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Commentary: Studies of prenatal antidepressant exposures: what can you recommend? A reflection on Sujan et al. (2019)

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Sujan et al. are to be congratulated for completing a monumental job reviewing the literature on a critical public health question: *are antidepressant medications safe to use during pregnancy from the perspective of their potential effects on the infant and growing child?* They have selected a problem of great magnitude because of the high prevalence of depression in childbearing years- especially in pregnancy, and because of the high use of medication for treating depression in pregnant women in the U.S. They have also chosen a challenging problem as depression itself can impact the fetus, clinical trials of medication in pregnancy are largely unfeasible, and animal work and a recent confirming study in humans suggest that some psychiatric problems in in utero exposed offspring may not emerge until adolescence (Ansorge, Zhou, Lira, Hen, & Gingrich, 2004; Malm et al., 2016).

What are we to do with this perplexing problem that affects the health of so many? The authors have done what most scientists would do: critically review what is known. Their review of the data and design issues will be valuable to others in the field, and their illustration in Figure 1 of the complex interaction of environmental and biological pathways is a teaching piece by itself. It also illustrates why clinical recommendations are so difficult to make. They have chosen to focus on offspring neurodevelopmental disorders, mainly autism and ADHD, and conclude that 'the findings may help women make informed decisions about antidepressant use during pregnancy by providing reassurance that use of these medications during pregnancy is unlikely to substantially increase the risk of ASD and ADHD.' Here we would depart from the authors of this otherwise seminal review. But first let's go through their review.

Animal studies

Sujan et al. provide an elegant summary of the value and limitation of animal studies. Their conclusion is that most rodent studies have found effects of perinatal antidepressant exposure on neuronal brain and behavior indices related to neurodevelopmental problems. They also note the problems of between-species differences. We would agree with their caution about making strong clinical conclusions based only on rodent studies. They might add a few more caveats. Most animal studies are not long term and therefore do not capture effects of exposure that potentially emerge later in development. In addition, animal models can never fully address the competing concerns most relevant to the clinician: namely, the potential risks of gestational antidepressant exposure *relative to* the likely alternative of exposure to untreated maternal depression itself.

Human observational studies

As the authors note, the question of how to determine whether antidepressants have adverse effects on the developing system poses a conundrum for scientists who rely on observational data. Common sense suggests that powerful drugs acting on neurotransmitter systems will affect the fetus and animal data provide some support for this intuition. Nevertheless, ethical concerns preclude scientists from randomly assigning pregnant women to clinical trials to test the safety of prenatal antidepressant use. Here again the authors provide a textbook of design and statistical strategies to tease out answers without experimenting on the mother or baby (for example, comparing exposed and unexposed siblings, comparing offspring exposed to maternal antidepressant use in pregnancy with those whose fathers used antidepressants in the corresponding period, comparing offspring exposed to antidepressants versus other psychotropic medications, etc.). Any newcomer to this field of fetal exposure should read these.

Implications for clinical practice

The authors conclude that the evidence for an increased risk of ASD or ADHD on offspring exposed to SSRI in utero is minimal, and that pregnant women can therefore be reassured that taking antidepressants during pregnancy is safe and will not substantially increase the risk of adverse

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neurodevelopmental outcomes. Here is where we depart from this valuable paper. While risk for ADHD and ASD may not be increased with fetal SSRI in utero exposure, there is other evidence that SSRI exposure may increase the risk for other problems including certain speech and language disorders in childhood (Brown et al., 2016), mood disorders in early adolescence (Malm et al., 2016), and a host of non-psychiatric conditions (see Gingrich et al., 2017 for review) beyond the risks associated with prenatal exposure to maternal depression itself. While we applaud the Sujan et al. review and agree that the evidence for the effects of SSRI in utero exposure for ASD and ADHD is equivocal, we argue that recommendations for antidepressant use during pregnancy must take into account other potential damaging effects on the offspring or other psychiatric or non-psychiatric complications. Effective treatment decisions require evaluation of a fuller portfolio of potential risks and benefits to the mother-child dyad in the context of the severity of the mother's symptoms. We agree that evidence-based psychotherapy should be on the menu as an alternate treatment, and the US Preventive Task Force in a recent report circulating for review (Force UPT, 2018) recommends several evidence-based psychotherapies for treatment and prevention of depression during the perinatal period.

Future directions: how do we move this important field forward?

Future studies should aim to replicate findings in diverse cohorts using as many of the study designs the authors describe, as the data will allow. Inclusion of different countries and cultures will allow better teasing apart of alternative mechanisms (e.g., genetic and environmental risks) that could be driving some of the observed associations.

Epidemiological studies should also be complemented with biological approaches, especially in the early postnatal period when the environment has had limited opportunities to reshape development. Recent studies for example have identified greater resting state functional (Rotem-Kohavi et al., 2019) and white matter (Lugo-Candelas et al., 2018) connectivity in newborns gestationally exposed to SSRIs over and above the effects of exposure to maternal depression. Such designs need to be scaled up within larger population studies, and findings followed up over time to test the longer-term implications of these early correlates of exposure.

In the absence of gold standard randomized trials, it is also important to strengthen the methodology of our observational studies. First is through a shift from binary classifications of exposure to a more granular, time-varying measure of medication use and of maternal illness across pregnancy. Because some depressed women who respond to SSRIs will discontinue medication while others will not, and women who do not respond could change doses or switch medications, neither depression symptoms nor medication doses are static parameters. Every fetus will likely receive a distinct temporal combination of exposure to maternal depression and maternal medications through the 9 months, and these exposures need to be rigorously modeled as curves rather than points. We also need to account for maternal depression symptoms after pregnancy as these can have independent effects on fetal development and behavior. Finally, we need to better account for the 'black box' that lies between what a mother takes and what the fetus receives. This is far from trivial: pregnancy-related changes in plasma volume and in activity of enzymes that metabolize SSRIs, coupled with variation in the placenta's ability to bio-transform and to pump SSRIs back into maternal circulation, means that for any given maternal dose, there can be myriad effective fetal doses (Shea, Oberlander, & Rurak, 2012). These potentially critical variations hardly ever make their way into the research equation, and we encourage future studies to collect biospecimens, ideally at multiple points in pregnancy, to quantify the many 'gates' that control medication access to the fetus.

Conclusion

Treating depression in pregnancy is a difficult problem that involves sometimes-competing interests, since what is better for the mother may not always be better for the fetus. Given these complexities, the authors have provided a good background for future studies that should be of interest to a range of clinicians and researchers.

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References

Ansorge, M.S., Zhou, M., Lira, A., Hen, R., & Gingrich, J.A. (2004). Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science*, *306*, 879–881.

Brown, A.S., Gyllenberg, D., Malm, H., McKeague, I.W., Hinkka-Yli-Salomaki, S., Artama, M., ... & Sourander, A.

(2016). Association of selective serotonin reuptake inhibitor exposure during pregnancy with speech, scholastic, and motor disorders in offspring. *JAMA Psychiatry*, *73*, 1163–1170.

Force UPT (2018). Perinatal depression: Preventing interventions. Retrieved from file:///C:/Users/talatia/Downloads/perinatal-depression-draft-evidence-review.pdf

Gingrich, J.A., Malm, H., Ansorge, M.S., Brown, A., Sourander, A., Suri, D., … & Weissman, M.M. (2017). New insights into how serotonin selective reuptake inhibitors shape the developing brain. *Birth Defects Research*, *109*, 924–932.

Lugo-Candelas, C., Cha, J., Hong, S., Bastidas, V., Weissman, M., Fifer, W.P., … & Posner, J. (2018). Associations between brain structure and connectivity in infants and exposure to selective serotonin reuptake inhibitors during pregnancy. *JAMA Pediatrics*, *172*, 525–533.

Malm, H., Brown, A.S., Gissler, M., Gyllenberg, D., Hinkka-Yli-Salomaki, S., McKeague, I.W., … & Sourander, A. (2016). Gestational exposure to selective serotonin reuptake inhibitors and offspring psychiatric disorders: A national register-based study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*, 359–366.

Rotem-Kohavi, N., Williams, L.J., Virji-Babul, N., Bjornson, B.H., Brain, U., Werker, J.F., … & Oberlander, T.F. (2019). Alterations in resting-state networks following in utero selective serotonin reuptake inhibitor exposure in the neonatal brain. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *4*, 39–49.

Shea, A.K., Oberlander, T.F., & Rurak, D. (2012). Fetal serotonin reuptake inhibitor antidepressant exposure: Maternal and fetal factors. *Canadian Journal of Psychiatry*, *57*, 523–529.

Sujan, A.C., Öberg, A.S., Quinn, P.D., & D'Onofrio, B.M. (2019). Maternal antidepressant use during pregnancy and offspring neurodevelopmental problems – a critical review and recommendations for future research. *Journal of Child Psychology and Psychiatry*, *60*, 356–376.

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