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SSRI TREATMENT DURING PREGNANCY: ARE WE ASKING THE RIGHT QUESTIONS?

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The title of this article is purposefully provocative. After several decades of clinical work and research related to the treatment of depressed childbearing women, a recurring series of questions demonstrate that antidepressant use in pregnant women evokes new concerns but often old dilemmas.^[1] This article is structured around these queries, with the goal of improving their sophistication and placing them in the context of broader public health ethics and policy.

WHAT IS THE PREVALENCE OF DEPRESSION AND ANTIDEPRESSANT USE DURING PREGNANCY?

The peak prevalence of major depressive disorder (MDD) in women is during the childbearing years. Gaynes et al.^[2] estimated that the prevalence of MDD ranged from 3.1–4.9% at different times during pregnancy. For major and minor depression, the combined estimates of point prevalence ranged from 8.5–11.0%. As many as 14.5% pregnant women have a new (incident) episode of either major or minor depression. Considering only MDD, 7.5% of pregnant women have a new episode. Therefore, the treatment of gestational depression is a commonly occurring situation in clinical medicine.

From National Birth Defects Prevention Registry data, approximately 2.3% of 4 million infants ($\approx 100,000$) born in the United States are exposed to SSRI antidepressants during fetal life, and about 30% of women who are taking an SSRI at conception discontinue it before the second month of pregnancy.^[3] Ideally, all pregnancies would be free of exposure to any potential toxicity, including medication, alcohol, smoking, maternal disease, violence, or environmental toxin exposure; however, this optimal situation is rarely the case. For example, 64% of 150,000 pregnant women in the United States received a prescription for a drug other than a vitamin or mineral supplement.^[4] In women who were pregnant in the past year, 14.6% had diagnoses of substance use disorder.^[5] About half of the pregnancies in the United States are unplanned.

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Although the prevalence of depression during pregnancy is high, women are usually neither identified nor treated.^[5] Pregnant women are even less likely than nonpregnant women to receive inpatient or outpatient psychiatric treatment.^[5] Multiple barriers contribute to the lack of treatment in childbearing women, such as attribution of distress to external causes (poverty and stress), which they believe mental health services cannot ameliorate. Lack of transportation, employment with inflexible time off, inability to afford copayments, concern about breastfeeding in public, no childcare, and infants being unwelcome at mental health appointments are practical barriers. Mothers also anticipate negative ramifications of care, such as labeling and custody loss. Although depression is the leading cause of disability for women worldwide, stigma remains a treatment barrier. Many physicians avoid pharmacologic treatment of depressed pregnant women due to concern about lack of expertise or medicolegal liability. The reality for many pregnant women is that accessible and acceptable mental health intervention is very limited.^[5] A more salient question is: Given the high prevalence of gestational depression, can a disease management system be constructed and implemented to identify and successfully treat women to remission?

WHAT ARE THE RISKS OF DEPRESSIVE DISORDER DURING PREGNANCY?

MDD is associated with physiological alterations and psychosocial sequelae that adversely impact pregnancy outcomes independent of drug exposure, such as inadequate maternal weight gain, underutilization of health care, smoking, substance use, pre-eclampsia, and suicide.^[6] Gestational depression increases the risk for preterm birth, lower birth weight, sudden infant death syndrome, and developmental delay in offspring.^[6] Neonates of mothers with depression have increased irritability, less activity and attentiveness, elevated cortisol, decreased peripheral dopamine levels, and lower vagal tone compared to infants of nondepressed women.^[7] The extensive literature on postpartum depression and its impact on development indicates a range of adverse child cognitive and emotional outcomes, particularly in male offspring of depressed women. Maternal interactional style, secondary to the mood disorder and/or social adversity, is the most potent causative agent.^[8] Women who were persistently depressed in pregnancy, but not after birth, had an increased risk for children with developmental delay independent of postpartum depression; therefore, some of the impact of depression on child developmental delay is attributable to gestational depression.^[9] MDD is an adverse exposure during pregnancy. Questions that remain to be answered are: When pregnant women with MDD are treated, is the risk for adverse reproductive outcomes decreased? Which treatments result in improved reproductive outcomes and can women who are likely to benefit be identified? Are mother–infant and familial interactions favorably impacted by treatments?

WHAT ARE THE TREATMENTS FOR GESTATIONAL DEPRESSION?

The patient, psychiatrist, and obstetrician must develop a treatment plan to address the pregnant woman's depression and often comorbid psychiatric conditions. The mainstays of treatment, psychotherapy and antidepressants, rarely have been studied for efficacy during pregnancy. Interpersonal, cognitive behavioral therapy and other forms of psychotherapy are

preferred initial interventions for mild-to-moderate depression.^[7] Antidepressant therapy is perceived to be less justifiable for pregnant women with depression than antibiotics or drugs used to treat gastric ailments.^[10] However, women who discontinue their antidepressant proximal to conception have a 68% recurrence rate compared to 26% for those who continue.^[11] No single treatment is uniformly efficacious for or acceptable to every depressed woman (pregnant or not), and expansion of the therapeutic armamentarium for gestational depression (particularly nonpharmacologic options) is needed. Novel treatment data are emerging; for example, fish oil, acupuncture, bright morning light therapy, and transcranial magnetic stimulation. No randomized comparative effectiveness studies of evidence-based psychiatric treatments during pregnancy have been published. Interventions for treatment resistant depression during gestation have not been defined; however, electroconvulsive therapy is an appropriate option for severe depression.

The goal of treatment is remission of MDD and return to optimal functioning. Both psychotherapy and pharmacotherapy have been shown to result in reduced depressive symptoms and improved maternal function during pregnancy.^[7,12] If psychotherapy is not feasible, or the woman prefers pharmacotherapy, decision making tends to focus on the potential adverse effects of medication rather than the possible adverse effects of the disorder. The result often is the choice by the pregnant woman or her prescriber to avoid or stop antidepressant treatment, to obviate fetal exposure without equal consideration of the risks of MDD to both the mother and fetus. Nowhere in medicine is the need for personalization of care so crucial than during pregnancy—personalization of the intervention for depression and comorbidities; for the course, characteristics, and treatment responses of the woman's illness; for pregnancy physiology; and for her capacity to provide sustenance for the growing fetus and interactive emotional care after the baby is born. The question is: What are the components of personalized treatment for the pregnant depressed woman that inform the risk benefit decision-making process, and how are they “weighted” by women and their prescribers to arrive at a treatment course?

ARE SSRI SAFE TO USE DURING PREGNANCY?

The word *safe* has no operational definition in this context. The establishment of any exposure as harmless presents the impossible task of proving no effect on a monumental number of reproductive and developmental outcomes throughout the exposed offspring's lifespan. Studies that estimate the magnitude of a subset of reproductive risks in SSRI-treated women are available. From the population-level data, the physician must communicate the nature and probability of the risks of treatment and of disease exacerbation. The desired information is the individual woman's set of reproductive risks that are reduced by SSRI treatment (through reduced disease expression) and the set of risks that are increased. Benefits must also be described objectively; for example, the lack of certainty about the treatment response to a drug that the patient has not received earlier. The physician's task is bridging the gap between population-level numerical risk estimates and the individual woman's subjective input, such as the values she assigns to specific reproductive outcome risks and benefits.

Because of ethical concerns, pharmacologic studies of gestational MDD are observational rather than randomized trials. Therefore, confounding related to residual symptoms and functional capacity from the underlying MDD and the characteristics of women who accept versus decline medication treatment are constant methodological concerns. Examples of potential confounds include behaviors associated with depression, such as smoking, alcohol, and other substance use, which also impact reproductive outcomes. Women with continuous gestational MDD are more likely to be younger, African-American, unmarried, and less educated than SSRI-treated women.^[12] Women with continuous MDD have higher mean preconception body mass index and a higher proportion of obesity than women treated with SSRI or women without either exposure during pregnancy.^[12] Maternal obesity is associated with a small absolute increase in the risk for multiple birth defects^[13] and other complications of pregnancy.

Two landmark large-scale case-control studies^[14,15] demonstrated that overall SSRI exposure was not associated with congenital heart or the majority of other categories of birth defects. The investigators and an accompanying editorial author^[16] concluded that SSRI exposure is associated with a small absolute risk (*if any*) for major defects beyond the population-level risk for birth defects of about 3%. The convergence of such studies in identifying low levels of absolute risk has evolved for the SSRI medications,^[7] and is crucial information in making risk-benefit decisions.

Third trimester ultrasound fetal neurobehavioral studies demonstrated that fetuses exposed to SSRI had higher activity levels and an increased heart rate response to a vibroacoustic stimulus compared to nonexposed fetuses.^[17] Fetuses exposed to untreated maternal MDD had lower baseline heart rates and prolonged fetal heart rate reactivity to the stimulus. Both SSRI and maternal MDD are associated with less optimal fetal neurobehavior at the time of exposure than nonexposed fetuses.^[17] Low infant birth weight has been associated inconsistently with both SSRI treatment and MDD.^[7,12] In infants exposed continuously to either SSRI or MDD (no SSRI), the rate of preterm birth was slightly more than 20% in both groups, which was about three times that in the control group.^[12] Neonates exposed in late pregnancy have a three-fold higher risk for a transient neonatal syndrome (central nervous system, motor, and respiratory signs) that resolves within 2 weeks post-birth.^[7] The highest reported rates for neonatal syndrome after in utero exposure are for paroxetine and fluoxetine. No consensus definition for neonatal syndrome has emerged, and it has not been consistently observed following SSRI exposure or after propensity score matching for illness variables that account for depressed women electing drug treatment.^[7] A risk ratio of 6 with a low absolute risk (6–12/1,000 births) was associated with late pregnancy SSRI exposure and persistent pulmonary hypertension of the newborn. This risk ratio was lower (2.4–3.6) in a subsequent study, but no association was reported in another.^[18]

Few data about the post-birth development of individuals exposed in utero to SSRI have been published. However, all converge on the finding that mental development (on the Bayley Scales of Infant Development) is similar in exposed compared to nonexposed children. Pedersen et al.^[19] reported a slight delay (within normal limits) to achievement of motor milestones in children exposed during gestation to SSRI, and no differences were observed between the exposed and control groups at 19 months. Long-term follow-up

studies have not identified global developmental problems, but no data are available in exposed children through puberty, a major neurodevelopmental stage.

More information about drug use and disease impacts upon reproductive outcomes will always be desirable. To some extent, having data about SSRI medications is a double-edged sword in that publications that define small absolute risks (which may not be replicated as the literature evolves) create concern in patients and physicians, and are highlighted in both scientific publications and the media. The temptation is to use less well-studied or newer antidepressant agents, which may seem to be more favorable treatment choices because we are ignorant of the risks.

Gestational MDD and SSRI exposure both impact reproductive outcomes. SSRI treatment is a reasonable option for some women when balanced against the risks of depression. The goal of SSRI treatment is to improve a set of pregnancy outcomes through reduction of the sequelae of MDD but also creates risk for others. A more relevant question is: How do we individualize the decision-making process to maximize the overall pregnancy and post-birth outcomes for the mother–infant pair?

HOW CAN WE IMPROVE OUR TREATMENT OF DEPRESSED PREGNANT WOMEN?

Once the decision to treat pharmacologically has been made, the standard clinical approach to use the minimum effective dose must be used—with emphasis on *effective*. Clinicians tend to use lower doses of medications during pregnancy, which often results in exposure to both the drug and to inadequately treated MDD and its sequelae. A contribution to the 26% recurrence rate during pregnancy for antidepressant treated women^[11] may be an unrecognized need for dose increases across gestation. Alterations in maternal physiology affect drug absorption, distribution, metabolism, and excretion, which impact pharmacokinetic and pharmacodynamic characteristics of the agent. For antidepressants, specifically tricyclics and SSRIs, increased dose requirements across the latter part of gestation have been demonstrated.^[20] The need for such studies in pregnant women is similar to that of populations with altered physiologic states (such as hepatic disease), children or the elderly, and a guidance document was developed by the Food and Drug Administration (FDA) (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072133.pdf). The FDA also proposed a classification system for drugs in pregnancy and lactation to replace the current letter (A,B,C,D,X) format (<http://www.fda.gov/DrugsDevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093311.htm>). Information will be standardized and summarize teratological and clinical data to support informed drug treatment during pregnancy. Registry enrollment to support postmarketing prospective data collection to assess a drug's impact on reproductive outcomes will be encouraged.

Mental health is fundamental to health! A comprehensive screening and management program model from depression identification through intervention provision and maternal recovery has yet to be developed. Supporting women and families through treatment choices during this crucial developmental life stage is the epitome of the art of medicine.

FREE RESOURCES

Organization of Teratology Information Specialists (www.otispregnancy.org), a nonprofit organization made up of individual services throughout North America, is dedicated to providing accurate evidence-based clinical information to patients and health care professionals about exposures during pregnancy and lactation.

National Library of Medicine (<http://toxnet.nlm.nih.gov>), Developmental and Reproductive Toxicology Database, and Drugs and Lactation database.

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Biography

She also serves as an investigator at the Magee-Womens Research Institute. Dr. Wisner obtained an M.S. in Nutrition and an M.D. from Case Western Reserve University, followed by a categorical pediatric internship and general and child psychiatry residency at Children's Hospital of Pittsburgh and WPIC. She completed a post-doctoral fellow in Epidemiology at the University of Pittsburgh Graduate School of Public Health and a fellowship in Professional Ethics at Case Western Reserve University in 1996.

Dr. Wisner's research is focused on the psychiatric evaluation and treatment of women of childbearing age. She is recognized as an expert in the treatment of mood disorders during pregnancy and the postpartum period. She is the principal investigator on several National Institute of Mental Health and foundation-funded research projects. As the current President of the Marce International Society (for the understanding, prevention, and treatment of mental illness related to childbearing), Dr. Wisner is hosting a conference in October 2010 (www.marcesodety.com). She has authored more than 150 peer-reviewed articles and book chapters.

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