HHS Public Access

Author manuscript

Clin Pharmacol Ther. Author manuscript; available in PMC 2020 March 17.

Published in final edited form as:

Clin Pharmacol Ther. 2009 October ; 86(4): 362–365. doi:10.1038/clpt.2009.160.

Pharmacotherapy for Depressed Pregnant Women: Overcoming Obstacles to Gathering Essential Data

KL Wisner[1,2], **PS Appelbaum**[3], **K Uhl**[4], **SF Goldkind**[5]

[1]Departments of Psychiatry, Obstetrics, Gynecology and Reproductive Sciences, Epidemiology, and Women's Studies, Pittsburgh, Pennsylvania, USA;

[2]Women's Behavioral HealthCARE, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA;

[3]Division of Law, Ethics, and Psychiatry, Department of Psychiatry, Columbia University and New York State Psychiatric Institute, New York, New York, USA;

[4]Office of Women's Health, US Food and Drug Administration, Rockville, Maryland, USA;

[5]Good Clinical Practice Program, Office of the Commissioner, US Food and Drug Administration, Rockville, Maryland, USA.

Abstract

Approximately 3% of pregnant women take antidepressant medications. information on the impact of antidepressants on short- and long-term maternal and offspring outcomes is highly desirable but neglected. The position that the dearth of treatment information is of greater concern than the risks to pregnant subjects involved in medical research is gaining support. Mandating the collection of reproductive outcome data in exposed childbearing women is an overdue step toward societal responsibility to our most vulnerable members.

Major depressive disorder (MDD) accounts for more than 15% of the disease burden in established economies and is second only to ischemic heart disease. Although depression is the leading cause of disability for women throughout the world, it (with other mental disorders) continues to be associated with stigma in our society. Stigma contributes to the perception that antidepressant drug therapy is less justifiable for pregnant women with depression than, for example, antibiotics or drugs used to treat gastric ailments.[1] Although nondrug treatments for major depression exist, no single treatment is uniformly acceptable or efficacious in every depressed woman. In fact, for many pregnant women the availability of accessible and affordable mental health intervention of any type is limited.

The peak prevalence of MDD in women is during the childbearing years, and approximately 3% of pregnant women are exposed to antidepressant medications. Of 4 million infants born in the United States, nearly 100,000 are exposed prenatally to selective serotonin reuptake

Correspondence: KL Wisner (wisnerkl@upmc.edu).

CONFLICT OF INTEREST

K.L.W. has received a donation of estradiol and placebo transdermal patches from Novogyne for a randomized clinical trial supported by the National Institute of Mental Health. The other authors declared no conflict of interest.

inhibitors (SSRIs). Ideally, all pregnancies would be free of exposure to any potential toxicity, including medications; however, this ideal is rarely realized. Nearly two-thirds of women take at least one prescription drug during pregnancy, and many take multiple medications.

The SSRI antidepressants have been available in the United States since the release of fluoxetine more than 20 years ago. Accumulating information to scaffold the risk–benefit decision-making process has been a lengthy process involving a largely uncoordinated sequence of studies with increasingly complex designs (Table 1). The types of reproductive outcomes investigated in these studies have also evolved over time. Initial reports focused on possible associations between the drug and birth defects, with subsequent studies targeting the impact of the drug on fetal growth, preterm birth risk, and neonatal adaptation and behavior. A robust understanding of the impact of antidepressant pharmacotherapy on short- and long-term maternal, fetal, neonatal, and pediatric outcomes is highly desirable but, unfortunately (and surprisingly), neglected in our current research environment.

The constantly evolving landscape of information about antidepressant drug exposure creates a complex decisional challenge for the individual woman, the prescribing physician, and, at some level, society. Population-level data about the risks of drug exposure must be individualized to determine a pregnant woman's valuation of the acceptable degree of risk compared with the anticipated benefit of drug treatment. Estimates of risk must be derived from populations; however, a patient (and her physician) desire to ascertain that particular woman's risk. For example, if the risk of preterm birth in women who take SSRIs continuously during pregnancy is 23% (ref. 2), a woman will want to know whether her infant will be among that 23%—which is not knowable. The strategic plan developed by the National Institute of Mental Health prioritizes investigations to personalize psychiatric treatment through identification of factors associated with response (or adverse events, such as adverse reproductive outcomes) among individuals in a population.

Depression is associated with physiological alterations and psychosocial sequelae that have the potential to adversely impact pregnancy outcomes independent of drug exposure.[2] Understudied, but fundamental, is whether depression during pregnancy is responsive to antidepressant pharmacotherapy. Some investigators have reported that pregnant women treated with antidepressants have levels of depressive symptoms similar to those in unmedicated depressed women, although a recent study showed the expected improvement in depressive symptoms and functional status in SSRI-treated women.[2] Additionally, even women who choose to *continue* antidepressant treatment during pregnancy have a 26% rate of relapse.[3] These disparate observations require explanation and dispute the essentially unchallenged assumption that antidepressant efficacy during pregnancy is similar to that in nongravid women.

The benefit of antidepressant treatment is reduction or elimination of exposure to the psychiatric disorder and its sequelae. Untreated antenatal depression has been associated with maternal inadequate weight gain, underutilization of health care, substance use, preeclampsia, and suicide. Antenatal depression increases the risk for preterm birth, lower birth weight, sudden infant death syndrome, and developmental delay in offspring. The

patient and physician must decide whether treatment with antidepressants yields a more favorable outcome than not treating with medication. No studies comparing antidepressants with other evidence-based treatments have been conducted during pregnancy. With minimal data to balance the risks of pharmacotherapy with the risks of unmedicated depression, decision making tends to focus on the potential for adverse effects of the drug. A frequent result is the choice by the pregnant woman to discontinue medication to avoid ongoing fetal exposure without equivalent consideration of the woman's risks related to depression recurrence. Discontinuation of antidepressants proximal to conception results in a 68% risk of rapid recurrence.[3] Finally, few studies of risk perception and risk communication that integrate the psychiatric, obstetrical, pediatric, and patient perspectives have been published.

Avoidance of enrollment of gravid women in clinical research, as well as removal of women who become pregnant after study entry, reflect well-intentioned decisions to prevent drug exposure to this vulnerable population, independent of the disease entity. However, the result of this practice is that drugs are approved and released to the general public without information about their use in pregnancy. In the clinical setting, pregnant women are subsequently exposed to medications without the benefit of rigorous data to inform their use or mandated surveillance to capture reproductive-outcome information. Because MDD is so prevalent during the childbearing years, women with this disorder are differentially affected. Stika and Fredericksen[4] wrote, "The pregnant woman is perhaps the last true therapeutic orphan. Because of the ethical, medicolegal and fetal safety concerns regarding pregnant women, few pharmacokinetic, pharmacodynamic, or clinical trials are conducted during pregnancy."

The research and regulatory communities currently do not require inclusion of pregnant women in drug studies, even for conditions that are prevalent in pregnancy. A factor sustaining this situation is that no one person or entity is "responsible" (and therefore liability is unlikely to be imposed) if a woman "accidentally" becomes pregnant during treatment after the newly released drug is prescribed. However, fear of liability is pervasive when deliberate inclusion of pregnant women in research is contemplated.

Information about the impact of antidepressant pharmacotherapy on reproductive outcomes is crucial to optimal antenatal care, as are data on potential changes in dose requirements related to substantial metabolic changes across gestation. Alterations in maternal physiology affect drug absorption, distribution, metabolism, and excretion, which impact the pharmacokinetic and pharmacodynamic characteristics of the agent. The need for such studies in pregnant women is no less than for other subjects with altered physiological states (such as hepatic disease) and special populations (such children and the elderly), and a guidance document has been issued by the US Food and Drug Administration (FDA) (http://www.fda.gov/downloads/Drugs/GuidanceComplicanceRegulatory-Information/Guidances/ucm072133.pdf). In clinical practice, dosing requirements for nonpregnant individuals are used to direct the care of childbearing women. For antidepressants, specifically the tricyclics and SSRIs, the need for increased dose requirements across gestation has been demonstrated.

Returning to the query implicit in this article's title, can we overcome the obstacles to obtaining the data essential for optimizing treatment for depressed pregnant women? It is unlikely that a pharmaceutical company will conduct trials with pregnant women after an agent achieves FDA approval unless it is required to do so, and even less likely that such data will be collected before FDA approval. Congress recently empowered the FDA through legislative authority under the FDA Amendments Act (FDAAA) of 2007 to require (i) postmarketing studies to obtain data in vulnerable and understudied populations (which could be interpreted to include pregnant women) and (ii) adverse event–related labeling changes. In addition, the FDAAA mandates the establishment of databases that can subsequently be mined for drug-associated adverse-event rates. The goal is to collect information on tens of millions of patients within the next few years. Because of the prevalence of psychiatric disorders in childbearing-aged women, depressed gravid women are likely to be captured in this database, which has the potential to advance our understanding of the benefits and risks of pharmacotherapy with antidepressants during pregnancy.

Recent policy proposals provide additional hope for new knowledge to guide the pharmacological treatment of pregnant women. The FDA has proposed labeling changes for drug use in pregnancy and lactation that require regular updating of reproductive outcome data (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093307.htm) The new format will be standardized and designed to summarize teratological and clinical data to support informed drug treatment during pregnancy. Registry enrollment to enable ongoing data collection to assess a drug's impact on reproductive outcomes will be encouraged, and the FDAAA provides the authority for the FDA to mandate such studies. Others have advocated for a comprehensive teratogen surveillance system that goes beyond routine voluntary surveillance under the auspices of the FDA.[5]

The position that the absence of information (which in itself generates risks for all pregnant women and their unborn children) is of greater concern than the risks to subjects involved in research is gaining support from multiple stakeholders. Mandating the collection of reproductive outcomes in exposed childbearing women is an overdue step toward societal responsibility to our most vulnerable members.

References

1. Bonari L, Koren G, Einarson TR, Jasper JD, Taddio A & Einarson A Use of antidepressants by pregnant women: evaluation of perception of risk, efficacy of evidence based counseling and determinants of decision making. Arch. Women's Mental Health 8, 214–220 (2005).
2. Wisner K et al. Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. Am. J. Psychiatr 166, 557–556 (2009). [PubMed: 19289451]
3. Cohen L et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 295, 499–507 (2006). [PubMed: 16449615]
4. Stika C & Frederiksen M Drug therapy in pregnant and nursing women In Principles of Clinical Pharmacology (eds. Atkinson A, Daniels C, Grudzinskas C & Markey S) 227–291 (Academic Press, San Diego, CA, 2001).
5. Mitchell A Systematic identification of drugs that cause birth defects—a new opportunity. N. Engl. J. Med 349, 2556–2559 (2003). [PubMed: 14695418]

Table 1

Reproductive-outcome information sources

Study type[a]	Description
Single-case report	Women with adverse pregnancy outcomes may become subjects of case reports. Positive case reports are signals that require further study. The total number of exposures associated with the adverse outcome is unavailable; therefore, the strength of the association is unknown. Publication of case reports creates concern and avoidance of the implicated drug, which make it difficult to collect data to define the true risk.
Case series	Case series reports provide information about several women with similar patterns of adverse pregnancy outcomes. The signal is stronger, because rare exposures and rare defects are not likely to occur by chance in a small sample. This mechanism was used to identify the association of birth defects, especially limb-reduction anomalies, with thalidomide in the 1960s.
Registries	Registries require large numbers of patients, and often years, to yield information. They must include women whose exposures were documented before knowledge of pregnancy outcomes in order to provide accurate information about the ratio of adverse events to the number of exposures. Registries allow generation of a meaningful rate of adverse outcomes that can be compared with background adverse-event rates. Registries are useful for monitoring—for example, to rapidly identify or exclude a drug as a major teratogen.
Retrospective, case-control	Sample populations of patients with and without an outcome of interest (e.g., congenital cardiovascular defects) are compared for exposure to an agent suspected of being associated with the outcome (e.g., paroxetine). The exposure occurrence is derived from interviews or records. Data from cases and controls may be derived from existing population data, such as registries. These studies yield an odds ratio.
Prospective, cohort	Prospective observational studies are focused on the study of samples of exposed and nonexposed women followed prospectively to compare the rate of the outcome(s). Ideally, women not exposed (to antidepressants) are assessed for the level of activity of the underlying disease condition (depression). These studies generally require large samples and lengthy observational periods, and they are difficult to implement for rare events, such as birth defects. They yield relative risk.
Meta-analysis	A meta-analysis combines data from studies of similar design based on predetermined inclusion/exclusion rules to create a summary effect size from the resulting larger sample.

[a]These are observational studies, rather than experimental studies, because the investigator cannot specify exposure conditions, i.e., assign pregnant women to be exposed vs. not exposed to antidepressant medication.

Clin Pharmacol Ther. Author manuscript; available in PMC 2020 March 17.