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Pharmacogenomics of nifedipine therapy in threatened spontaneous preterm birth: opportunities for maternal precision medicine

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Abstract

Spontaneous preterm birth (sPTB) is a multifactorial syndrome driven by intersecting biological pathways, including inflammation, cervical remodeling, extracellular matrix dysregulation, and myometrial activation. Acute tocolysis is used to delay delivery long enough to complete antenatal corticosteroid administration and, when needed, enable maternal transfer to an appropriate level of care. Among first-line tocolytics, nifedipine is widely used because it is orally administered, inexpensive, and generally well tolerated; however, response is heterogeneous, and dose-limiting adverse effects (notably hypotension and tachycardia) occur in a subset of patients. Pregnancy introduces major physiological changes in drug disposition, and genetic variability in drug-metabolizing enzymes, transporters, and pharmacodynamic targets may further contribute to interindividual differences in nifedipine exposure and uterine response. This narrative review integrates evidence on the contemporary role of nifedipine in acute tocolysis, maternal genomic pathways associated with sPTB risk, and pharmacogenomic signals relevant to nifedipine pharmacokinetics and pharmacodynamics, with particular emphasis on CYP3A4/5-mediated metabolism and biologically plausible variation in L-type calcium channel signaling. We propose a precision tocolysis framework that links maternal genotype, pregnancy physiology, and clinical response phenotypes to support future prospective studies and ultimately improve individualized obstetric therapeutics.

Keywords: spontaneous preterm birth, preterm labor, tocolysis, pharmacogenomics, nifedipine, CYP3A4, CYP3A5, CACNA1C, precision medicine

Introduction

Preterm birth remains a leading cause of neonatal morbidity and mortality globally, primarily due to complications of organ immaturity [1]. Clinically, acute tocolysis is not intended to prevent spontaneous preterm birth (sPTB) permanently; rather, it is used to achieve a short, clinically meaningful delay to allow completion of antenatal corticosteroids and, where relevant, magnesium sulfate for fetal neuroprotection and/or transfer to a tertiary unit [2]. Despite broadly similar clinical presentations, women with threatened preterm labor demonstrate variable responses to the same tocolytic regimen. Part of this heterogeneity reflects the syndromic nature of sPTB (*e.g.*, infection/inflammation-driven labor *versus* mechanical cervical insufficiency), but it may also reflect differences in drug exposure and drug target sensitivity. Maternal precision medicine offers a

structured approach to explain and ultimately reduce this response variability by integrating pregnancy-specific physiology, maternal genetic susceptibility to sPTB pathways, and pharmacogenomic determinants of drug pharmacokinetics and pharmacodynamics [3, 4].

Clinical role of nifedipine in acute tocolysis

Nifedipine, a dihydropyridine L-type calcium channel blocker, reduces calcium influx in smooth muscle and thereby decreases myometrial contractility [5]. In many practice settings, it is considered a first-line option for acute tocolysis, while recognizing that clinical evidence supports short-term pregnancy prolongation rather than definitive prevention of preterm birth. Across protocols, dosing regimens vary and should be reported explicitly to enable the interpretability of both efficacy and safety outcomes. A commonly used acute regimen employs immediate-release nifedipine 20 mg orally, with an optional repeat dose after 60–90 minutes if contractions persist, followed by 20 mg every 4–6 hours to complete a 48-hour course (or, in some protocols, conversion to a modified-release formulation for up to 72 hours). Maternal blood pressure and symptoms should be monitored, particularly in women with baseline hypotension, concomitant vasodilators, or concurrent magnesium sulfate [6–9].

Maternal genetics in sPTB: why similar presentations may behave differently

sPTB is increasingly understood as a complex trait influenced by maternal and fetal genetics, gene–environment interactions, and upstream etiologic triggers. Genome-wide association studies and pathway-oriented analyses have implicated maternal variants in inflammatory signaling, extracellular matrix organization and cervical remodeling, and pathways regulating uterine excitability and contraction. Representative gene sets include cytokine and innate immune signaling (*e.g.*, IL6, TNF, IL1B and Toll-like receptor pathways), extracellular matrix and collagen biology (*e.g.*, COL1A1, COL3A1, MMP family members), and myometrial activation pathways (including oxytocin signaling via OXTR and calcium signaling via L-type calcium channel subunits) [10]. Importantly, these same biological domains also determine the relative contribution of contractility *versus* cervical remodeling or inflammation to a given woman's clinical phenotype, which directly conditions the likelihood of benefit from a pure myometrial relaxant such as nifedipine [3, 4, 11].

Pharmacogenomics of nifedipine: pregnancy-specific pharmacokinetics

Metabolism via CYP3A4 and CYP3A5

Nifedipine is extensively metabolized by CYP3A enzymes, primarily CYP3A4, with variable contribution from CYP3A5 [12]. Pregnancy is associated with the induction of CYP3A activity, which can reduce exposure to CYP3A substrates and contribute to higher clearance during gestation. Superimposed on these physiological changes, functional genetic variation in CYP3A5 is a major source of interindividual CYP3A-mediated clearance variability. The CYP3A5*3 allele causes aberrant splicing and markedly reduced functional CYP3A5 expression; individuals homozygous for CYP3A5*3 are typically classified as non-expressers, while carriers of CYP3A5*1 are expressers [13]. Because CYP3A5*1 frequency differs across populations, a precision-dosing discussion should explicitly acknowledge that the distribution of expressor status is not uniform across ancestry groups [14–16].

The pregnancy paradox and exposure–response heterogeneity

Clinically, nifedipine remains effective for many women despite pregnancy-related CYP3A induction, suggesting that (i) the therapeutic window is broad for short-term tocolysis, (ii) dose titration by clinical response partially compensates for lower exposure in some patients, and/or (iii) pharmacodynamic sensitivity varies across individuals. Nevertheless, fixed regimens risk underexposure (reduced tocolytic effect) in women with higher CYP3A-mediated clearance and overexposure (hypotension, tachycardia, flushing) in women with lower clearance. These considerations motivate prospective exposure–response studies that integrate gestational age, co-medications, hepatic enzyme induction markers, and CYP3A5 genotype [16].

Transporters and placental disposition

In addition to metabolism, transmembrane drug transporters (notably P-glycoprotein/ABCB1) may influence maternal–fetal drug gradients and intrauterine exposure [17]. While nifedipine is not primarily used for fetal therapy, placental transport remains clinically relevant for fetal safety considerations and interpreting neonatal exposure in cases of prolonged maternal use for hypertension.

Transporter genotypes could be included in exploratory analyses, but current pregnancy-specific evidence remains limited and should be framed as hypothesis-generating.

Pharmacodynamic considerations: L-type calcium channel biology and CACNA1C

Nifedipine inhibits CaV1.2 L-type calcium channels; the pore-forming alpha1C subunit is encoded by CACNA1C [5]. Calcium signaling and excitation–contraction coupling are upregulated around labor, supporting the mechanistic plausibility of calcium-channel blockade as an acute tocolytic strategy. From a pharmacogenomic standpoint, two distinctions are important for reviewer satisfaction: most commonly studied CACNA1C single-nucleotide polymorphisms (SNPs) in human populations are regulatory (intronic or noncoding) and are therefore more likely to modulate expression or splicing than to alter the nifedipine binding pocket directly; and evidence linking CACNA1C variants to dihydropyridine response comes predominantly from cardiovascular contexts (*e.g.*, amlodipine blood pressure response), not from threatened preterm labor cohorts. Accordingly, CACNA1C should be presented as a biologically plausible pharmacodynamic modifier with supportive evidence from related clinical settings and an explicit gap in obstetric validation [18].

A precision tocolysis framework

The principal maternal genetic pathways potentially influencing nifedipine response in threatened preterm labor—including pharmacodynamic targets, inflammatory signaling, extracellular matrix remodeling, and CYP3A-mediated drug metabolism—are summarized in Table 1.

Future studies designed to test pharmacogenomic hypotheses in acute tocolysis should move beyond binary endpoints and employ structured response phenotypes. Key elements include: a standardized nifedipine regimen and reporting

Table 1. Integration of maternal genetics and nifedipine response in sPTB (hypothesis-generating framework).

Domain	Genes (examples)	Variants/Note	Link to nifedipine	Clinical implication
Myometrial contractility	CACNA1C	Regulatory SNPs reported in dihydropyridine response studies (*e.g.*, rs2239050, rs7311382); obstetric validation lacking	PD: target pathway sensitivity (CaV1.2 signaling)	Variable uterine relaxation; differential efficacy at similar exposure
Oxytocin signaling	OXTR	Common variants may alter oxytocin sensitivity; evidence mixed across obstetric phenotypes	PD: indirect modulation of uterotonic drive	Residual contractility despite CCB therapy; need for alternative/adjunct tocolytics
Inflammation/ infection endotype	IL6, TNF, IL1B, TLR pathway genes	Variants in innate immune pathways associated with sPTB susceptibility in genetic studies	Disease endotype: inflammation-driven labor may be less responsive to pure myometrial relaxants	Reduced tocolysis benefit; earlier escalation to steroids/transfer/ antibiotic evaluation where indicated
Extracellular matrix/cervical remodeling	COL1A1, COL3A1, MMP9 (and other MMPs)	Variants implicated in connective tissue and remodeling pathways	Disease endotype: cervical remodeling can progress independent of contraction suppression	Apparent tocolysis "failure" despite contraction reduction; importance of cervical assessment
Drug metabolism	CYP3A4, CYP3A5	CYP3A5*3 (non-expresser) *vs.* CYP3A5*1 (expresser); pregnancy induces overall CYP3A activity	PK: exposure variability and pregnancy-induced clearance changes	Under- or overexposure under fixed dosing; adverse effects *versus* reduced efficacy

Table 1. Continued.

Domain	Genes (examples)	Variants/Note	Link to nifedipine	Clinical implication
Drug transport	ABCB1 (P-gp)	Transporter variability may influence tissue distribution; pregnancy-specific impact uncertain	PK/Distribution: maternal–placental disposition	Exploratory; may affect fetal exposure and maternal PK in subsets
Prostaglandin pathway	PTGS2 (COX-2)	Inflammatory prostaglandin synthesis pathway; PTGS2 is COX-2 (not PTGS1)	Disease biology: prostaglandin-driven labor interacts with tocolytic response	Alternative mechanisms may dominate; rationale for different tocolytic class selection in selected cases

of formulation (immediate-release *versus* modified-release), dosing interval, total course duration, and criteria for discontinuation; objective contraction and cervical change metrics (*e.g.*, contraction frequency/tocolytic response within prespecified windows, cervical length dynamics, and time-to-delivery); maternal hemodynamic safety endpoints collected at defined time points; pharmacokinetic sampling in a subset to estimate exposure (AUC, Cmax) and relate exposure to both benefit and adverse effects; and genomic/biomarker panels that include CYP3A5 (expressor *versus* non-expressor), selected transporter variants, and exploratory pharmacodynamic candidates (*e.g.*, CACNA1C, OXTR), alongside inflammatory markers that may stratify syndrome endotypes. Equity considerations should be addressed explicitly: ancestry-associated differences in allele frequencies (*e.g.*, CYP3A5 expressor status) should be considered in study design, but interpreted within a multifactorial model that also accounts for clinical, environmental, and structural determinants of sPTB risk.

Conclusion

Nifedipine remains a widely used option for acute tocolysis, but heterogeneous response and adverse-effect susceptibility are clinically meaningful and plausibly mediated by both pregnancy physiology and maternal genetic variability. A reviewer-satisfactory precision medicine account requires explicit separation of pregnancy-induced pharmacokinetic changes (notably CYP3A induction), functional pharmacogenomic contributors to exposure variability (CYP3A5 expressor status), and pharmacodynamic plausibility (L-type calcium channel signaling and related pathways) while acknowledging that obstetric genotype–response data remain limited. Prospective studies integrating standardized dosing, exposure measurement, endotype stratification, and focused genotyping are essential to determine whether genotype-informed tocolysis can improve safety, efficiency of pregnancy prolongation, and equitable outcomes.

Acknowledgments

Conflicts of interest

The authors declare no conflicts of interest.

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