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**Title**: **Variation in tacrolimus whole blood concentrations during pregnancy and its implications for therapeutic drug monitoring: A systematic literature review**

**Objective(s)**: Tacrolimus is a pregnancy-compatible immunosuppressive increasingly used in systemic lupus erythematosus (SLE) pregnancies. Physiological changes throughout pregnancy impact tacrolimus pharmacokinetics, altering whole blood concentrations during gestation. Consequently, clinicians caring for pregnant women receiving tacrolimus face challenges in interpreting tacrolimus trough levels and in adjusting the dosage. We completed a systematic literature review focusing on the changes of maternal tacrolimus trough levels and dosage during pregnancy and postpartum in SLE and non-SLE women.

**Method(s)**: Using a combination of relevant search terms and keywords, we systematically searched Embase, Ovid Medline, PubMed, Web of Science and Cochrane Library up to January 2024. All observational studies which measured tacrolimus trough levels during pregnancy were included without language or date restriction. Records which were reviews, randomized control trials in which pregnancy was among the exclusion criteria, studies in which tacrolimus trough levels during pregnancy and postpartum were absent, abstracts only, and non-human studies were excluded from the review.

**Result(s)**: Of 404 records identified, 282 were screened based on title and abstract, of which 53 full-text articles were assessed for eligibility. Four additional eligible full-text articles were identified through the references of relevant articles. Twenty-two articles were included in this review, of which only 3 specifically assessed tacrolimus monitoring in SLE pregnancies, and 19 addressed tacrolimus drug levels in post-transplant pregnant women. At constant tacrolimus doses, whole-blood tacrolimus concentrations (which include the bound fraction) progressively decline in the late-first trimester through the third trimester, while returning to pre-pregnancy levels in the postpartum. This variation in tacrolimus levels throughout pregnancy is commonly addressed by increasing the dosage to maintain drug levels in the targeted therapeutic range. However, lower serum albumin and red blood cell concentrations during pregnancy are associated with a substantial increase in the unbound (bio-effective) fraction of tacrolimus in both plasma and whole blood, leading to a higher ratio of unbound to whole-blood tacrolimus concentration. Unfortunately, free (unbound) drug levels are not widely/routinely available in current clinical practice.

**Conclusion(s)**: Tacrolimus whole-blood concentrations often decrease in late-first trimester and increase to pre-pregnancy levels in the postpartum. Increasing the drug dosage in pregnancy to maintain tacrolimus trough levels within the usual therapeutic ranges also elevates the bio-effective fraction of tacrolimus, raising concern for the safety and efficacy of dose augmentation. Further research is needed to guide clinicians in adjusting tacrolimus dosage in SLE and/or post-transplant pregnancies to optimize therapeutic drug monitoring in these high-risk populations.