# Population pharmacokinetics of antibiotics to prevent group B streptococcal disease: from mother to neonate

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Chapter 4

# Amoxicillin pharmacokinetics in pregnant women with preterm premature rupture of the membranes.

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## Abstract

*Objective:* To study the pharmacokinetics of intravenously administered amoxicillin in pregnant women with preterm premature rupture of the membranes (PPROM).
*Study design:* Healthy women with PPROM were recruited and treated with amoxicillin (2 gram initially and 1 gram subsequently). Blood samples were obtained from the opposite arm and concentrations determined using HPLC. Nonlinear mixed-effects modeling was performed in NONMEM.
*Results:* The pharmacokinetics of seventeen patients was described by a 3-compartment model. Clearance and volume of distribution at steady state were 22.8 L/h and 21.4 L respectively, similar to values in non-pregnant individuals. There was little variability between patients. No relationship was observed between values of individual pharmacokinetic parameters and various covariates.
*Conclusion:* The pharmacokinetics of amoxicillin in pregnant patients with PPROM is similar to non-pregnant individuals. Given the small inter-individual variability in pharmacokinetics, no dose adjustments are required to account for differences between subjects under normal circumstances.

## Introduction

Preterm premature rupture of the membranes (PPROM) complicates approximately 3% of pregnancies and is responsible for one third of all preterm births[1]. Subclinical intra-amniotic infection has been implicated as a major etiological factor in the pathogenesis of PPROM[2]. The consequential maternal and neonatal morbidity are attributed to ascending infections from the vagina after rupture of the membranes. Antibiotic therapy has been recommended in the management of patients with PPROM to prevent or treat ascending intra-amniotic infection[3,4].

Amoxicillin, a penicillin derivative, is an antibiotic frequently used in the management of PPROM. It is active against common pathogens that can cause infection in neonates, in particular *Streptococcus agalactiae*. The currently recommended amoxicillin dosages in pregnancy are derived from studies using ampicillin[5,6]. These dosage regimens essentially do not differ from regimens employed in non-pregnant individuals and are based on the assumption that pharmacokinetics in pregnancy and in young men are similar[5,6]. In non-pregnant individuals a slow elimination phase has been suggested for penicillin G and amoxicillin[7,8]. Especially for bacteria with a low MIC, like *Streptococcus agalactiae*, a slow elimination phase would be of clinical importance. In women with PPROM the presence of such elimination phase would be beneficial for efficacy of the prophylaxis by increasing the time the amoxicillin concentration remains above the MIC. However, during pregnancy physiological changes occur that may modify the pharmacokinetics of drugs, such as increase in plasma volume, increase in fat content, presence of the fetus, changes in elimination rate or metabolism[9]. These changes can be expected to affect the pharmacokinetics of drugs in various ways. If changes in pharmacokinetics indeed occur, pregnant women and their fetus are inherently at risk for under- or overdosing when they are treated with dosage regimens developed for non-pregnant individuals. A clear example is the drastic decrease in concentration of the antiepileptic drug lamotrigine during pregnancy[10].

Despite the widespread use of amoxicillin in pregnant women, the pharmacokinetics in patients with PPROM has not been adequately studied. The objective of this study is to describe the pharmacokinetics in this vulnerable patient group and to develop a population pharmacokinetic model. Since the pharmacokinetics in individual patients may be affected by various factors, it is important that the method of data analysis allows identification of such factors. Therefore, pharmacokinetic data analysis using Non-Linear Mixed Effects ('population') modeling was applied. This method has distinct statistical advantages, especially for such patient groups. The data of the whole population are simultaneously analysed, while taking into account inter-individual and intra-individual variability in respectively the model parameters and the observations by assuming a stochastic distribution[11]. The influence of specific characteristics on

the individual PK parameters can be assessed by including these characteristics as covariates in the PK-model[12,13]. A more detailed background of population modelling can be found elsewhere[14,15].

## Material and methods

### Patients

In the period between February 7, 2005 and February 14, 2006, all women with PPROM who needed antibiotic treatment with amoxicillin were eligible for this study. Following the local guidelines, all women with PPROM (gestational age <37 weeks) were admitted to the hospital and monitored for fetal condition and signs of infection. Women with proven or unknown *Streptococcus agalactiae* carriage were treated with antibiotics. Delivery was induced only when signs of infection were present. The study was approved by the Medical Ethics Committee. Written informed consent was obtained from all patients. Women were excluded from the study when i) they had been treated with oral or intramuscular antibiotics within 2 days before starting therapy, ii) were unwilling to comply with the requirements of the study, iii) were known to be allergic to amoxicillin or other penicillins, or iv) were receiving co-medication that exhibits interaction with amoxicillin. All patients were at least 18 years of age and not in labor.

### Drug administration and blood sampling

Before the administration of amoxicillin an intravenous catheter was placed in each arm. Amoxicillin was administered following local guidelines. The treatment started with an intravenous infusion of 2 gram amoxicillin (50 mg/mL) administered over 30 minutes, followed by a second infusion after 4 hours of 1 gram amoxicillin over 15 minutes. Bloodsamples of 2 mL were collected from the second catheter in the contralateral arm at timed intervals beginning at 1 min after the start of the infusion and, at 7 and 15 min (1 gram infusion) or 15 and 30 min (2 gram infusion) during the first two amoxicillin administrations. After the infusion sampling was scheduled at 3, 6, 10, 16 and 36 minutes, and afterwards every 30 minutes until the next antibiotic dosage. The exact sampling times were recorded.

Blood samples were placed immediately on ice, allowed to clot and processed within one hour after collection. The samples were centrifuged at 1200 g for approximately 10 minutes. The supernatants were transferred into plastic storage tubes and frozen at –70° C until analysis.

### Patient information

All patients received a standard work-up which included a medical history, biochemical and hematological examination. Furthermore blood pressure, pulse, oral temperature, and body weight were recorded. The amount of edema was scored

semiquantitatively from 0 (no edema) to 3 (above the knee). Before the start of the antibiotics a rectovaginal culture was taken to determine GBS carriage.

## Amoxicillin HPLC assay

Amoxicillin concentrations were determined by an isocratic high-pressure liquid chromatography (HPLC) (Shimadzu, Den Bosch, The Netherlands (NL)) method, using an ODS Gemini column (Bester, Amstelveen,NL) with 0.066 M KH2PO4 solution containing 10% methanol as a mobile phase. A perchloric acid solution of 0.1 ml was added to the sample in an equal volume and after vortexing, added to 0.56 ml 0.028 M citric acid containing cefadroxil (Sigma, Zwijndrecht,NL) as an internal standard. The assay was linear over the concentration range measured. Controls were included in every run. The lower limit of detection was 0.2 mg/L and the between run CV < 4%.

## Pharmacokinetic analysis

Pharmacokinetic parameters were estimated by means of NonLinear Mixed Effect (population) Modeling (NONMEM). The model was implemented in the NONMEM ADVAN5 subroutine and the analysis was performed using the FOCE method. All fitting procedures were performed with the use of the Compaq Visual FORTRAN standard edition 6.6 (Compaq Computer Cooperation, Euston, Texas, USA) and NONMEM® software package (version V, release 1.1, GloboMax, Hanover, USA).

To determine the basic structural pharmacokinetic parameters various 1-, 2- and 3-compartment models were tested. Model selection and identification of variability was based on the likelihood ratio test, pharmacokinetic parameter point estimates, and their respective confidence intervals, and goodness-of-fit plots. For the likelihood ratio test on differences between two models, the objective function value (OFV) with a pre-specified level of significance of $P<0.001$ was used. NONMEM minimizes an objective function in performing nonlinear regression analysis. To detect systematic deviations in the model fits the goodness-of-fit plots were visually inspected. The data of individual observations versus individual or population predictions should be randomly distributed around the line of identity. The weighted residuals versus time or population predictions should be randomly distributed around zero. Population values were estimated for the parameters clearance (CL), the volumes of distribution (V) and the intercompartmental clearances (Q).

Individual estimates for pharmacokinetic parameters were assumed to follow a log normal distribution. Therefore an exponential distribution model was used to account for inter-individual variability. Possible correlation between inter-individual variability coefficients on parameters was estimated and if present accounted for in the stochastic model (NONMEM Omega block option).

Selection of an appropriate residual error model was based on the likelihood ratio test and inspection of the goodness-of-fit plots. The residual variability between the observed concentrations and those predicted by the model was described using a proportional error model. The residual error term contains all the error terms which cannot be explained and refers to, for example, measurement and experimental error and structural model misspecification.

To refine the model covariate analysis was also performed. The estimated pharmacokinetic parameters were plotted independently against the covariates bodyweight, body mass index, duration of amenorrhea, blood pressure, pulse, oral temperature, and the amount of edema to determine whether this influenced the pharmacokinetics. The effects of covariates were tested for statistical significance using the likelihood ratio test and the residual intra- and inter-individual variability were visually evaluated. The volume of distribution at steady state ($V_{ss}$) and terminal half-life ($T_{1/2}$) were calculated following standard procedures[16].

The accuracy of the final population model was established using a bootstrap method in NONMEM, consisting of repeated random sampling with replacement from the original data. This resampling was repeated 100 times. The estimated parameters from the bootstrap analysis were compared to the estimates from the original data.

## Results

In total 17 patients were included. The population consisted of 15 singleton and 2 twin pregnancies. The gestational age at the time of PPROM ranged from 29.4 to 36.9 weeks of pregnancy. The patients were born in 8 different countries, illustrating the heterogeneity of the hospital population as well as the study population. The characteristics of the study patients are presented in table I.

A total of 416 blood samples was collected, which was close to the predefined sampling schedule. The 2 g and 1 g infusions resulted in mean peak concentrations of 96.7 mg/L (range 73.5- 136.6 mg/L) and 70.9 mg/L (n=16, range 49.1-107.1 mg/L), respectively. A three-compartment open model best described the data. The estimates of the pharmacokinetic parameters and their respective coefficients of variation (cv) are summarized in table II. The cv's were relatively small with values between 4.5 and 30.8%. Inter-individual variability was explained by variation in the parameters CL and $V_2$ (18% for CL and 33% for $V_2$). This means that the variability between subjects was in fact very small. A correlation between the random parameters for inter-individuality was found and accounted for in the stochastic model. Values of $T_{1/2}$ and $V_{ss}$ were 1.10 h and 21.4 L, respectively.

None of the covariates tested, gestational age, bodyweight, body mass index, blood pressure, pulse, oral temperature, and the amount of edema could

| Data | Units | Number of patients | Mean | SD | Range |
|---|---|---|---|---|---|
| Maternal age | year | 17 | 29.4 | 4.64 | 19.6-35.1 |
| Gestational age | week | 17 | 35.1 | 1.75 | 29.4-36.9 |
| Body Mass Index | $kg/m^2$ | 17 | 29.1 | 3.86 | 21.5-35 |
| Weight | kg | 17 | 80.6 | 12.03 | 56.2-98.9 |
| Edema (no/around the ankle/up to the knee) | - | 16 | 10/5/1 | | |
| Leucocytes | $x10^9/L$ | 17 | 11.8 | 4.43 | 6-25.9 |
| Creatinin | μmol/L | 17 | 44.4 | 10.11 | 37-74 |
| Nulliparity | - | 11 | - | - | - |
| Twin pregnancy | - | 2 | - | - | - |
| Positive maternal GBS culture | - | 7 | - | - | - |

***Table 1****: Baseline patients demographic data of the 17 pregnant patients with PPROM. GBS: group B streptococcus (Streptococcus agalactiae)*

improve the model. Finally, no difference in pharmacokinetics between the 2 g and 1g infusion was observed.

The observed and population-predicted profiles for the final model are shown in figure 1. The scatter plot of the observed concentrations versus model-predicted concentrations is shown in figure 2.

The bootstrap validation of the final model was performed with 100 runs. The mean parameter estimates of the runs obtained from the bootstrap analysis did not differ significantly from the predicted values from the NONMEM pharmacokinetic analysis. The standard error obtained from the bootstrap analysis was also comparable to those estimated by the model, except for the intercompartimental clearance between the central and second compartment ($Q_1$). This value differs significantly from the standard error estimated by the model due to the small size of the study population. The mean values and standard errors are represented in table II.

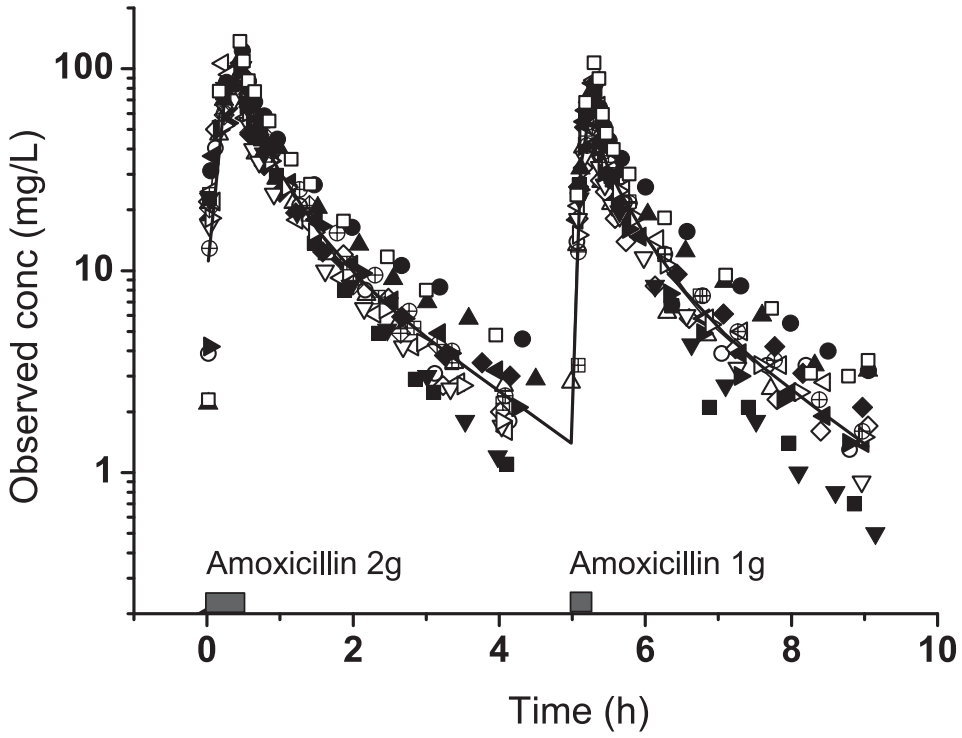


***Figure 1**: Observed concentration-time profiles.*

*The superimposed bold line shows the predicted profile obtained with the final model. The blocks indicate the time at which the infusions of the amoxicillin was started and stopped. Because there was variation in the start-time of the second infusion due to the clinical situation, in this graph the data were adapted assuming that the second infusions started at t=5.05h for all patients. (See color inlay for a full color version of this figure.)*

## Comment

In this study a PK-model was developed to describe the pharmacokinetics of amoxicillin in pregnant women with PPROM. The pharmacokinetics in our population appears to be only slightly different from non-pregnant individuals with a $V_{ss}$ of 21.4 L and a $T_{1/2}$ of 1.10 h. The variability between the patients was small.

| **parameter** | **units** | **Final model estimates** | | **Bootstrap estimates*** | |
|---|---|---|---|---|---|
| | | **mean** | **SE** | **mean** | **SE** |
| *structural model parameters* | | | | | |
| CL | L/h | 22.8 | 1.03 | 22.8 | 1.04 |
| $V_1$ | L | 5.59 | 0.826 | 5.26 | 1.32 |
| $V_2$ | L | 7.43 | 1.06 | 7.75 | 1.16 |
| $V_3$ | L | 8.61 | 0.768 | 9.07 | 0.99 |
| $Q_1$ | L/h | 60 | 18.5 | 82.2 | 69.8 |
| $Q_2$ | L/h | 7.72 | 1.72 | 7.92 | 1.78 |
| *variance model parameters* | | | | | |
| interpatient variability in CL | | 0.0317 | 0.0112 | 0.0300 | 0.0106 |
| interpatient variability in $V_2$ | | 0.108 | 0.00440 | 0.0982 | 0.0476 |
| residual variability | | 0.0365 | 0.00492 | 0.0359 | 0.00508 |
| *derived pharmacokinetics parameters* | | | | | |
| $T_{1/2}$ | h | 1.10 | - | - | - |
| $V_{ss}$ | L | 21.4 | - | - | - |

SE: standard error of the estimate; * mean of 100 bootstrap analyses. The parameter values were compared with the bootstrap estimates using the unpaired t-test.

***Table 2**: Population model parameter values and bootstrap estimates.*

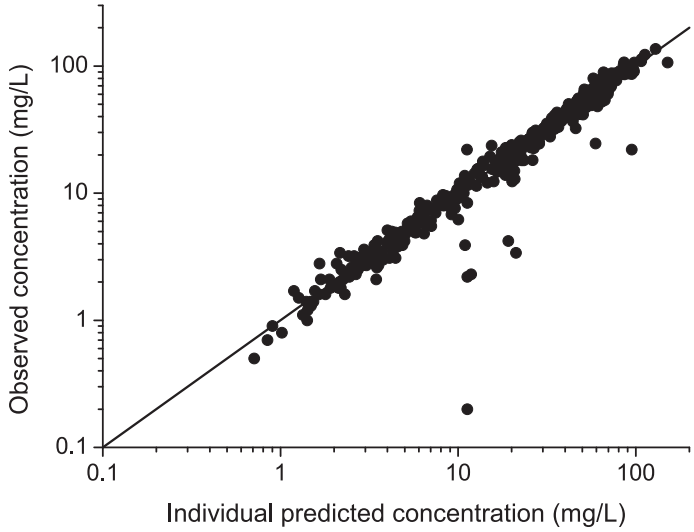


***Figure 2****: Scatter plot of the individual predicted versus observed concentrations of amoxicillin for 17 patients. The correlation coefficient was 0.97. The figure shows the individual data points for the entire population and the line of identity (x=y).*

With regard to amoxicillin, values for volumes of distribution, clearance and terminal half-life were all within the ranges reported in the literature for healthy non-pregnant individuals (table III). Only slightly lower peak serum concentrations were observed compared to 7 healthy non-pregnant individuals[17], i.e. 96.7 mg/L and 139.3 mg/L respectively for the 2 gram infusion. The value for $V_{ss}$ in our study was slightly larger than values found by Dalhoff et al. in healthy volunteers[8], who also used a 3-compartment model. Possibly this was due to the increased extracellular fluid in pregnant women and the pregnancy itself.

To our knowledge this is the first study on the pharmacokinetics of amoxicillin in pregnant women. Therefore, direct comparison with other studies under the same conditions is not possible. However, a comparison can be made to studies on ampicillin, which is closely related to amoxicillin (p-hydroxyampicillin). The two compounds differ very little in pharmacokinetics in healthy volunteers, except with respect to absorption after oral administration[18,19]. Several studies have been performed on the pharmacokinetics of ampicillin in pregnancy. In contrast to our study most studies on ampicillin did show differences in the pharmacokinetics during pregnancy, e.g. shorter half-life and higher plasma clearance during pregnancy[20-24]. This dissimilarity is intriguing; possible explanations are the use of different methods of analysis or the inclusion of patients at different gestational age and circumstances.

Two studies have noted that the clearance of amoxicillin after an intravenous dose exhibited a statistically significant dose effect[17,25]. However, the 2 studies are inconsistent with respect to the range where deviation of linearity occurs. Mastrandrea et al. described a difference in clearance in the range from 500 mg to 1000 mg[25], whereas Hill et al. found a slight deviation from linearity after a 5 g dose compared with doses of 250-1000 mg[17]. In a study by Sjövall et al. the pharmacokinetics after infusions in doses ranging from 1.9 g and 2.8 g were linear[19]. In our data, covering the range of 1-2 g, there was no evidence for a dose effect on the clearance. It is unlikely that therapeutic consequences are to be expected.

In general, inter-individual variability in pharmacokinetic parameters observed in clinical study populations are due to biochemical and physiological differences between subjects. In association with pregnancy, additional physiological alterations occur, which may further increase the variation in parameters between individuals in pregnant populations[26]. Surprisingly, the inter-individual variation in our data was remarkably small. While this was an unexpected finding, from the clinical perspective this is convenient, because specific adjustments are unnecessary for this patient group.

An important question is whether this dosing regimen is adequate to treat or prevent morbidity in both mother and fetus. The efficacy of the penicillins is determined by the time the concentration exceeds the minimum inhibitory concentration (T>MIC) and, in general, T>MIC for 40-50% of the dosing-interval is required for efficacy[27-29]. The breakpoint MIC value of an antibiotic used is the highest MIC value of different causative microorganisms that results in a high probability of cure, as follows from the target T>MIC. Since rectovaginal carriage of *Streptococcus agalactiae* has been described in up to 30% of pregnant women, this is an important microorganism after PPROM in the development of neonatal infection[3,30]. MIC values of amoxicillin for *Streptococcus agalactiae* are scarce, but vary from 0.03 to 0.12 mg/L[31,32]. The peak serum concentrations in our pregnant population were slightly lower than in non-pregnant individuals, but nevertheless well above the MIC. More importantly, maternal serum concentrations remained above the MIC for sufficient percentage of the dosing interval (>95%), even taking into account the protein binding of amoxicillin. The presence of a slow elimination phase, represented by the third compartment, significantly contributes to the high value for T>MIC. Because amoxicillin reaches the fetus after transplacental transport, it should be noted that adequate maternal levels are a prerequisite for the prevention of fetal infection, but no guarantee. In treatment of the mother, the added value of a 2 g loading dose above a 1 g dose is doubtful. However, it remains to be confirmed that by using this dosing schedule adequate fetal and AF levels are established as well.

| Author | Dose (mg) | Infusion Time (min) | $V_1$ (L/kg) | $V_2$ (L/kg) | $V_3$ (L/kg) | $V_{ss}$ (L/kg) | CL (L $kg^{-1}$ $h^{-1}$) | $T_{1/2}$ (h) | Number of Patients (F/M) |
|---|---|---|---|---|---|---|---|---|---|
| Zarowny[33] | 250 | 33 | 0.187 | 0.095 | - | 0.282 | 0.264 | 1.05 | 0/8 |
| Spijker[34] | 250 | 0.17 | 0.17 | 0.12 | - | 0.29 | 0.32 | | 0/8 |
| Spijker[34] | 500 | 0.17 | 0.22 | 0.24 | - | 0.46 | 0.32 | | 0/8 |
| Spijker[34] | 1000 | 0.17 | 0.22 | 0.27 | - | 0.49 | 0.34 | | 0/8 |
| Dalhoff[8] 1* | 250/500/1000 | 0.5 | 0.093 | 0.100 | - | 0.193 | | | 0/7 |
| Dalhoff[8] 1* | 2000/5000 | 30 | 0.129 | 0.084 | - | 0.213 | | | 0/7 |
| Dalhoff[8] 2* | 250/500/1000 | 0.5 | 0.075 | 0.06 | 0.069 | 0.205 | | 1.63 | 0/7 |
| Dalhoff[8] 2* | 2000/5000 | 30 | 0.119 | 0.056 | 0.069 | 0.246 | | 3.32 | 0/7 |
| Adam[35] | 4000 | 5 | 0.077 | 0.065 | - | 0.14 | - | 1.11 | 6/6 |
| Arancibia[36] | 500 | 0.17 | 0.18 | 0.070 | - | 0.25 | 0.20 | 1.08 | 2/7 |
| Mastrandrea[25] | 500 | bolus | | | | | 14.8 (L/h) | 1.16 | 0/20 |
| Mastrandrea[25] | 1000 | bolus | | | | | 20.7 (L/h) | 1.26 | 0/20 |
| Hill[24] | 250/500/1000 | 0.5 | | | | | | 1.18 | 0/7 |
| Hill[24] | 2000/5000 | 30 | | | | | | 1.26 | 0/7 |
| **This study** | **1000/ 2000** | **15/30** | **0.0694** | **0.0923** | **0.107** | **0.268** | **0.283** | **1.10** | **17/0** |

* Dalhoff et al. analyzed the same concentration-time data using a two-compartment model (1) and a three-compartment model (2). $V_1$ Volume of distribution of central compartment; $V_2$ Volume of distribution of first peripheral compartment; $V_3$ Volume of distribution of second peripheral compartment; $V_{ss}$ Volume of distribution at steady state; CL clearance; $T_{1/2}$ terminal half-life; F female, M male

***Table 3**: Pharmacokinetic parameters of amoxicillin in healthy (non-pregnant) volunteers reported in the literature and the results from our study.*

It is surprising that the pharmacokinetics in pregnant women with PPROM did not differ significantly from non-pregnant individuals. However, it should be noted that this is only valid for pregnant women with PPROM who are otherwise healthy. It has been suggested previously that it is not the state of pregnancy that influences the pharmacokinetics, but being in labor[6]. Since our patients were not in labor, this might explain why our data were similar compared to previously reported data of non-pregnant individuals.

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