

Introduction: Misoprostol is the first-line agent for cervical ripening in late pregnancy, with oral administration increasingly superseding traditional vaginal routes in international clinical guidelines^[1, 2]. Current oral dosing regimens are not derived from dose-exposure-response relationships but are empirically extrapolated from vaginal protocols. Dosing intervals (typically 2–4 hours) are based on an elimination half-life of 20–40 minutes, adhering to the principle that the preceding dose must be fully eliminated before subsequent administration^[3, 4]. In real-world practice, this approach yields unsatisfactory cervical ripening rates (failure rates of 15–20%) and is concomitant with a high risk of uterine hyperstimulation (approximately 10%)^[4, 5].

Objective: To address this critical gap between guideline recommendations and clinical outcomes, this study utilized prospective cohort data to develop a population pharmacokinetic (PopPK) model characterizing oral misoprostol disposition in late pregnancy and performed model-informed optimization of dosing regimens.

Methods: A prospective cohort of term-pregnant women (37–41 weeks gestation) receiving oral misoprostol for cervical ripening was enrolled. Serial plasma samples were systematically collected following standardized protocols and quantified using a validated HPLC-MS/MS assay (lower limit of quantification: 2.5 pg/mL). A nonlinear mixed-effects (NLME) population pharmacokinetic model was developed using NONMEM® and R software. Covariate analysis employed forward inclusion and backward elimination to identify significant predictors. Model robustness was rigorously assessed through bootstrap validation and internal diagnostic checks. Subsequently, Bayesian estimation was applied to simulate the guideline-recommended dosing regimen, characterize misoprostol pharmacokinetics under current clinical practice, and inform evidence-based regimen optimization.

Results: The study included 87 pregnant women with 228 plasma samples. Contrary to the first-order absorption reported in the literature^[6], the final PopPK model incorporated a lagged absorption time (T_{lag}), parallel zero-order and first-order absorption kinetics, a one-compartment distribution, and first-order elimination. The observed nonlinear absorption was hypothesized to be primarily influenced by food intake during pregnancy in real-world settings. Following adequate evaluation of the model, simulations of current guideline-recommended dosing regimens were conducted. Results demonstrated that repeated administration of 25 µg every 2 hours or 50 µg every 4 hours led to incomplete drug elimination between doses due to nonlinear absorption, resulting in drug accumulation. Furthermore, simulations identified the C_{max} following a 50 µg dose as a safety threshold. Based on this, two optimized regimens (initial-day and subsequent-day dosing) were designed, with a total daily dose cap of 200 µg. Compared to guideline-recommended regimens, the optimized regimens reduced the total cervical ripening duration (9.5 hours vs. 12 hours) while maintaining safety.

Conclusions: This study establishes the first PopPK model for oral misoprostol in late pregnancy cervical ripening. Real-world data revealed nonlinear absorption kinetics, which underpin the drug accumulation observed with current guideline-recommended regimens, thereby increasing safety risks. Model-informed optimization yielded regimens that improved safety while significantly reducing cervical ripening duration.