

# Medication Use During Pregnancy & Lactation

Karen Horst, M.D.

# Disclosures

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■ None

# Goal of Treatment

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Wellness for mom that then translates into health for her child.



“... it is not possible to talk about an infant without at the same time talking about infant-care and the mother.”

D.W. Winnicott, M.D. 1965

# Questions About Medication Use in Pregnancy

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- What do we know about safety?
- Are some antidepressants safer than others?
- Does it make sense to avoid use of antidepressants during certain stages of pregnancy?
- Is keeping the dosage as low as possible important?
- What are the risks if antidepressants are not prescribed?
- Are there alternative treatments?
- What about patients with bipolar depression?

# Studies Looking at Safety of Medications

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- Most are retrospective case-control designs using large birth registry information or managed health care databases.
- Prospective case-control data review studies.
- Few small, prospective observational studies.
- Meta-analyses of above.
- Recent studies compare exposure to antidepressants with exposure to depression, look at biomarkers for stress and the complexity of genes and environment.

# 2008 ACOG Opinion on Psychiatric Medication Use During Pregnancy

- “The potential risk of SSRI use throughout pregnancy must be considered in the context of the risk of relapse of depression if maintenance treatment is discontinued.”
- Avoid paroxetine due to concerns about heart defects, but do not discontinue abruptly.
- Association of SSRI use and PPHN is “unconfirmed”.
- Recent studies have not shown a link between prenatal exposure to TCAs and perinatal problems.

# Agency for Healthcare Research & Quality Report, 2013 (draft)

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- Identifies the risks of untreated depression in pregnancy/postpartum period:
  - Poor nutrition, poor prenatal care, tobacco, alcohol and drug use, risk of suicide.
  - Adverse obstetric complications (pre-eclampsia, PTD, LBW, miscarriage, SGA, low Apgars, neonatal complications).
  - Postpartum: diminished maternal-infant interactions leading to negative infant development, infant mortality, neglect, abuse, homicide, domestic violence.

# AHRQ report contd.

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- Poses 3 questions regarding treatment:
  - What are the comparative **benefits** of medications and nonpharmacological txs?
  - What are the comparative **harms**?
  - What patient characteristics (eg: SES, BMI, comorbidities), intervention characteristics and provider characteristics predict positive response to treatments?

# AHRQ Findings

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- Very few studies show **direct** evidence for outcomes of antidepressants.
- Studies using indirect evidence compare outcomes for women taking ADs **for any reason** with women not on ADs where presence of depressive symptoms are rarely reported and not analyzed.
- RCT studies meeting criteria for efficacy have drawbacks (exclude pts with co-morbidities, lack health outcomes, lack comprehensive assessment of adverse events, are short in duration and small.)
- Studies of non-pharmacologic treatments have a “lack of detail” regarding the characteristics of the treatment.

# AHRQ Conclusions

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- Pharmacologic treatment for pregnant women “may offer benefits.”
- Regarding harms:
  - There is direct evidence that SSRIs **are** associated with respiratory distress, and are **not** associated with neonatal convulsions.
  - 5 quality, indirect studies (low bias, systemized classification of malformation, controlled for 3 out of 4 major confounders) found no evidence for association of SSRIs and cardiac malformations.

# AHRQ Conclusions contd.

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- No direct evidence for Neonatal Abstinence Syndrome, but 5 small cohort studies with medium risk for bias show evidence for NAS.
- Encourage concurrent breastfeeding with SSRIs
  - Negligible amounts get through breast milk
  - No evidence of adverse events in children

# Respiratory Distress & PPHN

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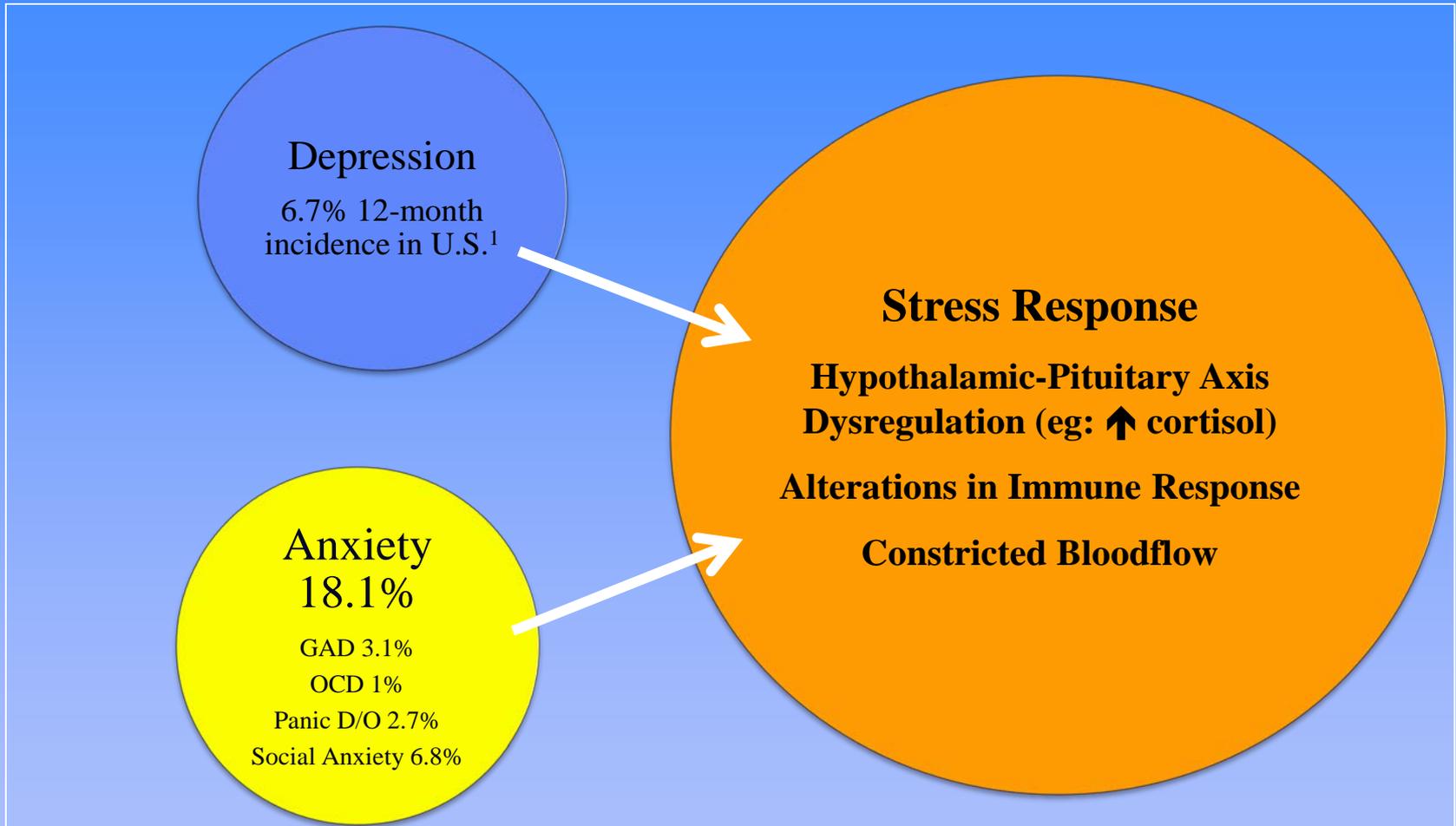
## ■ Respiratory Distress

- Infants require supportive measures like O<sub>2</sub> due to apneic spells (non-life threatening and transient)

## ■ PPHN rare, heterogeneous failure of neonatal lung circulation to dilate. Incidence of 2/1000.

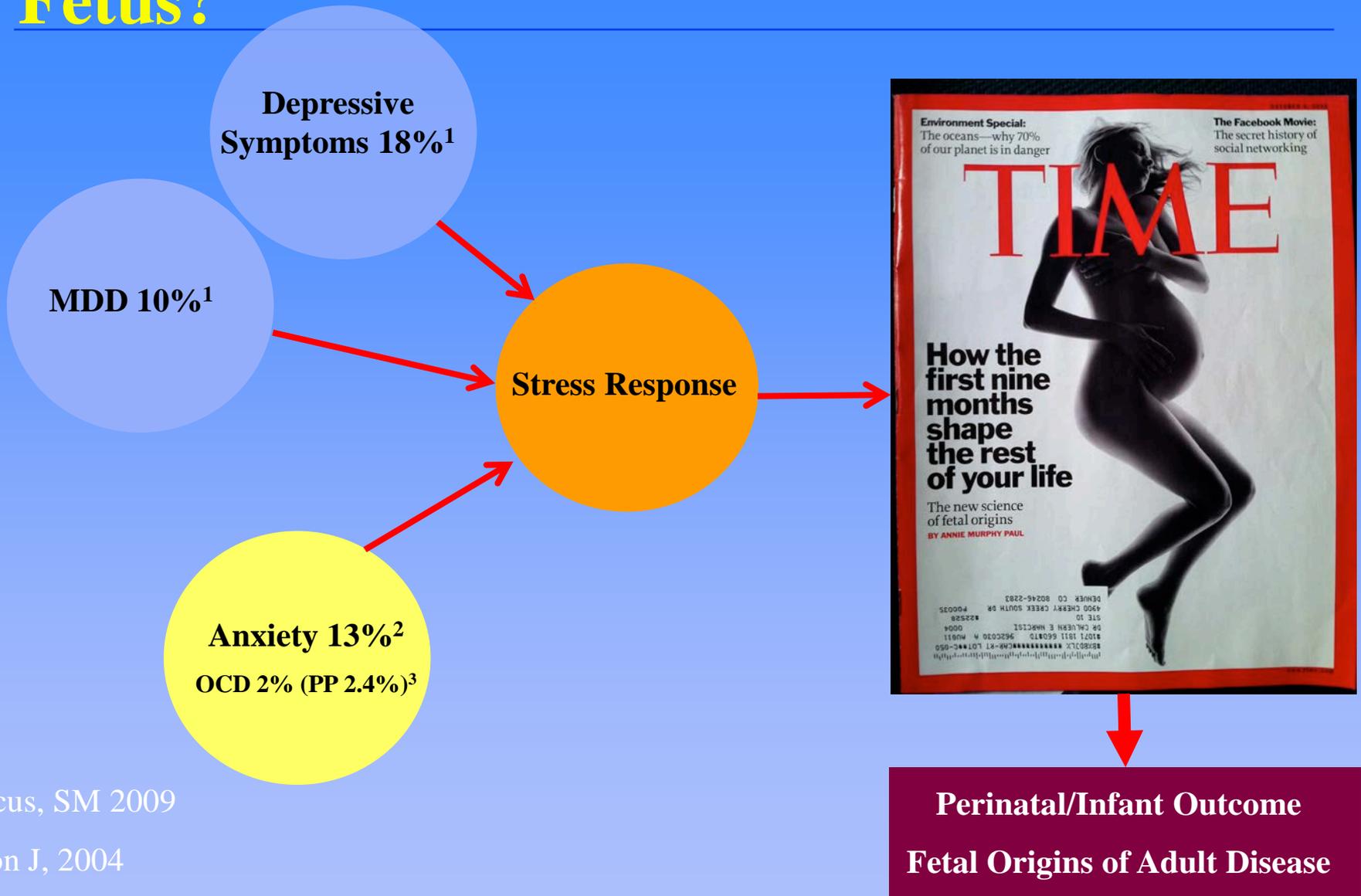
- 6 indirect studies with conflicting findings: 3 find association but have conflicting timing for exposure risk and 3 find no association.
- 50 neonates w/ PPHN/25,000 exposed to SSRI (2/1000 incidence equivalent to population statistics.)

# Depression and Anxiety as Physical Stress



<sup>1</sup>Kessler et al, 2005.

# Does Maternal Mental Distress Harm the Fetus?

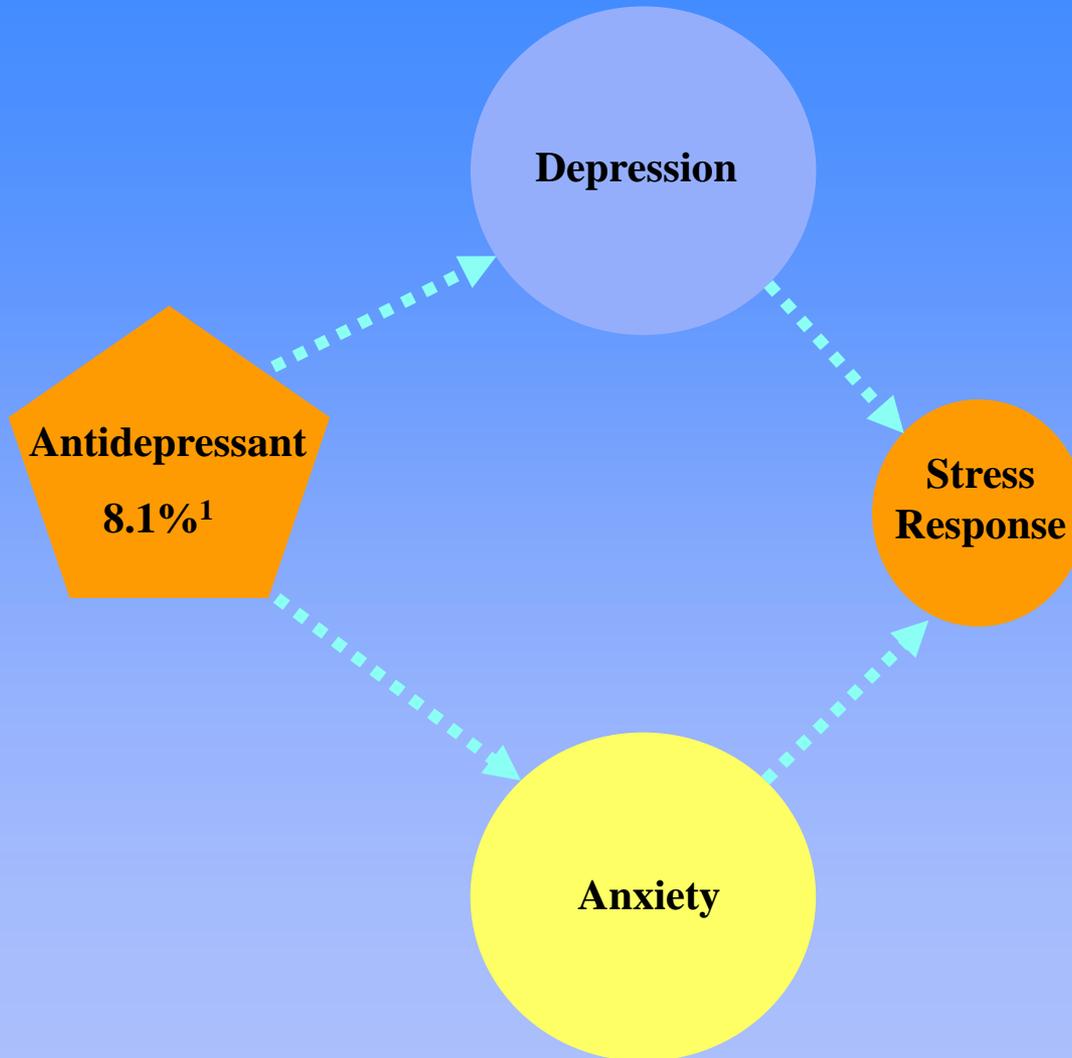


<sup>1</sup>Marcus, SM 2009

<sup>2</sup>Heron J, 2004

<sup>3</sup>Russell, FJ 2013

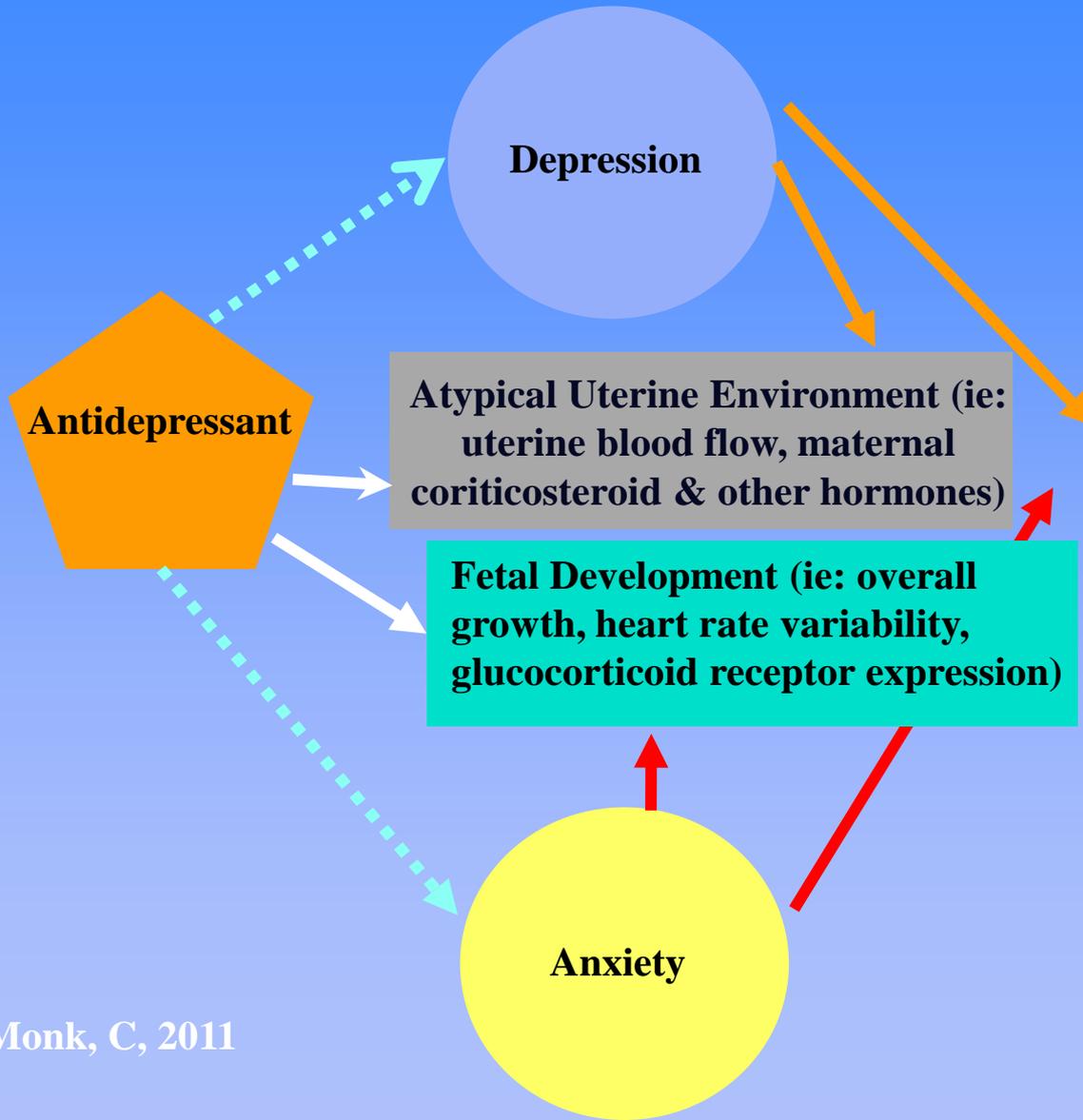
# Does Medication for Maternal Emotional Distress Harm or Protect the Fetus?



**Perinatal/Infant Outcome**  
**Fetal Origins of Adult Disease**

<sup>1</sup>Alwan, S, 2011

# What Exposure Poses More Risk to Fetus?



**Perinatal/Infant Outcome**  
**Adult Disease (FOAD)**

# Fetal Origins of Adult Disease

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- Dutch Famine during WWII led to a marked ↑ in schizophrenia & CNS abnormalities in offspring
  - malnutrition & maternal stress as causes?
- ALSPAC study: cohort of families from pregnancy to teens in the UK:
  - mothers with high levels of anxiety during late pregnancy produced a higher rate of children with behavioral & emotional problems at ages 4 & 7 <sup>1</sup>

# Fetal Origins of Adult Disease

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- Prospective, longitudinal study of 35 pregnant women assessed for anxiety at 19, 25 and 31 weeks. MRIs of their children done at 6-9 y.
  - Anxiety at 19 weeks GA associated with ↓ gray matter volume, esp. in prefrontal cortex.<sup>1</sup> No association with anxiety at 25 and 31 weeks GA.
  - Psychobiological markers of maternal stress associated with disrupted emotional regulation & impaired cognitive development in offspring.<sup>2</sup>

<sup>1</sup>Sandman CA et al, 2010

<sup>2</sup>Sandman CA et al, 2011

# Fetal Origins of Adult Disease

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## ■ ALSPAC (n: 3,442)<sup>1</sup>

- Pregnant women & partners (to control for intrauterine effects vs. general environment in home) tested for anxiety during pregnancy.
- Positive association between antenatal maternal depression & anxiety with attention and behavioral problems in 3-4 year old children.
- Confounders such as smoking, SES & postnatal depression also factors in severity of child difficulties

<sup>1</sup>Van Batenburg-Eddes et al, 2013

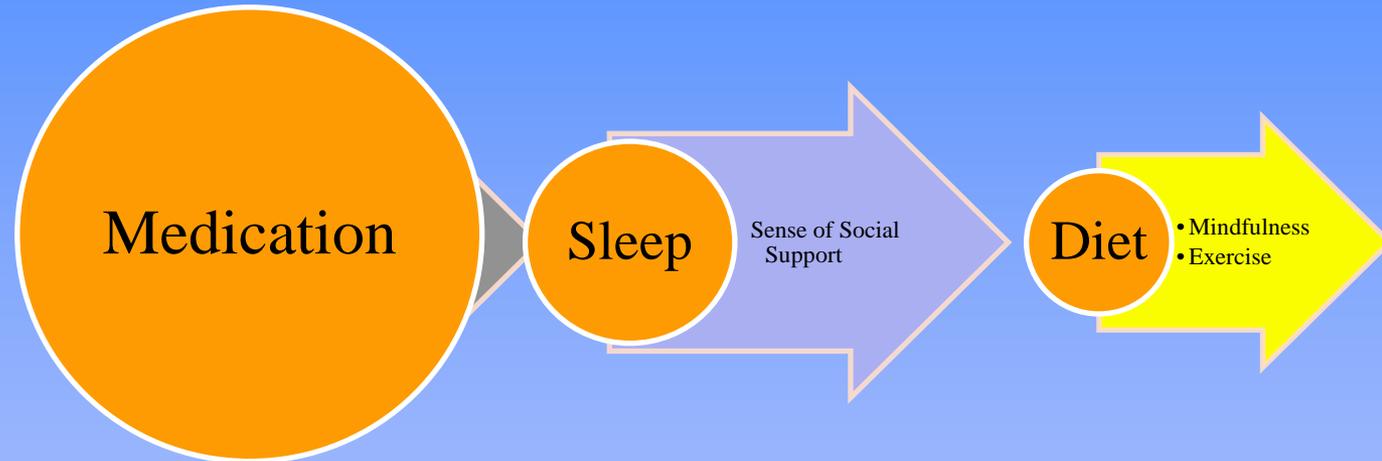
# Factors Supporting Wellness

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# Sometimes Medication is Key to Recovery

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# Current FDA Safety Categories Are Not Helpful

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- Teratogens have historically been identified not through animal studies but through astute clinicians noting patterns of malformations (examples: Fetal Alcohol Syndrome, Thalidomide, Retinoic Acid).
- Studies currently used to identify risk are indirect and prone to bias.
- Privileges medications with less data.
- Do not help clinicians weigh the strength of the data.

# New FDA Categories are coming!

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- 2008, FDA announced a new system with 3 sections<sup>1</sup>
  1. “Fetal Risk Summary” – conclusion as to risk of fetus based on quality & quantity of studies
  2. “Clinical Considerations” – compares risks to mother and fetus of exposure to illness vs. exposure to medication
  3. “Data” – what Fetal Risk Summary is based upon

<sup>1</sup>FDA News Release, May 28, 2008

# Benzodiazepines

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- Reports of increased risk of oral clefts, though extent of risk remains controversial<sup>1</sup>
- Perinatal dependence syndrome of low Apgar scores, hypotonia, and hypothermia<sup>2</sup>
- Perinatal withdrawal syndrome of hypertonia, hyperreflexia, restlessness, irritability, seizures, bradycardia, abdominal distention, and inconsolable crying<sup>3</sup>
- Neurobehavioral teratogenicity data limited
  - Some studies suggest developmental delays<sup>4,5</sup>, while others do not<sup>6</sup>

1. Altshuler et al. Am J Psychiatry 1996;153:592-606

2. Altshuler LL et al. AJP 1996;153:592-606

3. Pediatrics 2000;105:880-887.

4. Laegreidet al. Dev Med Child Neurol 1990;32:432-441

5. Viggedal et al. J Child Psychol Psychiatry 1993;34:295-305

6. Hartz et al. N Engl J Med 1975;292:726-728

# Epidemiology of Bipolar Disorder

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- Common illness (~1-2% lifetime prevalence)
- Early onset (Peak onset: 15-24 years)
- Recurrent in >90%
- Long average duration of mood episodes
  - depression: 19 weeks
  - mania: 10 weeks
  - mixed: 36 weeks
- High comorbidity
- High suicide risk (10-15% completion rate)

Keller MB, et al. *JAMA*. 1986;255(22):3138-3142.

Goodwin FK, Jamison KR. *Manic-Depressive Illness*, 1<sup>st</sup> ed. NY:Oxford Univ. Press, 1990

Kessler RC, et al. *Arch Gen Psychiatry* 1994;51:8-19

American Psychiatric Association. *Am J Psychiatry* 2002;159 suppl:1-50

# Bipolar Disorder

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## Recurrence Risk During Pregnancy

- Pregnancy does not consistently protect against recurrence of mania or depression
  - 45-50% of women may have an exacerbation of illness during pregnancy<sup>1,2</sup>
- Factors associated with higher risk of relapse during pregnancy include<sup>3,4</sup>:
  - abrupt discontinuation of mood stabilizers
  - a history of 4 or more prior mood episodes
  - prior intrapartum mood episode(s)

1. Blehar et al. *Psychopharmacol Bull* 1988;34:239-243

2. Freeman et al. *J Clin Psychiatry* 2002;63:284-287.

3. Viguera, et al, *Can J Psychiatr*, June 2002.

4. Viguera et al. *Am J Psychiatry* 2000;157:179-184

# Bipolar Disorder

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## Recurrence Risk During Postpartum Period

- 60-80% recurrence rates in the first three to six months postpartum<sup>1-3</sup>
- 10-20% risk of postpartum psychosis (compared to 0.1-0.2% in general population)<sup>4-6</sup>
  - Risk of recurrent postpartum psychosis in subsequent pregnancy may be as high as 90%<sup>7,8</sup>

1. Blehar et al. *Psychopharmacol Bull* 1988;34:239-243.

2. Freeman et al. *J Clin Psychiatry* 2002;63:284-287.

3. Viguera, et al, *Can J Psychiatr*, June 2002.

4. Viguera et al. *Can J Psychiatry* 2002;47:426-436.

5. Kendell et al. *Br J Psychiatry* 1987;150:662-673

6. Brockington et al. *Arch Gen Psychiatry* 1981;38:829-833.

7. Stewart et al. *J Nerv Ment Dis* 1988;176:485-489.

8. Stewart et al. *Br J Psychiatry* 1991;158:393-397.

# General Guidelines for the Management of Medication During Pregnancy

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- Planning prenatally is optimal
- If unplanned pregnancy occurs while on meds:
  - Don't panic
  - Avoid abrupt medication change
  - Discuss benefits v. risks of stopping meds
    - Highest risk period may have already passed
  - If discontinuing medication, taper slowly
  - Create timeline from LMP to delivery that documents medication exposures, Etoh/drug use, PNV use, and Obstetric visits

# Summary

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- What do we know about safety?
- Are some antidepressants safer than others?
- Does it make sense to avoid use of antidepressants during certain stages of pregnancy?
- Is keeping the dosage as low as possible important?
- What are the risks if antidepressants are not prescribed?
- Are there alternative treatments?
- What about patients with bipolar depression?

# Case Discussion #1

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- 28 year G0 woman with a history of anxiety and depression treated successfully with sertraline seeks preconception counseling.

# Case Discussion #2

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- 35 year old G1P0 at 20 weeks gestation whose mother died suddenly a month ago, struggling with insomnia, low energy, inability to enjoy herself, difficulty concentrating at work and preoccupied with negative outcome with the pregnancy.

# Case Discussion #3

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- 22 year old G1P1 at 2<sup>nd</sup> day postpartum feels like something is very wrong with her mood and can't sleep even when infant is sleeping.

# Case Discussion #4

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- 38 year old G1P1 at 3 months postpartum who keeps presenting to pediatrician with concerns about the health and development of her baby.

# Case Discussion #5

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- Family member calls concerned about odd behavior of a 30 year old 3-week postpartum mom exhibiting paranoia about anyone but her caring for the baby.