Clinical Pharmacokinetics (2025) 64:619–630
https://doi.org/10.1007/s40262-025-01498-0

ORIGINAL RESEARCH ARTICLE

Pharmacokinetics and Safety of Levofloxacin for Treatment of Rifampicin-Resistant Tuberculosis During Pregnancy and the Postpartum Period: Results from IMPAACT P1026s

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Accepted: 6 March 2025 / Published online: 28 March 2025

Abstract

Background and Objective Treatment of rifampicin-resistant tuberculosis (RR-TB) often includes fluoroquinolones, but data on long-term exposure during and after pregnancy are limited. We examined the pharmacokinetics and safety of levofloxacin in an observational cohort of pregnant and postpartum women receiving treatment for RR-TB.

Methods Participants were enrolled in their second or third trimester and underwent intensive pharmacokinetic sampling to quantify levofloxacin plasma concentrations at 20–26 weeks' and 30–38 weeks' gestation and at 2–8 weeks postpartum. The levofloxacin plasma concentration target was 7 µg/mL. Pharmacokinetic parameters over 12 and 24 h were described using non-compartmental analysis and within-participant comparison during pregnancy versus postpartum. Adverse events were extracted from medical records. Infants were enrolled in utero and followed on study for 4–6 months after birth.

Results A total of 11 pregnant women, with a median age of 31 years, received RR-TB treatment including levofloxacin; 6 (55%) were living with HIV. In the second trimester, third trimester, and postpartum, median maximum plasma drug concentration values were 10.3, 10.6, and 10.6 µg/mL, and area under the concentration time curve over 12 h ($AUC_{0–12}$) were 69.0, 77.6, and 80.2 µg·h/mL, respectively. Compared with postpartum, median AUCs were lower and clearance was higher in the second but not the third trimester. Eight (72%) women and seven (64%) infants experienced severe or life-threatening adverse events or outcomes that were unlikely to be related to levofloxacin.

Conclusions Levofloxacin $AUC_{0–12}$ was lower in the second trimester than the third trimester of pregnancy and the postpartum period, but exposures overall were within target ranges. Further research is warranted to explore the clinical significance of these findings.

1 Introduction

Rifampicin-resistant tuberculosis (RR-TB), caused by *Mycobacterium tuberculosis* resistant to at least rifampicin, with or without resistance to other antituberculosis drugs, affected 410,000 people globally in 2022 [1]. The burden of RR-TB during pregnancy and postpartum is rarely reported in national treatment programmes and surveillance data, whereas the incidence of tuberculosis appears to be highest during the reproductive years [1]. Therefore, a considerable proportion of people with RR-TB globally are likely to require treatment while pregnant and/or breastfeeding.

Treatment of RR-TB is challenging and requires a multidrug regimen containing at least three second-line antituberculosis drugs for a minimum of 6 months but is frequently extended to ≥18 months based on disease severity, prior drug exposure, and treatment response [2]. The newer-generation fluoroquinolones, levofloxacin and moxifloxacin, classified by the World Health Organization as 'Group A' antituberculosis drugs, are critical for the management of RR-TB [3]. An individual patient data meta-analysis reported that newer-generation fluoroquinolones were significantly associated with a higher rate of RR-TB treatment success and decreased mortality in adults [4]. Therefore, unless the *M. tuberculosis* isolate is proven or suspected to be resistant to fluoroquinolones, levofloxacin or moxifloxacin is recommended in RR-TB treatment regimens, including

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Key Points

A total of 11 pregnant women with drug-resistant tuberculosis receiving a multidrug treatment regimen including the antibiotic levofloxacin were followed up over several months during and after pregnancy, and no serious side effects were considered related to this drug.

Overall, the blood concentrations of levofloxacin in the pregnant women were similar to those reported in non-pregnant adults treated for drug-resistant tuberculosis; however, we noted a trend towards lower drug concentrations during the second trimester compared with postpartum.

The implications of suboptimal blood concentrations of levofloxacin are that treatment may be less effective than anticipated or may lead to acquisition of mycobacterial resistance to the drug; therefore, levofloxacin exposures should be explored further in larger cohorts of pregnant women with drug-resistant tuberculosis.

for pregnant and postpartum individuals [2, 5]. Levofloxacin and moxifloxacin are considered equally effective against susceptible strains of RR-TB, but levofloxacin is usually preferred because of its superior safety profile [6]. The bactericidal activity of levofloxacin is concentration dependent, so maximum plasma concentration (C_{max}) and area under the concentration time curve (AUC) are important pharmacokinetic parameters for this drug. Levofloxacin is rapidly absorbed after oral dosing and is cleared primarily via renal elimination [7].

Very few studies have described the pharmacokinetics of quinolones administered for any duration or indication during pregnancy, and a recent systematic literature review could present no conclusions about pharmacokinetics and exposure changes of levofloxacin in pregnant women [8]. Published pharmacokinetic data to inform fluoroquinolone dosing for the treatment of RR-TB during pregnancy are limited to a single case report that described lower moxifloxacin exposure during pregnancy, particularly in the second trimester, than in the postpartum period in a woman without HIV [9]. Physiological changes during pregnancy can alter drug pharmacokinetics because renal and hepatic clearance and volume of distribution are increased, risking sub-therapeutic dosing during this period [10]. Low plasma concentrations of antituberculosis drugs may compromise the therapeutic efficacy of the RR-TB treatment regimen and lower the likelihood of treatment success [11]; this may in turn pose a potential risk of tuberculosis transmission to the infant, either in utero or after birth. Furthermore, inadequate drug exposure increases the risk of the infecting *M. tuberculosis* isolate acquiring more extensive drug resistance through selective drug pressure, particularly if the treatment regimen is otherwise compromised or inadequate [12]. The effect of HIV and antiretroviral therapy (ART) on the pharmacokinetics of second-line antituberculosis drugs during pregnancy remains largely unknown [13].

We investigated the pharmacokinetics and safety of levofloxacin in an observational cohort of people treated for RR-TB during pregnancy and the postpartum period and reported on birth and infant outcomes.

2 Methods

2.1 Study Design and Setting

This analysis is part of the P1026s phase IV observational cohort study, Pharmacokinetic Properties of Antiretroviral and Related Drugs during Pregnancy and Postpartum (ClinicalTrials.gov NCT00042289), conducted within the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network [14]. Between 2017 and 2019, the P1026s study included an arm that enrolled pregnant women receiving RR-TB treatment during pregnancy and the postpartum period, and their infants. Participants were enrolled in either the second trimester (2T: 20–26 weeks' gestation) or the third trimester (3T: 30–38 weeks' gestation) and were followed on study until the completion of postpartum pharmacokinetic sampling (PP: 2–8 weeks postpartum). Infants were enrolled in utero, with maternal consent, at the same time as their mothers and were followed on study for 16–24 weeks after birth. RR-TB treatment and routine clinical care was provided through national treatment programmes in accordance with national guidelines and local policies in each setting; no dosing restrictions were applied, no study-specific levofloxacin was provided, and no RR-TB treatment was modified by the research teams in this observational study.

2.2 Participants

Pregnant women, living with or without HIV, were eligible for enrolment if they were receiving at least two second-line antituberculosis drugs for at least 2 weeks before study entry. Exclusion criteria included the use of medications known to interfere with the absorption, metabolism, or clearance of the drugs being evaluated; documented multiple gestation; and clinical or laboratory toxicity that would likely require a change in treatment during the study period.

2.3 Clinical and Laboratory Monitoring

Maternal age, ethnicity, weight, medical history, concomitant medications, CD4 counts, and plasma HIV viral load assay results were recorded at enrolment and during study follow-up. Clinical history, physical examination, and renal, hepatic, and haematologic laboratory tests were used to monitor maternal adverse events (AEs) on each pharmacokinetic sampling day and around the time of delivery. Additional AEs and available treatment modification information obtained from medical records and/or care providers were recorded. Adherence to RR-TB treatment was not objectively measured, but participants were asked to record the time of ingestion of the two drug doses before the pharmacokinetic sampling day. Previous duration of drug exposure and treatment interruption was extrapolated from available medical records. Infants did not undergo pharmacokinetic sampling for antituberculosis medications at any point but were clinically evaluated at 0–3 days, 5–9 days, and 16–24 weeks of life. Infant data, including birth weight and gestational age, HIV status, growth assessment, and details of AEs, were collected from available medical records. Classification of weight for gestational age at birth was calculated using the INTERGROWTH-21st foetal growth standards [15]. The site investigator assessed AEs, assigned causality, and graded for severity using the Division of AIDS AE grading table [16]. Every month, AE reports were reviewed by multiple members of the protocol team, and each event was assessed for a relationship to the study drugs of interest. Causality was finally assigned by consensus between the site investigators and the protocol team, and AEs were followed until resolution or stabilisation.

2.4 Sample Collection and Drug Concentration Assays

Each participant had pharmacokinetic sampling performed during the second trimester (if applicable), third trimester, and postpartum. On the day of pharmacokinetic sampling, administration of all medication was observed by the study team, with or without food, and in the order and mode of administration (swallowed whole, crushed, or chewed) preferred by the participant. Blood samples were collected predose (time 0) and at 1, 2, 4, 6, 8, and 12 h after the dose. Blood samples were centrifuged, aliquoted, and stored at −70 °C or lower within 60 min of collection.

Plasma levofloxacin assays were performed at the University of Cape Town Pharmacokinetic Research Laboratory using a validated, high-performance liquid chromatography tandem mass spectrometry method [17]. The lower limit of quantification (LLOQ) for levofloxacin was 0.078 µg/mL.

2.5 Pharmacokinetic Analyses

Pharmacokinetic parameters were estimated with non-compartmental methods in Microsoft Excel and R (http://www.R-project.org/), and results were cross-checked using Phoenix™ WinNonlin software. The AUC through 12 h after dose ($AUC_{0–12}$) was calculated using a linear-up log-down trapezoidal approach. Other parameters calculated were the C_{max} and corresponding time to C_{max} (t_{max}), plasma concentration at 12 h after dose (C_{12}), plasma terminal half-life ($t_{½}$), apparent clearance (CL/F), and apparent volume of distribution (Vd/F). Concentrations below the LLOQ were substituted using half of the LLOQ (0.039 µg/mL). As levofloxacin is usually dosed once daily, and to allow for comparability with published data, exposures through 24 h after dose were extrapolated from the terminal slope of the curve (λ_2) using the line of best fit. Pharmacokinetic parameters through both 12 and 24 h after dose were thus reported.

2.6 Statistical Methods

AEs and clinical and demographic characteristics were described using summary statistics: the median and upper and lower quartiles (Q1–Q3) were reported for continuous variables, and frequencies and percentages were reported for categorical variables.

Descriptive statistics were calculated for pharmacokinetic parameters during each sampling window. Pharmacokinetic parameters were assessed via within-participant comparison (second or third trimester vs. postpartum) using geometric means of the antepartum to postpartum ratios (GMRs) and corresponding 90% confidence intervals (CIs). GMRs were calculated as the exponentiated mean of the log-transformed ratio between antepartum and postpartum pharmacokinetic values calculated via within-participant comparison, and the 90% CIs were estimated using the *t*-statistic. If the 90% CIs for the GMRs did not include 1.0, this indicated that the antepartum and postpartum pharmacokinetic parameter differed at the two-sided 0.10 significance level. The CIs also described the range of percentage changes between the two sampling periods that were consistent with the observed data to assess whether there was a significant difference in exposure.

The C_{max} target within the dosing interval for levofloxacin was based on the lowest C_{max} concentration (7 µg/mL) observed among non-pregnant patients receiving levofloxacin at standard doses of 750 or 1000 mg in a dose-ranging clinical trial of adults with RR-TB in Peru and South Africa [18]. McNemar's test was used to compare proportions of maternal participants with levofloxacin plasma concentrations above the C_{max} target during pregnancy and

postpartum. The levofloxacin dose was calculated in mg/kg using the dose and the participant's weight on the day of sampling. The calculated levofloxacin dose in mg/kg, both as a continuous variable and as a dichotomous variable above or below a pre-specified cut-off of 15 mg/kg, was also summarised according to whether the participant's corresponding C_{max} was above or below the target of 7 ug/mL. *p*-Values were provided based on the two-sample Wilcoxon rank sum test and Fisher's exact test, respectively. Data were analysed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

2.7 Ethics

The National Institutes of Health, applicable national authorities, and local institutional review boards reviewed the protocol. Written informed consent was obtained from all pregnant participants for themselves and their infants.

3 Results

3.1 Participant Characteristics

In total, 11 pregnant women (10 from South Africa and 1 from Tanzania), of whom 6 (55%) were living with HIV, were receiving treatment with levofloxacin at enrolment. Over half of the participants (6/11 [55%]) self-reported their race as mixed, and 4 (36%) self-reported as Black African; 1 participant did not report their race. Six (55%) participants were enrolled in 2T and five (45%) in 3T. The median age at the time of delivery was 30.7 (Q1–Q3: 26.2–35.1) years. Cohort characteristics, per trimester sampling window, are summarised in Table 1 [19, 20].

One participant enrolled in 2T was receiving a daily levofloxacin dose of 750 mg (weight 50.0 kg), but this increased to 1000 mg daily at the time of 3T sampling (weight 53.1 kg). Another participant received a daily levofloxacin dose of 750 mg throughout pregnancy and postpartum (weight range 45.5–47.4 kg). All other participants weighed more than 50 kg and received levofloxacin 1000 mg daily throughout the study.

3.2 Levofloxacin Pharmacokinetics

Pharmacokinetic data were available for six participants in the second trimester, ten in the third trimester, and eight during the postpartum period. Three (27%) of 11 participants did not have pharmacokinetic sampling after delivery as they had either completed RR-TB treatment, stopped levofloxacin, or withdrawn from the study before the scheduled postpartum sampling visit. Figure 1 displays the mean plasma concentrations of levofloxacin measured over 12 h at steady state in the second and third trimesters and postpartum; see Resource 1 in the electronic supplementary material (ESM) for individual concentration–time curves demonstrating the interindividual variability of the data. Levofloxacin pharmacokinetic parameters are summarised in Table 2 and Fig. 2. See Resource 2 in the ESM for these parameters stratified by HIV status.

Among four women with available paired data, the median levofloxacin $AUC_{0–12}$, C_{12}, and $t_{½}$ were 25% (90% CI 5–40), 29% (90% CI 20–36), and 16% (90% CI 3–27) lower, respectively, in the second trimester than postpartum, and the median CL/F was 33% (90% CI 5–67) higher. The GMRs for the third trimester and postpartum comparison among seven women with paired data did not suggest a statistically significant difference for any of the pharmacokinetic parameters over 12 h. The findings from the second and third trimesters versus postpartum comparisons were consistent with extrapolated estimates through 24 h after dose.

Of the 11 participants, 10 (91%) achieved C_{max} above the target of 7 µg/mL at all available sampling timepoints (Table 1 and Fig. 2b). One participant, enrolled in the third trimester and receiving levofloxacin doses of ≥15 mg/kg, had a C_{max} below the target of 7 µg/mL at the time of sampling in both the third trimester and postpartum; however, on both occasions, the pre-dose concentrations were below the LLOQ, suggesting non-adherence in the days before pharmacokinetic sampling.

3.3 Maternal and Infant Safety

The median duration of maternal exposure to levofloxacin before study entry in the second trimester ($n = 6$) was 7 months, and median levofloxacin duration was 5 months among the total of 10 women reviewed on study or newly enrolled in the third trimester (Table 1). Eight (72%) of 11 mothers experienced 10 severe (grade 3) or life-threatening (grade 4) AEs during their time on study; none were considered by the site investigators and protocol team to be related to levofloxacin. Four of the 10 AEs (from four different women) were serious AEs (SAEs). Grade 3 and 4 maternal AEs included postpartum haemorrhage (SAE), major depressive disorder (SAE), genital warts, low haemoglobin ($n = 2$ participants), probable urinary tract infection, nausea and vomiting, raised alanine transaminase, and tachycardia (SAE). Obstetric ultrasonography in one mother identified a suspected life-threatening foetal cardiac abnormality (SAE), leading to planned preterm delivery of the infant at 35.7 weeks' gestation; the birth weight was 1815 g. After acute respiratory distress syndrome was resolved in the neonatal intensive care unit, no clinical cardiac concerns were identified before discharge. Echocardiography in the infant at 10

Table 1 Cohort characteristics of participants receiving levofloxacin-containing treatment regimens for rifampicin-resistant tuberculosis during pregnancy and postpartum ($N = 11$)

Characteristic at the time of pharmacokinetic evaluation	2nd trimester (2T) $N = 6$	3rd trimester (3T) $N = 10$	PP $N = 8$
Maternal age, years	34.1 (28.5–36.8)	30.0 (26.0–33.7)	30.7 (24.6–36.2)
Gestational age during pregnancy (2T or 3T) or time after delivery (PP), weeks	24.7 (22.9–25.1)	33.6 (32.9–35.0)[a]	6.6 (3.9–7.4)
Maternal weight at the time of sampling, kg	53.6 (50.0–61.9)	64.4 (58.3–67.3)	62.9 (56.1–68.4)
Serum creatinine, μmol/L	34.5 (33.0–44.0)	47.5 (40.0–51.0)	58.5 (53.0–66.5)
eGFR, mL/min/1.73 m^3	132.3 (126.7–139.1)	127.9 (123.9–131.4)	117.3 (110.1–123.3)
Levofloxacin dose, mg/kg	16.0 (15.0–18.2)	15.5 (14.9–17.2)	15.9 (14.7–16.8)
Number receiving levofloxacin <15 mg/kg	1 (17)	3 (30)	2 (25)
Number receiving levofloxacin ≥15 mg/kg	5 (83)	7 (70)	6 (75)
Duration on levofloxacin, weeks	27.9 (10.4–48.3)	20.1 (14.4–41.7)	34.2 (23.9–46.2)
Number of mothers taking levofloxacin, along with other antituberculosis drugs listed below	6 (100)	10 (100)	8 (100)
Bedaquiline	3 (50)	8 (80)	5 (63)
Clofazimine	5 (83)	10 (100)	7 (88)
Cycloserine/terizidone	5 (83)	5 (50)	5 (63)
Ethambutol	2 (33)	4 (40)	2 (25)
Ethionamide	1 (17)	1 (10)	2 (25)
Isoniazid	2 (33)	6 (60)	3 (38)
Kanamycin	1 (17)	0	0
Linezolid	1 (17)	4 (40)	3 (38)
Para-aminosalicylic acid	1 (17)	2 (20)	2 (25)
Pyrazinamide	4 (67)	6 (60)	5 (63)
Number HIV positive	4 (67)	6 (60)	4 (50)
Number with VL ≤ 400 copies/mL (% of HIV positive)	3 (75)	4 (67)	3 (75)
CD4 count, cells/mm^3	95 (65–391)	324 (41–660)	534 (158–859)
Number on ART (% of HIV positive), with ARVs listed below	4 (100)	6 (100)	4 (100)
Lopinavir or atazanavir	4 (100)	6 (100)	4 (100)
Ritonavir	4 (100)	6 (100)	4 (100)
Lamivudine or emtricitabine	4 (100)	6 (100)	4 (100)
Abacavir	2 (50)	1 (17)	1 (25)
Tenofovir disoproxil fumarate	1 (25)	4 (67)	3 (75)
Zidovudine	1 (25)	1 (17)	0

Data are presented as median (Q1 = lower quartile, Q3 = upper quartile) or N (%) unless otherwise indicated

ART = antiretroviral therapy; ARVs = antiretroviral drugs; eGFR = estimated glomerular filtration rate (using the Chronic Kidney Disease Epidemiology Collaboration 2021 equation without race adjustment) [17, 18]; PP = postpartum; VL = viral load

[a]Data are missing for one participant

months of age reported normal cardiac structure and function with no evidence of cardiac malformation.

Of the 11 participants, 10 (91%) delivered live infants: 9 singletons and 1 set of twins (unexpected, as no ultrasonography was carried out during pregnancy). No outcome was recorded for the singleton infant of one participant who withdrew consent and exited the study just before delivery. Of the remaining 11 infants, the median gestational age at birth was 38.9 weeks (Q1–Q3: 34.7–40.4), with 7 (64%) born at term (≥37 weeks) and 4 (36%, including the set of twins) born between 32 and 37 weeks' gestation. The median birth weight was 2540 g (Q1–Q3: 2000–2790), with a median birth length of 46 cm (Q1–Q3: 43–48). Five (45%) infants had low birth weight (<2500 g [21]), but none weighed <1500 g; six (55%) were considered small for gestational age (three with birth weight <10th percentile and three with birth weight <3rd percentile for gestational age). All six HIV-exposed infants were reported to be without HIV infection at the end of study follow-up (see Table 1 for maternal viral loads and ART regimens). Seven (64%) of 11 infants experienced grade 3 or higher AEs at or after birth (Table 3).

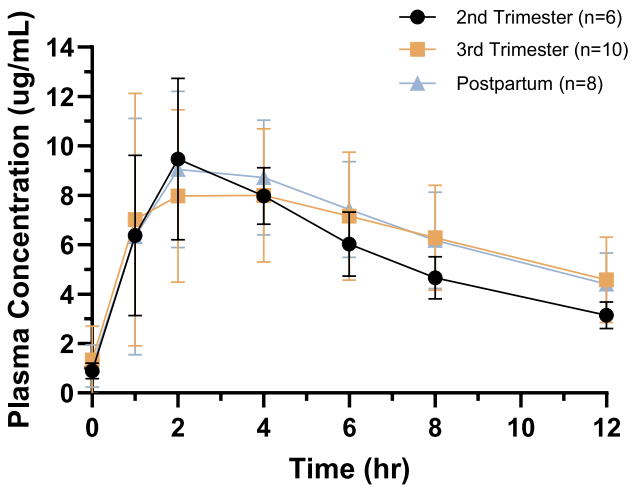

Fig. 1 Mean (standard deviation) plasma levofloxacin concentration–time profiles through 12 h after dose by trimester

4 Discussion

We described the pharmacokinetics and safety of levofloxacin among 11 women receiving treatment for RR-TB during the second and third trimesters of pregnancy and the postpartum period. Other published pharmacokinetic data on the use of the newer-generation fluoroquinolones during pregnancy are limited to one case report of a woman with RR-TB and three single-dose exposure studies (total of 48 women without tuberculosis or HIV) [13]. Two of the studies measured levofloxacin concentrations after a single oral dose of levofloxacin 500 mg given 2 h before amniocentesis ($n = 10$) [22] and after an intravenous infusion of levofloxacin 500 mg given 25 min before planned Caesarean delivery ($n = 12$) [23]. The mean ± standard deviation plasma concentration of levofloxacin was 3.95 ± 0.77 µg/mL when measured at a single timepoint during amniocentesis (at 16–20 weeks' gestation) and 8.18 ± 1.68 µg/mL at the time of clamping the umbilical cord during Caesarean delivery (median gestational age 38 weeks). Fluoroquinolones exhibit concentration-dependent bactericidal activity, and these single-point levofloxacin concentrations, which are lower than the median levofloxacin C_{max} measured at steady state in our cohort, reflect the limitations of single-dose pharmacokinetic studies where steady state is not achieved.

Early pharmacokinetic data from 60 pregnant and 30 lactating women receiving either ciprofloxacin, pefloxacin, or ofloxacin found lower serum quinolone concentrations among women in the second trimester of pregnancy than among lactating women [24]. More recently, a population pharmacokinetic model based on pharmacokinetic sampling over 24 h from 47 South African women with RR-TB demonstrated that renal clearance of levofloxacin during pregnancy may be increased by up to 38.1% above non-pregnant concentrations [25]. Levofloxacin is cleared by renal elimination [7], so the physiological changes of pregnancy, particularly higher blood flow to the kidneys resulting in increased glomerular filtration, may explain this variation. Levofloxacin $AUC_{0–12}$ and $AUC_{0–24}$ in our cohort were lower, with higher drug clearance, during both trimesters of pregnancy, with a more notable difference in the second trimester, than at 2–8 weeks postpartum. These differences may be due in part to variations in glomerular filtration, which peaks in mid-pregnancy [26]; this is supported by the observed renal clearance estimates at the different sampling points in our study.

In our cohort, the median (Q1–Q3) levofloxacin $AUC_{0–24}$ of 90.5 µg·h/mL (82.3–98.6) and 111.9 µg·h/mL (90.8–121.5) in the second and third trimesters, respectively, were comparable to the $AUC_{0–24}$ range of 77.3–295.9 µg·h/mL reported in a pharmacokinetic study of 10 non-pregnant adults with tuberculosis who had received levofloxacin 1000 mg daily monotherapy over 7 days [27]. Other pharmacokinetic parameters from the same study by Peloquin et al. [27], such as t_{max} of 1 h, a median $t_{½}$ of 7.37 h, and a C_{max} range of 9–43 µg/mL, were also similar to those observed in our cohort; however, we reported a shorter half-life for levofloxacin among participants sampled during the second trimester of pregnancy.

The minimum C_{max} target we used for this study was based on results of non-compartmental pharmacokinetic analyses from the Tuberculosis Trials Consortium/National Institute of Allergy and Infectious Diseases Opti-Q trial (a phase II randomised dose-finding trial), in which adults receiving therapy for RR-TB were randomised to four levofloxacin doses of 11, 14, 17, or 20 mg/kg/day with an optimised background regimen [18]. We opted for the lower limit of the C_{max} range (6.90–21.03 µg/mL) observed in 26 non-pregnant patients receiving levofloxacin doses of either 750 mg or 1000 mg daily (i.e., 14 mg/kg/day) [18], as this reflected the range of doses received by participants in our cohort. C_{max} concentrations in our cohort were mostly above the minimum target of 7 µg/mL, except for one patient, who received a levofloxacin dose of > 15 mg/kg and the measured C_{max} during the third trimester (4.3 µg/mL) and postpartum (4.7 µg/mL) were considerably lower than expected. This discrepancy was attributed to potential poor adherence to treatment and lower pre-dose drug concentrations on intensive sampling days, highlighting the study limitation that direct observation of study drug administration and adherence support were not required to be implemented by the research teams. Nevertheless, median C_{max} and $AUC_{0–24}$ values measured in pregnancy and postpartum in our study were within the ranges reported in the Opti-Q trial ($AUC_{0–24}$ 70–248 µg·h/mL for the group receiving 14 mg/kg/day) [18], despite the demonstrated interindividual variability in levofloxacin exposures in our cohort.

Table 2 Maternal levofloxacin pharmacokinetic parameters in the second and third trimesters and postpartum ($N = 11$)

Pharmacokinetic parameter	2nd trimester (2T) $N = 6$	3rd trimester (3T) $N = 10$	PP $N = 8$	Comparison 2T vs PP, $N = 4$ GMR (90% CI)	Comparison 3T vs PP, $N = 7$ GMR (90% CI)
Based on actual measurements over 12 h					
C_0, µg/mL	0.94 (0.85–1.03)	1.45 (0.04–1.59)	1.41 (0.16–1.72)	0.72 (0.17–3.00)	1.23 (0.24–6.23)
C_{12}, µg/mL	3.20 (2.74–3.60)	4.74 (4.30–5.03)	4.76 (3.58–5.34)	0.71 (0.64–0.80)	0.98 (0.80–1.20)
C_{max}, µg/mL[a]	10.31 (9.33–12.10)	10.55 (7.71–11.00)	10.61 (8.20–12.70)	0.86 (0.59–1.25)	0.98 (0.85–1.12)
t_{max}, h	2 (2–2)	2 (2–6)	3 (2–4)	–	–
$t_{½}$, h	6.28 (5.70–6.64)	8.71 (6.85–10.09)[b]	8.17 (6.42–9.30)	0.84 (0.73–0.97)	1.11 (0.83–1.50)[b]
$AUC_{0–12}$, µg·h/mL	69.01 (60.12–77.14)	77.64 (70.51–85.05)	80.23 (71.80–97.73)	0.75 (0.60–0.95)	0.4 (0.81–1.08)
CL/F, L/h	13.43 (12.03–15.45)	12.88 (11.76–14.18)	11.38 (9.96–13.64)	1.33 (1.05–1.67)	1.07 (0.93–1.23)
CL/F normalised by weight, L/h/kg[c]	0.23 (0.21–0.27)	0.21 (0.19–0.24)	0.19 (0.16–0.21)	1.31 (1.05–1.65)	1.02 (0.87–1.12)
Vd/F, L	108.92 (97.39–159.31)	167.86 (125.56–206.43)[b]	134.96 (107.43–198.01)	1.12 (0.86–1.44)	1.16 (0.79–1.72)[b]
Vd/F normalised by weight, L/kg[c]	2.18 (1.95–2.41)	2.78 (2.20–3.07)[b]	2.14 (2.02–2.65)	1.11 (0.85–1.44)	1.10 (0.76–1.60)[b]
Including estimated measurement extrapolated at 24 h[d]					
C_{24} (estimated), µg/mL	0.87 (0.49–1.01)	1.69 (0.56–2.17)	1.65 (1.10–2.08)	0.56 (0.50–0.64)	0.84 (0.49–1.44)
$t_{½}$, h	6.28 (5.70–6.64)	8.18 (5.06–10.09)	8.17 (6.42–9.30)	0.84 (0.73–0.97)	0.95 (0.63–1.41)
$AUC_{0–24}$, µg·h/mL	90.47 (82.26–98.55)	111.86 (90.80–121.53)	118.39 (98.98–137.13)	0.73 (0.60–0.88)	0.94 (0.80–1.10)
$CL/F_{0–24}$, L/h	10.89 (9.41–11.35)	8.94 (8.23–11.01)	8.08 (7.29–9.18)	1.38 (1.14–1.67)	1.07 (0.91–1.25)
$Vd/F_{0–24}$, L	85.77 (74.46–116.45)	110.70 (85.42–132.25)	94.35 (80.53–129.89)	1.16 (0.94–1.44)	1.01 (0.70–1.46)

Data are presented as median (Q1 = lower quartile, Q3 = upper quartile) unless otherwise indicated

AUC = area under the plasma concentration-time curve; $AUC_{0–12}$ = AUC up to 12 h after dose; $AUC_{0–24}$ = AUC up to 24 h after dose; CI = confidence interval; CL/F = apparent clearance; C_{max} = maximum plasma concentration; C_0 = plasma concentration pre-dose; C_{12} = plasma concentration at 12 h after dose; C_{24} = plasma concentration at 24 h after dose; GMR = geometric mean ratio; h = hour(s); PP = postpartum; t_{max} = time to maximum plasma concentration; $t_{½}$ = plasma terminal half-life; Vd/F = apparent volume of distribution; $Vd/F_{0–24}$ = apparent volume of distribution up to 24 h after dose

[a]Ten participants achieved C_{max} above the target of 7 µg/mL at all available sampling timepoints

[b]Data missing for one participant

[c]Normalised for weight using the following calculations: CL/F in L/hr divided by each participant's weight in kg, or V/F in L divided by each participant's weight in kg

[d]Median C_0, median C_{max}, and median t_{max} were identical to these parameters based on actual measurements over 12 h and so are not duplicated in the table

The established pharmacokinetic–pharmacodynamic relationship between the AUC, minimum inhibitory concentration (MIC), and anti-mycobacterial response of levofloxacin must be considered when determining the clinical relevance of lower drug exposures during pregnancy. The $AUC_{0–24}$/MIC ratio is a robust predictor of fluoroquinolone efficacy, favourable clinical outcomes, and acquisition of mycobacterial drug resistance [28, 29]. In a hollow fibre system model described by Deshpande et al. [28], an $AUC_{0–24}$/MIC ratio of 146 was identified as the optimal target exposure for achieving at least 80% maximal microbial kill, and a higher dose of levofloxacin ≥ 20 mg/kg/day was considered necessary to achieve suppression of acquired levofloxacin resistance. Similarly, a prospective pharmacokinetic study of 23 patients with RR-TB who received levofloxacin 750–1000 mg daily (equivalent to 11–14 mg/kg/day) found that one-third of patients did not attain target drug exposures at these doses. Only one-half of the patients with MICs ≥ 1 mg/L achieved optimal target exposures, prompting suggestions for higher levofloxacin doses (17–20 mg/kg/day) for these individuals [29]. Furthermore, pharmacokinetic modelling studies have consistently suggested that adults with RR-TB may require higher levofloxacin doses for maximum *M. tuberculosis* kill [30–33]. These findings underscore concerns regarding potentially suboptimal treatment efficacy and increased risk for *M. tuberculosis* isolates to acquire further drug resistance [34], especially among people with lower than expected drug exposures with currently recommended fluoroquinolone doses. This scenario is particularly relevant during pregnancy, when drug exposures may be lower because of the

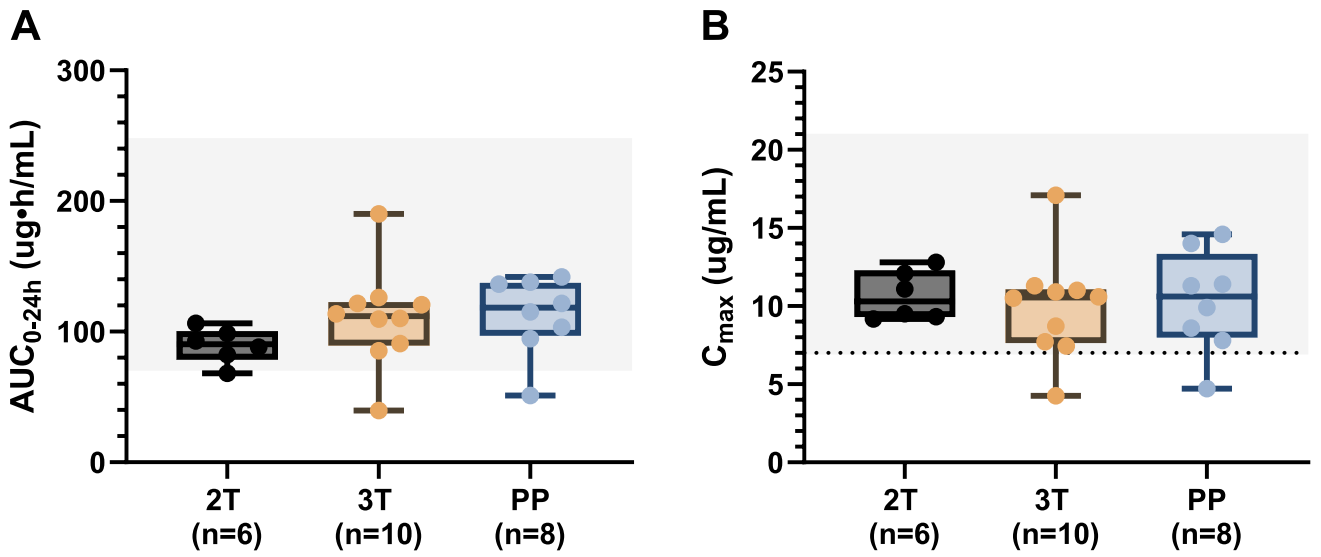

Fig. 2 Box-and-whisker plots of **A** levofloxacin area under the concentration time curve from 0 to 24 h (AUC_{0-24}) and **B** levofloxacin maximum plasma drug concentration (C_{max}), by trimester. Grey shading indicates typical values measured in non-pregnant adults [16]. The dotted line on (**B**) indicates the minimum target of 7 µg/mL

Table 3 Severe or life-threatening adverse events reported among seven of eleven infants born to women receiving levofloxacin-containing treatment for rifampicin-resistant tuberculosis during pregnancy

Participant (in utero HIV exposure)	AE description (per DAIDS grading table [16])	AE grade[a]	Status at final study visit (4–6 mo)	Relatedness to antituberculosis medication[b]
1 (HIV exposed)	Meconium aspiration syndrome	4	Resolved	Not related
2 (HIV unexposed)	WFL z-score <−3	3	Resolved	Possibly related
	Respiratory distress syndrome	4	Resolved	Not related
3 (HIV exposed)	WFL z-score <−3	3	Resolved	Possibly related
4 (HIV unexposed)	Respiratory distress syndrome and tachypnoea	4	Resolved	Not related
	WFL z-score <−3	3	Resolved	Possibly related
	Neonatal sepsis	3	Resolved	Not related
	Neutropenia	3	Ongoing	Not related
	Hypotension	3	Resolved	Not related
5 (HIV exposed)	Neonatal seizures	3	Resolved	Not related
	Hypoxic ischaemic encephalopathy	3	Resolved	Not related
	Neurodevelopmental delay	3	Ongoing	Not related
6 (HIV unexposed)	Weight loss ≥9% from baseline	3	Resolved	Not related
7 (HIV unexposed)	Neonatal respiratory distress	3	Resolved	Not related
	Neonatal jaundice and hyperbilirubinemia	3	Resolved	Not related
	Acute gastroenteritis	3	Resolved	Not related

AE = adverse event; DAIDS = Division of AIDS; mo = months; WFL = weight-for-length

[a]Grade 3 = severe, grade 4 = life-threatening per the DAIDS adverse events grading table [16]

[b]As determined by the protocol team on monthly team calls to assess infant and maternal toxicity; relatedness to individual drugs could not be determined

increased volume of distribution and drug clearance. Our study was not designed to assess the MIC of levofloxacin and RR-TB treatment outcomes. However, our findings of lower levofloxacin exposures in mid-pregnancy, although modest and among only four women, still warrant further research into the optimal dosing of this drug and clinical implications of lower exposures during pregnancy.

The limited sample size of our cohort meant that a direct comparison of levofloxacin exposures between participants with or without HIV (all on protease inhibitor-based ART regimens) was not feasible. The presence and magnitude of potential drug–drug interactions between fluoroquinolones and antiretrovirals remain poorly understood, and our study did not address these. Although ritonavir may potentially diminish moxifloxacin concentrations, a clinically significant interaction with levofloxacin is considered unlikely [35]. Nonetheless, the clinical implications of potential differences in second-line tuberculosis drug exposures between people without HIV and those with HIV and on ART can change during pregnancy [36] and remains a topic for further research.

The Opti-Q study findings demonstrated that escalating levofloxacin doses increased drug exposures and increase the likelihood of successful RR-TB treatment outcomes in adults [18]; this benefit must be weighed against the potential for an increased risk of adverse effects. Fluoroquinolones generally exhibit good tolerability over short dosing durations in pregnancy among people without RR-TB. Levofloxacin use has been linked to gastrointestinal disturbances, arthropathies, tendonitis, photosensitivity, and central nervous system toxicity, including seizures, headaches, dizziness, sleep disorders, and hallucinations [37, 38]. AEs are common among adults receiving treatment for RR-TB [39], and establishing causality to a specific drug within a multidrug treatment regimen can be challenging, particularly when such events may also be attributed to HIV, pregnancy complications, and other comorbid conditions or concomitant medications. However, levofloxacin is relatively well tolerated compared with most other second-line antituberculosis drugs in adults [40], and none of the severe or life-threatening maternal AEs observed in our cohort were assessed by the site investigators and protocol team as attributable to levofloxacin during or after RR-TB treatment.

Fluoroquinolones can cross the foetal–placental barrier and reach the foetal compartment, albeit with low observed levels of in utero foetal drug exposure [23]. Case reports have raised concerns regarding teratogenicity in animals and potential risks of impaired foetal cartilage development and erosion with prolonged in utero levofloxacin exposure [37, 41–43]. However, these concerns have not been supported by subsequent clinical studies of children receiving fluoroquinolones for extended periods [44]. A systematic review and meta-analysis involving 2821 pregnant women exposed to fluoroquinolones at any stage of pregnancy for any indication found no significant increase in major anomalies or adverse pregnancy outcomes compared with unexposed pregnant women [42]. However, a notable decrease in live birth rates and an increased rate of elective terminations, possibly influenced by perceived teratogenicity risks, was observed. Another meta-analysis corroborated these findings, revealing no significant association between quinolone use and risk of birth defects, stillbirths, preterm births, or low birth weight [43]. Many of the studies that met inclusion criteria in both meta-analyses focused on the early stages of pregnancy, with relatively short durations of drug exposure compared with the minimum 6-month treatment duration of therapy for RR-TB. The observation of low birth weight in over half of the infants in our cohort is consistent with findings from an observational study among 108 pregnant women treated for RR-TB in a South African province, where in utero exposure to levofloxacin and bedaquiline emerged as significant, independent predictors of low birth weight [45]. These findings underscore the need for integrated pregnancy and tuberculosis treatment registries, alongside coordinated surveillance systems to identify and address adverse pregnancy outcomes among such cohorts, particularly in South African and analogous settings.

Our study has several strengths and limitations. This was one of very few pharmacokinetic studies assessing levofloxacin for the treatment of RR-TB during pregnancy and the postpartum period. Pregnant women enrolled in the RR-TB treatment arm of the IMPAACT P1026s study were monitored throughout pregnancy and postpartum, with regular clinical evaluation of pregnant and postpartum women and their infants during and after exposure to levofloxacin. However, enrolment of participants with RR-TB was slower than for other arms of the study (which enrolled pregnant women with drug-susceptible tuberculosis and/or HIV) because of the relatively lower disease prevalence and the inherent challenges in timing enrolment with the limited duration of drug exposure during pregnancy. At the time of study closure, the enrolment target for this arm had not been reached, and the modest number of participants reduced the study's power to detect significant differences in pharmacokinetic parameters during pregnancy and postpartum. Additionally, incomplete pharmacokinetic sampling further decreased the sample size for within-participant comparison between trimesters. In addition, 24-h sampling was not carried out despite once-daily dosing of levofloxacin. All participants received generic versions of levofloxacin from different suppliers over different time periods, and inconsistencies in drug formulations could theoretically have affected pharmacokinetic findings. However, this is unlikely as 10 of 11 participants were enrolled in South Africa, where all generic medicines are required to meet strict regulatory standards to ensure bioequivalence to their brand name counterparts.

Selection of participants was biased towards those who could tolerate levofloxacin, and drug dosages were prescribed by routine healthcare providers and therefore not standardised to a specific mg/kg dose for all participants. Our study was not designed to assess pharmacodynamic

parameters because levofloxacin MICs were not available, and RR-TB treatment outcomes were not recorded. Infant and breastmilk pharmacokinetic sampling were not conducted to assess levofloxacin passage to neonates, and drug–drug interactions between levofloxacin and other concomitant medications were not assessed in this cohort. Safety assessment was limited by the extended intervals between study visits and reliance on clinical information from routine medical records. Determining the causality of AEs was challenging because of the multiple comorbidities and many concomitant antituberculosis and antiretroviral medications. We assessed potential relationships of AEs to specific study drugs but did not actively collect comprehensive data on other attributable causes or on the discontinuation or reintroduction of antituberculosis drugs in response to AEs.

In conclusion, levofloxacin appeared well tolerated despite the high number of unrelated AEs in this small cohort of women treated for RR-TB during pregnancy. Although levofloxacin exposures were lower in the second trimester than in the postpartum period, C_{max} and AUC were within the ranges reported among non-pregnant adults with RR-TB. Registration and monitoring of pregnant women with RR-TB, and regular reporting of pregnancy outcomes and neonatal and infant health, alongside RR-TB treatment outcomes, must be implemented through routine tuberculosis surveillance and integrated reporting systems. Further exploration of levofloxacin exposures during pregnancy, as well as maternal–infant drug transfer of levofloxacin, both in utero and through breastfeeding, is warranted.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40262-025-01498-0.

Acknowledgements The IMPAACT P1026s protocol team gratefully acknowledge the women and their infants who volunteered to participate in this study. We also acknowledge the hard work and contributions of the clinical research site investigators and study teams who implemented the study in South Africa (site 31790 Desmond Tutu TB Centre [Jennifer Hughes, Petra De Koker, and Ragmat Saul] and site 8051 Wits RHI Shandukani Research Centre [Lee Fairlie and Faeezah Patel]) and Tanzania (site 5118 Kilimanjaro Christian Medical Centre [James Samwel Ngocho, Blandina T. Mmbaga, and Boniface Njau]). JAH would like to acknowledge Kamunkhwala Gausi at the University of Cape Town, South Africa, who assisted with technical guidance on the non-compartmental analyses of these data.

Declarations

Funding Open access funding provided by Stellenbosch University. Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health, all components of the National Institutes of Health, under award numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC), and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The University of Cape Town Clinical PK Laboratory has been granted funding as an International Pharmacology Specialty Laboratory by the IMPAACT network.

Conflicts of Interest The authors have no conflicts of interest to declare.

Ethics Approval Ethics review board approvals for the IMPAACT P1026s study were received from the Stellenbosch University Health Research Ethics Committee (N13/02/025_DTTC; 24 November 2016) and the University of the Witwatersrand Human Research Ethics Committee: Medical (160913; 24 March 2017). This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to Participate All pregnant participants provided written informed consent for themselves and their infants to take part in this study.

Consent for Publication Not applicable (data are presented in aggregate and no personally identifiable information has been included in this manuscript).

Author's Contributions AS, BMB, MM, and DES contributed to the conceptualisation of the study and study design. RB, KG and NC contributed to the study implementation and oversight. PDK, LW, JSN, and LF contributed to the study implementation, data collection, and sample processing at the highest enrolling study sites. JH and ACE contributed to the literature search for the manuscript. KK contributed to the data extraction. JH, MP, KMB, DES, and MvS contributed to the data analysis. JH, ACE, ACH, and ED contributed to the writing of the manuscript. All authors contributed to reviewing the manuscript, and all authors have read and approved the final version.

Data Availability The data that support the findings of this study cannot be made publicly available because of the ethical restrictions in the study's informed consent documents and in the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network's approved human subjects protection plan; public availability may compromise participant confidentiality. However, data are available to all interested researchers upon reasonable request to the IMPAACT Statistical and Data Management Center's data access committee (email: sdac.data@fstrf.org) with the agreement of the IMPAACT Network.

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