}24h}$ area under the concentration–time curve from administration of drug to 24 hours after administration, C_{max} maximum concentration of drug, C_{mean} mean concentration of drug, *CI* confidence interval, *CL* clearance, *D* at delivery, *GA* gestational age, *HIV* human immunodeficiency virus, *HIV+* patients with human immunodeficiency virus, *HIV−* patients without human immunodeficiency virus, *N* total number of study participants, *P2* pregnancy at second trimester, *P3* pregnancy at third trimester, *PK* pharmacokinetic, *PP* postpartum, *PTA* probability of target attainment, $t_{½}$ half-life, t_{max} time to reach maximal concentration, *Vd* volume of distribution

[a]Value given as median (interquartile range)

Table 7 Study, patient characteristics, PK and exposure parameters, probability of target attainment and dose advice of the included studies of sulfonamides

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Reid et al. (1975) [24]	Sulfamethoxazole (with and without trimethoprim)	*Sulfamethoxazole* 4.8 g every 12 h orally *Trimethoprim:* 960 mg every 12 h orally	Prospective cohort study	Sulfamethoxazole: 13 Sulfamethoxazole with trimethoprim: 7	Sulfamethoxazole: 34.77 ± 4.07 (25–41) Sulfamethoxazole with trimethoprim: 35.00 ± 6.88 (27–40) Trimethoprim: 35.64 ± 5.39 (22–43)		Pregnant women admitted for abortion or tubal ligation	Sulfamethoxazole P1/P2: 13.69 ± 3.68 (9–22) weeks' GA Sulfamethoxazole with trimethoprim: P2: 14.86 ± 1.68 (13–18) weeks' GA Trimethoprim: P2: 14.50 ± 2.85 (10–19) weeks' GA	Sulfamethoxazole urine: 222.0–852.8 mg/24 h Sulfamethoxazole maternal serum: 7.67–78.57 y/mL Trimethoprim urine: 17.98–218.40 mg/24h Trimethoprim maternal serum: 0.60–3.85 y/mL		

Values given as mean (standard deviation) or median [range] unless otherwise specified

GA gestational age, *N* total number of study participants, *NP* non-pregnant, *P1* pregnancy at first trimester, *P2* pregnancy at second trimester, *PK* pharmacokinetic, *PTA* probability of target attainment

minocycline, oxytetracycline, tetracycline, and tigecycline) in pregnancy.

3.11 Tuberculostatic Drugs

No PK or exposure studies have been found for bedaquiline, cycloserine, delamanid, para-aminosalicylic acid, and prothionamide in pregnant women. It must be noted that other drugs like moxifloxacin, ofloxacin, and linezolid also belong to the tuberculostatic drugs. These are described in Sects. 3.4 and 3.12, respectively.

3.11.1 Ethambutol

One prospective cohort study reported on the PK and exposure during pregnancy. This study included 18 samples from pregnant women with HIV infection treated for tuberculosis, which were studied both in third trimester and/or at delivery and postpartum. Women received a calculated number of 275-mg tablets orally daily (Rifafour® and Rifinah® combination preparation), with the dose adjusted for weight to 15–25 mg/kg (Table 8) [25]. Both the C_{max} and AUC of ethambutol were slightly, but not significantly, increased by 13% during pregnancy. As for Vd/*F* and CL/*F*, no significant differences were observed between pregnant and postpartum women. No *p*-values were reported in this study [25].

In summary, it is very likely that the PK or exposure of ethambutol does not change during pregnancy. This also suggests that pregnant women could be treated with the same dose of ethambutol as postpartum women.

3.11.2 Isoniazid

Three studies reported on the PK and exposure of isoniazid during pregnancy [25]. Two studies were prospective cohort studies and one was a phase I/II trial. The first prospective study by Abdelwahab et al. [25] included a total of 29 samples, 18 during third trimester, 3 during delivery, and 8 postpartum. All women were pregnant and HIV positive, treated for tuberculosis by administering a calculated number of 75-mg tablets orally daily (Rifafour® and Rifinah® combination preparation), with the dose adjusted for weight to 4–6 mg/kg. The other prospective study of Gausi et al. [26] included 847 HIV-positive pregnant women. They received 300 mg orally daily for 28 weeks (immediately during pregnancy or starting at 12 weeks postpartum). A total of 420 levels were measured during second or third trimester and 637 levels were measured postpartum. In 210 patients, levels were measured both during pregnancy and postpartum. In the phase I/II trial by Mathad et al. [23], 50 pregnant women treated for tuberculosis were included. The women received isoniazid 900 mg weekly orally in combination with rifapentine in a combination preparation named 3HP for 12 weeks. Twenty-five women were in the second trimester, of whom 10 were HIV positive. Twenty-five women were in the third trimester, of whom ten were also HIV positive (Table 8).

The study by Mathad et al. reported no significant differences in model-estimated C_{max} and AUC between second- and third-trimester pregnant and postpartum women [23]. The model-estimated C_{max} was slightly, but non-significant (*p*-value was not reported), higher (2–14%) in two studies comparing postpartum with second/third trimester [25, 26]. Abdelwahab et al. [25] reported a model-estimated non-significant increase of 27% in AUC (no *p*-value reported) during the third trimester compared with the postpartum phase. On the contrary, Gausi et al. [26] found a decrease in AUC of 23% (no *p*-value reported) when comparing the second/third trimester with postpartum. However, both studies also showed a wide range of AUC values. The studies of Abdelwahab et al. [25] and Mathad et al. [23] reported no differences in Vd/F and CL/*F* between pregnant and postpartum women. Contradictory results were reported by Gausi et al. [26], who reported a 26% increase ($p < 0.001$) in CL/*F* during pregnancy.

In summary, there are conflicting results concerning PK and exposure changes of isoniazid during pregnancy. Abdelwahab et al. [25] concluded that the PK and exposure of isoniazid were, overall, not affected by pregnancy. However, the largest study by Gausi et al. [26] did conclude a reduction in isoniazid exposure during pregnancy and postpartum. The effect of PK and exposure on dosing of isoniazid is not stated and should be studied further.

3.11.3 Pyrazinamide

One prospective cohort study reported on the PK and exposure of pyrazinamide during pregnancy. This study included a total of 18 samples, all from pregnant women with HIV infection treated for tuberculosis. Pyrazinamide was administered as 400-mg tablets orally daily (Rifafour® and Rifinah® combination preparation), with the dose adjusted for weight to 20–30 mg/kg. Thirteen samples were taken during the third trimester, two while the patient was in labor, and three samples were collected postpartum (Table 8) [25]. The PK parameters for pyrazinamide showed that AUC and C_{max} could be slightly decreased during pregnancy, by 2.8% and 3.9%, respectively. The Vd and CL was not different between pregnant and postpartum women. No *p*-values were reported [25].

In summary, it seems that the PK and exposure of pyrazinamide do not change during pregnancy and that therefore the dose can remain the same as for non-pregnant women.

Table 8 Study, patient characteristics PK and exposure parameters, probability of target attainment and dose advice of the included studies of tuberculostatic drugs, in alphabetical order by antimicrobial drug followed by author

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Abdelwahab et al. (2020) [25]	Ethambutol	275 mg tablets orally daily (Rifafour® and Rifinah® combination preparation), dose adjusted for weight to 15–25 mg/kg	Prospective cohort study Population PK model	18 P3: 13 D: 2 PP: 3	26.7 (24.8–29.5)[a]	PreP: 66 (58–77)[a] PP: 66 (59–72)[a]	All: pregnant women with HIV infection treated for TB with isoniazid, ethambutol, and pyrazinamide		C_{max}: P3/D: 1.82 mg/L (1.61–2.14)[a] PP: 2.11 mg/L (1.85–2.46)[a] $AUC_{0\text{-}24h}$: P3/D: 16.5 mg•h/L (14.3–20.6)[a] PP: 19.0 mg•h/L (16.5–21.6)[a] *Vd:* $Vd_{central}$: 268 L (95% CI 154–419) $Vd_{peripheral}$: 334 L (95% CI 217–490) *CL:* intermediate NAT2 acetylators: 60.2 L/h (95% CI 53.7–68.5)		No dose adjustment during pregnancy

Table 8 (continued)

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Abdelwahab et al. (2020) [25]	Isoniazid	75 mg tablets orally daily (Rifafour® and Rifinah® combination preparation), dose adjusted for weight to 4–6 mg/kg	Prospective cohort study	29 P3: 18 D: 3 PP: 8	28.1 (25.2–29.9)[a]	PreP: 66.0 (60.0–80.0)[a] PP: 63.5 (57.3–72.8)[a]	All: pregnant women with HIV infection treated for TB with isoniazid (some in combination with ethambutol and pyrazinamide)	P3: 2.71 (1.29–3.57)[a] weeks before delivery PP: 6.64 (4.96–7.18)[a] weeks after delivery	C_{max}: P3/D: 1.39 mg/L (1.13–1.60)[a] PP: 1.43 mg/L (1.09–1.86)[a] $AUC_{0\text{-}24h}$: P3/D: 6.88 mg•h/L (3.63–10.40)[a] PP: 5.01 mg•h/L (2.89–8.03)[a] *Vd:* $Vd_{central}$: 130 L (95% CI 106–162) $Vd_{peripheral}$: 28.5 L (95% CI 10.8–50.1) *CL:* Rapid NAT2 acetylators: 97.1 L/h (95% CI 68.6–144) Intermediate NAT2 acetylators: 75.7 L/h (95% CI 59.4–95.8) Slow NAT2 acetylators: 29.0 L/h (95% CI 24.3–34.8)		No dose adjustment during pregnancy

Table 8 (continued)

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Gausi et al. (2021) [26]	Isoniazid	300 mg orally daily for 28 weeks (immediately during pregnancy or starting 12 weeks PP)	Prospective, double-blind, placebo-controlled, randomized, noninferiority trial in 8 countries	847 P2/P3: 420 PP: 637 210 had levels during P2/P3 and PP	P2/P3: 29 [18–45] PP: 29 [19–42]	P2/P3: 68 [39–167] PP: 62 [38–165]	All: HIV-positive pregnant women aged ≥18 y with GA of 14–34 weeks	P2/P3: 26 [14–34] weeks' GA PP: 16 [7–23] weeks postpartum	*C_{max}:* P2/P3: 2.89 mg/L (1.97–4.13)[a] PP: 3.69 mg/L (2.64–5.13)[a] *AUC:* P2/P3: 8.05 mg·h/L (4.43–16.7)[a] PP: 11.1 mg·h/L (6.26–23.9)[a] *Vd:* $Vd_{central}$: 37.6 L (95% CI 33.9–40.7) $Vd_{peripheral}$: 13.3 L (95% CI 10.5–16.9) *CL:* Rapid NAT2 acetylators: 72.3 L/h (95% CI 61.5–86.7) Intermediate NAT2 acetylators: 38.5 L/h (95% CI 34.6–43.2) Slow NAT2 acetylators: 14.5 L/h (95% CI 13.1–16.0)		
Mathad et al. (2022) [23]	Isoniazid	900 mg/week orally with rifapentine in combination preparation 3HP for 12 weeks	Phase I/II trial	50 P2: 25 (10 HIV+) P3: 25 (10 HIV+)	27 (20–32)[a] P2: 26 (22–33)[a] P3: 27 (20–31)[a]	61 (56–67)[a] P2: 59 (55–66)[a] P3: 61 (58–67)[a]	All: pregnant women with indications for tuberculosis preventative therapy in Haiti, Kenya, Malawi, Thailand, and Zimbabwe with or without HIV	26 (20–30)[a] weeks' GA P2: 20 (16–24) weeks' GA[a] P3: 30 (28–31) weeks' GA[a]	*C_{max}:* 7.74 mg/L (5.68–10.6)[a] *AUC:* At steady-state: 78.2 mg•h/L (21.9–78.2)[a]		No dose adjustment during pregnancy

Table 8 (continued)

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Abdelwahab et al. (2020) [25]	Pyrazinamide	400 mg tablets orally daily (Rifafour® and Rifinah® combination preparation), dose adjusted for weight to 20–30 mg/kg	Prospective cohort study	18 P3: 13 D: 2 PP: 3	26.7 (24.8–29.5)[a]	PreP: 66 (58–77)[a] PP: 66 (59–72)[a]	All: pregnant women with HIV infection treated for TB with isoniazid, ethambutol, and pyrazinamide		*C_{max}*: P3/D: 35.9 mg/L (32.7–38.1)[a] PP: 34.5 mg/L (29.9–41.3)[a] *$AUC_{0\text{-}24h}$*: P3/D: 419 mg•h/L (370–541)[a] PP: 407 mg•h/L (336–514)[a] *Vd:* $Vd_{central}$: 43.8 L (95% CI 39.7–47.2) *CL:* intermediate NAT2 acetylators: 3.39 L/h (95% CI 2.96–3.87)		No dose adjustment during pregnancy

Values given as mean (standard deviation) or median [range] unless otherwise specified

AUC area under the concentration–time curve, *$AUC_{0\text{-}24h}$* area under the concentration–time curve between 0 and 24 hours after administration, *C_{max}* maximum concentration of drug, *CI* confidence interval, *CL* clearance, *D* at delivery, *GA* gestational age, *HIV* human immunodeficiency virus, *HIV+* patients with human immunodeficiency virus, *HIV−* patients without human immunodeficiency virus, *N* total number of study participants, *NAT2* N-acetyltransferase 2, *NP* non-pregnant, *P1* pregnancy at first trimester, *P2* pregnancy at second trimester, *P3* pregnancy at third trimester, *PK* pharmacokinetic, *PP* postpartum, *PreP* prepartum, *PTA* probability of target attainment, *$t_{½}$* half-life, *TB* tuberculosis, *$Vd_{central}$* volume of distribution of central compartment, *$Vd_{peripheral}$* volume of distribution of peripheral compartment, *Vd* volume of distribution

[a]Value given as median (interquartile range)

3.12 Other Antimicrobial Drugs

No PK or exposure studies have been found that were performed in pregnant women for dapsone, clofazimine, aztreonam, daptomycin, fidaxomicin, fosfomycin, fusidic acid, methenamine, mupirocin, and tedizolid.

3.12.1 Chloramphenicol

One paper reported on the PK and exposure of chloramphenicol in which chloramphenicol 100 mg was vaginally administered daily in tablet form for 7 days, indicated for bacterial vaginosis in 37 pregnant women [27] (Table 9). This study reported maternal plasma levels that ranged from 0.043×10^{-3} to 0.0731 mg/L. This remained under the therapeutic concentration of 5.0–20.0 mg/L [27]. Due to these limited findings, no conclusions can be drawn regarding whether the PK or exposure of chloramphenicol changes during pregnancy.

3.12.2 Clindamycin

Three prospective cohort studies with a total of 44 subjects investigated the PK and exposure of clindamycin [28–30]. Fourteen subjects received clindamycin 450 mg orally after 8 or more hours of fasting as prophylaxis right before undergoing abortion [29]. The other 30 subjects received clindamycin intravenously as prevention for diagnosed Group B Streptococcus (GBS) (900 mg/kg every 8 h) or for prevention of endocarditis (600 mg every 6 h). The studies were all performed during different stages of pregnancy ranging from the first trimester to delivery (Table 9) [28–30]. From the maternal serum levels found, it can be seen that in the study of Wear et al., all maternal levels were above the target of >0.5 mg/L [30]. This concentration is also exceeded in the other two studies [28, 29]. Further PK or exposure parameters were not reported. Only the study by Muller et al. [28] studied other PK parameters. The Vd/F found in pregnant women in the third trimester reported by Muller et al. was $6.32 \bullet 10^3$ L at steady state [28]. The elimination of clindamycin was not compared with non-pregnant women in this study, but the CL (10.0 L/h) was lower compared with values found in literature (19.8–26.4 L/h) [28].

Overall, it cannot be assessed if PK and exposure of clindamycin changed during pregnancy, as no comparison has been made with non-pregnant women. However, the study by Muller et al. [28] specified that an MIC of 0.5 mg/L can be reached when the protein binding is not higher than 65% after a dose of 900 mg every 8 hours intravenously. This finding was also supported by Wear et al. [30]. It should be noted that the possibility exists that protein binding is higher, and that the current dosing regimen is not adequate to protect all neonates from GBS [28].

3.12.3 Linezolid

One case report was found of a 25-year-old pregnant woman with tuberculosis, receiving linezolid 300 mg twice daily starting at 20 weeks' gestational age. This treatment was stopped at 5 months postpartum (Table 9) [16]. Only the AUC is reported in this case report. The exposure was decreased during the second (by 76%) and third (by 48%) trimester compared with postpartum. In this case report, there was evidence of a change in the PK and exposure of linezolid for this single patient; however, further studies are needed to confirm this result. No conclusions on PTA and dose adjustments for pregnant women are provided.

3.12.4 Nitrofurantoin

One prospective cohort study of 17 pregnant women in labor reported on the PK and exposure of nitrofurantoin. Nitrofurantoin 90 mg was given intravenously over 30 minutes [31]. It has to be noted that currently the intravenous formulation is no longer available. This study did not report any PK and exposure parameters besides the half-life measured in 11 women and maternal serum levels (Table 9). Any conclusive changes in PK or exposure during pregnancy cannot be derived from this study.

4 Discussion

Antimicrobial drugs are some of the most prescribed drugs for pregnant women [4]. Based on this systematic literature review we can conclude that a very limited number of studies have been performed on the PK of antimicrobials drugs—other than penicillins [6] and cephalosporins (data unpublished)—in pregnant women. Therefore, only limited interpretations are possible. Of the 62 drugs included in the search strategy of this systematic review, PK and exposure parameters during pregnancy of only 18 drugs were reported; this means that 71% of the antimicrobial drugs—other than penicillins and cephalosporins—have not been studied during pregnancy. For 11 out of these 18 drugs, primary PK parameters such as Vd and/or CL were reported. The limited PK studies performed with these antimicrobial drugs in pregnant women show that overall PK is altered, especially during the second and third trimester compared with non-pregnant or postpartum women, resulting in lower exposure. For linezolid, gentamicin, tobramycin, and moxifloxacin, altered PK throughout pregnancy, especially in second and third trimester, has been reported. However, no target attainment was studied and no evidence-based dosing developed. On the other hand, the ability to reach adequate targets and assess the need for evidence-based dosing was assessed for vancomycin, clindamycin, rifampicin,

Table 9 Study, patient characteristics, PK and exposure parameters, probability of target attainment and dose advice of the included studies of other antimicrobial drugs, in alphabetical order by antimicrobial drug followed by author

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Harauchi et al. (2017) [27]	Chloramphenicol	100 mg daily vaginally in tablet form for 7 days	Prospective cohort study	37	31 (28–36)[a]	54.4 (49.3–63.0)[b]	All: pregnant Japanese women receiving chloramphenicol vaginal tablets for bacterial vaginosis	P2/P3: 30 weeks 3 days GA (24 weeks 2 days GA – 32 weeks 5 days GA)	*Maternal plasma:* 0.043 • 10^{-3}–0.731 mg/L C_{24h}: 0.101 mg/L (0.00406–0.180) *Dose normalized plasma concentration:* 0.00571 mg/L/mg/kg (0.00234–0.00885)		
Muller et al. (2010) [28]	Clindamycin	For the prevention of endocarditis: 600 mg IV over 20 min every 6 h For prevention of GBS disease: 900 mg IV over 30 min every 8 h	Prospective cohort study	Total: 7 Prevention of endocarditis: 2 Prevention of GBS disease: 4 Prevention of endocarditis and GBS disease: 1 Blood samples from 6 due to occlusion of catheter	36.1 ± 4.24 (31.3–41.8)[b]	86.1 ± 14.2 (59.5–104.8)[b]	All: pregnant women >26 weeks' GA with proven or unknown GBS carriage with one or more of the following six factors: preterm premature rupture of the membranes, rupture of the membranes for >18 hours, prematurity, fever (temperature >37.8 °C), bacteriuria in the current pregnancy, or a previous delivery of a child with invasive GBS disease	P3: 38.3 (34–42.3) weeks' GA	*Maternal blood*: 2.8 mg/L (2.4) *Vd:* $Vd_{central}$: 12.4 L (95% CI 9.83–14.9) $Vd_{first\ peripheral}$: 52.2 L (95% CI 45.8–58.6) $Vd_{second\ peripheral}$: 6250 L (95% CI 3447–9052) *CL :* 10.0 L/h (95% CI 2.65–17.35)	*f*AUC/MIC ratio for MIC of 0.5 mg/L (65% protein binding): 55.8 (lowest 95% CI 24.6) *f*AUC/MIC ratio for MIC of 0.5 mg/L (75% protein binding): 39.7 (lowest 95% CI 17.3) *f*AUC/MIC ratio for MIC of 0.5 mg/L (85% protein binding): 23.9 (lowest 95% CI 10.2)	900 mg IV every 8 h is adequate for MIC 0.5 mg/L and protein binding of 65% Not for higher protein binding

Table 9 (continued)

Author (year) [citation]	Antibiotic	Dose	Study design	*N*	Age (years)	Weight (kg)	Condition	Trimester	PK parameters	PTA	Dose advice
Philipson et al. (1973) [29]	Clindamycin	Single doses or multiple doses of 450 mg orally after fast of ≥8 h	Prospective cohort study	14	15–43	Not reported	All: pregnant women admitted for abortions All had normal renal, hepatic, and hematologic functions	P1/P2:10–22 weeks' GA	C_{max} : Single dose: 5.16 mg/L (2.9–9.0)[a] Multiple dose: 2.55 mg/L (0.38–7.2)[a]		
Wear et al. (2016) [30]	Clindamycin	900 mg IV every 8 h	Prospective cohort study	23	Not reported	Not reported	All: pregnant women that entered labor with positive GBS culture, a high-risk penicillin allergy, sensitivity to clindamycin and erythromycin	D: 36–41 weeks' GA	*Maternal serum levels:* 4.46 mg/L [0.7–8.4]	>0.5 mg/L; 100% maternal levels and 96% umbilical cord blood levels	900 mg IV every 8 h
Van Kampenhout et al. (2017) [16]	Linezolid	300 mg twice daily orally	Case report	1	25		Pregnant woman with tuberculosis	P2: 25+5 weeks' GA P3: 35+5 weeks' GA (1 month before delivery) PP: 18 weeks postpartum	$AUC_{0\text{-}24h}$: P2: 48 mg•h/L P3: 106 mg•h/L PP: 203 mg•h/L		
Perry and Leblanc (1967) [31]	Nitrofurantoin	90 mg IV over 30 min	Prospective cohort study	17			Women in labor	At delivery, not further specified	$t_{½}$: 32 min (16) ($n = 13$)		

Values given as mean (standard deviation) or median [range] unless otherwise specified

AUC area under the concentration–time curve, $AUC_{0\text{-}24h}$ area under the concentration–time curve from administration to 24 hours after administration, C_{24h} plasma concentration 24 hours after administration, C_{max} maximum concentration of drug, *CI* confidence interval, *CL* clearance, *D* at delivery, *f* free fraction of drug, *GA* gestational age, *GBS* Group B streptococci, *IV* intravenously, *MIC* minimal inhibitory concentration, *N* total number of study participants, *NP* non-pregnant, *P1* pregnancy at first trimester, *P2* pregnancy at second trimester, *P3* pregnancy at third trimester, *PK* pharmacokinetic, *PP* postpartum, *PTA* probability of target attainment, $t_{½}$ half-life, *TB* tuberculosis, *Vd* volume of distribution, $Vd_{central}$ volume of distribution of central compartment, $Vd_{first\ peripheral}$ volume of distribution of first peripheral compartment, $Vd_{second\ peripheral}$ volume of distribution of second peripheral compartment

[a]Value given as median (interquartile range)

[b]Value given as mean ± standard deviation (range)

Table 10 Recommendation for use of non-penicillin and non-cephalosporin antibiotics during pregnancy with results of animal and human studies [32]

Drug	Pregnancy recommendation	Animal studies	Human studies
Aminoglycosides			
Amikacin	Human Data Suggest Low Risk	Dose-related nephrotoxicity in pregnant rats and their fetuses. No evidence of impaired fertility or teratogenicity in rats and mice.	No reported congenital defects. Potentially eighth cranial nerve toxicity in the human fetus (other aminoglycosides; kanamycin and streptomycin).
Framycetin	-	-	-
Gentamicin	Human Data Suggest Low Risk	Dose-related nephrotoxicity and increased blood pressure in fetal rats. No evidence of impaired fertility or teratogenicity in rats and rabbits.	One report of congenital defect: abnormal nephrogenesis (after co-administration of prednisolone). Potentially eighth cranial nerve toxicity in the human fetus (other aminoglycosides; kanamycin and streptomycin).
Neomycin	Human Data Suggest Low Risk	-	No reported congenital defects. Potentially eighth cranial nerve toxicity in the human fetus (other aminoglycosides; kanamycin and streptomycin).
Paromomycin	Limited Human Data - Probably Compatible	-	No reported congenital defects.
Streptomycin	Human Data Suggest Risk	-	Fetal ototoxicity (eighth cranial nerve toxicity) resulting in deafness in newborns. Risk is lowered by dose monitoring and limited duration of fetal exposure.
Tobramycin	Human Data Suggest Low Risk	Dose-related maternal and fetal nephrotoxicity in rats.	No reported congenital defects. Potentially eighth cranial nerve toxicity in the human fetus (other aminoglycosides; kanamycin and streptomycin).
Carbapenems			
Ertapenem	No Human Data - Probably Compatible	No evidence of structural teratogenicity in mice and rats. Maximum dose in mice (three times MRHD on BSA) resulted in decreased fetal weight and decreases in the average number of ossified sacrocaudal vertebrae.	No reported use of ertapenem during pregnancy.
Imipenem (-cilastatin sodium)	Limited Human Data—Animal Data Suggest Low Risk	No evidence of adverse fetal effects in rats and rabbits. No maternal toxicity or teratogenicity in monkey, except for increase in embryonic loss.	No reported use during first trimester. Considered safe and effective during perinatal period by four sources.
Meropenem	Limited Human Data—Animal Data Suggest Low Risk	No evidence of impaired fertility or fetal harm in rats and cynomolgus monkeys, except for slight changes in fetal weight in rats at doses of >0.4 times the MRHD.	No reported use during first trimester. Most likely considered safe during perinatal period.

Table 10 (continued)

Quinolones			
Ciprofloxacin	Contraindicated (Use only if no other alternatives)	Fetal cartilage damage and subsequent arthropathies after administration to both pregnant and immature rats and dogs. No evidence for embryotoxicity or teratogenicity in mice, rats and rabbits.	No association with an increased risk of major congenital malformation due to a lack of pattern in defects. Causal relationship with birth defects cannot be excluded. FDA added a warning for risk of disabling and potentially permanent effects involving the tendons, muscles, joints, nerves, and central nervous system.
Levofloxacin	Contraindicated (Use only if no other alternatives)	No evidence for teratogenicity in rabbits. Increased fetal mortality and decreased fetal weight in rats, when receiving >9.4 times the MRHD based on BSA.	No association with an increased risk of major congenital malformation due to a lack of pattern in defects. Causal relationship with birth defects cannot be excluded. FDA added a warning for risk of disabling and potentially permanent effects involving the tendons, muscles, joints, nerves, and central nervous system.
Moxifloxacin	Contraindicated (Use only if no other alternatives)	No evidence of teratogenicity in rats and cynomolgus monkeys. Increased number of rib and vertebral malformations in rabbits. Fetal growth restriction in cynomolgus monkeys after oral doses up to 2.5 times the MRHD based on the AUC. Fetal toxicity in rats at 0.24 times the MRHD based on AUC (prenatal loss, reduced pup birth weight, decreased neonatal survival, and treatment related maternal death during gestation). Maternal toxicity and a marginal effect on fetal and placental weights at 2 times the MRHD based on BSA in rats.	Limited human pregnancy experience. Assumingly no association with an increased risk of major congenital malformation. FDA added a warning for risk of disabling and potentially permanent effects involving the tendons, muscles, joints, nerves, and central nervous system.
Norfloxacin	-	-	-
Ofloxacin	Contraindicated (Use only if no other alternatives)	No evidence for teratogenicity and malformations at high doses in pregnant rats and rabbits. Fetotoxicity in rats and rabbits after 11 and 4 times the MRHD based on AUC, respectively, causing reduced birth weight, increased mortality, and, in rats only, minor skeletal variations.	No association with an increased risk of major congenital malformation due to a lack of pattern in defects. Causal relationship with birth defects cannot be excluded. FDA added a warning for risk of disabling and potentially permanent effects involving the tendons, muscles, joints, nerves, and central nervous system.

Table 10 (continued)

Glycopeptides			
Dalbavancin	No Human Data - Animal Data Suggest Moderate Risk	No embryo or fetal toxicity in rats and rabbits with doses 1.2 and 0.7 times, respectively, the MRHD based on exposure. Decreased fetal maturation in pregnant rats, at doses 3.5 times the MRHD based on exposure. Reduced fertility, increased embryo resorption, and parental toxicity in male and female rats.	No reported use during pregnancy.
Oritavancin	-	-	-
Teicoplanin	-	-	-
Vancomycin	Compatible	No evidence of teratogenicity or fetotoxicity in rats and rabbits.	No cases of congenital defects reported attributable to vancomycin.
Macrolides			
Azithromycin	Compatible	No evidence of teratogenicity or fetotoxicity in mice and rats.	Data do not suggest an embryo-fetal risk of developmental toxicity. No association with an increased risk of pyloric stenosis.
Clarithromycin	Compatible	No evidence of teratogenicity in one strain of rats in four studies. Low incidence of cardiovascular anomalies in second train of rats in two studies. Variable incidence of cleft palate in mice at dose of 2-4 times the MRHD. Fetal death in rabbits at dose 17 times less than MRHD. Embryonic loss caused by maternal toxicity in monkeys at dose 2.4 times the MRHD	Sufficient experience during pregnancy. No evidence for congenital defects. No association with an increased risk of pyloric stenosis.
Erythromycin	Compatible (Excludes estolate salt)	No evidence of teratogenicity in female rats.	Most reports found no evidence of developmental toxicity. One report found an association with cardiovascular defects. However, this could not be a true drug effect. No evidence for development of infantile hypertrophic pyloric stenosis after use late in pregnancy. The estolate salt of erythromycin has been observed to induce hepatotoxicity in pregnant patients
Polypeptides			
Bacitracin	Compatible (Topical)	-	No reports linking the use of bacitracin with congenital defects. One study with 18 exposed pregnant women, but route of administration is not specified. No association with malformations
Colistin	Limited Human Data - Animal Data Suggest Moderate Risk	No evidence of teratogenicity in rats. Talipes varus in 2.6-2.9% of rabbits at dose of 0.25 and 0.55 times the MRHD based on BSA.	No reports linking the use of colistimethate with congenital defects. The drug crosses the placenta at term
Gramicidin	-	-	-
Polymyxin B	Compatible (Topical)	-	No reports linking the use of polymyxin B with congenital defects.

Table 10 (continued)

Rifamycines			
Rifabutin	No Human Data - Animal Data Suggest Low Risk	No evidence of teratogenicity in rats and rabbits up to 40 time the MRHD. Highest dose caused a decrease in fetal viability in rats. Increase in fetal skeletal variants at 8 times the MRHD in rats. Maternal toxicity and increase in fetal skeletal variants at 16 times the MRHD in rabbits.	No reports describing the use of rifabutin in human pregnancy.
Rifampicin	Compatible	No evidence of teratogenicity in rabbits. Evidence of teratogenicity in rodents (mice and rats) with oral doses 15-25 times the human dose. Spina bifida and cleft palates in mouse fetuses at doses >150 mg/kg.	No evidence of linking the use of rifampicin to congenital defects. Rifampin has been implicated as one of the agents responsible for hemorrhagic disease of the newborn. Vitamin K1 is recommended to prevent this complication.
Rifapentine	Limited Human Data - Animal Data Suggest Risk	Teratogenic and toxic effects in rats and rabbits. Cleft palates, right aortic arch, increased incidence of delayed ossification and increased number of ribs in rats at doses 0.6 times the human dose based on BSA. Also, embryo and fetal toxic effects in rats (resorption rates, post-implantation losses, stillbirths, decreased fetal weight). Decreased pup weights and stillbirths at 0.3 times the human dose based on BSA in rats. Ovarian agenesis, pes varus (i.e., talipes varus), arrhinia, microphthalmia and irregularities of the ossified facial tissues in rabbits at doses 0.3-1.3 times the human dose. Post-implantation losses and stillbirths at 1.3 times the human dose in rabbits.	Limited human data (3 cases reported). Two of the three cases ended in spontaneous abortions during the first trimester. Therefore, caution is needed in prescribing rifapentine early in pregnancy. Rifapentine has been linked to hemorrhagic disease in the newborn and mother secondary to a vitamin K1 deficiency. Vitamin K1 is recommended to prevent this complication.
Rifaximin	No Human Data - Animal Data Suggest Risk	Teratogenicity in rats and rabbits at 2.5-5 times and 2-33 times the MRHD, respectively. The effects included cleft palate, jaw shortening, agnathia, hemorrhage, partially open eye, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar vertebrae. Carcinogenic in male rats, but not in mice. No effect on the fertility of male and female rats.	No reports describing the use of rifaximin in human pregnancy.
Sulfonamides			
Sulfonamides (o.a. sulfadiazine, sulfamethoxazole, sulphametrole, sulphapyridine)	Human Data Suggest Risk in 3rd Trimester	Teratogenic in rats primarily resulting in cleft palates given oral doses of 533 mg/kg. The highest dose that did not produce cleft palates was 512 mg/kg.	Sulfonamides, as single agents, do not appear to be linked to a significant teratogenic risk. One study has found associations with birth defects, but a causative association cannot be determined with this type of study, since the birth defects may have been due to

Table 10 (continued)

			other factors, particularly if the sulfonamide was combined with trimethoprim. Sulfonamides should be avoided near term, because of the potential toxicity to the newborn.
Tetracyclines			
Tetracyclines (o.a. demeclocycline, doxycycline, eravacycline, minocycline, oxytetracycline, tetracycline, tigecycline)	Contraindicated in 2nd and 3rd Trimesters	-	Reported problems attributable to tetracyclines: adverse effects on fetal teeth and bones, maternal liver toxicity, congenital defects and miscellaneous effects.
Tuberculostatic drugs			
Bedaquiline	No Human Data - Animal Data Suggest Low Risk	No evidence of fetal harm in rats and rabbits.	No reports describing the use of bedaquiline in human pregnancy.
Cycloserine	Limited Human Data - Animal Data Suggest Moderate Risk	No evidence of teratogenicity in rats given doses up to 100 mg/kg/day through two generations.	No evidence of adverse fetal effects of three exposed pregnant women during the first trimester. Avoidance is recommended due to lack of information on the fetal effects of the drug.
Delamanid	-	-	-
Ethambutol	Compatible	-	No reports linking the use of ethambutol with congenital defects.
Isoniazid	Compatible - Maternal Benefit >> Embryo-Fetal Risk	No evidence of teratogenicity in mice, rats and rabbits. Embryocidal effects observed in rats and rabbits.	No evidence of teratogenicity. Possible association between isoniazid and hemorrhagic disease of the newborn. Vitamin K1 is recommended at birth to prevent this complication.
Para-aminosalicylic acid	Human and Animal Data Suggest Risk	Occipital malformations in rats at doses within human dose range. No adverse effects on the fetus in rabbits treated with 5 mg/kg/day.	Reports have associated para-aminosalicylic acid with structural anomalies (ear, limb and hypospadias), but confirming studies are required. Therefore para-aminosalicylic acid should be avoided in the first trimester.
Prothionamide	-	-	-
Pyrazinamide	Compatible - Maternal Benefit >> Embryo-Fetal Risk	No reproduction studies were performed in animals. Not carcinogenic in rats and male mice.	Limited data about use in human pregnancy. No adverse effects on fetuses or newborns reported. Induction of chromosomal aberrations in human lymphocyte cell cultures.
Others including			
Dapsone	Compatible - Maternal Benefit >> Embryo-Fetal Risk	No reproduction studies were performed in animals.	A few fetal or newborn adverse effects directly attributable to dapsone have been reported (hemolytic anemia, neonatal hyperbilirubinemia), but no congenital anomalies caused by the dapsone.

Table 10 (continued)

Clofazimine	Limited Human Data - Animal Data Suggest Low Risk	No evidence of teratogenicity in mice, rats and rabbits. Fetotoxicity in mice at doses 12-25 times the human dose (retardation of fetal skull ossification, increased incidence of abortions and stillbirths, and decreased neonatal survival).	No evidence of linking the use of clofazimine to congenital defects in the limited data of human pregnancies.
Aztreonam	No Human Data - Animal Data Suggest Low Risk	No evidence of teratogenicity, fetotoxicity and embryotoxicity in rats and rabbits. Slightly reduced survival rate in rat offspring during lactation at doses 2.9 times higher than human doses.	No reports describing the therapeutic use of aztreonam in human pregnancy.
Chloramphenicol	Compatible	-	Chloramphenicol seems apparently non-toxic to fetuses. One study reported cardiovascular collapse (gray syndrome) in babies delivered from mothers treated with chloramphenicol during the final stage of pregnancy. Additional reports of this severe adverse effect have. It is well known that newborns exposed directly to high doses of chloramphenicol may develop the gray syndrome. Some authors consider the drug to be contraindicated during pregnancy.
Daptomycin	Limited Human Data - Animal Data Suggest Low Risk	No evidence of fetal harm in rats and rabbits. Maternal toxicity (decreased food intake and weight) seen at highest dose in rats and rabbits at 3 an 6 times the MRHD, respectively. No effect on fertility in male and female rats.	Limited human data (three reports during 2nd an 3rd trimester). No abnormalities were reported.
Fidaxomicin	No Human Data—Animal Data Suggest Low Risk	No evidence of fetal harm in rats and rabbits. No effects on fertility in male and female rats	No reports describing the use of fidaxomicin in human pregnancy.
Fosfomycin	Compatible	No evidence of teratogenicity in rats. Fetotoxicity in pregnant rabbits at doses up to 1000 mg/kg/day, about 9 and 2.7 times the human dose.	No evidence of linking the use of fosfomycin to congenital defects.
Fusidic acid	-	-	-
Linezolid	Compatible - Maternal Benefit >> Embryo-Fetal Risk	No evidence of teratogenicity in mice and rats. Fetotoxicity, embryotoxicity and maternal toxicity in mice at a dose of 4 times the expected human dose based on the AUC. In rats slight fetal toxicity (decreased pup survival and decreased fertility in offspring) and slight maternal toxicity at 0.13 and 0.64 times the human dose based on AUC, respectively.	One case-report has described the use of linezolid during human pregnancy. No adverse effects were reported.

Table 10 (continued)

Methenamine	Compatible	-	Limited human data. No evidence of linking the use of methenamine to congenital defects.
Mupirocin	No Human Data - Probably Compatible	No evidence of fetal harm in rats and rabbits. No evidence of impaired fertility or reproductive performance.	No reports describing the use of any mupirocin formulations in human pregnancy.
Nitrofurantoin	Human Data Suggest Risk in 3rd Trimester	Animal teratogen with doses close to those used in humans. No evidence of teratogenicity, impaired fertility or fetal adverse effects in rats and rabbits at a dose 6 times the human dose based on body weight. In mice, a dose 68 times the human dose based on body weight was associated with fetal growth restriction and a low incidence of minor and common malformations. A dose 19 times the human dose based on body weight induced lung papillary adenomas in mice offspring.	No confirmed data suggesting that nitrofurantoin is a human teratogen. Two retrospective studies reported associations with congenital anomalies. There is a risk at hemolytic anemia in newborns, who are exposed in utero to nitrofurantoin close to delivery. Therefore, nitrofurantoin should be avoided in the third trimester.
Tedizolid	No Human Data - Maternal Benefit >> Embryo-Fetal Risk	Reduced fetal weight and increased costal cartilage anomalies in mice at dose 4 times the human exposure based on AUC. Decreased fetal weight, increased skeletal variations including reduced ossification of the sternebrae, vertebrae, and skull, and maternal toxicity in rats at dose 6 times the human exposure based on AUC. Reduced fetal weight resulted after exposure to doses that induced maternal toxicity. No evidence of impaired fertility in rats.	No reports describing the use of tedizolid in human pregnancy.
Trimethoprim	Human and Animal Data Suggest Risk	Cleft palates in rats at a dose of. 200 mg/kg. Resorptions, fetal death, and malformations in rabbits at a dose 6 times the human dose.	Defects like cardiovascular defects and neural tube defects (NTDs), and possibly oral clefts, are associated with use of trimethoprim during pregnancy.

Abbrevations: AUC, area under the curve; BSA, body surface area; FDA, Food and Drug Administration; MRHD, maximum recommended human dose.

(simplified) color legend

Compatible	
Probably compatible	
Low risk	
Moderate risk	
Risk	
Contraindicated	

rifapentine, ethambutol, pyrazinamide, and isoniazid. For the first six of these drugs, no dosage adaptations during pregnancy seem to be needed. Studies on isoniazid provide contradictory results. It is not surprising that very limited data is available in the pregnant population on drugs outside of the penicillin and cephalosporin classes. This is due to the fact that these classes are frequently prescribed and, based on human and animal studies, appear to be safe [32]. For many of the non-penicillin and non-cephalosporin drugs, there is animal data suggesting fetal toxicity. This data does not support the use of these drugs in pregnant women and hence there is very limited human data. To guide clinicians, in Table 10 we have provided recommendations for the use of these drugs during pregnancy, based on results from human and animal studies, and Briggs' 'Drugs in Pregnancy and Lactation' was used as major source to formulate these recommendations [32]. For example, aminoglycosides such as amikacin, gentamicin, tobramycin, and streptomycin are generally recommended to be avoided due to their teratogenic effects (e.g., ototoxicity and nephrotoxicity) reported from human or animal studies (Table 10). PK data, and even safety data, for aminoglycosides are limited as for this class the risk often outweighs the benefit to the fetus/mother when other antimicrobials are available. As a consequence, the possibility of studying these drugs in pregnant women is limited, as is supported by the results obtained from our systematic review. Both amikacin and framycetin PK have not been studied during pregnancy, while limited PK studies ($N = 3$) are available for tobramycin and gentamicin during pregnancy [10–12]. For neomycin, it has to be noted that this is mainly topically administered. Paromomycin can be studied in pregnant women as no fetal toxicity has been reported (Table 10). This probably relies on the fact that it is applied orally and overall absorption is poor with almost 100% recovery in the feces. Therefore, it is likely to have little to no effect on the fetus [33]. For the carbapenems, such as ertapenem, some fetal abnormalities such as decreased fetal weight and decreases in average number of ossified sacrocaudal vertebrae (Table 10) have been reported in animal studies; this hinders the use of ertapenem in humans. This is also supported by the results from our systematic review. However, for both meropenem and imipenem, limited human and animal data suggest low risk, indicating that PK of those drugs can be further investigated. For all quinolones, strict contraindications are provided for use in pregnant women, mainly due to the fact that cartilage and joint abnormalities are reported in animal studies in the earlier stages of pregnancy (Table 10). Thus, PK data is limited, but PK studies performed with quinolones ($N = 6$) overall included pregnant women in later stages of pregnancy such as at caesarean section/delivery [15–17], showing no fetal risks after maternal quinolone exposure. For glycopeptides, dalbavancin seems to be teratogenic based on animal studies (decreased fetal maturation, reduced fertility). For oritavancin and teicoplanin, no data from human and animal studies is presently available in Briggs' 'Drugs in Pregnancy and Lactation' [32]. It has to be noted that dalbavancin and oritavancin have weekly or longer dosing intervals, so studies are very challenging in any population. This is also supported by our systematic review as no PK studies could be found for these drugs. For the glycopeptide vancomycin, no evidence for teratogenicity or fetotoxicity from human and animal studies has been reported, therefore vancomycin is considered safe for all pregnancy states (Table 10). Although four PK studies on vancomycin during the last trimester of pregnancy reported similar PK and exposure in late-trimester pregnant and non-pregnant women, indications are still present to further investigate the PK of this drug in earlier stages of pregnancy as PK data is still absent in those trimesters. For macrolides, erythromycin is the only macrolide recommended in the clinical pregnant population; but data are controversial for azithromycin and clarithromycin. Both have been linked to cardiovascular anomalies (Table 10). It is surprising that no PK data for these three macrolides could be found for pregnant women. Therefore, PK (and safety data) for mother/fetus should be collected for these three macrolides. For polypeptides, both bacitracin and gramicidin are used topically and thus no PK studies are available. For colistin and polymyxin B, no data from human and animal studies seems to be available in the current edition of Briggs' 'Drugs in Pregnancy and Lactation' (Table 10). For the rifamycines, rifaximin and rifabutin have a low to moderate risk based on animal data (Table 10) and thus both are not used in clinical practice. For rifapentine, teratogenic effects mainly occur in early stages of pregnancy (Table 10). Therefore, caution is needed in prescribing rifapentine in early stages of pregnancy. Currently, one PK study has been performed for the PK of rifapentine in the third trimester showing similar PK and exposure compared with post-partum. Rifampicin, however, is reported to be safe in pregnancy based on human and animal studies (Table 10) and one PK study reported similar PK and exposure in late-trimester pregnant compared with postpartum women. Thus, PK (and safety information for the fetus) should be further studied in earlier stages of pregnancy. For sulfonamides, no distinction in risk was made between the various sulfonamides within this specific class. Data from both human and animal studies suggest a risk, especially in the third trimester of pregnancy (Table 10).It has to be noted that one prospective study has been found investigating sulfamethoxazole PK in first- and second-trimester pregnant women undergoing termination of pregnancy [24]. Also, for tetracyclines, no distinction in risk was made between the various tetracyclines within this specific class. All tetracyclines are contra-indicated in the second and third trimester of pregnancy; mainly because of fetal abnormalities, dental and bone issues, and maternal

hepatotoxicity (Table 10). If a tetracycline is strictly indicated during pregnancy, doxycycline should be used only in the first trimester of pregnancy. These findings are in line with the results from our systematic literature review in which no studies were found that have investigated the PK or exposure of tetracyclines. For the tuberculostatic drugs, ethambutol is considered compatible in pregnancy as no teratogenic effects have been reported from human and animal studies (Table 10). Pyrazinamide and isoniazid are also labeled as compatible with pregnancy, although human studies have reported induction of chromosomal aberrations in human lymphocyte cell cultures and animal studies have reported embryonical effects, respectively, for these drugs (Table 9). However, it has to be noted that despite these safety issues, maternal benefit is more important compared with the embryo-fetal risk [32]. The PK of these three tuberculostatic drugs has been studied in more detail during pregnancy, including the ability to reach adequate target concentrations andthe need to develop evidence-based dosing [22–26]. For all these drugs, except for isoniazid, exposure during pregnancy is unchanged, making dose adaptations unnecessary. For isoniazid, contradictory results on altered PK have been reported [23, 25] and more studies are needed. For the tuberculostatic drugs bedaquiline and cycloserine, low and moderate fetal risks are suggested due to limited available data from human and animal studies (Table 10) [32]. Based on human and animal studies, para-amino salicylic acid has been reported to have a risk for malformations, which again limits the possibility of studying the PK in pregnancy. This is also supported by the fact that no papers have been published on the PK in pregnant women. For delamanid and prothionamide, no data from human and animal studies are available in the current edition of Briggs' 'Drugs in Pregnancy and Lactation' [32]. For the other antimicrobial drugs not belonging to a specific class, various labeling has been reported based on risk assessments in human and animal studies. Chloramphenicol, fosfomycin, methenamine, linezolid, and dapsone are labeled as compatible in pregnancy. No human data, but probably compatible in pregnancy, has been reported for mupirocin and tedizolid, while no human data but based on animal data, a fetal risk for clofazimine, aztreonam, daptomycin, and fidaxomicin is reported. Finally, for nitrofurantoin and trimethoprim, a fetal risk for use during pregnancy has been reported based on human or animal studies. In general, the PK of the drugs belonging to 'other antimicrobial drugs' (Sect. 3.12) is not investigated throughout pregnancy.

It has to be concluded that for most drugs, other than penicillins and cephalosporins, the predefined PK/PD relationships ($fT_{>MIC}$, fC_{max}/MIC or fAUC/MIC) [9] currently used to develop evidence-based dosing regimens need to be further investigated, as these are mainly based on theoretical concepts and studies in critically ill patients [34]. Attainment of targets is a challenge to investigate. Target attainment mainly depends on the sensitivity of the micro-organisms in combination with the net exposure to the antibiotic. Thus, both bacterial sensitivity (MIC) and free concentration of the antibiotic need to be studied in pregnancy. It has to be noted that protein binding is a less well studied topic. A problem may be that microbial sensitivity can vary per area and dose recommendations established in high-income countries where these studies can be performed also need to be applicable in low- and middle-income countries where measurement of target attainment is less possible.

The limited number of PK studies found by performing this systematic literature search is a limitation. It has to be concluded that for most drugs, other than penicillins and cephalosporins, limited PK data is available. In addition, these PK studies have been performed with small numbers of pregnant and non-pregnant/postpartum patients. As a consequence, significant differences between these two populations are difficult to prove and bias can occur when interpreting the results. Focus should be on the primary PK parameters Vd and CL between pregnant and non-pregnant patients. Population-PK modelling in combination with simulations is a valuable tool to not only demonstrate clinically relevant differences in PK parameters but also to develop evidence-based dosing schemes to attain adequate targets in pregnant patients [5]. Another reason for the limited PK data being available is mainly due to maternal and/or fetal risks as there is no possibility of obtaining these data throughout pregnancy. This does not mean that no data is available at all. The possibility exists that drugs with a high safety risk will be incidentally used (e.g., when a patient is unaware that she is pregnant; has allergies for safer drugs, or no alternatives are available due to the nature of the infection). It is of the utmost importance to report these cases, including possible PK and safety data. When limited PK data is available, this information can serve as a basis to validate PK predictions from developed physiological-based PK (PBPK) models. Fetal–maternal PBPK (fm-PBPK) modeling is a pragmatic approach combining available compound models with a virtual maternal–fetal physiology model [35]. It can be an attractive tool to predict PK and increase knowledge on both maternal and fetal drug exposure, especially when combined with clinically collected short- and long-term safety data [35]. Another logical next step for future research is to study the PK of those antimicrobial drugs that are considered to be safe (such as meropenem, imipenem, erythromycin, azithromycin and clarithromycin), based on animal or human studies, in a larger heterogenous pregnant population to better describe exposure targets.

A final limitation of the studies found is the fact that only total concentrations of non-penicillin and non-cephalosporin drugs have been measured. It goes without saying that a

changed protein binding will not affect the clearance of the free drug (as this usually stays the same), but the apparent clearance of the total drug. In future research, it is relevant to not only measure the total fractions, but also the free fraction of drugs with high (> 80%) protein binding being the active part.

5 Conclusion

This systematic literature overview shows that currently many knowledge gaps exist for almost all antimicrobial drugs, other than penicillins and cephalosporins, in the pregnant patient population. With this systematic review we hope to stimulate other researchers to fill these missing gaps by providing both PK data and dosing guidances for clinical implementation. Optimization of antibiotic treatment is vital for this vulnerable population.

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Declarations

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