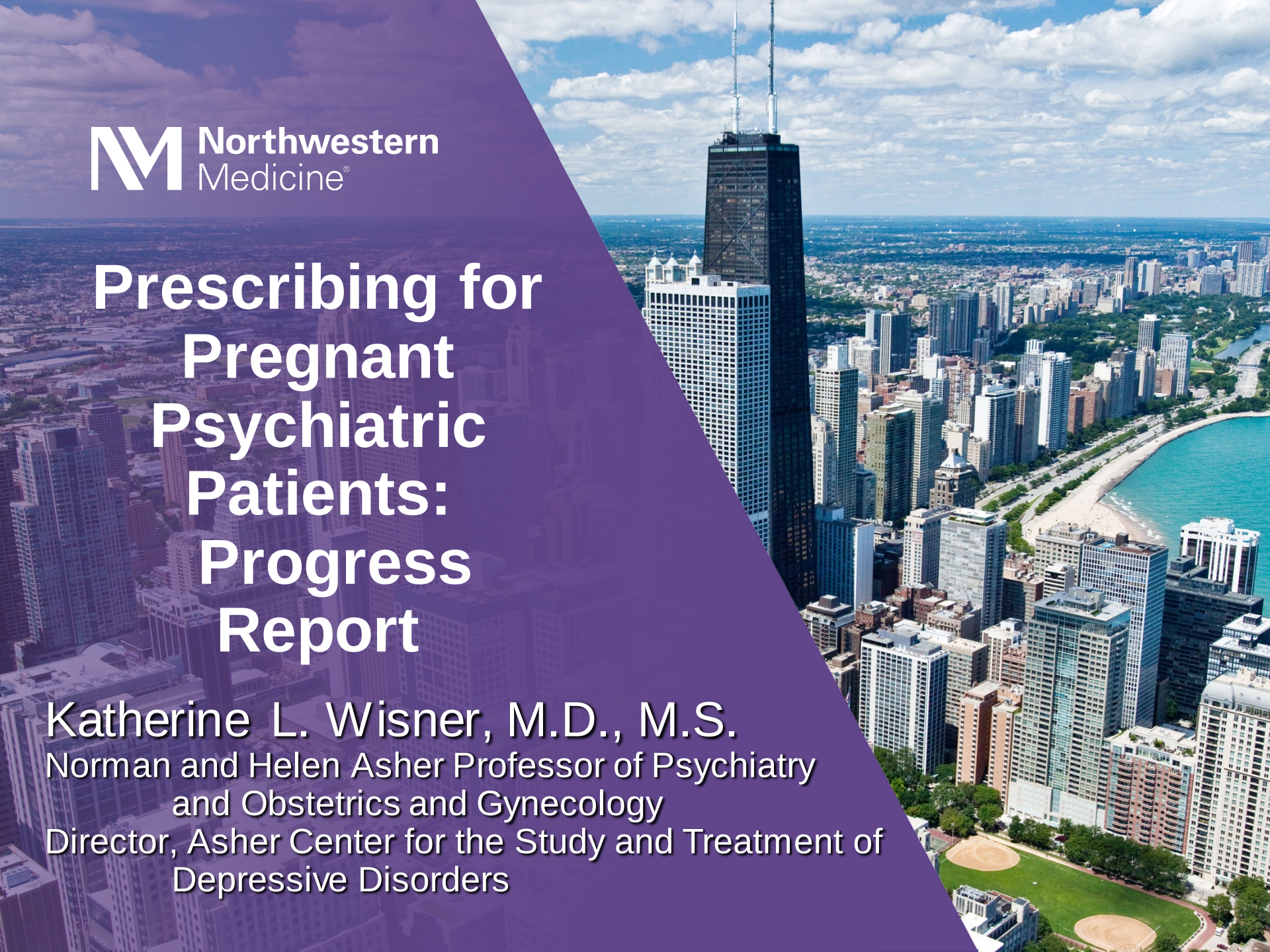


Northwestern Medicine®

Prescribing for Pregnant Psychiatric Patients: Progress Report

Katherine L. Wisner, M.D., M.S.
Norman and Helen Asher Professor of Psychiatry and Obstetrics and Gynecology
Director, Asher Center for the Study and Treatment of Depressive Disorders

Goals

- Review public health burden of psychiatric illness in pregnancy.
- Discuss factors that influence patient acceptance or decline of treatment.
- Comment on what psychiatrists want to see in labeling.

Epidemiology Major Depression- Major Public Health Impact

- Depression is the **leading cause of disability in women worldwide.**
- Lifetime, Female (F)=21%; Male (M)=12%
- Annual, F=13%, M=8%
- Pregnancy-related death rate in the United States **increased** across the last 3 decades.
  www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html
- Self-harm is the most common cause of pregnancy-associated fatalities in first year postpartum.
  https://www.ncbi.nlm.nih.gov/pubmed/27824771

Maternal Disease Burden: Depression

You say that I'm depressed
I wonder if you understand
You've never lived, I think
In this God-forsaken land
I always fight to function
I'm fighting to survive
I'm trying desperately to remember
What it's like to feel alive
You say I'm carrying life inside
How can that really be?
How could life possibly survive
In a non-existent me?

Prognosis

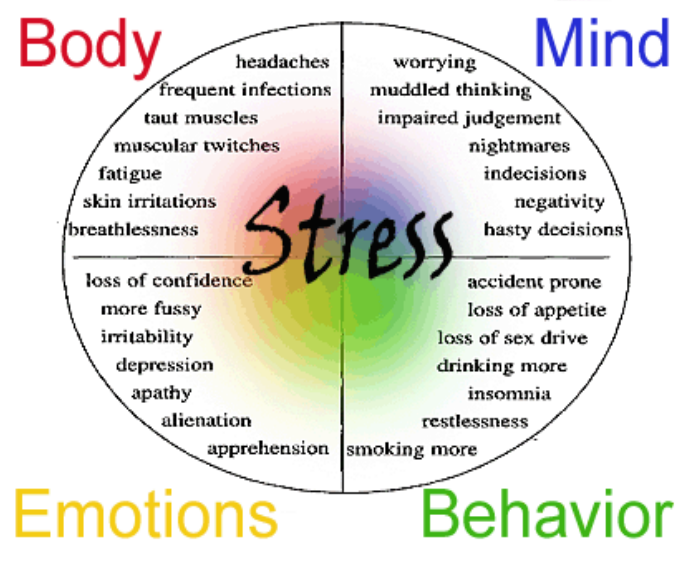
Recurrence Risk increases with the number of episodes:

- With 1 episode of major depression, the individual has a 60% probability of another
- If 2 episodes, 70%
- If 3 episodes, 90%, likely to be chronic, consider maintenance treatment
- Treat to Remission - not Response

Risks of Maternal Mental Illness

Obstetric/Neonatal Complications

- Miscarriage
- Hypertensive Disorders/ Preeclampsia
- Preterm birth
- Operative deliveries
- Low birth weight
- Birth defects
- NICU admission
- Sudden infant death syndrome



MDD Impacts Attachment and Development

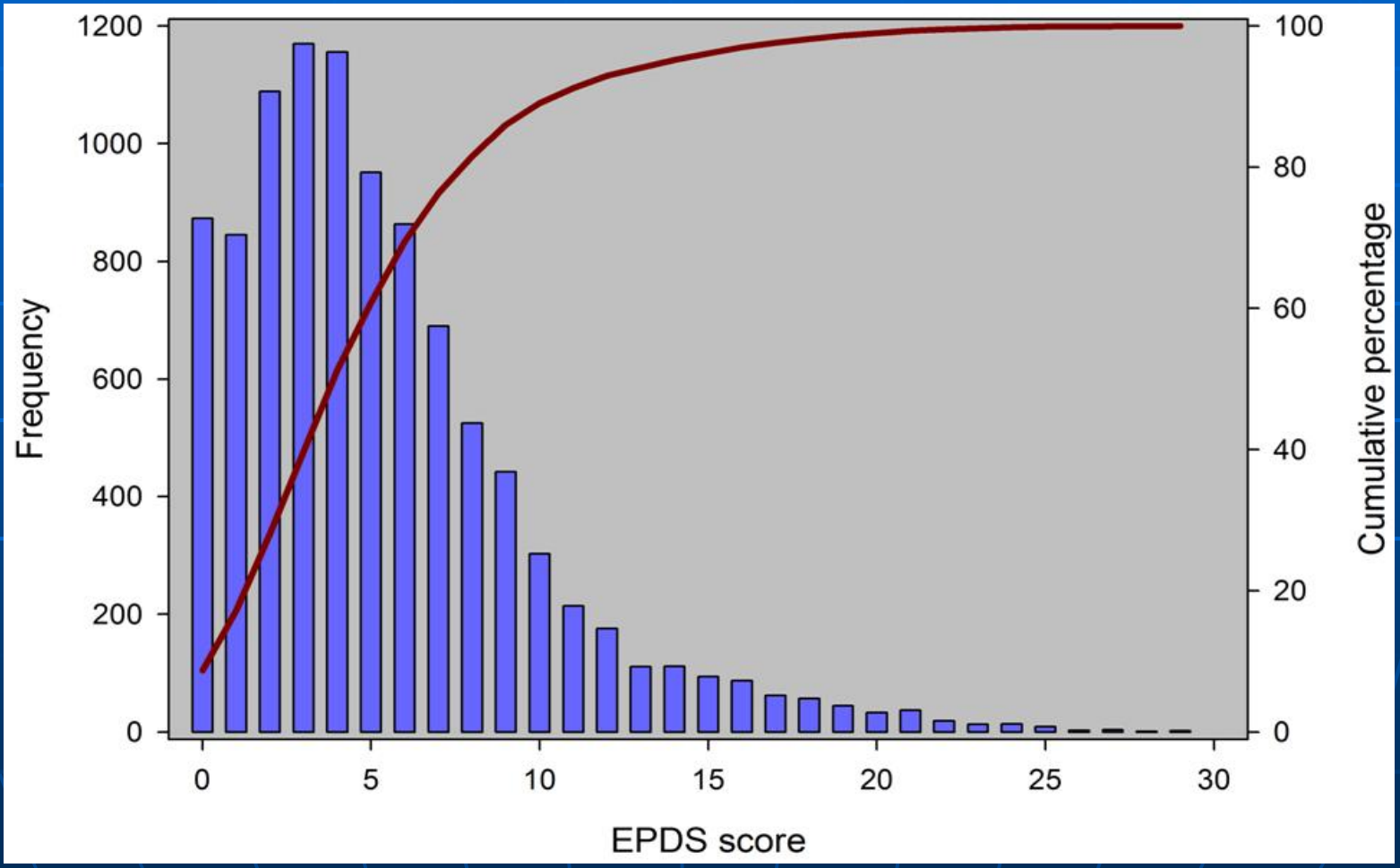
- **Early Social – Emotional Impact**
  - Poor infant self-regulation
  - Less secure attachments to caregivers
  - Infants cry more, smile less
  - Less interactive, few vocalizations, less physically active
  - Depressed moms less responsive, perceive infants as bothersome
- **Long Term Impairments:**
  - Developmental delays
  - Cognitive deficits
  - Behavioral problems
  - Social deficits
  - Poorer physical health
  - Increased risk for child psychopathology

Wisner et al (1999) *JAMA*, 282: 1264-9, Brockington et al. (2006) *Arch Women's Ment Health* 9: 243-251
Murray et al (2003) *Br J Psychiatry*, 2003.182: 420-427.
Beebe et al (2008) *Infant Mental Health Journal*, 2008. 29 (5): 442-471.

The Scope of the Problem

- Women approached for education and screening permission during maternity hospitalization
- Women given EPDS at 4 to 6 weeks post-birth by telephone by research team
- Women with positive screens offered home visit
- SCID psychiatric DSM4 diagnostic interview to evaluate women with EPDS $\geq$ 10
- Magee Women's Hospital, Pittsburgh, PA USA
- 10,000 deliveries/year

Composite Screen Results



At ≥ 10, 14% of population screened
At ≥ 13, 7% of population screened

Timing of Episode Onset for Depression Identified Post-birth

The onset of the identified episodes for the 826 home-visited women was:

- during pregnancy, N=276 (33.4%)
- **postpartum (within 4 weeks of birth), N= 331 (40.1%)**
- prior to pregnancy, N=219 (26.5%)

Primary Axis 1 SCID Diagnoses

Primary Diagnoses, N = 826		
	N	%
Depressive Disorders	**566**	**68.5**
Major Depression- Recurrent	368	65.0
Major Depression - Single Episode	146	25.8
Depressive Disorder NOS	38	6.7
Adjustment Disorder With Depressed Mood	11	1.9
Mood Disorder NOS	2	0.4
Dysthymic Disorder	1	0.2
Bipolar Disorders	**187**	**22.6**
Bipolar 2 Disorder	58	31.0
BPD1-Recent Episode Depressed	54	28.9
Bipolar Disorder NOS	35	18.7
BPD1-Recent Episode Mixed	32	17.1
BPD1-Single Manic Episode	7	3.7
Schizoaffective Disorder	1	0.5
Anxiety Disorders	**46**	**5.6**
Generalized Anxiety Disorder	24	52.2
Obsessive-Compulsive Disorder	8	17.4
Anxiety Disorder NOS	8	17.4
Adjustment Disorder With Anxiety	3	6.5
Panic Disorder Without Agoraphobia	1	2.2
Post-traumatic Stress Disorder	1	2.2
Specific Phobia	1	2.2
Substance Use Disorders	**4**	**0.5**
Substance-Induced Mood Disorder	1	25.0
Alcohol Abuse/Dependence	1	25.0
Opioid Abuse/Dependence	1	25.0
Polysubstance Dependence	1	25.0
Other Disorders	**6**	**0.7**
No Diagnosis	**17**	**2.1**

The Myth of Protection from Mental Illness during Pregnancy

- Recurrence risk for women who either maintained or discontinued antidepressants proximal to conception (*Cohen et al- JAMA. 2006;295:499-507)*
- Significantly more women who discontinued (44/65, 68%) compared to women who maintained (21/82, 26%) antidepressant treatment suffered recurrent major depressive disorder.
- Recurrences emerged rapidly (50% in the first trimester, and 90% by the end of second trimester).

Risk-Benefit Decision-Making for Depression during Pregnancy: A Framework

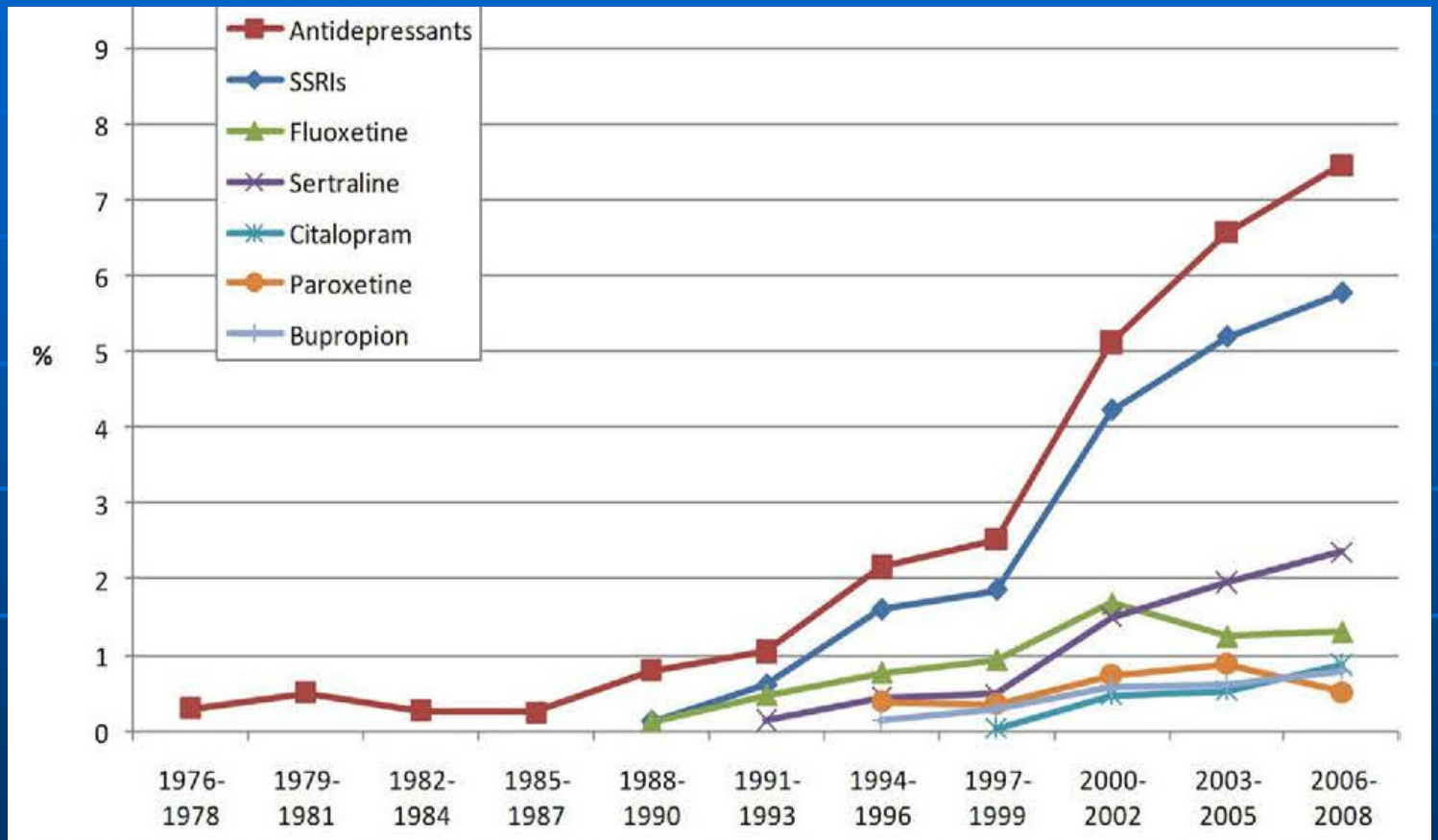
- Wisner et al: Risk-benefit decision-making for treatment of depression during pregnancy. *Am J Psych 157: 1933-1940, 2000*
- Healthy outcomes for mother and baby are the rule rather than the exception!

Non-Pharmacologic Treatments

- Short-term, 12-16 sessions, focused psychotherapy
- Cognitive Behavior Therapy – correct distorted and dysfunctional automatic thoughts *www.beckinstitute.org/what-is-cognitive-behavioral-therapy/*
- Interpersonal Psychotherapy targets interpersonal distress and effect on mood *www.apa.org/divisions/div12/rev_est/ipt_depr.html*
- Mindfulness/Yoga *Clin Psychol Rev 2018 Feb;59:52-60. doi: 10.1016/j.cpr.2017.10.011. Epub 2017 Nov 8.*
- Acupuncture for depression during pregnancy *Manber et al. Obstet Gynecol. 2010; 115(3):511-20.*
- Aerobic Exercise (> 30 minutes of moderate intensity exercise, 3-5 days/wk) *Dunn et al, Am J Prev SRI 2005;28:1-8, 2005*
- Bright Morning Light Therapy *Wirz-Justice et al: J Clin Psychiatry 2011;72(7):986-993*

BDS, 1976-2008, Secular patterns of selected antidepressant use during the first trimester

Mitchell et al, Am J Obstet Gynecol 2011



BDS, 1976-2008, Boston and Philadelphia centers. Secular patterns of selected **A,** antinausea medications and **B,** antidepressants during the first trimester are shown. Proportion of women exposed (n = 25,313) is also shown.

BDS, Birth Defects Study.

Mitchell. Overall medication use in pregnant women. Am J Obstet Gynecol 2011.

Initial Structure to Consultation

- Woman (partner) expectations of consultation, primary concerns
- Knowledge of pregnancy physiology
- Knowledge of risk concepts
- Awareness of birth outcome information (defects 3%, no guarantee of normally formed child even without exposures
- Understanding of disease and treatment exposures during pregnancy
- Decision process preferences (*Patel and Wisner, Depression and Anxiety 28:589-95, 2011)*

Data Collection

- Diagnostic Assessment
- History: Medical, Treatment, Substance Use, Reproductive
- Current - Standardized Measure of Symptom severity/type and Function
- Exposures since conception (smoking, alcohol, other drugs, environmental)
- Disease exposure (hyperglycemia/ diabetes, obesity, hypothyroidism, other)
- Pregnancy Course, Testing

Data Analysis

- Evidence-based treatment for individual situation
- Discussions of modifications of above due to pregnancy (if appropriate)
- Non-drug interventions to augment impact of drug treatment/improve pregnancy outcome
- Document the woman's questions/ feedback/ rationale for decision

Risk- Benefit Consultation during Pregnancy

Wisner et al, Am J Psychiatry 2000; 157:1933–1940

PHYSICIAN: STRUCTURE OF PROBLEM

- ▶ Diagnostic Formulation
- ▶ Treatment Options
  - ● Somatic
    - Antidepressants
    - ECT
    - Other
  - ● Psychotherapy
  - ● No treatment

PHYSICIAN: LIKELIHOOD OF OUTCOMES

- ▶ Fetal Toxicity
  - ● None
  - ● Intrauterine death
  - ● Physical malformations
  - ● Growth impairment
  - ● Behavioral teratogenicity
  - ● Neonatal toxicity
- ▶ Depression Outcomes
  - ● Full remission
  - ● Partial remission
  - ● No improvement
  - ● Worsening

PATIENT: CHARACTERISTICS INFLUENCING DECISION

- ▶ Relative Values of Outcomes
- ▶ Perception of Risk
- ▶ Competence to Consent

DECISION AND ACTION
Physician and Patient

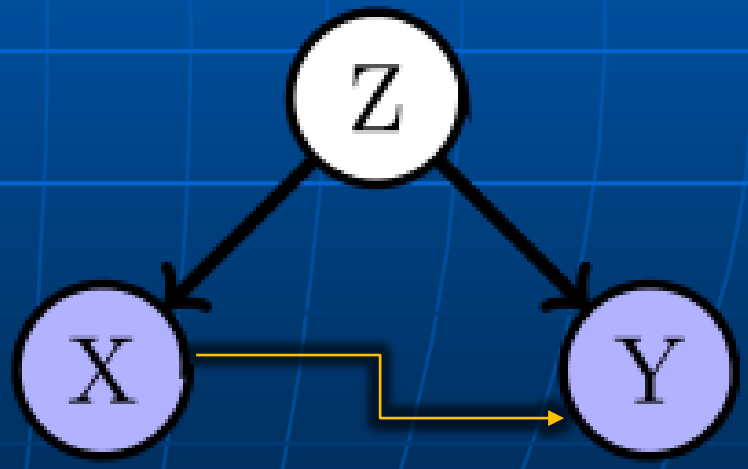
INTEGRATION
Physician/Obstetrician
Patient
Significant Other

REVISED DECISION AND ACTION
Physician and Patient

CONTINUOUS INTEGRATION
Physician/Obstetrician
Patient
Significant Other

Explaining Confounding

- A confounding variable (Z) is correlated with both the dependent variable (X) and independent variable (Y) in a way that "explains away" the correlation between them.
- Common unmeasured variables (Z):
  - maternal psychiatric illness severity
  - medical comorbidity
  - obstetric comorbidity
  - tobacco, drug, alcohol use
  - other medications
  - paternal factors
  - nutrition
  - poverty, stress



SSRI

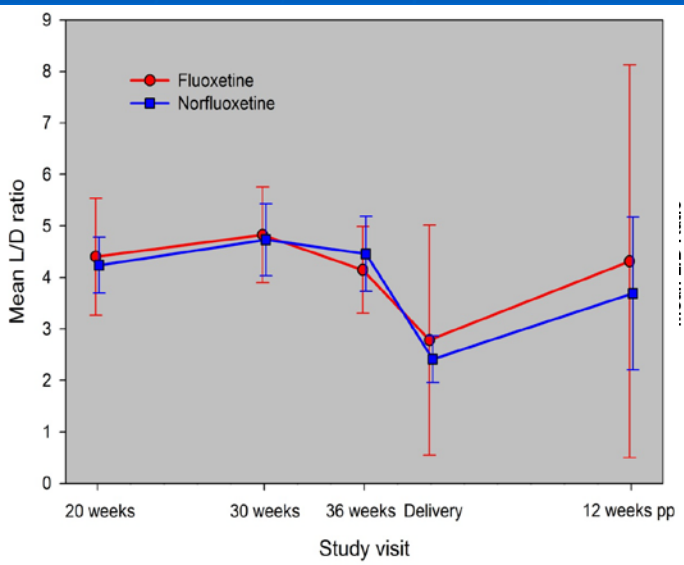
Birth Defects

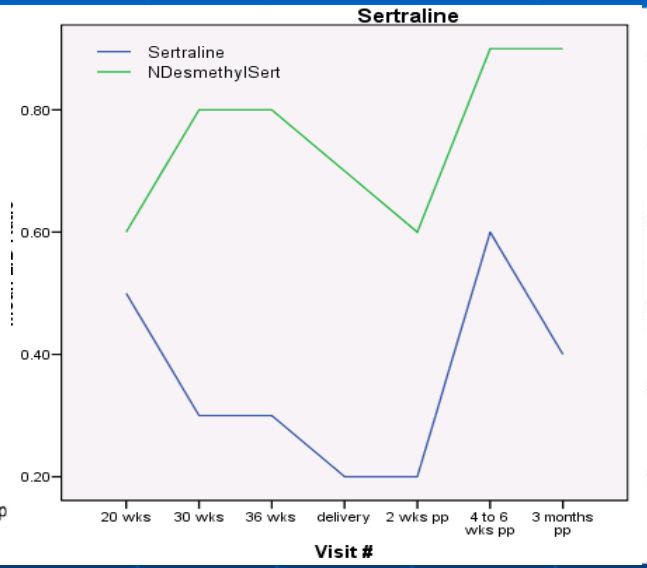
Optimize Maternal Treatment

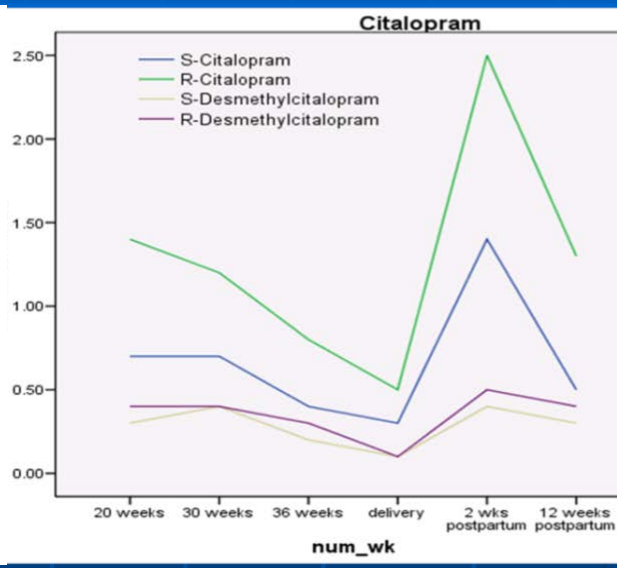
- Minimum **effective** dose through pregnancy!
- Standardized measure throughout pregnancy to monitor for symptom change
- Pharmacokinetic changes due to pregnancy, an evolving literature
- Postpartum management of dosing
- Breastfeeding (Surgeon General's report; excess risks with not breastfeeding *http://www.ncbi.nlm.nih.gov/books/NBK52680/)*

Optimal Dosing in Pregnancy: Drug levels Decline

Monitor Symptoms monthly !







Sit, D.K., et al., *Changes in antidepressant metabolism and dosing across pregnancy and early postpartum.* J Clin Psychiatry, 2008. 69(4): p. 652-8.

Sit, D., et al., *Disposition of chiral and racemic fluoxetine and norfluoxetine across childbearing.* J Clin Psychopharmacol, 2010. 30(4): p. 381-6.

For the Practitioner

- One source for relevant information immediately available at time of encounter
  - Reproductive adverse effects (domains) assoc with drug and rates
  - Reproductive adversity effects (domains) due to disease and rates
  - Drugs commonly prescribed with the drug of interest and above
- NY State model – visit preparation
- Consultation on application of this information to clinical practice (such as Organization of Teratology Information Specialists, https://mothertobaby.org/)
- Consultation on application of disease specific information to the individual
- Documentation that serves medicolegal standards of drug prescribing in pregnancy
- Curriculum: Obstetrical pharm for prescribers

Mental Health is **Fundamental** to Health

David Satcher, M.D.

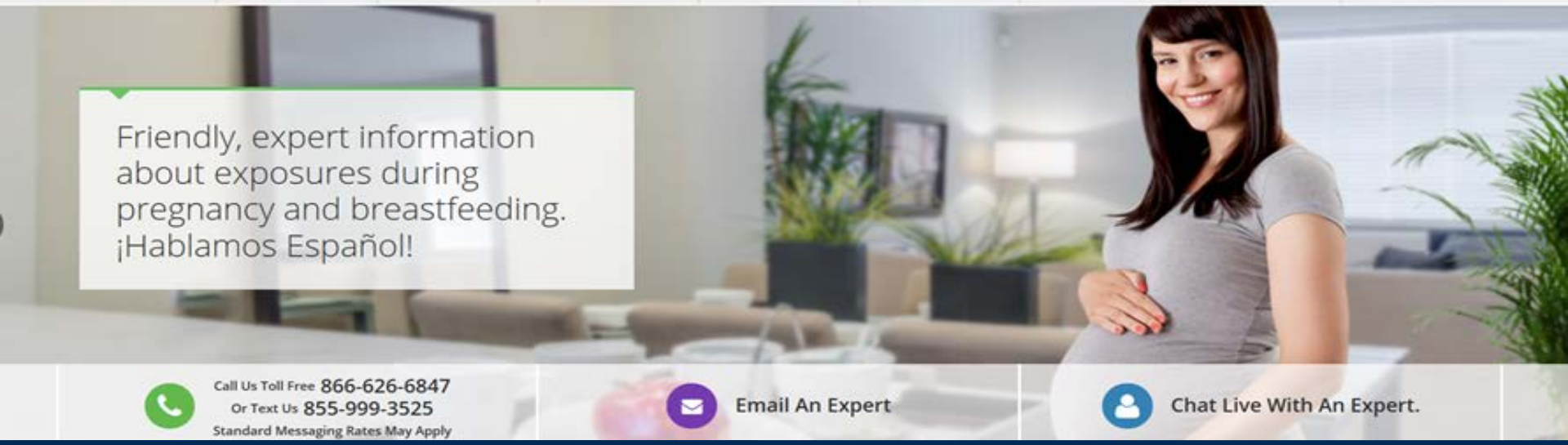
We must prioritize the mental health of the mothers of our next generation!

Slides for Discussion as needed

Risks are More Heavily Weighted Than Benefits

Antidepressant treatment during pregnancy: Are we asking the right questions?

Wisner, Depression and Anxiety: 27:695-698, 2010



MotherToBaby
Medications & More During Pregnancy & Breastfeeding
Ask The Experts

Fact Sheet
by the **Organization of Teratology Information Specialists (OTIS)**
For more information about us or to find a service in your area, call **(866) 626-6847**. Visit us online at **www.MotherToBaby.org**.
Find us! Facebook.com/MotherToBaby or @MotherToBaby on Twitter

Fluoxetine (Prozac®) and Pregnancy

In every pregnancy, a woman starts out with a 3-5% chance of having a baby with a birth defect. This is called her background risk. This sheet talks about whether exposure to fluoxetine may increase the risk for birth defects over that background risk. This information should not take the place of medical care and advice from your health care provider.

What is fluoxetine?

Fluoxetine is a medication commonly used to treat depression. Fluoxetine is also used to treat obsessive-compulsive disorders, Tourette's syndrome, eating disorders (bulimia nervosa), and Premenstrual Dysphoric Disorder (PMDD). Brand names for fluoxetine are Prozac® and Sarafem®. Fluoxetine belongs to the class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs).

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Depression

In every pregnancy, a woman starts out with a 3-5% chance of having a baby with a birth defect. This is called her background risk. This sheet talks about whether exposure to depression may increase the risk for birth defects over that background risk. This information should not take the place of medical care and advice from your health care provider.

What is depression and how common is it in pregnancy?

Depression is a serious medical illness. It can change how someone feels, thinks and acts. The most common symptoms of depression are long-lasting and strong feelings of sadness and not being able to feel pleasure or happiness. Other symptoms of depression are anxiety, irritability, difficulty concentrating, fatigue (feeling very tired), and thoughts of death or self-harm. Physical symptoms of depression can include increased heart rate, loss of appetite, stomach pain, and headaches.

The chance for a woman to develop depression during her lifetime is about 10-25%. The highest risk occurs during the childbearing years. Pregnancy may be a possible trigger for the development of depression in some women. This may be due to changes in hormone levels during pregnancy and the stress that comes with this major life event. Treatment for depression usually includes counseling/psychotherapy and/or medications.

Major Depression

- For two weeks, most of the day nearly every day, 5 of these (one must be mood or interest):
- **Depressed mood**
- **Diminished interest/pleasure**
- Weight loss/ gain unrelated to dieting
- Insomnia/ hypersomnia
- Psychomotor agitation/ retardation
- Fatigue or loss of energy
- Feelings of worthlessness/guilt
- Diminished ability to concentrate
- Recurrent thoughts of death

NIMH--MDD in Women for patients:

www.nimh.nih.gov/health/publications/women-and-depression-discovering-hope/index.shtml

Figure 4. Demographic Characteristics of Women with Positive vs. Negative EPDS Screens

Characteristic	Total (N=9998)*	EPDS score ≥10 (positive) (N=1396)	EPDS score ≤ 9 (negative) (N=8602)	Analyses Test statistic	df	P
EPDS	5.3 ± 4.4	13.8 ± 3.8	4.0 ± 2.6	$H = 3631$	1	<.0001
Age	29.6 ± 5.6	28.8 ± 5.9	29.7 ± 5.5	$H = 36.25$	1	<.0001
Race				$x^2 = 71.83$	3	<.0001
White	8016 (80.3)	1005 (72.0)	7011 (81.6)			
African-American	1456 (14.6)	282 (20.2)	1174 (13.7)			
Asian	212 (2.1)	40 (2.9)	172 (2.0)			
Other	301 (3.0)	68 (4.9)	233 (2.7)			
Hispanic	199 (2.2)	36 (2.8)	163 (2.1)	$x^2 = 2.96$	1	0.0851
Education (level)				$x^2 = 182.2$	4	<.0001
<High school	436 (4.4)	117 (8.4)	319 (3.7)			
High school	1474 (14.8)	294 (21.1)	1180 (13.8)			
Some college	2566 (25.7)	421 (30.2)	2145 (25.0)			
College	3125 (31.3)	333 (23.9)	2792 (32.6)			
Graduate school	2368 (23.8)	228 (16.4)	2140 (25.0)			
Medical insurance				$x^2 = 212.8$	2	<.0001
Private	7179 (71.9)	777 (55.7)	6402 (74.5)			
Public	2751 (27.5)	600 (43.0)	2151 (25.0)			
None	60 (0.6)	18 (1.3)	42 (0.5)			
Marital status				$P < 0.0001$	3	<.0001
Single	2854 (29.6)	587 (42.7)	2267 (27.4)			
Married/cohabiting	6706 (69.5)	756 (55.0)	5950 (71.9)			
Divorced/separated	91 (0.9)	32 (2.3)	59 (0.7)			
Widowed	2 (0.0)	0 (0.0)	2 (0.0)			

*Two subjects had incomplete EPDS data

Descriptive statistics based on available data. Test statistic P indicates Fisher's exact.

Reproductive Outcome Domains

- Major birth defects
- Preterm Birth
- Neonatal Adaptation Syndrome
- Behavioral and Developmental Effects

These domains are impacted by both psychiatric disorders and antidepressants

Birth Defects

- **Physical Malformations-** Specific defects (if any) are rare and absolute risks are small. *Greene, M. F. (2007). Teratogenicity of SSRIs -- Serious Concern or Much Ado about Little? NEJM 356: 2732-2733*

No Association of SSRI with Birth Defects: Key Publication

- Huybrechts KF et al, Antidepressant Use in Pregnancy and the Risk for Cardiac Defects, NEJM 370:2397-2407, 2014.
- AHRQ study, Medicaid Data, 949,504 pregnant women
- Exposed to antidepressants T1 vs. nonexposed
- Unadjusted, Restricted to MDD, Propensity score matched
- 6.8% used antidepressants T1
- **Cardiac defect SSRI OR=1.25 (1.13-1.38) unadjusted**
- **Cardiac defect MDD only OR=1.12 (1.00–1.26) NS**
- **Cardiac defect MDD/PPS OR=1.06 (.93-1.22) NS**
- Paroxetine and RVOTO OR=1.07 (.59-1.93) NS
- Sertraline and Septal defects OR=1.04 (.76-1.41) NS
- No relationship to dose

Preterm Birth

- *Malm H et al, Am J Psych 172:1224-32, 2015*
- SSRI Rx during pregnancy- lower risk for late preterm birth (OR=0.84, 95% CI=0.74-0.96)
- very preterm birth (OR=0.52, 95% CI=0.37-0.74)
- cesarean section (OR=0.70, 95% CI=0.66-0.75) compared to:
- No medications/psychiatric disorders
- SSRI-treated mothers, higher risk neonatal for complications, including low Apgar score (OR=1.68, 95% CI=1.34-2.12) and monitoring in NICU (OR=1.24, 95% CI=1.14-1.35).

Neonatal Adaptation Signs

- Poor neonatal adaptation in 31.5% of infants in late-exposed group, 8.9% in early-exposure group for fluoxetine (*Chambers et al, NEJM 335:1010-1015, 1996)*
- Acute effects or discontinuation signs possible from any antidepressant (*Moses-Kolko et al, JAMA 293:2372-2382, 2005)*
- Paroxetine- most common drug in the case literature
- Venlafaxine – also multiple cases
- No consensus definition
- Mechanism(s) not elucidated

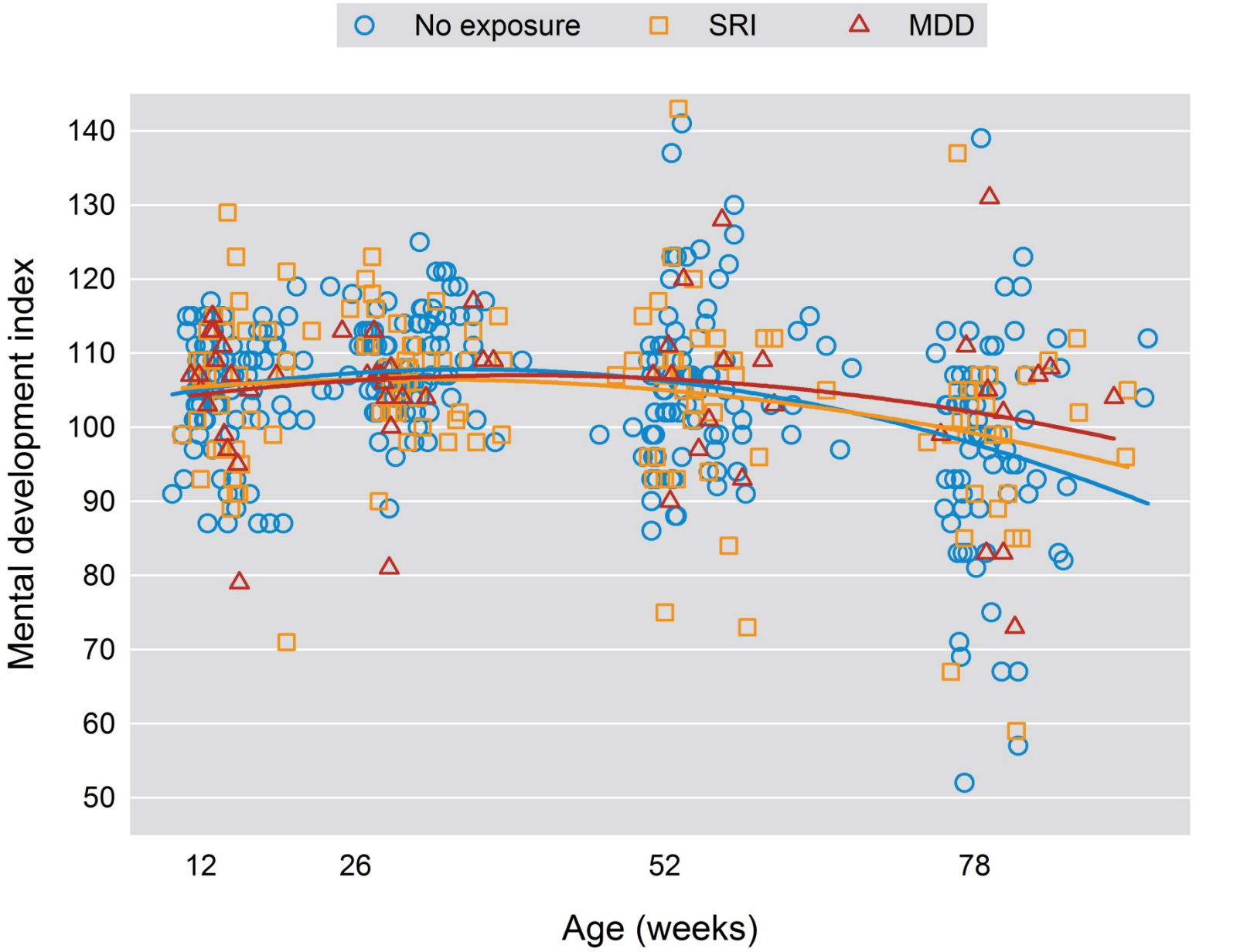
Development of Children Prenatally Exposed to SRI

- *Nulman I et al, J Clin Psychiatry 2015 Jul;76(7):e842-7*
- IQ/ behavior of sib pairs (n=45, age 3- 7) discordant for SRI exposure
- Assessments: WPPSI, CBCL
- Mothers with MDD: IQ testing and depressive sx (CES-D).
- FS IQs -NS (103±13 vs 106±12; P=.30)
- No difference in rates of problem behaviors
- Signif predictor of child IQ was maternal IQ
- Severity of prenatal maternal MDD predicted CBCL Internalizing (P=.019), Externalizing (P=.003), Total scores (P = .001).
- Prenatal drug doses/ durations of exposure, child's age, sex, birth order, symptom severity included in analyses

Bayley Scales of Infant Development

- ADUP- *Wisner et al. J Clin Psych 2014;75:1088-1095.*
- BSID-II-Mental Development Index (MDI) and Psychomotor Development Index (PDI)
- Longitudinal Assessments at 12, 26, 52 and 78 weeks
- Raters blind to exposure
- UDS done at intake in pregnancy (20 wks)
- No SRI, no MDD (N=98), SRI (N=41)-Majority treated continuously (29); MDD, No SRI (N=27)
- Models included main effect of postnatal depression score (SIGH-ADS) and interaction term for postnatal SIGH-ADS by prenatal exposure (SRI, MDD, neither)

Bayley MDI in ADUP, p=0.8254



Bayley PDI in ADUP, p=0.12

Age^2 X exposure intx (p=.0376)

Conceptual Evolution

- Both SSRI and MDD impact maternal, fetal and infant outcomes – potentially in different ways in different mother-offspring dyads
- We want to know whether the maternal and fetal outcomes are **better with drug treatment (reduced disease burden)?**
- **Optimal** treatment of pregnant women!
- We must maximally reduce the disease burden that justifies the drug's use.

Breastfeeding and Antidepressants

- The benefits of breastfeeding are legion and long-term. www.cdc.gov/breastfeeding/promotion/calltoaction.htm
- Data consist of mother and infant serum levels; some breastmilk
- Usually below limit of quantifiability in infant serum: sertraline (zoloft), paroxetine (paxil), tricyclic nortriptyline
- Routine pediatric monitoring for full-term infants
- (*Weissman et al, 2004; Lanza di Scalea and Wisner, 2009)*
- LactMed: http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

Autism

Sorenson MJ, Clin Epid 2013:5 449–459

Danish Registry 1996–2006 (n=668,468)

- Children exposed had an adj hazard ratio of 1.5 (95% CI, 1.2–1.9) for ASD vs. unexposed
- Restricting to children of women with affective disorder, the adjusted hazard ratio was 1.2 (95% CI 0.7–2.1),
- Risk reduced when exposed children compared with unexposed sibs (adj hazard ratio 1.1; 95% CI 0.5–2.3).

Rai, D: BMJ 2013;346

- Maternal depression (aOR 1.49, 95% CI 1.08 to 2.08) assoc'd with increased risk of ASD in offspring.
- Assuming an unconfounded, causal association, antidepressant use during pregnancy explained 0.6% of cases of ASD.

More Information- Pregnancy

- Developmental and Reproductive Toxicity: www.toxnet.nlm.nih.gov (DART database-free)
- Organization of Teratology Information Specialists (OTIS) www.otispregnancy.org, (866) 626-OTIS, or (866) 626-6847
- ACOG Practice bulletin: Use of psychiatric medications during pregnancy and lactation. *Obstetrics and Gynecology 110:1179-1198*
- Wisner KL et al: Psychiatric Disorders, in Obstetrics: Normal and Problem Pregnancies, 5th edition. Gabbe SG, Niebyl JR, Simpson JL, Galan H, Goetzl L, Jauniaux ERM, Landon M, Editors; Elsevier, pages 1249-1288, 2007.