PERINATAL MEDICATION USE: Considerations for Health Care Providers

CAMT
Coalition to Advance Maternal Therapeutics

There are more than 5.5 million pregnancies and more than 3.5 million births in the United States every year.[1] More than 90% of women take medication during some point in pregnancy, whether it is prescription or over-the-counter drugs,[2] and more than 50% of postpartum women require at least one medication, including those who are breastfeeding.[3] Yet, of the 213 drugs approved by the U.S. Food and Drug Administration (FDA) from 2003 to 2012, just 5% contained human data in their pregnancy section and almost half did not contain information about medication use for lactating women.[4] Limited data on the perinatal safety and efficacy of medications creates challenges for women, their families, and health care providers who are striving to achieve optimal outcomes for both mother and baby.

While efforts are being made to improve the representation of pregnant and lactating populations in research—and thus, enhance the evidence base surrounding medication use—there are steps that health care providers can currently take when considering a medication regimen for patients who are planning to become pregnant, pregnant, or lactating.

Perinatal Counseling

Preconception Counseling

Preconception counseling is a series of conversations that should involve risk assessment, including medical and family history, interventions to reduce the risk of perinatal transmission of disease, and ways to optimize long-term health for both mother and baby.

TOPICS THAT MAY BE ADDRESSED IN PRECONCEPTION COUNSELING	
Lifestyle Modifications	• Dietary recommendations • Exercise guidelines • Healthy weight obtainment • Stress management techniques • Smoking, alcohol, and substance abuse resources
Medication Management	• Explore risks vs. benefits of medication use • Medication adherence and follow up • Vitamin recommendations • Medication's potential impact on pregnancy (e.g., for mediations that can cause fetal anomalies may need to be stopped months prior to conception)
Pre-Existing Condition Management	• Seeking appropriate specialists • Assessments and screenings • Optimal pregnancy timing • Setting and managing expectations

1 Births: Final Data for 2022 (April 2024). National Vital Statistics Report, Volume 73, Number 2. https://www.cdc.gov/nchs/data/nvsr/nvsr73/nvsr73-02.pdf
2 Sachdeva P, Patel BG, Patel BK. Drug use in pregnancy; a point to ponder! Indian J Pharm Sci. 2009 Jan;71(1):1-7. doi: 10.4103/0250-474X.51941. PMID: 20177448; PMCID: PMC2810038.
3 Saha MR, Ryan K, Amir LH. Postpartum women's use of medicines and breastfeeding practices: a systematic review. Int Breastfeed J. 2015 Oct 28;10:28. doi: 10.1186/s13006-015-0053-6. PMID: 26516340; PMCID: PMC4625926.
4 Moore K L, Persaud T VN, Torchia M G.The Developing Human: Clinically Oriented Embryology10th ed.Philadelphia, PA: Elsevier; 2015

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Prenatal Counseling

For low-risk pregnancies, the current model for prenatal care includes 12-14 obstetric visits over the span of a 40-week pregnancy. This involves visits every 4 weeks until 28 weeks, then visits every 2 weeks until 36 weeks, and weekly visits thereafter. These visits allow for obstetric providers to monitor the health and growth of mother and baby, manage the health of the mother, and treat any issues that may arise as soon as possible. They can also serve as anticipatory checkpoints for the rest of a pregnant patient's health care team.

For pregnant individuals who develop a condition during pregnancy or who had an existing chronic health condition prior to becoming pregnant, health care providers can support patients by helping to coordinate care across the mother's health care team. A multidisciplinary, collaborative approach to care can optimize medication use and improve outcomes.

Postpartum Counseling

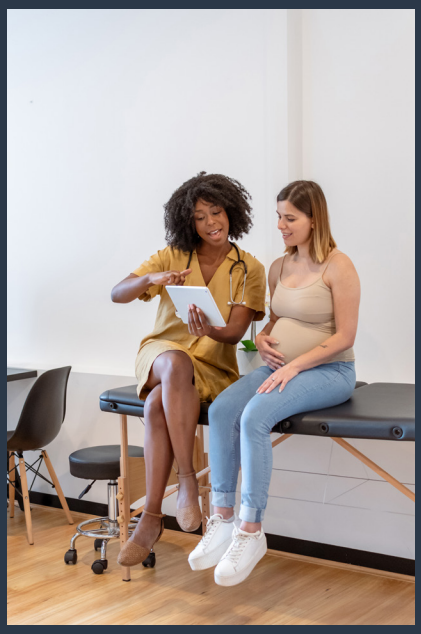
While the World Health Organization and the American Academy of Pediatrics recommend exclusively breastfeeding infants for the first six months of life, there are considerations that mothers—particularly those with chronic health conditions—and their health care providers must weigh when it comes to making the decision about whether to breastfeed. Some of these considerations may include:

- Patient's lactation goals
- Patient's health following delivery
- How breastfeeding might affect any pre-existing health conditions
- Evidence-based risks and benefits surrounding the proposed medication use while breastfeeding

A study of rheumatoid arthritis patients[5] suggests that breastfeeding for the first time could be a cause of an arthritic flare.

Engaging in Conversations with Patients

Discussing medication use before, during, and after pregnancy can be sensitive, given safety concerns, lack of clear guidance, possible risks, or fear of judgment. Health care providers navigating these conversations with patients may wish to implement the following strategies:



- Ensure that resources being provided are written in a way that is easy for the patient and their family to understand
- Repeat information consistently and sensitively, since mothers are getting information from multiple sources
- Build trust so that advice holds weight amongst social advice and external conversations
- Acknowledge concerns and fears
- Discuss risks and benefits of medications comprehensively
- Involve the patient in the decision-making process and respect their preferences
- Consult with specialists, including maternal-fetal medicine specialists, and build consensus amongst clinicians and patient if necessary to support decision-making
- Encourage the patient to seek peer and/or community support from condition-specific advocacy groups to support their health journey

5 Barrett JH, Brennan P, Fiddler M, Silman A. Breast-feeding and postpartum relapse in women with rheumatoid and inflammatory arthritis. Arthritis Rheum. 2000 May;43(5):1010-5. doi: 10.1002/1529-0131(200005)43:5<1010::AID-ANR8>3.0.CO;2-O. PMID: 10817553.

Medication Understanding and Review

Given the paucity of research on specific medications in pregnant and lactating populations, it is critical for health care providers to understand how different drugs may interact with the placenta and how drugs interact with one another to promote positive health outcomes.

Nutrients, as well as clinical compounds in drugs, can transfer across the placenta in four ways – simple diffusion, facilitated diffusion, pinocytosis, and active transport – depending on the physical properties of the placental membrane and on the pharmacological properties of the drug.[6,7] Factors that may affect how much a drug transmits across the placental membrane include:

- **Weight**. Drugs less than 500 g/mol can typically move freely across the placental membrane, whereas those 500-1000 g/mol cross the membrane incompletely or less easily, and those >1000 g/mol do not cross it.[8]
- **Electrical Charge**. Ionized drugs do not cross the placenta as easily as nonionized drugs.[9]
- **Lipid Solubility**. Lipid-soluble drugs (<500Da) tend to cross the placenta more easily.[10]
- **Protein Binding**. Drugs associated with protein complexes experience slower transfer to the fetus, whereas unbound drugs are better able to cross and quickly bind to fetal protein targets. In such cases, drugs that bind to fetal proteins can prolong fetal exposure.[11]
- **Acidity**. Drugs with a pKa >7.4 are associated with less placental transfer, whereas drugs with a pKa near 7.4 are associated with higher placental transfer.[12]

6 Sheffield JS, Siegel D, Mirochnick M, Heine RP, Nguyen C, Bergman KL, Savic RM, Long J, Dooley KE, Nesin M. Designing drug trials: considerations for pregnant women. Clin Infect Dis. 2014 Dec 15;59 Suppl 7(Suppl 7):S437-44. doi: 10.1093/cid/ciu709. PMID: 25425722; PMCID: PMC4303056.

7 Griffiths SK, Campbell JP. Placental structure, function and drug transfer. Contin Educ Anaesth Crit Care Pain. 2015;15(2):84-89. doi: 10.1093/bjaceaccp/mku013.

8 Kraemer K. Placental transfer of drugs. Neonatal Netw. 1997 Mar;16(2):65-7. PMID: 9087012.

9 Sheffield JS, Siegel D, Mirochnick M, Phillips RH, Nguyen C, et al. Designing Drug Trials: Considerations for Pregnant Women, *Clinical Infectious Diseases*, Volume 59, Issue suppl_7, December 2014, Pages S437–S444, https://doi.org/10.1093/cid/ciu709

10 Winters E. Placental drug transfer: determinants. Open Anesthesia. 2020 June 3. https://www.openanesthesia.org/keywords/placental-drug-transfer-determinants/. Accessed 2024 June 5.

11 Garland M. Pharmacology of drug transfer across the placenta. Obstet Gynecol Clin North Am. 1998;25(1):21-42. doi: 10.1016/S0889-8545(05)70356-9.

12 Pharmacology of the Placenta. Open Anesthesia. 2013 March 3. https://www.openanesthesia.org/keywords/pharmacology-of-the-placenta/. Accessed 2024 June 5.

Perinatal Pharmacology Resources for Health Care Providers

Health care providers may not always have easy access to someone with expertise in maternal-fetal medicine to ask questions about the existing evidence base on medications for pregnant or lactating patients. In these cases, health care providers can consult the following resources:

SOURCE	DESCRIPTION *Pulled from respective websites, where applicable*
Drugs and Lactation Database (LactMed®)	The LactMed® database contains information on drugs and other chemicals to which breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant. Suggested therapeutic alternatives to those drugs are provided, where appropriate. All data are derived from the scientific literature and fully referenced. A peer review panel reviews the data to assure scientific validity and currency. ▸ **For more information visit:** https://www.ncbi.nlm.nih.gov/books/NBK501922/
MotherToBaby® Fact Sheets	MotherToBaby, a service of the non-profit Organization of Teratology Information Specialists (OTIS), is the nation's leading authority and most trusted source of evidence-based information on the benefit or risk of medications and other exposures during pregnancy and while breastfeeding. MotherToBaby's Fact Sheets answer frequently asked questions about many common exposures during pregnancy and breastfeeding, including medications, recreational substances, cosmetic treatments, health conditions, infections, vaccines, and more. ▸ **For more information visit:** https://mothertobaby.org/fact-sheets/
Prescribing Information/ Package Inserts	Package inserts contain important information about medications or medical devices, including Highlights of Prescribing Information, Table of Contents, and the Full Prescribing Information about the specific drug. ▸ **More information can be found at** Drugs@FDA database or DailyMed, or can appear as a printed version that is included in the medication packet form the pharmaceutical company
REPROTOX®	REPROTOX® contains summaries on the effects of medications, chemicals, infections, and physical agents on pregnancy, reproduction, and development. The REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. ▸ **For more information, visit:** https://reprotox.org/
U.S. Food and Drug Administration (FDA) Medication Guides	A Medication Guide is patient labeling that is part of the FDA-approved prescription drug labeling for certain prescription drugs when the FDA determines that: patient labeling could help prevent serious adverse reactions; the drug has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product; or patient adherence to directions for use is crucial to the drug's effectiveness. ▸ **For more information visit:** https://dps.fda.gov/medguide

*Note: These resources do not typically include information on drug-drug interactions. Some drug combinations lead to increased teratogenic effects. For information about potential drug-drug interactions, consult your health care provider.

Engaging Patients to Improve Research Base

According to the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), "The pace of research across all types and methods has not been sufficient to ensure that pregnant women and lactating women and their providers have enough scientific evidence for well-informed clinical decisions."[13] To ensure the inclusion of these populations in clinical trials, thereby informing subsequent health decision-making, health care providers can equip themselves with information about resources and ongoing studies that are enrolling these populations in order to provide informed counsel to pregnant and lactating patients.

13 National Institute of Child Health and Human Development (NICHD). Report of the Pregnancy and Neonatal Loss Awareness Committee (PRGLAC). Bethesda (MD): NICHD; 2018 Sep. Available from: https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf

Recommendations for health care providers include the following:

- **Familiarize yourself with federal agency communications related to pregnancy, breastfeeding, and lactation**. Several federal agencies have reports and resources to assist health care providers in learning about medical conditions and health issues as they relate to pregnancy. For example, AHRQ's Effective Health Care Program provides comprehensive, science-based information on drugs, devices, and more, and has several reports related to pregnancy.
- **Make note of studies enrolling pregnant and lactating patients through pregnancy registries and clinicaltrials.gov**. Pregnancy exposure registries collect health information on exposure to medical products and vaccines during pregnancy. The FDA Office of Women's Health has compiled an online list of registries.
- **Encourage pregnant and lactating patients to enroll in studies**. Having pregnant and lactating individuals voluntarily participate in observational and/or pharmacokinetic studies will promote the collection of invaluable information to improve outcomes for these populations for generations to come. Opportunities might be available to anyone who is taking medications during pregnancy – whether from a pre-existing health condition or one that develops during pregnancy.

Federal Agency Resources on Medication Use for Pregnant and Lactating Populations

- **Agency for Healthcare Research and Quality (AHRQ)**
  - Effective Health Care Program
- **Centers for Disease Control and Prevention (CDC)**
  - Medicine and Pregnancy: An Overview
- **Department of Health and Human Services (HHS)**
  - Pregnancy and Medicines
- **Department of Veterans Affairs (VA)**
  - Maternity Care
  - Pre-Pregnancy Health
- **Food and Drug Administration (FDA)**
  - Index to Drug-Specific Information
  - List of Pregnancy Exposure Registries
  - Pregnancy and Lactation Labeling Final Rule
  - Pregnancy and Lactation Medication Information for the Healthcare Provider
- **National Institutes of Health (NIH)**
  - Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub
  - Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) and PRGLAC Implementation Working Group

Additional Resources and Information

Population-Based Surveillance and National Registries

- ClinicalTrials.gov
- List of Pregnancy Exposure Registries | FDA Office of Women's Health
- Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)

Informational Resources and Guidance Documents

- Clinical Lactation Studies: Guidance for Industry (May 2019) | FDA
- Developing a Framework to Address Legal, Ethical, Regulatory, and Policy Issues for Research Specific to Pregnant and Lactating Persons | NASEM
- Postapproval Pregnancy Safety Studies: Guidance for Industry (May 2019) | FDA
- Pregnancy and Lactating Labeling Rule (PLLR) Guidelines
- Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials (April 2018) | FDA

Obstetric and Professional Organizations

- American College of Nurse-Midwives
- American College of Obstetricians and Gynecologists (ACOG)
- Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)
- National Association of Nurse Practitioners in Women's Health
- Society for Maternal-Fetal Medicine (SMFM)

This resource was developed from materials and discussions from the Perinatal Patient Engagement Forum of the Coalition to Advance Maternal Therapeutics, held in April 2024.