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Depression and SSRI Treatment During Pregnancy—Prioritizing Maternal Mental Health

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IMPORTANCE In the US, 5% to 6% of pregnant patients are treated with selective serotonin reuptake inhibitors (SSRI), primarily for major depressive disorder (MDD), which has a prevalence of about 12%. Psychiatric conditions are a leading cause of maternal morbidity and mortality. MDD is a common disorder that must be treated during pregnancy to improve outcomes for the mother, infant, family, and community.

OBSERVATIONS MDD is a complex, multifactorial brain disease arising from genetic, environmental, and epigenetic factors. Factors unique to the perinatal period are associated with additional pathophysiologic changes specific to MDD. Maternal stress and psychiatric illnesses adversely affect fetal and infant outcomes. SSRI are an essential component of perinatal mental health care. Studies that define the benefits of SSRI treatment in pregnancy are fewer than those defining risks; however, several describe adverse effects with drug discontinuation in women with moderate to severe MDD. Evaluating the safety of SSRI treatment during pregnancy has been challenging due to the potential for confounding in observational studies by the underlying indication and associated factors. Once the impact of the drug is disentangled from that of MDD and its sequelae, accumulated evidence suggests that SSRI carry little or no risk for serious adverse outcomes. The thrust of the field has shifted to prioritize treatment of MDD to optimize maternal health.

CONCLUSIONS AND RELEVANCE Meaningful advances in the treatment of perinatal MDD require coordinated attention to multiple aspects of clinical care delivery and research, informed by a perspective accounting for the health needs of 2 generations. Expanding access to care—particularly in maternity, child health, and psychiatric care deserts—is a public health imperative. A structured decision-making process facilitates the provision of balanced information on the potential maternal and fetal risks of untreated or undertreated illness, the benefits of treatment, and the risks associated with SSRI exposure.

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The US Food and Drug Administration (FDA) panel on selective serotonin reuptake inhibitors (SSRI) during pregnancy in July, 2025,[1] focused attention on pharmacotherapy for major depressive disorder (MDD). In the US, 5% to 6% of pregnant patients are treated with an SSRI,[2] most commonly for MDD, which has a prevalence of about 12%.[3] Maternal MDD is a brain disease that adversely affects maternal function and physiology. We review the effects of both MDD and SSRI treatment on pregnancy and offspring outcomes and highlight research supporting evidence-informed treatment decisions. Although large-scale nonrandomized studies have inherent constraints, the preponderance of data demonstrate that associations between SSRI treatment and most adverse pregnancy and child developmental outcomes are largely due to confounding by the effects of maternal MDD rather than SSRI exposure. We harness current evidence to focus on optimizing mental health during pregnancy and, by extension, improving developmental outcomes for children.

Pathophysiology of MDD

MDD is a multifactorial disorder arising from complex genetic, epigenetic, and environmental factors, which interact to disrupt communication in the functional connectome of the brain. The heritability of MDD is 30% to 40%. Single-nucleotide variations (formerly single-nucleotide polymorphisms) have been associated with MDD, including the serotonin transporter (*SLC6A4*) and brain-derived neurotrophic factor (BDNF) genes. *SLC6A4* is involved with serotonin reuptake, and BDNF affects neuroplasticity and neuronal survival.[4] Stressful life events (eg, early life adversity, the COVID-19 pandemic, poverty, social isolation) substantially increase the risk for MDD.[4,5] Hyperactivity of the hypothalamic-pituitary-adrenal axis stress response and disruption of its negative feedback loop and glucocorticoid receptors are characteristic of MDD. Stress responsivity is also associated with neuroactive steroids and the γ-aminobutyric acid (GABA) system.

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Investigators in neuroscience, neuroimaging, and multiomics have explored the mechanisms underlying MDD. Positron emission tomography studies demonstrated alterations within corticolimbic and corticostriatal circuits that are mitigated in treatment responders.[6] Transcranial magnetic stimulation targeted to the left dorsolateral prefrontal cortex increases brain connectivity in patients with MDD.[7] Alterations in the frontoparietal network, default mode network, dorsal attention network, salience network, and the central executive network have been consistently identified in neuroimaging studies. Pioneering work in precision medicine identified 6 clinically distinct biotypes of MDD characterized by neurocircuit and behavioral profiles that define MDD as a brain disease, with diverse symptom clusters that can be mapped to specific task-derived circuits.[8]

Pathophysiologic studies of the effects of SSRI and MDD exposures have included alterations in placental function. Placentas of women with MDD compared with those from healthy women exhibited an increase in antioxidant enzymes, senescence-associated secretory phenotypes, and a decrease in histone proteins, implying placental aging.[9] Placentas from women with MDD are characterized by an upregulation of proteins involved in platelet activation, degranulation, amyloid fiber formation, and the coagulation cascade. In placentas of SSRI-treated women compared to those of untreated women with MDD, placental function is characterized by downregulation of proteins related to senescence, amyloid fiber formation, and platelet activation, suggesting that SSRI treatment may mitigate the placental alterations observed in MDD.[9]

These pathophysiologic mechanisms are further altered during pregnancy. The neuroactive steroid metabolites of progesterone and their target, the GABA-A receptor, are dramatically modified in pregnancy and at childbirth, which results in changes in neural circuit responses[10] and structural, functional, and metabolic alterations in key brain regions.[11] MDD is a brain disease of disrupted communication among functional brain networks that differ among subtypes. The separation of MDD from other medical disorders represents stigma rather than science.

The pharmacologic action of antidepressants is to increase synaptic levels of monoamines, including serotonin, norepinephrine, and dopamine. Newer, rapid-acting drugs (eg, ketamine, brexanolone, and zuranolone) affect concentrations of other neurotransmitters, such as glutamate, or transmission through receptors for transmitters, such as GABA.[12] The beneficial effects of SSRI on symptoms of depression derive not only from alterations in neurotransmitter levels, but also by influencing the dynamic interplay of downstream neurodevelopmental systems, including adaptive changes in receptor sensitivity and function across time that facilitate neuronal connectivity.

Key Points

Question How can the effects of exposure to major depressive disorder (MDD) and selective serotonin reuptake inhibitors (SSRI) treatment be balanced during pregnancy?

Findings The goal of this Special Communication is to synthesize accumulated evidence, which suggests that when the impact of the drug is disentangled from that of MDD and its sequelae, SSRI alone carry little or no risk for the most serious averse outcomes for mothers and their offspring.

Meaning Treatment of maternal depression must be prioritized, and SSRI are an essential component of perinatal mental health care.

Maternal Stress and MDD Affect Offspring Development Independent of SSRI

The growing literature on fetal sensitivity to maternal stress and its impact on lifelong health[13] has fueled research on maternal psychiatric conditions, which are the leading causes of maternal morbidity and mortality in the US.[14] Independent of antidepressant treatment, women with MDD have higher rates of pregnancy complications, such as preterm birth (PTB; odds ratio [OR], 1.46; 95% CI, 1.20-1.78),[15] low birth weight (OR, 1.90; 95% CI, 1.31-2.74),[15] cesarean delivery (risk difference, 3.5 percentage points higher; 95% CI, 2.7-4.3),[15] and hyperemesis gravidarum (OR, 5.2; 95% CI, 4.3-6.3).[16] Depressive symptoms confer a 3-fold higher risk for hypertension and preeclampsia due to the increase in adrenergic activity inherent in emotional distress.[17] The symptoms of MDD (eg, concentration problems, fatigue, amotivation) compromise the pregnant person's capacity to function and manage care for complications, comorbid disorders, labor and delivery, lactation, and care of the newborn in the challenging postbirth period.

Exposure to maternal MDD in utero is associated with alterations in fetal and infant neurodevelopment and functional connectivity of key brain structures and networks involved in stress processing.[18] Other sequelae of stress are infant emotion dysregulation, sleep problems, and disorganized attachment.[19] In the US National Institutes of Health (NIH) Environmental influences on Child Health Outcomes (ECHO) study, prenatal stress and elevated depressive symptoms were associated with higher rates of child psychiatric symptoms and reductions in cognitive abilities.[20] Prenatal maternal depression significantly predicted childhood mental health problems after accounting for shared genetic risk and confirmed that maternal mental illness is a robust predictor of offspring mental problems.[21] In an imaging study of fetal brain development, elevated maternal psychological distress was associated with significantly smaller fetal left hippocampal volume and accelerated fetal cortical gyrification in the frontal and temporal lobes.[22] Maternal depressive and anxiety symptoms alter gene expression of the placental human serotonin transporter (*SLC6A4*), which suggests a potential mechanism for the impact of maternal symptoms on fetal neurodevelopment.[23] The association between increased maternal stress, MDD, and adverse childhood outcomes is a continuum that begins in pregnancy.

Generation of Evidence and Interpretation for Treatment Decisions

The safety of SSRI in pregnancy remains a source of debate because randomized placebo-controlled trials—the cornerstone of causal inference—are not available in pregnancy due to (debatable) ethical concerns.[24] Animal studies are valuable for hypothesis generation,[25] and most report alterations in fetal neurodevelopment and behavior in association with SSRI exposure; however,

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the relevance to human exposure is unclear. These studies rarely use depressionlike exposure conditions as comparators, which reduces their translational relevance.[26] Studies of SSRI in animal models have understandably prioritized studies to explore the potential for toxicity[27] and occasionally benefit.[28]

Translational challenges include differences in placentation, pharmacokinetics, developmental timing, and dose equivalence. Hypotheses must be tested in observational studies that evaluate the effects of treatments administered in routine clinical care. As data accumulate, investigations with sizeable samples and expanding tools (eg, biological markers, epigenetics, artificial intelligence[29]) will add to our knowledge about maternal and offspring outcomes, including both benefits and harms.

Nearly 70 years ago, exposure to thalidomide caused malformations, primarily limb-reduction anomalies, in more than 10 000 children. Fear of another drug-associated devastating fetal effect has overshadowed concern about the impact of maternal disorders on maternal-fetal health. Inattention to maternal psychiatric disorders is reflected in studies using inadequate reference groups, such as comparing SSRI-treated women with MDD to disease-free women. The effect of the underlying disease on the health and function of the mother, on whom the fetus is completely dependent, must be a primary consideration. As stated by the Society of Maternal-Fetal Medicine, "While all pregnant patients deserve individualized counseling, the risks of SSRI are, in general, greatly overshadowed by the profound risk that untreated depression has for both pregnant people and their children."[30]

Multiple biological and behavioral factors associated with MDD influence pregnancy outcomes and render pharmacoepidemiologic studies susceptible to confounding by indication. The reason MDD acts as a strong confounder is not clear and is a critical area for study. Explanations include physiologic changes and risk factors associated with MDD, such as smoking, substance use, poor nutrition, obesity, chronic medical comorbidities, reduced prenatal care engagement, and socioeconomic adversity, which independently affect pregnancy and offspring outcomes. Women who continue SSRI treatment during pregnancy often have more severe, recurrent, or chronic illness than women who discontinue treatment or remain untreated, and many do not achieve remission despite treatment.[31] These women may also differ with respect to social determinants of health that are independently associated with maternal and child health outcomes.[32,33]

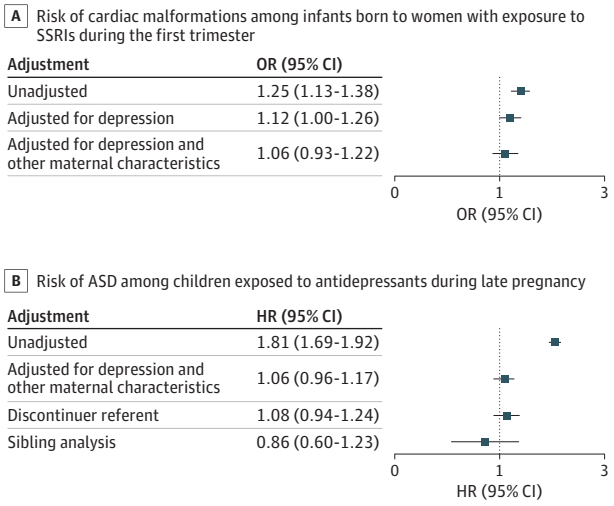
When these factors are not accounted for or imperfectly measured, their influence can be assigned erroneously to a drug effect, leading to conflicting findings and academic and public concern. Cardiac malformations serve as a salient example. Studies in the 2000s reported 2- to 3-fold increases in the rate of heart defects following first-trimester SSRI exposure, most notably with paroxetine.[34,35] Many studies relied on retrospective interviews with mothers, which raises the possibility of recall bias; that is, women bearing a child with a congenital malformation are more likely to recall exposures than those with a healthy infant. Additionally, adjustments were made only for factors known at that time to be risk factors for malformations (ie, maternal MDD was not adjusted for), resulting in residual confounding. The reports lead to widespread concern about SSRI teratogenicity.

As large cohort studies became available, these associations weakened substantially. Maternal MDD accounted for most of the excess risk originally assigned to SSRI. After further adjustment for sociodemographic and clinical characteristics, the association with cardiac malformations disappeared (**Figure 1**A). These findings suggest that associations between SSRI and cardiac malformations were not causal but attributable to confounding by MDD and associated factors. A reanalysis of one of the original studies found that comparing first-trimester SSRI users with women who stopped their medication before conception substantially attenuated the associations, further supporting the role of confounding by factors associated with MDD.[38]

Investigations of long-term outcomes, such as autism spectrum disorder (ASD), involve substantial challenges because MDD and ASD share genetic and environmental vulnerability. Without adjustment, the association between SSRI and ASD appears strong, but again, the strength of association is substantially reduced or eliminated after accounting for confounding by MDD and genetic and/or familial factors. Examples of such approaches include comparing outcomes of women who continue vs discontinue SSRI treatment during pregnancy or comparing siblings, only 1 of whom was exposed in utero to an SSRI (Figure 1B).

Any effect in a neonate whose mother took psychotropic medications in pregnancy is a combination of the direct impact of psychiatric illness, stress, genetic and epigenetic processes, effects of maternal health behaviors associated with MDD, factors attributable to medications (or lack of medication), and/or other environmental exposures. The impact of the drug must be disentangled from that of MDD and its sequelae to accurately quantify the excess risk attributable to the antidepressant. The inevitably imperfect and evolving knowledge regarding SSRI safety in pregnancy must be weighed against the consequences of untreated or undertreated maternal MDD. Even sophisticated observational research cannot fully exclude small or moderate risks. Confidence intervals around risk estimates may encompass clinically meaningful effects even when

Figure 1. Forest Plot Showing Impact of Adjustment for Confounding on Effect Estimates for Antidepressant Use in Pregnancy and the Risk of Cardiac Malformations (A) and Autism Spectrum Disorder (ASD) (B)



Panel A adapted from Huybrechts and colleagues[36]; panel B adapted from Suarez and colleagues.[37] HR indicates hazard ratio; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.

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point estimates are null (see the upper bound of the 95% confidence interval in Figure 1).[36,37] Exposure and outcome misclassification and incomplete adjustment for confounders persist as fundamental limitations. While the preponderance of evidence indicates that SSRI are unlikely to cause congenital malformations or ASD, residual uncertainty is unavoidable, as is the case for observational studies of any drug exposure in pregnant women.[39] Decisions must be made with best estimates of risk levels from SSRI treatment compared to that of the underlying disease and its sequelae for the individual patient—no zero-risk option exists.

SSRI Are Critical Tools for Treatment of Maternal MDD

In addition to antidepressants, interventions studied in pregnant women include psychotherapy, with cognitive behavioral, interpersonal, and behavioral activation therapies having consistent evidence of efficacy[40]; electroconvulsive therapy; and nonpharmacologic treatments, including bright light therapy and transcranial magnetic stimulation.[41] Access to a variety of single and combination treatments to respect patient preference and optimize effectiveness and tolerance is essential to achieving remission of MDD. SSRI are first-line drugs and an essential component of perinatal MDD care. They may be the only treatment available in underresourced communities.

Although the literature on SSRI efficacy in pregnant women is scarce due to the lack of randomized clinical trials,[42] the rarity of studies does not mean these drugs are ineffective. Informative data come from studies comparing relapse rates in women who continue vs discontinue antidepressant treatment. Patients in a perinatal psychiatry program who discontinued medication relapsed significantly more frequently compared with those who maintained treatment (hazard ratio [HR], 5.0; 95% CI, 2.8-9.1).[43] In a Danish cohort study, women who discontinued antidepressants during pregnancy had an increased risk for psychiatric emergencies (HR, 1.25; 95% CI, 1.00-1.55) compared to a propensity score–matched group who continued treatment.[44] In contrast, a study including participants recruited from community and hospital-based prenatal care clinics did not show a difference in MDD relapse in women treated compared to those untreated with antidepressants (HR, 0.88; 95% CI, 0.51-1.50).[45] In this study, a risk factor for relapse was 4 or more episodes of MDD prior to pregnancy (HR, 1.97; 95% CI, 1.09-3.57), which converges with the findings derived from a specialty program cited previously.[43] Other risk factors included Black race (HR, 3.69; 95% CI, 2.16-6.30) and Hispanic ethnicity (HR, 2.33; 95% CI, 1.47-3.69).[45] In a systematic review and meta-analysis,[46] a higher relapse risk of depression for pregnant women who discontinued compared to continued antidepressant treatment was observed (risk ratio [RR], 1.74; 95% CI, 0.97-3.10). The relapse risk was substantially higher for populations with severe or recurrent depression (RR, 2.30; 95% CI, 1.58-3.35) but less so for those with mild or moderate depression severity (RR, 1.59; 95% CI, 0.83-3.04), further supporting the importance of these factors in relapse risk.[46] Moreover, women who continue antidepressants are likely to be more symptomatic than those who discontinue, and a third of women who continue SSRI treatment in pregnancy continue to screen positive for depression,[31] which tends to attenuate the difference in recurrence risk between groups of women who continue vs discontinue treatment.

Maintaining treatment is an important consideration, since the occurrence of MDD can adversely affect employment, social mobility, insurance status, and personal income, with disposable income losses for women of 10.2% (95% CI, 10.0%-10.4%) 10 years after MDD diagnosis.[47]

Future investigations evaluating the effectiveness of SSRI treatment of pregnant women with MDD must capture their real-world experiences, including the suffering they endure, their functional capacity at home and/or work, and their ability to cope with pregnancy appointments, labor and delivery, and the challenging postbirth period.

SSRI Treatment and Pregnancy Morbidity, Neonatal, and Child Outcomes

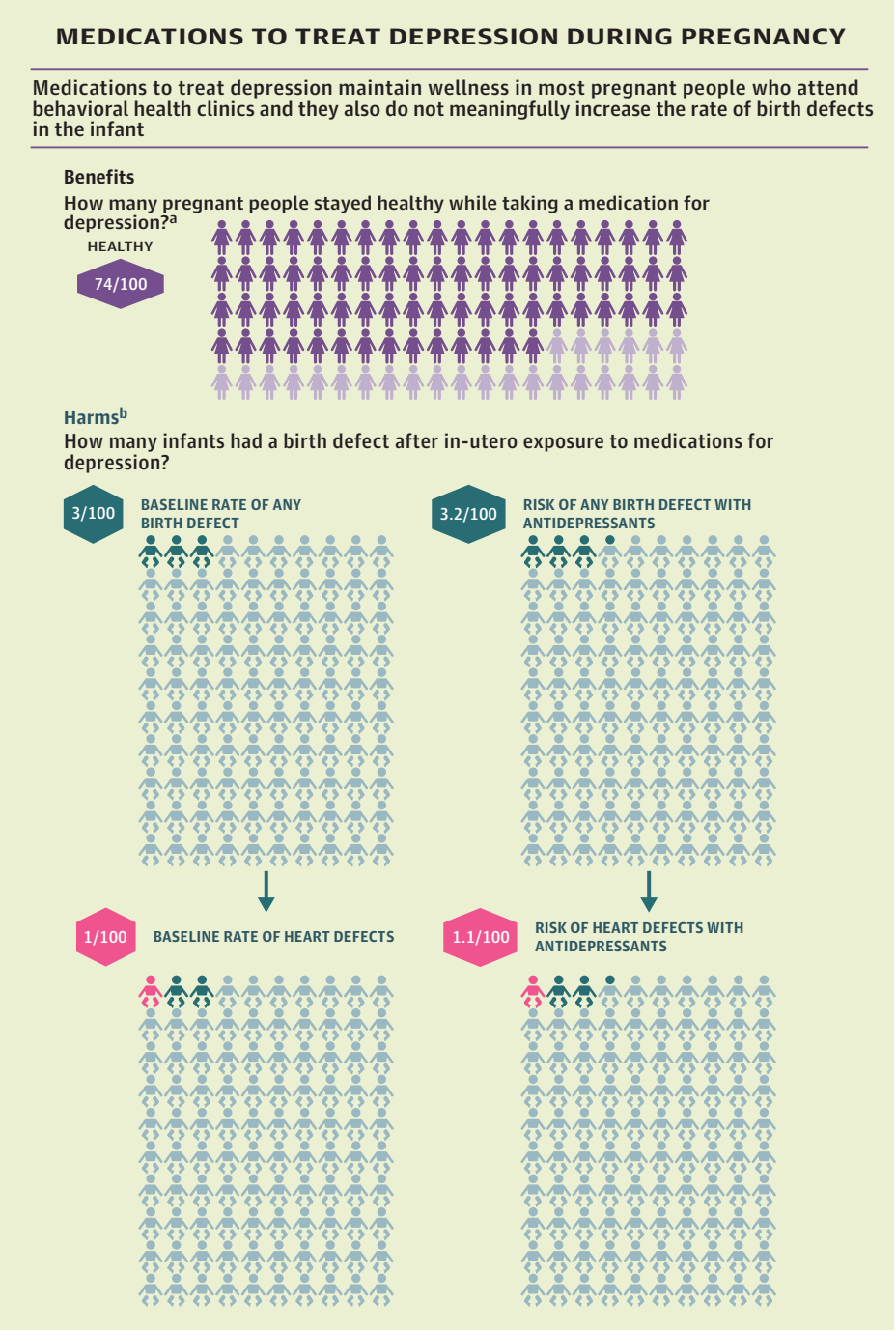
Confounding by indication contributes to the level of risk for SSRI-treated pregnant individuals in studies of miscarriage,[48] stillbirth,[49] fetal growth,[50] cardiac defects,[36] persistent pulmonary hypertension of the newborn (PPHN),[51] and postpartum hemorrhage.[52] The adjusted OR for primary PPHN for SSRI exposure is 1.28 (95% CI, 1.01-1.64).[51] While a meta-analysis concluded that a small increase in the risk of PTB in women treated with antidepressants in the second and third trimesters could not be ruled out,[53] another study found no effect.[50] A large-scale prospective study from Finland showed that SSRI treatment had 16%, 48%, and 30% lower risks for late PTB, early PTB, and cesarean delivery, respectively, compared to mothers with mental illness without pharmacological treatment.[54] A possible explanation is that most of the participants in the treated group were in remission, which removed risk associated with active depressive disorder. Unfortunately, no depressive symptom data were reported, and future studies must include symptom and functional level outcomes.

Poor neonatal adaptation signs (PNAS) appear in up to 30% of newborns with prenatal exposure to SSRI. PNAS is characterized by jitteriness, respiratory distress, irritability, tachycardia, feeding problems,[55] and an increased rate of neonatal intensive care unit admission (OR, 1.5; 95% CI, 1.4-1.5)[56] A recent meta-analysis found that the rate of PNAS is higher in infants following in-utero SSRI compared to MDD exposure.[57] The risk is significantly higher when maternal treatment includes SSRI plus benzodiazepines.[58] PNAS is self-limited in most cases, is rarely associated with adverse development, and resolves within 2 weeks with supportive care.[59] The signs associated with PNAS are not specific to this syndrome and also occur in association with obstetric complications.[60,61] No consensus operational definition for PNAS exists—formulating one would be a step toward facilitating research.

The critical role of serotonin in embryologic growth of neural systems compels studies of the neuropsychiatric effects of in-utero SSRI exposure. Compared with nonexposed controls, children exposed to SSRI during fetal life had less cerebral gray matter, particularly within the corticolimbic circuit, which persisted through 15 years of age.[62] Exposed children showed a steeper increase in volumes of the amygdala and fusiform gyrus from 7 to 15 years of age, and these volumetric differences resolved by early adolescence. Prenatal depression was associated with a smaller volume in the rostral anterior cingulate gyrus. Postnatal depression was associated with reduced fusiform gyrus volume. Both depressive symptoms and in-utero SSRI expo-

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Figure 2. Fact Box With Qualitative, Numeric, and Visual Data for Simplified Communication of the Risk for Congenital Malformations Associated With Antidepressants to Prescribers and Patients



Adapted from Moses-Kolko and colleagues.[72]

[a]Cohen and colleagues.[73]

[b]Excludes other domains (ie, pregnancy loss, preterm birth, neonatal adaptation).

sure were associated with altered developmental trajectories of brain regions involved in emotional regulation. SSRI-treated pregnant women had higher depression scores and rates of exposure to benzodiazepines, underscoring the interpretive challenges associated with confounding by indication. Another research team reported that SSRI-exposed children had a larger left parietal surface area and thicker occipital cortex, although effect sizes were small.[63] The functional effects of these brain changes are not clear.[64]

The risk of neurodevelopmental disorders (NDD) associated with SSRI exposure was explored in a cohort study of publicly and commercially insured women with control for confounding by indication, environment, and genetics.[37] SSRI-exposed offspring had a 2-fold greater risk of NDD; however, adjustment for confounders and comparison to a group of women who discontinued SSRI substantially reduced the associations. Comparison of exposed and unexposed siblings resulted in null estimates for any NDD,

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ASD, attention-deficit/hyperactivity disorder, learning and intellectual disability, and language and behavior disorders (except for *S*-citalopram exposure). In contrast, a large-scale Danish study showed no association between *S*-citalopram and any child psychiatric disorder.[65] While an association between in utero SSRI exposure and elevated risk for adolescent-onset depression or anxiety was reported, recent studies have not supported this association.[66,67] The risk for affective disorders in children whose fathers continued vs discontinued antidepressant use during the mothers' pregnancies was similar to the risk for maternal continuation vs discontinuation, implicating factors other than drug exposure.[68] Similarly, in the NIH Adolescent Brain Cognitive Development Study (ABCD Study), SSRI exposure was not independently associated with offspring depression.[63]

In summary, investigations of the long-term impact of SSRI exposure on diagnosis or functional impairment in childhood or adolescence have not yielded consistent evidence of adversity.[69] Rather than searching for specific child neurobehavioral outcomes associated with prenatal SSRI exposure, maternal MDD must now be regarded as an exposure rather than merely an ever-present confounding variable. The question must shift from whether SSRI treatment is associated with an elevated risk for adverse pregnancy outcome to whether SSRI treatment resulting in remission of MDD is associated with more positive maternal-fetal short- and long-term outcomes than those observed in undertreated or untreated women.

Advancing Care for Perinatal MDD

Meaningful advances in the treatment of perinatal MDD require coordinated attention to multiple aspects of clinical management with a perspective that incorporates the health needs across 2 generations. Expanding access to treatment, particularly in maternity and child health and psychiatric care deserts, is a public health imperative. Obstetric care is reimbursed as a bundle (pregnancy and delivery paid with 1 fee)—unbundling (planned for January 2027) will allow coverage of adequate time to support benefit-harm decision-making with patients, which now rarely takes place outside of specialized reproductive psychiatry settings.

A structured process to guide decision-making facilitates provision of balanced information.[70] The prescriber and patient must consider the maternal-fetal risks of untreated or undertreated illness and the potential risks (safety and tolerability) of SSRI exposure along with the potential benefits of treatment. In women treated with SSRI prior to pregnancy, the decision will focus on the relapse risk of discontinuation and whether and when to restart medication if symptoms emerge.

Decision-making can be optimized by advising patients about treatment options (including no treatment with symptom monitoring), supporting identification of their values and preferences, and allowing time for discussion. Comfort in providing estimates of efficacy and safety in absolute terms when possible (eg, 1 in 1000) and acknowledging uncertainty are important skills.[71] Structured summaries of absolute risk in the form of fact boxes (**Figure 2**)[72,73] that combine quantitative, visual, and textual elements strengthen clinicians' knowledge, facilitate confident risk communication, and assist patients in the interpretation of research.[72] These decisions are highly individual, and the values assigned to choices vary by woman's circumstances, preferences, and access to mental health care.

Using evidence-based strategies, such as collaborative care, algorithm-guided treatment, and frequent monitoring of symptom severity with validated instruments to adapt treatment, improves remission rates.[74] Changes in drug pharmacokinetics during pregnancy generally result in lower plasma concentrations, which may reduce the drug's efficacy,[75] and studies to guide dosing across pregnancy and post partum are needed. Genotyping of cytochrome isoforms and therapeutic drug monitoring may be valuable pathways to individualize dose management during pregnancy.[76]

Pregnancy is an opportune time to conceptualize the treatment of MDD with the goals of remission and relapse prevention. The Canadian Network for Mood and Anxiety Treatments recently published treatment guidelines reflecting meaningful advances in evidence-informed care for perinatal mental disorders.[71] Centering treatment decisions on factors aligned with the patient's values and beliefs, while recognizing the life course perspective and the broader implications for family and societal well-being, is essential for effective patient-centered care of perinatal MDD.

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