Physiological changes during pregnancy may alter drug pharmacokinetics. Therefore, mechanistic understanding of these changes and, ultimately, clinical studies in pregnant women are necessary to determine if and how dosing regimens should be adjusted. Because of the typically limited number of patients who can be recruited in this patient group, efficient design and analysis of these studies is of special relevance. This paper is a summary of a conference session organized at the American Conference of Pharmacometrics in April 2011, around the topic of applying pharmacometric methodology to this important problem. The discussion included both design and analysis of clinical studies during pregnancy and in silico predictions. An overview of different pharmacometric methods relevant to this subject was given. The impact of pharmacometrics was illustrated using a range of case examples of studies around pregnancy.

Introduction

The American Conference on Pharmacometrics (ACoP) held its third meeting in April 2011 and included a conference session on ‘Pharmacometrics in Pregnancy: Quantifying Maternal/Fetal Pharmacology’. This manuscript, prepared by the organizers and presenters of that session, summarizes the discussion on the application of pharmacometric methodologies in efficient design and analysis of studies in order ultimately to optimize drug therapy during pregnancy. For further details, presentation materials are available in electronic form on the conference’s website, http://www.go-acop.org.

Need for clinical studies in pregnant women

Pregnant women have long been orphaned from drug studies, yet need drug treatment. Drug use during pregnancy can be required for either pregnancy-related or unrelated conditions. Examples of pregnancy-related conditions that require treatment are hypercoagulability, gestational diabetes and pre-eclampsia. Moreover, a wide range of conditions unrelated to pregnancy, such as either chronic conditions including epilepsy, depression, asthma, hypertension, diabetes and HIV, or acute conditions such as infections (e.g. bronchitis, herpes, malaria) and cancer may occur during pregnancy. As a consequence, drug use during pregnancy is common. One recent study reported that drugs were prescribed during 64% of all deliveries [1]. Ethical objections for conducting clinical studies in pregnant women may exist, given the risk of potentially harmful fetal exposure, as was seen in the past with thalidomide and diethylstilbestrol [2]. However, continued off-label treatment with drugs during pregnancy may also be considered unethical [3], as it may be done in the absence of clinical evidence.
of well-controlled clinical studies that can ascertain efficacy and safety. This dilemma could be compared with the historical hesitation of conducting clinical studies in the paediatric population, which was addressed through a concerted effort, and led to the Paediatric Rule.

Physiological changes during pregnancy
During pregnancy, pharmacokinetics may be altered due to changes in physiology. For instance, during pregnancy, renal function (in terms of glomerular filtration rate and renal tubular activity) is increasing, leading to increased clearance for renally eliminated drugs. Also, the apparent activities of a number of cytochrome P450 and UGT drug metabolizing enzymes are increased. Increased plasma volume and low albumin concentrations may impact on the volume of distribution and in some cases total drug clearance. Depending on the physicochemical properties of a drug, such changes may substantially impact on the pharmacokinetics (PK) [4]. In principle, this may lead to either medication under- or over-dosing, with varying consequences for safety and efficacy. The coupled maternal-fetal physiology imposes unique concerns for both efficacy and safety of drug treatment [5]. In summary, for clinicians, substantial uncertainty exists regarding the risks for fetal and maternal exposure and the need for individually adjusted dosing regimens during pregnancy.

Pharmacometrics and pregnancy
In principle, pharmacometric approaches may be applied both in silico and in vivo. Model-based, analytical modelling and simulation approaches can be used to quantify the effects of pregnancy in clinical studies and mechanistically relate measured exposure to clinical response. Moreover, computer simulation of in silico pregnant subjects can integrate mechanistic data from several sources, thus maximizing the available information for use in designing therapies for mother, placenta and/or fetus. The ACoP session highlighted the state of the art and current needs in design and analysis of pharmacokinetic studies in pregnant women by (i) addressing the clinical implications and challenges of maternal-fetal pharmacology, (ii) illustrating how pharmacometric approaches can improve the efficiency of clinical study data analysis and (iii) demonstrating how applications of physiologically-based PK models can be used to predict maternal-fetal exposure.

In this brief review we will first provide an overview of different pharmacometric tools available for design and analysis of clinical studies during pregnancy. Then, case examples, which were presented during the session will be used to illustrate where pharmacometric methods may provide useful information. Finally, challenges and opportunities for conduct of studies in pregnant women and associated use of pharmacometric technologies will be discussed.

Pharmacometric tools
The pharmacometrics discipline applies a collection of interdisciplinary quantitative tools and methodologies in three main functional areas broadly defined as pharmacokinetics, pharmacodynamics (PD) and disease modelling (DM). Conceptually, a mechanistic description of drug pharmacokinetics can be coupled to the signalling eliciting a pharmacodynamic effect or response, which then can be modelled accounting for the context of the temporal physiological changes occurring during pregnancy.

In this review, we focus on the pharmacometric tools that support PK analysis, the kind of pharmacometric analysis most widely applied to the special population of pregnant women. These tools include non-compartmental analysis (NCA), compartmental individual PK analysis (IPK) and population level PK analysis (PPK), clinical trial simulation (CTS) and optimal design (OD). We also will address physiologically based pharmacokinetic (PBPK) modelling, which is an extension of compartmental modelling. Each of these methods is described below. The role of these tools in study design and analysis, is illustrated in Figure 1.

Non-compartmental analysis
Non-compartmental analysis [6] is a data driven method of analysis that requires densely sampled PK data in order to calculate empirically integral measures (moments) such as the area under the concentration–time curve (AUC). These can then be used to obtain estimates for valuable PK parameters such as mean residence time (MRT) and clearance (CL). Other informative non-compartmental parameters include the peak concentration (Cmax) and the time at which the peak concentration occurs (tmax). NCA based methods work well if data are dense and with enough resolution to estimate the above parameters reliably. Moreover, few prior assumptions are used in calculation of PK parameters, for example the well-known ‘equivalent source–equivalent sink’ assumption [7]. These assumptions need to be carefully understood to evaluate the appropriate domain of validity for the non-compartmental model.

Compartmental PK analysis
Drug concentration–time profiles may also be described using compartmental models, which allow the simultaneous estimation of mechanistic or semi-mechanistic PK parameters using least squares or maximum likelihood procedures. These models are based on (linear or non-linear) differential equations and balance of mass principles [8].

Compartmental or, more in general, differential equation-based PK models may either be describing PK on an individual level or on a population level. Individual level PK analyses require relatively dense data for each subject, whereas population level PK models allow simultaneous estimation of mean population PK parameters, as well as
between subject variability (of biological origin) and residual unexplained variability (including other stochastic factors, e.g. assay variation) [9]. Population level PK models also allow the incorporation of covariates to understand the influence of physiological factors on PK parameters (e.g. estimated gestational age). Unlike NCA approaches, PPK models are able to handle heterogeneous and sparsely sampled data, and may therefore be especially suitable to analyze data from clinical studies such as in pregnancy where data often may have a sparse character. Experiments may also be designed optimally to maximize the probability to achieve useful information from the data, as we will mention below.

Once a PPK model has been developed and informed from prior knowledge or data, stochastic simulation approaches may be used to answer questions related to the need and the magnitude of potential dosing adjustments during different periods of pregnancy.

Physiologically-based PK modelling
PBPK models are multi-compartmental models that aim to describe mechanistically major tissues and organs in an organism, in order to predict and quantify PK characteristics of a drug. They may be used for predictive purposes or to support study design. PBPK model predictions are based on the physiological characteristics of drugs and

---

**Figure 1**
Overview of pharmacometrics approaches in design and analysis of clinical studies in pregnant women
tissues, and on the intrinsic physicochemical drug properties. PBPK models are generally not driven by clinical data, such as in NCA or PPK models. Because PBPK models have a mechanistic character, they are considered most suitable for producing extrapolations to new populations. PBPK models are intensely studied and used in drug development and in the study of environmental toxin exposures. A review by Corley et al. [10] described the general PBPK model structures which have been reported to describe the physiological changes during pregnancy. These models have been utilized predominantly to explore disposition of environmental chemicals in humans and across various species. These previously reported model structures do have some recognized limitations, for example they typically have not considered changes in drug metabolizing or transporting proteins. More recently, PBPK models were also developed specifically for selected compounds, such as for midazolam [11] and caffeine [12].

Because of their complexity PBPK models require rich supporting experimental data and/or make use of in silico prediction tools to obtain required physiochemical parameters. Since drug-specific supporting data to inform model parameters and structure may not always be available, assumptions are often made based on general knowledge. Thus it is important to verify or validate model predictions with available data, and also to assess the sensitivity of model predictions to key parameters in the model. Reported PBPK models therefore have recognized limitations. For example the models summarized by Corley et al. [10] typically did not consider changes in drug metabolizing or transporting proteins. The midazolam model developed by Andrew et al. included changes in metabolism based on a wealth of metabolic data and time-dependent physiological changes due to gestation. However, many assumptions were made to incorporate a detailed fetal structure. Sensitivity analysis was used to assess how these and other model parameters affected the model output [13].

**Clinical trial simulation**

Clinical trial simulation (CTS) [14] uses Monte Carlo sampling methods to identify trial designs that are most likely to achieve trial goals. At a minimum, a clinical trial simulation may consist of an input-output model and a trial execution model. The input-output model concerns the stochastic simulation of pharmacokinetic profiles based on a prior or assumed PPK model, and a dosing schedule. The trial execution model concerns other random events such as dropout rate, or other events related to trial execution, which may have an impact on the trial outcome. Using CTS, different trial designs may be explored to determine which is most likely to meet the objectives of the study.

**Optimal design**

OD [15] is a statistical methodology that aims to optimize the design of a trial with respect to a design criterion, e.g. PK parameter precision. ODs may be identified based on prior information, which is typically a compartmental PK model. Moreover, design characteristics and design optimization boundaries need to be defined, e.g. the number of subjects, number of groups, sampling time boundaries or dose levels. An important advantage of OD is they are often less computationally intensive, and optimization is not bound to a priori defined designs such as for CTS. Additionally, ODs can be defined on either an individual or a population level.

**Case examples**

**Gestational diabetes**

One clinical area in which pharmacometric techniques, including PK–PD modelling, have been applied is in the investigation of the commonly used oral hypoglycaemic agent, glyburide, in the treatment of women with gestational diabetes mellitus. Glyburide is a substrate for CYP2C9, CYP3A and CYP2C19 in vitro [16, 17]. The activities of both CYP2C9 and CYP3A appear to be markedly increased during pregnancy, in contrast to CYP2C19 activity, which appears to be decreased during pregnancy [18–20]. Mary Hebert’s presentation at the ACoP session described how a study run by the Obstetric-fetal pharmacology Research Unit Network showed that the dose-normalized glyburide AUC was approximately 50% lower during pregnancy than in the non-pregnant control subjects. Utilizing PPK model based stochastic simulations, the maximum dosage would need to be more than doubled [21], in order to obtain the same concentrations during pregnancy as were observed in the non-pregnant subjects.

The clinical situation requires additional considerations beyond observed or expected changes in maternal PK. For example fetal and neonatal safety must be taken into consideration because the safety of higher dosages has not been evaluated during pregnancy and glyburide does cross the placenta [21]. Another consideration is the impact of pregnancy on the PD response to glyburide during pregnancy. The physiologic changes that occur even during normal pregnancy lead to a state of insulin resistance and hyperinsulinaemia [21]. These changes likely result in alterations in response to glyburide and perhaps in the PK–PD relationship, and should be further investigated. This is of course a general consideration.

**Antibiotics**

Another published pharmacometric application presented by Mary Hebert was to evaluate amoxicillin prophylaxis for *Bacillus anthracis* exposure. The antibiotic amoxicillin has been recommended by the American Academy of Obstetrics and Gynecology for pregnant women who have been exposed to anthrax, once penicillin-sensitivity has been confirmed [22]. However, amoxicillin is primarily eliminated unchanged in the urine and pregnancy is known to
increase renal filtration, with creatinine clearance increasing to 150–160% of non-pregnant values [23–27]. In a small study of amoxicillin exposure, NCA PK evaluation of amoxicillin, single dose (500 mg orally) has demonstrated that amoxicillin AUC is significantly lower in both the second and third trimesters of pregnancy than in the same women 3 months post partum. In addition, the average half-life during pregnancy was 1.2 h in the second trimester and 1.3 h in the third trimester, compared with 1.6 h 3 months post partum, raising concerns about the recommended dosage of amoxicillin for both pregnant on non-pregnant individuals.

PPK modelling and simulation allowed investigation of optimized dosing regimens. Based on these analyses, amoxicillin would need to be dosed every 4 h to keep amoxicillin trough concentrations above 0.12 µg mℓ⁻¹, which is the minimum inhibitory concentration for sensitive B. anthracis isolates. These simulations suggest that, given the prolonged course of 60 days needed in the setting of anthrax exposure prophylaxis, an every 4 h dosing regimen would be particularly challenging if not impossible to implement [28].

**Anti-malarial drugs**

Malaria is one of the most important infectious diseases in the world and affects the population of many of the poorest countries. Pregnant women are especially vulnerable to malaria, with an estimated 85 million pregnancies occurring in areas with P. falciparum transmission during 2007 [29]. The physiological changes during pregnancy also tend to result in altered PK properties of many of the anti-malarials used today. In Joel Tarning’s presentation, it was shown how previous studies reported that artesunate, artemether, dihydroartemisinin, sulfadoxine, atovaquone, proguanil, cycloguanil, pyrimethamine and lumefantrine concentrations and cure rates were lower in pregnant women compared with non-pregnant adults [20, 30–34]. A meta-analysis by McGready et al. [35] showed that nine out of 12 included PK studies recommended dose optimization in pregnant women with malaria. Unacceptably high polymerase chain reaction (PCR)-corrected failure rates of 16.5% (95% CI 9.9, 25.1) after artemether-lumefantrine treatment (Coartem®) in pregnant women with malaria in Thailand [33] have been reported.

Joel Tarning illustrated how PPK modelling of lumefantrine was used to quantify altered PK parameters during pregnancy, which resulted in low drug concentrations in the terminal phase. Results of stochastic simulations using the developed PPK model suggested that this combination treatment needs to be administered for an extended period of time in pregnant women, in order to kill residual parasites efficiently. The lower drug concentrations of lumefantrine in the terminal phase are likely to explain the high recrudescence (regrowth of the same parasite) rate seen in pregnant women and emphasize the need for dose optimization in this especially vulnerable group.

Finally, given the challenging conditions in the often remote areas where the studies of anti-malarials in the pregnant population are performed, Joel Tarning suggested that the use of informative sparse sampling designs is highly relevant for the conduct of PK studies in this particular area. Jamsen et al. [36] described this approach for anti-malarial studies.

**Influenza drugs**

Pregnant women who contract influenza face a significantly increased risk for admission to hospital and associated morbidity and mortality [37]. Identifying more effective influenza therapies or regimens during pregnancy is of special interest. While oseltamivir is recommended for use during pregnancy, until recently no data were available regarding its disposition during pregnancy. Consequently, it was not known whether the recommended adult prophylaxis and treatment dosages were adequate.

Oseltamivir is a pro-drug, metabolized by carboxylesterases in the gut and liver to the active drug oseltamivir carboxylate. Simple approximations for changes in disposition during pregnancy for both oseltamivir and oseltamivir carboxylate were predicted using compartmental approaches, as described in Donald Mattison’s presentation. This was done using available adult drug disposition data [38–52], in which model clearances were modified based on the knowledge of physiological changes during pregnancy. Glomerular filtration rate increases about 50%, renal plasma flow increases about 70% and extracellular fluid volume increases about 30–40% by the third trimester of pregnancy. Drug disposition could then be predicted in pregnant women. The volume of distribution was predicted to change from 120 to 170 l and the apparent clearance was predicted to change from 27 to 41 l h⁻¹. Using the estimated changes in maternal physiological parameters, exposure during pregnancy could be compared with that in non-pregnant adults. Overall, these results predicted that the AUC was reduced by 30% in pregnancy compared with the non pregnant individual. Subsequently, these simulated observations were validated using recent clinical data from a small study of oseltamivir and oseltamivir carboxylate PK during pregnancy [53–55], illustrating the utility of quantitative approaches to the evaluation of clinical therapeutics during pregnancy.

**Challenges and opportunities**

Design and conduct of an ethical yet informative study in this special population can be challenging. Capturing changes in PK during pregnancy may be complicated due to practical difficulties such as limited recruitment of subjects, limited numbers of feasible blood samples or sampling occasions. When designing and analyzing a clinical study, ideally pregnancy should not be treated as a
dichotomous covariate, since changes in physiological parameters and PK are continuous. Moreover, the combination of small sample sizes and large inter- and intra-patient variability in PK parameters may further complicate the detection of significant changes in PK parameters during pregnancy.

As illustrated in the case examples covered during the ACoP session, pharmacometric approaches such as optimal design [56] or simulation studies may be used to support design of informative studies in this vulnerable population in various ways. These include sparse sampling designs, leveraging of physiological data to quantify anticipated changes in PK, conducting the trial in silico before its execution in vivo, and the overall evaluation of potential study designs for their likelihood of quantifying the (changes in) PK parameters of interest. All these approaches generate information or hypotheses that can be rigorously tested as data become available from controlled experiments. As clinical studies have been performed, these data may also be used to evaluate or validate the performance of developed models and further improve these models based on observed data.

Relevant methods available for analyzing PK studies were briefly discussed, each with their own benefits and drawbacks. It is important to consider carefully an appropriate method, or combination of methods, specific to the question to be answered. Semi-physiological approaches may sometimes be considered, offering benefits of both PPK and PBPK methods. Further advances in PBPK models are expected to be useful in further exploration of both maternal and fetal exposure in silico. Increased understanding of maternal-fetal transport processes and gestationally-induced changes in drug metabolism and transport would be especially helpful in improving the utility of PBPK models.

Optimizing drug treatment in (pregnant) patients is related ultimately to observed variability within and between patients, both in PK and PD. Such variations are the sum of the interplay between differences in physiological changes during pregnancy and other causes such as differences in metabolism (e.g. pharmacogenetic variation), patient compliance or obesity. The multitude of factors influencing PK and PD complicates the assessment of changes in the pharmacology of drugs during pregnancy.

The session and this review focused on changes in PK in the pregnant women. Post partum changes in maternal PK were not specifically discussed, but should ideally also be investigated in any clinical study aiming to investigate changes in PK during pregnancy, as it is not expected that PK will change back to the non-pregnant baseline instantaneously. Another subject which was discussed in this review was assessment of fetal exposure through the placenta and drug exposure through breast milk. However, as indicated, PBPK methods would be expected to be the most appropriate methodology to provide quantitative predictions for these events.

We discussed the specific challenges related to the design, conduct and analysis of clinical studies in pregnant women, underlining the unmet need for pharmacometric analysis approaches and examples of impact to date. There have been significant developments in pharmacometric models over the past three decades, as well as increased understanding of the profound physiological changes which occur during pregnancy. The pharmacometric approaches discussed allow design and analysis of more informative studies. However, effective application of pharmacometric methods is dependent on interdisciplinary expertise and collaboration, in order ultimately to support the improvement in care for pregnant women and their offspring.

### Competing Interests

PV is employed by and owns stock in Pfizer Inc. but the topic of this conference report is unrelated to his employment with Pfizer. The other authors declare no conflict of interest.

We thank the ACoP 2011 organizing and programming committee for making this session possible. DRM was supported by the intramural research program of the NICHD. Some of the data presented by MFH was supported by grant #U10HD047892 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health & Human Development or the National Institutes of Health.

### REFERENCES

1. Andrade SE, Gurwitz JH, Davis RL, Chan KA, Finkelstein JA, Fortman K, McPhillips H, Raebel MA, Robin D, Smith DH, Yood MU, Morse AN, Platt R. Prescription drug use in pregnancy. Am J Obstet Gynecol 2004; 191: 398–407.

2. Saunders EJ, Saunders JA. Drug therapy in pregnancy: the lessons of diethylstilbestrol, thalidomide, and bendectin. Health Care Women Int 1990; 11: 423–32.

3. McCullough LB, Coverdale JH, Chervenak FA. A comprehensive ethical framework for responsibly designing and conducting pharmacologic research that involves pregnant women. Am J Obstet Gynecol 2005; 193: 901–7.

4. Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. Clin Pharmacokinet 2005; 44: 989–1008.

5. Feghali MN, Mattison DR. Clinical therapeutics in pregnancy. Br J Clin Pharmacol 2011; 20: 253–62.

6. Gillespie WR. Noncompartmental versus compartmental modelling in clinical pharmacokinetics. Clin Pharmacokinet 1991; 20: 253–62.
7 DiStefano JJ. Noncompartmental vs. compartmental analysis: some bases for choice. Am J Physiol 1982; 243: R1–6.

8 Jang GR, Harris RZ, Lau DT. Pharmacokinetics and its role in small molecule drug discovery research. Med Res Rev 2001; 21: 382–96.

9 Sheiner L, Wakefield J. Population modelling in drug development. Stat Methods Med Res 1999; 8: 183–93.

10 Corley RA, Mast TJ, Carney EW, Rogers JM, Daston GP. Evaluation of physiologically based models of pregnancy and lactation for their application in children’s health risk assessments. Crit Rev Toxicol 2003; 33: 137–211.

11 Andrew MA, Hebert MF, Vicini P. Physiologically based pharmacokinetic model of midazolam disposition during pregnancy. Annual International Conf Proc IEEE Eng Med Biol Soc 2008; 2008: 5454–7.

12 Gaohua L, Abduljalil K, Furness P, Jamei M, Rostami-Hodjegan A, Soltani H. A Time-Varying Physiologically-Based Pharmacokinetic Model of Caffeine during Pregnancy. The John Rylands University Library, The University of Manchester, Manchester, 2010.

13 Andrew M, Hebert M, Vicini P. Physiologically based pharmacokinetic (PBPK) modeling of midazolam disposition in pregnant and postpartum women. Abstracts of the Annual Meeting of the PAGE 2010; 19: 1760.

14 Holford N, Ma SC, Ploeger BA. Clinical trial simulation: a review. Clin Pharmacol Ther 2010; 88: 166–82.

15 Duffull SB. Design of clinical pharmacology trials. Clin Exp Pharmacol Physiol 2001; 28: 905–12.

16 Naritomi Y, Terashita S, Kagayama A. Identification and relative contributions of human cytochrome P450 isozymes involved in the metabolism of glibenclamide and lansoprazole: evaluation of an approach based on the in vitro substrate disappearance rate. Xenobiotica 2004; 34: 415–27.

17 van Giersbergen PLM, Treiber A, Clozel M, Bodin F, Dingemans E. In vivo and in vitro studies exploring the pharmacokinetic interaction between bosentan, a dual endothelin receptor antagonist, and glyburide. Clin Pharmacol Ther 2002; 71: 253–62.

18 Hebert MF, Easterling TR, Kirby B, Carr DB, Buchanan ML, Rutherford T, Thummel KE, Fishbein DP, Unadkat JD. Effects of pregnancy on CYP3A and P-glycoprotein activities as measured by disposition of midazolam and digoxin: a University of Washington specialized center of research study. Clin Pharmacol Ther 2008; 84: 248–53.

19 Erby MS, Friel PN, McCormick K, Koerner M, Van Allen M, Leavitt AM, Sells CJ, Yerby JA. Pharmacokinetics of anticonvulsants in pregnancy: alterations in plasma protein binding. Epilepsy Res 1990; 5: 223–8.

20 McGready R, Stepniewska K, Seaton E, Cho T, Cho D, Ginsberg A, Edstein MD, Ashley E, Looareesuwan S, White NJ, Nosten F. Pregnancy and use of oral contraceptives reduces the biotransformation of proguanil to cycloguanil. Eur J Clin Pharmacol 2003; 59: 553–7.

21 Hebert MF, Ma X, Naraharissetti SB, Krudys KM, Umans JG, Hankins GDV, Caritis SN, Mi lodovnik M, Mattison DR, Unadkat JD, Kelly EJ, Blough D, Cobelli C, Ahmed MS, Snodgrass WR, Carr DB, Easterling TR, Vicini P. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. Clin Pharmacol Ther 2009; 85: 607–14.

22 American College of Obstetricians and Gynecologists. Management of asymptomatic pregnant or lactating women exposed to anthrax. Obstet Gynecol 2002; 99: 366–8.

23 Gordon C, Regamey C, Kirby WM. Comparative clinical pharmacology of amoxicillin and ampicillin administered orally. Antimicrob Agents Chemother 1972; 1: 504–7.

24 Croydon EA, Sutherland R. Amino-p-hydroxybenzylpenicillin (BRL 2333), a new semisynthetic penicillin: absorption and excretion in man. Antimicrob Agents Chemother 1970; 10: 427–30.

25 Sjövall J, Alván G, Westerlund D. Dose-dependent absorption of amoxicillin and bacampicillin. Clin Pharmacol Ther 1985; 38: 241–50.

26 Davison JM, Dunlop WEM. 24-hour creatinine clearance during the third trimester of normal pregnancy. Br J Obstet Gynaecol 1989; 87: 106–9.

27 Davison JM, Noble MCB. Serial changes in 24 hour creatinine clearance during normal menstrual cycles and the first trimester of pregnancy. Br J Obstet Gynaecol 1981; 88: 10–7.

28 Andrew MA, Easterling TR, Carr DB, Shen D, Buchanan ML, Rutherford T, Bennett R, Vicini P, Hebert MF. Amoxicillin pharmacokinetics in pregnant women: modeling and simulations of dosage strategies. Clin Pharmacol Ther 2007; 81: 547–56.

29 Dellicour S, Tatem A, Guerra C, Snow R, ter Kuile F. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. PLoS Med 2010; 7: e1000221.

30 McGready R, Stepniewska K, Ward SA, Cho T, Gilvery G, Looareesuwan S, White NJ, Nosten F. Pharmacokinetics of dihydroartemisinin following oral artesunate treatment of pregnant women with acute uncomplicated falciparum malaria. Eur J Clin Pharmacol 2006; 62: 367–71.

31 McGready R, Stepniewska K, Lindegardh N, Ashley EA, La Y, Singhahivan P, White NJ, Nosten F. The pharmacokinetics of artemether and lumefantrine in pregnant women with uncomplicated falciparum malaria. Eur J Clin Pharmacol 2006; 62: 1021–31.

32 Karunajeewa HA, Salman S, Mueller I, Bawilag F, Gomorrai S, Law I, Page-Sharp M, Rogerson S, Siba P, Ilett KF, Davis TME. Pharmacokinetic properties of sulfadoxine-pyrimethamine in pregnant women. Antimicrob Agents Chemother 2009; 53: 4368–76.

33 Tarning J, McGready R, Lindegardh N, Ashley EA, Pimanpanarak M, Kamanikom B, Annerberg A, Day NPJ, Stepniewska K, Singhahivan P, White NJ, Nosten F. Population pharmacokinetics of lumefantrine in pregnant women treated with artemether-lumefantrine for uncomplicated Plasmodium falciparum malaria. Antimicrob Agents Chemother 2009; 53: 3837–46.
34 Nyunt MM, Adam I, Kayentao K, van Dijk J, Thuma P, Mauff K, Little F, Cassam Y, Guirou E, Traore B, Doumbo O, Sullivan D, Smith P, Barnes KL. Pharmacokinetics of sulfadoxine and pyrimethamine in intermittent preventive treatment of malaria in pregnancy. Clin Pharmacol Ther 2010; 87: 226–34.

35 McGready R, White NJ, Nosten F. Parasitological efficacy of antimalarials in the treatment and prevention of falciparum malaria in pregnancy 1998 to 2009: a systematic review. BJOG 2011; 118: 123–35.

36 Jamsen KM, Duffull SB, Tarning J, Lindegardh N, White NJ, Simpson JA. Optimal designs for population pharmacokinetic studies of oral artesunate in patients with uncomplicated falciparum malaria. Malar J 2011; 10: 181.

37 Mosby LG, Rasmussen SA, Jamieson DJ. 2009 Pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. Am J Obstet Gynecol 2011; 205: 10–8.

38 Morrison D, Roy S, Rayner C, Amer A, Howard D, Smith JR, Jamsen KM, Duffull SB, Tarning J, Lindegardh N, White NJ. Pharmacokinetics of high-dose oseltamivir in healthy volunteers. Antimicrob Agents Chemother 2009; 53: 945–52.

39 Wattanagoon Y, Stepniewska K, Lindegårdh N, Pukrittayakamee S, Silachamroon U, Pyiaphanees W, Singtorojo T, Hanpithakpong W, Davies G, Tarning J, Pongtavornpinyo W, Fukuda C, Singhasivanon P, Day NPJ, White NJ. Pharmacokinetics of high-dose oseltamivir in healthy volunteers. Br J Clin Pharmacol 2005; 59: 598–601.

40 Rayner CR, Chanu P, Gieschke R, Boak LM, Jonsson EN. Population pharmacokinetics of oseltamivir when coadministered with probenecid. J Clin Pharmacol 2008; 48: 935–47.

41 Jhee SS, Yen M, Ereshefsky L, Leibowitz M, Schulte M, Kaeser B, Boak L, Patel A, Hoffmann G, Prinssen EP, Rayner CR. Low penetration of oseltamivir and its metabolite oseltamivir from capsule delivery in healthy volunteers: a cross-over, randomised, open-label study. Vaccine 2006; 24: 6660–3.

42 Snell P, Dave N, Wilson K, Rowell L, Weil A, Galitz L, Robson R. Lack of effect of moderate hepatic impairment on the pharmacokinetics of oral oseltamivir and its metabolite oseltamivir carboxylate. Br J Clin Pharmacol 2005; 59: 598–601.

43 Hill G, Chlair T, Oo C, Ho ES, Prior K, Wiltshire H, Barrett J, Liu B, Ward P. The anti-influenza drug oseltamivir exhibits low potential to induce pharmacokinetic drug interactions via renal secretion-correlation of in vivo and in vitro studies. Drug Metab Dispos 2002; 30: 13–9.

44 Oo C, Hill G, Dorr A, Liu B, Boellner S, Ward P. Pharmacokinetics of anti-influenza produg oseltamivir in children aged 1–5 years. Eur J Clin Pharmacol 2003; 59: 411–5.

45 Robson R, Buttimore A, Lynn K, Brewster M, Ward P. The pharmacokinetics and tolerability of oseltamivir suspension in patients on haemodialysis and continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 2006; 21: 2556–62.

46 Massarella JW, He GZ, Dorr A, Nieforth K, Ward P, Brown A. The pharmacokinetics and tolerability of the oral neuraminidase inhibitor oseltamivir (Ro 64-0796/GS4104) in healthy adult and elderly volunteers. J Clin Pharmacol 2000; 40: 836–43.

47 Snell P, Oo C, Dorr A, Barrett J. Lack of pharmacokinetic interaction between the oral anti-influenza neuraminidase inhibitor produg oseltamivir and antacids. Br J Clin Pharmacol 2002; 54: 372–7.

48 Oo C, Barrett J, Dorr A, Liu B, Ward P. Lack of pharmacokinetic interaction between the oral anti-influenza produg oseltamivir and aspirin. Antimicrob Agents Chemother 2002; 46: 1993–5.

49 Schentag JJ, Hill G, Chu T, Rayner CR. Similarity in pharmacokinetics of oseltamivir and oseltamivir carboxylate in Japanese and Caucasian subjects. J Clin Pharmacol 2007; 47: 689–96.

50 Holodniy M, Penzk SR, Straight TM, Davey RT, Lee KK, Goetz MB, Raisch DW, Cunningham F, Lin ET, Olivo N, Deyton LR. Pharmacokinetics and tolerability of oseltamivir combined with probenecid. Antimicrob Agents Chemother 2008; 52: 3013–21.

51 Brewster M, Smith JR, Dutkowski R, Robson R. Active metabolite from Tamiflu solution is bioequivalent to that from capsule delivery in healthy volunteers: a cross-over, randomised, open-label study. Vaccine 2006; 24: 6660–3.

52 Abe M, Smith J, Urea A, Barrett J, Kinoshita H, Rayner CR. Pharmacokinetics of oseltamivir in young and very elderly subjects. Ann Pharmacother 2006; 40: 1724–30.

53 Greer LG, Leff RD, Rogers VL, Roberts SW, McCracken GH, Wendel GD, Sheffield JS. Pharmacokinetics of oseltamivir according to trimester of pregnancy. Am J Obstet Gynecol 2011; 204: (Suppl. 1): S89–93.

54 Beigi RH, Han K, Venkataramanan R, Hankins GD, Clark S, Hebert MF, Easterling T, Zajicek A, Ren Z, Mattison DR, Caritis SN. Pharmacokinetics of oseltamivir among pregnant and nonpregnant women. Am J Obstet Gynecol 2011; 204: (Suppl. 1): S84–8.

55 Mirochnick M, Clarke D. Oseltamivir pharmacokinetics in pregnancy: a commentary. Am J Obstet Gynecol 2011; 204: (Suppl. 1): S94–5.

56 van Hasselt JGC, Green B, Morrish GM. Leveraging physiological data from the literature into a pharmacokinetic model to support informative clinical study design in pregnant women. Pharm Res 2012; DOI: 10.1007/s11199-012-0671-2. [Epub ahead of print].