Anti-Infective Dosing in Special Populations: Pregnancy

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Substantial anatomical and physiological changes occur during pregnancy and labor, which impact on drug absorption, distribution, metabolism, and elimination. Reduced maternal concentrations may have a clinically important impact on the efficacy of anti-infectives for mother, fetus, and neonate, with potential dosing implications. However, there is a paucity of pregnancy-specific data examining this. Existing data on the pharmacokinetics of anti-infectives in pregnancy are summarized and evaluated, with emphasis on agents that are used in treatment of HIV, tuberculosis, malaria, and common bacterial infections. Limitations and challenges in achieving ideal study designs in pregnant populations are highlighted, and key quality considerations for the generation of the highest quality evidence are outlined. PubMed was searched for each chosen anti-infective. Pharmacokinetic studies which either compared pharmacokinetics from pregnant women against nonpregnant controls, or which assessed concentrations against a known minimum inhibitory concentration were included. Two independent reviewers extracted data from each study and appraised them using the 24-point ClinPK Checklist. The main finding was that there is a lack of published data for anti-infectives in pregnancy, despite their clinical importance. Of the studies identified, only those investigating cobicistat-boosted antiretroviral regimens firmly concluded that these should not be used in pregnancy. Most studies concluded either that further research was needed, or that there were significant pharmacokinetic differences between pregnant and nonpregnant participants which had uncertain clinical significance. Challenges in applying existing quality grading systems to these studies were noted, suggesting a development of a refined system for appraisal of pharmacokinetic studies in "special populations" may be warranted.

Infections in pregnancy are common and are associated with numerous consequences for the mother, fetus and the neonate, including miscarriage, congenital abnormalities, fetal growth restriction, preterm birth, and significant neonatal morbidity and mortality. Furthermore, the immunological changes in pregnancy confer a greater risk of acquiring infection, or reactivating latent infection. It is estimated that in some parts of Southern Africa, over 30% of pregnant women have human immunodeficiency virus (HIV). While 80% of HIV-infected women worldwide are on antiretroviral treatment, there remains a 14% mother-to-child HIV transmission rate. In 2011, there were an estimated 216,500 active tuberculosis (TB) cases in pregnant women globally, with increased mortality during both pregnancy and the puerperium. In 2018, 11 million pregnancies were exposed to malaria in sub-Saharan Africa, associated with higher risk of maternal anemia and low birth weight. Urinary tract infections and preterm prelabor rupture of membranes with the risk of ascending infection, chorioamnionitis, and maternal sepsis are common worldwide and pose significant risks to mother, fetus, and neonate. Anti-infective drugs are an established part of clinical care in pregnancy, but has robust pharmacokinetic evidence informed the dosing schedules currently used?

During pregnancy, substantial physiological changes which impact on drug absorption, distribution, metabolism, and elimination become evident by the second trimester (Figure 1); where severe systemic illness results from infection, further pharmacokinetic perturbations may occur. Furthermore, pregnancy is a unique situation, balancing the interests of two (or more) participants. While the aim of some anti-infectives is solely to treat the mother, others, such as antiretrovirals, must prevent vertical transmission, while also ensuring safety from adverse effects on the fetus. Traditionally, there has been reluctance to conduct drug trials in pregnant women due to the perceived risk to the fetus; dosing recommendations are often extrapolated from pharmacokinetic data derived from nonpregnant populations. While preclinical evaluation and assessment of potential teratogenicity and adverse fetal effects are centrally important, it is imperative that, as far as possible, studies are undertaken in the population in which the drug will be used. We believe that the pharmacokinetic data and evidence for dosing regimens for new and existing anti-infectives used in pregnancy should be rigorously evaluated to determine whether therapeutic maternal concentrations are achieved in pregnancy, or whether dose adjustment is required. To interpret existing data, it is necessary to understand the study objectives and design; whether target concentrations are known; whether the pharmacokinetic sampling schedule was sufficient to address the research questions; whether the

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pharmacometric analysis was appropriate; and whether the study data are transparent.

This review aimed firstly to summarize and evaluate existing data on the pharmacokinetics of anti-infectives in pregnancy, focusing on agents that are commonly used worldwide. Secondly, we discuss some of the limitations and challenges in study design with reference to existing studies. Finally, we present approaches to overcome these challenges, to improve the quality of future pharmacokinetic studies conducted in pregnancy.

**CHOICE OF DRUGS AND METHODS TO SYNTHESIZE DATA**

The following anti-infectives were chosen based on commonly used treatment guidelines:

- Antituberculous drugs from World Health Organization (WHO) guidelines, first line: rifampicin, isoniazid, pyrazinamide, and ethambutol; second line: moxifloxacin, linezolid, bedaquiline, and delamanid
- Antimalarials from WHO guidelines: quinine (first trimester), artemether-lumefantrine (second and third trimester), and intravenous artesunate (severe malaria at any stage)
- Antibiotics: benzylpenicillin administered during labor for prophylaxis against early-onset neonatal group B streptococcus (GBS) infection, erythromycin prescribed following preterm labor rupture of membranes, amoxicillin for urinary tract infection, amoxicillin/clavulanic acid, and gentamicin or metronidazole for maternal sepsis
- Antiretrovirals: all licensed antiretroviral drugs.

The terms “pharmacokinetics” AND “pregnancy” AND “[selected drug]” were entered into PubMed for each chosen anti-infective, without date or language restrictions. Titles and abstracts were screened against the study question with evaluation of potentially relevant full text articles. Inclusion criteria were (i) primary pharmacokinetic study; (ii) comprising pregnant women at any stage of gestation; and (iii) including a nonpregnant control group, and/or direct comparison against a known target concentration, for example the minimal inhibitory concentration (MIC) to be achieved in pregnant women. The nonpregnant control group could comprise historical controls if these data were presented and analyzed within the study itself, vs. in the discussion only. Studies in only nonpregnant participants, animal studies, or those focused only on placental, amniotic fluid, or neonatal pharmacokinetics were excluded.

The pharmacokinetics of antiretrovirals were recently reviewed by Hodel and colleagues.9 From this comprehensive overview, studies of drugs which showed clinically significant differences in pharmacokinetics between pregnant and nonpregnant participants were selected for our review. Further searches of these selected antiretrovirals were conducted to ensure that any subsequent studies were included. Similarly, a recent meta-analysis assessed artemether-lumefantrine pharmacokinetics in pregnant women and children,10 so only studies undertaken subsequently were included as individual items.

Two independent reviewers (P.H. and C.W.) extracted the following data points: population studied, control group, sampling occasion/s (2nd trimester/3rd trimester/intrapartum/...
postpartum), number of sampling timepoints, pharmacometric method, conclusion, and limitations. Both reviewers also appraised each study and graded the quality of evidence using the ClinPK scoring system (Table S1). Drug concentrations within cord, amniotic fluid, breastmilk, and neonates/infants were beyond the scope of this review. Intrapartum studies were included, but women undergoing elective (prelabor) caesarean section (ELCS) were classed as being participants in their third trimester, rather than in labor. Finally, all authors discussed the limitations of existing literature and sought to succinctly present the key design considerations for high-quality pharmacokinetic studies in pregnancy.

FINDINGS FROM REVIEW OF PHARMACOKINETIC LITERATURE
Search results are shown in Figure 2. The most frequent reason for exclusion of full text articles was lack of a nonpregnant comparator group.

Table 1 summarizes the included studies. Further detail regarding the study design, pharmacokinetic sampling schedule, and results of each of these studies is provided in Table S2.

Antituberculous drugs
Only three studies were identified, all of which involved HIV-infected pregnant women receiving first-line TB treatment. One of these evaluated pharmacokinetics of isoniazid, pyrazinamide, and ethambutol and concluded that no changes were needed in dosing for pregnant women, as there were no significant differences between women antenataally and 7-weeks postpartum. However, there were very few paired sampling occasions where the woman acted as her own control postpartum: eight for isoniazid and one each for pyrazinamide and ethambutol. This relates to the four-drug intensive period of TB treatment being only 2 months long; by the postpartum sampling occasion, many women were on the continuation phase of treatment comprising only rifampicin and isoniazid.

**Quality Considerations for All PK Studies**

| Study rationale, design and objectives clearly stated |
|-------------------------------------------------------|
| Choice of study population (and where appropriate, control group) justified |
| Eligibility criteria stated |
| Concurrent medication or food requirements/ restrictions described |
| Details on drug formulation, preparation and administration |
| Sampling schedule for blood (and other body fluids) clear and sufficient to answer research questions. Where a ‘sparse’ sampling schedule used, statement on verification of time of dose and selection of timepoints |
| Validation of quantitative bioanalytical methods referenced or described |
| Pharmacokinetic and statistical modelling methods and software described |
| Pharmacokinetic ‘target’ concentrations stated and referenced |
| Study withdrawals, loss to follow-up and missing data reported |
| Methods used to handle missing data described |
| Limitations and sources of bias discussed |
| Data made Findable, Accessible, Interoperable and Reusable (FAIR) |

**Additional Considerations for Pregnancy PK studies**

- Prospective study designed specifically for pregnancy PK
- Study population reflective of wider population (age, ethnicity, comorbidities)
- For long-term medication, sampling in pregnancy and again > 4-6 weeks postpartum
- Includes free and unbound concentrations of drug if possible

**Additional Considerations for PK studies in Labour**

- Informed consent and recruitment to study prior to active labour
- Flexibility within consent – to enable choice to participate in selected aspects of study
- Flexibility and adaptability for missed time points or change in maternal preferences
- Actual time points accurately recorded
- Paired cord and maternal blood samples where possible
- Consider sampling amniotic fluid and placenta

Figure 2 Flowchart of search outcomes for each anti-infective. PK, pharmacokinetics.
| Author/Year | Population | Pregnant/Nonpregnant control | Sampling occasion | Number of samples post dose | Method | Conclusion | ClinPK score | Limitations |
|-------------|------------|-------------------------------|-------------------|----------------------------|--------|------------|--------------|-------------|
| Denti 2015  | HIV-positive women with TB in T2 or T3 | 48/48 (all paired) | T3 and PP | 3 | Comp | No dose adjustment needed | 21 | Inaccurate timing of doses |
| Abdelwahab 2020 | HIV-positive women with TB in T2 or T3 | 18/8 | T3 and PP | 3 | Comp | No dose adjustment needed | 16 | Lack of paired samples; Inaccurate timing of doses |
| Gausi 2020 | HIV-positive women with TB in T2 or T3 | 420/637 (210 paired) | T3 and PP | Intensive = 6 (32 samples) Sparse = 1 (815) | Comp | Reduced levels in pregnancy, unclear clinical relevance | 18 | Unclear timing of sparse sampling visits |
| Abdelwahab 2020 | HIV-positive women with TB in T2 or T3 | 13/3 (1 paired) | T3 and PP | 3 | Comp | No dose adjustment needed | 16 | Lack of paired samples |
| Pyrazinamide |
| Abdelwahab 2020 | HIV-positive women with TB in T2 or T3 | 13/3 (1 paired) | T3 and PP | 3 | Comp | No dose adjustment needed | 16 | Lack of paired samples |
| Ethambutol |
| Abdelwahab 2020 | HIV-positive women with TB in T2 or T3 | 13/3 (1 paired) | T3 and PP | 3 | Comp | No dose adjustment needed | 16 | Lack of paired samples |
| Artemether-Lumefantrine |
| Nyunt 2016 | Falciparum in T2 or T3 | 30/30 (not paired) | T2 or T3 | 10 | NCA | Further research needed | 20 | Males in control group |
| Mutagonda 2019 | Falciparum in T2 or T3 | 205/72 (not paired) | T2 or T3 | 1 | Other | Lower levels in pregnancy; unclear clinical relevance | 14 | Single timepoint; lack of paired samples |
| Mosha 2014 | Falciparum in T2 or T3 | 33/22 (not paired) | T2 or T3 | 4 | Comp + simulation | Consider modified 5-day regimen | 19 | Lack of paired samples |
| Adegbola 2018 | Falciparum, T2/T3, HIV positive on efavirenz | 35/34 (not paired) | T2 or T3 | 9 | NCA | Further research needed | 15 | Lack of paired samples |
| Tarning 2013 | Falciparum in T2 or T3 | 26/17 (not paired) | T2 or T3 | 24 | NCA | Further research needed | 17 | Lack of paired samples |
| Kloprogge 2013 | Falciparum in T2 or T3 | 116/17 (not paired) | T2 or T3 | 24 | Comp + simulation | May need alteration, further research needed | 18 | Lack of paired samples |
| Quinine |
| Abdelrahim 2007 | Falciparum in T2 or T3 | 8/8 (not paired) | T2 or T3 | 7 | NCA | No dose adjustment needed | 15 | Small sample size |
| IV artesunate |
| McGready 2012 | Falciparum in T2 or T3 | 20/14 (all paired) | T2 or T3 | 8 | NCA | No dose adjustment needed | 17 | Small sample size |

(Continued)
| Author/Year | Population | Sampling occasion | Number of samples post dose | Method | Conclusion | ClinPK score | Limitations |
|-------------|------------|-------------------|----------------------------|--------|------------|--------------|-------------|
| **Antibiotics** | | | | | | | |
| **Amoxicillin** | Andrew 2007 | Healthy, T2 or T3 | 16/16 (all paired) | T2 and T3 and PP | 11 | Comp + simulation | Further research needed | 19 | Single dose of drug given |
| | Muller 2008 | T3 with PROM/ in labor, GBS positive | 25/8 (not paired) | 9 IP (8 paired) | T3/IP and PP | 8 | Comp | No dose adjustment needed | 14 | Lack of paired samples; PP dose was 4 hours after labor |
| **Benzylpenicillin** | Johnson 2001 | Healthy, T3 | 15/0 | T3 | 11 | NCA | Concentration > MIC achieved, further research needed | 14 | No controls; short length of sampling |
| **Erythromycin** | Bulska 2015 | GBS positive, ELCS or VD | 34/8(IP)/42 | PP | 1 | Other | Concentration > MIC achieved in maternal serum, not in umbilical vein serum | 15 | Single timepoint; unclear analysis |
| | Larsen 1998 | T2 or T3 with C trachomatis | 10/0 | T2/T3 | 5 | Not stated | Subtherapeutic concentration with gastrointestinal side effect | 10 | No controls; unclear analysis; interindividual variability not shown |
| **Gentamicin** | Popovic 2007 | Undergoing gynecological surgery/ELCS (T3) | 18/4 (not paired) | PP or postoperative | 2 | Comp | Concentration < MIC achieved | 15 | Lack of paired samples; both timepoints PP |
| **Metronidazole** | Wang 2010 | T1, T2, or T3 | 20/0 | T1, T2, or T3 | 10 | Comp | No dose adjustment needed | 17 | No controls—compared with previous data |
| **Antiretrovirals** | Elvitegravir-Cobicistat | HIV positive T2 or T3 | 30/30 (paired) | T2 and T3 and PP | 7 | Other | Should not be used in pregnancy | 17 | Meals given at time of drug not standardized |
| | Momper 2018 | HIV positive T2 or T3 | 14/12 (paired) | T3 and PP | 9 | NCA | Should not be used in pregnancy | 14 | Small sample size |
| | Bukkems 2020 | HIV positive T2 | 6/6 (paired) | T2 and T3 and PP | 8 | NCA | Should not be used in pregnancy | 16 | Small sample size |

Comp, compartmental analysis; ELCS, elective caesarean section; GBS, group B streptococcus; IP, intra-partum (during labor); IV, intravenous; MIC, minimum inhibitory concentration; NCA, noncompartmental analysis; PP, postpartum; PROM, premature rupture of membranes; T2, second trimester; T3, third trimester; VD, vaginal delivery.
Using the 24-point ClinPK scale, the median score of these studies was 18 (range 16–21).

**Antimalarial drugs**
The 2018 meta-analysis of artemether-lumefantrine pharmacokinetics in children and pregnant women concluded that day-7 plasma lumefantrine concentrations were 20% lower in pregnant women than in nonpregnant controls. However, despite using data from 1,347 participants to generate the lumefantrine population pharmacokinetic model, only 40 of these were pregnant (3.12%).

Six studies published following this meta-analysis were identified. Out of these, five were inconclusive regarding need for dose adjustments but rather commented that the clinical relevance of statistically significant differences in pharmacokinetic parameters warrants further evaluation. All the studies used day-7 lumefantrine concentrations of either >175 ng/mL or >280 ng/mL as a proxy for adequate dosing to avoid treatment failure, based on the demonstrated correlation between concentrations below these targets and risk of recrudescence malaria. Mosha and colleagues found that with the standard 3-day regimen, 9% of pregnant women had day-7 lumefantrine concentrations <280 ng/mL, compared with 2% of nonpregnant women. Thresholds of 175 and 280 ng/mL have both been considered.

However, the precise pharmacodynamic relationship has not been elucidated, and other studies have failed to demonstrate clear clinical correlation of subtherapeutic concentrations. While further data may determine the optimal target, the more conservative threshold of 280 ng/mL is logical as it seems likely to reduce the risk of subtherapeutic effects on the parasite and reduce selection for drug-resistant parasites. Supporting this, Mosha and colleagues demonstrated that a modified regimen could optimize concentrations for pregnant women initially below this threshold. Simulation from their models demonstrated that a modified 5-day regimen may result in only 2% of pregnant women having a day-7 lumefantrine concentration of <280 ng/mL.

One study each was identified for artesunate and quinine. Both concluded that no dose adjustment was needed in pregnancy, but both were limited by small sample size.

The median ClinPK Score for the antimalarial studies was 17 (range 14–20).

**Antibiotics**
Despite clinical guidelines recommending amoxicillin, benzylpenicillin, erythromycin, gentamicin, and metronidazole for treatment of infection in pregnancy, only seven appropriate studies were identified. Three studies did not use pregnant controls but were included as they measured concentrations against a target MIC. In one study, women undergoing gynecological surgery were compared with women undergoing ELCS. There was no formal matching between these groups, but rather an assumption that nonpregnant women undergoing elective gynecological surgery would provide a comparator to women in their third trimester undergoing ELCS. Two studies were conducted during active labor. One examined use of amoxicillin for GBS colonization in women both prior to the onset of labor (with PROM) and during labor. Eight women sampled following a dose during labor received an additional dose postpartum, followed by further sampling. However, this “postpartum” dose was given within 4 hours after delivery. The second labor study, by Bulska and colleagues was limited through use of a single sampling timepoint, which was immediately postpartum.

Most studies concluded that either there were no significant differences between pregnant women and nonpregnant controls, or that therapeutic concentrations were achieved in pregnant women. When comparing gentamicin pharmacokinetics between nonpregnant women undergoing surgery and women undergoing ELCS, Popovic and colleagues concluded that subtherapeutic concentrations were achieved in pregnancy, but they drew this conclusion from samples taken at two timepoints subsequent to delivery.

For these studies, the median ClinPK score was 15 (range 10–19).

**Antiretroviral treatment**
The 2019 review by Hodel evaluated 45 clinical studies, excluding those where treatment was initiated in labor, and studies using nonpregnant adults as comparators. Therefore, all studies compared the same women during pregnancy and postpartum. No dose adjustments for nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and ritonavir-boosted protease inhibitors were recommended, as despite some significant differences in pharmacokinetics, drug exposures remained adequate to suppress viral replication. However, clinically significant reductions in cobicistat-boosted regimens mean that these are not recommended for use in pregnancy due to the risk of virologic failure.

We further evaluated these clinically significant studies; there are no new antiretroviral compounds with pregnancy-specific data. Concentrations of cobicistat and cobicistat-boosted elvitegravir and darunavir were significantly lower during pregnancy. This finding was reiterated in an additional study published in 2020. Cobicistat is a potent cytochrome P450 3A4 (CYP3A4) inhibitor used in combination with darunavir and elvitegravir to increase their plasma concentrations. The progesterone-mediated induction of CYP3A4 during pregnancy accelerates cobicistat clearance, resulting in lower concentrations of itself and the partner drugs.

For these studies, the median ClinPK score was 16 (range 14–17).

**STUDY DESIGN, DATA MANAGEMENT, ETHICAL AND REGULATORY CONSIDERATIONS**
We aimed to summarize and evaluate existing literature on pharmacokinetics of anti-infectives used during pregnancy. The limited amount of published data for these drugs, despite their clinical importance in pregnant women, was striking. Substantially more data exist for antiretrovirals than for antibiotics, antimalarial, and antituberculous drugs, perhaps because a major goal of maternal treatment has been to prevent vertical transmission to the infant, as well as strong research partnerships and community advocacy compared with the other drug groups or diseases.

Very few studies firmly concluded that drugs should not be used at the same doses as in nonpregnant patients, with these data...
relating to cobicistat-boosted antiretroviral regimens. Others, particularly regarding antimalarials, concluded that the significant differences between concentrations in pregnant and nonpregnant patients had uncertain clinical relevance. In the antibiotic category, Bulska et al. found that maternal erythromycin concentrations were higher than the target MIC, but the limited transplacental transfer of the drug suggested compromised efficacy in treatment of intrauterine infections.\textsuperscript{23} Most stated that further research was needed to determine adequate dosing in this population.

The European Medicines Agency has highlighted the need for more pharmacokinetic studies in women (nonpregnant, pregnant, and lactating), stating that there should be an “all-encompassing approach regarding the inclusion and follow-up of pregnant women in well-designed clinical trials and post authorization, rather than excluding them systematically.”\textsuperscript{33} However, no legislation exists to make these studies mandatory and often pregnancy is a major exclusion criterion for clinical trials, with mandatory withdrawal should a pregnancy occur.\textsuperscript{6} Guidance from the US Food and Drug Administration (FDA) states that there either must be a prospect of direct benefit for the woman or fetus or, if no direct benefit, the risk to the fetus is minimal and the knowledge cannot be obtained by any other means.\textsuperscript{34} Consequently, the fear of harm to the fetus from drugs often outweighs the potential benefits for the pregnant woman. However, in many situations, these adverse effects are only a possibility, whereas adverse outcomes of infections on the mother, fetus, and neonate are well established.\textsuperscript{1}

It was not until 2018 that the FDA issued warnings on the use of cobicistat-containing antiretroviral regimens in pregnancy,\textsuperscript{6} despite them having been registered and in clinical use including in pregnancy for up to 6 years. The median delay between registration of a new antiretroviral agent and published data on pharmacokinetics and safety in pregnancy is 6 years.\textsuperscript{6} During this interval, healthcare professionals face a difficult choice: prescribing a drug “off-label” with potential risks to mother and infant, or denying them access to a drug that could bring significant benefit.

During labor, additional physiological changes occur, further altering the concentration-time profile of drugs.\textsuperscript{26} Guidance recommends use of antibiotics during labor in all pregnant women at increased risk of transmitting GBS to their baby during delivery. Despite the organism being carried in the genito-anal tract of 20–40% of UK women,\textsuperscript{7} only two studies evaluating the influence of labor on pharmacokinetics of anti-infectives used against GBS were identified. There are ethical and practical barriers to conducting these studies, but nonetheless, it is critically important to verify that adequate concentrations of antibiotic are reached to prevent neonatal sepsis.

High-quality pharmacokinetic studies require rigorous attention to study design and reporting. Several additional challenges are seen in pregnant or laboring women. For example, the physiological changes that occur during pregnancy take ~6 weeks after birth to resolve; therefore it is imperative to allow adequate time before the postpartum sampling occasion.\textsuperscript{35} This was a particular limitation for the intrapartum studies which used the immediate postpartum timepoint. Figure 3 outlines some key study design considerations. In this review, quality of evidence was appraised using the ClinPK Checklist, a list of 24 items describing the quality of design and reporting of pharmacokinetic studies. The median score obtained was 16, with a range of 10 to 21. Most studies were limited by small sample size and unmatched control populations. Those which evaluated anti-infectives which are used long-term, such as antiretrovirals or antituberculous drugs, could measure concentrations in the same women antepartum and postpartum. This comparison is more challenging to attain for drugs which are given as a short treatment course in late pregnancy or around delivery, unless for research purposes a repeat dose or treatment course is given around 6 weeks postpartum. In this scenario, the participant would no longer require the treatment for her own health and might be breastfeeding; participation in such studies would therefore present different risk–benefit considerations. To overcome these challenges, matched nonpregnant women could be used as controls.

Most studies measured total plasma concentration of drugs. However, some drugs, such as the protease inhibitor class of antiretrovirals, are more than 90% protein bound, with activity depending on unbound drug entering cells.\textsuperscript{9} In late pregnancy, decreased maternal albumin and occupation of binding sites by steroids and hormones may result in increased free drug fraction. If only total drug concentration is measured, this may be incorrectly interpreted as increased elimination. Ideally, both bound and unbound concentrations should be measured.

Most identified studies employed noncompartmental analysis or population pharmacokinetic modeling. Some studies, particularly on antimalarials, used simulation in their analysis to predict an adjusted dosing regimen to achieve therapeutic concentrations in pregnant women with a range of clinical covariates. Future clinical studies could evaluate the real-life efficacy of this simulated regimen. Data sharing enables data from previous clinical trials to be used in both physiologically-based pharmacokinetic and population pharmacokinetic modeling.\textsuperscript{36} However, most studies do not make their primary data sets available. Increasing awareness of the need to make data findable, accessible, interoperable, and reusable (FAIR) has not yet translated to improved access to data in studies relating to anti-infective exposure in pregnancy.

Furthermore, alongside pharmacokinetic parameters, studies should ideally evaluate clinical outcomes to enable concentrations to be correlated with efficacy. Sample size or study duration can make this challenging within the design of a pharmacokinetic study (for example end of treatment outcomes in the case of TB treatment). Additionally, when considering the risk–benefit ratio in the mother–infant dyad, other measurements such as cord-blood-to-maternal-blood ratios, breastfeeding, and infant plasma concentrations provide valuable information. While this current review focuses on the pharmacokinetic differences encountered during pregnancy, these other measurements should be considered in relation to the overall goals of the clinical study.

A final observation from this review is the difficulty in grading quality of evidence of pharmacokinetic studies. Clinical trials are frequently appraised against GRADE (Grading of Recommendations, Assessment, Development and Evaluations) criteria, but many criteria are not applicable for pharmacokinetic studies. The Grading and Assessment of Pharmacokinetic-Pharmacodynamic Studies (GAPPS) system was developed for use in pediatric drug development studies.\textsuperscript{37} However, in practice, the
**Figure 3**  Key study design considerations in pharmacokinetic studies during pregnancy and labor. IV, intravenous; TB, tuberculosis.

**Records identified through database search**

| Drug                          | N   |
|-------------------------------|-----|
| Rifampicin                    | 42  |
| Isoniazid                     | 16  |
| Pyrazinamide                  | 2   |
| Ethambutol                    | 4   |
| Artemether-Lumefantrine       | 30  |
| Quinine                       | 33  |
| IV Artesunate                 | 8   |
| Amoxicillin                   | 23  |
| Amoxycillin/clavulanic acid   | 0   |
| Benzylpenicillin              | 144 |
| Erythromycin                  | 49  |
| Gentamicin                    | 34  |
| Metronidazole                 | 29  |

**Records removed as not relevant**

| Drug                          | N   |
|-------------------------------|-----|
| Rifampicin                    | 37  |
| Isoniazid                     | 13  |
| Pyrazinamide                  | 1   |
| Ethambutol                    | 2   |
| Artemether-Lumefantrine       | 20  |
| Quinine                       | 27  |
| IV Artesunate                 | 6   |
| Amoxicillin                   | 17  |
| Benzylpenicillin              | 142 |
| Erythromycin                  | 42  |
| Gentamicin                    | 29  |
| Metronidazole                 | 27  |

**Records removed as not relevant**

| Drug                          | N   |
|-------------------------------|-----|
| Rifampicin                    | 37  |
| Isoniazid                     | 13  |
| Pyrazinamide                  | 1   |
| Ethambutol                    | 2   |
| Artemether-Lumefantrine       | 20  |
| Quinine                       | 27  |
| IV Artesunate                 | 6   |
| Amoxicillin                   | 17  |
| Benzylpenicillin              | 142 |
| Erythromycin                  | 42  |
| Gentamicin                    | 29  |
| Metronidazole                 | 27  |

**Full text articles considered**

| Drug                          | N   |
|-------------------------------|-----|
| Rifampicin                    | 5   |
| Isoniazid                     | 3   |
| Pyrazinamide                  | 1   |
| Ethambutol                    | 2   |
| Artemether-Lumefantrine       | 10  |
| Quinine                       | 6   |
| IV Artesunate                 | 2   |
| Amoxicillin                   | 6   |
| Benzylpenicillin              | 2   |
| Erythromycin                  | 7   |
| Gentamicin                    | 5   |
| Metronidazole                 | 2   |

**Full text articles excluded**

| Drug                          | N   |
|-------------------------------|-----|
| Rifampicin                    | 4   |
| Isoniazid                     | 1   |
| Pyrazinamide                  | 0   |
| Ethambutol                    | 1   |
| Artemether-Lumefantrine       | 4   |
| Quinine                       | 5   |
| IV Artesunate                 | 1   |
| Amoxicillin                   | 4   |
| Benzylpenicillin              | 1   |
| Erythromycin                  | 5   |
| Gentamicin                    | 4   |
| Metronidazole                 | 1   |

**Articles included in review**

| Drug                          | N   |
|-------------------------------|-----|
| Rifampicin                    | 1   |
| Isoniazid                     | 2   |
| Pyrazinamide                  | 1   |
| Ethambutol                    | 1   |
| Artemether-Lumefantrine       | 6   |
| Quinine                       | 1   |
| IV Artesunate                 | 1   |
| Amoxicillin                   | 2   |
| Benzylpenicillin              | 1   |
| Erythromycin                  | 2   |
| Gentamicin                    | 1   |
| Metronidazole                 | 1   |

*Antiretrovirals* data primarily drawn from existing review (Hodel et al.) and therefore not detailed in our search strategy.
allocation of greater weight to studies which used pooled data sets and simulation, irrespective of sample size, type of control group, and number of sampling timepoints meant that studies that used paired participants antenatally and postpartum, but did not use simulation, were deemed as "weak," when arguably these are higher quality. Ultimately, the ClinPK scale was considered to emphasize the key quality characteristics which would indicate optimal study design for a pharmacokinetic study comparing drug exposure between pregnancy and nonpregnant controls (See Table S1).

However, this scoring system still does not fully address considerations of sample size, appropriateness of sampling schedule, or type of control group, highlighting that there is a need for a specific grading system for studies which compare pharmacokinetics between populations. In conclusion, there is a paucity of high-quality research surrounding the pharmacokinetics of anti-infectives in pregnant women. This lack of knowledge results in medications being used in this population off-label, without information on efficacy. If gender equity is ever to be achieved in research, in addition to including pregnant women in trials of new drugs, specific studies to evaluate pharmacokinetics of important drugs with established and emerging use in pregnancy (such as anti-infectives) must be undertaken. Experienced women's health trialists must collaborate with pharmacokinetic-pharmacodynamic and infectious disease experts to design robust studies with suitable controls, sample types, and sampling schedules.

SUPPORTING INFORMATION
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CONFLICT OF INTEREST
PH and CW designed the structure for the review, performed the searches and analysed data. PH, CW, PB and KN wrote the manuscript and formulated the ideal study design for PK studies in pregnancy.

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