Chapter 5

The influence of labor on the pharmacokinetics of intravenously administered amoxicillin in pregnant women.

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Abstract

Aim: Many physiological changes take place during pregnancy and labor. These might change the pharmacokinetics of amoxicillin, necessitating adjustment of the dose for prevention of neonatal infections. We investigated the influence of labor on the pharmacokinetics of amoxicillin.

Methods: Pregnant women before and during labor were recruited and treated with amoxicillin intravenously. A postpartum dose was offered. Blood samples were obtained and amoxicillin concentrations were determined using high-pressure liquid chromatography. The pharmacokinetics was characterized by nonlinear mixed-effects modeling using NONMEM.

Results: The pharmacokinetics of amoxicillin in 34 patients was best described by a 3-compartment model. Moderate inter-individual variability was identified in CL, central and peripheral volumes of distribution. The volume of distribution increased with an increasing amount of edema. Labor influenced the parameter estimate of peripheral volume of distribution ($V_2$). $V_2$ was decreased during labor, and even more in the immediate postpartum period. For all patients the population estimates (mean +/- SE) for CL and the volumes of distribution (V) were 21.1+/-4.1 L/h (CL), 8.7+/-6.6 L ($V_1$), 11.8+/-7.7 L ($V_2$) and 20.5+/-15.4 L ($V_3$) respectively.

Conclusion: The peripheral distribution volume of amoxicillin in pregnant women during labor and immediately postpartum is decreased. However, these changes are not clinically relevant and do not warrant deviations from the recommended dosing regimen for amoxicillin during labor in healthy pregnant patients.
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Introduction

The use of antibiotics during labor for prevention of neonatal infections has increased substantially in the last decades. Current guidelines from the Centers of Disease Control and Prevention (CDC) to prevent neonatal group B streptococcal (GBS) disease recommend the use of antibiotics during labor in all pregnant women carrying GBS1. The prevalence of GBS carriage varies according to the geographical region from 10% to 35% of all pregnant women, resulting in antibiotic use for this purpose in up to one of every three women2-5. Amoxicillin, a penicillin derivative, is one of the antibiotics used in the prevention of GBS disease. Amoxicillin is widely used in Europe, while ampicillin is more commonly used in the US. Amoxicillin is a bactericidal antibiotic and is primarily excreted unchanged in the urine both by glomerular filtration and by tubular secretion in the kidneys.

Adequate dosing of antibiotics to the mother is essential to prevent the neonate from GBS disease. Antibiotics reach the fetus after transplacental passage. An adequate concentration-time profile in maternal serum is therefore a prerequisite for an adequate concentration-time profile in the fetus. Current dosing regimens are similar for non-pregnant individuals, pregnant women before the onset of labor and for pregnant women during labor. Many physiological changes take place during pregnancy, which may modify the concentration-time profile of specific drugs, such as an increase in plasma volume, presence of the fetus and changes in elimination rate or metabolism6. In a previous study we found no differences in the pharmacokinetics (PK) of amoxicillin between pregnant women with preterm premature rupture of the membranes (PPROM) and values reported in the literature for non-pregnant individuals7. During labor additional physiological changes occur of which many are expected to change the PK behavior of drugs8. Uterine contractions, mechanical compression of blood vessels by the gravid uterus as well as hyperventilation, might all have their separate circulatory influences affecting blood flow through the body and especially to the eliminating organs. The consequential change in concentration-time profile of the antibiotic for both mother and neonate are unpredictable.

Despite the regular use of amoxicillin during labor, the influence of labor on the PK has not been adequately studied. PK studies during labor face considerable ethical and practical difficulties, limiting the collection of blood samples. The number of blood samples collected in women during labor will therefore be smaller compared to pregnant women before the onset of labor. Unbalanced study groups harbor statistical problems. Non-Linear Mixed Effects Modeling (NONMEM)9 allows weighted analysis of observations from unbalanced study designs and incorporation of patients with small or incomplete datasets10, 11. Studying the whole population as one group, the influence of specific circumstances, such as the presence of labor, on the individual PK parameters can be assessed using covariate
analysis\textsuperscript{12,13}. A more detailed background of population modeling can be found elsewhere\textsuperscript{14,15}. The objective of this study is to investigate the influences of labor on the PK of intravenously administered amoxicillin.

**Methods**

**Patients**

In the period between February 7, 2005 and February 28, 2007, all women with gestational age of minimally 26 weeks who needed antibiotic treatment with amoxicillin were eligible for the study. From a subset of patients a part of the data was used in a previous study\textsuperscript{7}. These patients were all diagnosed with preterm premature rupture of the membranes and therefore before the onset of labor (in total 416 samples). Following the local guidelines, all women with proven or unknown *Streptococcus agalactiae* carriage were treated with antibiotics when pregnancy was complicated by one of the following factors: preterm premature rupture of the membranes, rupture of the membranes for \(>18\) hours, prematurity, fever \((>37.8^\circ\text{C})\), bacteriuria in current pregnancy and a previous child with invasive GBS disease. The choice of the antibiotic for this study was dictated by the local guidelines, which recommend amoxicillin as first choice. Women were admitted to the hospital and monitored for fetal condition, onset of labor and signs of infection. When intra-amniotic infection was suspected, delivery was induced. The study was approved by the Medical Ethics Committee of the Medical Center Haaglanden, the Hague, the Netherlands. 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 year of age.

Both pregnant patients before the onset of labor and patients in labor were included in the study. Patients included before the onset of labor or during labor, who agreed to receive an additional dose of amoxicillin after their delivery for study purposes only were kept in the study until maximally 28 hours after delivery. Being in labor was defined as the presence of uterine contractions resulting in progressive cervical dilatation. The vaginal examinations were performed by the physician responsible for the delivery. When labor started during the study period, the time of the onset of labor was recorded.

All patients received a standard work-up that included a medical history, biochemical and hematological examination. Furthermore blood pressure, pulse, oral temperature, and body weight were recorded at the onset of the study. Furthermore blood pressure, pulse, oral temperature, and body weight were recorded at the onset of the study. Temperature and pulse were recorded to register the possibility of
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intra-amniotic infection, whereas the blood pressure and the amount of edema were recorded to account for differences in distribution volumes. The amount of edema was scored semiquantitatively from 0 (no edema) to 3 (above the knee).

**Drug administration and blood sampling**

Before the administration of the amoxicillin, an intravenous catheter was placed in each arm. Amoxicillin was administered according to local guidelines in the hospital. Treatment started with an intravenous infusion of 2 gram amoxicillin (50 mg/mL) administered over 30 min, followed by an infusion of 1 gram amoxicillin over 15 minutes every 4 hours until delivery. In the prevention of GBS, antibiotics were administered until delivery. For the purpose of this study only, a single additional dose of 1 gram amoxicillin was administered after delivery 4 hours after the last dose before child birth. Blood samples 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). After the infusion, sampling was scheduled at 3, 6, 10, 16 and 36 minutes, and afterwards every 30 minutes until the next antibiotic dosage. Blood samples were collected when possible, taking into consideration the physical and emotional inconvenience to the woman. 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 min. The supernatants were transferred into plastic storage tubes and frozen at -70˚C until analysis.

**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 Non-Linear Mixed Effect Modeling (NONMEM). The model was implemented in the NONMEM ADVAN5 subroutine and the analysis was performed using the FOCE with INTERACTION method. All fitting procedures were performed with the use of the Compaq Visual FORTRAN standard edition 6.6 (Compaq Computer Cooperation, Euston,
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Texas, USA) and NONMEM® software package (version VI, release 1.2, ICON Development Solutions, Ellicott City, Maryland, USA).

To determine the basic structural pharmacokinetic parameters various 2- and 3-compartment models were tested. Model selection and identification of variability was based on evaluation of the mean objective function value (OFV), pharmacokinetic parameter point estimates, and their respective confidence intervals, and goodness-of-fit plots. For differences between two structural models, the OFV with a pre-specified level of significance of $p<0.001$ was used (corresponding to a difference in OFV of 10 points). 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. A proportional error model, additive error model and a combined proportional-additive error model were tested to describe the residual variability between the observed concentrations and those predicted by the 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, on which a random effect has been identified, were plotted against the covariates bodyweight, body mass index, gestational age, blood pressure, pulse, oral temperature, and the amount of edema, single or twin pregnancy, creatinin, the renal function calculated with the Cockcroft-Gault (CG) and the modified Modification of Diet in Renal Disease (MDRD) equation to determine whether this influenced the pharmacokinetics\textsuperscript{16,17}. Covariate analysis was performed by forward addition of each candidate covariate into the model structure until no further improvement of goodness of fit was observed. A significance level of 0.05 was selected (corresponding to difference in OFV 3.84 points). A further criterion for acceptance of covariate effects was that the estimated 95% confidence interval of the covariate effect did not overlap with zero. Contribution of each covariate to the final model was the confirmed by backward elimination of each covariate from
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the model to account for possible interaction between covariates. 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.$^{18}$

Finally, the effect of the presence of labor was investigated on structural PK parameters. The state of being pregnant but before the onset of labor, being in labor and being in the immediate postpartum period were implemented in the model as covariate in the entire group of patients. A significance level of 0.05 was selected (corresponding to difference in OFV of 3.84 points). A further criterion for acceptance of the influence of labor was that the estimated 95% confidence interval of its effect did not overlap with its null value. Contribution of an effect of labor to the final model was the confirmed by backward deletion of both the effect of labor and the continuous covariates from the model to account for possible interaction between covariates and the effect of labor.

The accuracy of the final population model for the entire population 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, 34 patients were included. From 8 patients blood samples were taken both before the onset of labor and during labor. From 17 patients blood samples were taken only before the onset of labor and from 9 patients only during labor. Eight patients agreed with a postpartum dose of amoxicillin as well. The postpartum doses of amoxicillin were administered between 1.5-3.8 hours after child birth. The study population consisted of 31 singleton and 3 twin pregnancies. All 17 patients participating in the study during labor, delivered vaginally. The gestational age at the time of the study ranged from 30.0 to 40.6 weeks. The characteristics of the study patients are presented in Table 1.

Peak concentrations were comparable in patients during labor and in patients before the onset of labor. Peak concentrations after the 2 gram infusion were 97.4 +/- 20.7 mg/L in patients before the onset of labor and 92.3 +/- 16.6 mg/L in patients during labor (mean +/- SD). Peak concentrations after the 1 gram infusion were 71.8 +/- 14.8 mg/L, 62.8 +/- 7.9 mg/L, and 65.7 +/- 15.5 mg/L, respectively, in patients before labor, during labor and postpartum. The terminal half-lives for the three stages of labor were not significantly different (1.1 +/- 0.3 h during labor, 1.2 +/- 0.2 h before labor and 1.2 +/- 0.2 h postpartum). The volume of distribution in steady state was 40.4 L.
A total of 898 blood samples were collected in this study. Of these samples 550 were taken before the onset of labor, 187 during labor and 161 in the immediate postpartum period. For patients included before the onset of labor between 7 and 34 samples were obtained per patient, during labor between 5 and 24 samples and in the postpartum period between 12 and 25 samples. A three compartment open model best described the data. The residual error was found to be proportional to the blood concentrations. Inter-individual variability was mainly observed in clearance (CV 19.8%), V1 (CV 23.1%) and V2 (CV 31.6%). Correlations between the random parameters for inter-individual variability were found and implemented in the model. For the selected continuous covariates, there was a significant effect of edema on the total volume of distribution. The volume of distribution increased with an increasing amount of edema (Figure 2b). Furthermore, the effect of renal function on CL was found inconsequential. Using the serum creatinin concentration and the estimated creatinin clearance calculated with the CG-formula, no influence on the CL of amoxicillin was seen. However, renal clearance was found to have a small, but significant effect on CL when calculated using the modified MDRD formula. CL was inversely correlated with an increased MDRD (Figure 2C). In figure 1 the observed concentrations are plotted versus the model-based population predicted concentrations, illustrating the unbiased model-fit.
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Figure 1
Scatter plot of the population predicted vs observed concentrations of amoxicillin for 34 patients. The figure shows the individual data points for the entire population and the line of identity (x=y) with linear scale (Fig 1A) and logarithmic scale (Fig 1B).

Figure 2
Plots of values for $V_2$ for the three stages of labor (figure 2a), values of $V_1$ versus the amount of edema (figure 2b) and values of MDRD versus CL (figure 2c).
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Labor status in patients was found to have a small but significant effect on peripheral distribution volume ($V_2$). $V_2$ was larger in women before the onset of labor compared to women during labor and in the postpartum period. Compared to women before the onset of labor, $V_2$ was decreased with 13.7% during labor and 29.5% in the immediate postpartum period. Figure 2a shows the different values for $V_2$ for the three stages of labor. Figure 3a shows the observed concentrations of patients before and after the onset of labor for the first 4 h after the 2 gram infusion, whereas figure 3b shows the observed concentration for all three stages of labor after a 1 gram dose. The estimates of the pharmacokinetic parameters of the final model and the relative standard errors derived from the bootstrap analysis are presented in Table 2.

The bootstrap validation of the model of the entire population 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 PK analysis (data not shown). The bootstrap validation was successful for 95 runs. The standard errors obtained from the bootstrap analysis were also comparable to those estimated by the model.

Figure 3
Figure 3a shows the observed amoxicillin concentrations after a 2 gram dose and figure 3b after a 1 gram dose. Time of infusion is indicated by black bars. The open squares represent all data points of the patients before the onset of labor; the filled dots data points of patients during labor and data points of patients in the postpartum period are indicated by the open triangles. Because there was variation in the start-time of the second infusion, in figure 3b the data were adapted assuming that the 1 gram infusions started at $t=0$ for all patients. (See color inlay for a full color version of this figure.)
Table 2: Population model parameter values with standard error of 34 women presented with SE% or CV% and 95% confidence interval as derived from the bootstrap analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Mean (model)</th>
<th>SE% (bootstrap)</th>
<th>95%CI (bootstrap)</th>
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<td>CL</td>
<td>L/h</td>
<td>21.1</td>
<td>4.1</td>
<td>19.6 - 23.0</td>
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<td>V₁</td>
<td>L</td>
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<td>7.5 - 9.8</td>
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<td>V₂</td>
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<td>11.8</td>
<td>7.7</td>
<td>9.9 – 13.4</td>
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<tr>
<td>V₃</td>
<td>L</td>
<td>20.5</td>
<td>15.4</td>
<td>14.3 – 26.7</td>
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<tr>
<td>Q₁</td>
<td>L/h</td>
<td>21.9</td>
<td>16.9</td>
<td>15.0 – 29.8</td>
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<tr>
<td>Q₂</td>
<td>L/h</td>
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<td>41.3</td>
<td>0.28 – 2.69</td>
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<td><strong>Variance model parameters</strong></td>
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<tr>
<td>IIV in CL</td>
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<td>4.2</td>
<td>19.8</td>
<td>1.6 – 6.1</td>
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<td>23.1</td>
<td>-0.16 – 10.6</td>
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<td>IIV in V₂</td>
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<td>31.6</td>
<td>1.1 – 17.9</td>
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<td>Residual variability</td>
<td></td>
<td>4.6</td>
<td>21.5</td>
<td>3.3 – 5.7</td>
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</table>

SE: standard error of the estimate, SE%: relative SE (%), 95%CI: 95% confidence interval, CL: clearance, V₁: volume of distribution of the central compartment, V₂: volume of distribution of the first peripheral compartment, V₃: volume of distribution of the second peripheral compartment, Q₁: intercompartmental clearance between V₁ and V₂, Q₂: intercompartmental clearance between V₁ and V₃, IIV: Inter-individual variability, CV%: relative coefficient of variation (%)
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Discussion

The PK of intravenously administered amoxicillin of our entire study population was best described by a three-compartment open model. Volume of distribution increased with an increasing amount of edema. An effect of labor was seen on the peripheral volume of distribution (V₂). When compared to pregnant women before the onset of labor, V₂ was decreased during labor and even more decreased in the immediate postpartum period. For our patients dose adjustments were not indicated, but it can not be excluded from this study that the current dosing schedule is adequate for patients with pregnancy-related disorders.

Estimation of glomerular filtration rate (GFR) in pregnant women is difficult. Serum creatinin levels are often used to estimate GFR, especially in conjunction with either the Cockcroft-Gault (CG) or Modification of Diet in Renal Disease (MDRD) formulae. Both the CG and MDRD formulae are based on cohort studies of patients with mild to moderate renal insufficiency, and none of the subjects was pregnant. Unfortunately, estimation of GFR in the pregnant population using either the CG or the MDRD formula has not been validated. There have been several reports demonstrating that the MDRD formula tends to underestimate GFR in subjects with normal or near-normal renal function. Whereas the CG formula is weight based, and weight gain in pregnancy will obviously exaggerate estimated GFR. Alper et al. investigated the GFR in preeclamptic patients. Neither the CG or the MDRD formula were very accurate in predicting GFR in this group of patients, although the MDRD formula performed modestly better. In our analysis, both serum creatinin values and estimated GFR using the CG-formula did not have a significant effect on CL, but when GFR was estimated with the MDRD formula the CL decreased with an increasing GFR. This is unlikely, and therefore illustrates the importance of the use of validates formulas in special patient groups. Pharmacokinetic parameter estimates did not change after the implementation of GFR calculated with the MDRD formula. Based on the absence of an effect of serum creatinin values and the GFR estimated using the CG formula, we concluded that CL is not influenced by renal function.

Other studies on the influence of labor on the PK of amoxicillin are not available. One study has investigated the PK of oral amoxicillin after a single dose both in the second and third trimester of pregnancy as well as postpartum. It was found that during pregnancy the renal clearance was increased compared to the postpartum period. However, in the study of Andrew et al. patients were included 3 months after delivery, while our patients were measured within the first 27 hours after delivery. This probably explains the difference between the two studies. The PK of ampicillin, an antibiotic closely related to amoxicillin, has been studied both during pregnancy and during labour. Differences in PK of ampicillin between pregnant and non-pregnant individuals have been described, such as a shorter
Influence of labor on Amoxicillin PK half-life and higher plasma clearance during pregnancy\textsuperscript{25,26,28}. Furthermore, an effect of labor on the terminal half-life of ampicillin has been described\textsuperscript{24}. Labor increased the terminal half-life in patients in labor, compared to pregnant women before the onset of labor from 39.2 +/- 4.27 min to 58.3 +/- 4.98 min\textsuperscript{24}. Unlike other studies\textsuperscript{25,26,28}, these investigators also could not demonstrate differences in the PK of ampicillin between non-pregnant individuals and pregnant women before the onset of labor\textsuperscript{24}. In contrast to this study, we did not find differences in terminal half-life of amoxicillin between women before and after the onset of labor. Differences in study design might explain the discrepancy between the results. In the ampicillin study four blood samples were collected from each patient, whereas in our study an average of 18 blood samples was obtained for each patient per stage of labor. More intensive sampling will result in more reliable estimates of the inter-individual variability. The pharmacokinetic description of studies with a high sampling density are expected to be more accurate and harbor the possibility of detecting also small differences in pharmacokinetic parameters between various patients. Whether differences in methodology or true differences between the study populations underlies the different conclusions of the studies remains to be determined. Alternatively, differences in chemical structure or features of the two drugs might also explain differences in the results. However, since the pharmacokinetics of ampicillin and amoxicillin after intravenous administration in non-pregnant individuals has been shown to be similar in previous studies\textsuperscript{29,30}, this is unlikely.

Clinically relevant pharmacokinetic changes during pregnancy have also been demonstrated for other drugs. For example, the plasma concentration of the antiepileptic drug lamotrigine has been shown to decrease during pregnancy. Subsequently, in the immediate postpartum period, the plasma concentration increases rapidly, resulting in a risk for toxicity\textsuperscript{31}. This indicates that changes of specific drugs during pregnancy and labor cannot be readily extrapolated on the basis of results obtained with other drugs.

The inter-individual variability in amoxicillin pharmacokinetics between the patients was remarkably moderate. In figure 1 the observed concentrations are plotted versus the population predicted concentrations. The majority of the data points are located near the line of identity. However, for some observed concentrations the predicted concentrations are overestimated. These blood samples were taken during the antibiotic infusion. The antibiotic concentration increases very fast during the infusion. We recorded the sampling times with a precision of 0.5-1 minute. Therefore, the model will predict concentrations during the antibiotic infusion less accurately compared to concentrations in blood samples collected after the antibiotic infusion.

An important question for the clinical practice is whether the recommended amoxicillin dosing regimen is adequate in the prevention of GBS disease. The
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efficacy of amoxicillin 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\textsuperscript{32,34}. The MIC value of an antibiotic is the highest MIC value of different microbial strains that results in a high probability of cure. MIC value of amoxicillin for GBS as indicated by the EUCAST is 0.25 mg/L\textsuperscript{35}. All concentrations remained well above the MIC of GBS for a sufficient percentage of the dosing interval, even when taking into account the plasma protein binding of approximately 18-20%\textsuperscript{36,37}.

After delivery, the pregnancy-induced physiological adaptations will change back to normal. This process starts immediately postpartum, but will continue for several weeks\textsuperscript{38,39}. In the first days after delivery, this includes an increase in blood volume and cardiac output. We found only minor differences in pharmacokinetic behavior of amoxicillin in the immediate postpartum period when compared to pregnant women. This supports our earlier study that demonstrated a similar PK of amoxicillin in pregnant women with PPROM compared to values reported for non-pregnant individuals.

In our study, in none of the patients toxic or sub-therapeutic concentration-profiles were reached. For this reason the differences in PK in the three stages of labor were considered not clinically relevant. This finding supports the current practice that the dosing regimen is not adjusted during the course of labor. However, it should be noted that we included only healthy patients and that only 8 patients were included both before and during labor. Our patient group may be considered to be small, but taking into account the situation in which the patients had to be studied this is a relatively large population. Antibiotics in the prevention of GBS are also used to protect the fetus. Therefore, adequate fetal concentrations are imperative. Since uterine contractions might influence the blood flow in the umbilical cord, studies investigating the transplacental transfer of amoxicillin during vaginal deliveries are needed to describe the PK in umbilical cord serum and ultimately in the fetus.

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