World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Check for updates

# Pharmacogenomics and Pregnancy Pharmacokinetics: Toward Precision Drug Therapy in Obstetrics

Malachy Nwaeze Ezenwaeze [1,*], Sylvester Onuegbunam Nweze [2] and Chibugo Ndidiamaka Nwankwo [3]

[1] *Department of Pharmacology and Therapeutics, Enugu State University of Science and Technology College of Medicine.*
[2] *Department of Obstetrics and Gynaecology, Enugu State University Teaching Hospital /College of Medicine.*
[3] *Department of Paediatrics, Alberta Children Hospital, Calgary, Canada.*

World Journal of Biology Pharmacy and Health Sciences, 2025, 23(03), 514-522

Publication history: Received on 20 August 2025; revised on 25 September 2025; accepted on 29 September 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.23.3.0874

## Abstract

**Background**: Pregnancy profoundly reshapes drug disposition through physiologic changes in absorption, distribution, metabolism, and excretion. Maternal, placental, and fetal genomes add additional layers of variability, creating challenges for safe and effective pharmacotherapy in obstetrics. Objective: To synthesize current evidence on how pharmacogenomics and pregnancy related pharmacokinetics can be integrated to optimize drug therapy in obstetrics, and to highlight clinical, safety, and research implications.

**Methodology**: This narrative review draws from clinical guidelines (e.g., CPIC, ACOG, FDA), systematic assessments, pharmacokinetic and pharmacogenomic studies, and implementation reports. Key therapeutic domains were examined, including analgesia/anesthesia, antiepileptics, antimicrobials, and antidepressants, with a focus on pregnancy induced pharmacokinetic remodeling and genotype driven variability.

**Results**: Pregnancy increases CYP2D6 and CYP3A activity, decreases CYP1A2 activity, and enhances glucuronidation, leading to altered drug exposure that may mask or amplify pharmacogenomic effects. Clinically, CYP2D6 genotype significantly impacts opioid safety in the peripartum and lactation period, while HLA-B15:02 and HLA-A31:01 genotypes strongly predict carbamazepine/oxcarbazepine induced cutaneous reactions. NAT2 polymorphisms modify isoniazid metabolism and toxicity risk, while CYP2C9 and UGT variants influence sulfamethoxazole exposure. CYP2C19 and CYP2D6 variants affect antidepressant efficacy and tolerability, with pregnancy further altering drug clearance. Implementation studies demonstrate that pre-emptive pharmacogenomic testing (e.g., HLA genotyping in Thailand) reduces adverse outcomes, while clinical decision support tools facilitate translation into practice.

**Conclusion**: Pharmacogenomics, when combined with the physiologic realities of pregnancy and lactation, provides a pathway toward precision pharmacotherapy in obstetrics. High-value opportunities already exist, including avoidance of CYP2D6-dependent prodrugs in breastfeeding and pre-emptive HLA testing for carbamazepine/oxcarbazepine. Future priorities include integrating maternal–placental–fetal genomics, developing pregnancy-specific dosing algorithms, and ensuring equitable implementation across diverse populations.

**Keywords:** Pharmacogenomics; Pharmacokinetics; Obstetric Pharmacotherapy; Precision Medicine

## 1. Introduction

Medication use during pregnancy is pervasive. Recent estimates suggest that 93.9 % of pregnant women take at least one medication during gestation, with an average of 4.2 medications per pregnancy [1]. Use of prescription medications

* Corresponding author: Ezenwaeze, Malachy Nwaeze

during pregnancy also shows wide variability across studies, with prevalence rates ranging from 27 % to 93 % [2]. Commonly used therapeutic classes include analgesics, antibiotics, antihypertensives, antiepileptics, and antidepressants reflecting the breadth of acute and chronic conditions encountered in obstetric care [3].

Although medications are often essential for maternal and fetal health, pregnancy imposes profound physiologic changes that complicate optimal pharmacotherapy. The gestational state is characterized by increased plasma volume, altered hepatic enzyme activity (such as induction or suppression of various CYP enzymes), enhanced renal glomerular filtration, and shifts in protein binding, all of which can significantly influence drug absorption, distribution, metabolism, and excretion [4,5]. These dynamic alterations may lead to subtherapeutic exposure or elevated drug levels (and toxicity) if dosing is not appropriately adjusted.

Overlaying these pregnancy specific changes, interindividual genetic variation further modulates drug response. Polymorphisms in genes encoding cytochrome P450 enzymes, drug transporters (such as ABCB1, SLCO1B1), and immune related pathways influence pharmacokinetics, pharmacodynamics, and susceptibility to adverse drug reactions [3,6]. For instance, CYP2D6 genotype significantly alters the metabolic conversion of codeine to morphine a clinically important issue for maternal analgesia and risk of opioid exposure to the neonate [7]. Genetic variants influencing folate metabolism or drug transport have also been implicated in differential teratogenic risks associated with certain antiepileptic agents [8,9].

Recent systematic reviews continue to highlight extensive pregnancy-associated pharmacokinetic shifts yet also underscore the persistent lack of pregnancy-tailored dosing guidelines [5,10]. Because obstetric prescribing frequently relies on extrapolation from nonpregnant populations, this practice may poorly capture the interplay between maternal genotype and altered gestational physiology. The underrepresentation of pregnant women in pharmacogenomic trials perpetuates uncertainty and potential inequities in therapy [11,12].

Given these challenges, a truly personalized obstetric therapeutic paradigm must move beyond “one size fits all” models toward integration of both genetic and pregnancy specific determinants of drug response. A precision medicine framework grounded in pharmacogenomics holds promise for optimizing maternal treatment efficacy, minimizing drug related adverse events, and protecting fetal development. To realize this vision, coordinated efforts are needed to expand pharmacogenomic testing in pregnant populations, conduct longitudinal pharmacokinetic studies across gestation, and develop robust, pregnancy adapted clinical decision support tools [3,13,14].

## 2. Pharmacokinetic remodeling in pregnancy

Pregnancy induces substantial physiological and biochemical changes that remodel pharmacokinetics. These include increases in plasma volume, cardiac output, and glomerular filtration rate, as well as alterations in hepatic enzyme activity. Recent in vivo and modeling studies show that CYP2D6 and CYP3A activities increase in pregnancy, while CYP1A2 activity decreases; glucuronidation (phase II metabolism) is often enhanced. Collectively, these changes can alter drug exposures independent of genotype, meaning that pharmacogenomic effects may be masked or magnified [15,16].

For example, a probe study using dextromethorphan in pregnant women showed that CYP2D6 activity was 43% higher during pregnancy compared with postpartum, and CYP3A activity was 92% higher, whereas CYP1A2 activity was reduced. Vitamin A supplementation did not modify these changes, although higher endogenous retinoic acid levels correlated with CYP2D6 activity (17). In vitro work with primary human hepatocytes exposed to pregnancy related hormones confirmed a dose dependent increase in CYP3A4 protein and activity for substrates such as midazolam, nifedipine, and buprenorphine, with variability depending on CYP3A5 background [18].

Physiologically based pharmacokinetic (PBPK) models predict that CYP1A2 activity declines progressively across pregnancy, falling to 70%, 44%, and 30% of baseline in the first, second, and third trimesters, respectively. In contrast, CYP2D6 and CYP3A4 activities increase throughout gestation [19]. Measurement of endogenous biomarkers, such as the plasma 4β-hydroxycholesterol/cholesterol ratio, also confirms increased CYP3A activity in pregnancy, with gestational age dependent variation [20].

### 2.1. Three genomes and a placenta

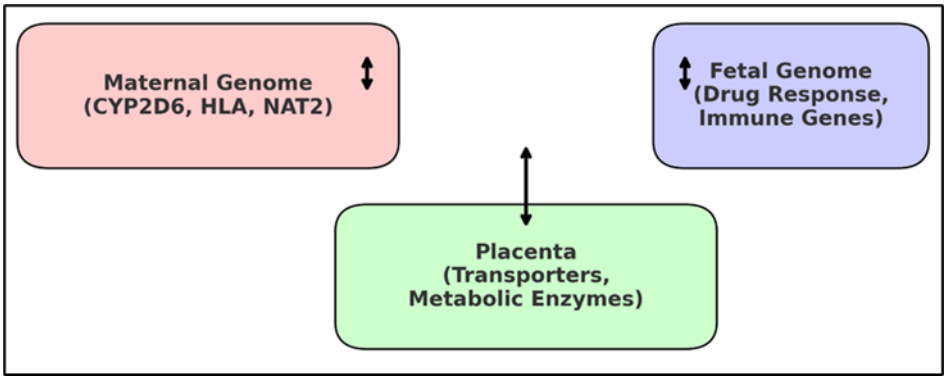


**Figure 1** Drug disposition and response in pregnancy

Drug response in obstetrics reflects the interplay of maternal, placental, and fetal genomes:

Maternal genotype: Variants in CYP2D6, NAT2, UGTs, and HLA can influence drug metabolism and adverse drug reactions. PBPK modeling of dolutegravir, which is metabolized by UGT1A1, predicted that maternal UGT1A1 poor metabolizers would have 1.6-fold higher maternal and cord blood exposures than extensive metabolizers, although standard dosing remained effective across genotypes [21].

Placental biology: The placenta expresses metabolic enzymes and transporters that shape fetal exposure. Quantitative proteomics demonstrated that efflux transporters such as P-gp and BCRP decrease with gestational age, while some uptake transporters, including OCT3 and OAT4, increase [22]. Recent reviews confirm that Phase II enzymes and transporter expression shift dynamically across gestation, highlighting gaps in our understanding of maternal–placental drug handling [16]. A vascularized placenta on a chip model has further demonstrated the feasibility of studying transplacental transport of large molecules and biologics [23].

Fetal genotype: Although rarely considered clinically, fetal polymorphisms may contribute to immune mediated reactions or altered developmental drug responses. This remains a research frontier, with limited application in routine care [14,25].

At present, most pharmacogenomic decisions in pregnancy are based on maternal genotype, while placental transporter biology and fetal genomics remain largely investigational.

## 3. The Obstetric Pharmacogenomics Landscape by Therapeutic Domain

### 3.1. Analgesia and anesthesia: CYP2D6 and opioid safety in the peripartum and lactation

Postpartum pain management is common, opioids may be needed in some patients but pose unique risks in lactation when prodrugs depend on CYP2D6 activation (e.g., codeine, tramadol). Ultra rapid CYP2D6 metabolizers can generate high morphine (or O-desmethyltramadol) concentrations, which pass into breast milk and may cause infant sedation, respiratory depression, or rarely death. Regulatory and professional guidance has therefore shifted away from codeine/tramadol in breastfeeding [26–29]. The United States Food and Drug Administration (FDA) added a contraindication for codeine/tramadol in certain pediatric settings and recommended against use in breastfeeding because infant harm can occur and most mothers will not know their CYP2D6 status [26]. The American College of Obstetricians and Gynecologists (ACOG) and anesthesia societies echo this, prioritize multimodal non opioid analgesia and avoid codeine/tramadol during breastfeeding [27].

It recommends that, if an opioid is necessary postpartum, prefer agents not reliant on CYP2D6 bioactivation (e.g., morphine), use the lowest effective dose for the shortest duration and support with robust non opioid multimodal strategies [28]. Also to document any known CYP2D6 genotype in the electronic health record and to avoid prodrug opioids altogether in the breastfeeding period if a patient is a known ultrarapid metabolizer [28,29]. Health-system evaluations observed utilization changes after the 2017 FDA communication, and case reports include a breastfed infant death linked to maternal codeine use, reinforcing a conservative approach with prodrug opioids in lactation [26,28].

### 3.2. Antiepileptics: preventing life threatening cutaneous reactions (HLA-B15:02 / HLA-A31:01)

Carbamazepine (CBZ) and oxcarbazepine (OXC) are sometimes used in women of reproductive age. Certain HLA genotypes confer high risk of serious cutaneous adverse reactions (SCAR), including Stevens Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) [29–31].

The CPIC guideline gives strong recommendations to avoid CBZ/OXC in HLA-B15:02 carriers and to consider alternatives or enhanced caution in HLA-A31:01 carriers [30,31]. Implementation studies (e.g., Thailand's national policy) show that pre-emptive HLA-B 15:02 testing reduces SCAR by steering therapy away from CBZ/OXC in carriers an instructive model for obstetric clinics managing epilepsy or trigeminal neuralgia in pregnancy or preconception [32,33].

Where antiepileptic therapy is indicated in pregnancy, preconception pharmacogenomics testing is ideal; if unavailable, consider HLA testing before initiating CBZ/OXC in at-risk ancestries. Pharmacogenomics guides safety (risk of SCAR) rather than teratogenicity; teratogenic risk remains a separate consideration in antiepileptic selection [30–33].

### 3.3. Antimicrobials: Large Pharmacokinetic Shifts and Emerging Pharmacogenomic Intersections

Systematic reviews emphasize that pregnancy frequently alters antimicrobial pharmacokinetics, typically leading to increased clearance and expanded volume of distribution. These physiological changes can result in suboptimal drug concentrations, necessitating dose adjustments to achieve therapeutic targets. For instance, β-lactam antibiotics often require dose intensification during late pregnancy to maintain effective plasma concentrations [34].

Pharmacogenomic factors can further complicate this variability:

Isoniazid (INH) and NAT2 Acetylation: Genetic polymorphisms in the NAT2 gene categorize individuals as slow, intermediate, or rapid acetylators. Slow acetylators may experience elevated INH concentrations, increasing the risk of hepatotoxicity, while rapid acetylators might have subtherapeutic levels, risking treatment failure. Pregnancy can alter INH clearance; however, NAT2 genotype remains a significant determinant. Integrating pharmacogenomic data with pregnancy adjusted dosing could optimize therapy, particularly in high tuberculosis burden regions [35,36].

Trimethoprim Sulfamethoxazole (TMP-SMX) and CYP2C9/UGT Polymorphisms: Sulfamethoxazole is metabolized by CYP2C9 and UGT enzymes. Variants such as CYP2C9*2/*3 can reduce clearance and elevate toxicity risk. TMP-SMX is utilized in HIV prophylaxis and urinary tract infections during pregnancy. While pharmacokinetic studies indicate increased clearance in late gestation, pharmacogenomic differences may still influence maternal toxicity or drug–drug interactions with antiretrovirals [37].

### 3.4. Antidepressants and Other CNS Agents: Genotype and Physiology

Beyond pregnancy, CYP2D6 and CYP2C19 genotypes influence the metabolism and dosing of many SSRIs and tricyclic antidepressants. During pregnancy, increased CYP2D6 activity and variable CYP2C19 activity can further alter drug exposure, impacting both efficacy and relapse prevention in mood and anxiety disorders [3,39]. Clinicians should integrate available genotype information with close symptom monitoring and, where feasible, therapeutic drug monitoring (TDM).

For example, sertraline is commonly used in pregnancy for depression and anxiety. CYP2C19 poor metabolizers have higher plasma concentrations and greater risk of dose related adverse effects, whereas ultrarapid metabolizers may have subtherapeutic exposure. Pharmacokinetic studies demonstrate that sertraline clearance increases during late pregnancy, often necessitating dose escalation to maintain symptom control. Thus, a CYP2C19 ultrarapid metabolizer may be particularly vulnerable to treatment failure in pregnancy unless TDM or symptom guided titration is applied. Conversely, poor metabolizers may still experience elevated exposure despite pregnancy induced clearance changes, emphasizing the importance of combining pharmacogenomics with clinical monitoring [39,40].

For tricyclic antidepressants like nortriptyline and amitriptyline, CYP2D6 genotype strongly influences dosing outside pregnancy, and increased CYP2D6 activity in pregnancy can further lower plasma concentrations, reinforcing the need for TDM and pharmacogenomics informed dose adjustments [38,40].

Clinical Implications is that when pharmacogenomic information is available, it should be layered onto pregnancy physiology. In case of ultrarapid CYP2C19 metabolizers, there will be higher risk of relapse if sertraline dose is not optimized therefore closer monitoring or alternative SSRI may be warranted [39]. In case of poor metabolizers, consider

lower starting dose and vigilant monitoring for adverse effects, even during pregnancy [39,40]. In all genotypes, anticipate increased clearance during late gestation and reassess dosing postpartum as metabolism normalizes [45-47].

**Table 1** Key Pharmacogenes in Obstetric Pharmacotherapy

| Gene(s) | Drug(s) | Pregnancy Considerations | Pharmacogenomic Implications |
|---|---|---|---|
| CYP2D6 | Codeine, Tramadol (prodrugs) | ↑ CYP2D6 activity in pregnancy; risk of infant exposure via breast milk in lactation | Ultra-rapid metabolizers produce excessive active metabolites → neonatal sedation/respiratory depression; avoid codeine/tramadol in breastfeeding; prefer non-CYP2D6 opioids (e.g., morphine) |
| HLA-B15:02, HLA-A31:01 | Carbamazepine, Oxcarbazepine | Pregnancy does not mitigate SCAR risk; preconception or early testing ideal | Strong CPIC recommendation to avoid CBZ/OXC in carriers; consider alternatives; risk applies regardless of pregnancy status |
| NAT2 | Isoniazid | Pregnancy alters INH clearance but not genotype effect; TB therapy common in high-burden settings | Slow acetylators → ↑ risk of hepatotoxicity; rapid acetylators → ↓ exposure and possible treatment failure; PGx may guide individualized dosing |
| CYP2C9, UGT1A6/9 | Sulfamethoxazole (TMP-SMX) | Increased clearance in late pregnancy; used for HIV prophylaxis and UTIs | Reduced-function CYP2C9 alleles (*2, *3) or UGT variants → ↑ risk of adverse effects (e.g., hypersensitivity, hepatotoxicity); genotype may refine risk stratification |
| CYP2C19, CYP2D6 | SSRIs (e.g., sertraline, paroxetine), tricyclics | ↑ CYP2D6 activity and variable CYP2C19 activity during pregnancy; risk of reduced antidepressant efficacy | Genotype influences metabolism (e.g., poor vs ultrarapid metabolizers); consider PGx + therapeutic drug monitoring for dose optimization |

## 4. Lactation Pharmacogenomics: Translating Maternal Genotype to Infant Exposure

Lactation introduces a second "patient," the infant, requiring careful consideration of pharmacogenomic (PGx) factors in medication choices. CYP2D6 dependent prodrug opioids, such as codeine and tramadol, are particularly concerning due to variable activation to potent metabolites and potential transfer into breast milk. Maternal CYP2D6 ultra-rapid metabolizers (UMs) can convert codeine into morphine at higher rates, leading to increased risk of infant sedation and respiratory depression [41,42]. The FDA has issued warnings against breastfeeding during treatment with codeine or tramadol due to these risks [43]. For tramadol specifically, LactMed summarizes the FDA/manufacturer stance against breastfeeding exposure and discusses safer alternatives [42].

## 5. Implementation: From Genotype to Bedside in Obstetrics

### 5.1. Timing and Test Parameters (When and What to Test)

Preconception or early prenatal visits are ideal to obtain durable pharmacogenomic data (e.g., CYP2D6, HLA-B, HLA-A), enabling safe choices should new indications arise later (e.g., intrapartum analgesia, infections) [44]. Targeted testing is warranted when starting high-risk drugs (e.g., carbamazepine/oxcarbazepine in at-risk ancestries) or when a lactating person requires analgesia and has a known risky genotype [44,45].

### 5.2. Application of Result

The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides actionable, drug specific tables mapping genotype, phenotype, and recommendation (dose change, alternative, or avoidance) [44,45]. Integrating these into the electronic health record (EHR) with clinical decision support is feasible and has supporting resources [44].

*5.2.1. Layering Pregnancy Physiology on Top of Genotype*

Even with genotype guided selection/dosing, pregnancy associated pharmacokinetic changes can push exposures below targets. Combining PGx with stage of pregnancy pharmacokinetic knowledge (e.g expect higher CYP2D6 activity and higher renal clearance), therapeutic drug monitoring where available, and postpartum reassessment as physiology normalizes are the key [46].

Practical peripartum pharmacogenomic algorithms can guide safe and effective medication use. For postpartum analgesia in a breastfeeding parent, management should begin with non-opioid multimodal therapy, avoiding codeine and tramadol. If an opioid is necessary, non-CYP2D6-prodrug options should be preferred, with conservative dosing, counseling, and documentation of any CYP2D6 genotype, supported by clinical decision rules [45]. When initiating or switching antiepileptic therapy, populations with appreciable HLA-B 15:02 frequency should undergo testing before receiving carbamazepine or oxcarbazepine, and carriers should avoid these medications, with alternative antiepileptic drugs selected according to obstetric neurology guidance [47].

Safety, ethics, and equity considerations are essential in peripartum pharmacogenomics. Informed consent should encompass the full range of pharmacogenomic implications, including incidental findings and potential impacts on family members, such as shared HLA risks [45]. Equity requires offering testing without using race as a proxy, while ensuring that panels are validated across diverse populations to prevent widening disparities [45]. Data stewardship involves storing pharmacogenomic results as lifetime data, which can retain relevance for future pregnancies and non-obstetric care. Targeted testing, such as HLA-B 15:02 screening before carbamazepine in high prevalence groups, has been shown to be both clinically impactful and cost effective [45,47].

## 6. Research Priorities

Future research in obstetric pharmacogenomics should prioritize several domains. First, there is a need to develop maternal placental fetal triad models that clarify how placental transporters and fetal genotypes modulate maternal drug exposure and fetal outcomes [46]. Second, pregnancy specific pharmacogenomic dosing strategies must move beyond extrapolation from non-pregnant populations by integrating pharmacogenomics with physiologically based pharmacokinetic (PBPK) modeling and validating these approaches through pragmatic clinical trials. Third, lactation pharmacokinetics and pharmacogenomics require further investigation to quantify milk to plasma transfer and infant drug exposure across maternal pharmacogenomic phenotypes, extending research beyond opioids. Fourth, real world implementation should focus on embedding pharmacogenomic information into electronic health records, including obstetric-specific clinical decision support tools and outcomes tracking [45]. Finally, diversity in study populations must be improved by expanding representation of African, Asian, and admixed ancestries in obstetric pharmacogenomics research [46].

## 7. Conclusion

Pharmacogenomics is a practical lever for safer, more effective obstetric pharmacotherapy when paired with the physiologic realities of pregnancy and lactation. High value opportunities already exist (e.g., avoiding codeine/tramadol in breastfeeding, pre-emptive HLA testing for CBZ/OXC), and broader integration via CPIC-aligned decision support can improve care now while the evidence base for other drug classes grows.

## Compliance with ethical standards

*Acknowledgments*

We extend our gratitude to all whose steadfast support and encouragement were invaluable to the completion of this review.

*Disclosure of conflict of interest*

The authors declare no conflict of interest.

## References


[1] Hwang Y-M, Barreto EA, Smith NL, et al. Accelerating adverse pregnancy outcomes research amidst legacy cohort constraints: global perspectives and priorities. *BMC Med*. 2024; 22:354.

[2] Thunbo MØ, Petersen KS, Jørgensen JS, et al. Use of medication in pregnancy on the rise: Study on 1.4 million pregnancies. *Acta Obstet Gynecol Scand*. 2024. doi:10.1111/aogs.14805

[3] Hudson RE, Unadkat JD, Priceman S, et al. Drug exposure during pregnancy: Current understanding and approaches to advance maternal–fetal pharmacology. *Front Pharmacol*. 2023; 14:1111601.

[4] Eke AC, Gramkow L, Jaber N, et al. Pharmacometrics in obstetrics and maternal–fetal medicine. *CPT Pharmacometrics Syst Pharmacol*. 2024;13: e13267.

[5] Siccardi M, Kearney BP, Lovern H, et al. Pharmacokinetic evaluation in pregnancy: Current status and future directions. *J Clin Pharmacol*. 2023;63(7):793-806.

[6] Chaemsaithong P, Romero R, Veerbeek JHW, et al. Pharmacogenomics of preeclampsia therapies. *Pharmacogenomics*. 2024;25(6):357-369.

[7] Madadi P, Ross CJD, Hayden MR, Carleton BC, Gaedigk A, Leeder JS, Koren G. Pharmacogenetics of neonatal opioid toxicity following maternal codeine use during breastfeeding: a case–control study. *Clin Pharmacol Ther*. 2020;107(1):136-142.

[8] Meador KJ, Pennell PB, May RC, et al. Effects of periconceptional folate supplementation on cognitive outcomes in children of women with epilepsy: NEAD study. *Neurology*. 2020;95(12): e1759-e1769.

[9] Coles LD, Gaedigk A, Leeder JS, et al. Genetic and clinical factors affecting risk for major congenital malformations with antiepileptic drug exposure. *Epilepsia*. 2021;62(4):915-926.

[10] Eyal S, Easterling TR, Carr D, Umans JG, Miodovnik M, Hankins GDV, et al. Pharmacokinetics of drugs in pregnancy: A systematic review and meta-analysis. *Clin Pharmacokinet*. 2021;60(9):1101-1116.

[11] van der Graaf PH, Kerbusch T, Allegaert K, et al. Precision dosing in pregnancy: Are we ready to move forward? *Clin Transl Sci*. 2022;15(5):1068-1077.

[12] Wang J, Panchaud A, Pariente G, et al. Drug safety in pregnancy: A review of global pharmacovigilance reporting systems. *Drug Saf*. 2022;45(8):841-856.

[13] Pariente G, Leibson T, Adams-Webber T, et al. Pregnancy-associated changes in pharmacokinetics: A systematic review. *PLoS Med*. 2020;17(11):e1003305.

[14] Ryu RJ, Eyal S, Easterling TR, Caritis SN, Venkataramanan R. Pharmacogenomics and pregnancy: Moving toward individualized pharmacotherapy. *Clin Pharmacol Ther*. 2021;110(1):36-44.

[15] Pariente G, Leibson T, Carls A, Adams-Webber T, Ito S, Koren G. Pregnancy-associated changes in pharmacokinetics: a systematic review. PLoS Med. 2016;13(11):e1002160.

[16] Gong C, Bertagnolli LN, Boulton DW, Coppola P. Literature review of changes in Phase II drug-metabolizing enzyme and drug transporter expression during pregnancy. Clin Transl Sci. 2023;16(10):1840-1854.

[17] Colicchia M, Zajicek A, Unadkat JD, Ke AB. Impact of pregnancy and vitamin A supplementation on CYP2D6 and CYP3A activity using dextromethorphan phenotyping. Clin Transl Sci. 2022;15(12):2831-2842.

[18] Fashe T, Lutz JD, Isoherranen N, et al. Pregnancy-related hormones alter CYP3A expression and activity in human hepatocytes in a substrate- and donor-dependent manner. Drug Metab Dispos. 2023;51(8):803-813.

[19] Ke AB, Greupink R, Abduljalil K, et al. Prediction of maternal pharmacokinetics using physiologically based pharmacokinetic models: assessing the impact of the longitudinal changes in the activity of CYP1A2, CYP2D6, and CYP3A4 enzymes during pregnancy. Clin Pharmacokinet. 2020;59(12):1601-1616.

[20] Palandra J, Chowdhury SK, Nordmark A, et al. Plasma 4β-hydroxycholesterol/cholesterol ratio as an endogenous biomarker of CYP3A activity in pregnant women. Br J Clin Pharmacol. 2022;88(4):1590-1599.

[21] Duan J, Rowland Yeo K, Zhang H, et al. Physiologically based pharmacokinetic modeling to inform dolutegravir dosing in pregnancy across UGT1A1 phenotypes. CPT Pharmacometrics Syst Pharmacol. 2023;12(10):1400-1410.

[22] Mao Q, Unadkat JD, Mao J, et al. Gestational age-dependent abundance of human placental transporters quantified by LC-MS/MS proteomics. Drug Metab Dispos. 2020;48(8):571-580.

[23] Celik A, Ramamoorthy P, Park J, et al. A vascularized placenta-on-a-chip model for evaluating maternal–fetal drug transfer. Lab Chip. 2025;25(4):812-826.

[24] Bérard A, Sheehy O, Zhao JP, et al. Fetal genetic polymorphisms and adverse drug reactions in pregnancy. Pharmacoepidemiol Drug Saf. 2019;28(9):1231-1242.

[25] Colicchia M, Unadkat JD, Ke AB. Placental pharmacogenomics: current insights and future directions. Pharmacogenomics J. 2021;21(4):401-412.

[26] U.S. Food and Drug Administration. Use of codeine and tramadol products in breastfeeding women: questions and answers. FDA; 2019 Aug 1.

[27] American College of Obstetricians and Gynecologists. Leading women's health organizations recommend strategies to enable adequate pain control and continued breastfeeding. ACOG; 2017 Apr 28.

[28] Clinical Pharmacogenetics Implementation Consortium. CPIC guideline for codeine and CYP2D6: 2020 update. Available from: https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/

[29] Dhesi M. Tramadol. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.

[30] Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. CPIC guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update. Clin Pharmacol Ther. 2018;103(5):567–75.

[31] Nguyen AH, Sukasem C, et al. The pharmacogenomics of carbamazepine-induced cutaneous adverse drug reactions. Front Pharmacol. 2023;14:1217516.

[32] Tiwattanon K, Sukasem C, et al. Implementation of HLA-B*15:02 genotyping as standard practice in Thailand: a retrospective cohort study. Front Pharmacol. 2022;13:867490.

[33] Liu Y, et al. Association between HLA-B*15:02 and oxcarbazepine-induced severe cutaneous adverse reactions. Pharmacogenomics J. 2018;18(3):380–5.

[34] Hesse MR, et al. Pharmacokinetics and target attainment of antimicrobial drugs during pregnancy. Clin Pharmacokinet. 2023;62(1):1-12. doi:10.1007/s40262-023-01143-4.

[35] Zhu R, et al. The pharmacogenetics of NAT2 enzyme maturation in South African infants with perinatal HIV exposure. Clin Pharmacol Ther. 2012;91(2):234-241. doi:10.1038/clpt.2011.245.

[36] Hein DW, et al. Arylamine N-acetyltransferase acetylation polymorphisms and their clinical relevance. Pharmacogenomics J. 2021;21(3):231-239. doi:10.1038/s41397-020-00152-1.

[37] Huang YS, et al. Sulfamethoxazole-trimethoprim-induced liver injury and genetic polymorphisms in a Han Chinese population. Pharmacogenet Genomics. 2021;31(5):123-130. doi:10.1097/FPC.0000000000000315.

[38] Yue M, et al. Pharmacokinetics of antidepressants in pregnancy. J Clin Pharmacol. 2023;63(7):890-899. doi:10.1002/jcph.2282.

[39] Milosavljević F, et al. Association of CYP2C19 and CYP2D6 poor metabolizer status with antidepressant response during pregnancy. JAMA Psychiatry. 2021;78(4):423-431. doi:10.1001/jamapsychiatry.2020.4482.

[40] Hicks JK, et al. Clinical pharmacogenetics implementation consortium guideline for CYP2D6 and CYP2C19 genotypes and SSRI dosing: 2023 update. Clin Pharmacol Ther. 2023;114(3):497-507. doi:10.1002/cpt.2903.

[41] Madadi P, Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder JS. Safety of codeine during breastfeeding: Fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. CMAJ. 2007;176(13): 185–191.

[42] Drugs and Lactation Database (LactMed). Codeine. Bethesda (MD): National Library of Medicine (US); 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501212/

[43] U.S. Food and Drug Administration. FDA Drug Safety Communication: Restricts use of prescription codeine pain and cough medicines and tramadol-containing products in children and breastfeeding women. Silver Spring, MD: FDA; 2017.

[44] Clinical Pharmacogenetics Implementation Consortium (CPIC). CPIC Guidelines. Available from: https://cpicpgx.org/guidelines/

[45] Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband S, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. 2022;111(1): 16–23.

[46] Pan X, Zhang X, Zhao P, Rostami-Hodjegan A. Physiologically based pharmacokinetic modeling in pregnancy: Advances and applications in precision dosing. Clin Pharmacokinet. 2021;60(6): 723–741.

[47] Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, Yang CC, et al. Carbamazepine-induced toxic effects and HLA-B*15:02 screening in Taiwan. N Engl J Med. 2011; 364:1126–1133.