MASSACHUSETTS GENERAL HOSPITAL
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Course and Treatment of Mood and Anxiety Disorders During Pregnancy : Lessons Learned Across Two Decades

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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: Alkermes Biopharmaceuticals ,Praxis Precision Medicines, Inc.(through MGH Clinical Trials Network Initiative); **Honoraria:** None
Royalty/patent, other income: None

Reproductive Psychiatry and the COVID-19 Pandemic

- Family planning and the pandemic
- Telemedicine and implications for pregnancy and postpartum period
- Infertility treatment and the pandemic
- 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

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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/

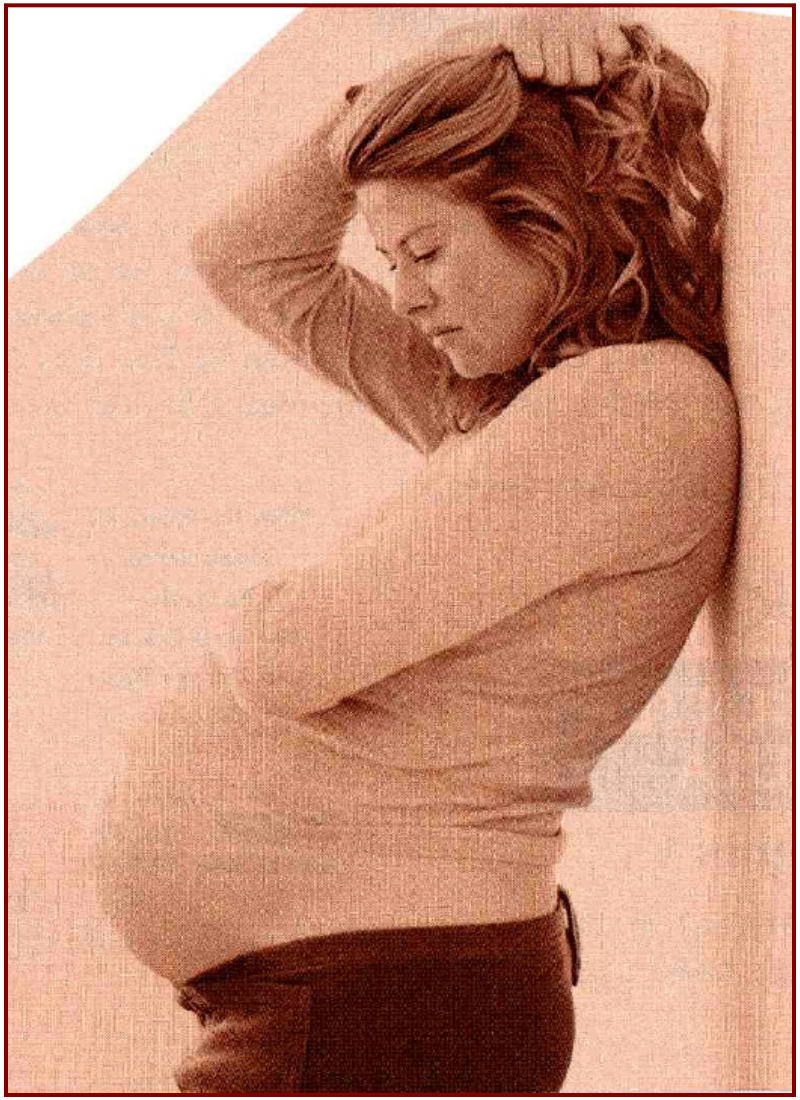
Treatment considerations for women with MDD in pregnancy and the postpartum period

- Depression during pregnancy is strongest predictor of postpartum depression
- **Nothing is more important maternal euthymia**

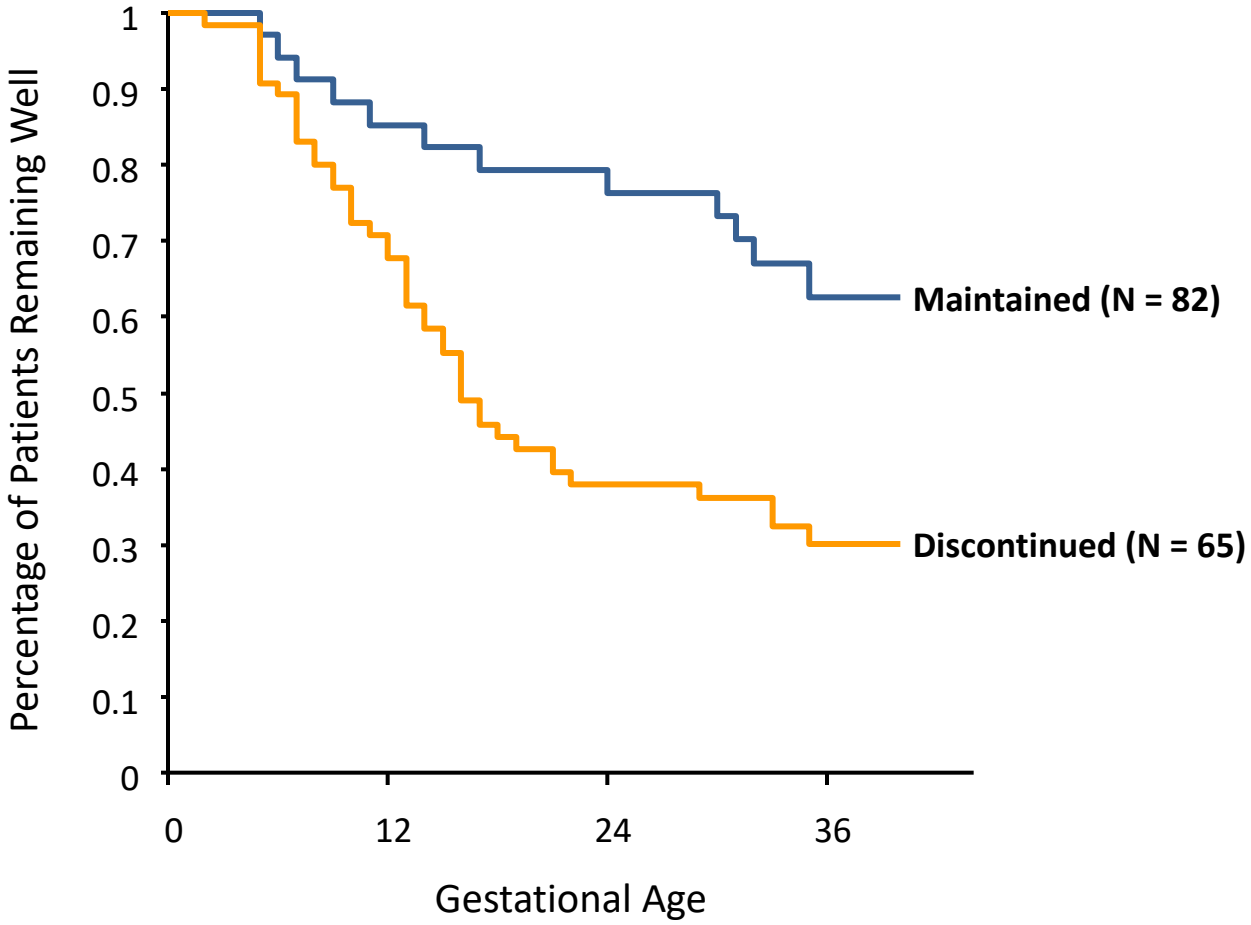
Major Depression During Pregnancy

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

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

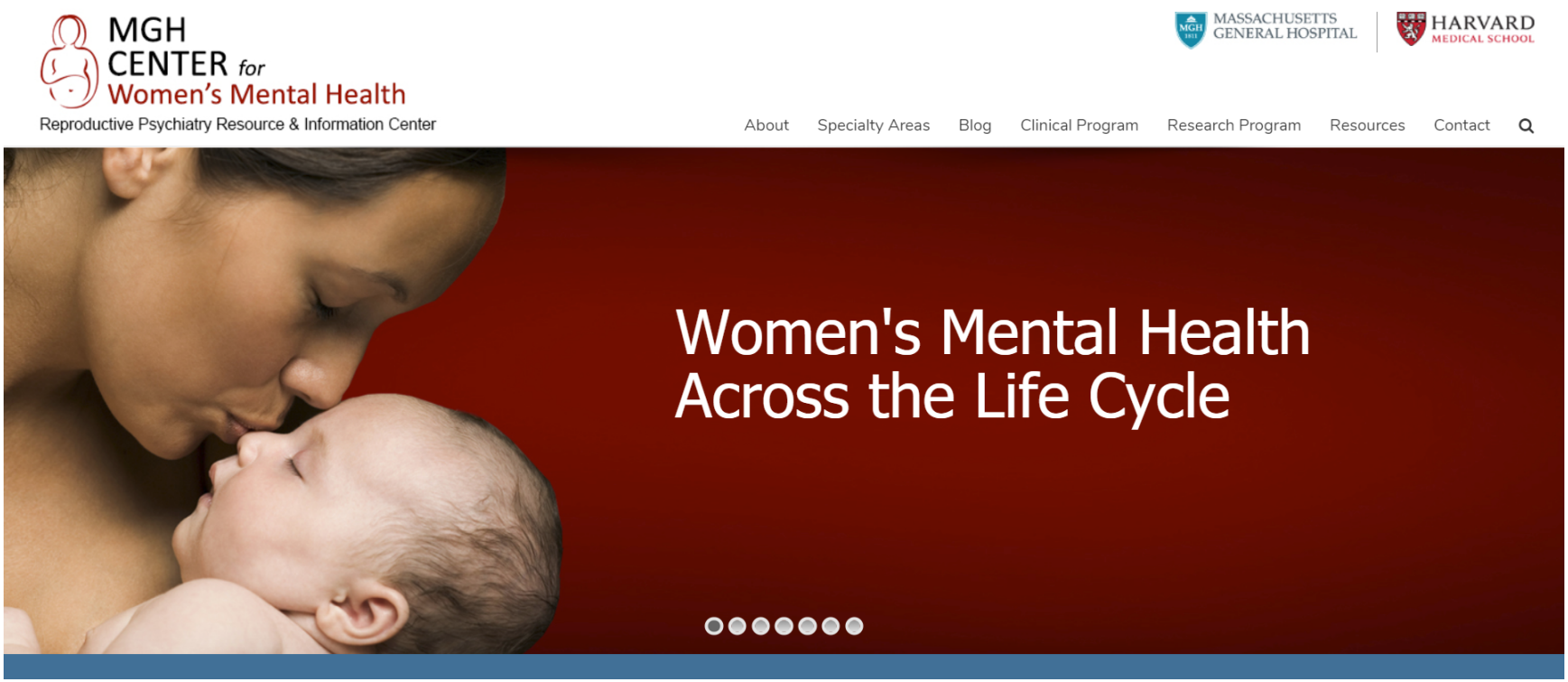


Time to Relapse in Patients Who Maintained or Discontinued Antidepressant



Cohen LS, et al. *JAMA*. 2006

Womensmentalhealth.org



Psychotropic Drug Use in Pregnancy

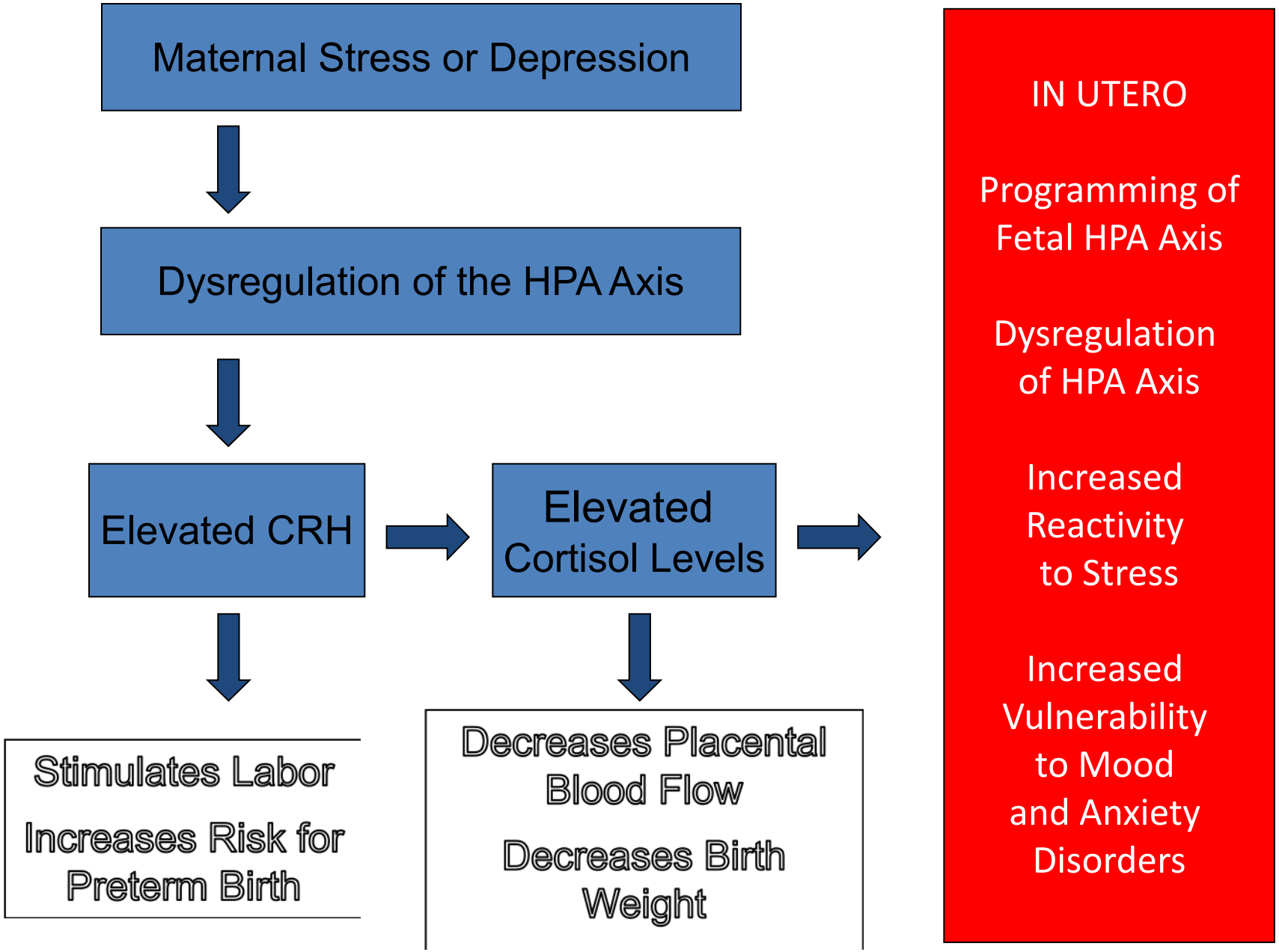
- Medications used when risk to mother and fetus from disorder outweighs risks of pharmacotherapy
- Optimum risk/benefit decision for psychiatrically ill pregnant women
- Patients with similar illness histories make different decisions regarding treatment during pregnancy
- No decision is risk-free
-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

Henshaw *Fam Plann Perspect*. 1998

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**


Maternal Stress or Depression
Dysregulation of the HPA Axis
Elevated CRH
Elevated Cortisol Levels
Stimulates Labor
Increases Risk for Preterm Birth
Decreases Placental Blood Flow
Decreases Birth Weight
IN UTERO
Programming of Fetal HPA Axis
Dysregulation of HPA Axis
Increased Reactivity to Stress
Increased Vulnerability to Mood and Anxiety Disorders

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.

What is the Safest Antidepressant for Women of Childbearing Age?

Phasing Out: FDA Pregnancy Categories

- **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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U.S. Food and Drug Administration
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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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http://womensmentalhealth.org/posts/fda-finalizes-guidelines-pregnancy-lactation-labeling-information/

Timeline to Changes in Product Labeling

	NDAs, BLA, ESs	Required Submission Date of PLLR Format
New Applications	Submitted on or after 6/30/2015	At time of submission
---------- PLLR Implementation Date (6/30/2015) ----------		
Older Approved Applications	Approved 6/30/2001 to 6/29/2002 Approved 6/30/2005 to 6/29/2007	6/30/2018
	Approved 6/30/2007 to 6/29/2015 Or pending on 6/30/2015	6/30/2019
	Approved 6/30/2002 to 6/29/2005	6/30/2020
	For applications approved prior to 6/30/2001 in old format labeling	Not required to be in PLLR format. However, must remove Pregnancy Category by 6/29/2018

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 small[1-3]
  - Consistent pattern of malformations with SSRI exposure is lacking
  - Case-control studies reveal inconsistent data regarding teratogenic risk of individual SSRIs[4-9]

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; [7]Wogelius 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

Research

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.

Editorial

Supplemental c

EDITORIAL

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

Katherine L. Wisner, MD, MS; Tim F. Oberlander, MD, FRCPC; 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?

Related article

Anderson et al[2] 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 diagnosis, which 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/

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.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

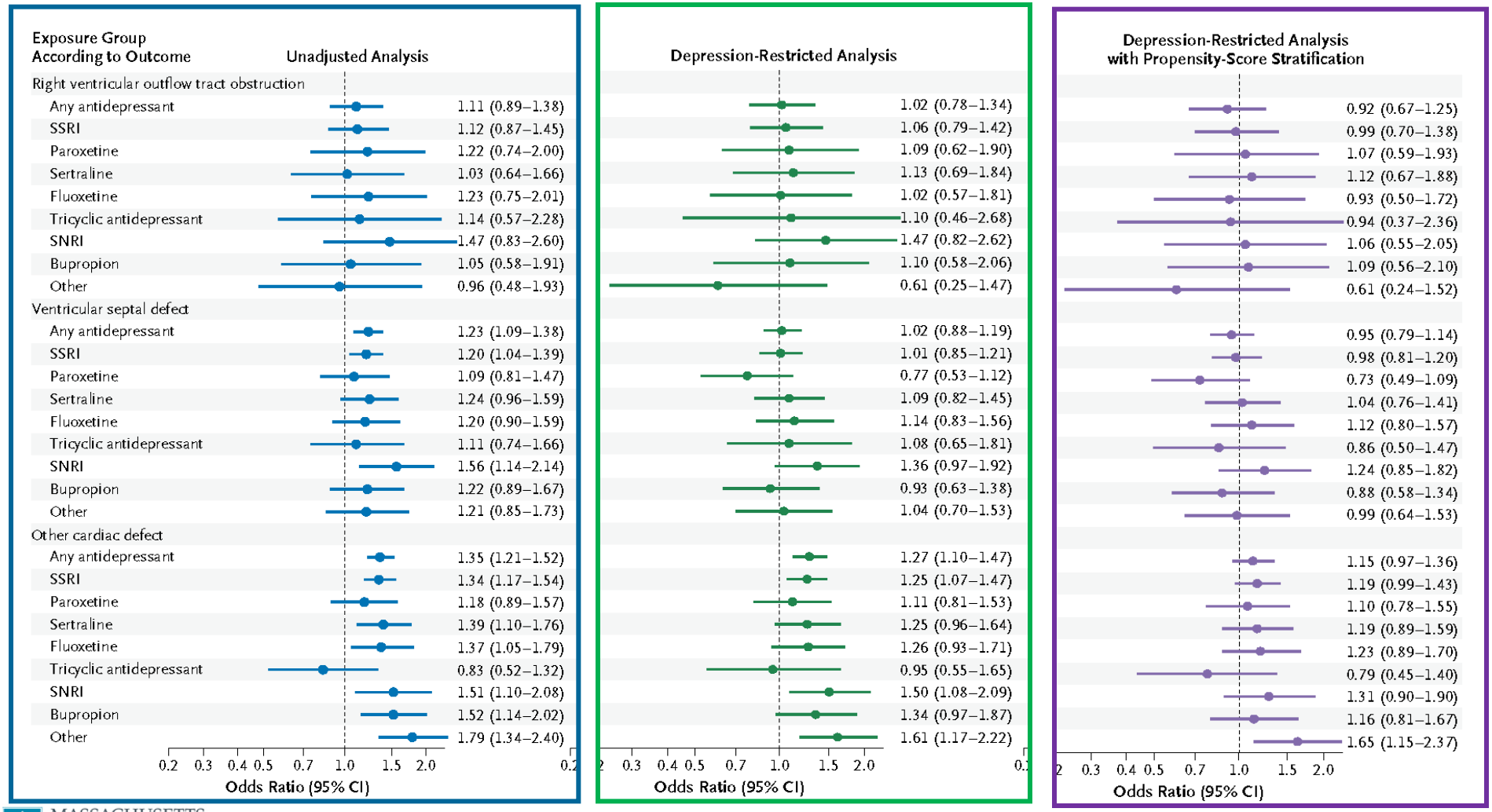
Antidepressant Use in Pregnancy and the Risk of Cardiac Defects

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



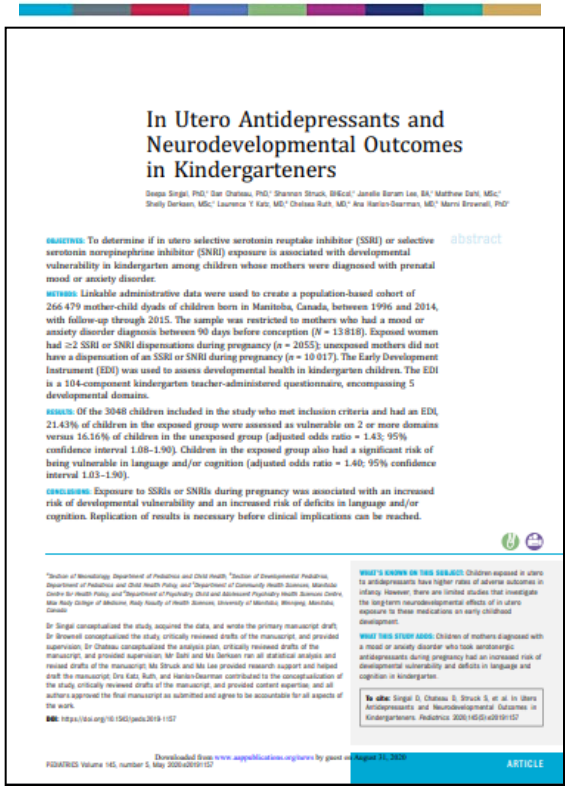
Huybrechts et al. *NEJM* 2014.

“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/

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



Neurodevelopmental Outcomes in Kindergartners 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 kindergartners with prenatal exposure to

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

Singal D, Chateau D, 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 Confounds 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.

Clinical and Practical **Psychopharmacology**

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 al[9]

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 al[9]

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).

Table 3. Important Findings From the Meta-Analysis of Brown et al[11]

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 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)

- **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

- 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 AD dose proximate to delivery is sparse

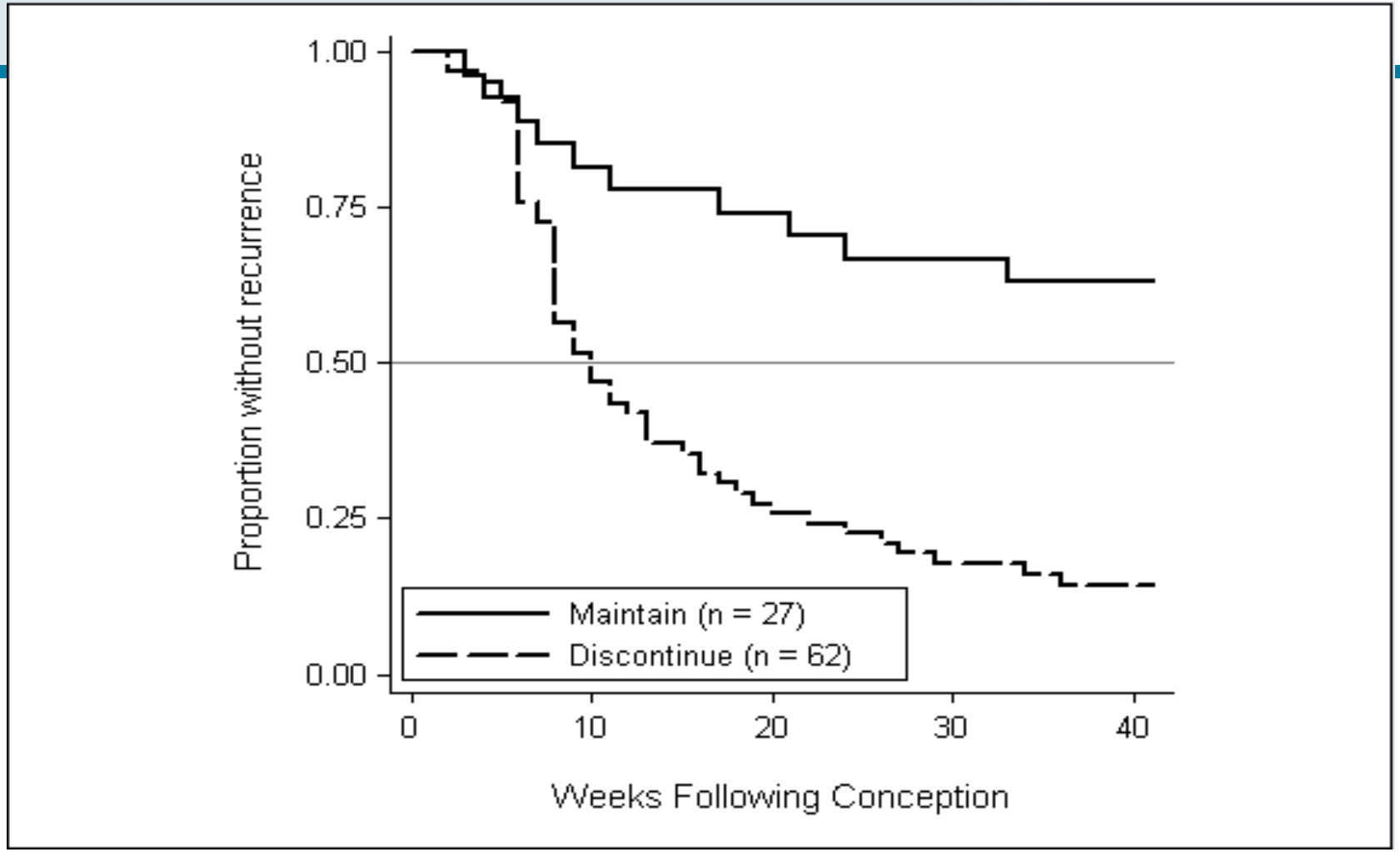
Kallen *Obstet Gynecol Int.* 2012
Palmsten and Hernandez-Diaz *Epidemiology* 2012

Summary of treatment considerations for women with MDD in pregnancy (cont.)

- Depression during pregnancy is strongest predictor of postpartum depression
- There are known and unknown risks associated with AD use during pregnancy
- Adverse effects of depression in pregnancy on patient, infant and families
- **Nothing trumps maternal euthymia**

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 sparse available reproductive safety data
- Risks of untreated psychiatric illness
- 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. C*lin Psychiatry*. 1996

National Pregnancy Registry for Atypical Antipsychotics

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

Call Toll-Free:
1-866-961-2388

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

The American Journal of Psychiatry

March 2016

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

Lee S. Cohen, M.D., Adele C. Viguera, M.D., M.P.H., Kathryn A. McInerney, Sc.M., Marlene P. Freeman, M.D., Alexandra Z. Sosinsky, B.S., Danna Moustafa, B.S., Samantha P. Marfurt, B.S., Molly A. Kwiatkowski, B.A., Shannon K. Murphy, B.A., Adriann M. Farrell, M.A., David Chitayat, M.D., Sonia Hernández-Díaz, M.P.H., Dr.P.H.

- Primary aim: determine the risk of major malformations among infants exposed to second-generation antipsychotics
- Prospectively enrolled 487 women
- The odds ratio for major malformations comparing exposed and unexposed infants was 1.25 (95% CI=0.13-12.19)
- Current data indicate that second-generation antipsychotics are not major teratogens
- Study is ongoing and continues to enroll women

National Pregnancy Registry for Atypical Antipsychotics: Interim Findings Aggregate Sample : May 2020

- Prospective study – current sample > 2000
- As of May, 2020:
  - 1906 subjects enrolled
  - 640 with 1st trimester exposures enrolled w/ evaluable data at time of analysis
  - 704 in comparison group (non-exposed)
  - Exposure group: 16 malformations (2.5% prevalence)
  - Control group: 14 malformations (2.0% prevalence)
  - Odds ratio major malformations (exposed versus controls) 1.48 (95% CI, 0.625 - 3.517)
- Preliminary conclusions: **atypical antipsychotics are not major teratogens but more data are needed to narrow the confidence interval**

National Pregnancy Registry for Atypical Antipsychotics: Interim Findings - Aripiprazole

- Prospective study
- As of May 2020:
  - 1906 enrolled
  - 163 1st trimester exposures enrolled w/ evaluable data at time of analysis, 7 cases malformations versus 14 of the 690 unexposed
  - Prevalence malformations = 4.29 % (exposed) vs. 1.99 %
  - Adjusted odds ratio; 1.35 (95% confidence interval [CI]= (0.433,4.197).
- Preliminary conclusions: **aripiprazole is not likely a major teratogen ;more data are needed to narrow the confidence interval**

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 suggests no meaningful increased risk with a pooled null risk ratio.

Cohen et al., 2018; Amer J Psychiatry

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lithium Use in Pregnancy and the Risk of Cardiac Malformations

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

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

Exposure Group	No. of Pregnancies	No. of Events	Prevalence per 100 Births	Propensity-Score-Adjusted Risk Ratio (95% CI)
No exposure	1,322,955	15,251	1.15	Reference
Exposure to lithium				
≤600 mg/day	305	<11	1.64	1.11 (0.46–2.64)
601–900 mg/day	235	<11	2.13	1.60 (0.67–3.80)
>900 mg/day	123	<11	4.88	3.22 (1.47–7.02)
Exposure to lamotrigine				
≤100 mg/day	904	<11	1.11	0.70 (0.38–1.30)
101–200 mg/day	620	<11	1.61	1.00 (0.54–1.86)
>200 mg/day	421	<11	1.66	1.02 (0.49–2.13)

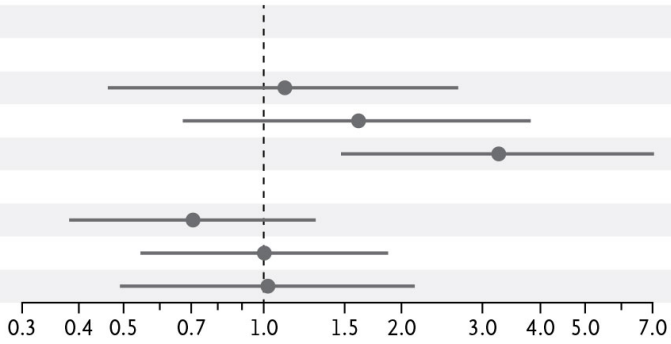


Figure 2. Absolute and Relative Risk of Cardiac Malformations among Lithium-Exposed and Lamotrigine-Exposed Infants as Compared with Unexposed Infants, Stratified According to the Mother's Dose of the Drug.

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 tautism 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 population s of reproductive age women

Other Antiepileptic Drugs and Pregnancy

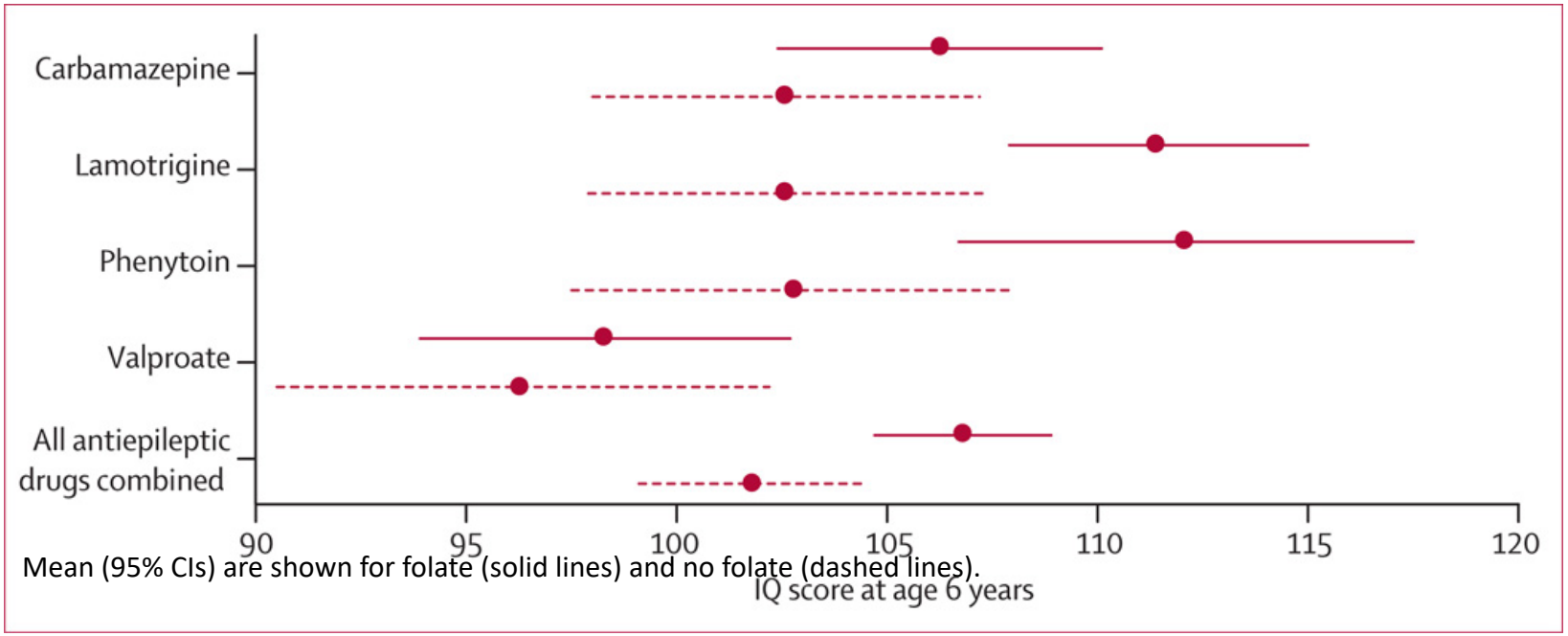
Recent study from EUROCAT

- 107 of 1957 for carbamazepine = 5·5%
- 6 of 152 for topiramate = 3·9%, oral clefts
- 10 of 333 for oxcarbazepine = 3·0%
- 74 of 2514 for lamotrigine = 2·9%

Inadequate data on the use of gabapentin, less than 350 exposures

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



Mean (95% CIs) are shown for folate (solid lines) and no folate (dashed lines).

Meador, et al. *Lancet Neurol*. 2013

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
  - More human pregnancy data available for older medications in the class
  - 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

Cohen LS, *J Clin Psychiatry* 2007 (suppl 9).

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%)
- Review of 12 studies (2001-2011): Most studies show no increase in malformations, no consistent pattern of defects

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

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

Cannibus and Pregnancy

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

FDA U.S. FOOD & DRUG ADMINISTRATION

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

ECT During Pregnancy

- Treatment of choice when expeditious management is imperative
- Use in delusional depression, mania
- External fetal monitoring, ultrasonography
- Comprehensive treatment team

MGH Perinatal Depression Scale