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Course and Treatment of Psychiatric Disorders During Pregnancy

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Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

12-Month Disclosure

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Advisory/Consulting: JDS Therapeutics LLC; As an employee of MGH, Dr. Cohen works with the MGH CTNI, which has had research funding from multiple pharmaceutical companies, including Praxis Precision Medicines, Inc., and the NIMH.

Honoraria: None

Royalty/patent, other income: None



Reproductive Psychiatry and the COVID-19 Pandemic: 2022

- Family planning and the pandemic
- Telemedicine and implications for pregnancy and postpartum period
- Perinatal anxiety during the COVID 19 crisis
- Importance of euthymia during pregnancy
- Reframing postpartum experience

JAMA Psychiatry. Published online July 15, 2020. doi:10.1001/jamapsychiatry.2020.1947
<https://womensmentalhealth.org/obgyn/reproductive-psychiatry-during-the-covid-19-pandemic/>

Virtual Rounds at CWMH during COVID: Wednesdays at 2 PM – Community in Reproductive Psychiatry



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Resource: Join us for Virtual Rounds at the Center for Women's Mental Health on Wednesdays

By MGH Center for Women's Mental Health | April 3rd, 2020 | [Resources](#) | [0 Comments](#)



As our faculty at the **Center for Women's Mental Health** (CWMH) have gone fully remote with respect to clinical and research activity, we have managed to stay connected these last three weeks with "virtual rounds". For over 25 years, our group has met on Wednesdays at midday to discuss clinical cases we have seen across the week and also to discuss recently published papers in reproductive psychiatry. We look forward to Wednesdays as we get to talk about how we think about treatment options with

respect to presented cases and the decisions patients make about treatment before, during, and after pregnancy. Particular attention is given to the safest use of psychiatric medications during pregnancy, the postpartum period and lactation. Three decades after founding the Center, I still love Wednesday rounds and always learn something by listening to cases and hearing how my colleagues think about perinatal psychiatric disorders. We are continuing to round during the COVID19 epidemic and Zoom proves to be the next best thing to being there.



<https://womensmentalhealth.org/posts/resource-join-us-for-virtual-rounds-at-the-center-for-womens-mental-health-on-wednesdays/>



Treatment considerations for women with MDD in pregnancy and the postpartum period: Take Homes

- Depression during pregnancy is strongest predictor of postpartum depression
- **Nothing is more important maternal euthymia**
- There are abundant data derived from multiple sources supporting safety of many psychiatric medications used during pregnancy with some particular exceptions (valproate)
- Impact of untreated depression and stress during pregnancy will continue to be increasingly appreciated as a toxic exposure with respect to obstetrical outcome and longer term neurodevelopmental outcomes



Major Depression During Pregnancy

Are pregnant women protected
against relapse or new onset of major
depression?

To maintain or to discontinue antidepressant?

O'Hara et al. *J Abnorm Psychol.* 1990

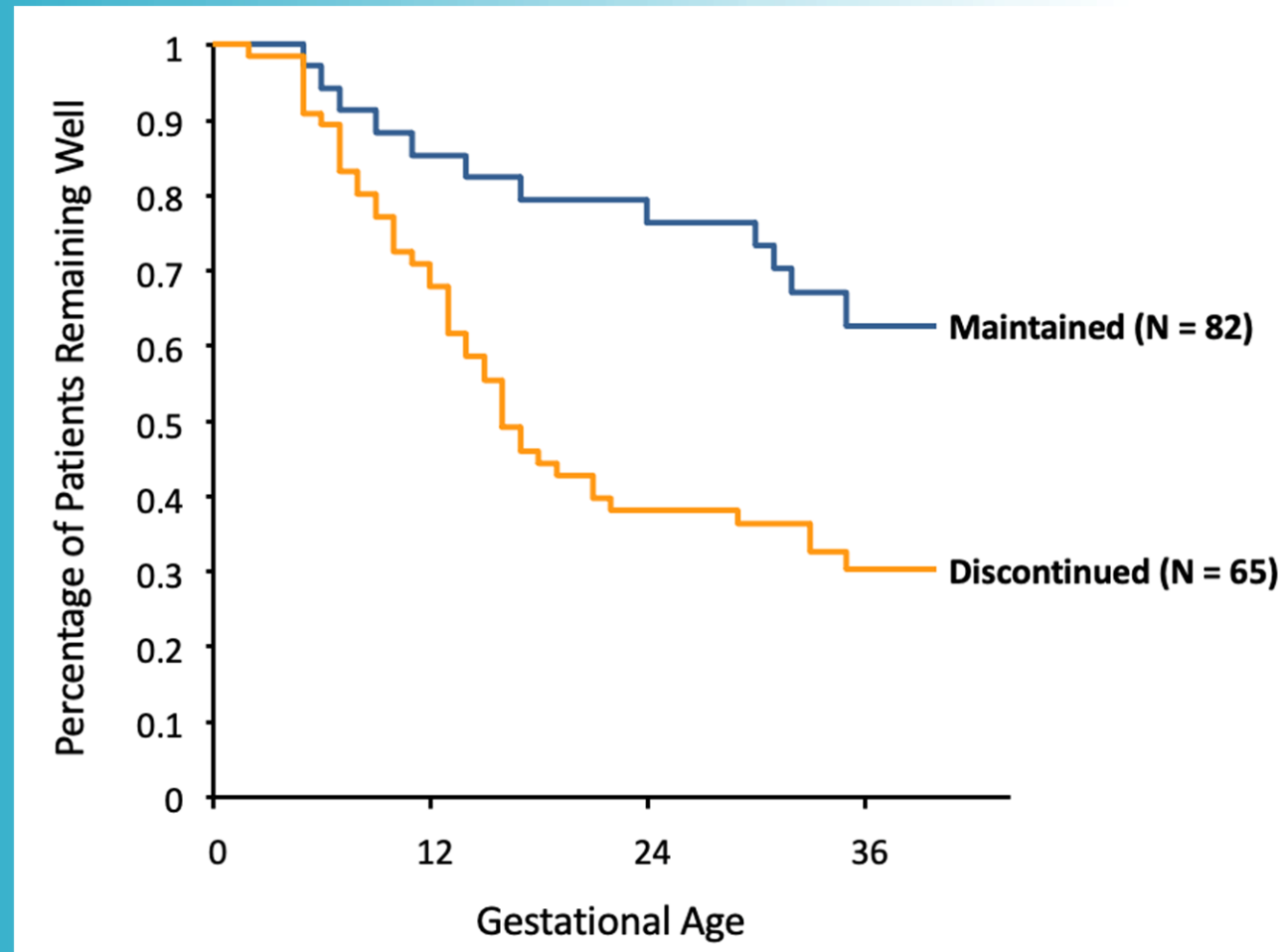
Evans et al. *BMJ.* 2001

Yonkers et al. *Epidemiology* 2011

Roca et al. *J Affective Disorders* 2013

Bayrampour et al. *J Clin Psychiatry* 2020

Time to Relapse in Patients Who Maintained or Discontinued Antidepressant



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Women's Mental Health Across the Life Cycle



WWW.MGHCMCME.ORG



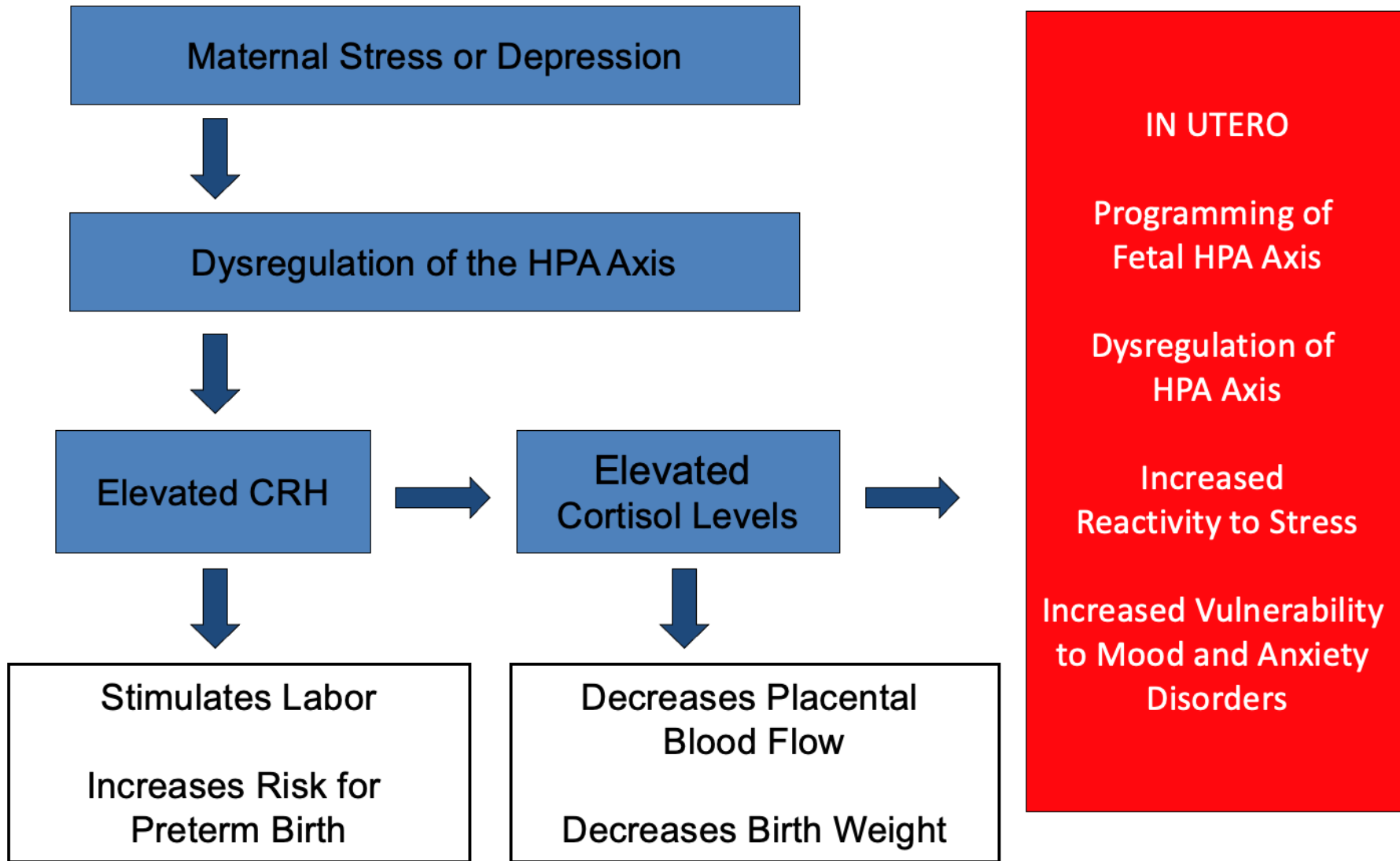
Psychotropic Drug Use in Pregnancy

- Medications used when risk to mother and fetus from disorder outweighs risks of pharmacotherapy
- Optimum risk/benefit decision for psychiatrically ill pregnant women
- Patients with similar illness histories make different decisions regarding treatment during pregnancy
- No decision is risk-free
- Collaborative, patient-centered approach required



Treatment of Depression During Pregnancy: Lessons Learned and New Directions

- Focus of concern regarding known and unknown risks of fetal exposure to psychiatric medications is increasingly balanced by data supporting risk of exposure to ***disorder, stress and HPA-axis dysregulation on fetoplacental unit***
- **Enhanced appreciation for impact of disorder and chronic stress on long term behavioral outcomes**



Implications of impact of stress associated with pandemic on long-term neurodevelopmental outcomes



Research

Original Investigation | META-ANALYSIS

Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression

A Systematic Review and Meta-analysis

Alexander Jarde, PhD; Michelle Morais, MD; Dawn Kingston, PhD; Rebecca Giallo, PhD; Glenda M. MacQueen, MD; Lucy Giglia, MD; Joseph Beyene, PhD; Yi Wang, BHSc; Sarah D. McDonald, MD

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2016.0934
Published online June 8, 2016.



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What is the Safest Antidepressant for Women of Childbearing Age?



FDA Pregnancy Categories – History

- **Category A:**

- Well controlled studies in human pregnancy show no increased risk to the fetus

- **Category B:**

- Animal studies show no increased risk to the fetus OR
- Animal studies show an increased risk to the fetus but well controlled human studies do not.

- **Category C:**

- Animal studies show an increased risk to the fetus and there are no well controlled studies in human pregnancy OR
- There aren't any animal studies or well controlled human studies.



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- Animal & Veterinary
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News & Events

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FDA News Release

FDA issues final rule on changes to pregnancy and lactation labeling information for prescription drug and biological products

For Immediate Release December 3, 2014

Release [Español](#)

The U.S. Food and Drug Administration published a [final rule](#) today that sets standards for how information about using medicines during pregnancy and breastfeeding is presented in the labeling of prescription drugs and biological

Inquiries

Media

✉ [Sandy Walsh](#)
☎ 301-796-4669

Consumers

☎ 888-INFO-FDA

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96

<http://womensmentalhealth.org/posts/fda-finalizes-guidelines-pregnancy-lactation-labeling-information/>



SSRI Use During Pregnancy

- Recent findings and more data inform the pharmacologic treatment of depression during pregnancy
 - Consistent conclusions that the *absolute* risk of SSRI exposure in pregnancy is small¹⁻³
 - Consistent pattern of malformations with SSRI exposure is lacking
 - Case-control studies reveal inconsistent data regarding teratogenic risk of individual SSRIs⁴⁻⁹

Reproductive safety data on SSRIs exceed what is known about most other medicines used in pregnancy

¹ Louik C et al. *N Engl J Med* 2007; ² Einarson TR, Einarson A. *Pharmacoepidemiol Drug Saf* 2005; ³ Einarson A, et al. *Am J Psychiatry* 2008; ⁴ Alwan S, et al. *N Engl J Med* 2007; ⁵ Greene MF. *N Engl J Med* 2007; ⁶ Hallberg P, Sjoblom V. *J Clin Psychopharmacol* 2005; ⁷Wogelius P, et al. *Epidemiology* 2006; ⁸ www.gsk.ca/english/docs-pdf/PAXIL_PregnancyDHCPL_E-V4.pdf Dear Healthcare Professional (3/17/08); ⁹ www.fda.gov/medwatch/safety/2005/Paxil_dearhcp_letter.pdf Dear Healthcare Professional (3/17/08); Grigoriadis et al. *J Clin Psychiatry* 2013.

JAMA Psychiatry | Original Investigation

Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects

Kayla N. Anderson, PhD; Jennifer N. Lind, PharmD, MPH; Regina M. Simeone, MPH; William V. Bobo, MD, MPH; Allen A. Mitchell, MD; Tiffany Riehle-Colarusso, MD, MPH; Kara N. Polen, MPH; Jennita Reefhuis, PhD

IMPORTANCE Antidepressants are commonly used during pregnancy, but limited information is available about individual antidepressants and specific birth defect risks.

OBJECTIVE To examine associations between individual antidepressants and specific birth defects with and without attempts to partially account for potential confounding by underlying conditions.

DESIGN, SETTING, AND PARTICIPANTS The population-based, multicenter case-control National Birth Defects Prevention Study (October 1997–December 2011) included cases with selected birth defects who were identified from surveillance systems; controls were randomly sampled live-born infants without major birth defects. Mothers of cases and controls participated in an interview after the expected delivery date. The data were analyzed after the completion of the National Birth Defects Prevent Study’s data collection.

EXPOSURES Self-reported antidepressant exposure was coded to indicate monotherapy exposure to antidepressants.

MAIN OUTCOMES AND MEASURES We used multivariable logistic regression to calculate adjusted odds ratios (aORs) and 95% confidence intervals for associations between maternal antidepressant use and birth defects. We compared early pregnancy antidepressant-exposed women with those without antidepressant exposure and, to partially account for confounding by underlying maternal conditions, those exposed to antidepressants outside of the birth defect development critical period.

RESULTS This study included 20 620 case mothers of infants with birth defects and 11 476

+ Editorial
+ Supplemental

Anderson KN, Lind JN, Simeone RM, Bobo WV, Mitchell AA, Riehle-Colarusso T, Polen KN, Reefhuis J. Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects. *JAMA Psychiatry*. 2020 Aug 5:e202453.

Huybrechts KF, Palmsten K, Avorn J, Cohen LS, Holmes LB, Franklin JM, Mogun H, Levin R, Kowal M, Setoguchi S, Hernández-Díaz S. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med*. 2014 Jun 19;370(25):2397-407.

Wisner KL, Oberlander TF, Huybrechts KF. The Association Between Antidepressant Exposure and Birth Defects—Are We There Yet? *JAMA Psychiatry*. 2020 Aug 5.



EDITORIAL

The Association Between Antidepressant Exposure and Birth Defects—Are We There Yet?

Katherine L. Wisner, MD, MS; Tim F. Oberlander, MD, FRCP; Krista F. Huybrechts, MS, PhD

Few moments are more concerning to parents than learning that their infant has a birth defect. Compounding this news is the possibility that the medication used to manage the mother’s mood disorder may have increased the risk for her infant developing a birth defect. As health care professionals, we have an enormous obligation to get the science right. In 2007, an editorial was published in response to 2 large case-control studies, “Teratogenicity of SSRIs: Serious Concern or Much Ado about Little?”¹ What have we learned over the ensuing 13 years?

Anderson et al² aimed to determine which antidepressants are associated with birth defects. They state, “such analyses can support work to identify medications with the highest and lowest birth defect risks independent of the underlying condition.”² This statement implies that the broad adverse effects of psychiatric illness can be distinguished from the effect of medications on the risk for birth defects, a formidable challenge in observational research.

Data from the National Birth Defects Prevention Study were used to compare the risks of congenital malformations in women exposed in early pregnancy to 2 reference groups: (1) unexposed women and (2) women treated with antidepressants 2 to 3 months before and/or after embryogenesis (months 4-9). The second group was included to account for confounding by indication, the major challenge plaguing observational studies. However, the National Birth Defects Prevention Study data set does not include psychiatric diag-

able is unlikely to change the effect estimate by at least 10%, several variables together might. Other principled approaches to confounder selection have been recommended over data-driven statistical methods.⁴ Selective serotonin reuptake inhibitor exposure may be a proxy for unidentified environmental and/or genetic factors associated with maternal mental illness that are associated with birth defects. The absence of information on characteristics, such as socioeconomic disadvantage, toxin exposures, and substance use that often accompany poor mental health, renders the results challenging to interpret owing to concern about residual confounding.

The second comparison focused on women exposed to antidepressants during the first trimester vs exposed outside of the first trimester. The validity of this comparison depends on equivalence of the groups relative to the severity and functional sequelae of the underlying psychiatric disorder. Using the same 10% change-in-estimate approach, the authors adjusted only for maternal education. The set of characteristics presented in Table 2 are helpful but insufficient to demonstrate their comparability with respect to the psychiatric disorder, comorbid conditions (eg, diabetes and/or hypertension), or concomitant drug exposures (eg, anticonvulsants and/or antimanic agents) that may be associated with increased risk for fetal malformations. The authors highlighted the results for the serotonin-norepinephrine reuptake inhibitor venlafaxine, which is not a first-line drug for pregnant women, as indicated by the relatively low frequency of use

Read our blog post on this topic: <https://womensmentalhealth.org/posts/antidepressant-birth-defects/>



ORIGINAL ARTICLE

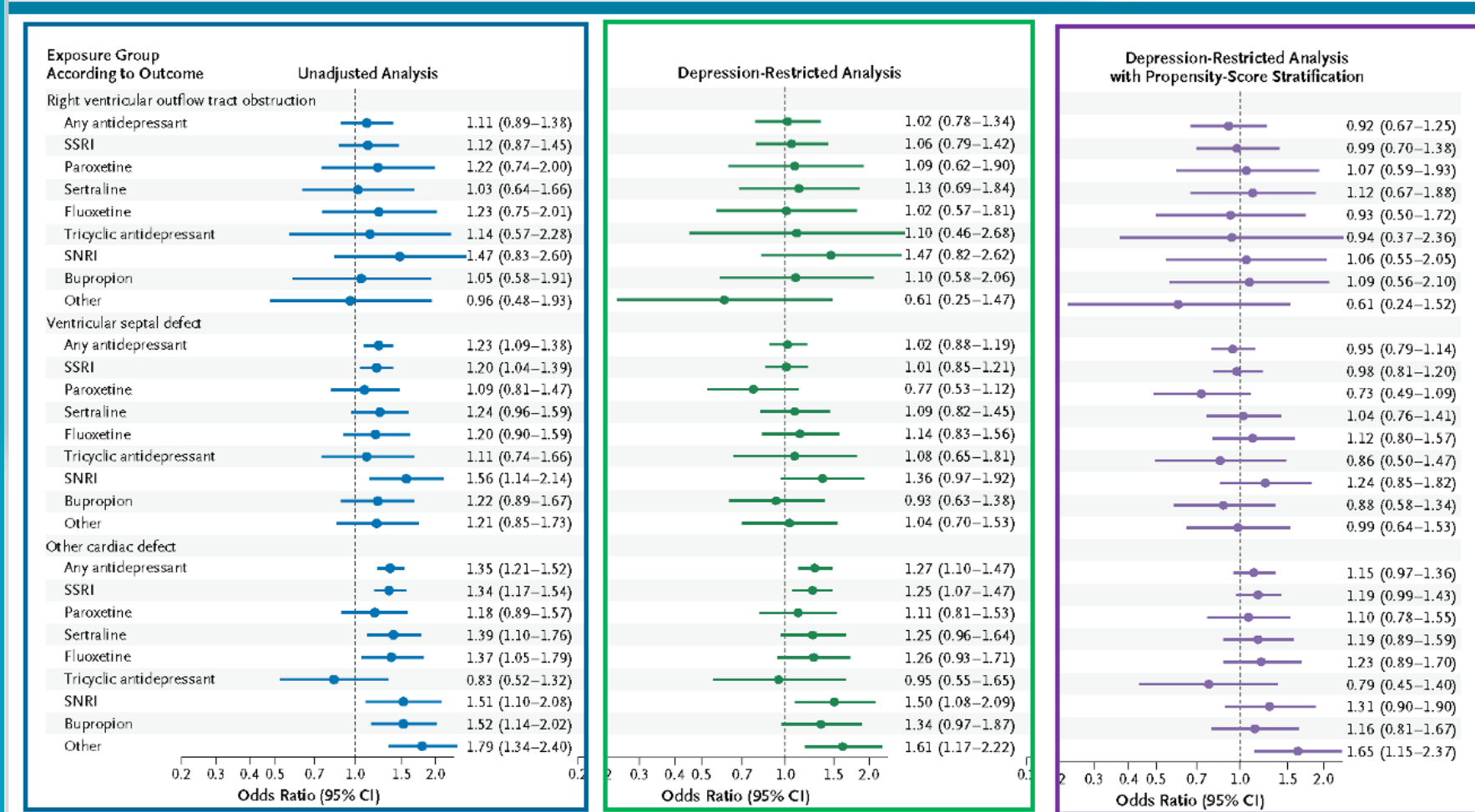
Antidepressant Use in Pregnancy and the Risk of Cardiac Defects

Krista F. Huybrechts, Ph.D., Kristin Palmsten, Sc.D., Jerry Avorn, M.D.,
Lee S. Cohen, M.D., Lewis B. Holmes, M.D., Jessica M. Franklin, Ph.D.,
Helen Mogun, M.S., Raisa Levin, M.S., Mary Kowal, B.A.,
Soko Setoguchi, M.D., Dr.P.H., and Sonia Hernández-Díaz, M.D., Dr.P.H.

N ENGL J MED 370;25 NEJM.ORG JUNE 19, 2014

- No evidence of increased risk for major malformations or cardiovascular malformations in children of pregnant women exposed to SSRIs

Cardiovascular Malformation and Fetal SSRI Exposure





Bupropion and Pregnancy

- Bupropion Pregnancy Registry, prospective birth outcome data
 - 3.6% (24/675) of the cohort experienced a congenital anomaly after first trimester exposure
 - There was no clear pattern of type of birth defects
- Small prospective study N=136 women who used bupropion in the first trimester, there was no evidence of increased rates of malformations compared with two groups of women, those who used other antidepressants or and those who had known nonteratogen exposures
- No malformations/ cardiovascular malformations seen in large study after controlling for confounding variables (Huybrechts et al. *NEJM* 2014)
 - Small but increased risk of cardiovascular left outflow defects was reported in a retrospective case control study from a birth defect registry (The absolute risk was approximately 2 out of 1000 pregnancies)

http://pregnancyregistry.gsk.com/documents/bup_report_final_2008.pdf. Chun-Fai-Chan B et al., Am J Obstet Gynecol. 2005;192(3):932-6. Cole et al., Pharmacoepidemiol Drug Saf. 2007;16(5):474-84. Alwan et al., Am J Obstet Gynecol. 2010;203(1):52.e1-6.; Huybrechts et al. *NEJM* 2014.



“Poor Neonatal Adaptation” and SSRI Use During Pregnancy

- **Consistent data:** Late trimester exposure to SSRIs is associated with *transient* irritability, agitation, jitteriness, and tachypnea (25-30%)
- Overall studies do not adequately control for maternal mental health condition, adequate blinding of exposure in neonatal assessments
- **Clinical implication: Should women be treated with antidepressants late in pregnancy and during labor and delivery (Warburton et al. 2010)**
- Are any subgroups of newborns vulnerable to enduring symptoms beyond the first days of life ?

Levinson-Castiel R, et al. *Arch Pediatr Adolesc Med.* 2006

Chambers CD, et al. *N Engl J Med.* 2006

Chambers, *BMJ*, 2009

CWMH Blog, July 27 2005: <http://womensmentalhealth.org/posts/neonatal-symptoms-after-in-utero-exposure-to-ssris/>



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What are the Long-term Neurobehavioral Effects of Prenatal Exposure to an Antidepressant?

In Utero Antidepressants and Neurodevelopmental Outcomes in Kindergarteners

Beena Singal, PhD,* Ben Chateau, PhD,¹ Sharon Struck, BS^{1,2}, Janelle Baran Lee, BA,³ Matthew Dahl, MSc,⁴ Shelly Derksen, MSc,⁵ Laurence Y Katz, MD,⁶ Chelsea Ruth, MD,⁷ Jea Hanlon-Dearman, MD,⁸ Marco Brownell, PhD⁹

OBJECTIVE: To determine if in utero selective serotonin reuptake inhibitor (SSRI) or selective serotonin norepinephrine inhibitor (SNRI) exposure is associated with developmental vulnerability in kindergarten among children whose mothers were diagnosed with prenatal mood or anxiety disorder.

METHODS: Linkable administrative data were used to create a population-based cohort of 266 479 mother-child dyads of children born in Manitoba, Canada, between 1996 and 2014, with follow-up through 2015. The sample was restricted to mothers who had a mood or anxiety disorder diagnosis between 90 days before conception (N = 13 818). Exposed women had ≥2 SSRI or SNRI dispensations during pregnancy (n = 2055); unexposed mothers did not have a dispensation of an SSRI or SNRI during pregnancy (n = 10 017). The Early Development Instrument (EDI) was used to assess developmental health in kindergarten children. The EDI is a 104-component kindergarten teacher-administered questionnaire, encompassing 5 developmental domains.

RESULTS: Of the 3048 children included in the study who met inclusion criteria and had an EDI, 21.43% of children in the exposed group were assessed as vulnerable on 2 or more domains versus 16.16% of children in the unexposed group [adjusted odds ratio = 1.43; 95% confidence interval 1.08–1.90]. Children in the exposed group also had a significant risk of being vulnerable in language and/or cognition (adjusted odds ratio = 1.40; 95% confidence interval 1.03–1.90).

CONCLUSIONS: Exposure to SSRIs or SNRIs during pregnancy was associated with an increased risk of developmental vulnerability and an increased risk of deficits in language and/or cognition. Replication of results is necessary before clinical implications can be reached.

abstract



*Division of Biostatistics, Department of Pediatrics and Child Health, †Section of Developmental Pediatrics, Department of Pediatrics and Child Health Policy, and ‡Department of Community Health Sciences, Manitoba Centre for Health Policy, and †Department of Psychiatry, Child and Adolescent Psychiatry Health Sciences Centre, †The Rady College of Medicine, †Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

Dr Singal conceptualized the study, acquired the data, and wrote the primary manuscript draft; Dr Brownell conceptualized the study, critically reviewed drafts of the manuscript, and provided supervision; Dr Chateau conceptualized the analysis plan, critically reviewed drafts of the manuscript, and provided supervision; Mr Dahl and Ms Derksen ran all statistical analysis and revised drafts of the manuscript; Ms Struck and Ms Lee provided research support and helped draft the manuscript; Drs Katz, Ruth, and Hanlon-Dearman contributed to the conceptualization of the study, critically reviewed drafts of the manuscript, and provided content expertise, and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: <https://doi.org/10.1542/peds.2019-1157>

WHAT'S KNOWN ON THIS SUBJECT: Children exposed in utero to antidepressants have higher rates of adverse outcomes in infancy. However, there are limited studies that investigate the long-term neurodevelopmental effects of in utero exposure to these medications on early childhood development.

WHAT THIS STUDY ADDS: Children of mothers diagnosed with a mood or anxiety disorder who took serotonergic antidepressants during pregnancy had an increased risk of developmental vulnerability and deficits in language and cognition in kindergarten.

Key words: Singal B, Chateau B, Struck S, et al. In Utero Antidepressants and Neurodevelopmental Outcomes in Kindergarteners. *Pediatrics* 2020;145(5):e20191157

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PEDIATRICS Volume 145, number 5, May 2020:e20191157

ARTICLE



Neurodevelopmental Outcomes in Kindergarteners with Prenatal Exposure to Antidepressants

By MGH Center for Women's Mental Health | June 2nd, 2020 | Antidepressants and Pregnancy, Child Development, Psychiatric Disorders During Pregnancy | 0 Comments



While we have data to support the use of antidepressants, including the selective serotonin reuptake inhibitors (SSRIs) and the serotonin norepinephrine reuptake inhibitors (SNRIs), during pregnancy, most studies have focused on risk of congenital malformations, and we have less information on longer term neurodevelopmental outcomes. In a recent study, Singal and colleagues look at neurodevelopmental outcomes in kindergarteners with prenatal exposure to

Full blog post: <https://womensmentalhealth.org/posts/antidepressants-neurodevelopment/>

Singal D, Chateau B, Struck S, Lee JB, Dahl M, Derksen S, Katz LY, Ruth C, Hanlon-Dearman A, Brownell M. In Utero Antidepressants and Neurodevelopmental Outcomes in Kindergarteners. *Pediatrics*. 2020 May;145(5).

Andrade C. Genes as Unmeasured and Unknown Confounders in Studies of Neurodevelopmental Outcomes After Antidepressant Prescription During Pregnancy. *J Clin Psychiatry*. 2020 May;26:81(3):20f13463. Free Article

Rommel AS, Bergink V, Liu X, Munk-Olsen T, Molenaar NM. Long-Term Effects of Intrauterine Exposure to Antidepressants on Physical, Neurodevelopmental, and Psychiatric Outcomes: A Systematic Review. *J Clin Psychiatry*. 2020 May;12:81(3):19r12965.

Andrade C. Offspring Outcomes in Studies of Antidepressant-Treated Pregnancies Depend on the Choice of Control Group. *J Clin Psychiatry*. 2017 Mar;78(3):e294-e297. Free Article



Research

JAMA Pediatrics | [Original Investigation](#)

Risk for Autism Spectrum Disorders According to Period of Prenatal Antidepressant Exposure

A Systematic Review and Meta-analysis

Antonia Mezzacappa, MD; Pierre-Alexandre Lasica; Francesco Gianfagna, MD, PhD; Odile Cazas, MD; Patrick Hardy, MD, PhD; Bruno Falissard, MD, PhD; Anne-Laure Sutter-Dallay, MD, PhD; Florence Gressier, MD, PhD

JAMA Pediatr. 2017;171(6):555-563. doi:10.1001/jamapediatrics.2017.0124
Published online April 17, 2017.



Antidepressant Exposure During Pregnancy and Risk of Autism in the Offspring, 1:

Meta-Review of Meta-Analyses

Chittaranjan Andrade, MD

Table 1. Important Findings From the Meta-Analysis of Kobayashi et al⁹

1. SSRI exposure during pregnancy was associated with an increased risk of ASD in the offspring in the case-control studies (5 studies; OR= 1.37; 95% CI, 1.08–1.74) and in one (2 studies; OR= 1.89; 95% CI, 1.28–1.88) but not the other (2 studies; OR= 1.69; 95% CI, 0.80–3.57) combination of the cohort studies.
2. There was no difference in ASD risk when exposure was compared between SSRIs and other antidepressant drugs in either case-control or cohort study analyses.
3. When analysis was restricted to datasets of mothers with psychiatric disorders, SSRIs were not associated with an increased risk of ASD in the case-control studies (1 study; OR= 1.86; 95% CI, 0.76–4.58) and in both sets of cohort studies (2 studies, each; OR= 0.79; 95% CI, 0.51–1.23 and OR= 1.03; 95% CI, 0.49–2.15).

Abbreviations: ASD = autism spectrum disorder, CI = confidence interval, OR = odds ratio, SSRI = selective serotonin reuptake inhibitor.

Kobayashi et al⁹

1. SSRI exposure during pregnancy was associated with an increased risk of ASD in the offspring in the case-control studies (5 studies; OR= 1.37; 95% CI, 1.08–1.74) and in one (2 studies; OR= 1.89; 95% CI, 1.28–1.88) but not the other (2 studies; OR= 1.69; 95% CI, 0.80–3.57) combination of the cohort studies.
2. There was no difference in ASD risk when exposure was compared between SSRIs and other antidepressant drugs in either case-control or cohort study analyses.
3. When analysis was restricted to datasets of mothers with psychiatric disorders, SSRIs were not associated with an increased risk of ASD in the case-control studies (1 study; OR= 1.86; 95% CI, 0.76–4.58) and in both sets of cohort studies (2 studies, each; OR= 0.79; 95% CI, 0.51–1.23 and OR= 1.03; 95% CI, 0.49–2.15).

Abbreviations: ASD = autism spectrum disorder, CI = confidence interval,



Table 3. Important Findings From the Meta-Analysis of Brown et al¹¹

1. In unadjusted analyses, exposure to SSRIs during pregnancy was associated with an increased risk of ASD in the offspring in both case-control (4 studies; OR= 1.7; 95% CI, 1.3–2.3) and cohort (2 studies; OR= 1.8; 95% CI, 1.3–2.6) studies.
2. In unadjusted analyses, exposure to SSRIs during the first trimester was associated with an increased risk of ASD in the offspring in both case-control (4 studies; OR= 2.0; 95% CI, 1.3–3.1) and cohort (2 studies; OR= 1.8; 95% CI, 1.3–2.6) studies.
3. After adjusting for potential confounders, exposure to SSRIs during pregnancy was associated with borderline significant risk of ASD in the offspring in the case-control studies (4 studies, OR, 1.4; 95% CI, 1.0–2.0) and with nonsignificant risk in the cohort studies (2 studies; OR= 1.5; 95% CI, 0.9–2.7).
4. After adjusting for potential confounders, exposure to SSRIs during the first trimester was associated with increased risk of ASD in the offspring in the case-control studies (4 studies, OR= 1.7; 95% CI, 1.1–2.6) and with nonsignificant risk in the cohort studies (1 study; OR= 1.4; 95% CI, 1.0–1.9).
5. In analyses restricted to datasets that controlled for maternal mental illness, SSRI exposure during pregnancy was not associated with an increased risk of ASD in the offspring in either case-control (3 studies; OR= 1.4; 95% CI, 0.9–2.2) or cohort (2 studies; OR= 1.5; 95% CI, 0.9–2.7) studies.
6. In analyses restricted to datasets that controlled for maternal mental illness, SSRI exposure during the first trimester was associated with an increased risk of ASD in the offspring in the case-control studies (3 studies; OR= 1.8; 95% CI, 1.1–3.1). In the cohort studies, the risk was not significant (1 study; OR= 1.4; 95% CI, 1.0–1.9).

Abbreviations: ASD = autism spectrum disorder, CI = confidence interval, OR = odds ratio, SSRI = selective serotonin reuptake inhibitor.

Treatment Guidelines Depression: Does Severity Drive Treatment Recommendations (and Patient Choice)



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- **Psychotherapy: First-line for mild to moderate MDD**
- Lifestyle components: Nutrition, weight management, prenatal care ; treatment for co-morbid substance abuse
- Evidence base for CBT , Behavioral Activation and MBCT (prevention)
- **Women trying to conceive who have histories of MDD:**
 - Encourage period of euthymia
 - Sustained remission: consider tapering and discontinuing ?
 - More recently depressed or with symptoms: consider remaining on medication, optimizing medication
- **Pregnant women with severe MDD: Medication is first-line**
- **Pregnant women on antidepressants during pregnancy:** take into account patient preferences, previous course of illness
- Medication selection should be based on known safety information

MDD, major depressive disorder.

Yonkers KA et al. *Obstet Gynecol.* 2009;114(3):703-713.

Treatment of Depression During Pregnancy: Lessons Learned



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- Treatment decisions are complex (maternal and fetal benefits and risks)
- Absolute quantification of risk associated with fetal exposure to medication or maternal disease is impossible
- No treatment decision is “perfect”
- Each treatment decision should try to optimize pregnancy outcomes for the mother and her child
- Consider the risks of untreated disease and the risks of medication treatment
- Wisdom of changing or discontinuing AD proximate to delivery is sparse

Kallen Obstet Gynecol Int. 2012

Palmsten and Hernandez-Diaz Epidemiology 2012

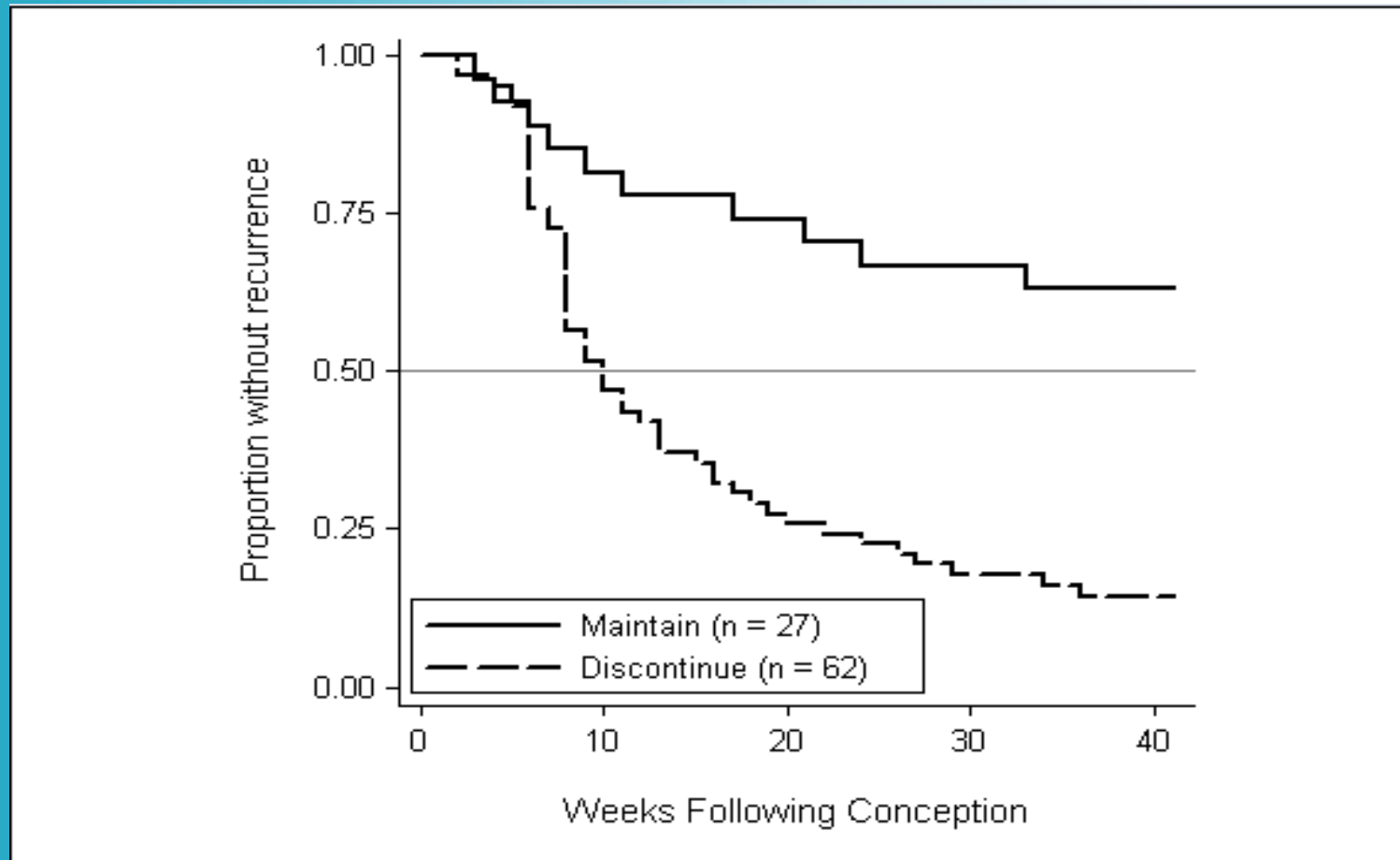


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Bipolar Disorder During Pregnancy

Relapse of Bipolar Disorder During Pregnancy



Viguera et al. *Am J Psychiatry* 2007



Pharmacologic Treatment of Pregnant Women with Bipolar Disorder: Weighing Imperfect Options

- Commonly employed antimanic agents are either known teratogens or have incomplete reproductive safety data
- Risks of untreated bipolar disorder during pregnancy
- Risk of discontinuing maintenance psychotropic medications

Cohen LS, et al. *JAMA*. 1994

Steer RA, et al. *J Clin Epidemiol*. 1992

Orr ST, et al. *Am J Prev Med*. 1996

Suppes T, et al. *Arch Gen Psychiatry*. 1991

Faedda GL, et al. *Arch Gen Psychiatry*. 1993

Baldessarini RJ, et al. *Clin Psychiatry*. 1996



Antipsychotic Use in Pregnancy and the Risk for Congenital Malformations

Krista F. Huybrechts, MS, PhD; Sonia Hernández-Díaz, MD, DrPH; Elisabetta Paterno, MD, DrPH;
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JAMA Psychiatry. 2016;73(9):938-946. doi:10.1001/jamapsychiatry.2016.1520
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- Primary aim: determine the risk of major malformations among infants exposed to atypical antipsychotics
- Examined Medicaid claim data from 1,341,715 pregnancies
- After adjustment for confounding, the risk ratio for congenital malformation in exposed versus unexposed infants was 1.05 (95% CI=0.96-1.16)
- A slightly increased risk in overall and cardiac malformations was noted for risperidone

National Pregnancy Registry for Atypical Antipsychotics



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A **NEW** Research Study at the
Massachusetts General Hospital
Center for Women's Mental Health

To determine the safety of atypical
antipsychotics in pregnancy for
women and their babies

Participation will involve **3** brief phone
interviews over approximately **8**
months

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Reproductive Safety of Second-Generation Antipsychotics: Updated Data From the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics

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Focus on Women's Mental Health



Table 4. Unadjusted and Adjusted Odds Ratios for Risk of Major Malformations Comparing Exposure Status With Second-Generation Antipsychotics (N = 1,344 Infants)

| Group | n | Prevalence of Malformations | Odds Ratio | 95% CI |
|--------------------------------------------|----|-----------------------------|--------------------------------------|----------------------------|
| First trimester exposure to SGAs (n = 640) | 16 | 2.50% | Adjusted: 1.483 Unadjusted: 1.264 | 0.625–3.517 0.612–2.610 |
| Unexposed to SGA (n = 704) | 14 | 1.99% | ... | ... |

Viguera et al 2021

ORIGINAL ARTICLE

Reproductive safety of aripiprazole: data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics

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Table 2 Odds ratio comparing number of malformations among infants exposed to aripiprazole ($N=163$) versus comparison group ($N=704$)

| Group | <i>N</i> | Prevalence | Odds ratio | 95% CI |
|----------------------------------------------------------|----------|------------|-------------------------------------|---------------------------|
| 1st trimester exposure to aripiprazole ($N=163$) | 7 | 4.26% | Unadjusted: 2.212 adjusted 1.349 | 0.878, 5.571 0.433, 4.917 |
| Unexposed to second-generation antipsychotic ($N=704$) | 14 | 1.99% | - | - |

Reproductive Safety of Quetiapine: NPRAA Findings



Table 4 – Pooled risk ratio of major malformations in babies exposed to quetiapine

| Data Source | Risk Ratio (95% Confidence Interval) |
|-------------------------------------------|--------------------------------------|
| Habermann 2013* | 1.46 (0.57-3.75) |
| Sadowski 2013* | 2.49 (0.64-9.71) |
| Huybrechts 2016# | 1.01 (0.88-1.17) |
| Cohen 2018 (current report)# | 0.90 (0.15-5.46) |
| Pooled risk ratio** | 1.03 (0.89-1.19) |
| P-value to assess homogeneity of the data | P=0.526 |

*healthy control group

#comparison group, adjusted for underlying psychiatric disorder

**accumulated evidence suggested no meaningful increased risk with pooled null risk ratio

Cohen et al., 2018; *Amer J Psychiatry*

- Updated risk estimate based on larger sample size (n=264) for quetiapine consistent with earlier data (2022)
- Presented at annual meeting of ASCP 2022 Phoenix, AZ



Reproductive Safety of Lurasidone: NPRAA Findings

- Recent data based on n=134 women exposed to lurasidone compared to controls (n=886) do not suggest increased risk for major congenital malformations

Presented at annual meeting of ASCP 2022 Phoenix, AZ

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Prevalence of ADHD and Autism Spectrum Disorders in Children with Prenatal Exposure to Antipsychotic Medications

By MGH Center for Women's Mental Health | August 31st, 2021 | Psychiatric Disorders During Pregnancy | 0 Comments



We have seen an increasing number of women of reproductive age treated with the newer atypical antipsychotic agents, and more women seek consultations regarding the reproductive safety of these newer medications. Over the last couple of years, we have seen a series of studies assessing the reproductive safety of this class of medications. However, we have very little information on the long-term effects of prenatal exposure to antipsychotic

medications.

From womensmentalhealth.org



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The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Lithium Use in Pregnancy and the Risk of Cardiac Malformations

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Helen Mogun, M.S., Lee S. Cohen, M.D.,
and Sonia Hernandez-Diaz, M.D., Dr.P.H.

https://womensmentalhealth.org/posts/12021/?doing_wp_cron=1506358912.7760159969329833984375

WWW.MGHCMC.ORG



Lithium and Pregnancy

- Lithium Register of Babies 1970s
- Ebstein’s Anomaly: 0.05 – 0.1% risk
- Recent analysis from Medicaid database shows dose-dependent increase in risk of cardiovascular anomalies

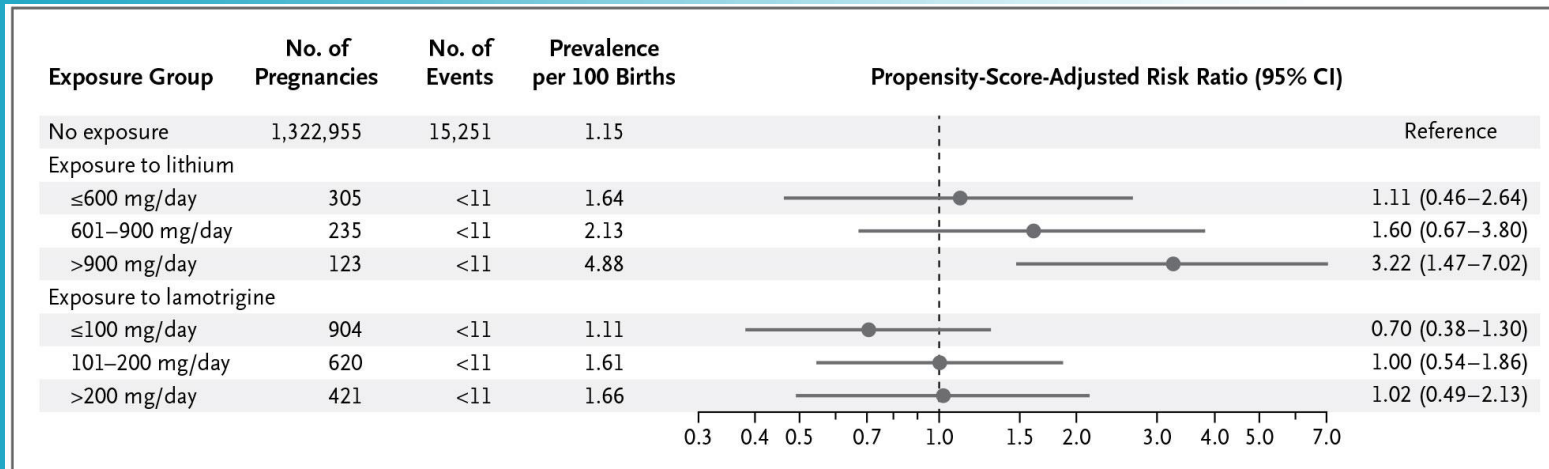


Figure 2. Absolute and Relative Risk of Cardiac Malformations among Lithium-Exposed and Lamotrigine-Exposed Infants as Compared with Unexposed Infants, Stratified According to the Mother’s Dose of the Drug.

Stratification was according to thirds of the first prescribed daily dose that was filled during the first trimester. A separate exposure propensity score was estimated in each dose stratum as the predicted probability of receiving the treatment-dose range of interest versus no treatment, conditional on the covariates reported in Tables S6 through S9 in the Supplementary Appendix. For each estimated propensity score, the population in the nonoverlapping areas of the propensity-score distributions was trimmed, and 50 strata were created on the basis of the distribution of the treated women. Weights for the reference group were calculated according to the distribution of the exposed women among propensity-score strata and were used to estimate adjusted risk ratios and 95% confidence intervals.



Valproic Acid and Pregnancy

- Overall risk of malformations elevated (6-10%): neural tube defects, cardiac anomalies, cleft lip/palate, limb abnormalities
- Dose dependent: Risk for major malformations highest (25.2%) in women on high dose valproate (above 1450 mg/day)
- Higher rates associated with polytherapy
- Neurodevelopmental sequelae: Increased risk of autism spectrum disorders, behavioral problems, lower IQ
- Folic acid appears to ameliorate risk of autism spectrum disorders but not risk of malformations
- UK and France have banned use of valproic acid in certain populations of reproductive age women



Other Antiepileptic Drugs and Pregnancy: North American AED Registry (2012)

- Of the 5,667 women taking an AED as monotherapy during the first trimester, 4,899 were eligible for analysis. The risks of major malformations were:
- 9.3% (30 of 323) for valproate (Depakote)
- 4.2% (15 of 359) for topiramate (Topamax)
- 3.0% (31 of 1,033) for carbamazepine (Tegretol)
- 2.4% (11 of 450) for levetiracetam (Keppra)
- 2.2% (4 of 182) for oxcarbazepine (Trileptal)
- 2.0% (31 of 1,562) for lamotrigine (Lamictal)

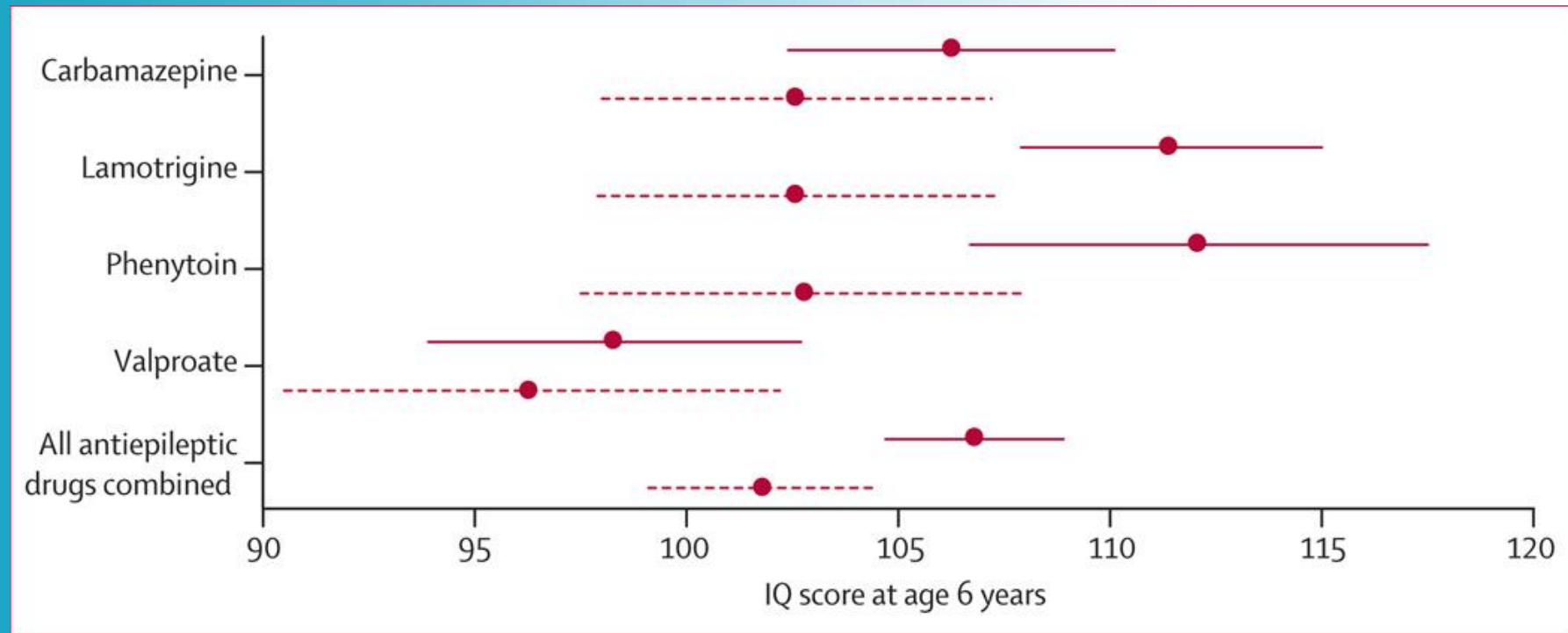
Growing data on safety of gabapentin (Patorno , 2020, PLoS1)

Hernandez-Diaz et al , Neurology , 2012



Cognitive Function in 6 year olds Following Fetal Exposure to AED's

Child IQ at 6 years, by exposure to maternal antiepileptic drug use and periconceptional folate



Meador, et al. *Lancet Neurol.* 2013



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Essential Reads: Neurodevelopmental Outcomes in Children with Prenatal Exposure to Antiepileptic Drugs

By MGH Center for Women's Mental Health | September 1st, 2021 | Child Development, Child Outcomes | 0 Comments



While much data focuses on the risk of prenatal exposure to antiepileptic drugs (AEDs) and the risk of congenital malformations, there is a growing body of literature to indicate that exposure to certain antiepileptic drugs, most notably valproic acid (VPA, Depakote) during critical periods of development may be associated with long-lasting neurodevelopmental deficits across multiple domains. While

From womensmentalhealth.org



Treatment of Bipolar Illness During Pregnancy: What is a Reasonable Strategy?

- Lithium and lamotrigine have well characterized reproductive safety profiles, low absolute risks
- Lithium may be the best characterized and reasonable alternative for women who require an anti-manic agent **but its use is declining**
- Lamotrigine appears reasonable for the prevention of depressive episodes (but not for mania per se)
- Atypical antipsychotics have growing body of data and do not at this time appear to be major teratogens
 - May be reasonable to continue during pregnancy, particularly if patient has had good response, psychotic symptoms, is a lithium non-responder, or atypical was critical in affording euthymia



Benzodiazepines

- Methodological issues have confounded reports: dose, duration, class of BZD, other drug exposures, recall bias
- Risk of oral clefts following first trimester exposure (0-0.6%)
- Most studies show no increase in malformations, no consistent pattern of defects
- Incidence of neonatal adverse sequelae is low

Altshuler, Cohen et al. *Am J Psychiatry*. 1996.
Dolovich, et al. *BMJ*. 1998.



Non-Benzodiazepine Hypnotics

- Much less studied than benzodiazepines
- Zolpidem
 - Largest study suggested increased association with obstetrical complications (low birth weight, preterm delivery)
 - No evidence of major malformations
- Class as a whole that has been studied does not appear to increase risk of teratogenicity, although there are few studies
 - Zopiclone, zolpidem, zaleplon do not appear to increase risk of major malformations

Wikner and Kallen. J Clin Psychopharmacol 2011; Wang et al., Clin Pharm Ther 2010; Wikner et al., Pharmacoepidemiol Drug Saf 2007.



Stimulants during Pregnancy

- From the current available data from prospective, retrospective and case control studies it can be concluded that **none of the medications (except guanfacine, where data is unavailable) used for the treatment of ADHD is a major human teratogen.**
- Available data do suggest the possibility that psychostimulants, especially amphetamines, may increase the risk of preeclampsia and possibly certain other adverse gestational outcomes; the absolute risk, however, is low.
- Long-term neurodevelopmental studies on the offspring are sparse
- If treatment is pursued, methylphenidate, amphetamine and bupropion appear to be better choices than other medication where reproductive safety data are sparse

Cannabis and Pregnancy



WOMEN'S HEALTH ALERT

FDA Office of Women's Health

October 17, 2019

www.fda.gov/womens

Message from the Acting Associate Commissioner

Dear Women's Health Colleagues,

Today, the Office of Women's Health is sharing an important announcement issued by FDA regarding the use of cannabis and cannabis-derived products while pregnant or breastfeeding. There are many potential negative health effects from using marijuana and other products containing tetrahydrocannabinol (THC) during pregnancy and while breastfeeding. Therefore, FDA strongly advises against the use of cannabidiol (CBD), THC, and marijuana in any form during pregnancy or while breastfeeding. I encourage you to read the consumer update below.

Sincerely,

Kaveeta Vasisht, M.D., Pharm.D.

Acting Associate Commissioner for Women's Health

What You Should Know About Using Cannabis, Including CBD, When Pregnant or Breastfeeding

Cannabis and Cannabis-derived products have become increasingly available in recent years, with new and different types of products appearing all the time. These products raise questions and concerns for many consumers. And if you are pregnant or breastfeeding, you might have even more questions about whether these products are safe for you.

FDA strongly advises against the use of cannabidiol (CBD), tetrahydrocannabinol (THC), and marijuana in any form during pregnancy or while breastfeeding.

[Read the full Consumer Update](#)



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Essential Reads: Guidelines for the Use of Electroconvulsive Therapy During Pregnancy

By MGH Center for Women's Mental Health | August 4th, 2021 | Depression, Essential Reads, Psychiatric Disorders During Pregnancy | 0 Comments



Electroconvulsive therapy (ECT) is one of the most effective treatments for depression, with response rates consistently higher than those observed in clinical trials of traditional antidepressants. Furthermore, ECT may be more effective than medications for treatment-refractory depression. The American Psychiatric Association (APA) recommends ECT for patients who have not responded to pharmacological treatments, as well as for those patients who experience severe psychiatric

symptoms, including psychosis, suicidal ideation, catatonia, and mania.

From womensmentalhealth.org

National Psychiatric Consultation Line



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A photograph of a pregnant woman's belly, which serves as the background for the PSI Psychiatric Consult Line information box.

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Perinatal Psychiatric Consult Service

Medical prescribers can call our free consultation line. Within 24 hours of calling you will be connected with an expert perinatal psychiatrist who can provide advice on diagnosis, treatment and medication management for preconception, pregnant and postpartum women.

For Medical Prescribers Only

- Free, expert consultation line.
- Connected with a perinatal psychiatrist within 24 hours who can provide advice on diagnosis, treatment, and medication management for preconception, and pregnant and postpartum women.
- **NOT** an emergency hotline.



Treatment Guidelines for Psychotropic Drug Use in Pregnancy

LEE S. COHEN, M.D.

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Despite the apparent risks of psychotropic drug exposure in pregnancy, many pregnant women receive psychotropics. The major concerns associated with the use of antipsychotics, antidepressants, benzodiazepines, and lithium carbonate in pregnancy are reviewed, with clinical approaches for assessing the relative risks and benefits of treatment of psychiatrically ill pregnant patients and for choosing and instituting therapy with these agents.