Pharmacokinetics of tacrolimus in pregnant solid organ transplant recipients

Versluis, Jorn; Bourgonje, Arno R.; Touw, Daan J.; Meinderts, Jildau R.; Prins, Jelmer R.; de Jong, Margriet F. C.; Mian, Paola

Published in:
The Journal of Clinical Pharmacology

DOI:
10.1002/jcph.2393

Publication date:
2024

ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology

Original Article

Pharmacokinetics of Tacrolimus in Pregnant Solid-Organ Transplant Recipients: A Retrospective Study

The Journal of Clinical Pharmacology
2024, 64(4) 428–436

DOI: 10.1002/jcph.2393

Jorn Versluis, PharmD[1], Arno R. Bourgonje, MD, PhD[2], Daan J. Touw, PharmD, PhD[1,3], Jildau R. Meinderts, BSc[4], Jelmer R. Prins, MD, PhD[5], Margriet F. C. de Jong, MD, PhD[4], and Paola Mian, PharmD, PhD[1]

Abstract

Data on the pharmacokinetics of tacrolimus during pregnancy are limited. Therefore, the aim of this retrospective study was to characterize the whole-blood pharmacokinetics of tacrolimus throughout pregnancy. In this single-center retrospective cohort study, whole-blood tacrolimus trough concentrations corrected for the dose (concentration-to-dose [C/D] ratios) were compared before, monthly during, and after pregnancy in kidney, liver, and lung transplant recipients who became pregnant and gave birth between 2000 and 2022. Descriptive statistics and linear mixed models were used to characterize changes in tacrolimus C/D ratios before, during, and after pregnancy. The total study population included 46 pregnancies (31 pregnant women). Nineteen, 21, and 6 pregnancies were following kidney, liver, and lung transplantation, respectively. Immediate-release or extended-release formulations were used in 54.5% and 45.5% of the women, respectively. Tacrolimus C/D ratios significantly ($P < .001$) decreased (−48%) compared to the prepregnancy state at 7 months of pregnancy. These ratios recovered within 3 months postpartum ($P = .002$). C/D ratios tended to be lower during treatment with an extended-release formulation than with an immediate-release formulation ($P = .071$). Transplantation type did not significantly affect C/D ratios during pregnancy ($P = .873$). In conclusion, we found that tacrolimus whole-blood pharmacokinetics change throughout pregnancy, with the lowest C/D ratios (48% decrease) in the 7th month of pregnancy. In general, the decrease in C/D ratios seems to stabilize from month 4 onward compared to prepregnancy.

Keywords

extended-release formulation, immediate-release formulation, organ transplantation, pharmacokinetics, pregnancy, tacrolimus

After solid-organ transplantation, patients are prescribed immunosuppressive drugs, such as tacrolimus, to prevent acute as well as long-term rejection of the allograft.[1] Tacrolimus is a calcineurin inhibitor and prevents allograft rejection by suppression of interleukin-2, a cytokine produced by activated T cells.[2] It is often referred to as one of the backbone drugs in standard immunosuppressive therapy after transplantation.[2,3] It has a half-life in adults of approximately 12 hours[4] and a narrow therapeutic range, and therefore therapeutic drug monitoring (TDM) of whole-blood concentrations is routinely used in clinical practice.[5,6] Subtherapeutic whole-blood concentrations can result in rejection of the allograft.[5] However, higher whole-blood concentrations are associated with nephrotoxic and neurotoxic effects as well as increased infection rates.[7,8]

A special group of patients using tacrolimus after solid-organ transplantation are pregnant women or those who wish to conceive. Over the past years, the number of solid-organ transplant recipients, including women in the fertile age, is increasing.[9] Pregnancy induces many physiological changes such as increased plasma volume, lowered serum protein and erythrocyte concentrations, altered metabolism (eg, increased cytochrome P450 3A4 activity), and increased renal flow rate.[10,11] These changes can significantly influence the pharmacokinetic behavior of tacrolimus during pregnancy. There is a growing body of evidence describing successful pregnancies in solid-organ transplant

[1]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen and University of Groningen, Groningen, The Netherlands
[2]Department of Gastroenterology and Hepatology, University Medical Center GroningenUniversity of Groningen, Groningen, The Netherlands
[3]Department of Pharmaceutical Analysis, Groningen Research Institute for Pharmacy, University of Groningen, Groningen, The Netherlands
[4]Department of Internal Medicine, Division of Nephrology, University Medical Center GroningenUniversity of Groningen, Groningen, The Netherlands
[5]Department of Obstetrics and Gynaecology, University Medical Center GroningenUniversity of Groningen, Groningen, The Netherlands

Submitted for publication 23 July 2023; accepted 6 December 2023.

Corresponding Author:
Paola Mian, PharmD, PhD, Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen and University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands.
E-mail: p.mian@umcg.nl

recipients with tacrolimus-based immunosuppression. Nevertheless, these pregnancies are at increased risk for maternal complications such as preeclampsia, hypertension, renal impairment, rejection, infection, postpregnancy graft loss, and miscarriage. Fetal and neonatal complications include preterm birth, stillbirth, intrauterine growth restriction, low birth weight, and reversible renal dysfunction, as well as hyperkalemia in the newborn and, rarely, neonatal death. Given the severity of the complications, a critical evaluation and optimization of tacrolimus therapy during pregnancy is warranted.[12]

Limited data are available on whole-blood pharmacokinetic changes of tacrolimus during pregnancy after solid-organ transplantation. Overall, tacrolimus dosages are being increased during pregnancy and decreased postpartum to maintain a whole-blood trough concentration within the target therapeutic range.[13] However, the increased dose need and the time frame during gestation that the dose should be increased might vary throughout pregnancy and between individual pregnancies. To increase the ability of reaching adequate target concentrations throughout pregnancy, Le et al[14] proposed increasing the frequency of TDM, which was supported by Hebert et al.[12] For "a priori" dose adjustments, more information about the change in whole-blood pharmacokinetics of tacrolimus during pregnancy after solid-organ transplantation is needed. In addition, after delivery, tacrolimus whole-blood pharmacokinetics may return to prepregnancy values, but timing may vary.[12] Therefore, the aim of this retrospective study was to characterize the change in whole-blood pharmacokinetics of tacrolimus throughout the various phases of pregnancy and after delivery.

Methods

This was a single-center retrospective cohort study performed in the University Medical Center Groningen (UMCG), The Netherlands. Kidney, liver, and lung transplant recipients who became pregnant and gave birth between 2000 and 2022 were selected. Inclusion criteria were solid-organ transplant recipients requiring tacrolimus during pregnancy. In addition, medical records should include at least 1 tacrolimus whole-blood trough concentration within the period of interest. Due to the retrospective and descriptive nature of this study, the need to provide informed consent was waived by the UMCG medical ethics committee (METc 2022/611).

Pregnancy-related characteristics were collected from the patients' medical records and included date of pregnancy outcome and weeks of gestation. The prepregnancy period was defined as the 6-week period prior to conception. Pregnancy was categorized into months, counting from the first day of pregnancy to pregnancy outcome. The postpartum period was defined up to 3 months after delivery. No postpartum data from pregnancies resulting in pregnancy loss were included in the results, since physiological changes in these pregnancies might deviate from live-birth pregnancies and thereby affect tacrolimus pharmacokinetics. No discrimination in data between patients with single (once pregnant after transplantation) or multiple (multiple pregnancies after transplantation) pregnancies was made. When periods of measurement from multiple pregnancies showed overlap, the tacrolimus whole-blood concentrations were used only once.

Tacrolimus whole-blood trough concentrations before, during, and after pregnancy were extracted from the patients' medical files, including the date and time of sampling. All tacrolimus whole-blood trough concentrations were determined as part of routine care by validated liquid chromatography-tandem mass spectrometry analysis at the UMCG.[15] Furthermore, other patient information including type and date of organ transplantation; tacrolimus formulation; date and time of tacrolimus administration; changes in tacrolimus dosage over time; height, weight, and comorbidities of pregnant women; comedication; and number and dosage of immunosuppressive drugs were collected.

Tacrolimus whole-blood trough concentrations show great variability between patients. Therefore, whole-blood trough concentrations (ng/mL) were divided by the dose (mg) given, resulting in a concentration-to-dose (C/D) ratio. This allows comparison of tacrolimus whole-blood pharmacokinetics between and within patients.[16] For patients with a whole-blood trough concentration below the lower limit of quantification of 1 ng/mL, half of the lower limit of quantification (0.5 ng/mL) was used for calculating the C/D value. When a patient had more than 1 C/D ratio, per-month averages were calculated per patient for that month. Finally, the average C/D ratios in prepregnancy, pregnancy (monthly), and postpartum periods were calculated. C/D ratios were calculated and presented for the immediate-release (Prograft) and 2 extended-release formulations (1, Advagraf; and 2, Envarsus) separately, because of their distinctive pharmacokinetic properties.

Baseline demographic and clinical characteristics were presented as means ± standard deviation (SD) for normally distributed continuous variables, medians with interquartile ranges for skewed continuous variables or as proportions n with corresponding percentages (%) in case of nominal variables. Assessment of normality was performed visually using kernel density plots and normal probability (Q-Q) plots and statistically using Shapiro-Wilk tests. Changes in tacrolimus

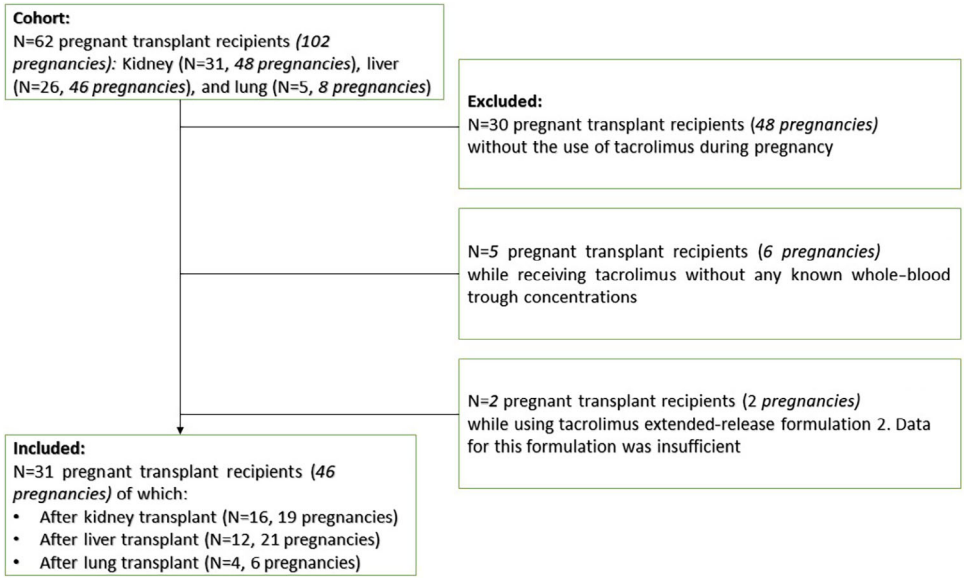

Figure 1. Flowchart indicating the total number of female transplant recipients, number of pregnancies, number of exclusions, reason for exclusion.

C/D ratios relative to prepregnancy baseline values over time were analyzed using linear mixed models, in which time (less than 6 weeks prepregnancy period, pregnancy months 1-9, and less than 3 months postpregnancy period), type of tacrolimus formulation (immediate and extended release), and type of transplantation (kidney, liver, or lung) were inserted as fixed effects and subject ID as a random effect. Time was entered as a factor to compare each time point against baseline. Akaike's information criterion was used to select the best-fitting covariance structure. Estimated marginal means were presented with standard errors and 95% confidence intervals. Data analysis and visualization were performed using SPSS Statistics software package Version 28.0 (SPSS Inc.) and Python Version 3.9.0 (Python Software Foundation), using the pandas (Version 1.2.3.), numpy (Version 1.20.0), matplotlib (Version 3.4.1), and seaborn (Version 0.11.1) packages. Two-tailed *P* values of .05 or less were considered statistically significant.

Results

A total of 62 female patients who received a lung (N = 5), kidney (N = 31), or liver (N = 26) transplant and became pregnant were identified for inclusion in the study. Pregnant patients not using tacrolimus were excluded (N = 0, 18, and 14, respectively). In addition, pregnant women receiving tacrolimus but without tacrolimus whole-blood trough concentrations were also excluded (N = 2, 1, and 3, respectively). Pregnancies while using extended-release formulation 2 were excluded as well because it was used in only 2 pregnancies. One woman with 2 pregnancies using the immediate-release formulation received a kidney as well as a liver transplant before her first pregnancy. This patient was included in both the kidney as well as the liver transplant cohort. Finally, the total study population included 31 women who became pregnant and a total of 46 pregnancies, of which 19 were following kidney transplantation, 21 following liver transplantation, and 6 following lung transplantation (Figure 1).

Characteristics of the study population are shown in Table 1.

In general, all pregnancies started at least 6 months after solid-organ transplantation. All pregnancies in this study were singleton pregnancies. Average gestational age in live births was 36 weeks 3 days (SD = 3 weeks 4 days). Pregnancy duration was shortest in lung (mean, 34 weeks 6 days; SD, 2 weeks 3 days) transplant recipients, followed by kidney (mean, 35 weeks 2 days; SD, 4 weeks 1 day), and liver (mean, 37 weeks 2 days; SD, 3 weeks 3 days). Preterm delivery (less than 37 weeks) was common (45%). Furthermore, 54.5% of women used tacrolimus as an immediate-release formulation, whereas the other 45.5% used the extended-release formulation (Table 1). The number of total pregnancy losses in our study population was 8, of which 7 were in the kidney transplant cohort, and 2 were in the liver transplant cohort (1 pregnancy loss from a patient who received a kidney as well as a liver transplant). The mean pregnancy period in pregnancy loss was 19 weeks 2 days (SD, 5 weeks 5 days). It must be noted that this pregnancy loss is in the late second trimester, while in the general population pregnancy loss is usually in the first trimester.

Table 1. Characteristics of the Study Population

Characteristics	Mean [SD] or proportions (%)
No. of pregnancies after organ transplantation	46 (49)[a]
Kidney (%)	19 (41.3)
Liver (%)	21 (45.7)
Lung (%)	6 (13.0)
Age (years) when giving birth	32.0 [4.00]
Kidney	32.8 [4.19]
Liver	31.3 [3.73]
Lung	30.9 (2.76)
Average gestational age in live births (n = 38)	36 weeks 3 days (3 weeks 4 days)
Kidney	35 weeks 2 days 4 weeks 1 day)
Liver	37 weeks 2 days (3 weeks 3 days)
Lung	34 weeks 6 days (2 weeks 3 days)
Tacrolimus formulation use (n = 46)	
Immediate-release formulation (Prograft)	24 (52.2)
Extended-release formulation 1 (Advagraf)	20 (43.5)
Extended-release formulation 2 (Envarsus)	2 (4.3)
Immunosuppressant therapy: (n = 46)[b]	
Single-drug therapy	10 (21.7)
Dual-drug therapy	12 (26.1)
Triple-drug therapy	24 (52.2)
Distribution of dates of pregnancy outcome per half a decade	
2005-2009	4 (8.7)
2010-2014	7 (15.2)
2015-2019	23 (50.0)
2020-2022	12 (26.1)

Data are presented as mean (SD) or n (%).
SD, standard deviation.
[a] The total number is corrected for multiple (3) pregnancies belonging to both a kidney as well as liver transplant recipient.
[b] Single-drug therapy: tacrolimus, dual-drug therapy: tacrolimus and prednisolone or azathioprine; triple-drug therapy: tacrolimus, azathioprine, and prednisolone.

Immunosuppressive therapies consisted of tacrolimus either alone or in combination with azathioprine or prednisolone or both (Table 1). The tacrolimus daily dose of the patients varied from 1 to 12 mg/day for Advagraf and 0.5 to 12 mg/day for Prograft. Single-drug immunosuppression was used only in liver transplant recipients. All lung transplant recipients were using a combination of 3 immunosuppressive agents. The azathioprine dose ranged between 25 and 150 mg/day, whereas the prednisolone dose was between 1 and 10 mg/day. Besides immunosuppressants, use of other medication during pregnancy varied between women. None of the comedications was found to have clinically relevant interactions with tacrolimus.

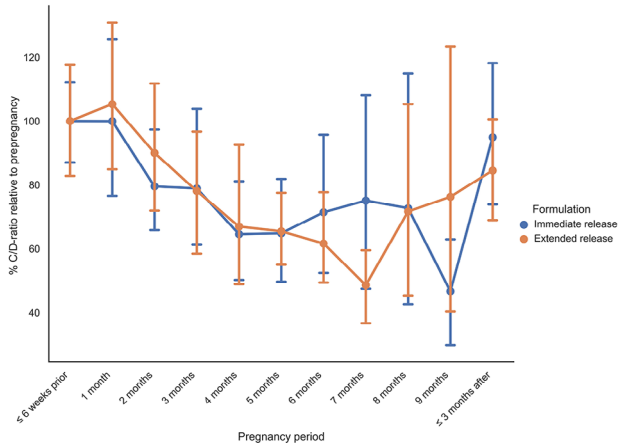

Figure 2. Changes in drug tacrolimus blood concentrations (ng/mL) divided by the daily dose (mg) of the immediate and extended-release formulation in total pregnant patients receiving solid-organ transplant. Results are given as mean percentage of this ratio 6 weeks prior to pregnancy. The error bars are the 95% confidence interval.

In Table 2, the number of C/D ratios are shown for both the immediate- and extended-release formulations specified by type of solid-organ transplantation. C/D ratios are calculated and plotted for both the immediate- and extended-release formulations before, during, and after pregnancy (Figure 2). Ratios are expressed as percentages compared to the prepregnancy period. When focusing on the immediate-release formulation (Figure 2), C/D ratios decreased steadily to approximately 65% of the prepregnancy value in Month 4 and remained stable until Month 8, followed by a decrease to 50% in Month 9. Postpartum, C/D ratios increased to more than 80% of the prepregnancy value. For the extended-release formulation (Figure 2), a trend was observed with decreasing C/D ratios over the course of the pregnancy period. It increased to approximately 110% in Month 1 and decreased to 50% in Month 7. In Months 8 and 9, C/D ratios were back at 75% and 80% but with large deviations. Within 3 months postpartum, C/D ratios recovered to approximately 85% of the prepregnancy value.

In Figure 3, the percentage of C/D ratios of tacrolimus relative to prepregnancy are shown specified for the immediate-release formulation for kidney, liver, and lung transplantation. In kidney transplant recipients (Figure 3a), C/D ratios in the immediate-release formulation users did not decline below the prepregnancy ratio except in Month 9. Postpartum However, the C/D ratio was increased to 130%. In liver transplant recipients (Figure 3b), C/D ratios decreased steadily to 50% after 4 months at this value until the end of the pregnancy. Postpartum C/D ratios increased back to 80% prepregnancy value. In lung transplant recipients receiving the immediate-release formulation, no tacrolimus trough concentrations were available in

Table 2. Total Number of Women with Solid Transplants and Total Number of Pregnancies Using Immediate- or Extended-Release Formulation, Including the Number of Pregnancies and C/D Ratios Specified as Before, Monthly During, and After Pregnancy

		≤6 weeks before pregnancy	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	≤3 months after pregnancy
Immediate-release formulation	Kidney transplant recipients, n = 7											
	Total pregnancies, n = 9											
	Pregnancies, N	5	5	4	6	5	7	5	5	4	3	8
	C/D ratios, N (range)	5 (0-1)	6 (0-2)	5 (0-2)	6 (0-1)	6 (0-2)	8 (0-2)	7 (0-2)	9 (0-5)	6 (0-3)	4 (0-2)	28 (0-7)
	Liver transplant recipients, n = 6											
	Total pregnancies, n = 11											
	Pregnancies, N	4	6	10	8	10	10	10	9	7	3	10
	C/D ratios, N (range)	5 (0-2)	6 (0-1)	11 (0-2)	8 (0-1)	12 (0-2)	11 (0-2)	21 (0-10)	22 (0-12)	8 (0-2)	4 (0-2)	38 (0-8)
	Lung transplant recipients, n = 4											
	Total pregnancies, n = 6											
	Pregnancies, N	3	0	3	5	0	4	2	3	1	0	5
	C/D ratios, N (range)	3 (0-1)	0	3 (0-1)	5 (0-1)	0	4 (0-1)	2 (0-1)	4 (0-2)	3 (0-3)	0	15 (1-4)
Extended-release formulation	Kidney transplant recipients, n = 9											
	Total pregnancies, n = 10											
	Pregnancies, N	2	4	7	5	5	6	7	5	4	4	7
	C/D ratios, N (range)	2 (0-1)	6 (0-3)	8 (0-2)	6 (0-2)	6 (0-2)	8 (0-2)	9 (0-2)	6 (0-2)	9 (0-4)	12 (0-5)	14 (0-4)
	Liver transplant recipients, n = 5											
	Total pregnancies, n = 10											
	pregnancies, N	4	3	6	7	8	8	8	7	8	6	10
	C/D ratios, N (range)	6 (0-2)	3 (0-1)	7 (0-2)	8 (0-2)	9 (0-2)	9 (0-2)	8 (0-1)	8 (0-2)	9 (0-2)	7 (0-2)	21 (0-4)

The 3rd row beneath every transplantation type indicates the number of separate pregnancies with at least 1 tacrolimus through level within this time period. The tacrolimus concentrations from these pregnancies were used to calculate the average C/D ratio. The 4th row beneath every transplantation type indicates the total number of tacrolimus trough concentrations within each period including the minimum and maximum number of repeated measurements within each period.

C/D, concentration-to-dose.

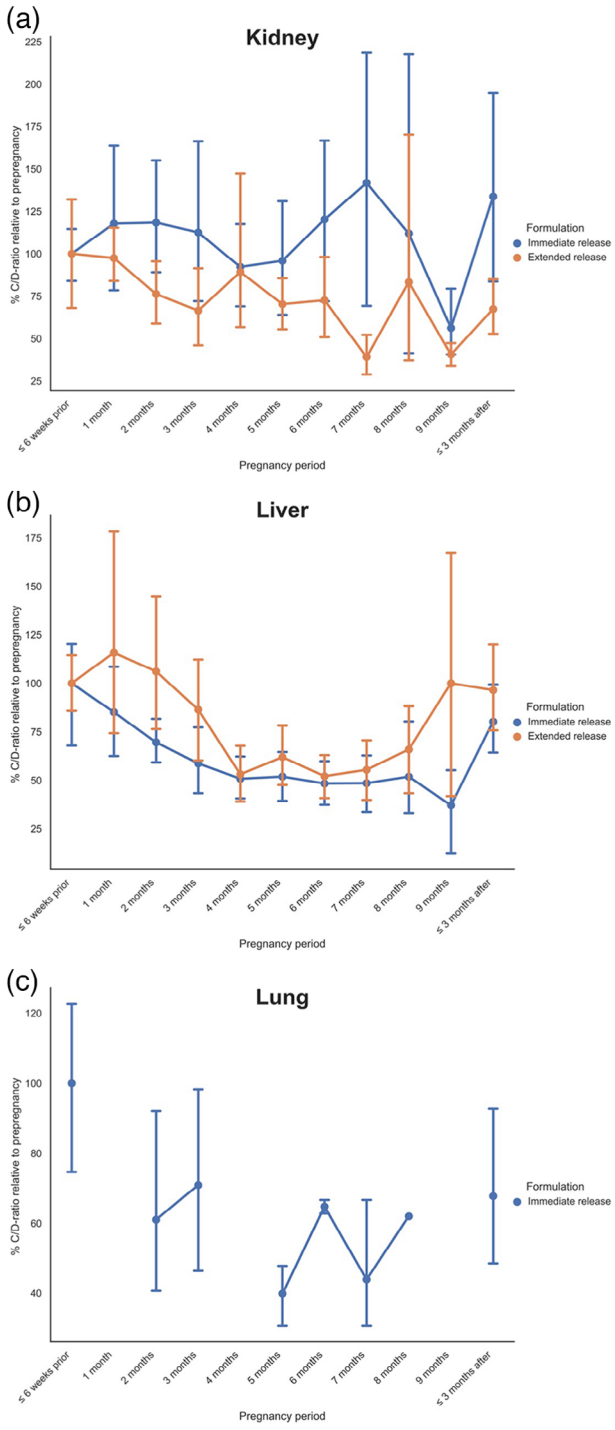

Figure 3. Changes in tacrolimus blood concentrations (ng/mL) divided by the daily dose (mg) of the immediate and extended-release formulation in pregnant patients receiving kidney (a), liver (b), and lung (c) transplants, respectively. Results are given as mean percentage of this ratio 6 weeks prior to pregnancy. The error bars are the 95% confidence interval. Note that no blood concentrations were known within the 1st, 4th, and th month in pregnant lung transplant patients. In addition, no extended release was used in pregnant lung.

Table 3. Estimated Marginal Means of Tacrolimus C/D Ratios Derived from Linear Mixed Model Analyses

Pregnancy state	Geometric EMM	Geometric 95% CI	*P* values*
Prepregnancy phase (6 weeks prior to pregnancy)	1.202	0.938-1.538	-
Month 1	1.268	0.986-1.629	1.000
Month 2	0.993	0.791-1.245	1.000
Month 3	0.929	0.741-1.164	1.000
Month 4	0.753	0.597-0.948	0.006
Month 5	0.764	0.611-0.955	0.002
Month 6	0.719	0.574-0.902	<0.001
Month 7	0.641	0.509-0.805	<0.001
Month 8	0.764	0.603-0.968	0.180
Month 9	0.671	0.520-0.869	0.027
Postpartum phase (3 months after pregnancy)	1.040	0.836-1.294	1

C/D, concentration-to-dose; CI, confidence interval; EMM, estimated marginal means.
*P values comparison with prepregnancy phase (=baseline).

Months 1, 4, and 9 of pregnancy. However, tacrolimus trough concentrations indicate a decline in C/D ratio during pregnancy to as low as 40% in Month 5. Postpartum recovery was 70% of the prepregnancy value (Figure 3c). In pregnant kidney transplant recipients taking the extended-release formulation (Figure 3a), C/D ratios decreased to 70% in Month 3 and further to less than 40% in Month 9. Postpartum recovery was not clearly observed. In liver transplant pregnancies (Figure 3b), C/D ratios of the extended-release formulation increased to 110%-120% in Months 1 and 2, before decreasing to approximately 60% between Months 4 and 8 of pregnancy. The postpartum C/D ratio increased to 100% prepregnancy value. No lung transplant recipients used the extended-release formulation.

Time period over the course of pregnancy was significantly associated with tacrolimus C/D ratios ($P < .001$). C/D ratios were on average lower for the extended-release formulation compared to the immediate-release formulation, albeit this was not statistically significant ($P = .071$). Type of transplantation did not significantly affect the tacrolimus C/D ratios ($P = .873$).

When comparing estimated marginal means throughout pregnancy (Table 3) with baseline (prepregnancy) tacrolimus C/D ratios, significantly decreased C/D ratios were observed at Month 4 ($P = .006$), 5 ($P = .002$), 6 ($P < .001$), 7 ($P < .001$), and 9 ($P < .05$) during pregnancy, with the lowest estimated marginal mean at 7 months during pregnancy. Tacrolimus C/D ratios significantly increased after pregnancy with 48% compared to 7 months ($P = .002$). In general, the decrease in C/D ratios seems to stabilize from Month 4 onward compared to prepregnancy.

Discussion

In this retrospective cohort study, we found that tacrolimus whole-blood pharmacokinetics change throughout pregnancy, with the lowest C/D ratios (48% decrease) in the 7th month of pregnancy. In general, the decrease in C/D ratios seems to stabilize from Month 4 onward compared to prepregnancy. On average, C/D ratios are higher in Month 8 of pregnancy compared to the previous month; however, this increase is not statistically significant and mainly caused by large variability. Overall, values recovered postpartum in all groups (although not yet fully back to prepregnancy state) except in kidney transplant recipients taking the immediate-release formulation and in lung transplant recipients. Although a large variability, which is also present in nonpregnant patients, between postpartum women has been observed, a reason for not fully recovering to prepregnancy values could be that more than 3 months postpartum are needed to reach these prepregnancy baseline values. The need to observe tacrolimus whole-blood trough concentration trajectories closely in both the pregnant and postpartum period, due to fluid shifts and hormonal changes, is critically important in the management of transplanted patients, since unintentional and unnoticed low or high tacrolimus whole-blood concentrations give a risk for allograft rejection or toxicity. The mechanisms behind this decrease throughout pregnancy compared to the nonpregnant state is the fact that pregnancy induces many physiological changes such as increased plasma volume, lowered serum protein and erythrocyte concentrations, altered metabolism (eg, increased cytochrome P450 3A4 activity), and increased renal flow rate.[10,11] After delivery, in the postpartum state, the body slowly recovers to prepregnancy state.

The clinical importance proved by our retrospective study is that the pharmacokinetics of tacrolimus change during pregnancy. Therefore, it is of the utmost importance to frequently, at least once a month, perform TDM in pregnant transplant recipients using tacrolimus to adjust dosing. Furthermore, it must be noted that the changed pharmacokinetics necessitates the development of evidence-based dosing for tacrolimus in pregnant women after transplantation. In this way, evidenced-based dosing can be developed reaching adequate target attainment instead of afterwards adjusting dosing using TDM. Insight in the pharmacokinetics is the first step needed before evidence-based dosing can be developed.[17] One way of moving to evidence-based dosing regimens based on pharmacokinetic data is by conducting a prospective study collecting concentration–time data, including accurate documentation of administration times of tacrolimus and sample times, after which a population pharmacokinetic model can be developed. Within this model, variables (also known as covariates) can be identified that influence the pharmacokinetics within and between patients. After that, simulations can be performed with this population pharmacokinetic model to determine how dosages should be adapted to obtain a certain target concentration.[18]

Until now, a limited number of studies investigated the whole blood pharmacokinetics of tacrolimus in pregnant transplant recipients.[11,19-21] Immediate-release formulations have different pharmacokinetics compared to extended-release formulations, and therefore we stratified C/D ratios for the immediate- and extended-release formulation within our results. However, we could not find a statistically significant difference between the 2 formulations. The same holds true for the type of transplantation. Therefore, within this discussion, we took the tacrolimus formulations as well as the type of transplant as a group and compared those with the published literature.[11,19-21] Our findings are in line with the findings of Aktürk et al,[19] who investigated tacrolimus whole blood trough concentrations in 16 pregnancies of 12 kidney transplant recipients. All women received tacrolimus as an immediate-release formulation. Similar to our work, the authors found that the dosage of tacrolimus needed to be increased to keep tacrolimus whole-blood trough concentrations similar to the prepregnancy value. Aktürk et al found that their dose had to be increased by 2-fold during pregnancy. This corresponds well with a decline in C/D ratio by approximately 50% found for the total cohort pregnancy transplant recipients in the second and third trimesters (Figure 2) in our population exposed to the immediate- and extended-release formulation (Figure 2). In line with our results, a case report by Fehrman-Ekholm and Nisell[20] found a need to increase the dose during pregnancy after kidney transplantation to maintain adequate trough concentrations. This was also supported by 1 pregnant case-within-a-case series of 2 patients after kidney transplantation reported by Midtvedt et al,[21] receiving immediate-release formulation. However, another pregnant case-within-a-case series of 2 patients reported unchanged tacrolimus dosage while maintaining stable therapeutic whole-blood concentrations during pregnancy.[22] In addition, Zheng et al[11] investigated the pharmacokinetics of whole-blood tacrolimus in mid- and late pregnancy; reporting that the mean oral clearance based on whole-blood tacrolimus concentration was 39% higher during mid- and late pregnancy compared with postpartum (47.4 ± 12.6 vs 34.2 ± 14.8 L/h; $P < .03$). Decreased C/D ratios during mid- and third pregnancy from our results correspond with the increase in clearance. Schagen et al[22] recently reported an increased

tacrolimus clearance during pregnancy, resulting in decreased tacrolimus exposure, which was explained by gestational age and hematocrit.[22] The authors' findings and conclusions were in line with our results, namely, to maintain prepregnancy target whole-blood tacrolimus predose concentrations during pregnancy, increasing the dose is required.

In this retrospective analysis, the focus has only been on the pregnant women without taking into account the placenta and the fetus. Tacrolimus can cross the placental barrier and was found in therapeutic concentrations in venous umbilical cord blood from offspring born to women who received a solid-organ transplantation.[22-25] One study compared the umbilical cord blood concentration with the maternal peripheral blood concentration around time of delivery. The authors found a concentration of 71% of the maternal concentration in the umbilical cord blood.[26] Furthermore, tacrolimus is also known to accumulate in the placenta of kidney and liver transplant recipients.[26,27] Freriksen et al[27] reported a greater than 10-fold accumulation of tacrolimus in placental tissue from kidney transplant recipients compared to the maternal whole-blood tacrolimus concentrations around the time of delivery in these patients. As investigating the pharmacokinetics before evidence-based dosing regimens of tacrolimus can be developed in pregnant transplant recipients,[17] future research should not only focus on describing the pharmacokinetics of tacrolimus in pregnant women only, but also take into account the placenta transfer and fetal drug exposure to tacrolimus.

Several limitations of our study need to be addressed. First, we measured tacrolimus in whole-blood samples. Therefore, changes in hematocrit,[28-31] occurring throughout pregnancy, could influence the interpretation of the whole-blood tacrolimus concentrations and thereby its pharmacokinetics. In essence, with whole-blood concentrations, the total concentration is measured; of which 95% is determined by the content of tacrolimus in or attached to red blood cells. With a lower hematocrit, as is often seen in pregnant women, there are overall fewer red blood cells and thereby consequently lower total concentrations, and therefore lower C/D ratios. The 5% of tacrolimus in the blood that is not bound to erythrocytes is bound to plasma proteins or is free. Only free molecules are able to cross cellular membranes and bind to receptors at the target sites. Therefore, only free tacrolimus is pharmacologically active. In whole blood, less than 0.1% of tacrolimus is not bound to proteins.[29] In the past, free tacrolimus concentrations could not be measured due to insufficient sensitivity of the analytical methods. However, plasma tacrolimus concentrations can now be measured,[29-31] although it is still not part of clinical practice. This could be a focus for future research. Second, the retrospective nature of this study could be seen as a limitation, since record keeping is not always accurately designed beforehand for the information needed in this study. However, strengths of our study include well-documented information about the patient and pregnancy such as date of pregnancy outcome, gestational age, up-to-date and complete medication lists, and dates and times of blood sampling.

Conclusions

In conclusion, we found that tacrolimus whole-blood pharmacokinetics change throughout pregnancy, with the lowest C/D ratios (48% decrease) in the 7th month of pregnancy. In general, the decrease in C/D ratios seems to stabilize from Month 4 onward compared to prepregnancy. Values recovered postpartum in all groups (although not yet fully back to prepregnancy state) except in kidney transplant recipients taking the immediate-release formulation and in lung transplant recipients. Overall, a large variation in pharmacokinetic properties of tacrolimus within patients was observed. The need to observe tacrolimus whole-blood trough concentration trajectories closely in both the pregnant and postpartum period is critically important in the management of transplanted patients, since unintentional and unnoticed low or high tacrolimus whole-blood concentrations give a risk for allograft rejection or toxicity.

Acknowledgments

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

Funding

This research received no external funding.

Data Availability Statement

Data are available upon reasonable request: p.mian@umcg.nl.

References

1. Lerut JP, Gondolesi GE. Immunosuppression in liver and intestinal transplantation. *Best Pract Res Clin Gastroenterol*. 2021;54-55:101767. doi:10.1016/j.bpg.2021.101767
2. Jasiak NM, Park JM. Immunosuppression in solid-organ transplantation essentials and practical tips. *Crit Care Nurs Q*. 2016;39(3):227-240. doi:10.1097/CNQ.0000000000000117
3. Farouk SS, Rein JL. the many faces of calcineurin inhibitor toxicity—what the FK? *Adv Chronic Kidney Dis*. 2020;27(1):56-66. doi:10.1053/j.ackd.2019.08.006
4. Wallemacq PE, Verbeeck RK. Comparative clinical pharmacokinetics of tacrolimus in paediatric and adult patients. *Clin Pharmacokinet*. 2001;40(4):283-295.

5. Tanzi MG, Undre N, Keirns J, et al. Pharmacokinetics of prolonged-release tacrolimus and implications for use in solid organ transplant recipients. *Clin Transplant*. 2016;30(8):901-911. doi:10.1111/ctr.12763
6. Quteineh L, Verstuyft C, Furlan V, et al. Influence of CYP3A5 genetic polymorphism on tacrolimus daily dose requirements and acute rejection in renal graft recipients. *Basic Clin Pharmacol Toxicol*. 2008;103(6):546-552.
7. Brunet M, van Gelder T, Asberg A, et al. Therapeutic drug monitoring of tacrolimus personalized therapy: second consensus report. *Ther Drug Monit*. 2019;41(3):261-307.
8. Wijdicks EFM, Wiesner RH, Dahlke LJ, et al. FK506-induced neurotoxicity in liver transplantation. *Ann Neurol*. 1994;35(4):498-501. doi:10.1002/ana.410350422
9. Transplant Pregnancy Registry International. Accessed March 11, 2023. http://transplantpregnancyregistry.org
10. Kazma JM, van den Anker J, Allegaert K, et al. Anatomical and physiological alterations of pregnancy. *J Pharmacokinet Pharmacodyn*. 2020;47(4):271-285. doi:10.1007/s10928-020-09677-1
11. Zheng S, Easterling TR, Umans JG, et al. Pharmacokinetics of tacrolimus during pregnancy. *Ther Drug Monit*. 2012;34(6):660-670. doi:10.1097/FTD.0b013e3182708edf
12. Hebert MF, Zheng S, Hays K, et al. Interpreting tacrolimus concentrations during pregnancy and postpartum. *Transplantation*. 2013;95(7):908-915. doi:10.1097/TP.0b013e318278d367
13. Kim H, Jeong JC, Yang J, et al. The optimal therapy of calcineurin inhibitors for pregnancy in kidney transplantation. *Clin Transplant*. 2015;29(2):142-148. doi:10.1111/ctr.12494
14. Le HL, Francke MI, Andrews LM, et al. Usage of tacrolimus and mycophenolic acid during conception, pregnancy, and lactation, and its implications for therapeutic drug monitoring: a systematic critical review. *Ther Drug Monit*. 2020;42(4):518-531. doi:10.1097/FTD.0000000000000769
15. Koster RA, Dijkers ECF, Uges DRA. Robust, high-throughput LC-MS/MS method for therapeutic drug monitoring of cyclosporine, tacrolimus, everolimus, and sirolimus in whole blood. *Ther Drug Monit*. 2009;31(1):116-125. doi:10.1097/FTD.0b013e318192304c
16. Veenhof H, Schouw HM, Besouw MTP, et al. Flucloxacillin decreases tacrolimus blood trough levels: a single-center retrospective cohort study. *Eur J Clin Pharmacol*. 2020;76(12):1667-1673. doi:10.1007/s00228-020-02968-z
17. Dallmann A, Mian P, Van den Anker J, et al. Clinical pharmacokinetic studies in pregnant women and the relevance of pharmacometric tools. *Curr Pharm Des*. 2019;25(5):483-495. doi:10.2174/1381612825666190320135137
18. Zeilmaker GA, Pokorna P, Mian P, et al. Pharmacokinetic considerations for pediatric patients receiving analgesia in the intensive care unit; targeting postoperative, ECMO and hypothermia patients. *Expert Opin Drug Metab Toxicol*. 2018;14(4):417-428.
19. Aktürk S, Çelebi ZK, Erdoɨmuş Ş, et al. Pregnancy after kidney transplantation: outcomes, tacrolimus doses, and trough levels. *Transplant Proc*. 2015;47(5):1442-1444. doi:10.1016/j.transproceed.2015.04.041
20. Fehrman-Ekholm I, Nisell H. A successful pregnancy in a kidney recipient with tacrolimus (Prograf, FK 506) therapy. *Nephrol Dial Transplant*. 1998;13(11):2982-2983. doi:10.1093/oxfordjournals.ndt.a027806
21. Midtvedt K, Hartmann A, Brekke IB, et al. Successful pregnancies in a combined pancreas and renal allograft recipient and in a renal graft recipient on tacrolimus treatment. *Nephrol Dial Transplant*. 1997;12(12):2764-2765. doi:10.1093/ndt/12.12.2764
22. Schagen MR, Ulu AN, Francke MI, et al. Modelling changes in the pharmacokinetics of tacrolimus during pregnancy after kidney transplantation: a retrospective cohort study. *Br J Clin Pharmacol*. 2023. doi: 10.1111/bcp.15886 Online ahead of print.
23. Aktürk, Serkan, Sadioğlu RE, et al. Acute kidney injury in an infant of a kidney allograft recipient. *Clin Kidney J*. 2019;13(1):123-124. doi:10.1093/ckj/sfz093
24. Resch B, Mache CJ, Windhager T, et al. FK 506 and successful pregnancy in a patient after renal transplantation. *Transplant Proc*. 1998;30(1):163-164. doi:10.1016/S0041-1345(97)01220-7
25. Zheng S, Easterling TR, Hays K, et al. Tacrolimus placental transfer at delivery and neonatal exposure through breast milk. *Br J Clin Pharmacol*. 2013;76(6):988-996. doi:10.1111/bcp.12122
26. Jain AB, Shapiro R, Scantlebury VP, et al. Pregnancy after kidney and kidney-pancreas transplantation under tacrolimus: a single center's experience. *Transplantation*. 2004;77(6):897-902. doi:10.1097/01.TP.0000117564.50117.FB
27. Freriksen JJM, Feyaerts D, van den Broek PHH, et al. Placental disposition of the immunosuppressive drug tacrolimus in renal transplant recipients and in ex vivo perfused placental tissue. *Eur J Pharm Sci*. 2018;119:244-248. doi:10.1016/j.ejps.2018.04.017
28. Pariente G, Leibson T, Carls A, et al. Pregnancy-associated changes in pharmacokinetics: a systematic review. *PLoS Med*. 2016;13(11):e1002160. doi:10.1371/journal.pmed.1002160
29. Zijp TR, van Hateren K, Kuiper H, et al. Ultra-high throughput dual channel liquid chromatography for quantification of four immunosuppressants in whole blood for therapeutic drug monitoring. *J Chromatogr A*. 2023;1702:454086.
30. Zijp TR, Knobbe TJ, van Hateren K, et al. Expeditious quantification of plasma tacrolimus with liquid chromatography tandem mass spectrometry in solid organ transplantation. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2023;1222:123709.
31. Zahir H, Nand RA, Brown KF, et al. Validation of methods to study the distribution and protein binding of tacrolimus in human blood. *J Pharmacol Toxicol Methods*. 2001;46(1):27-35. doi:10.1016/S1056-8719(02)00158-2