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Perspective

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Potential risks and benefits of prenatal selective serotonin reuptake inhibitor medications for maternal mental health and child development

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Depressed mood and anxiety are common in pregnancy, affect the health of pregnant mothers, and set pathways for health and disease for mothers and their children long after birth. While non-pharmacological treatments are effective options, pharmacotherapy is often unavoidable, especially when maternal symptoms become moderate or severe. Selective serotonin reuptake inhibitor (SSRI) medications are the most common antidepressants prescribed in pregnancy with the expectation that they benefit a mother's mental health and, by extension, child well-being. However, regardless of the impact of these medications on maternal mood and anxiety, research findings are often conflicting and contradictory and tend to focus on adverse developmental outcomes, leaving us with unresolved questions about whether such negative outcomes result from an enduring effect of maternal depressed mood, prenatal antidepressant exposure, or yet unknown environmental contextual or genetic factors. Ultimately, we need to ask whether SSRI treatment during pregnancy confers a developmental benefit over the effects of exposure to depression or anxiety in pregnancy. To answer this question, we need to ask what metholodolgical and conceptual approaches are needed to clarify the risks and benefits related to SSRI treatment in pregnancy. In this Perspective, we highlight key child developmental outcomes associated with prenatal SSRI exposure, outline methodological approaches needed to move beyond a search for prenatal SSRI-related adverse effects, and offer a conceptual framework that incorporates the role of multiple intersecting factors (that is, family relations, socioeconomic status and discrimination) that may also contribute to perinatal mental illness, the decision to use SSRIs as treatment during pregnancy, and child development.

Perinatal mood and anxiety disorders are estimated to affect one in four women and birthing parents[1,2], compared with one in ten non-birthing parents[3]. These disorders are disabling and increase risk for poor maternal health and poor child development long after pregnancy and birth[4–8]. Early detection and timely treatment are needed. Selective serotonin reuptake inhibitor (SSRI) medications are common antidepressant treatments for perinatal mood and anxiety disorders aimed at regulating the neurotransmitter serotonin and related systems and improving maternal mental health. Currently, 3.4% of pregnant women are prescribed these medications globally[9] and, in some reports, prescription rates in pregnancy rise to 10% (ref. 10). For many women, these medications are essential for their mental and physical well-being during pregnancy and the postpartum period. Given the key developmental role played by serotonin[11], altered gestational serotonergic signaling may conceivably have downstream developmental consequences, raising concern about how gestational exposure to SSRIs affects the

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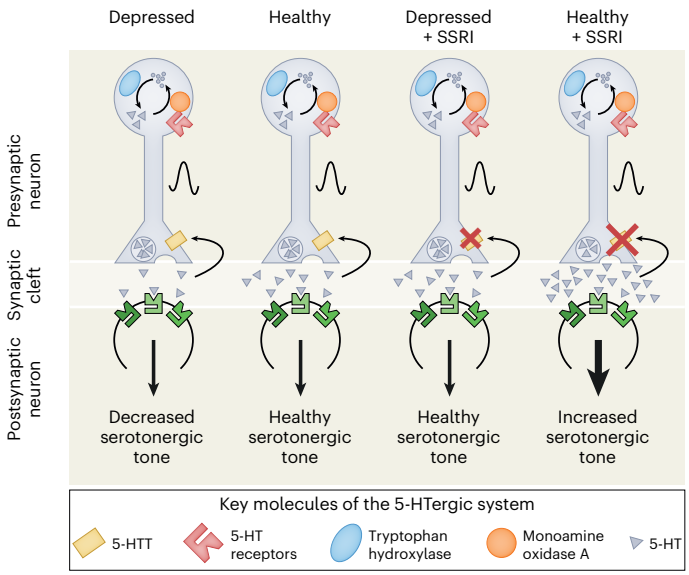

Fig. 1 | Schematic representation of the impact of depression and SSRI medications on serotonin signaling at a cellular level. The general idea for the treatment of depression is that SSRIs[76] 'normalize' serotonergic tone. However, we also know that there are many neurochemicals implicated in mental illnesses and development, and serotonin is only one of them. Other key factors include 5-HT receptors, the monoamine oxidase A enzyme, tryptophan hydroxylase enzyme, a rate-limiting enzyme crucial for serotonin synthesis, and the serotonin transporter 5-HTT, a presynaptic protein that transports serotonin back into the presynaptic neuron. Given the developmental inhibitory role of 5-HT, we also need to consider the downstream effects of constrained or enhanced 5-HT signaling in shaping complex neurodevelopmental outcomes in childhood. However, as emphasized in this schematic representation, for translational research on perinatal SSRI exposure using animal models, it is critical that models include some aspect of the stress that humans symptomatically experience as depression and do not simply investigate perinatal SSRI exposure to a healthy dam or offspring.

developing child[12] (Fig. 1). However, perinatal mood disorders can also impact the serotonergic system during critical developmental periods[13,14] and have developmental consequences[4–8].

Developing an evidence-based approach to guide the use of SSRIs in pregnancy continues to be constrained by inconclusive and contradictory findings that arise from research that fails to address the impact of the underlying perinatal mood disturbance or disentangle the effects of SSRI exposure from the mood disorder itself ('confounding by indication')[15]. As randomizing prenatal exposures to medication is not feasible, we are often left with methodological approaches to research and data analysis that attempt to estimate the effect of a treatment by accounting for multiple covariates (that is, high-dimensionality propensity score matching) to detect elements of residual confounding related to unmeasured factors that often underlie perinatal mental illness. In the end, we are left with unresolved questions about whether outcomes reflect an enduring effect of perinatal depressed mood, prenatal antidepressant exposure or yet unknown environmental contextual or genetic factors.

Discontinuing SSRIs during pregnancy increases the risk of relapse of mental illness and depression-related ongoing health risks for both the mother and her developing child[16,17]. This intensifies the uncertainty faced by mothers and their clinicians about whether to initiate, continue or discontinue SSRI treatment during pregnancy[16,17].

Recently, the Canadian Network for Mood and Anxiety Treatments published guidelines offering comprehensive approaches for clinical management of mood, anxiety and related disorders during and following pregnancy[18]. Reviewing the evidence, the guidelines report that "there are no consistent associations between fetal exposure to SSRIs and later developmental or mental health outcomes". Critically, they note that "links between most antidepressants and most adverse pregnancy outcomes are reduced significantly when confounding by indication is well-managed," highlighting the importance of recognizing and managing the persistent influence of underlying perinatal mood disorders.

SSRI medications are typically recommended to treat mood disorders in pregnancy when non-pharmacological therapies are ineffective, and as first-line treatment when the initial symptoms are moderate-to-severe or severe[18]. As such, there will always be a role for SSRI treatment in pregnancy; thus, we need to harness what evidence we have, acknowledge its limitations and develop approaches that optimize maternal mental health, accounting for variations in responses to antidepressant treatment and identifying ways to promote the healthy development of children of mothers with depression.

To date, research has frequently focused on identifying adverse child outcomes and has often failed to identify developmental benefits from maternal SSRI treatment during pregnancy. In this Perspective, we review key findings from studies examining associations between SSRI exposure and child development with an aim to stimulate a discussion that moves us beyond a search for identifying perinatal mood or SSRI-specific outcomes. In doing so, we need to acknowledge that developmental outcomes ultimately reflect an intersection of multiple factors that together contribute to perinatal mental illness, its treatment and, by extension, an inherently dyadic relationship between maternal health and child development that unfolds over time.

Early findings on prenatal SSRI effects

By the mid-1990s, nearly 2% of pregnant women were prescribed an SSRI[8,19], and case studies reporting a relationship between SSRI use in pregnancy, neonatal behavioral disturbances, lower birth weight[12], preterm birth[20] and congenital malformations[21] raised urgent questions about the developmental impact of prenatal SSRI exposure on the developing infant. Importantly, where SSRI-related outcomes were compared with outcomes among infants of mothers with depression, but not treated with an antidepressant, the SSRI effect became diminished[20,22–26]. Using well-defined prenatal exposures and developmental outcomes coupled with stringent approaches that address confounding by indication, SSRI-related findings are often attenuated. Where small differences remain, the clinical significance of such differences often remain uncertain.

By March 2000, even with limited clinical evidence, SSRI use in pregnancy was considered to be associated with minimal adverse effects, with the exception that high doses of SSRIs in the third trimester may be associated with an increasing risk of neonatal adaptation symptoms after birth[12].

Early preclinical research on prenatal SSRI effects, primarily using rodents, showed that SSRI exposure during a perinatal period in the rodent, akin to the human third trimester, alters serotonin signaling in the developing male rat brain[27] and may even, paradoxically, predispose the offspring to depression or anxiety later in life[28]. Importantly, female offspring were rarely used in these early studies, and conclusions arising from these preclinical studies frequently failed to control for, or compare with, animal models of maternal depressive symptoms; namely, a methodological failure to consider the impact of the underlying perinatal mental illness that was being treated with antidepressant medication[29]. This methodological failure is still common today with many preclinical studies treating a healthy dam or offspring with an SSRI and then concluding that the result of the study relates to the clinical situation where a mother with depression is prescribed an SSRI. A recent example of this is a study published this year looking at the link between prenatal SSRI exposure, anxiety and fear in offspring, using both preclinical and clinical studies[30]. Importantly, this study

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did not account for prenatal exposure to maternal mood disturbances in either the preclinical or clinical cohorts and resulted in erroneous associations between prenatal SSRIs and developmental outcomes. This type of research focusing on investigating only a medication effect leaves critical unanswered questions about the inherent confounding by indication, where the very indication for pharmacotherapy (depression) inherently influences both SSRI exposure and developmental outcomes.

Disentangling prenatal SSRI effects from impact of perinatal mental illness

Over the past two decades, a growing body of preclinical and clinical research studying the developmental effects of early-life SSRI exposure has attempted to disentangle the impact of prenatal antidepressant exposure from the impact of perinatal exposure to maternal mood disturbances on child outcomes[15,24,31–34]. Developing an evidence-based approach to guide the use of SSRIs in pregnancy continues to be constrained by inconclusive and contradictory findings that arise from research that fails to address the impact of the underlying mood disturbance and disentangle the effects of SSRI exposure from the mood disorder itself[15]. Given that randomizing an exposure to SSRIs in gestation is both ethically and medically not feasible, multiple methodological approaches have been used to identify whether a particular effect of SSRIs on child outcomes is due to biological and environmental factors related to perinatal mental illness severity. This typically involves attempts to estimate the effect of a treatment by accounting for multiple known covariates that seek to detect elements of residual confounding related to unmeasured factors that often underlie perinatal mental illness. These approaches include finding comparable groups of mothers with similar illness severity that are treated with an SSRI or not (propensity matching), comparing child outcomes after prenatal SSRI exposure with those in unexposed siblings (discordant sibling matching), as well as considering the timing and duration of the depressive symptoms and treatment[22,24–26]. At a pharmacological level, methodological approaches include considering the dose, type, potency and duration of SSRI use. Ultimately however, we may be left with unresolved questions about whether the outcomes we observe reflect an enduring effect of perinatal depressed mood, prenatal antidepressant exposure, or yet unknown environmental contextual or genetic factors or combinations of these factors. Thus, it remains crucial that we incorporate methodological approaches that consider maternal and environmental factors that influence timing of the illness, its duration, severity and symptom cluster such as relationship distress, paternal depression, neighborhood characteristics, access to greenspace and racial disparities, all factors that also influence maternal mental health and child development[35–38] (Fig. 2).

Animal models investigating the effects of perinatal SSRI exposure offer critical insights into timing of exposures and ways to distinguish perinatal mental illness from medication exposure that are not available to clinical research. SSRIs given to healthy pregnant rodents and by extension their offspring have very different effects on both mother and offspring[34,39,40]. For example, perinatal SSRI exposure can normalize the effects of gestational stress (a model of aspects of maternal depression) on depressive-like behavior in juvenile male and female rat offspring. However, perinatal SSRI exposure in the absence of gestational stress increases depressive-like behavior[40–42]. In addition, the dose, timing and duration of the treatment need to be considered to truly model the clinical situation. Injecting an SSRI directly into a rat or mouse pup, a technique that has been regularly used, is minimally comparable to perinatal human SSRI exposure through pregnancy when a mother takes her medication orally. While there are key lessons we can learn from animal models, translating animal findings to the clinic requires us to use animal models that reflect, as closely as possible, our clinical context.

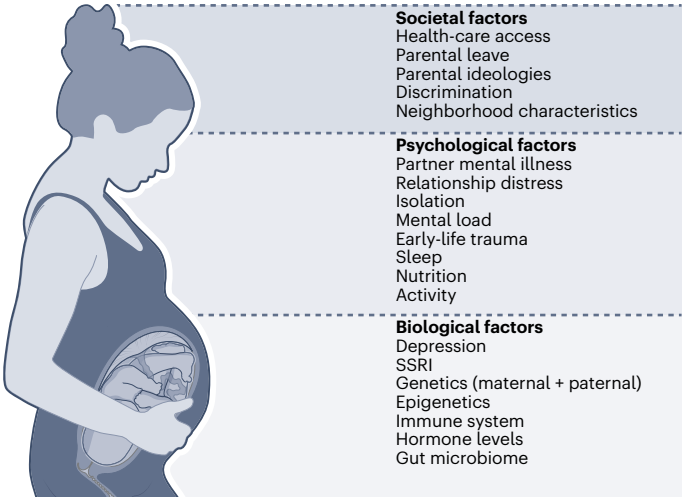

Fig. 2 | Schematic representation of some of the factors that can contribute to our understanding of how prenatal SSRIs and perinatal mental illness impact the mother and developing child. Broadening our understanding of these factors and how they intersect is vital to promote the health and well-being of parents and their children.

Prenatal SSRIs and child development

Prenatal SSRIs and autism spectrum disorder

Disentangling the impact of SSRI exposure from the effects of maternal depression remains challenging, and attempts to identify adverse developmental outcomes have met with varying degrees of success. A 2011 report of associations between prenatal SSRI use and increased risk for autism spectrum disorder (ASD)[43] raised urgent public and scientific concerns. These findings were based on a study using a small number of participants and a limited approach to controlling for the impact of maternal depression. More recent studies using rigorous methodologies, including population-based health-linked data and careful control for maternal mood symptoms, have failed to find similar associations between prenatal SSRI exposure and increased risk of ASD. When analyses account for maternal mood and illness-related factors—and compare outcomes with unexposed siblings—the observed risk for ASD is further reduced[24].

Using population-level data, studies have also failed to identify an association between prenatal SSRI exposure and increased ASD risk[44,45], leading to our current understanding that prenatal SSRIs are not associated with an increased risk of developing ASD in the general population. In addition, population-level studies using appropriate controls for perinatal mental illness have failed to demonstrate associations between prenatal SSRI exposure and the risk of developing attention deficit/hyperactivity disorder (ADHD), behavioral disorders or developmental conditions—including conditions related to speech, language, learning, coordination disorders or intellectual disabilities—in children through mid-adolescence[21,42,43].

The absence of evidence establishing a prenatal SSRI–ASD association might in one sense be reassuring, but in another sense only highlights the need to shift from methodological approaches that search for a 'main medication effect' to examining how multiple interrelated factors are indirectly attributable to prenatal SSRI exposure, per se, such as factors underlying perinatal mental illness risk or illness severity, or factors that contribute to the decision to begin SSRI treatment[46,47] and have a role in shaping neurodevelopmental outcomes[48,49].

Prenatal SSRIs and risk of depression and anxiety

Prenatal SSRI exposure is often associated with an increased risk of depression and anxiety in children, adolescents and adult offspring[32,50,51], and in some cases even when maternal mood symptoms

are controlled for. Importantly, population-based studies showing an association between prenatal SSRI exposure and increased risk of emotional disorders in adult children show that this relationship is related to either a mother's or father's use of an SSRI during the prenatal period[50]. This suggests that the association between prenatal SSRI exposure and the increased risk of depression in children is not linked to direct exposure to the SSRI but is likely to be driven by mental illness severity in either of the parents (mood measures were not available for use in the study), an underlying genetic propensity for the development of depression or anxiety, and/or gene-by-environment interactions[51].

Prenatal SSRIs and possible developmental benefits

Typically, studies of prenatal SSRI exposure and child development have been designed to identify adverse developmental outcomes, often ignoring the opportunity to study why exposed children are in fact developing in typical ways or that there could even be developmental benefits associated with prenatal SSRI exposure. In a prospective longitudinal birth cohort study, SSRI-exposed fetuses show accelerated perceptual development by being able to discriminate both vowels and consonants at 36 weeks of gestation, something that usually occurs later in development[52]. This developmental shift in speech perception then continued across the first year of infancy, reflecting a bidirectional effect that appears to differentiate between exposure to prenatal depressed maternal mood and SSRIs.

Prenatal SSRIs also appear to preserve or protect against the impact of perinatal depression on executive functions (including self-control, working memory and cognitive flexibility) in school-age children, thus possibly acting to 'buffer' the child from the adverse impact of untreated perinatal depression[53]. Interestingly, this effect appears to be linked to household chaos, whereby 6 year olds with prenatal SSRI-exposure have difficulty with executive functions in the context of a high degree of chaos in the home[54]. However, the effect of such everyday chaos only became particularly evident when mothers were depressed and treated with an SSRI during pregnancy. These intriguing, but limited, findings nevertheless point to the importance of accounting for maternal mood, both prenatally and across childhood, and everyday context that might reflect a differential susceptibility to prenatal SSRI exposure.

Preclinical studies also illustrate a potential prenatal SSRI benefit to offspring development. This is reflected in studies 'disentangling' drug from disease, comparing perinatal SSRI effects with maternal stress effects, showing that perinatal SSRIs prevent or even 'protect' against the effects of prenatal stress on neurobehavioral outcomes in both male and female juvenile and adolescent offspring[40,42,55]. In adult rat offspring, perinatal SSRIs have a greater and more 'positive' effect on neurobehavioral outcomes in female offspring, particularly by increasing social and reproductive behaviors, regardless of prenatal stress[55,56]. In adult male rat offspring, prenatal stress, regardless of perinatal SSRIs, has a more enduring impact by reducing social behaviors and hippocampal neurogenesis[55,57]. Thus, when modeling maternal stress in preclinical research, as a proxy for perinatal depression in women, developmental risk associated with perinatal SSRI exposure may point to a developmental advantage, telling quite a different story from the one that has typically focused on adversity or disordered developmental outcomes.

Importance of identifying and treating perinatal mental illness

Over 30 years of research has focused on identifying SSRI-related developmental outcomes, yet SSRI exposure reflects only one dimension of many factors associated with perinatal mental health that shape childhood outcomes. Many women (and men) will struggle with subthreshold mild to severe levels of depression and anxiety during pregnancy. Discontinuation of SSRI medication in pregnancy increases the risk of symptom relapse[17] and thereby confers additional developmental risks. This is particularly evident following antidepressant discontinuation among women with severe or recurrent depression[58], highlighting that regardless of pharmacotherapy continuation during pregnancy, developmental risk persists.

Together, these findings point to the need to treat and ultimately prevent perinatal mental illness in both mothers and fathers, birthing and non-birthing parents. Pharmacotherapy is often recommended for the treatment of moderate to severe depressive symptoms, particularly when the initial symptoms are severe and when non-pharmacological therapies are ineffective or not available. Prenatal SSRIs are an effective option for many, but for others, treatment with an SSRI may not be effective, and alternative pharmacotherapies are needed that are tailored to the neurophysiological effects of pregnancy and beyond the postpartum period.

Importantly, parents may remain symptomatic due to limited access to treatment or treatment options. For those with mild to moderate depressive or anxiety symptoms where non-pharmacological approaches are preferable, interventions that can aid in promoting mental health range from prioritizing sleep[59–61] to participating in evidence-based psychotherapeutic interventions that include interpersonal therapy, cognitive behavioral therapy, mindfulness-based interventions and group psychotherapies, such as Mom Power[62], all of which can improve mental health and parent–child interactions[63–68] and, ultimately, child outcomes. There is also emerging literature pointing to the importance of social support and relationship satisfaction for perinatal mental health[69,70] and an encouraging trial of transcranial direct current stimulation in pregnancy[71]. Importantly, while there are options for treatment and intervention, access to care is often not possible due to limited availability, cost, geographic isolation, lack of childcare and time burden[72,73].

Conceptual considerations and future directions

Our understanding of the impact of prenatal SSRIs and perinatal mental illness on the mother and child remains inherently and arguably, by necessity, interconnected. Without accounting for maternal (and paternal) mood effects in the context of SSRI treatment during pregnancy, we will only continue to observe erroneous associations between SSRIs and developmental outcomes.

Despite vigorous research approaches to distinguishing prenatal SSRI effects from the impact of prenatal maternal depression, maternal and paternal moods continue to influence outcomes across childhood[8,22,74]. Such findings raise intriguing questions about whether it is even possible to disentangle the impact of these prenatal influences (SSRI and mood) or whether it is even necessary given that development in children of mothers (and fathers) with depression remains disproportionately at risk, reflecting an enduring effect of perinatal illness-related factors and not SSRI exposure per se[22]. This raises critical concerns about what actually defines developmental risk in this context.

Is it possible that in our search for SSRI-related adverse developmental outcomes we have overlooked the need to study the impact of treatment responses (remission or a failure to achieve remission), maternal illness severity, genetic inheritance associated with prenatal depression, and drug metabolism as well as environmental influences that extend far beyond the family? If so, then we need to consider the possibility that even with SSRI treatment, a mother's depression itself continues to be adversely associated with child developmental health, or alternatively, that a mother benefits from treatment with an SSRI, as her mood improves, and by extension her child also benefits. Similarly, we need to consider that even if a mother's depressive symptoms persist despite treatment with an SSRI, the prenatal SSRI exposure may confer a neurodevelopmental benefit to the child that 'buffers' the child against the impact of maternal (or paternal) depression.

Furthermore, we need to consider that prenatal SSRI exposure may represent a 'proxy exposure' reflecting factors that underlie the need for SSRI treatment. Namely, a genetic propensity for intergenerational

transfer that increases risk for depression, or a cluster of factors that predispose to mental illness and lead to SSRI treatment in pregnancy, thereby become the 'exposures' of interest when investigating maternal mental health and child well-being (Fig. 2).

In this Perspective, we highlight the methodological and conceptual approaches needed to identify the risks and benefits associated with prenatal SSRI treatment based on sound science. We also need to consider the possibility, that maternal treatment with an SSRI could actually confer a developmental benefit within a conceptual framework that incorporates multiple intersecting factors (that is, genetics, paternal depression and socioeconomic status) inherently related to maternal health and healthy child development. Knowing this, we can move beyond a search focused on risks directly related to prenatal SSRI exposure and shift to identifying modifiable factors that promote maternal, parental and child well-being. This will allow us to investigate outcomes at the intersection of medication, mental health, genes and environment, and develop accessible interventions, strategies and policies that optimize the health of generations to come. As the American College of Obstetricians and Gynecologists recently reminded us, "Patients need access to evidence-based, compassionate treatment options so that they can continue their paths to parenthood in sound physical and mental health"[75].

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Competing interests

J.P. has consulted for Biogen Therapeutics and is on the advisory board of Strategies for Moms Inc. T.F.O. declares no competing interests.

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