Maternal-Fetal Psychiatry: Managing Psychiatric High-Risk Pregnancies

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FINANCIAL DISCLOSURE

RELATIONSHIP	LAST 2 YEARS
Research Support	Magnus Medical, Navitor, Reunion Neuroscience, Sage Therapeutics, Supernus Pharmaceuticals
Advisory Board	None
Consultant	None
Equity, Stock, or Options	None
Speakers' Bureau or Honoraria	None

Everything is permissible, but not everything is constructive. . . Do not cause anyone to stumble.

Apostle Paul

Learning Objectives

Objectives: The learning objectives for this activity have been designed to address clinician competence. Upon conclusion of this program, participants should be able to:

- Understand the **prevalence** of prenatal mental illness and maternal use of CNS active medications during pregnancy.
- Describe the potential adverse **impact of maternal mental illness** during gestation including its impact on maternal health behaviors, obstetrical and delivery complications, and fetal neurodevelopment.
- Identify the **risks and benefits of psychotropic treatment** during pregnancy and lactation.
- Use a model for rational application of psychotropic reproductive safety data to **prenatal decision-making**.

MATERNAL-FETAL PSYCHIATRY

Conclusion: Prenatal Decision-Making

Prevalence: Magnitude of the Issue

Risks of Prenatal Mental Illness

Risks & Benefits of Pharmacotherapy

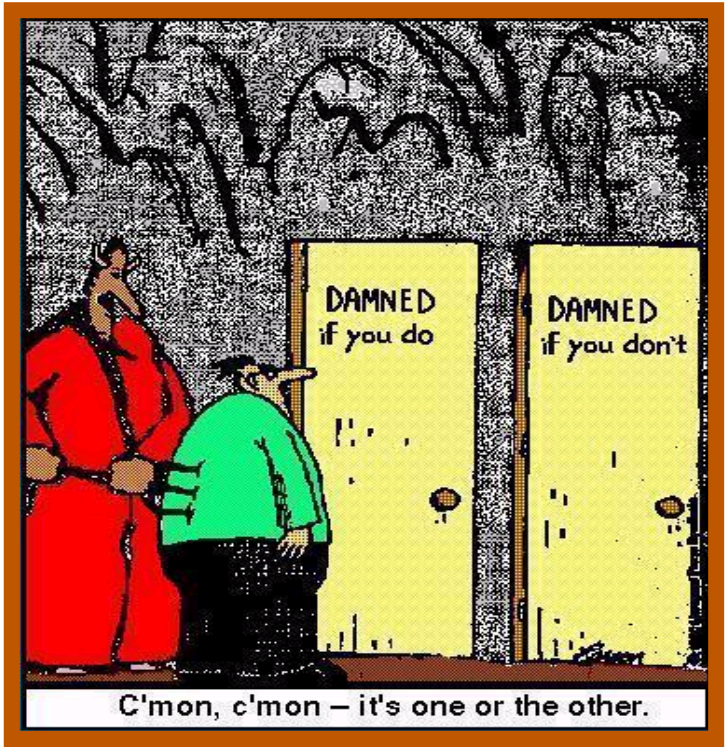
Working Assumptions: Prenatal Psychotropic Treatment

- **IF PREGNANT/LACTATING PT IS TREATED, INFANT IS EXPOSED.**
  - **Anything that crosses the maternal blood-brain barrier will also cross:**
    - Placenta
    - Blood-milk barrier
    - Fetal blood-brain barrier.
- **NO MEDICATION IS SAFE.**
  - **Risks include birth defects, adverse obstetrical & neonatal outcomes, neurodevelopmental affects.**
  - **Reproductive safety data derived from observational studies with varying degrees of scientific rigor.**
  - **No medication has complete safety data across the entire risk spectrum.**
- **MUST WEIGH RISK OF USING vs. NOT USING MEDICATION.**

Product Labelling

"Use in pregnancy is not recommended unless the potential benefits justify the potential risks to the fetus."

"When manufacturers & official agencies warn against drug treatment during pregnancy, their warnings serve to protect themselves and are of little use to clinically responsible physicians." Schou M. *J Affect Disord* 2001; 67: 21-32.



Guiding Principles for Prescription Decision-Making during Pregnancy

Concern	Primary Consideration	
	Safety	Efficacy
Should I prescribe medication?	✓	
What medication(s) should I prescribe?	✓	✓
At what dose should the medication(s) be prescribed?	✓	✓

- Avoid making false promises. NO MEDICATION IS SAFE.
- Avoid mother-infant conflict
- Maximize use of effective non-pharmacological treatments
- Weigh risk & likelihood of illness against risk of medication
- Consider duration of illness (if treatment is deferred)

- Use as few medications as possible
- Avoid ineffective medications

- Use minimal effective dose
- Avoid subtherapeutic dosing at all costs

Newport DJ et al. *The American Psychiatric Association Publishing Textbook of Psychiatry, 6th Edition*, 2024, 537-98

Most Common Initial Encounter Scenarios

PRECONCEPTION ON MEDS	PREGNANT ON MEDS	PREGNANT OFF MEDS & ILL	POSTPARTUM ILL
Are my meds safe?	Are my meds safe?	I need help.	I need help.
Options 1. Continue 2. Discontinue 3. Switch	Options 1. Continue 2. Discontinue ~~3. Switch~~	Options 1. Start/Restart 2. Don't Start/Restart	Options 1. Start/Titrate 2. Switch/Augment

Ranking Medication Choices

POTENTIAL EFFICACY	SAFETY CONCERNS
FDA indication(s) Research evidence Personal experience	Research evidence Prior fetal exposure Exacerbating preexisting conditions

Case: PeriPAN Consult with Obstetrical Provider

36yo G1P0, unplanned Pregnancy 8 weeks EGA. Psychiatric h/o of recurrent MDD, OCD, and ADHD with possible GAD. Using cannabis and tobacco daily.

At knowledge of conception, patient was taking paroxetine 40mg Qday, trazodone 50mg QHS, and atomoxetine 80mg qday. Patient immediately discontinued atomoxetine and trazodone at that time. She is trying to wean herself from tobacco and marijuana. Mood and anxiety symptoms remain well-controlled. Only previous treatment was with fluoxetine, which patient recalls working well.

Question: What should we advise regarding paroxetine?

PREGNANT ON MEDS

Are my meds safe?

Options
1. Continue
2. Discontinue
3. Switch

Ranking Options

TREATMENT OPTION	POTENTIAL EFFICACY	SAFETY
Continue Paroxetine 40mg		
Discontinue		
Switch to Fluoxetine ?mg		

MATERNAL-FETAL PSYCHIATRY

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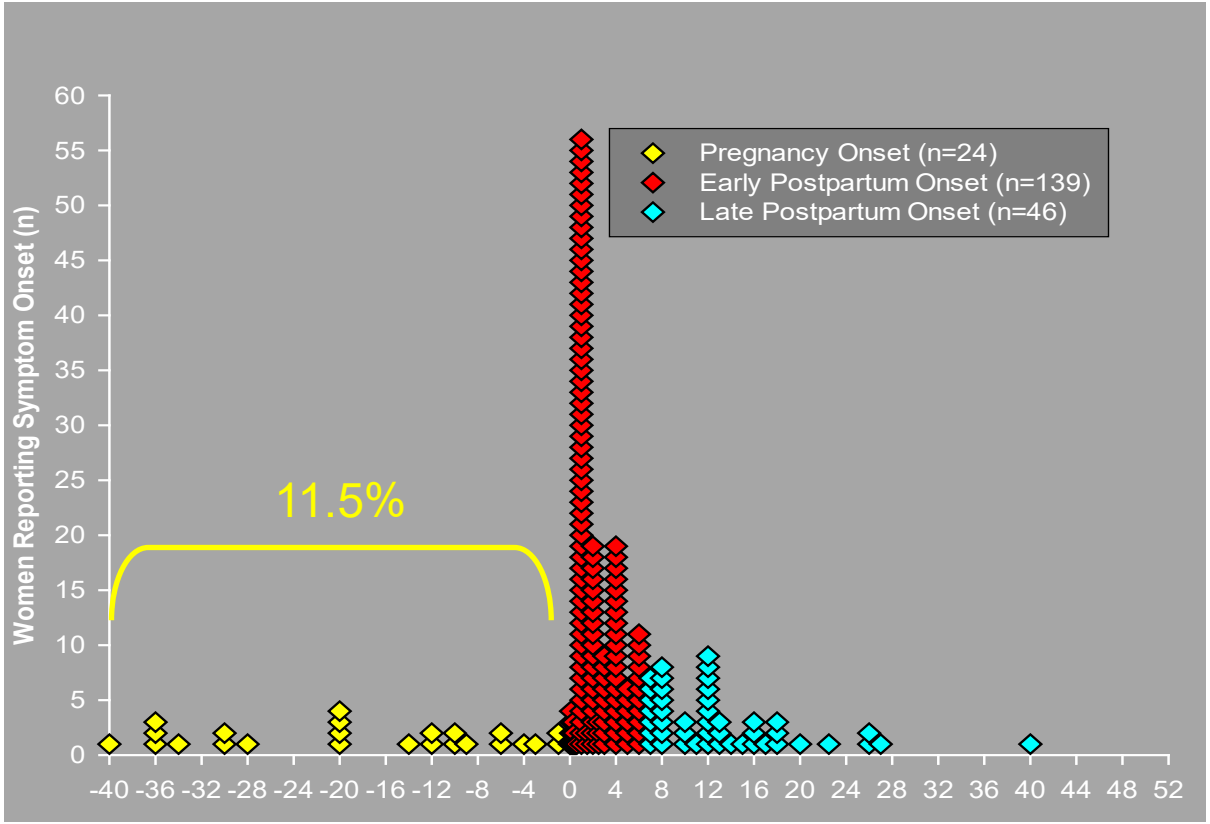
Risks of Prenatal Mental Illness

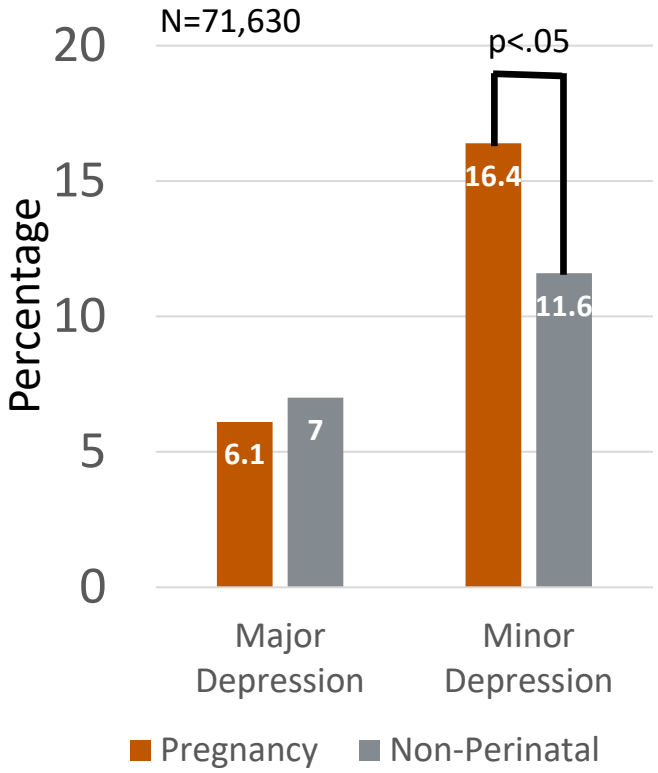
Risks & Benefits of Pharmacotherapy

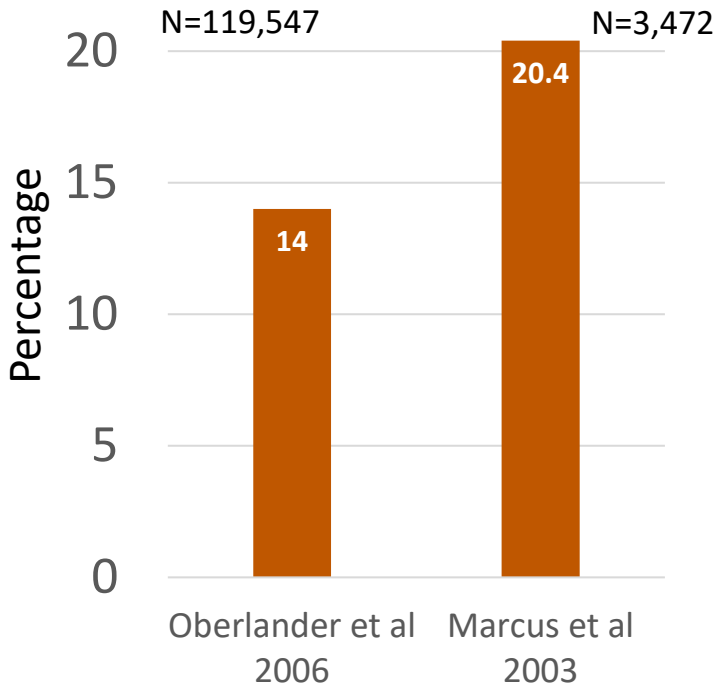
Timing of Onset of "Postpartum" Depression



Stowe Z et al. *Am J Obstet Gynecol* (2005)

Prevalence of Prenatal Depression





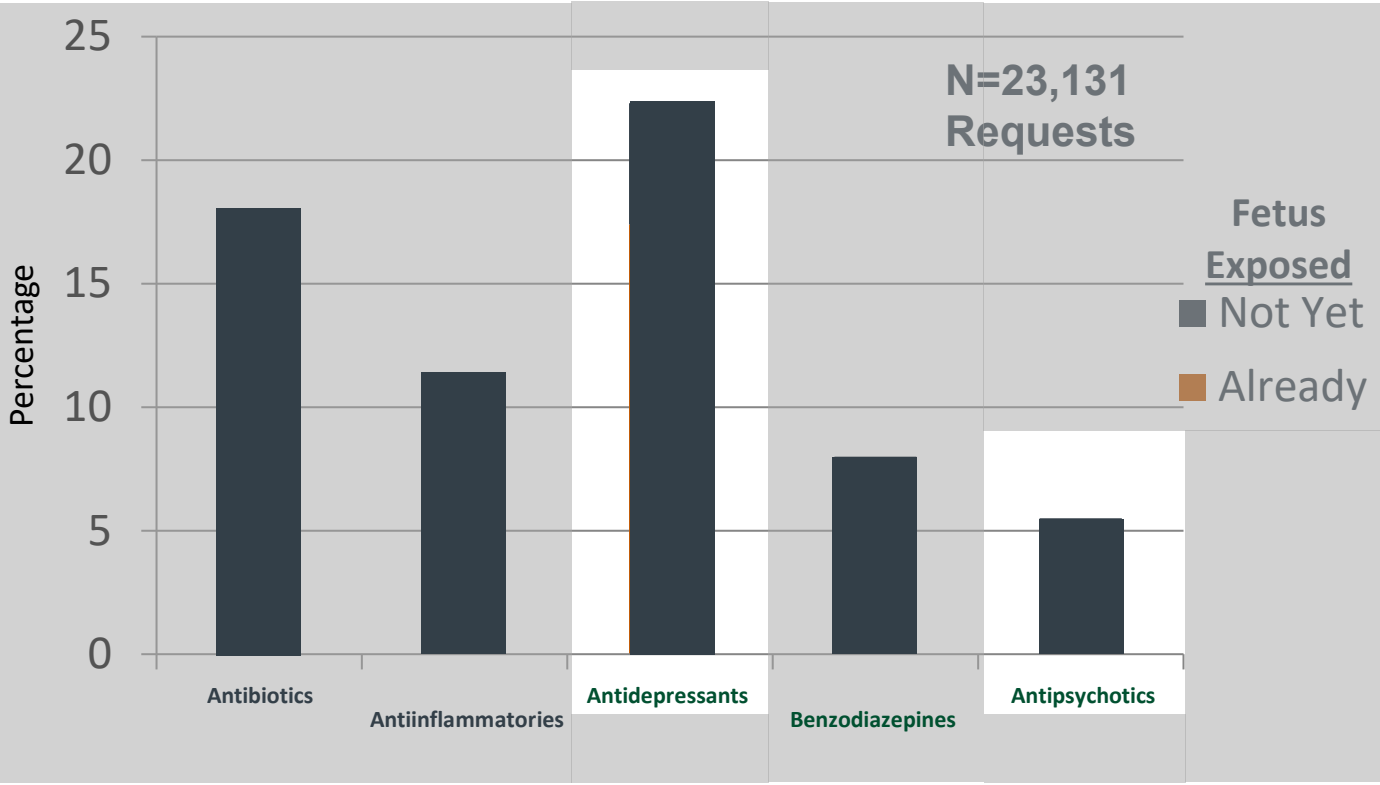
Ashley J et al. *Arch Womens Ment Health* 2016; 19: 395-400

Oberlander TF et al. *Arch Gen Psychiatry* 2006; 63: 898-906

Marcus SM et al. *J Womens Health* 2003; 12: 373-80

TIS Calls from Healthcare Providers

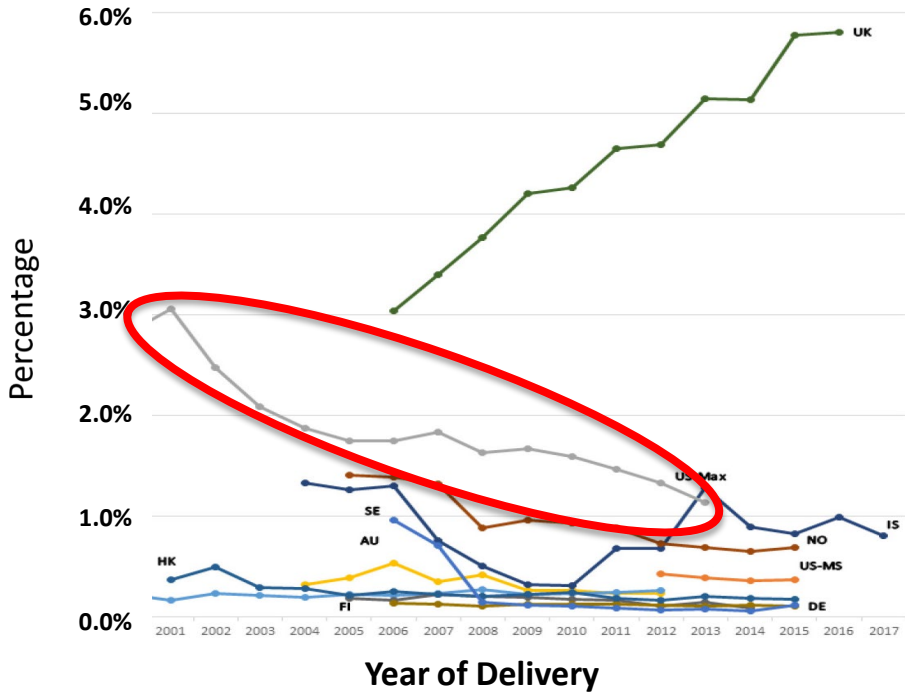
IMAGe Center, Montreal, Quebec



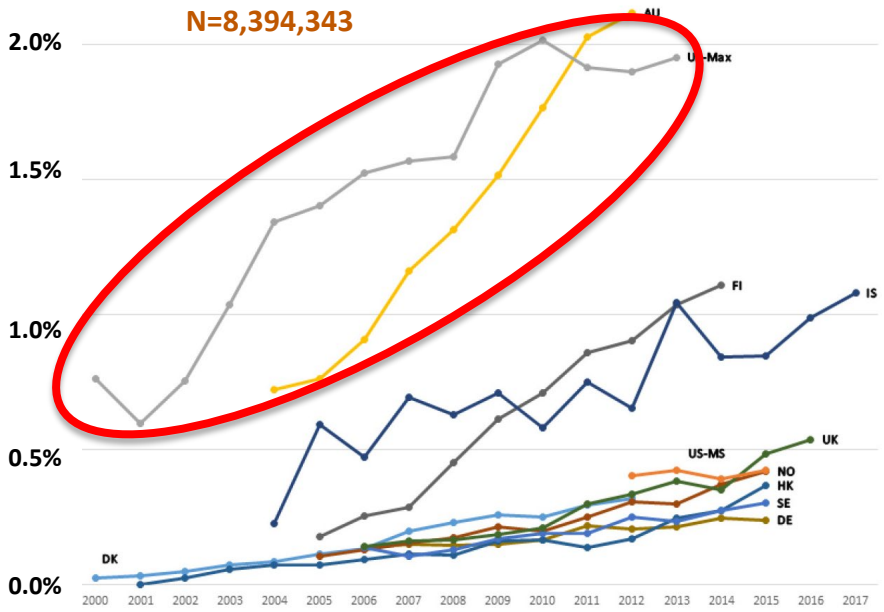
Gendron MP et al. *Eur J Clin Pharmacol* 2009; 65: 523-31

Prenatal Antipsychotic Use: Prevalence from 10 Countries

First Generation Antipsychotic



Second Generation Antipsychotic



Texas Births in 2025		390,203
First Generation	*1.18%*	*4,604*
Second Generation	*1.91%*	*7,452*
Total	*3.09%*	*12,057*

AU=Australia DK=Denmark FI=Finland DE=Germany HK=Hong Kong IS=Iceland NO=Norway SE=Sweden UK=United Kingdom USMS=US MarketScan USMAX=US Medicaid Analytic eXtract

Reutfors J et al. *Schiz Res* 2020; 220: 106-115

FDA Indications for Second Generation Antipsychotics

Agent	Schiz.	Schizo-affect.	Bipolar D/O			MDD (Adj)	Autism Irritability	Agitation
			Mania	Dep	Maint			
Aripiprazole	X		X			X	X	X
Asenapine	X		X					
Brexpiprazole	X					X		
Cariprazine	X		X					
Clozapine	X	X						
Iloperidone	X		X					
Lumateperone	X			X		X		
Lurasidone	X			X				
Olanzapine	X		X	X		X		X
Paliperidone	X	X						
Quetiapine	X		X	X	X	X		
Risperidone	X		X				X	
Ziprasidone	X		X		X			X

Scope of the Issue

- Mental disorders complicate pregnancy with harmful effects upon both mothers and infants
  ACOG Clinical Practice Guidelines 2023a, 2023b
- Leading contributor to pregnancy-related deaths (84% of preventable)
  Trost SL et al 2022
- Those from marginalized groups are less likely to receive care and have poorer pregnancy outcomes
  McGuire SL et al 2008; Sussman LK et al 1987; Zhang AY et al 1998
- Too few mental health care providers to meet the growing needs
  Olfson M 2016; Webb R et al 2023
- Lack of training leaves providers hesitant to provide clinical care for this population
  Webb R et al 2023
- Training often focuses on potential treatment risks without addressing benefits and barriers to treatment
  Griffen A et al 2021; Marshman A et al 2022

MATERNAL-FETAL PSYCHIATRY

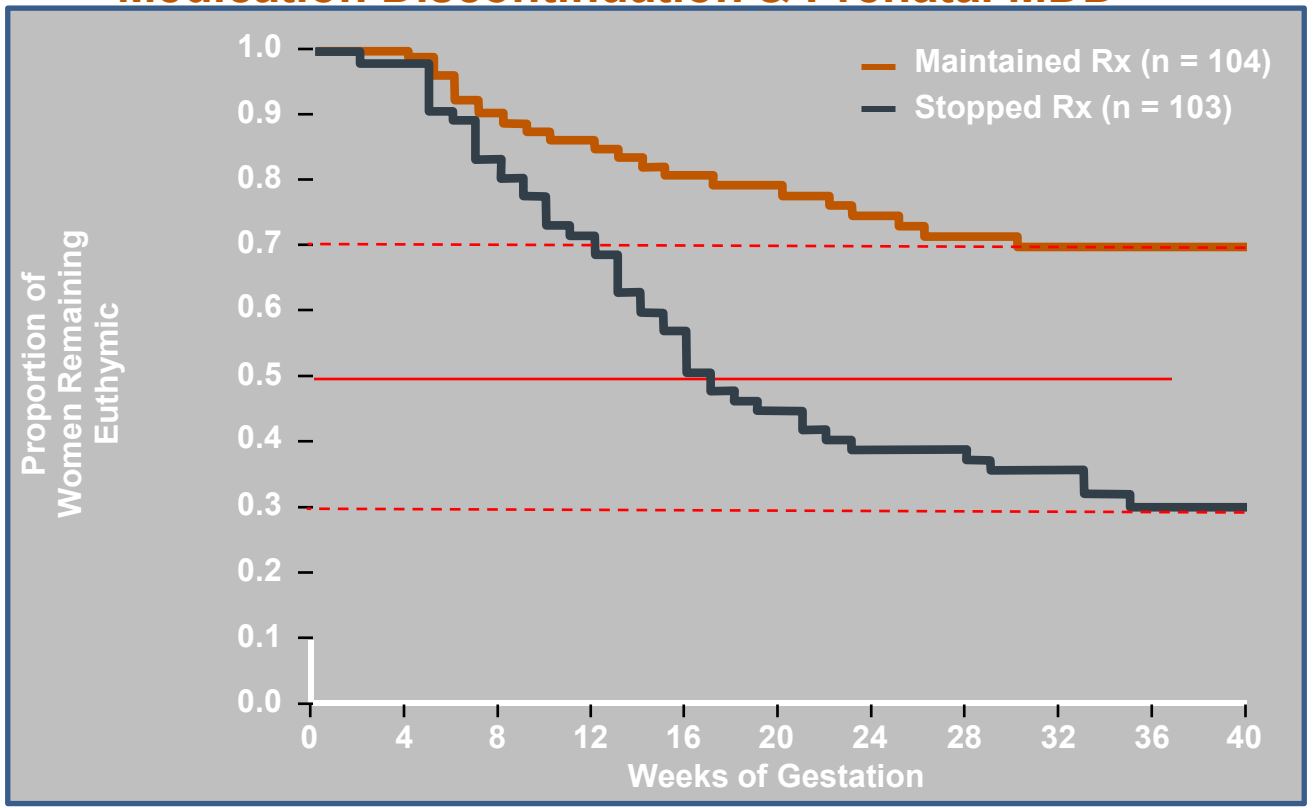
Conclusion: Prenatal Decision-Making

Prevalence: Magnitude of the Issue

Risks of Prenatal Mental Illness

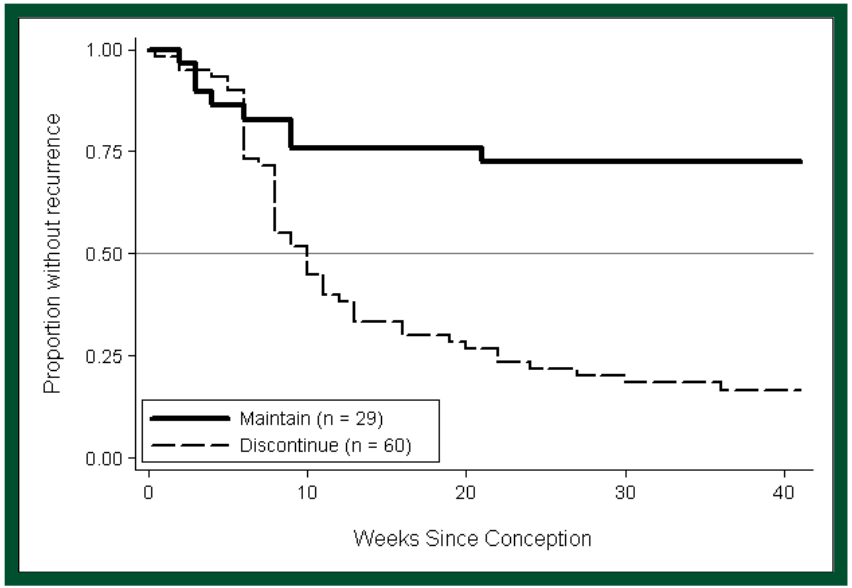
Risks & Benefits of Pharmacotherapy

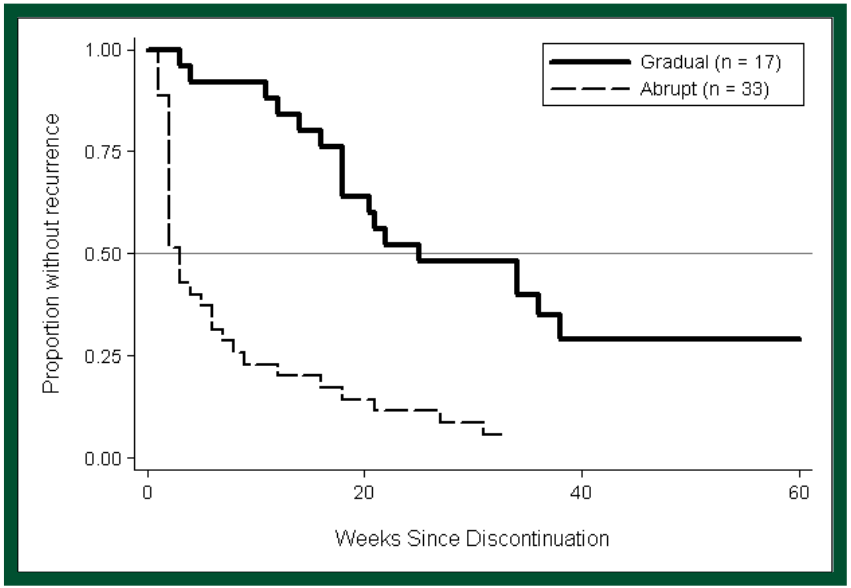
Likelihood of Illness
Medication Discontinuation & Prenatal MDD



Cohen LS et al. *JAMA* 2006; 295: 499-507

Likelihood of Illness
Mood Stabilizer Discontinuation





Viguera AC et al. *Am J Psych* 2007; 164: 1817-1824

Maternal Mental Illness

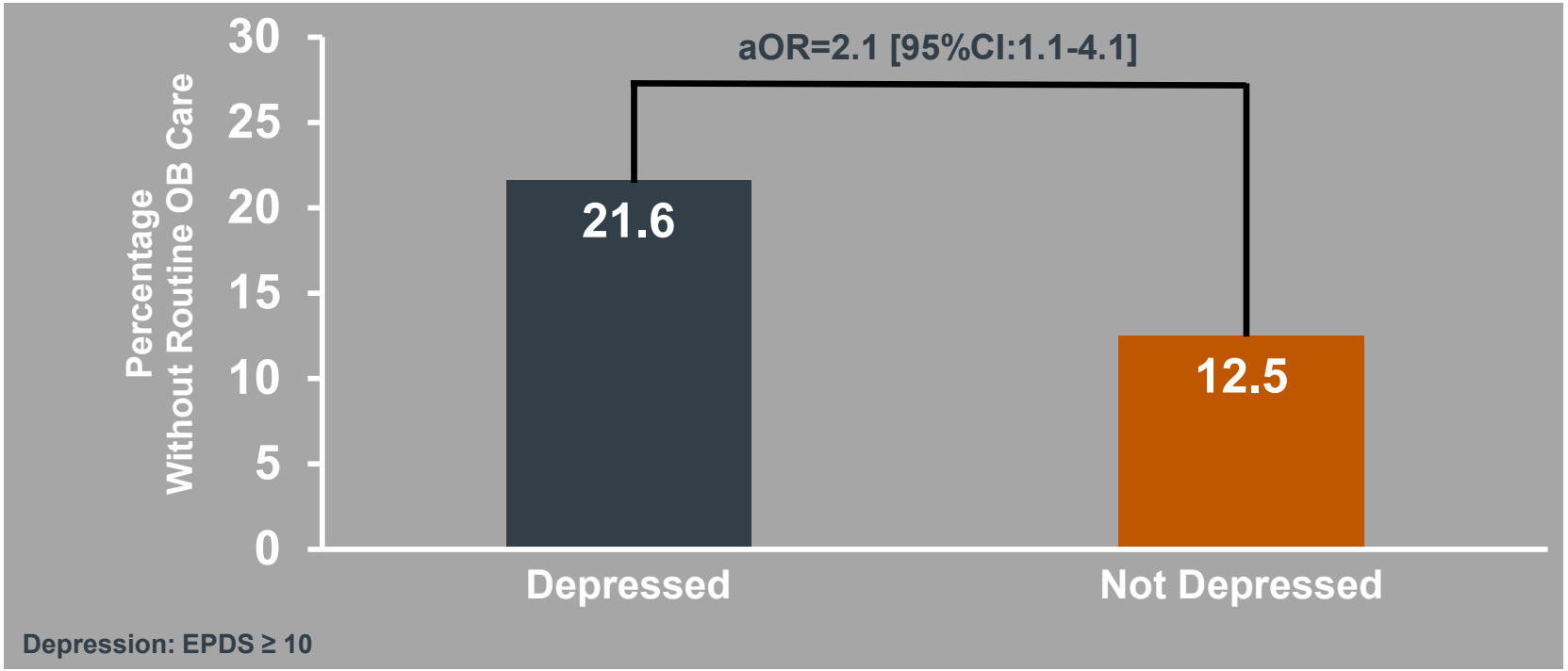
Risk of Adverse Pregnancy Outcomes

- **Schizophrenia**
  - Pregnancy: Preclampsia, Maternal Hemorrhage, Gestational Diabetes
  - Delivery: Emergency C/S, Uterine Atony
  - Infant: Low Birthweight, Reduced Head Circumference, Malformations, Lower APGAR
- **Depression**
  - Pregnancy: Preterm Birth, Gestational Hypertension
  - Delivery: Operative Delivery
  - Infant: Low Birthweight, Reduced Head Circumference, Lower APGAR, Poor Neurodevelopment
- **Bipolar Disorder**
  - Pregnancy: Maternal Hemorrhage, Gestational Hypertension
  - Delivery: Operative Delivery
  - Infant: Low Birthweight

Cannon M et al. *Am J Psychiatry* 2002; 159(7): 1080-92. Vlenterie R et al. Obstet Gynecol 2021; 138(4): 633-646.
Simonovich SD et al. Health Aff 2021; 40(10): 1560-5. Shay M et al. Psychol Med 2020; 50(13): 2128-40.
Power J et al. J Affect Disord 2021; 291: 218-34. Rusner M et al. BMC Preg Childbirth 2016; 16(1): 331

Consequences of Prenatal Depression
Impact on Access to Routine Obsetrical Care

N=1,103

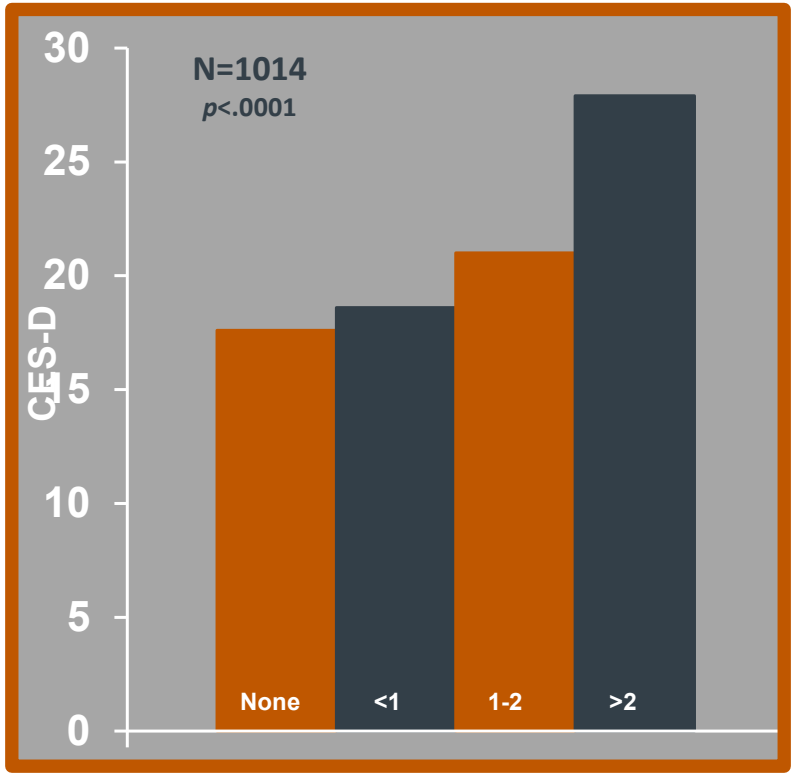


Masters GA et al. *J Womens Health* 2020; 29: 944-51

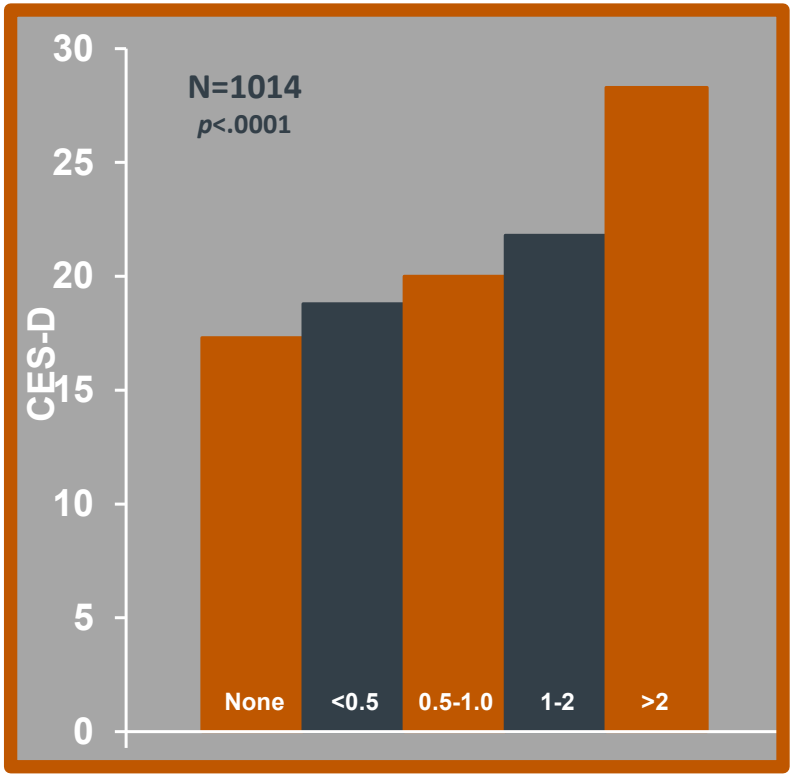
Consequences of Prenatal Depression

Tobacco/Alcohol Use

Prenatal Alcohol Use (Drinks per Day)



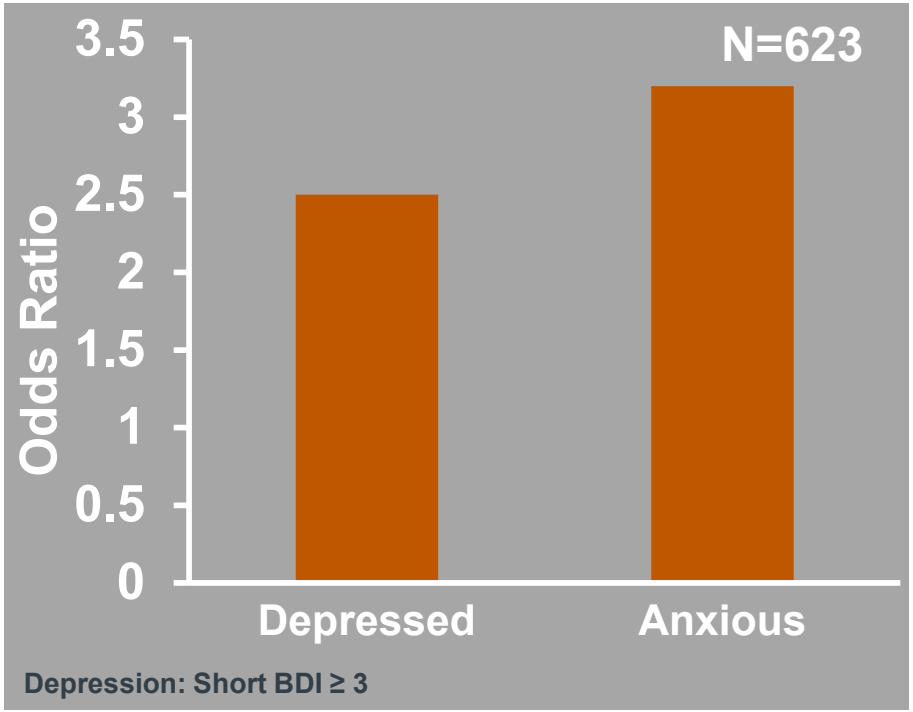
Prenatal Cigarette Use (Packs per Day)



Zuckerman B et al. *Am J Obstet Gynecol* 1989; 160: 1107-11

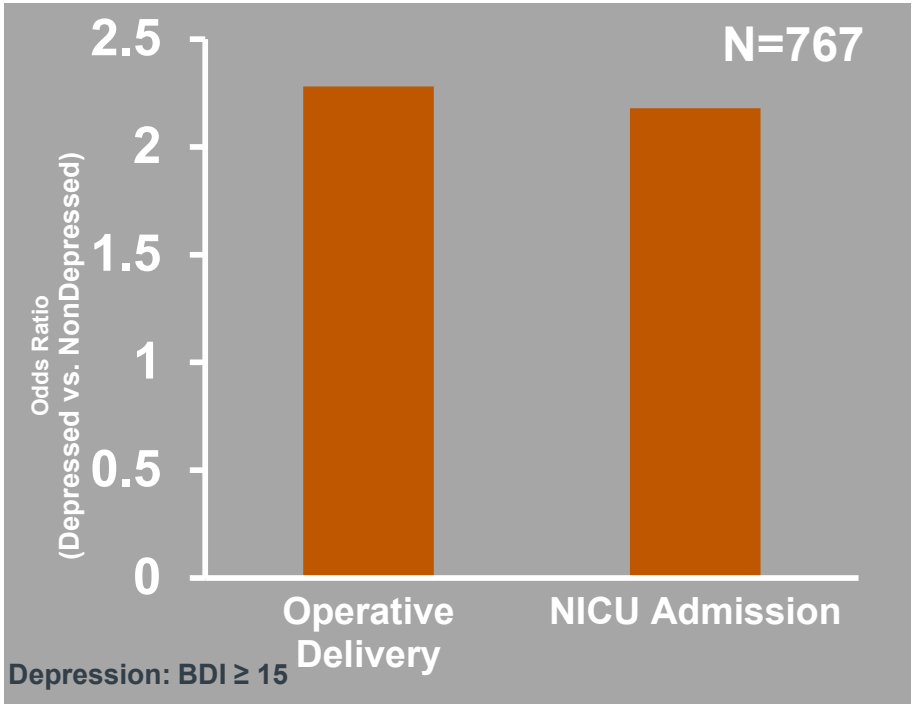
Consequences of Prenatal Depression
Obstetrical Complications

PREECLAMPSIA



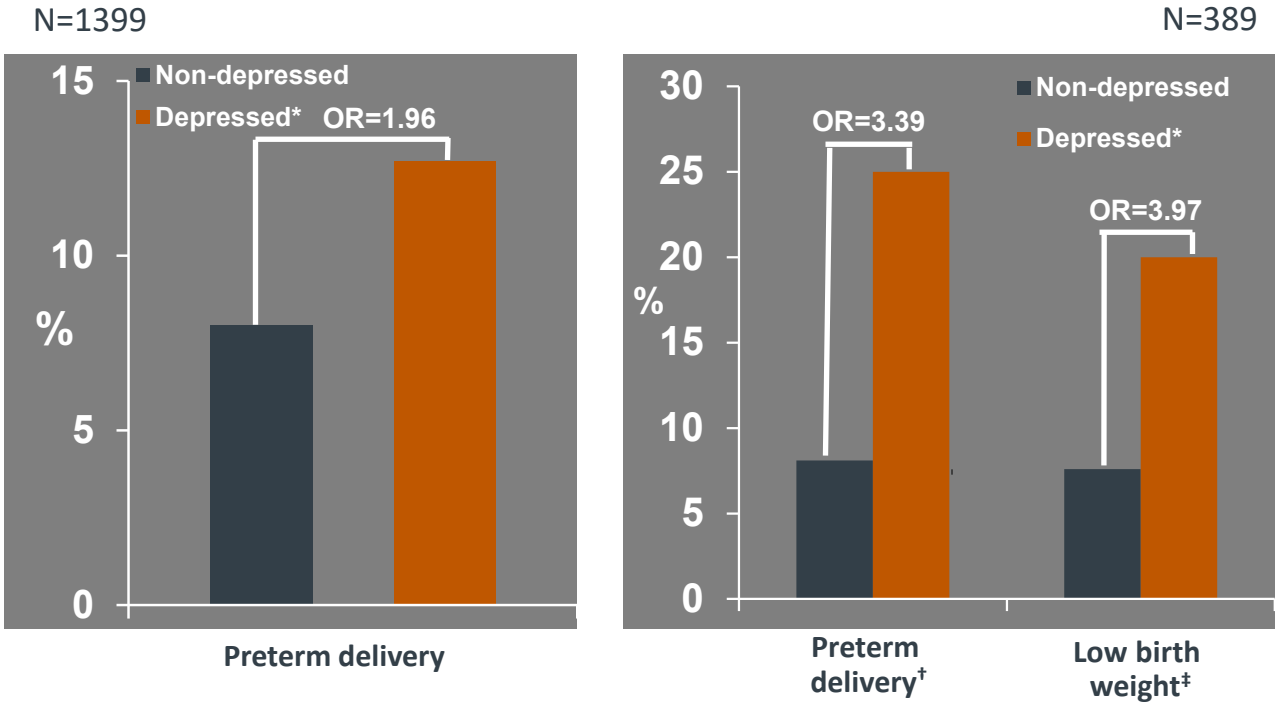
Kurki T et al. *Obstet Gynecol* 2000; 95: 487-490

DELIVERY



Chung TKH et al. *Psychosom Med* 2001; 63: 830-4

Consequences of Prenatal Depression
Obstetrical Complications



Orr ST et al. *Am J Epidemiol* 2002; 156: 797-802. Steer RA et al. *J Clin Epidemiol* 1992; 45: 1093-9.

*CES-D score in upper 10th percentile[1] or BDI score >21[2].
†<37 wks gestational age; ‡<2.5 kg.

Cumulative Longitudinal Exposure: Medication & Illness

Preterm Delivery

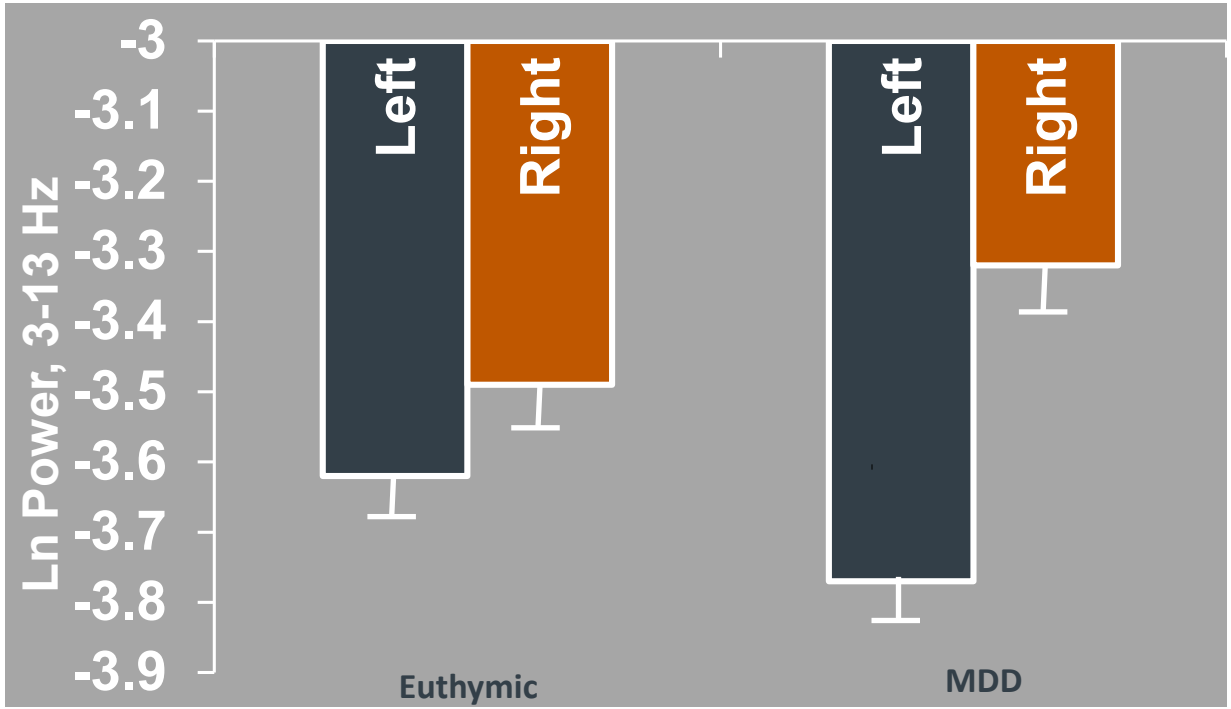
N=841

Predictor	Odds Ratio [95% CI]		X^2, P Value	
Severe Depression (Avg. HamD for 3rd Trimester* [21+ vs. 0-15])	8.82	[2.62 –29.8]	X^2=12.3	p=.0004
Placental Abruption	8.73	[1.08 – 70.3]	X^2=4.14	p=.04
Maternal Infection at Delivery (Other than Chorioamnionitis)	7.19	[1.75 – 29.5]	X^2=7.49	p=.006
History of Previous Preterm Delivery	4.64	[2.04 – 10.6]	X^2=13.4	p=.0003
Employed Full Time Outside Home	3.39	[1.76 – 6.53]	X^2=13.3	p=.0003
Zolpidem Exposure (during 3rd Trimester)	3.31	[1.39 – 7.90]	X^2=7.35	p=.007
Gestational Diabetes	2.90	[1.07 – 7.87]	X^2=4.35	p=.04
Moderate Depression (Avg. HamD for 3rd Trimester* [16-20 vs. 0-15])	2.76	[1.15 – 6.64]	X^2=5.17	p=.02
SRI Antidepressant Exposure (during 3rd Trimester)	2.31	[1.14 – 4.67]	X^2=5.40	p=.02

HamD=Hamilton Rating Scale for Depression SRI=Serotonin Reuptake Inhibitor

Newport DJ et al. Unpublished Data

Consequences of Prenatal Depression
EEG Asymmetry in 6-Week Infants



N=63

Jones NA. *Infant Behav Dev* 1998; 21: 537

Cognitive Development (Ages 15-71 Months)
Effects of Maternal Depression and/or Antidepressants

Predictor	ß	t	p	95% CI
Reynell Developmental Language Scales: Verbal Comprehension (n=93)				
Mother's ethanol consumption	+0.11	+0.49	0.62	–0.33 to +0.56
Severity of mother's depression	+0.09	+0.10	0.92	–0.02 to +0.02
Socioeconomic status (Hollingshead index)	–0.03	–0.25	0.80	–0.03 to +0.02
Mother's IQ	+0.82	+0.78	0.44	–0.01 to +0.03
Duration of prenatal depression	–0.04	–0.36	0.71	–0.54 to +0.38
Duration of prenatal antidepressant	+0.33	+1.30	0.20	–0.18 to +0.86
No. of postnatal depressive episodes	**–0.28**	**–2.50**	**0.01**	**–0.51 to –0.06**
Medicated patients vs comparison subjects	+0.01	+0.03	0.98	–0.90 to +0.89
Reynell Developmental Language Scales: Expressive Language (n=92)				
Mother's ethanol consumption	+0.04	+0.16	0.87	–0.40 to +0.48
Severity of mother's depression	+0.04	+0.40	0.69	–0.01 to +0.02
Socioeconomic status (Hollingshead index)	+1.43	+1.24	0.22	–0.01 to +0.04
Mother's IQ	+0.08	+0.08	0.94	–0.02 to +0.02
Duration of prenatal depression	–0.33	–1.43	1.16	–0.78 to +0.13
Duration of prenatal antidepressant	+0.05	+0.18	0.86	–0.46 to +0.55
No. of postnatal depressive episodes	**–0.26**	**–2.33**	**0.02**	**–0.05 to –0.04**
Medicated patients vs comparison subj	**+0.94**	**+2.19**	**0.03**	**+0.09 to +1.80**
McCarthy Scales of Children's Abilities: Global Cognitive Index (n=37)				
Mother's ethanol consumption	+3.30	+0.88	0.40	–4.40 to +10.98
Severity of mother's depression	–2.34	–0.12	0.91	–0.42 to +0.38
Socioeconomic status (Hollingshead index)	+9.25	+0.40	0.69	–0.38 to +0.56
Mother's IQ	+0.25	+1.08	0.29	–0.21 to +0.68
Duration of prenatal depression	**-16.67**	**–2.10**	**0.05**	**–32.94 to –0.40**
Duration of prenatal antidepressant	+9.94	+1.18	0.25	–7.33 to +27.21
No. of postnatal depressive episodes	–2.76	–0.93	0.36	–8.83 to +3.31
Medicated patients vs comparison subjects	+19.88	+1.45	0.16	–8.12 to +47.88

Nulman I et al. *Am J Psychiatry* 2002; 159: 1889-95

MATERNAL-FETAL PSYCHIATRY

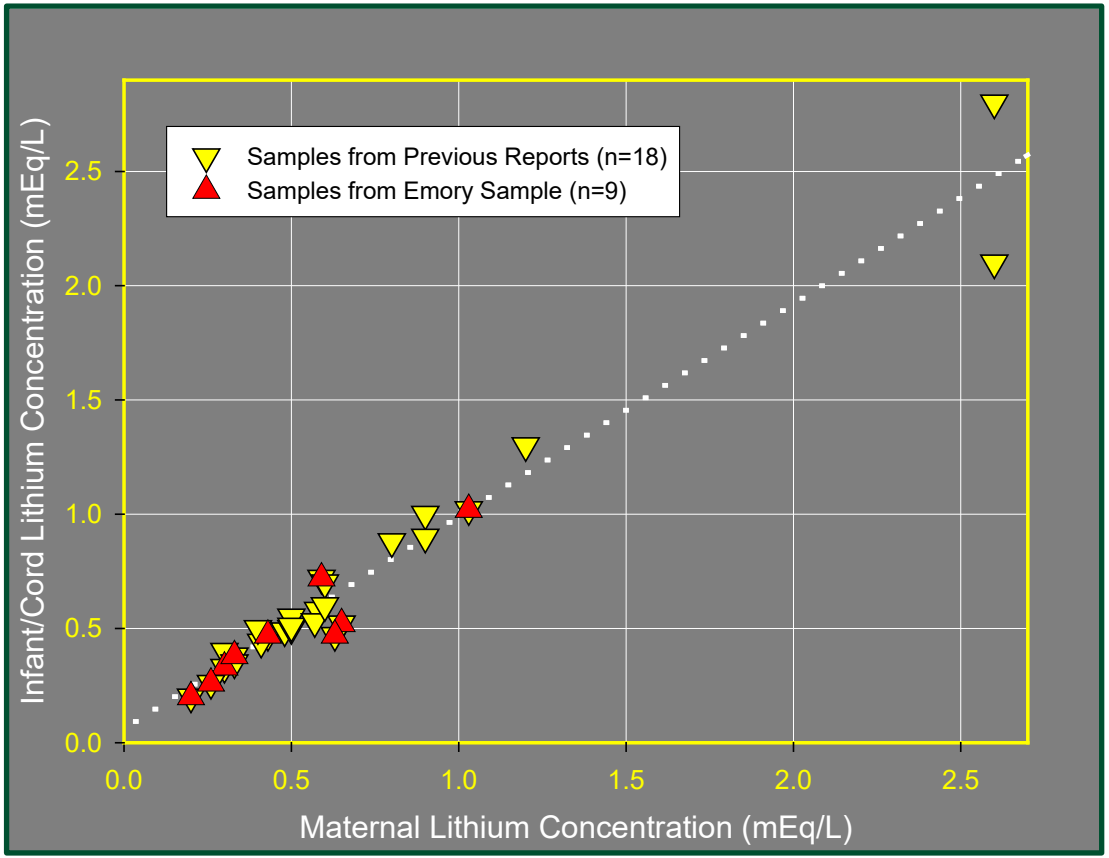
Conclusion: Prenatal Decision-Making

Prevalence: Magnitude of the Issue

Risks of Prenatal Mental Illness

Risks & Benefits of Pharmacotherapy

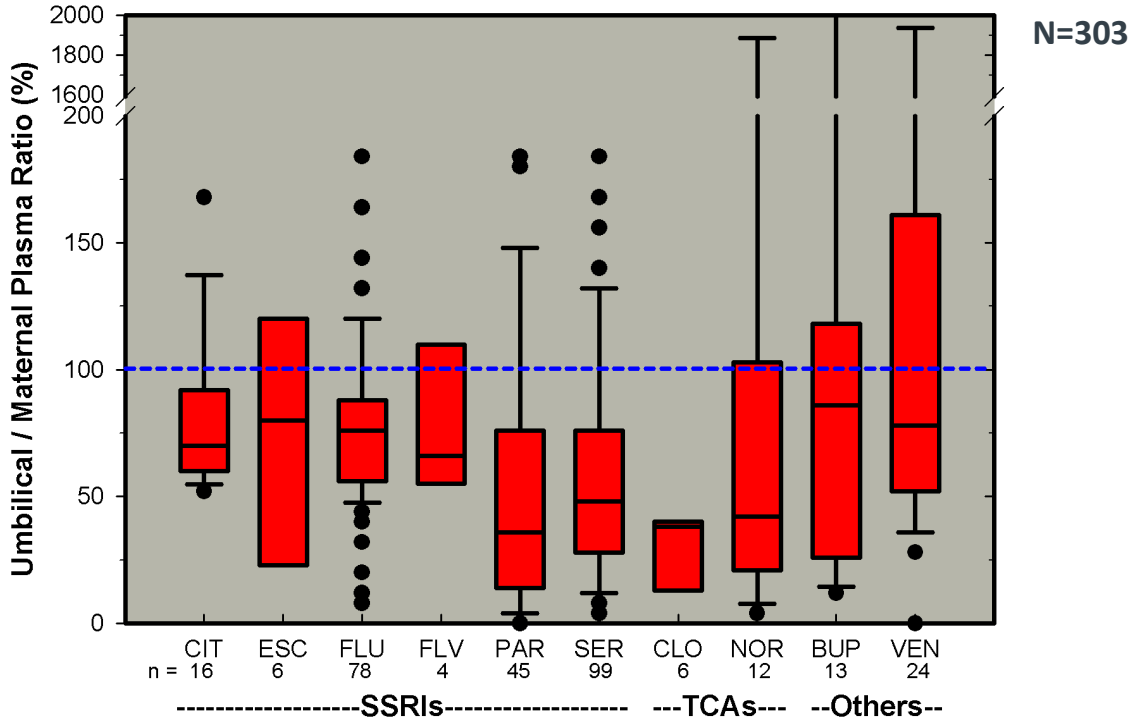
PK STUDIES: PLACENTAL PASSAGE
Lithium



Newport DJ et al. *Am J Psychiatry* 2005; 162: 2162-70

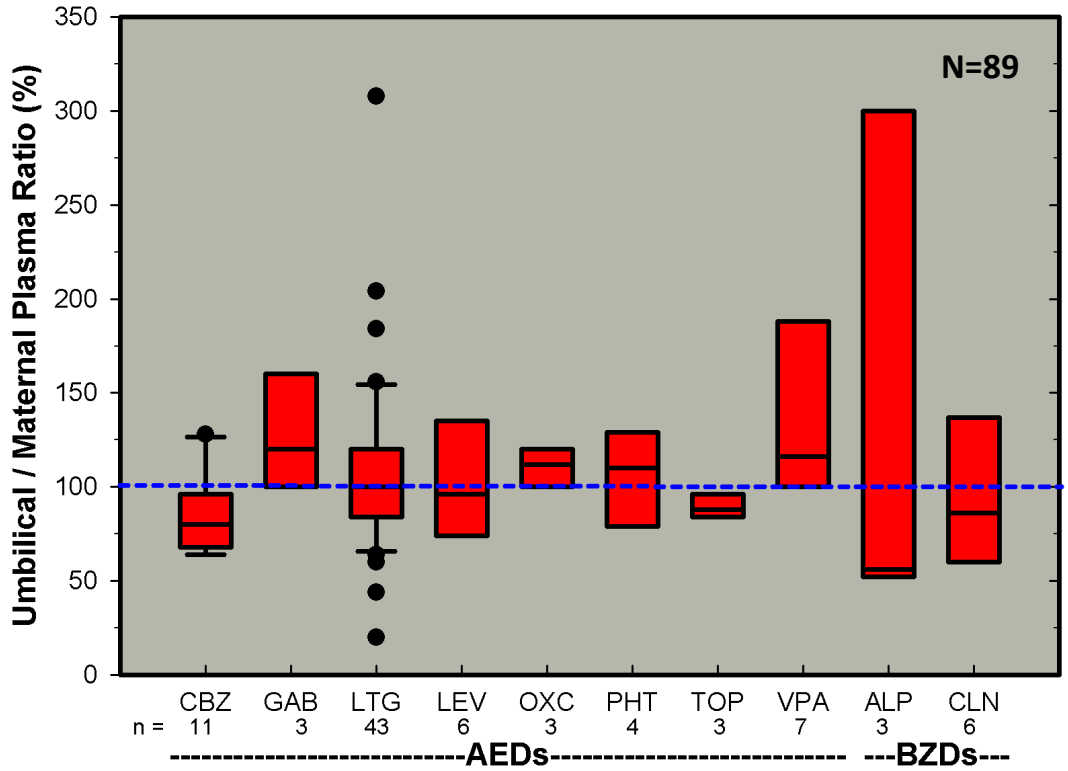
PK STUDIES: PLACENTAL PASSAGE

Antidepressants



Newport DJ et al. Unpublished Data

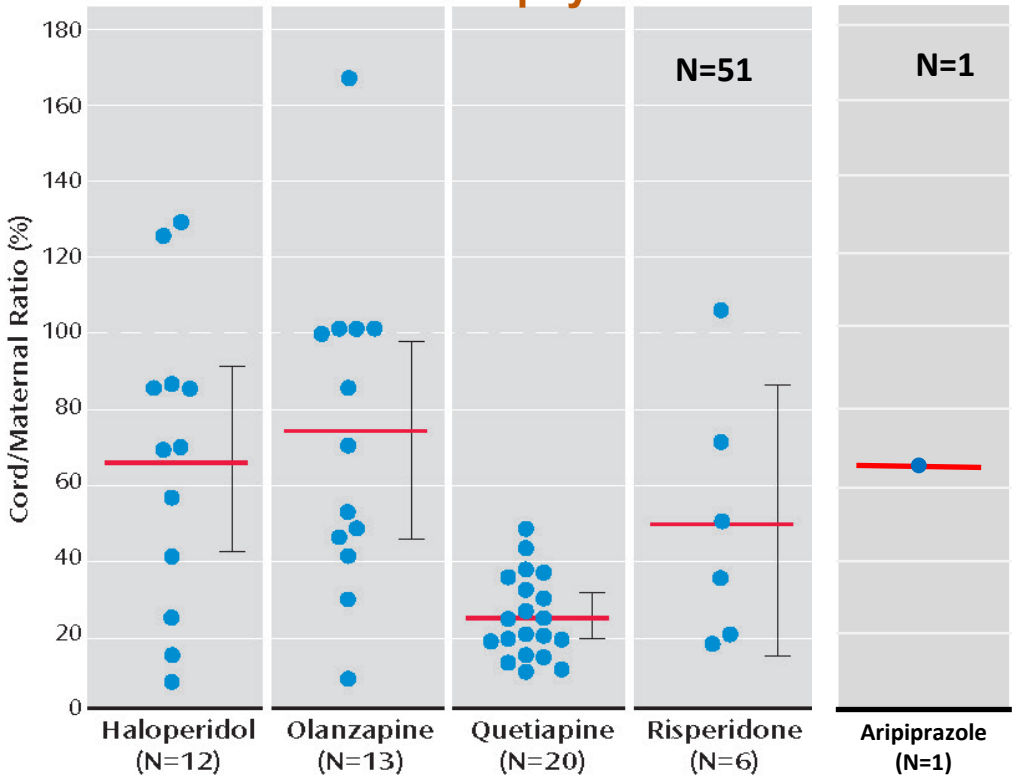
PK STUDIES: PLACENTAL PASSAGE
Antiepileptic Drugs & Benzodiazepines



Newport DJ et al. Unpublished Data

QUANTITATIVE STUDIES: PLACENTAL PASSAGE

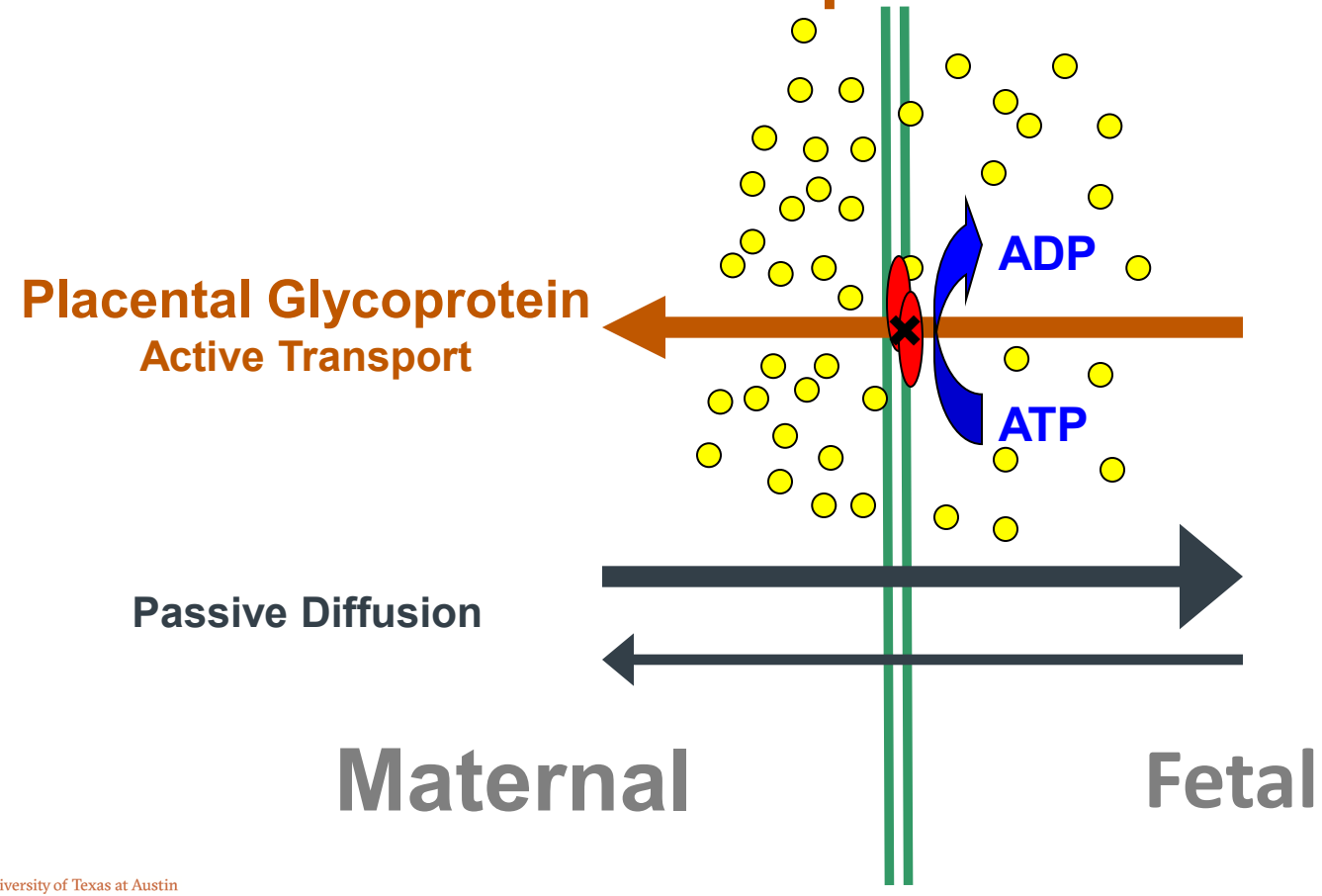
Antipsychotics



Newport DJ et al. *Am J Psychiatry* 2007; 164: 1214-20

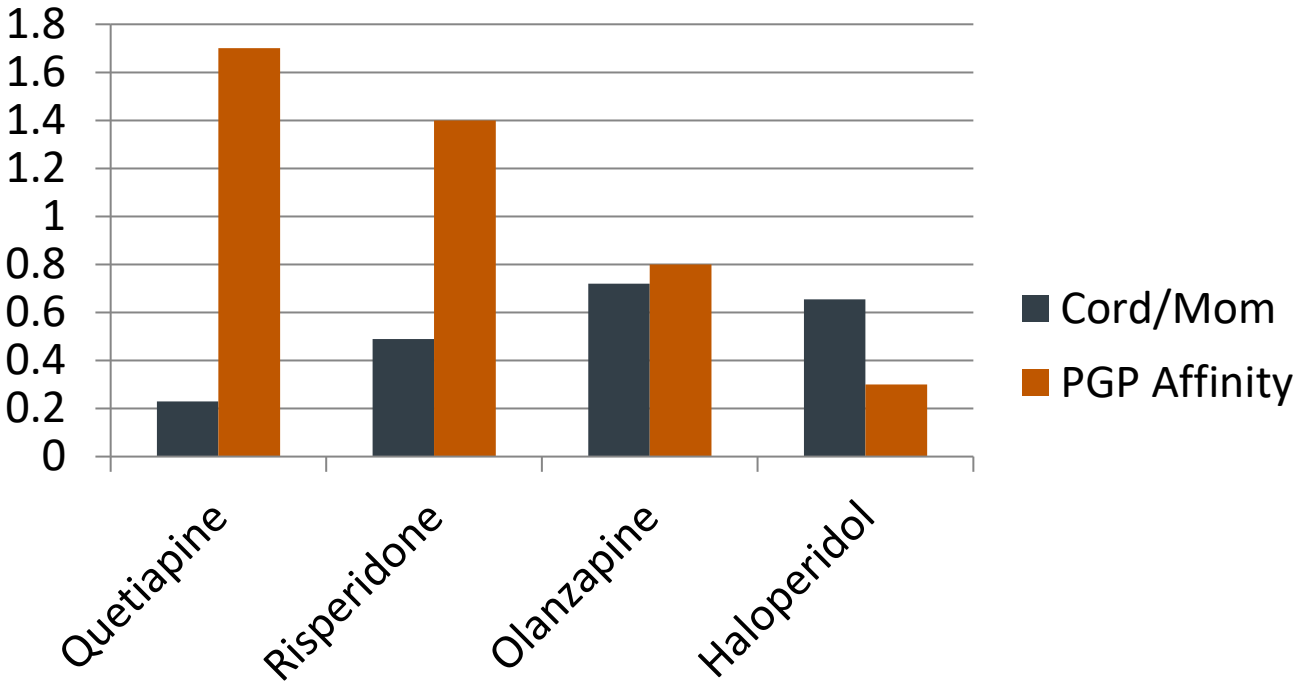
Nguyen T et al. *Aust NZ J Psychiatry* 2011; 45: 500-1

Placental Transport Mechanisms



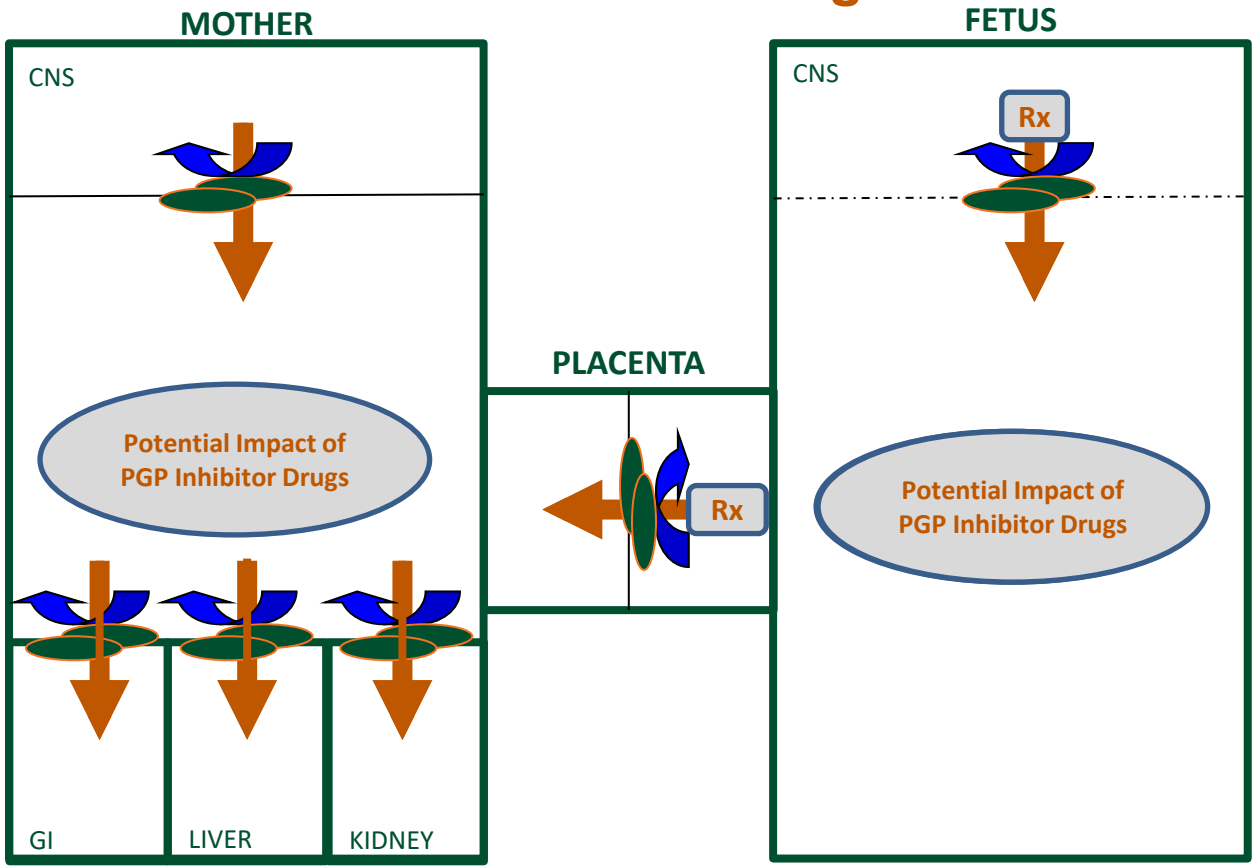
Placental Passage

Evidence for PGP Efflux Regulation



Newport DJ et al. Unpublished Data

Prenatal PGP Efflux Regulation

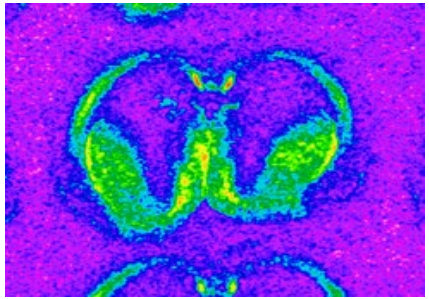
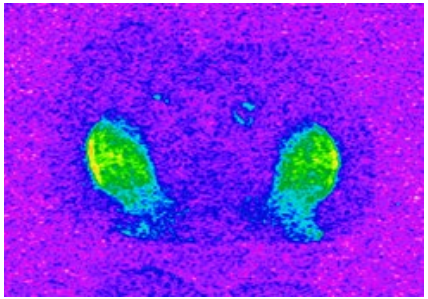
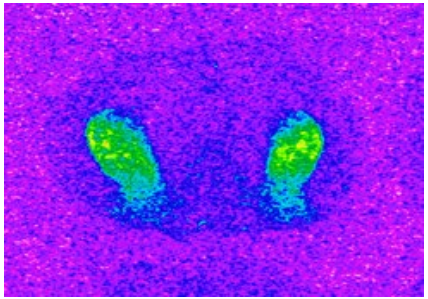


PGP INHIBITORS

- Amitriptyline
- Boceprevir
- Chlorpromazine
- Clarithromycin
- Desipramine
- Dexamethasone
- Erythromycin
- Glyburide
- Haloperidol
- Meperidine
- Methadone
- Nifedipine
- Progesterone
- Ritonavir
- Saquinavir
- Telaprevir

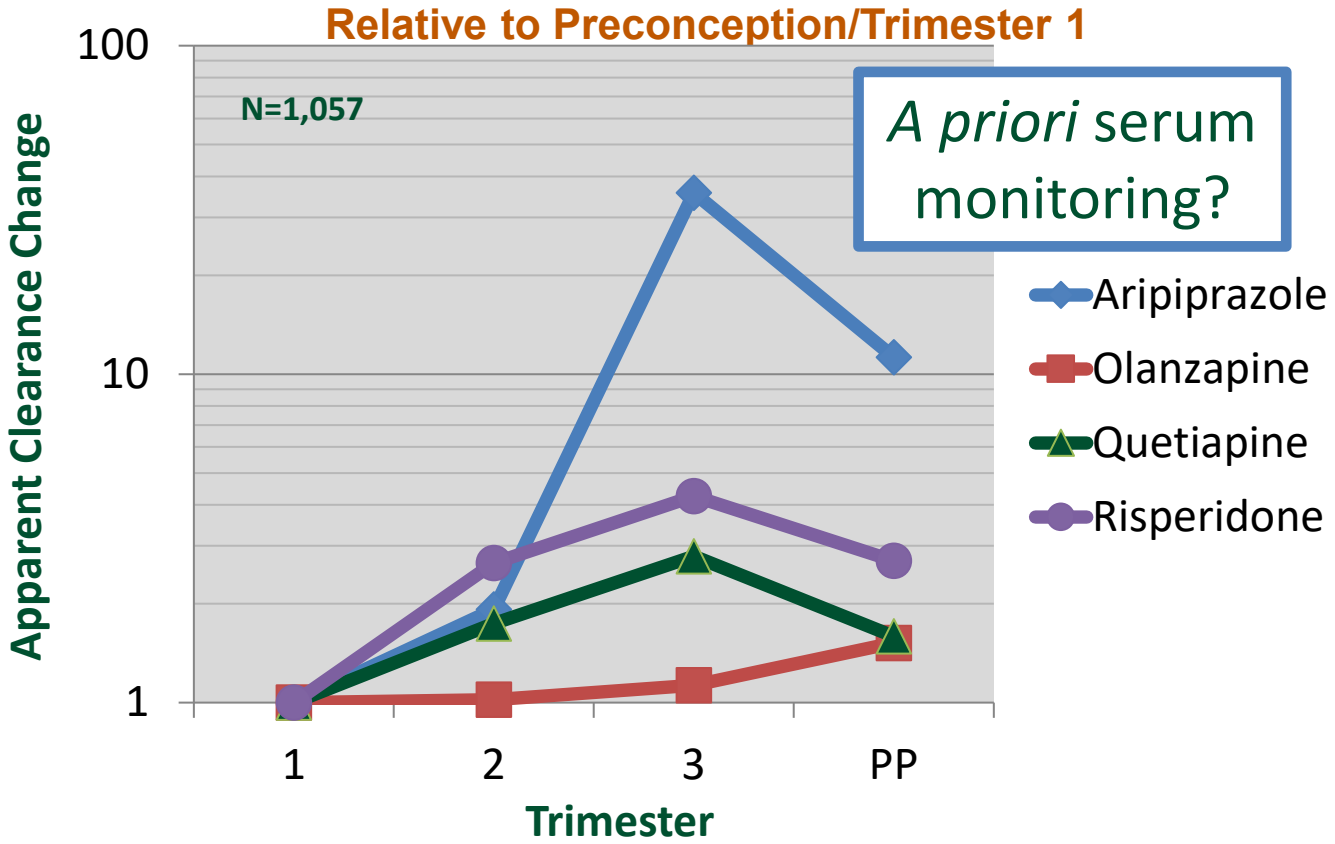
ANTIDEPRESSANT PLACENTAL PASSAGE

SERT Occupancy during *In Utero* Paroxetine Exposure

	Vehicle	Low Dose Paroxetine	High Dose Paroxetine
			
SERT Occupancy	98%	98%	
[Maternal Serum] (ng/ml)	43 ± 28	121 ± 16	
Human Dose Equivalent	28.9 mg/day	40.2 mg/day	

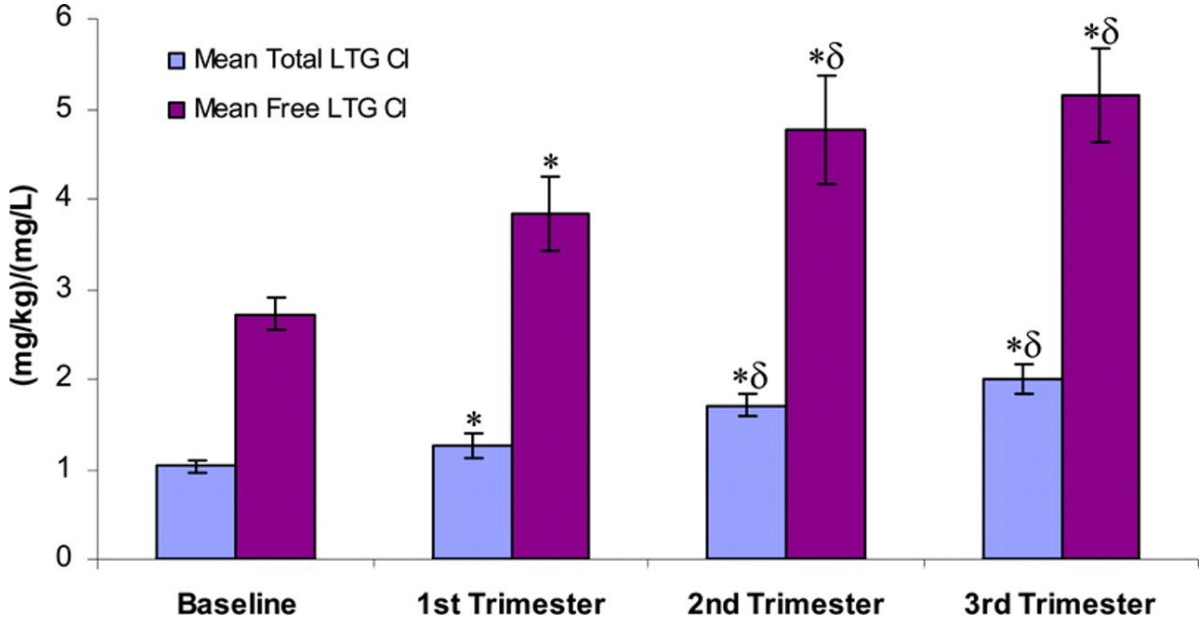
Capello CF et al. *J Pharmacol Exp Ther* 2011; 339: 275-85

Perinatal Alterations in Apparent Clearance



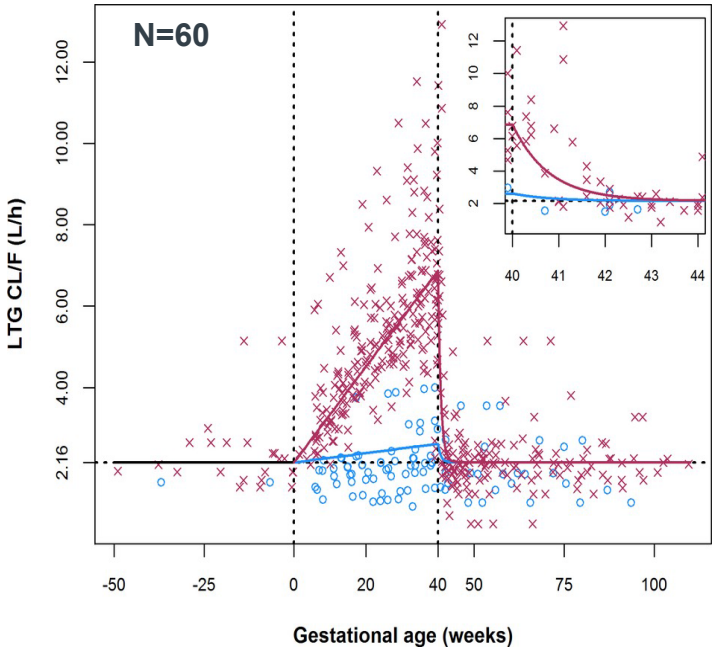
Newport DJ et al. Unpublished Data

LTG Clearance Change Across Pregnancy



Pennell PB et al *Neurology* 2008; 70(22 Pt 2): 2130-6

Modeling LTG Clearance Changes during Gestation: 2 Subpopulations



	Population I	Population II
N, %	46, 77%	14, 23%
CL/F @ Baseline	2.16 L/h	
CL/F Weekly Δ	0.118 L/h	0.0115 L/h
CL/F Overall Δ	4.72 L/h	0.46 L/h
CL/F @ Delivery	6.88 L/h	2.62 L/h
CL/F %Δ @ Delivery	219%	21%

Ratio to Target Concentration (RTC) = [LTG] / [LTG] @ Baseline
Lower RTC assoc'd with Increased Seizure Frequency ($p<0.001$).
RTC <0.65 significant predictor of seizure worsening

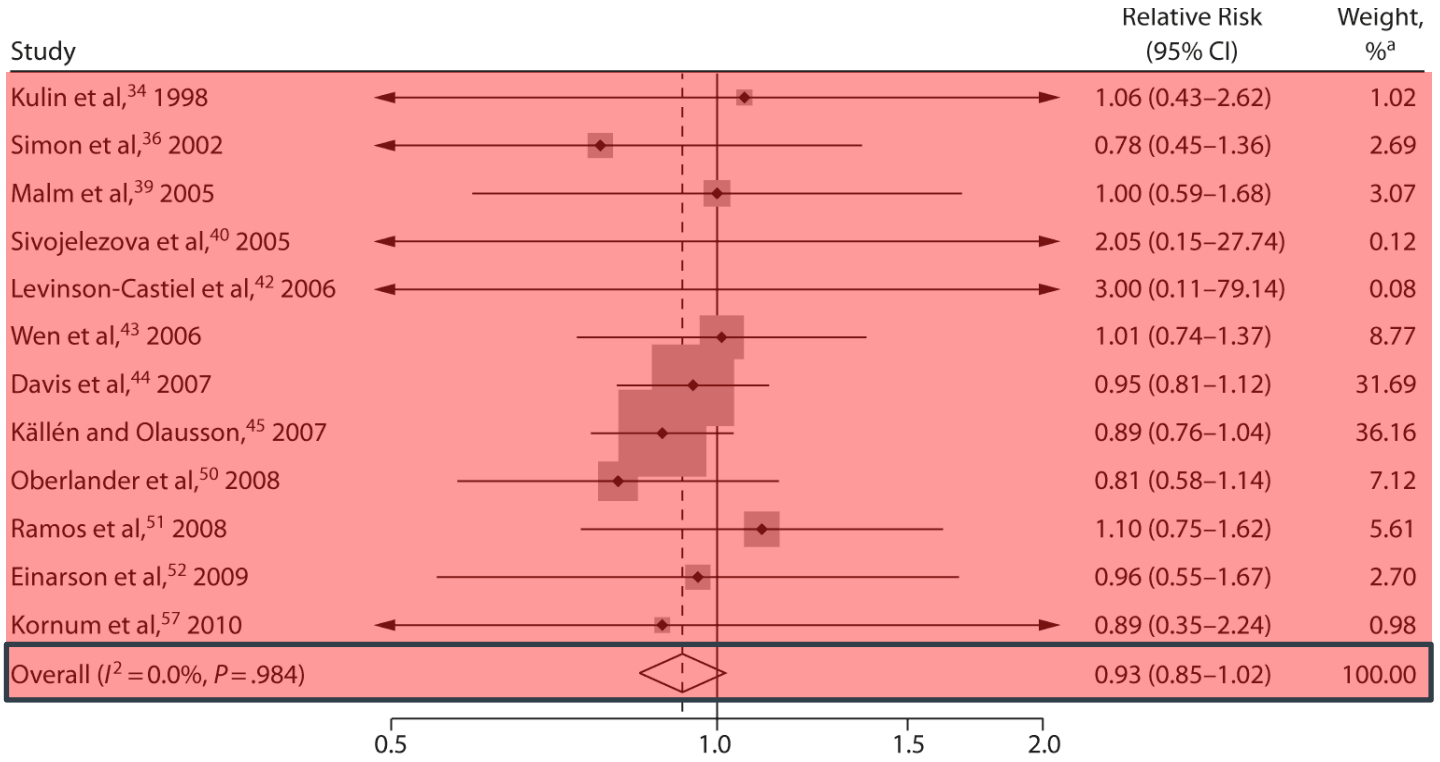
Polepally AR et al *Ann Clin Transl Neurol* 2014; 1(2): 99-106.

Perinatal Lamotrigine Dose Management
Seizure Disorder vs. Bipolar Disorder

	Seizure Disorder	Bipolar Disorder
N	46	73
LTG Dose at Conception (mg/day)	424 ± 207	243 ± 104
LTG Dose at Delivery (mg/day)	679 ± 202	268 ± 116
Change in LTG Dose (mg/day)	255 ± 139	25 ± 64
Change in LTG Dose (%)	111 ± 246	16 ± 42
LTG Dose Postpartum Week 2 (mg/day)	477 ± 139	265 ± 111
Change in LTG Dose (mg/day)	-200 ± 124	-2 ± 37
Change in LTG Dose (%)	-28 ± 13	1 ± 15

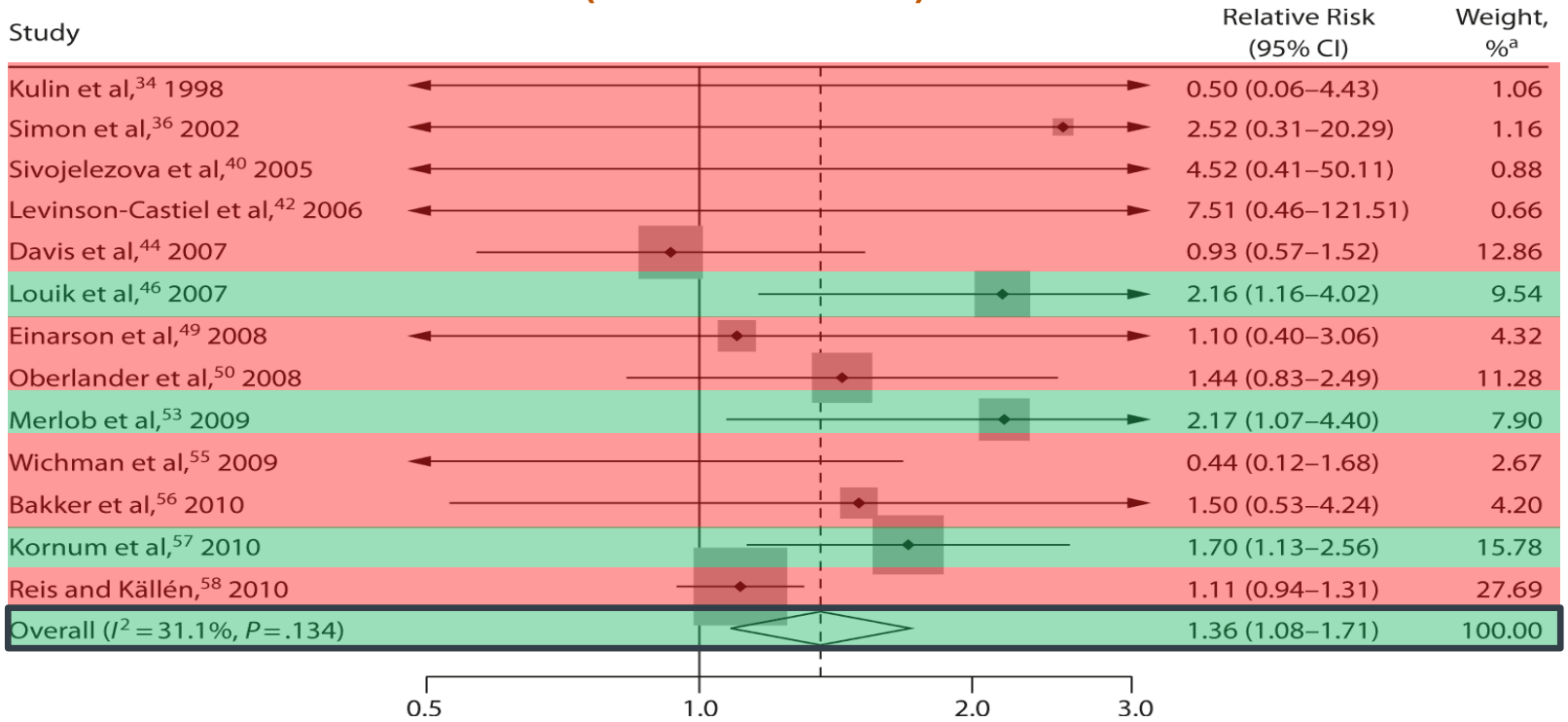
Newport DJ et al. Unpublished Data

Antidepressant Reproductive Safety Data
Birth Defects



Grigoriadis S et al. *J Clin Psychiatry* 2013; 74: 293-308

Antidepressant Reproductive Safety Data
Heart (Cardiovascular) Defects



Grigoriadis S et al. *J Clin Psychiatry* 2013; 74: 293-308

None of the significant RRs found were above 1.47, and the clinically significant benchmark for this field has been cited as being a 2-fold increase.

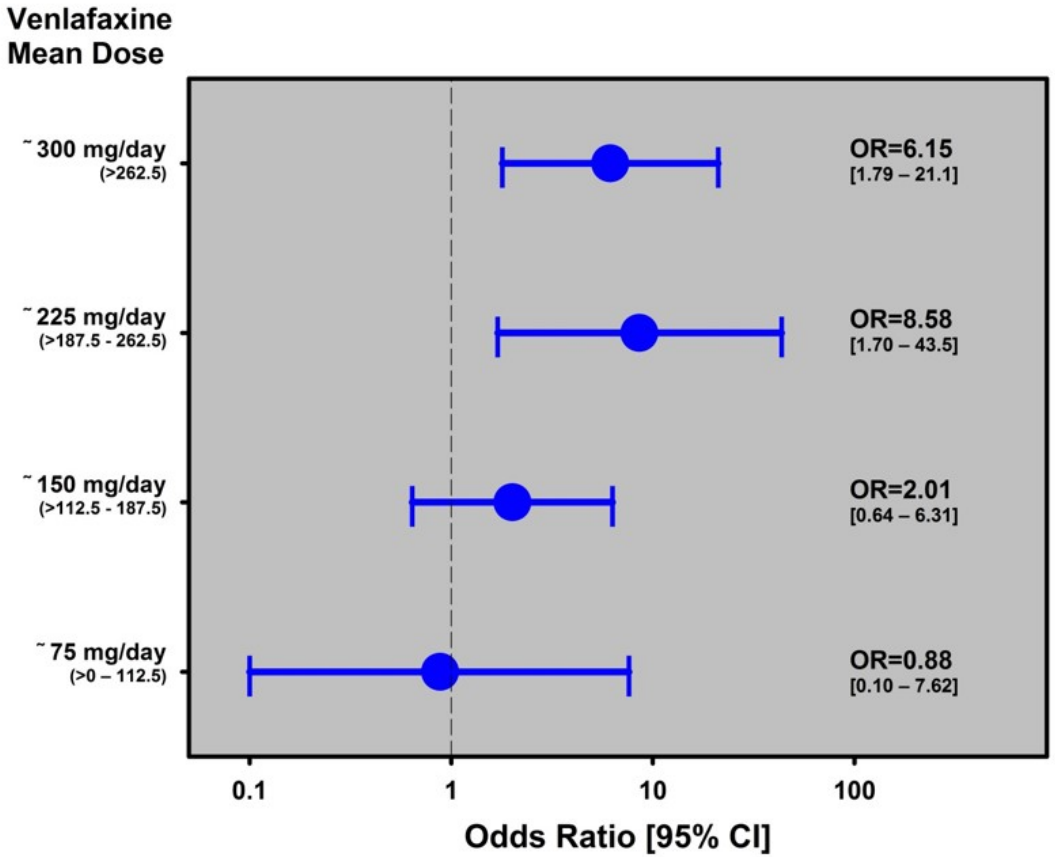
Reproductive Safety Data
Hypertensive Disorders of Pregnancy

Risk Factor		Odds Ratio [95% CI]		X^2, P Value	
Psychostimulant Exposure	After Pregnancy Week 20	6.11	[1.79 – 20.9]	X^2=8.32	p=.004
Cocaine Dependence	Lifetime History	2.99	[1.12 – 7.98]	X^2=4.76	p=.03
SNRI Exposure	After Pregnancy Week 20	2.57	[1.34 – 4.93]	X^2=8.12	p=.004
Advanced Maternal Age	≥ 40 Years Old at Conception	2.51	[1.21 – 5.20]	X^2=6.11	p=.01
African-American Race		2.33	[1.04 – 5.23]	X^2=4.23	p=.04
Nulliparity		2.18	[1.32 – 3.60]	X^2=9.18	p=.002
Obesity	Preconception BMI ≥ 30	2.14	[1.18 – 3.89]	X^2=6.24	p=.01
Panic Disorder	Lifetime History	1.78	[1.06 – 2.98]	X^2=4.76	p=.03

Exposure to depression and other psychotropics during gestation was not predictive of prenatal hypertension.

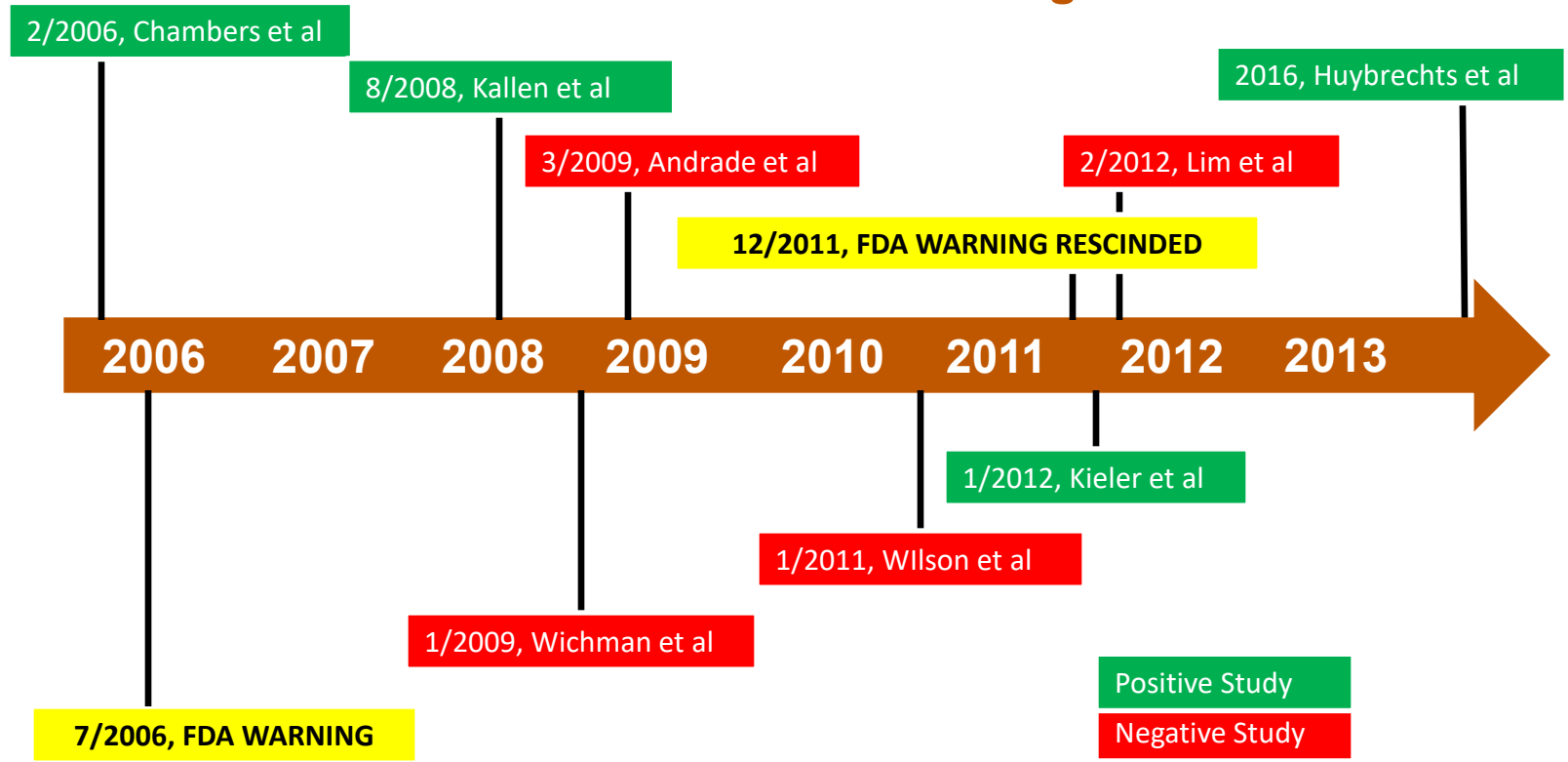
Newport DJ et al. *J Clin Psychiatry* 2016; 77: 1538-45.

Reproductive Safety Data
Venlafaxine & Hypertensive Disorders of Pregnancy



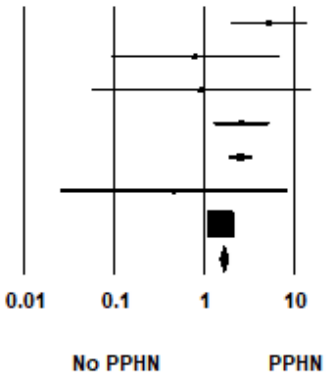
Newport DJ et al. *J Clin Psychiatry* 2016; 77: 1538-45.

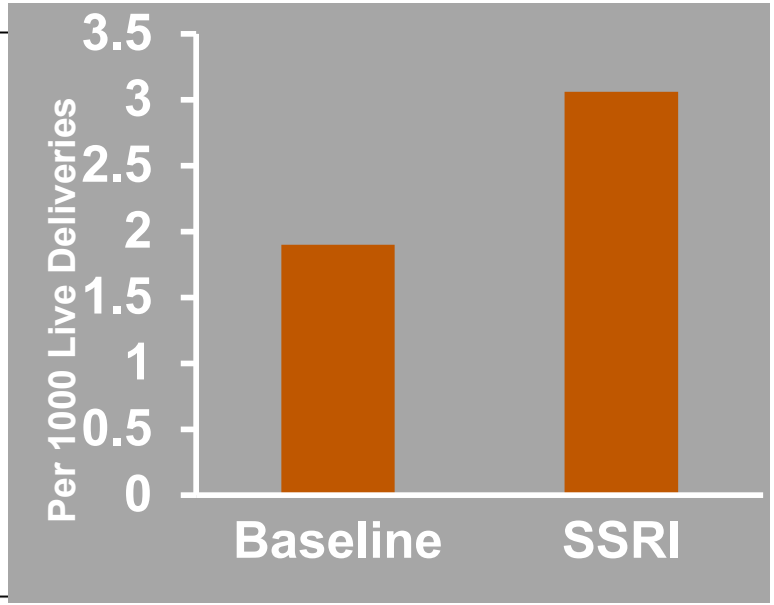
Reproductive Safety Data: Antidepressants
SSRIs & PPHN: Timeline of Findings



Reproductive Safety Data: Antidepressants
Controlled Studies of SSRI Exposure & PPHN

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Chambers et al 2006	5.100	1.928	13.493	3.282	0.001
Andrade et al 2009	0.790	0.091	6.890	-0.213	0.831
Wichman et al 2009	0.914	0.055	15.251	-0.062	0.950
Reis and Kallen 2010	2.560	1.259	5.206	2.596	0.009
Kieler et al 2011	2.500	1.800	3.472	5.467	0.000
Wilson et al 2011	0.452	0.025	8.336	-0.534	0.593
Huybrechts et al 2016	1.510	1.350	1.689	7.192	0.000
	1.623	1.463	1.802	9.110	0.000





Newport DJ. Unpublished meta-analysis

Reproductive Safety Data: Antidepressants
Controlled Studies of Neonatal Adaptation

Reference	Study Group	Control Group	Outcome	OR [95% CI] / Pct. Diff.
Chambers '96	Fluox (n=63)	Early Fluox (n=101)	Poor Adaptation	8.7 [2.9-26.6]
Costei '02	Parox (n=55)	Healthy/Early Parox (n=54)	Respiratory Distress	9.6 [1.1-79.3]
Laine '03	SSRI (n=20)	Healthy (n=20)	Serotonergic Sxs	6.9 [1.6-29.2]
Kallen '04	SSRI (n=563)	Historical (n>560K)	Respiratory Distress Jaundice Hypoglycemia Convulsions	2.0 [1.4-2.8] 1.0 [0.6-1.5] 1.4 [0.9-2.0] 3.6 [1.0-9.3]
Oberlander '04	SSRI (n=28)	Healthy (n=23)	Poor Adaptation	5.6 [1.1 – 25.3]
Zeskind '04	SSRI (n=17)	Healthy (n=17)	Tremulousness Behavioral state chg REM sleep epochs REM sleep bouts REM sleep startles Motor activity Heart rate variability	↑ 29% p<.04 ↓ 57% p<.005 ↑ 13% p<.13 ↓ 49% p<.001 ↑ 48% p<.13 ↑ 46% p<.08 ↓ 17% p<.07
Sivojelezova '05	Citalo (n=63)	Healthy/Early SSRI (n=158)	Any Complication	1.5 [1.0-2.4]
Oberlander '06	SSRI (n=37)	Healthy (n=47)	Respiratory Distress Jitteriness	46% vs. 13% p<.05 35% vs. 6% p<.05

Reproductive Safety Data: Antidepressants
Controlled Studies of Neurodevelopment

Ref.	Study Groups	Bayley Mental Development Index (MDI)	MDI Differences (vs. Control)	Bayley Psychomotor Development Index (PDI)	PDI Differences (vs. Control)
Nulman '97	Fluox (n=63) TCA (n=80) Healthy (n=84)	117 ± 17 118 ± 17 115 ± 14	n.s. n.s.		
Nulman '02	Fluox (n=46) TCA (n=40) Healthy (n=36)	104.4 ± 15.5 110.9 ± 18.0 104.1 ± 13.7	n.s. n.s.	97.7 ± 11.0 100.1 ± 12.5 98.3 ± 9.7	n.s. n.s.
Casper '03*	SSRI (n=31) MDD/No Med (n=13)	91.0 ± 13.3 94.3 ± 7.5	n.s.	90.0 ± 11.4 98.2 ± 9.1	t=2.30,p=.03
Oberlander '04 (@ 2 mos)	SSRI (n=28) SSRI+clonazepam (n=18) Healthy (n=23)	97.0 ± 8.3 94.0 ± 5.2 96.7 ± 7.8	n.s. n.s.	104.8 ± 6.1 102.9 ± 6.2 102.6 ± 7.3	n.s. n.s.
Oberlander '04 (@ 8 mos)	SSRI (n=28) SSRI+clonazepam (n=18) Healthy (n=23)	100.7 ± 6.4 97.2 ± 4.5 99.4 ± 5.6	n.s. n.s.	91.5 ± 9.6 93.1 ± 8.6 97.0 ± 9.1	n.s. n.s.

* 29% enrolled AFTER delivery

Autism & Prenatal Antidepressant Exposure

Initial Case-Control Study

SSRI Exposure Window	Adjusted OR
Preconception	2.1 [1.1 – 4.2]
First Trimester	3.8 [1.8 – 7.8]
Second Trimester	1.9 [0.7 – 5.6]
Third Trimester	2.9 [1.0 – 8.0]
Overall	2.2 [1.2 – 4.2]

Trait	Autism (N=298)	Controls (N=1507)	Test
Age (mean, sd)	31.6 (5.2)	30.2 (5.7)	*p*<.001
Race/Ethnicity (n, %)			*p*<.04
White Non-Hispanic	163 (54.7)	700 (46.4)	
White Hispanic	40 (13.4)	307 (20.4)	
Black	27 (9.1)	151 (10.0)	
Asian	28 (9.4)	149 (9.9)	
Other	40 (13.4)	200 (13.3)	
Education (≤HS n, %)	61 (20.5)	522 (34.6)	*p*<.001

Croen L et al. *Arch Gen Psychiatry* 2011

Racial/Ethnic Group	ASD Prevalence per 1000 [95% CI]
White (Non-Hispanic)	6.7 [6.4-7.0]
Black (Non-Hispanic)	5.9 [5.4-6.5]
Hispanic	3.9 [3.4-4.5]

Durkin MS et al. *Am J Public Health* 2017; 107(11): 1818-26

Methodological Concerns

Studies of Prenatal Antidepressant Exposure & Autism

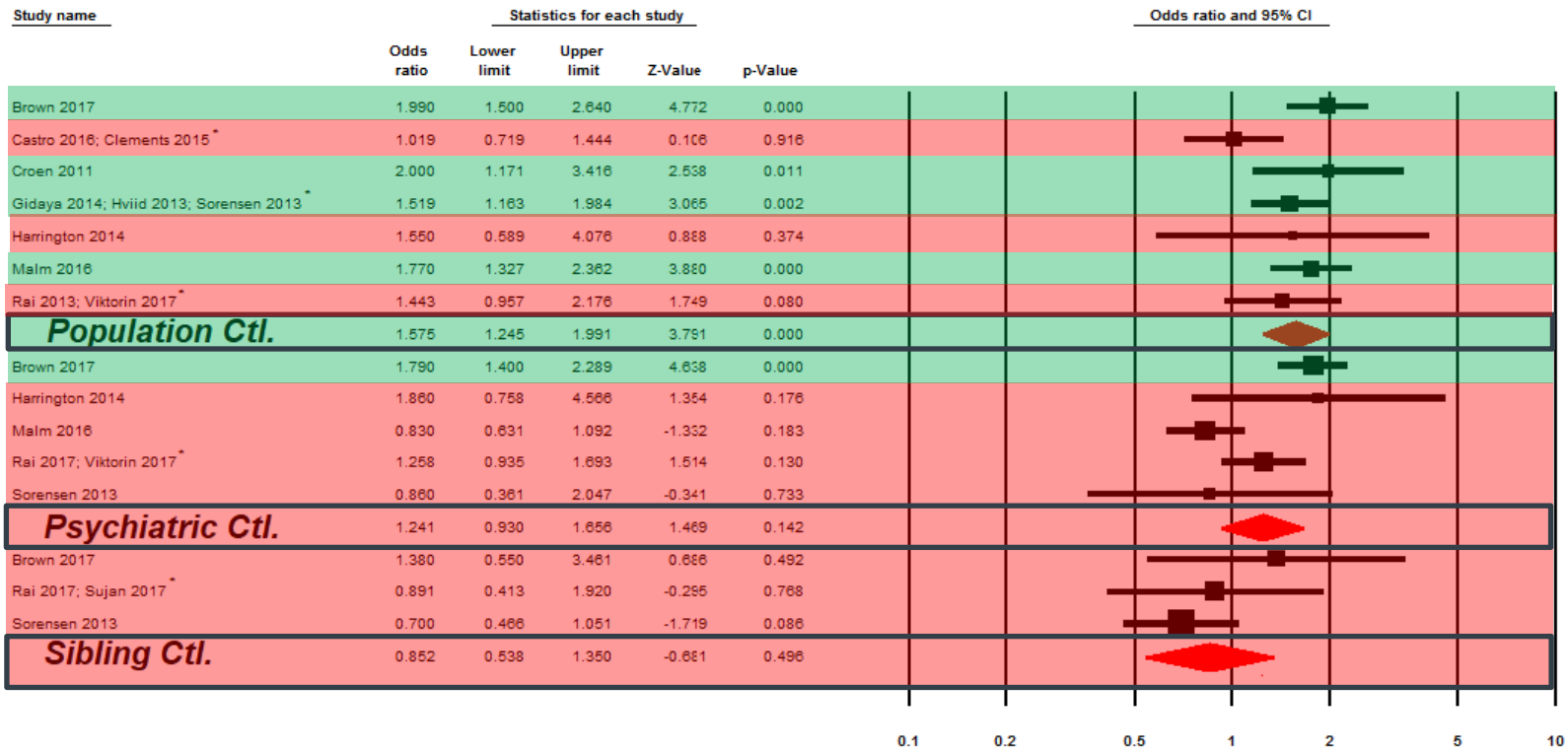
Study	Design	Group Distribution by Maternal Ethnicity / Nationality
Croen et al 2011	**Case-Ctl**	**Autism rate LOWER among Hispanics than non-Hispanics**
Hviid et al 2013	**Cohort**	**AD Exposure Rate LOWER among mothers born outside Denmark**
Malm et al 2016	**Cohort**	**AD Exposure Rate LOWER among mothers born outside Finland**
Rai et al 2013	**Case-Ctl**	**Autism rate LOWER among children of mothers born outside Sweden**
Rai et al 2017	**Cohort**	**AD Exposure Rate LOWER among mothers born outside Sweden**
Sujan et al 2017	**Cohort**	**AD Exposure Rate LOWER among mothers born outside Sweden**
Harrington et al 2014	**Case-Ctl**	**Autism rate HIGHER among children of mothers born outside US**
Castro et al 2016	**Case-Ctl**	**No Differences**
Clements et al 2016	**Case-Ctl**	**No Differences**
Boukhris et al 2016	Case-Ctl	Unreported
Brown et al 2017	Cohort	Unreported
Gidaya et al 2014	Cohort	Unreported
Sørensen et al 2013	Case-Ctl	Unreported
Viktorin et al 2017	Cohort	Unreported

Vega M et al. *Am J Psychiatry 2020; 177: 506-17*

Prenatal Antidepressant Exposure & Autism Risk

Advanced Methods in Reproductive Pharmacovigilance Reporting

Odds Ratios



Vega M et al. *Am J Psychiatry 2020; 177: 506-17*

LITHIUM

Lithium Registry

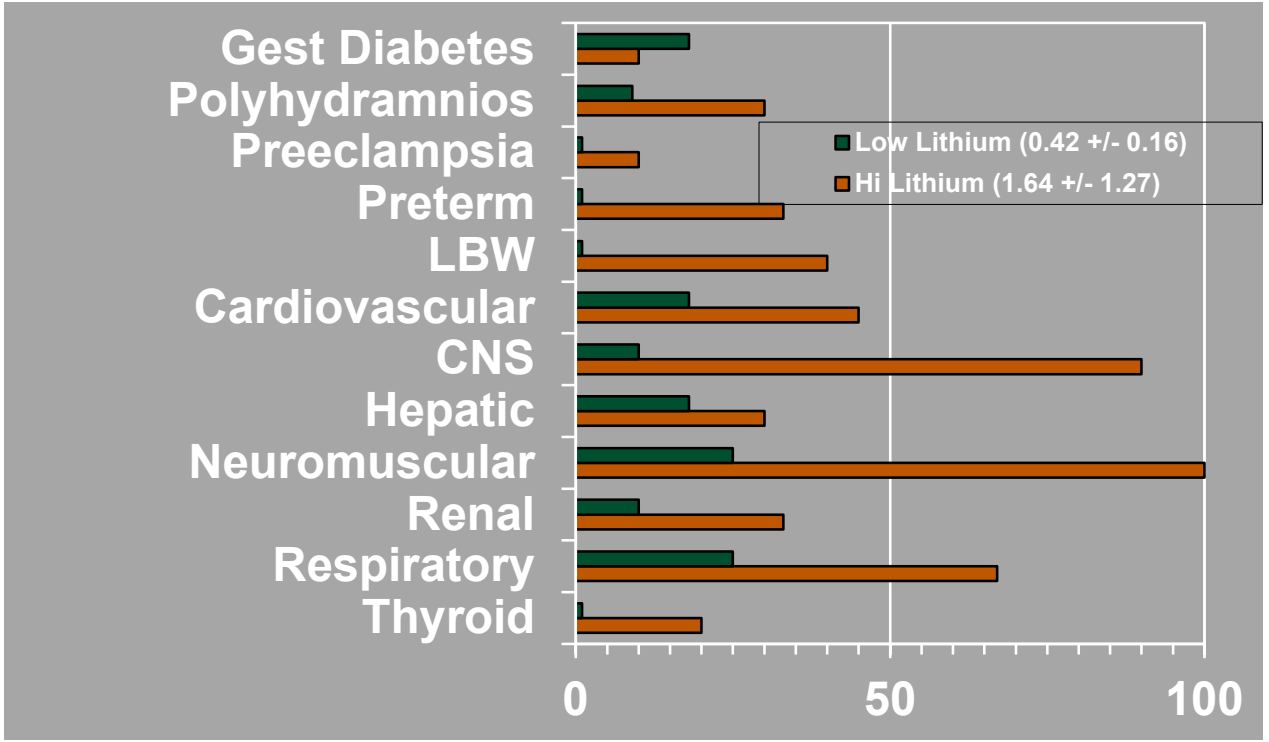
Ebstein's anomaly risk (<0.1%)
Cohen LS et al. *JAMA* 1994; 271: 146-50

Neurobehavioral Outcome

No concerns in school age kids (n=60)
Schou M. *Acta Psychiatr Scand* 1976; 54: 193-7

Delivery Complications

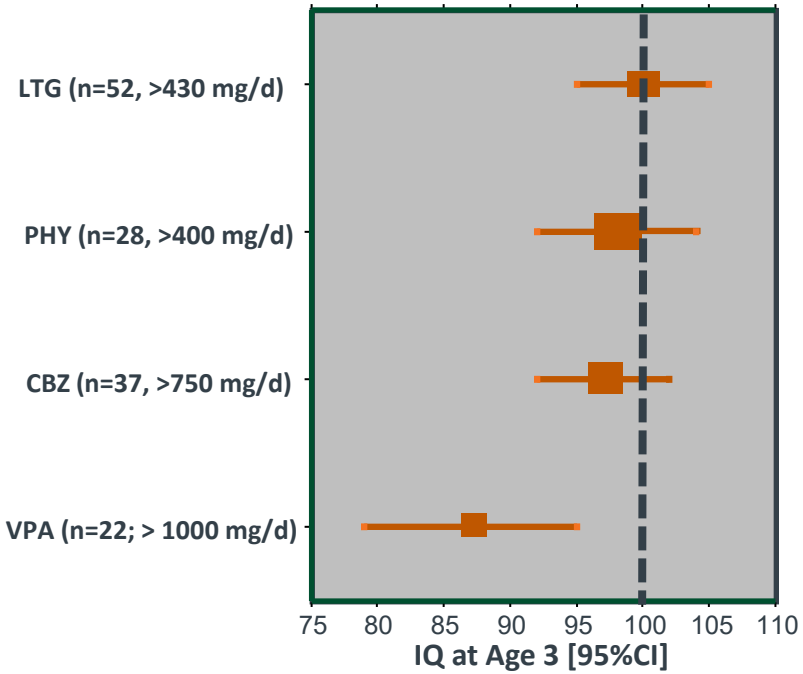
cyanosis, hypotonia, atrial flutter, bradycardia, fetal diabetes insipidus, hydronephrosis, fluid retention, neonatal hypoglycemia, neonatal goiter



Newport DJ et al. *Am J Psychiatry* 2005; 162: 2162-70

Valproate

- **Neural Tube Defects: 3.8% Risk**
  - Rosa FW. *New Engl J Med* 1991; 324: 674-7
  - Samren E et al. *Epilepsia* 1997; 38: 981-90
  - Reduced Risk: [VPA] ≤ 70, VPA daily dose ≤ 1000 mg
    - Kaneko S et al. *Epilepsy Res* 1999; 33: 145-58
    - Samren E et al. *Epilepsia* 1997; 38: 981-90
- **Fetal Valproate Syndrome**
  - McMahon CL, Braddock SR. *Teratology* 2001; 64: 83-6
  - Facial, Cardiovascular, & Limb abnormalities
  - Higher rate of homozygosity for MTHFR
    - Dean JCS et al. *Clin Genet* 1999; 56: 216-20
- **Delivery Complications**
  - hepatotoxicity, coagulopathy, hypogylcemia
- **Neurobehavioral Outcome**
  - Kozma C. *Am J Med Genet* 2001; 98: 168-75
  - Developmental Delay (20%)
  - Mental Retardation (10%)



Meador KJ et al. *N Engl J Med* 2009; 360: 1597–1605

Lamotrigine

Prospective Assessment of Teratogenicity

Source	Major Malformations		
	Mono-therapy	Polytherapy	VPA Polytherapy
Intl. Lamotrigine Pregnancy Registry [1]	28 / 1085 2.6%	9 / 350 2.6%	15 / 144 10.4%
UK Independent Pregnancy Registry [2]	21 / 647 3.2%	8 / 289 2.8%	13 / 141 9.2%
North Am. AED Pregnancy Registry [3]	15 / 564 2.7%		
European Registry AEDs Pregnancy Australian Registry AEDs Pregnancy [4] Danish Registry AEDs Pregnancy [5]	0 / 61 0.0%	1 / 51 2.0%	4 / 68 5.9%
Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study [6]	1 / 98 1.0%		
Dominguez-Salgado et al [7]	0 / 31 0.0%		
	65 / 2486 2.6%	**18 / 690 2.6%**	**32 / 353 9.1%**

83 / 3176 2.6%

1 Lamotrigine Pregnancy Registry. Interim Report. 9/92 – 3/07
2 Morrow J et al. *J Neurol Neurosurg Psychiatr* 2006;77:193-8
3.Holmes LB et al. *Birth Defects Res* 2006; 76:318
4 Vajda FJ et al. *J Clin Neurosci* 2003; 10: 543-9.
5 Sabers A et al. *Acta Neurol Scand* 2004; 109: 9-13.
6 Meador KJ et al. *Neurology* 2006; 67: 407-12.
7 Dominguez-Salgado M et al. *J Neurol* 2001; 248(suppl 2): 146.

Lamotrigine: Orofacial Clefts

Cohort Studies

Source	Orofacial Clefts	
Intl. Lamotrigine Pregnancy Registry [1]	2 / 1085	1.8 / 1000
UK Independent Pregnancy Registry [2]	1 / 647	1.5 / 1000
North Am. AED Pregnancy Registry [3]	5 / 564	8.9 / 1000
European Registry AEDs Pregnancy Australian Registry AEDs Pregnancy [4] Danish Registry AEDs Pregnancy [5]	 0 / 61 0 / 51	 0.0 / 1000 0.0 / 1000
Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study [6]	0 / 98	0.0 / 1000
Dominguez-Salgado et al [7]	0 / 31	0.0 / 1000
	8 / 2537	**3.2 / 1000**

1 Lamotrigine Pregnancy Registry. Interim Report. 9/92 – 3/07
2 Morrow J et al. *J Neurol Neurosurg Psychiatr* 2006;77:193-8
3.Holmes LB et al. *Birth Defects Res* 2006; 76:318
4 Vajda FJ et al. *J Clin Neurosci* 2003; 10: 543-9.
5 Sabers A et al. *Acta Neurol Scand* 2004; 109: 9-13.
6 Meador KJ et al. *Neurology* 2006; 67: 407-12.
7 Dominguez-Salgado M et al. *J Neurol* 2001; 248(suppl 2): 146.

EUROCAT Case-Control

Group	Cases	Controls	Total
LTG	2	43	45
No LTG	5,509	80,009	85,518
Total	5,511	80,052	85,563

AOR (Cleft | LTG Exposure)

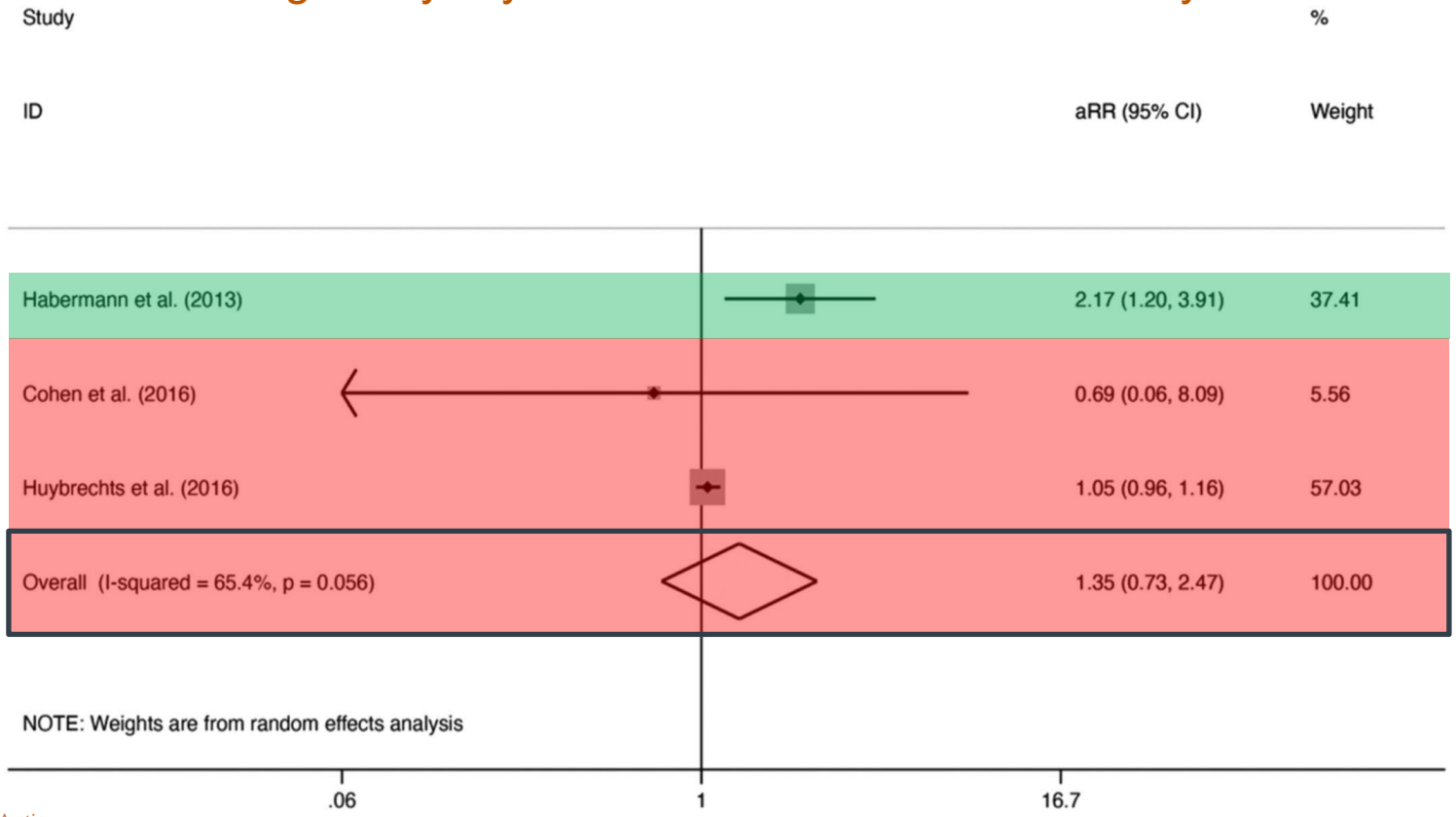
0.67 [95%CI: 0.10 – 2.34]

First Generation Antipsychotics
Reproductive Safety Profile Summary

- **Teratogenicity: Major Malformations**
  - No association with chlorpromazine, perphenazine, haloperidol
    Goldberg HL & DiMascio A 1978; Hill RM & Stern L 1979; Nurnberg HG & Prudic J 1984
  - Positive association with aliphatic phenothiazines
    Rumeau-Rouquette C et al. 1977
- **Preterm Birth & Birth Weight**
  - No association with haloperidol at antiemetic doses (1.2 mg/day)
    Van Waes A & Van de Velde EJ 1969
  - No association with trifluoperazine at antiemetic doses
    Moriarty AJ & Nance NR 1963; Rawlings WJ et al 1963
- **Neonate**
  - Case reports of EPS, NMS
    James ME 1988; Cleary MF 1977; Hill RM et al 1966; O'Connor MO et al 1981
  - Intestinal Obstruction
    Falterman CG & Richardson CJ 1980
- **Neurodevelopment (Clinical)**
  - No differences in IQ scores at 4yo (generally low antipsychotic doses)
    Kris EB 1965; Sloan D et al 1977
- **Neurodevelopment (Preclinical)**
  - Learning Deficits
    Hoffeld DR et al 1968; Ordy JM et al 1966; Robertson RT et al 1980
  - No Impact upon Learning
    Dallemagne G & Weiss B 1982

Prenatal Antipsychotic Exposure

Teratogenicity: Systematic Review and Meta-Analysis



Wang Z et al. *Brit J Clin Pharmacol* 87(11): 4101-23,

Prenatal Antipsychotic Exposure

Teratogenicity

"a detection bias cannot be ruled out . . .

exposed women might be more likely to be offered fetal echocardiography and postnatal diagnosis . . .

all septal defects detected in both the [SGA] cohort and [FGA] cohort were isolated in contrast to most infants of the control cohort where multiple malformations included septal defects"

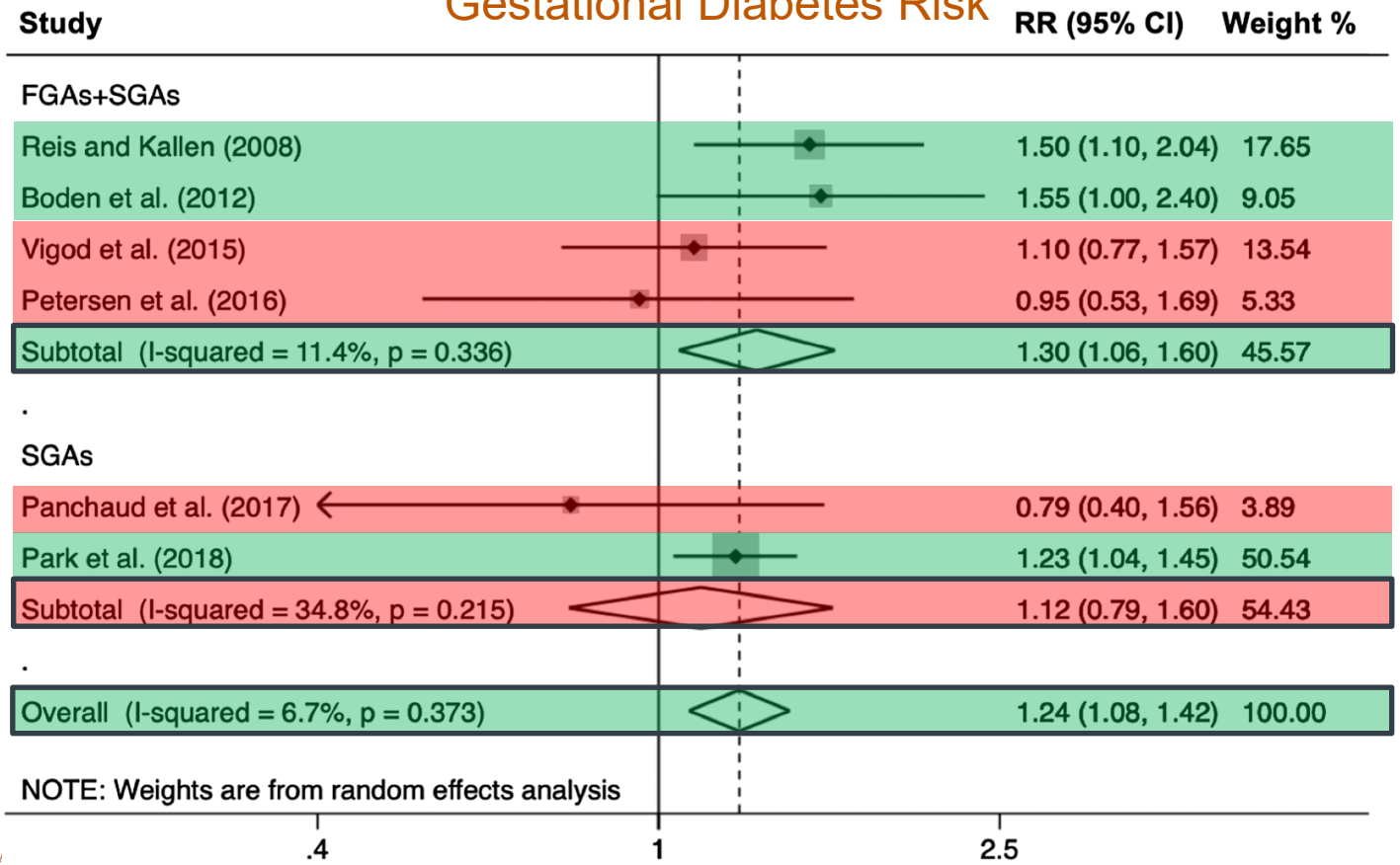
Systems Affected

System	SGA	FGA	Ctl
N	430	213	1014
Nervous	2 (0.5)	0 (0.0)	1 (0.1)
CV*	**12 (2.8)**	**3 (1.4)**	**6 (0.6)**
GI	2 (0.5)	0 (0.0)	5 (0.5)
Musc Skel	2 (0.5)	2 (0.9)	4 (0.4)
Face	2 (0.5)	0 (0.0)	1 (0.1)
ENT	0 (0.0)	0 (0.0)	0 (0.0)
Genital	0 (0.0)	0 (0.0)	1 (0.1)
Urinary	1 (0.2)	1 (0.5)	3 (0.3)
Skin	0 (0.0)	1 (0.5)	0 (0.0)
Multiple	1 (0.2)	2 (0.9)	4 (0.4)

Haberman F et al. *J Clin Psychopharmacol* 2013; 33: 453-62

Prenatal Antipsychotic Exposure

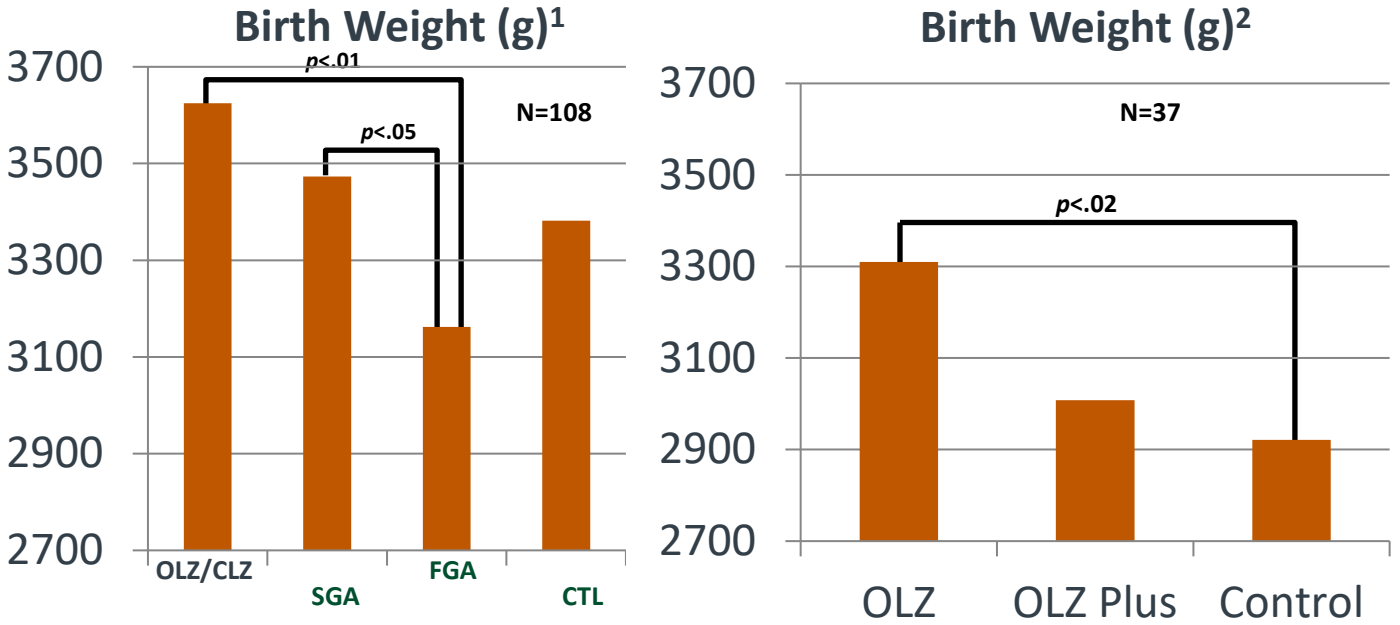
Gestational Diabetes Risk



Wang Z et al. *Brit J Clin Pharmacol* 87(11): 4101-23,

Prenatal Antipsychotic Exposure

Metabolic Effects: Birth Weight



[1]Newham JJ et al. *Br J Psychiatry* 2008; 192: 333-7

[2]Babu GN et al. J Psychopharmacol 2010; 30: 331-2

Prenatal Antipsychotic Exposure

Neurobehavioral Profiles at 2, 6, 12 Months

Bayley III Scales		SGA Exposed N=76	Control N=76	t	p
Cognitive	**2 Months**	**90.33 (6.92)**	**97.84 (7.74)**	**39.74**	**<.001**
	6 Months	99.03 (8.26)	101.42 (6.96)	3.74	.055
	12 Months	100.99 (8.17)	103.11 (7.84)	2.66	.105
Language	2 Months	94.43 (7.51)	96.18 (7.67)	2.02	.157
	6 Months	95.72 (7.28)	97.00 (7.16)	1.19	.278
	12 Months	97.26 (6.79)	98.18 (7.18)	0.66	.418
Motor	**2 Months**	**92.28 (7.89)**	**97.53 (7.67)**	**17.37**	**<.001**
	6 Months	100.46 (9.29)	102.79 (6.64)	3.16	.078
	12 Months	101.59 (8.53)	103.68 (7.19)	2.68	.104
Social Emotional	**2 Months**	**95.68 (9.38)**	**101.89 (8.67)**	**17.95**	**<.001**
	6 Months	**99.41 (9.97)**	**103.59 (8.71)**	**7.59**	**.007**
	12 Months	102.54 (9.72)	104.50 (8.63)	1.73	.191
Adaptive Behavior	**2 Months**	**93.14 (8.63)**	**99.32 (6.29)**	**25.38**	**<.001**
	6 Months	**97.57 (8.44)**	**100.66 (6.04)**	**6.74**	**.010**
	12 Months	99.80 (8.56)	101.24 (5.83)	1.46	.229

N=152

Peng M et al. *Psychopharmacology* 2013; 228: 577-84

Fetal Antipsychotic Exposure:
Risk of Neurodevelopmental Disorders

Aripiprazole

Any neurodevelopmental disorder	1.36 (1.14-1.63)
ASD	1.49 (0.91-2.47)
ADHD	1.36 (0.98-1.89)
Learning difficulty[b]	-
Speech/language disorder	1.61 (1.28-2.02)
DCD	1.05 (0.55-2.01)
Intellectual disability[b]	-
Behavioral disorder[a]	1.63 (1.18-2.26)

Olanzapine

Any neurodevelopmental disorder	0.95 (0.80-1.12)
ASD[a]	1.00 (0.60-1.69)
ADHD	0.98 (0.78-1.24)
Learning difficulty[a]	0.81 (0.33-2.00)
Speech/language disorder	0.90 (0.69-1.18)
DCD[a]	0.89 (0.40-2.01)
Intellectual disability[a]	0.41 (0.10-1.67)
Behavioral disorder[a]	0.90 (0.67-1.19)

Quetiapine

Any neurodevelopmental disorder	1.07 (0.96-1.19)
ASD	1.12 (0.81-1.54)
ADHD	1.08 (0.91-1.28)
Learning difficulty[a]	1.14 (0.62-2.12)
Speech/language disorder	1.06 (0.91-1.25)
DCD	1.03 (0.69-1.54)
Intellectual disability[a]	1.22 (0.59-2.54)
Behavioral disorder	1.10 (0.91-1.33)

Risperidone

Any neurodevelopmental disorder[c]	1.03 (0.86-1.23)
ASD[a]	0.62 (0.31-1.24)
ADHD[c]	1.01 (0.78-1.30)
Learning difficulty[a]	1.43 (0.66-3.10)
Speech/language disorder[a]	0.88 (0.66-1.19)
DCD[a]	1.44 (0.77-2.69)
Intellectual disability[a]	1.74 (0.75-4.06)
Behavioral disorder[a]	1.12 (0.84-1.48)

Straub L et al. *JAMA Int Med* 2022; 182: 522-33

MATERNAL-FETAL PSYCHIATRY

Conclusion: Prenatal Decision-Making

Prevalence: Magnitude of the Issue

Risks of Prenatal Mental Illness

Risks & Benefits of Pharmacotherapy

Case: PeriPAN Consult with Obstetrical Provider

36yo G1P0, unplanned Pregnancy 8 weeks EGA. Psychiatric h/o of recurrent MDD, OCD, and ADHD with possible GAD. Using cannabis and tobacco daily.

At knowledge of conception, patient was taking paroxetine 40mg Qday, trazodone 50mg QHS, and atomoxetine 80mg qday. Patient immediately discontinued atomoxetine and trazodone at that time. She is trying to wean herself from tobacco and marijuana. Mood and anxiety symptoms remain well-controlled. Only previous treatment was with fluoxetine, which patient recalls working well.

Question: What should we advise regarding paroxetine?

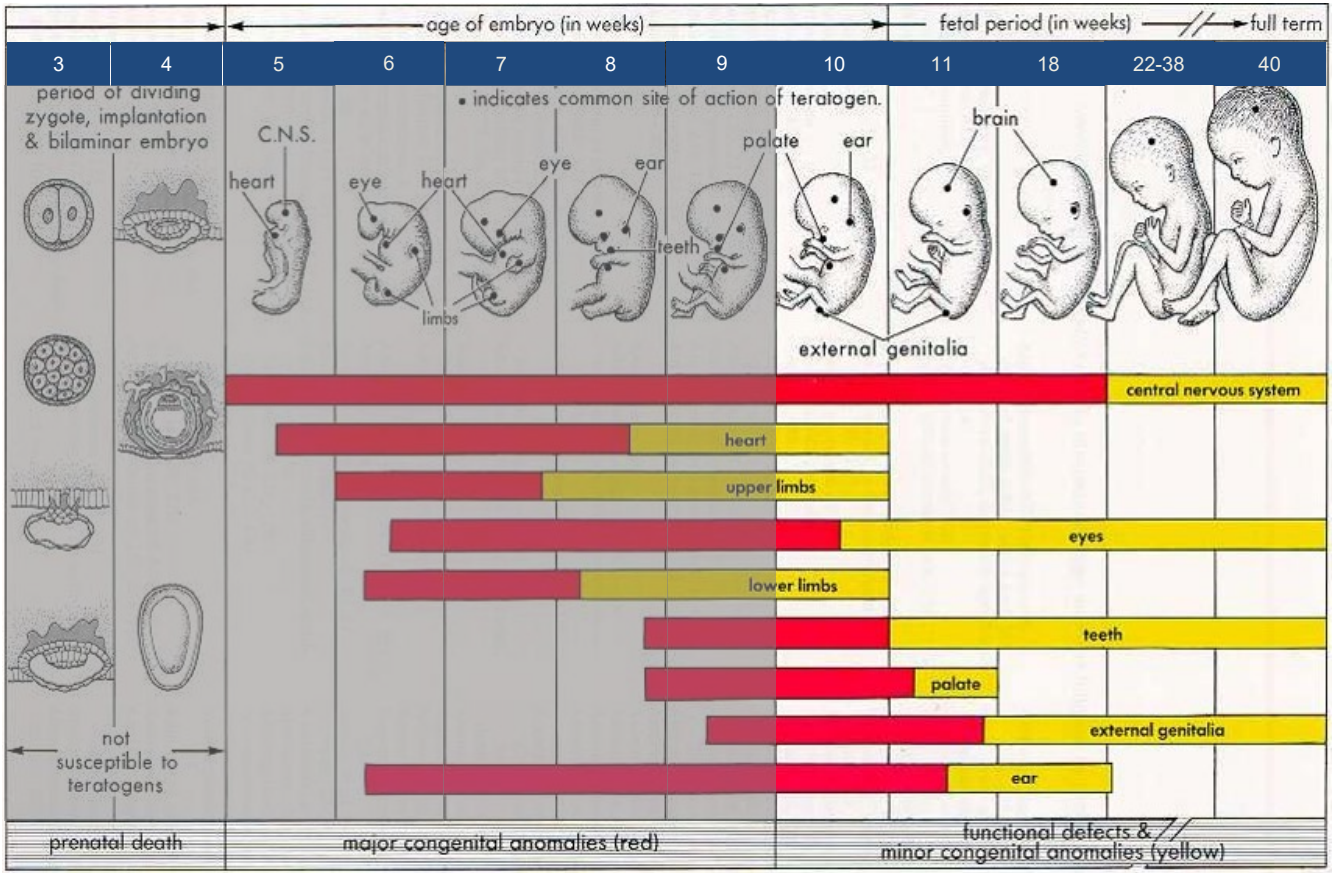
PREGNANT ON MEDS

Are my meds safe?

Options
1. Continue
2. Discontinue
3. Switch

Ranking Options

TREATMENT OPTION	POTENTIAL EFFICACY	SAFETY
Paroxetine 40mg		
Fluoxetine ?mg		
Discontinue		


age of embryo (in weeks)
fetal period (in weeks)
full term
3
4
5
6
7
8
9
10
11
18
22-38
40
period of dividing zygote, implantation & bilaminar embryo
• indicates common site of action of teratogen.
C.N.S.
heart
eye
heart
eye
ear
palate
ear
brain
teeth
limbs
external genitalia
central nervous system
heart
upper limbs
eyes
lower limbs
teeth
palate
external genitalia
ear
not susceptible to teratogens
prenatal death
major congenital anomalies (red)
functional defects & minor congenital anomalies (yellow)

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