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# Clinical Opinion Clinical Management of Medications in Pregnancy and Lactation

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## Abstract

Prescription and over the counter medication use during pregnancy and lactation is exceedingly common. There are many available resources to gather information and guide patient counseling. These include primary literature, online resources, professional society recommendations, and the drug label. One must consider both disease and drug characteristics when making decisions on medication use during pregnancy and lactation. Providers can then use this information to balance the risks of fetal or neonatal exposure against the potential benefits of maternal treatment and the risks of untreated disease.

### Keywords

medications in pregnancy; medications in lactation; psychiatric medications in pregnancy

An estimated 94% of women use at least one medication while pregnant or lactating, with nearly 70% taking a medication in the first trimester of pregnancy during organogenesis.[1] Many of these medications have not been adequately studied in human pregnancy and have an undetermined risk for birth defects or adverse fetal outcomes.[2] As the prevalence of medication use continues to rise, clinicians in obstetrics and primary care alike face a significant challenge to appropriately counsel patients on the safety and implications of medication use during pregnancy and in the postpartum period.

The importance of this topic was highlighted in a recent workshop on medications in pregnancy and lactation that included representatives from the Society for Maternal-Fetal Medicine (SMFM), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG). This workshop was held

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concurrently with the annual meeting of SMFM in San Diego, California, on February 3-4, 2015.

The purpose of this document is to highlight our suggested best available resources and to provide a clinical approach for decisions regarding medication use during pregnancy and lactation. This approach incorporates knowledge about the patient's disease and its impact on pregnancy both treated and untreated, efficacy and safety of treatment options, and potential impact of pregnancy on those treatments.

As framework for this discussion, imagine receiving a phone call from a long time patient. She is 30 years old and has a long standing history of depression that has recently been well controlled on citalopram and she has just had a positive pregnancy test. The patient wonders if she should stop taking the citalopram. This situation is exceedingly common, as nearly one third of all pregnant patients are exposed to psychotropic medications.[3] It presents the primary dilemma clinicians face regarding medication use during pregnancy and lactation: the need to balance the risks of fetal or neonatal exposure against the potential benefits of maternal treatment and the risks of untreated disease. Decisions regarding medication cessation, continuation, or dosage adjustments must be shared and can require a multidisciplinary team to design a treatment plan. [4] For psychotropic medications, this typically involves the patient, provider, mental health provider, pediatrician, and available community support services. The case presented here is an example for discussion of available sources of information, but the information discussed could be considered for all medications used during pregnancy and lactation.

## Information on Medication Safety

There are several resources available to providers to evaluate medication safety. We will discuss some of the available electronic resources, the usage and limitations of the drug label, as well as resources available from ACOG and AAP to provide information about medications. Additional electronic resources available as applications for the iphone or android phone as well as additional telephone based resources can be seen in table 1.

Primary literature is often a good place to begin the evaluation of any medication used in pregnancy and lactation. This is most commonly accessed via MEDLINE, which is maintained by the National Library of Medicine and is typically searched via PubMed or other platforms, including Ovid, ProQuest, Embase, and Web of Science. Such searches can be limited to human data, clinical trials, or meta-analyses to narrow the scope of the search. Although the method of narrowing a search depends on the platform used, generally, one can customize a search by limiting the species to humans and the article types to those suggested above. In PubMed, these customizable options appear on the left side of the search screen. There are cases where the data is less mature in the primary literature and the need for research is ongoing and this usually becomes evident by performing a search of MEDLINE.

Providers may also consider the use of available online databases with information regarding medication use during pregnancy. One such source is REPROTOX, an online database of summaries regarding drugs and known toxic effects, which is owned by a non-profit

foundation and accessible at www.reprotox.org. [5] Individual and institutional group subscriptions are available at a nominal fee, and are generally free for those in training. REPROTOX provides a brief summary of the available primary literature on a medication, and then provides details on available animal and human studies with citations. It also provides details regarding the impact of medication use during lactation for most agents.

For more detailed information on medication use during lactation, providers can access LactMed at http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm. LactMed is a peer reviewed, free database that is maintained by the National Library of Medicine and updated monthly. It provides information on medications that may be used during lactation, drug levels in breast milk and infant blood, and reviews possible adverse effects in nursing infants.[6] Additionally, LactMed reviews the drug effect on milk supply and lactation success. LactMed suggests therapeutic alternatives to drugs that may be harmful and provides summaries, details, and citations of available studies on medications.

Another source of information on medication safety is the drug label. Since 1979, the US Food and Drug Administration (FDA) has provided regulation for drug labeling for pregnancy and lactation, with the use of a categorical system to guide health care providers regarding the risks and benefits of medications.[7] The system consists of five letter categories (A,B,C,D, and X), which designate drugs as ranging from no evidence of risk demonstrated by adequate and well-controlled studies (A) to animal and human studies showing clear evidence of fetal risk with the risk of drug use outweighing any possible benefit (X). There is a long history of criticism of the drug labeling system based on the absence of information on the nature, severity, timing, incidence and treatability of fetal injury, as well as the inclusion of drugs with a wide range of risks in the same category.[7]

In part due to these concerns, the FDA passed a rule for new labeling requirements starting July 1, 2015. [8] The new label removes the letter-based system and provides information about medications regarding patients in three categories: pregnancy, lactation, and females and males of reproductive potential. The label will provide general information, including contact information for a pregnancy registry where available, followed by a fetal risk summary, which details the likelihood that drugs increase the risk of developmental abnormalities. The label also provides specific clinical considerations, including effects of dose, timing, and duration of exposure as well as data from human and animal studies.[9] The label will provide details of any clinical trials and postmarketing data available. The FDA will phase out the old category system. New medications approved after June 2015 are not assigned a safety category, and drugs previously approved after June 30, 2001 have 3 years to submit updated labeling information. Overall, these changes are designed to give information beyond just the category of drug. The new label should encourage providers to use a range of information combined with considerations of risks, benefits, and patient specific counseling to make decisions regarding medication usage.

There are also resources available from ACOG and the AAP regarding medications in pregnancy and lactation. ACOG has several publications which are available to members via www.acog.org, and are otherwise available via MEDLINE. For instance, there are practice bulletins and committee opinions addressing the use of psychiatric, diabetic, analgesic,

asthma, thyroid, antihypertensive and antiemetic medications during pregnancy. These documents provide not only the rationale for using certain drugs and an assessment of the safety data but also a recommendation about use in pregnancy. The AAP recommends the use of the LactMed resource and routinely publishes clinical reports on the transfer of medications into human breast milk. The most recent publication includes information on antidepressants, anxiolytics, antipsychotics, drugs for smoking cessation and substance abuse, diagnostic imaging, vaccines, and herbal products used during lactation. The AAP publications are available via the AAP website or MEDLINE.

## Addressing Safety for our Case

In regards to the clinical scenario of advising a patient on citalopram use during early pregnancy, we turn first to the primary literature. After selective serotonin reuptake inhibitors (SSRIs) were introduced, a prospective, controlled, multi-center study showed no increase in teratogenesis or congenital anomalies.[10] Subsequent large epidemiologic studies found no evidence of increased risk of birth defects from SSRI exposure. [11, 12] A metaanalysis of nine cohort studies suggested an association with a self-limited neonatal behavioral syndrome when SSRIs, are used in the last trimester of pregnancy, and found that this syndrome can be generally managed with supportive care. [13] A large, case control study suggested the association of SSRIs with persistent pulmonary hypertension of the newborn (PPHN).[14] However, an even larger, subsequent nested cohort study showed that the absolute risk of PPHN was small and that PPHN is rare, usually self-limited and typically successfully treated. [15] Finally, there had been controversy regarding SSRI use and increased risk for congenital cardiac defects. A large, nested cohort study containing nearly 1 million pregnant women in the US found no substantial increased risk of cardiac malformations in patients using SSRIs.[16] In addition to these large studies which included several SSRIs, a prospective case-control study found no evidence of teratogenicity with citalopram. One pharmacokinetics study found very low serum concentrations of citalopram in lactating infants suggesting no safety concerns for breastfed neonates.[17, 18]

When searching online sources for information, REPROTOX confirms the primary literature findings that citalopram does not increase congenital anomalies. REPROTOX mentions a mild, transient poor neonatal adaptation syndrome with central nervous system effects and states that citalopram has been associated with the risks of PPHN in some, but not all, studies. Overall, REPROTOX concludes that the incidence and severity of any neonatal adverse effects is low and women should not avoid citalopram if it is otherwise indicated.[19] LactMed states that low levels of citalopram are detectable in the breastmilk, with small amounts ingested by the infant, and occasionally low levels are detectable in neonatal serum. It concludes that if the mother was taking citalopram during pregnancy, it should be continued while breastfeeding.[20]

The ACOG practice bulletin on psychotropic medications in pregnancy reports that there are no confirmed birth defects associated with citalopram, and conflicting data regarding a small increase in risk of cardiac defects, particularly ventricular septal defects. ACOG points out that these studies are confounded by ascertainment bias and likely retrospective overestimation of exposure, which results in overestimated risk.[3] Additionally, ACOG

comments on the decreased serum concentrations of SSRIs during pregnancy which may affect dosing, mentions the risk of neonatal withdrawal syndrome, and states that citalopram is moderately safe for use during lactation. [3] AAP reports that there are low concentrations of citalopram in human milk, with relative infant doses reported to be low, although found in some studies to be ~10% of maternal serum concentration. The AAP comments that the long-term effects on developing infants of maternal citalopram use during lactation are understudied. [21]

In summary, the information obtained from primary literature, online sources, ACOG and AAP about citalopram suggests that citalopram has been studied and that it is relatively safe. However, the information about citalopram from these various sources highlights the challenges facing providers when gathering and interpreting information on most medications used in pregnancy and lactation. An additional challenge facing providers will be the time it takes to acquire this information in the context of a busy clinical setting. While many of the above resources may be accessed fairly quickly, for some patients with complex medical problems and medications, a referral for maternal and fetal medicine consultation may be appropriate.

## Considerations in Disease Treatment and Drug Choice

In addition to evaluating available information about drugs, providers consider both disease and drug characteristics when advising patients on initiation, continuation, discontinuation or modification of dosing of medications used during pregnancy and lactation.

In some cases, the most important consideration is the disease being treated, and one must consider the risk to the pregnancy of untreated disease balanced against the risks, or theoretical risks, of the medication. The disease process must also be considered in interpreting outcomes of medication studies: in many cases the disease being treated confounds outcomes attributed to medication use. In the case of depression, providers must consider the risks of untreated disease. Uncontrolled depression is associated with increased risks of spontaneous pregnancy loss, preterm birth, and low birth weight.[22] Women who discontinue antidepressants “cold turkey” out of concern for teratogenic effects have higher rates of morbidity and hospitalization, and such discontinuation can lead to suicidal ideation or even maternal death.[22] The provider must balance these risks against the risks of the drug. For citalopram, these are essentially 1) the rare risk of persistent pulmonary hypertension, which is usually self-limited and successfully treated, 2) the very small risk of the self-limited neonatal adaptation syndrome, which is higher with exposure late in pregnancy, and 3) the unknown and theoretic risk of long-term neurodevelopmental effects, for which studies are limited and confounded by effects on the neonate of maternal depression.[13-15, 21, 22]

Additionally, the characteristics of the medication being used and other drug characteristics affecting dosing and metabolism during pregnancy and lactation must be considered. General information regarding pharmacokinetics of particular medications may be found in many of the resources listed above, with more detailed discussion of pharmacokinetics available in other sources.[23] The increase in hepatic enzymes during pregnancy that

metabolize citalopram may necessitate higher doses later in pregnancy, although the flat dose response curves of SSRIs suggest lower levels may not abruptly lower efficacy.[22] The patient should be monitored for symptom changes as pregnancy progresses. Because all SSRIs have low molecular weight, they all cross into the breast milk to some degree. The relative infant dose is unknown, but unlikely to cause adverse effects.[4, 18, 21] The potential effect of decreased bonding if maternal depression worsens as well as the benefits of breastfeeding outweigh the risks of SSRI use for the infant during breastfeeding.

In applying all of these characteristics to the patient taking citalopram, the potential benefits of citalopram use in terms of treatment of depression far outweigh the drug related risks, and a reasonable recommendation would be to continue. Of the SSRIs, citalopram is preferred both because of its relatively low risk profile, because it is highly effective, and because the patient is already taking it.[4]

Finally, a recent review from the US showed that over half of pregnant women use four or more medications during pregnancy, with many using over the counter or herbal medications for which there is limited pregnancy information. [1, 24] Although not mentioned in our case, counseling patients regarding polypharmacy and the use of over the counter medications is a significant challenge facing providers. In general, providers should work with patients and other prescribers to attempt to limit the overall number of medications used to the minimum necessary to control symptoms. This is frequently an issue with psychotropic medications and antihypertensive medications, and consult with the patient's other providers or specialist may be necessary.[24] Regarding over the counter medications, they are most commonly taken during pregnancy and lactation for analgesia, allergy, respiratory, gastrointestinal or skin conditions. [25] There is limited data available on some of these drugs and medications such as acetaminophen, loratadine, famotidine, and diphenhydramine. Although they are generally considered safe for pregnancy and lactation, the long term effects as well as effects of various drug combinations is unknown.[25] Therefore, providers should consider each medication using the resources suggested above in the context of the drug's effectiveness, and do so for both prescription and over-the-counter medications. There is a continued need for research regarding both polypharmacy and over the counter medication use during pregnancy and lactation.

## Conclusion

Our patient's question of whether to discontinue her SSRI during pregnancy is one that patients and their providers face daily. There are a number of resources available to guide decision-making. When approaching clinical decision making regarding both over the counter and prescription medications in pregnancy and lactation, a dedicated discussion about the safety of medications in the context of the disease being treated is optimal. These discussions ideally consider the impact of untreated disease on pregnancy as well as the possible limitations of the available data for many medications. Patients using newer medications with little safety data, medications associated with known risk, or combinations of medications may benefit from maternal-fetal medicine consultation or referral for genetic counseling to explore the complex risk-benefit profile and arrive at a recommendation for an individual patient.

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## Table 1

Selected Telephone Resources and Selected iphone and android applications for information on medications in pregnancy and lactation

| Resource | How to Access | Fees Associated/Availability | Features |
|---|---|---|---|
| **Select Telephone Resources** | | | |
| Infant Risk Center | 1-806-352-2519 www.infantrisk.com | Free/M-F 8 am-5pm CST | • Provided by Texas Tech University Institute for Women's Health<br>• Provides accurate, up to date information regarding medications and other exposures to providers and patients |
| MotherToBaby | 1-866-626-OTIS www.mothertobaby.org | Free, Hours vary by State | • Provided by the Organization of Teratology Information Specialist<br>• Provides evidence based information on medications and other exposures<br>• Provides information about pregnancy registries and ongoing medication studies<br>• National Call center routes to state based centers |
| **Select iPhone and Android Applications** | | | |
| InfantRisk Center | www.infantrisk.com | Application is $9.99 | • Provided by Texas Tech University Institute for Women's Health<br>• Provides information on prescription drugs, vitamins and supplements, and non-prescription drugs<br>• Application designed for patients, MommyMeds, also available for $3.99, with feature to scan product barcodes to gain information |
| REPROTOX | www.reprotox.org | Application is free, requires individual and institutional subscriptions available at a nominal fee, free for those in training | • Provides quick overview<br>• Provides summary of primary literature, details on available animal and human studies |
| LactMed | http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm | Application is free | • Peer reviewed, maintained by National Library of Medicine<br>• Information about maternal and infant drug levels, effects on lacation and breast fed infants, and alternative drugs to consider |