Article type : Mini-Review

# Anti-infective Dosing in Special Populations: Pregnancy

[1]Phoebe Hazenberg, [2]Kate Navaratnam, [2]Paula Busuulwa, [3,4]Catriona Waitt

[1]Faculty of Health and Life Sciences, University of Liverpool, UK

[2] Centre for Women's Health Research, Institute of Translational Medicine, University of Liverpool, UK

[3] Department of Pharmacology and Therapeutics, Institute of Systems, Molecular & Integrative Biology, University of Liverpool, UK

[4] Infectious Diseases Institute, Makerere University College of Health Sciences, Kampala, Uganda

Dr Phoebe Hazenberg, Faculty of Health and Life Sciences, University of Liverpool, 07308 598628, phoebehazenberg@liverpoolft.nhs.uk

Dr Kate Navaratnam, Centre for Women's Health Research, Institute of Translational Medicine, University of Liverpool, Kate.Navaratnam@liverpool.ac.uk

Dr Paula Busuulwa, Centre for Women's Health Research, Institute of Translational Medicine, University of Liverpool, paula.busuulwa@liverpool.ac.uk

Dr Catriona Waitt, Department of Pharmacology and Therapeutics, 70 Pembroke Place, Liverpool L69 3GF. +447581417744 cwaitt@liverpool.ac.uk

The authors declared no competing interests for this work.

CW is a Wellcome Clinical Research Career Development Fellow 222075/Z/20/Z. KN is a funded NIHR ACL and holds a Wellbeing of Women Postdoctoral Fellowship.

Keywords: Pregnancy, Pharmacokinetics, Dosing, Antibiotics, Antiretrovirals, Antimalarials, Antituberculous drugs

**Abstract**

Substantial anatomical and physiological changes occur during pregnancy and labour, 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 summarised and evaluated, with emphasis on agents that are used in treatment of HIV, TB, 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 non-pregnant 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 the 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 non-pregnant 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.

**Introduction**

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(1). 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)(2). Whilst 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 cases in pregnant women globally, with increased mortality both during pregnancy and the puerperium (3). In 2018, 11 million pregnancies were exposed to malaria in sub-Saharan Africa, associated with higher risk of maternal anaemia and low birth weight(4). Urinary tract infections (UTI) and preterm prelabour rupture of membranes (PPROM) 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 (5) Furthermore, pregnancy is a unique situation, balancing the interests of two (or more) participants. Whilst the aim of some anti-infectives is solely to treat the mother, others, such as antiretrovirals, must prevent vertical transmission, whilst also ensuring safety from adverse effects on the fetus (6). 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 non-pregnant populations. Whilst pre-clinical 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 pharmacometric analysis was appropriate; and whether the study data are transparent.

This review aimed firstly to summarise and evaluate existing data on the pharmacokinetics of anti-infectives in pregnancy, focussing 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 Synthesise Data**

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

- Antituberculous drugs from WHO guidelines: first line: rifampicin, isoniazid, pyrazinamide, ethambutol; second line: moxifloxacin, linezolid, bedaquiline, 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 labour for prophylaxis against early-onset neonatal group B streptococcus (GBS) infection (7), erythromycin prescribed following PPROM (8), amoxicillin for urinary tract infection (UTI), amoxicillin/clavulanic acid, 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: 1) primary pharmacokinetic study; 2) comprising pregnant women at any stage of gestation; 3) including a non-pregnant 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 non-pregnant control group could comprise historical controls if these data were presented and analysed within the study itself, versus in the discussion only. Studies in only non-pregnant participants, animal studies or those focussed 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 non-pregnant 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 (PH and CW) extracted the following data points: population studied, control group, sampling occasion/s (2nd trimester/3rd trimester/intrapartum/postpartum), number of sampling time points, pharmacometric method, conclusion and limitations. Both reviewers also appraised each study and graded the quality of evidence using the ClinPK scoring system(11) (Table S1). Drug concentrations within cord, amniotic fluid, breastmilk and neonates/infants were beyond the scope of this review. Intra-partum studies were included, but women undergoing elective (pre-labour) caesarean-section (ELCS) were classed as being participants in their third trimester, rather than in labour. 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 non-pregnant comparator group.

Table 1 summarises 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 (12-14). 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 antenatally and 7-weeks postpartum(12). 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 two months long; by the postpartum sampling occasion, many women were on the continuation phase of treatment comprising only rifampicin and isoniazid.

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 non-pregnant controls(10). However, despite using data from 1347 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(15-20). 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 >175ng/ml or >280ng/ml as a proxy for adequate dosing to avoid treatment failure, based on the demonstrated correlation between concentrations below these targets and risk of recrudescent malaria(16). Mosha and colleagues found that with the standard 3-day regimen, 9% of pregnant women had day-7 lumefantrine concentrations <280ng/ml, compared with 2% of non-pregnant women (17).

Thresholds of 175 ng/ml and 280 ng/ml have both been considered (16). However, the precise pharmacodynamic relationship has not been elucidated and other studies have failed to demonstrate clear clinical correlation of subtherapeutic concentrations. Whilst 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 (16). Supporting this, Mosha and colleagues demonstrated that a modified regime could optimise concentrations for pregnant women initially below this threshold (17). Simulation from their models demonstrated that a modified 5-day regimen may result in only 2% of pregnant women having day-7 lumefantrine concentration of <280ng/ml(17).

One study each was identified for artesunate and quinine(21, 22). 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(23-

29). Three studies did not use non-pregnant controls but were included as they measured concentrations against a target MIC(23, 24, 28). In one study, women undergoing gynaecological surgery were compared against women undergoing ELCS(27). There was no formal matching between these groups, but rather an assumption that non-pregnant women undergoing elective gynaecological surgery would provide a comparator to women in their third trimester undergoing ELCS. Two studies were conducted during active labour(23, 26). One examined use of amoxicillin for GBS colonisation in women both prior to the onset of labour (with PROM) and during labour(26). Eight women sampled following a dose during labour received an additional dose postpartum, followed by further sampling. However, this "postpartum" dose was given within four hours after delivery. The second labour study, by Bulska and colleagues was limited through use of a single sampling time point, which was immediately postpartum.

Most studies concluded that either there were no significant differences between pregnant women and non-pregnant controls, or that therapeutic concentrations were achieved in pregnant women. When comparing gentamicin pharmacokinetics between non-pregnant women undergoing surgery and women undergoing ELCS, Popovic and colleagues concluded that sub-therapeutic concentrations were achieved in pregnancy, but drew this conclusion from samples taken at two time points subsequent to delivery(27).

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 labour, and studies using non-pregnant adults as comparators(9). 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 (30, 31). This finding was reiterated in an additional study published in 2020(32). Cobicistat is a potent CYP3A4 inhibitor used in combination with darunavir and elvitegravir to increase their plasma concentrations(9). 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 summarise 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 to the other drug groups or diseases.

Very few studies firmly concluded that drugs should not be used at the same doses as in non-pregnant patients, with these data relating to cobicistat-boosted antiretroviral regimens. Others, particularly regarding antimalarials, concluded that the significant differences between concentrations in pregnant and non-pregnant 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(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 (non-pregnant, 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-authorisation, rather than excluding them systematically”(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(6). Guidance from the US Food and Drug Administration (FDA) states that there either must be 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(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(1).

It was not until 2018 that the FDA issued warnings on the use of cobicistat-containing antiretroviral regimens in pregnancy(6), despite them having been registered and in clinical use including in pregnancy for up to six years. The median delay between registration of a new antiretroviral agent and published data on pharmacokinetics and safety in pregnancy is six years(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 which could bring significant benefit.

During labour, additional physiological changes occur, further altering the concentration-time profile of drugs(26). Guidance recommends use of antibiotics during labour 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(35), only two studies evaluating the influence of labour 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 labouring women. For example, the physiological changes that occur during pregnancy take approximately six weeks after birth to resolve, therefore it is imperative to allow adequate time before the postpartum sampling occasion (36) ; 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 six 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 non-pregnant 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(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 non-compartmental analysis or population pharmacokinetic (pop-PK) modelling. 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 (PBPK) and pop-PK modelling(37). However, most studies do not make their primary datasets 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: maternal blood ratios, breastmilk and infant plasma concentrations provide valuable information. Whilst 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 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 paediatric drug development studies(38). However, in practice, the allocation of greater weight to studies which used pooled datasets and simulation, irrespective of sample size, type of control group and number of sampling time points 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 emphasise the key quality characteristics which would indicate optimal study design for a pharmacokinetic study comparing drug exposure between pregnancy and non-pregnant 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, sampling schedules.

**Acknowledgements**

We would like to thank Owen Neve for the design of the pregnant woman in Figure 1.

**References**

(1) Barinov, S.V., Tirskaya, Y.I., Kadsyna, T.V., Lazareva, O.V., Medyannikova, I.V. & Tshulovski, Y.I. Pregnancy and delivery in women with a high risk of infection in pregnancy. *The Journal of Maternal-Fetal & Neonatal Medicine*, 1-6 (2020).

(2) McIntyre, J. HIV in Pregnancy: A Review. *World Health Organisation* (1998).

(3) Bates, M., Ahmed, Y., Kapata, N., Maeurer, M., Mwaba, P. & Zumla, A. Perspectives on tuberculosis in pregnancy. *International Journal of Infectious Diseases* **32**, 124-7 (2015).

(4) (2019). *World Malaria Report 2019* (World Health Organisation Geneva, 2019).

(5) Roberts, J.A. & Lipman, J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Critical care medicine* **37**, 840-51; quiz 59 (2009).

(6) Colbers A, M.M., Schalkwijk S, Penazzato M, Townsend C, Burger D. . Importance of Prospective Studies in Pregnant and Breastfeeding Women Living With Human Immunodeficiency Virus. . *Clin Infect Dis* **69**, 1254-8 (2019).

(7) Hughes, R., Brocklehurst, P., Steer, P., Heath, P. & Stenson, B. Prevention of early-onset neonatal group B streptococcal disease. Green-top Guideline. *BJOG* **124**, e280-e305 (2017).

(8) Tsakiridis, I., Mamopoulos, A., Chalkia-Prapa, E.M., Athanasiadis, A. & Dagklis, T. Preterm Premature Rupture of Membranes: A Review of 3 National Guidelines. *Obstet Gynecol Surv* **73**, 368-75 (2018).

(9) Hodel, E.M., Marzolini, C., Waitt, C. & Rakhmanina, N. Pharmacokinetics, Placental and Breast Milk Transfer of Antiretroviral Drugs in Pregnant and Lactating Women Living with HIV. *Curr Pharm Des* **25**, 556-76 (2019).

(10) Kloprogge, F. *et al.* Artemether-lumefantrine dosing for malaria treatment in young children and pregnant women: A pharmacokinetic-pharmacodynamic meta-analysis. *PLoS Med* **15**, e1002579 (2018).

(11) Kanji, S. *et al.* Reporting Guidelines for Clinical Pharmacokinetic Studies: The ClinPK Statement. *Clin Pharmacokinet* **54**, 783-95 (2015).

(12) Abdelwahab, M.T. *et al.* Population Pharmacokinetics of Isoniazid, Pyrazinamide, and Ethambutol in Pregnant South African Women with Tuberculosis and HIV. *Antimicrob Agents Chemother* **64**, (2020).

(13) Denti, P. *et al.* Population Pharmacokinetics of Rifampin in Pregnant Women with Tuberculosis and HIV Coinfection in Soweto, South Africa. *Antimicrob Agents Chemother* **60**, 1234-41 (2015).

(14) Gausi, K. *et al.* Pharmacokinetics and drug-drug interactions of isoniazid and efavirenz in pregnant women living with HIV in high TB incidence settings: importance of genotyping. *Clin Pharmacol Ther*, (2020).

(15) Adegbola, A. *et al.* Effect of Pregnancy on the Pharmacokinetic Interaction between Efavirenz and Lumefantrine in HIV-Malaria Coinfection. *Antimicrob Agents Chemother* **62**, (2018).

(16) Kloprogge, F. *et al.* Population Pharmacokinetics of Lumefantrine in Pregnant and Nonpregnant Women With Uncomplicated Plasmodium falciparum Malaria in Uganda. *CPT Pharmacometrics Syst Pharmacol* **2**, e83 (2013).

(17) Mosha, D. *et al.* Population pharmacokinetics and clinical response for artemether-lumefantrine in pregnant and nonpregnant women with uncomplicated Plasmodium falciparum malaria in Tanzania. *Antimicrob Agents Chemother* **58**, 4583-92 (2014).

(18) Mutagonda, R.F. *et al.* Pregnancy and CYP3A5 Genotype Affect Day 7 Plasma Lumefantrine Concentrations. *Drug Metab Dispos* **47**, 1415-24 (2019).

(19) Nyunt, M.M. *et al.* Artemether-Lumefantrine Pharmacokinetics and Clinical Response Are Minimally Altered in Pregnant Ugandan Women Treated for Uncomplicated Falciparum Malaria. *Antimicrob Agents Chemother* **60**, 1274-82 (2015).

(20) Tarning, J. *et al.* Pharmacokinetic properties of artemether, dihydroartemisinin, lumefantrine, and quinine in pregnant women with uncomplicated plasmodium falciparum malaria in Uganda. *Antimicrob Agents Chemother* **57**, 5096-103 (2013).

(21) Abdelrahim, II, Adam, I., Elghazali, G., Gustafsson, L.L., Elbashir, M.I. & Mirghani, R.A. Pharmacokinetics of quinine and its metabolites in pregnant Sudanese women with uncomplicated Plasmodium falciparum malaria. *J Clin Pharm Ther* **32**, 15-9 (2007).

(22) McGready, R. *et al.* Artesunate/dihydroartemisinin pharmacokinetics in acute falciparum malaria in pregnancy: absorption, bioavailability, disposition and disease effects. *Br J Clin Pharmacol* **73**, 467-77 (2012).

(23) Bulska, M., Szcześniak, P., Pięta-Dolińska, A., Oszukowski, P. & Orszulak-Michalak, D. The placental transfer of erythromycin in human pregnancies with group B streptococcal infection. *Ginekol Pol* **86**, 33-9 (2015).

(24) Larsen, B. & Glover, D.D. Serum erythromycin levels in pregnancy. *Clin Ther* **20**, 971-7 (1998).

(25) Andrew, M.A. *et al.* Amoxicillin pharmacokinetics in pregnant women: modeling and simulations of dosage strategies. *Clin Pharmacol Ther* **81**, 547-56 (2007).

(26) Muller, A.E. *et al.* The influence of labour on the pharmacokinetics of intravenously administered amoxicillin in pregnant women. *Br J Clin Pharmacol* **66**, 866-74 (2008).

(27) Popović, J., Grujić, Z. & Sabo, A. Influence of pregnancy on ceftriaxone, cefazolin and gentamicin pharmacokinetics in caesarean vs. non-pregnant sectioned women. *J Clin Pharm Ther* **32**, 595-602 (2007).

(28) Johnson, J.R., Colombo, D.F., Gardner, D., Cho, E., Fan-Havard, P. & Shellhaas, C.S. Optimal dosing of penicillin G in the third trimester of pregnancy for prophylaxis against group B Streptococcus. *Am J Obstet Gynecol* **185**, 850-3 (2001).

(29) Wang, X. *et al.* Pharmacokinetics of metronidazole in pregnant patients with bacterial vaginosis. *J Matern Fetal Neonatal Med* **24**, 444-8 (2011).

(30) Crauwels, H.M., Osiyemi, O., Zorrilla, C., Bicer, C. & Brown, K. Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant women receiving a darunavir/cobicistat-based regimen. *HIV Med* **20**, 337-43 (2019).

(31) Momper, J.D. *et al.* Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV. *Aids* **32**, 2507-16 (2018).

(32) Bukkems, V. *et al.* Clinically significant lower elvitegravir exposure during third trimester of pregnant patients living with HIV: data from the PANNA study. *Clin Infect Dis*, (2020).

(33) Saint-Raymond, A. & de Vries, C.S. Medicine safety in pregnancy and ambitions for the EU medicine regulatory framework. *Clin Pharmacol Ther* **100**, 21-3 (2016).

(34) (2018 ). *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry* (U.S Department of Health and Human Services: Food and Drug Administration Maryland 2018 ).

(35) Hughes RG, B.P., Steer PJ, Heath P, Stenson BM. . (2017). *Prevention of early-onset neonatal group B streptococcal disease* e280-e305 (Royal College of Obstetricians and Gynaecologists BJOG, 2017).

(36) Eke, A.C. *et al.* Optimizing Pharmacology Studies in Pregnant and Lactating Women Using Lessons from HIV: A Consensus Statement. *Clin Pharmacol Ther*, (2020).

(37) Turner, M.A., Kenny, L. & Alfirevic, Z. Challenges in Designing Clinical Trials to Test New Drugs in the Pregnant Woman and Fetus. *Clin Perinatol* **46**, 399-416 (2019).

(38) Gastine, S. *et al.* GAPPS (Grading and Assessment of Pharmacokinetic-Pharmacodynamic Studies) a critical appraisal system for antimicrobial PKPD studies - development and application in pediatric antibiotic studies. *Expert Rev Clin Pharmacol* **12**, 1091-8 (2019).

**Figure Legends**

**Figure 1.** Physiological changes during pregnancy and labour and their impact on pharmacokinetics

**Figure 2.** Flowchart of search outcomes for each anti-infective

**Figure 3.** Key study design considerations in pharmacokinetic studies during pregnancy and labour

**Supplementary Information**

1. Supplemental Material Table S1.
2. Supplemental Material Table S2.

| Author/Year | Population | Pregnant/Non-pregnant control | Sampling Occasion | Number of samples post dose | Method | Conclusion | ClinPK Score | Limitations |
|---|---|---|---|---|---|---|---|---|
| **Anti-TB drugs** | | | | | | | | |
| **Rifampicin** | | | | | | | | |
| 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 |
| **Isoniazid** | | | | | | | | |
| 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 |
| **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 |
| **Anti-malarials** | | | | | | | | |
| **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 time point; 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 | 18 | Lack of paired samples |

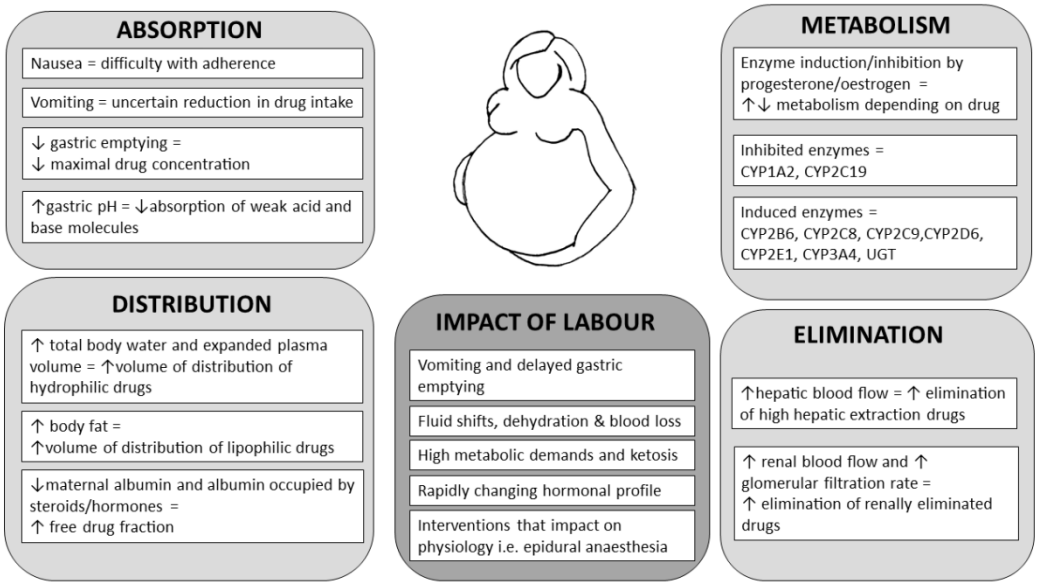
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | research needed | | |
| **Quinine** | | | | | | | | |
| Abdelrahim 2007 | Falciparum in T2 or T3 | 8/8 (not paired) | T2 or T3 | 7 | NCA | No dose adjustment needed | 15 | Small sample size |
| **IV artesunate** | | | | | | | | |
| McGready 2012 | Falciparum in T2 or T3 | 20/14 (all paired) | T2 or T3 | 8 | NCA | No dose adjustment needed | 17 | Small sample size |
| **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 labour, GBS positive | 25/8 (not paired)<br>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 labour |
| **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 time point; unclear analysis |
| Larsen 1998 | T2 or T3 with C trachomatis | 10/0 | T2/T3 | 5 | Not stated | Sub-therapeutic concentration with gastrointestinal side effect | 10 | No controls; unclear analysis; inter-individual variability not shown |
| **Gentamicin** | | | | | | | | |
| Popovic 2007 | Undergoing gynaecological surgery/ELCS (T3) | 18/4 (not paired) | PP or post-operative | 2 | Comp | Concentration<MIC achieved | 15 | Lack of paired samples; both time-points PP |
| **Metronidazole** | | | | | | | | |
| Wang 2010 | T1, T2 or T3 | 20/0 | T1, T2 or T3 | 10 | Comp | No dose adjustment needed | 17 | No controls – compared to previous data |
| **Antiretrovirals** | | | | | | | | |
| **Elvitegravir-Cobicistat** | | | | | | | | |
| Momper 2018 | HIV positive T2 or | 30/30 (paired) | T2 and T3 | 7 | Other | Should not be used | 17 | Meals given at time of drug |

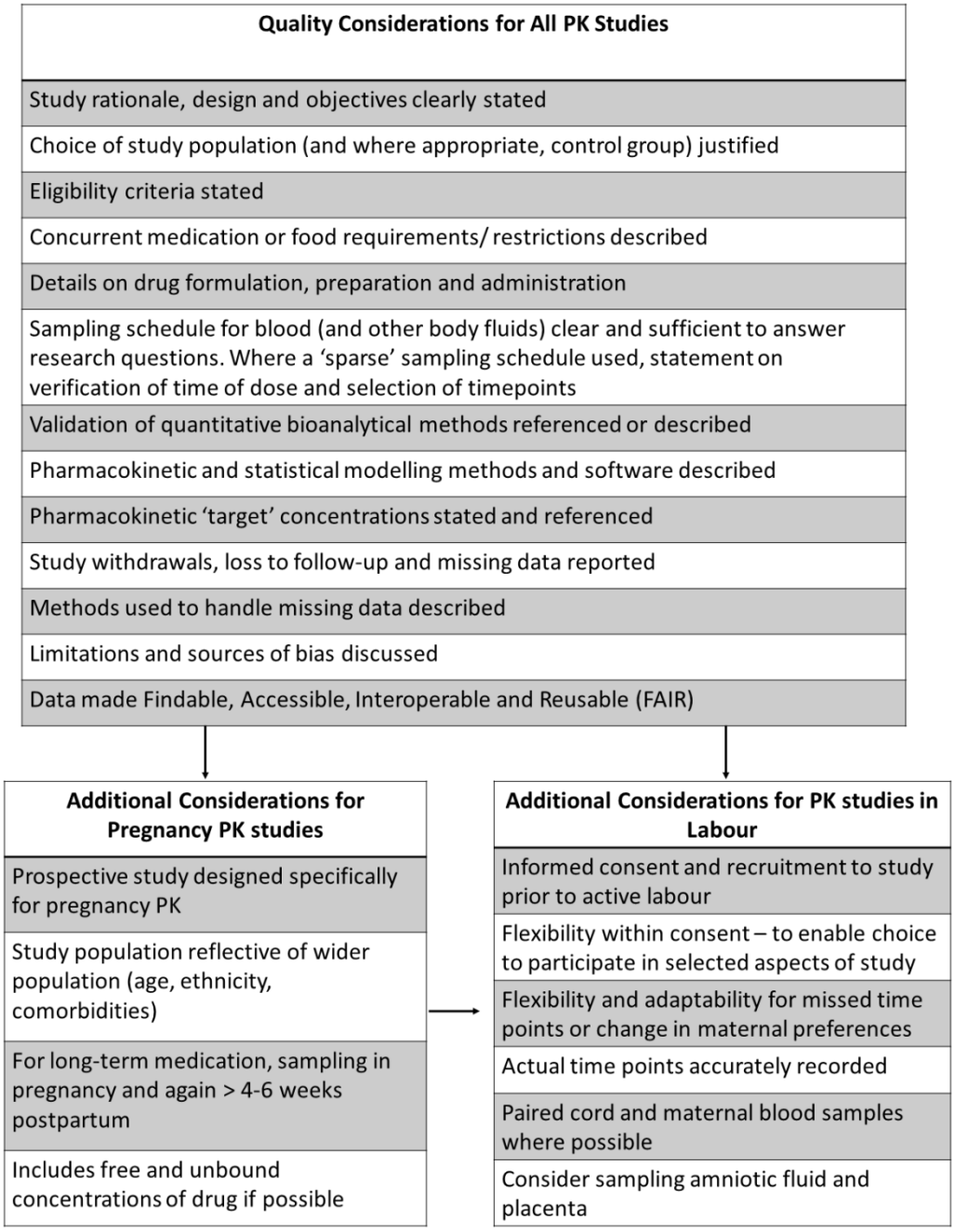
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | T3 | | and PP | | | in pregnancy | | not standardised |
| Bukkems 2020 | HIV positive T3 | 14/12 (paired) | T3 and PP | 9 | NCA | Should not be used in pregnancy | 14 | Small sample size |
| **Darunavir-Cobicistat** | | | | | | | | |
| Crauwels 2018 | HIV positive T2 | 6/6 (paired) | T2 and T3 and PP | 8 | NCA | Should not be used in pregnancy | 16 | Small sample size |

**Table 1. Key data points extracted from included pharmacokinetic studies**

Comp = compartmental analysis; ELCS = elective C section; GBS = group B streptococcus; IP = intra-partum (during labour); MIC = minimum inhibitory concentration; NCA = non-compartmental analysis; PP = post-partum; PROM = premature rupture of membranes; T2 = second trimester; T3 = third trimester; VD = vaginal delivery.




cpt_2192_f1.tif




cpt_2192_f2.tif