Mood Disorders in Women of Child Bearing Age

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Pre-Lecture Exam
Question 1

1. Which of the following are true regarding the known risks to antidepressant use in pregnancy?

a. SSRI neonatal adaptation syndrome in 20-30% of infants exposed in the last trimester of pregnancy

b. Paroxetine has been associated with congenital heart defects and is now category D

c. SSRIs may be associated with an increased risk for spontaneous abortion according to metanalysis

d. All of the above

Pre-Lecture Exam
Question 2

2. Double blind placebo controlled studies of the treatment options for premenstrual dysphoric disorder include:

a. SSRIs all month

b. SSRIs luteal phase only

c. Yasmin oral birth control pill

d. All of the above

e. None of the above

Pre-Lecture Exam
Question 3

3. Risks of congenital malformations with mood stabilizers in the treatment of bipolar women have been estimated to be the following:

a. Lamotrigine 1.3% at <100 mg day and 5.4% at > 200 mg day

b. 1-2% in Lithium exposed infants

c. 20-30% in valproic acid exposed infants

d. Atypical antipsychotics have been studied extensively and have been shown to be risk free, and are category A

Pre-Lecture Exam
Question 4

4. Which of the following factors about postpartum depression are true?

a. Anxiety during pregnancy has been associated with postpartum depression

b. Postpartum depression is clearly linked to hormone changes postpartum in all women

c. Marital problems have been associated with treatment resistant postpartum depression

d. All SSRIs have been extensively studied and no metabolites have been found in infant serum in mother nursing pairs

Pre-Lecture Exam
Question 5

5. Treatment options for postpartum depression include:

a. Interpersonal psychotherapy

b. Cognitive behavioral therapy

c. Antidepressant medication

d. Group psychotherapy

OUTLINE

1. Premenstrual Dysphoric Disorder: definition, differential diagnosis and treatment
2. Depression in Pregnancy and Postpartum
3. Psychotropic Medications Use in Pregnancy and Postpartum
4. Bipolar Disorder and Pregnancy

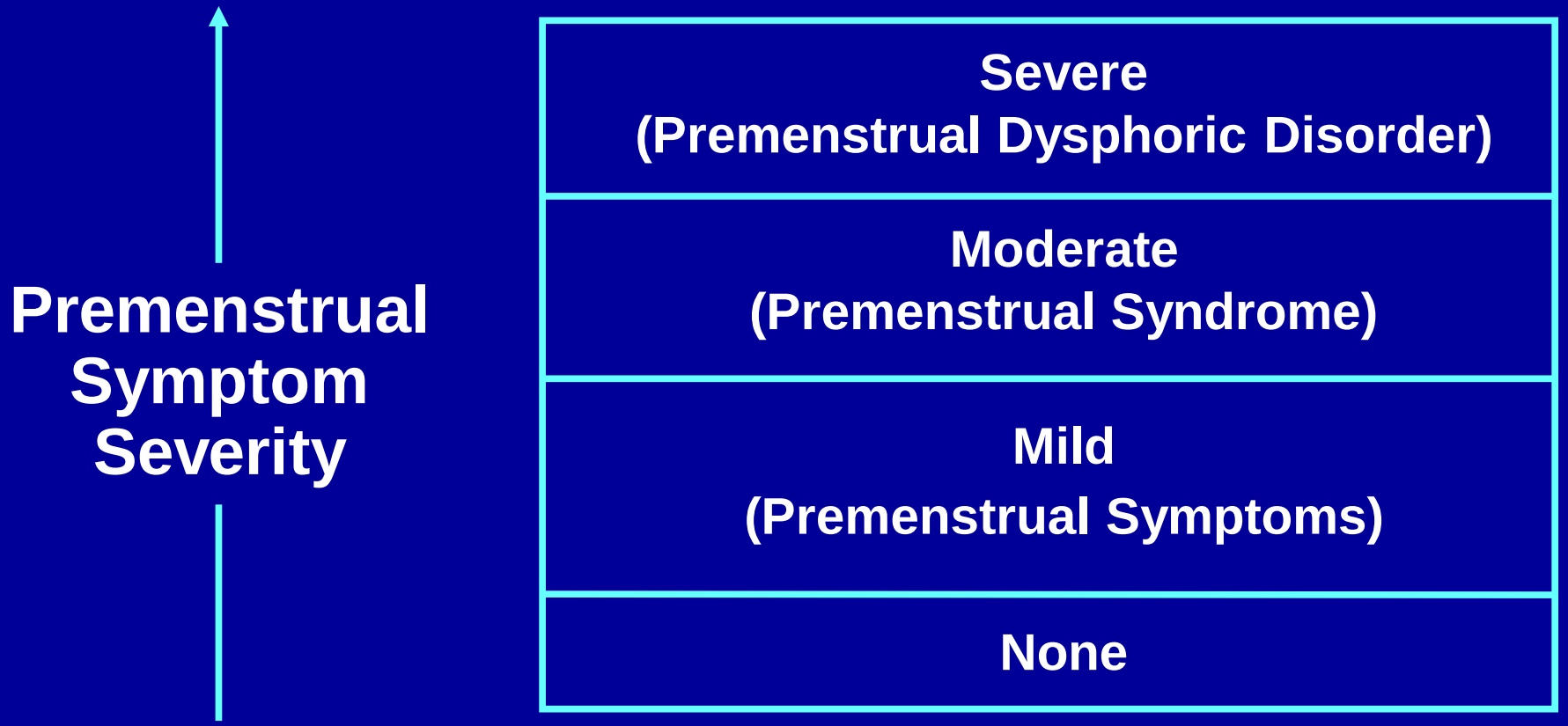
Overview

- Women are twice as likely as men to suffer from mood disorders.
- Gender differences exist in prevalence, expression, co-morbidity and course of the illnesses.
- Gender differences may be due to psychosocial factors and biological factors.
- Estrogens and progestegins may play a role in psychiatric disorders.

Major Teaching Points

- To gain a better understanding of:
  - the relationship between reproductive function and mood.
  - how to effectively manage and treat depression in pregnancy and postpartum.
  - the risks associated with using psychotropic medications during pregnancy and while breastfeeding.

Spectrum of Premenstrual Symptoms[1-3]



1. Johnson S, et al. *J Reprod Med.* 1988;33(4):340-346.
2. Gise L. The premenstrual syndromes. In: Sciarra JJ, Ed. *Gynecology and Obstetrics.* Philadelphia PA: Lippincott-Raven; 1997:6:1-14.
3. ACOG Practice Bulletin. Number 15, April 2000.

PMDD, PMS, and Depression[1,2]

	Mood Symptoms	Functional Impairment	Physical Symptoms	Monthly Periodicity
Premenstrual Dysphoric Disorder (PMDD)	✓	✓ ✓	✓	✓
Premenstrual Syndrome (PMS)	✓	✓	✓	✓
Depression and Dysthymia	✓ ✓	✓ ✓	✓	—

1. Gise L. The premenstrual syndromes. In: Sciarra JJ, Ed. *Gynecology and Obstrics.* Philadelphia PA: Lippincott-Raven; 1997:6:1-14.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994.

Diagnostic Criteria for PMDD

Five of the following symptoms (with at least 1 of these*) must occur during the week before menses and remit within days of menses:

- Irritability*
- Affective lability* (sudden mood swings)
- Decreased interest in activities
- Difficulty concentrating
- Lack of energy
- Change in appetite, eg, food cravings
- Depressed mood or hopelessness*
- Tension or anxiety*
- Change in sleep
- Feeling out of control or overwhelmed
- Other physical symptoms, eg, breast tenderness, bloating

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994.

Diagnostic Criteria for PMDD (Cont'd)

- Interferes markedly with work, school, usual activities, or relationships
- Not an exacerbation of another disorder
- All criteria should be confirmed for 2 consecutive menstrual cycles

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994.

PMDD Distinct from Depression[1]

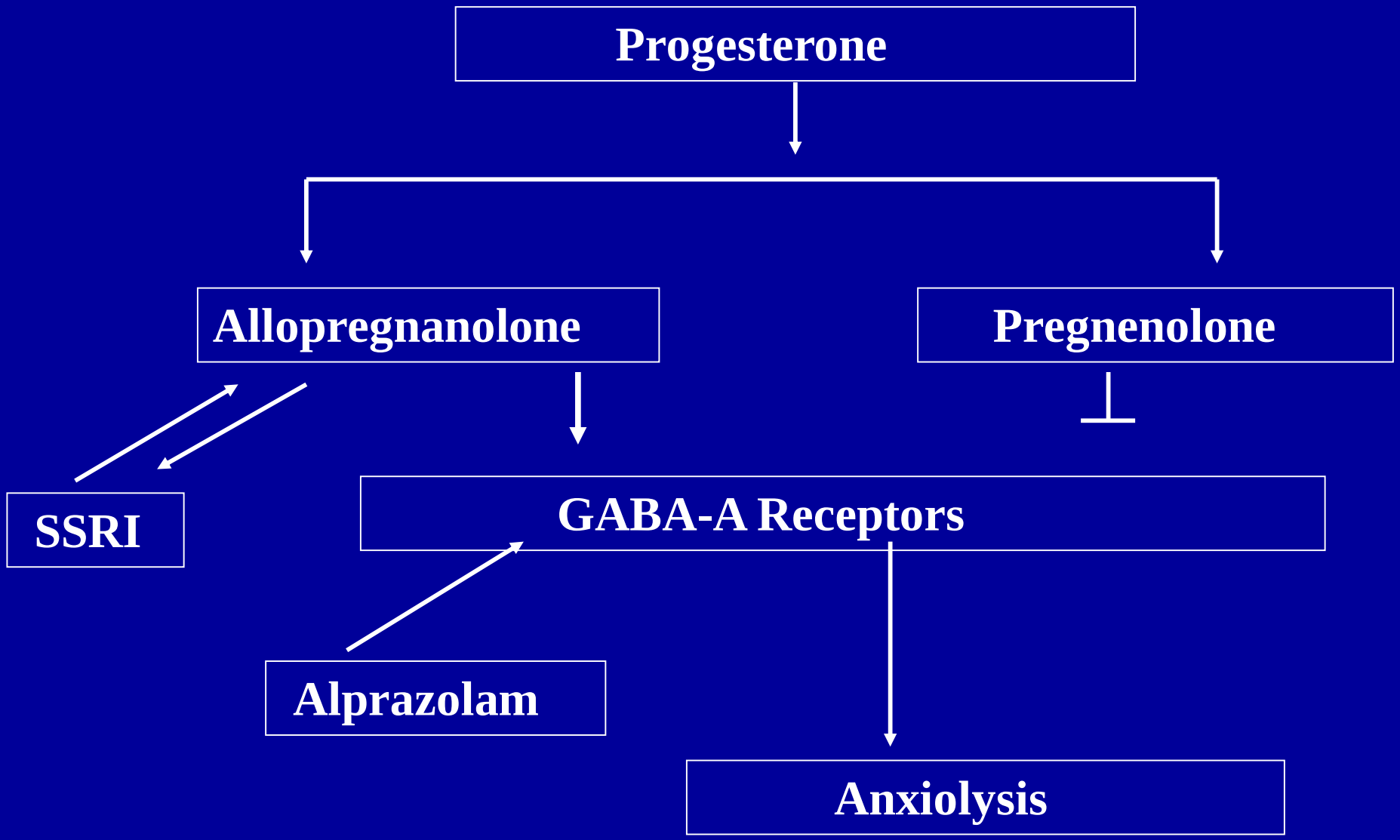
- Symptoms resolve within days of the onset of menses
- Tied to the menstrual cycle; does not occur in men
- Pregnancy resolves symptoms in PMDD
- Symptoms usually return within one to two cycles after cessation of treatment
- Unique physical symptoms (eg, breast tenderness and bloating)

Endicott J, et al. *J Womens Health GendBased Med.* 1999;8:663-679.

Relationship Between PMDD and Sex Steroids

- Recent studies on the treatment of PMDD lend strong support to serotonin being key in modulation of sex-steroid-related behavior
- Major argument for involvement of serotonin in PMDD is that SSRIs are very effective in reducing symptoms
- SSRIs' onset of action is shorter (1-2 days) than when used to treat other indications

Eriksson E, et al. *CNS Spectrums.* 2001; 6(2):141-149.


Progesterone
Allopregnanolone
Pregnenolone
SSRI
GABA-A Receptors
Alprazolam
Anxiolysis

Physiologic Responses to Neurosteroid Challenge in Women With PMDD

- Patients with severe PMDD had a reduced sensitivity to GABAergic substances[1]
- Similarly, panic disorder patients exhibit reduced sensitivity to benzodiazepines[2]
- Fluoxetine and paroxetine selectively change rat brain steady-state levels of ALLO and 5alpha-DHP[3,4]
- Fluoxetine and fluvoxamine treatment of major depression for 8-10 weeks increased ALLO content in CSF[5]

1) Sundstrom I, et al, 1997
2) Roy-Byrne PP, et al, 1990
3) Guidotti A, et al, 1996;
4) Uzunov DP, et al, 1996
5) Uzunova A, et al, 1998

Conclusions, cont.

- Increased levels of ALLO in response to 5-HT challenge support the postulate that SSRIs exert their anxiolytic effects through modulation of neuroactive steroids
- PMDD is a model of interactions between reproductive and serotonergic systems in humans

Clinical Evaluation of PMDD

- Daily Rating Forms are invaluable in diagnosis
- Most difficult psychiatric differential diagnosis is Bipolar Disorder, rapid cycling subtype
- DDx of PMDD from Bipolar Spectrum Disorders includes an extensive life time mood chart, detailed family history and psychiatric history
- Medical DDx includes thyroid disease, prolactinemia

Treatment of PMDD

- Pharmacologic
  - SSRIs have been extensively studied and all have been found to be effective in decreasing PMDD symptoms
  - Limited studies of SNRIs show efficacy
  - Luteal phase dosing effective and may be treatment of choice initially
  - Augmentation of SSRI for symptom specific residual symptoms. Gabapentin or Benzodiazepine or Buspirone useful for residual anxiety

Nutritional and Lifestyle Modifications and PMDD

- Calcium supplementation 1200 mg/day has been shown to improve symptoms in DBPCTs
- Exercise has been shown to decrease symptoms
- Limit caffeine and alcohol intake
- Stress reduction techniques are helpful

Ovulation Suppression and PMDD

- Several placebo controlled studies have demonstrated that suppression of the menstrual cycle via GnRH agonists is effective in 50-70% “pure” PMDD patients
- Patients with premenstrual worsening of MDE do not respond to GnRH treatment, but may improve with OCPs
- Early data suggests that the new contraceptive “Yasmin” containing estradiol and drosperinone, a spironolactone analogue, improves PMDD

  (Freeman et al., 2002)

  “Yaz” for PMDD

  - COC 3 mg drospirenone and 20 micrograms ethinylestradiol
  - 24/7 and 120/7 day cycles have been shown to be effective

Major Depression in Pregnancy

- Cohen et al (2006) recently conducted an investigation using longitudinal psychiatric assessments across pregnancy to determine risk of relapse in pregnant women who discontinued antidepressant medication compared with those who maintained treatment with these medications.
- 201 pregnant women were enrolled who
  - had a history of major depression prior to pregnancy,
  - were less than 16 weeks' gestation,
  - were euthymic for at least 3 months prior to their last menstrual period, and
  - were currently or recently (<12 weeks prior to last menstrual period) receiving antidepressant treatment.

Relapse of Major Depression During Pregnancy

Table 3. Relapse of Major Depression During Pregnancy

Relapse Status	All Women	Medication Status			
		Maintained	Increased	Decreased	Discontinued
No relapse	115 (57.2)	61 (74.4)	11 (55.0)	22 (64.7)	21 (32.3)
Relapse by trimester					
All	86 (42.8)	21 (25.6)	9 (45.0)	12 (35.3)	44 (67.7)
First	44 (51.2)	11 (52.4)	7 (77.8)	5 (41.7)	21 (47.7)
Second	31 (36.0)	9 (42.9)	2 (22.2)	3 (25.0)	19 (43.2)
Third	11 (12.8)	1 (4.8)	0 (0.0)	4 (33.3)	4 (9.1)

Cohen, L. S. et al. JAMA 2006;295:499-507.

Relapse of Major Depression in Pregnancy

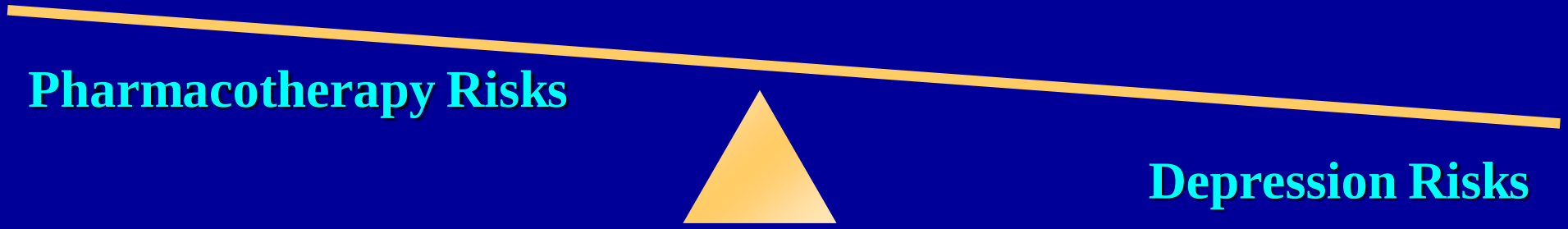
- 86 (43%) experienced a relapse of major depression during pregnancy.
- Among the 82 women who maintained their medication throughout their pregnancy, 21 (26%) relapsed compared with 44 (68%) of the 65 women who discontinued medication.
- Women who discontinued medication relapsed significantly more frequently over the course of their pregnancy compared with women who maintained their medication.

How Generalizable are the Results?

- Methodological Issues
  - HAM-D as a measure of depression: emphasis on symptoms of depression that are also consistent with normal pregnancy
  - Failure to control for concurrent psychotherapy treatment effects
- Population Characteristics: Highly recurrent illness
  - 44% reported > 5 episodes of major depression
  - High comorbidities:
    - 53% met criteria for current or past anxiety disorders and eating disorders (17%)

Depression in Pregnancy: Risk of Treatment vs No Treatment With Medications

- Teratogenesis
- “Behavioral teratogenesis”
- Perinatal complications
- Miscarriage
- Endocrine effects
- Mothers’ poor self care
- ? Low birth weight
- ? Premature labor



Risks Associated With Pharmacotherapy During Pregnancy

- Teratogenicity: gross evidence of organ dysgenesis (eg, Ebstein's anomaly with lithium)
  - Occurs 2-8 weeks after conception, but can extend into 2nd trimester (craniofacial)
- "Behavioral teratogenicity": subtle functional disturbances (eg, developmental delays, neurologic deficits)
  - Occurs throughout pregnancy
- Perinatal complications: effect of drug on labor and delivery and immediate neonatal outcomes

Risks Associated with Antidepressant Use in Pregnancy

- Antidepressants and Spontaneous Abortion (SA)
  - Variable findings in individual studies of differing antidepressants
  - Results of metanalysis evaluating all published studies reported the following risks for SA in 6 carefully evaluated cohort studies:
    - Nonexposed = 8.7% (7.5%-9/9%); N=1,534
    - Exposed= 12.4% (8.8%-14/1%); N=2,033
    - Relative Risk = 1.45
    - No difference between antidepressants (Nefazadone. Trazodone, Venlafaxine, SSRIs)
      - Hemels et al, 2005; *Ann Pharmacother* 39: 803-9

Risks for Spontaneous Abortion

- Estimated risk in general population: 12% of pregnancies
- Estimated risk is less in patients with previous history of successful pregnancy

(4-5%) and greatest in a history of recurrent miscarriage (24-50%)

Regan et al, BMJ, 1989; 26: 54-58

Getting Closer…….

- 937 women on antidepressants (AD) vs. 937 not on antidepressants (NAD)
- Spontaneous abortion AD=13% vs. 8% NAD
- 338 women in the sample had h/o miscarriage
- Comparison SA in women with history of SA:

  20% AD vs. 13% NAD (RR=1.63)

Study limitations:

- What is the contribution of depression?
- What comorbidities are associated with increased risk of SA ?(i.e. subclinical hypothyroidism?)

Einarson et al. *J Obstet Gynaecol* Can 2009; 31: 452-6.

Are Antidepressants Associated with Congenital Malformations?

History of the Controversy:

- Pre-2005:
  - No studies showed an increased risk of major congenital malformations
  - Chambers et al. reported an increased risk of “minor” malformations (Chambers et al, 1996 *NEJM*; 335: 1010-5) in babies exposed to fluoxetine in utero
- September 2005: Preliminary GSK Report:
  - Increased rate of congenital malformationsin Paroxetine exposed infants compared to other antidepressants (4%) OR=1.82
  - Increased risk of cardiac malformations compared to other antidepressants (2%) OR=1.79

Paroxetine and Pregnancy

- A new study utilizing the Swedish national registry data has reported a 2-fold increased risk of cardiac defects (contributed mainly by ventricular septal defects [VSD] and atrial septal defects [ASD]) in infants exposed to paroxetine, compared with the general population.

- Unlike the U.S. epidemiologic study, this study found no increase in the risk of overall congenital malformations after maternal use of paroxetine -- an observation consistent with previous published analyses.

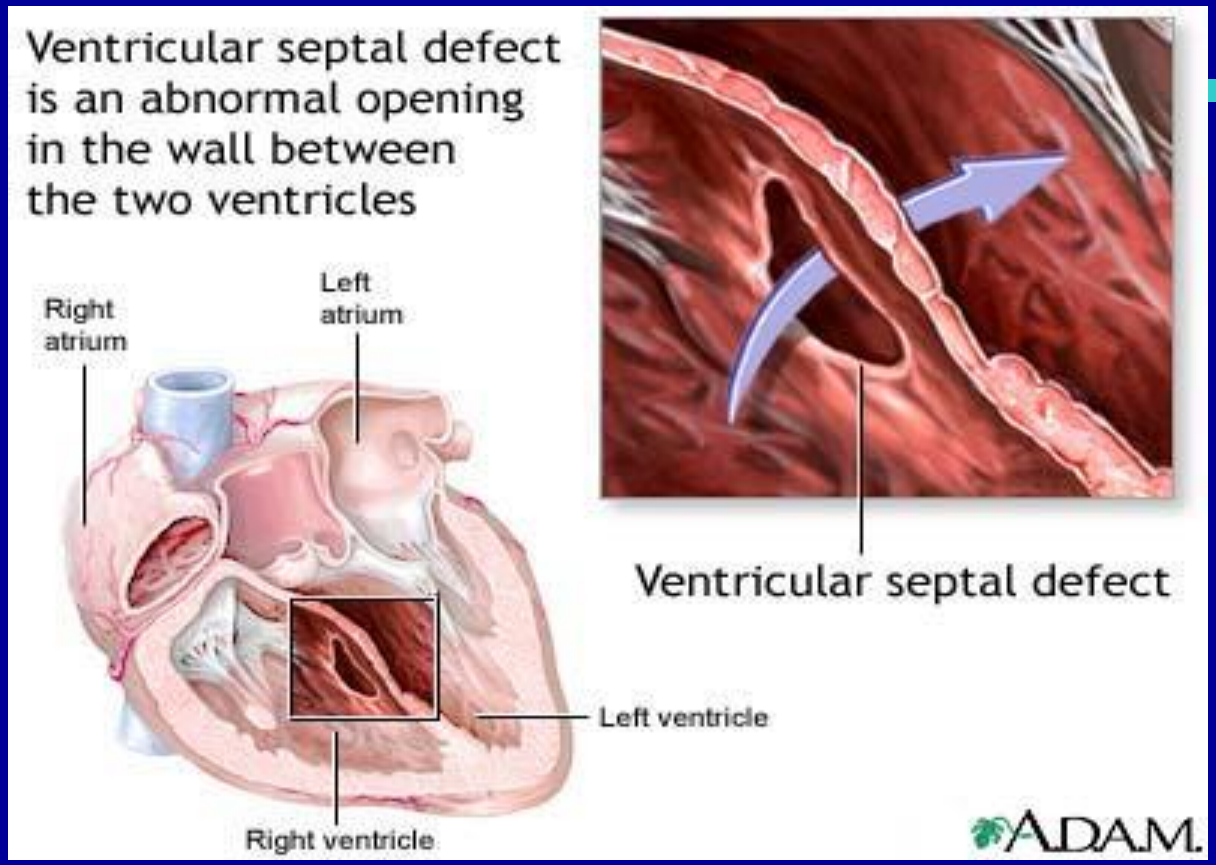
Paroxetine and Cardiac Congenital Malformations

- Paroxetine and Cardiovascular Defects Update:
- Swedish Medical Birth Registry
  - 6,481 women delivered 6,555 infants exposed to SSRIs during 1st trimester of pregnancy
  - No increased relative risk for any cardiac defect in SSRI exposed infants compared to unmedicated total population

    RR=.7 (78/6,555 vs. 11,367/873,876)
  - Relative risk for any cardiac defect in Paroxetine subgroup compared to Sertraline or Fluoxetine or Citalopram: 1.63
  - Paroxetine infants w/cardiac defect in select group

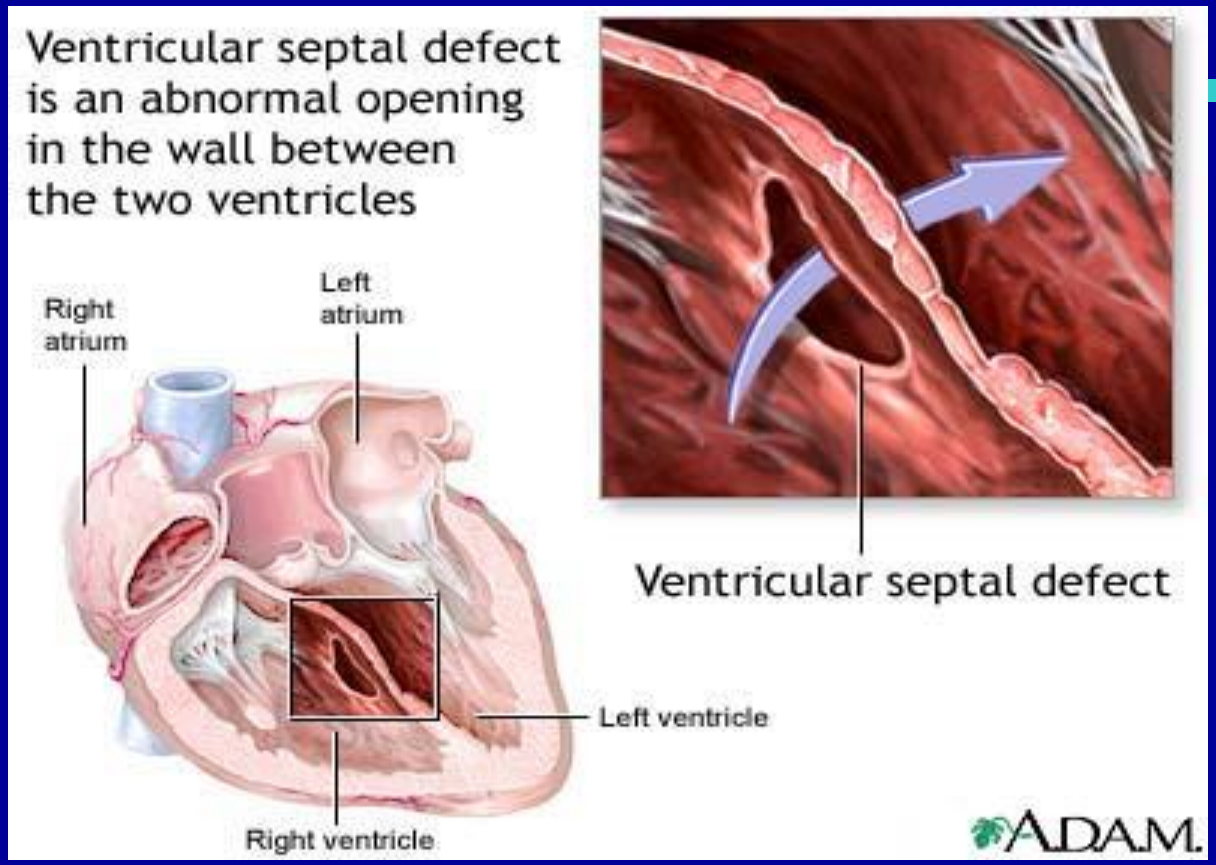
    (normal BMI) compared to general population RR = 2.63 (13/405 vs. 4.9/405)

Kallen and Olausson, 2007 Birth Defects Re A Clin Mol Teratol



- Most common congenital heart defect
- Estimated to occur in 1% of births in general population
- Small defects are most common (80-90%)
- 30-50% small defects close spontaneously prior to 4 years old
- Small muscular defects are more likely to close than small membranous (80% vs. 35%)
- Risk factors include maternal alcohol use, valproic acid

•Williams et al, 2004



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•Williams et al, 2004

National Birth Defects Prevention Study

- 9622 infants with major birth defects compared to 4092 control infants without defects
- No significant associations found between maternal use of SSRIs overall in early pregnancy and congenital heart defects

Alwan S, et al. *NEJM* 2007; 356:2684-2692

Slone Epidemiology Center Birth Defects Study

- Case control surveillance study of 9849 infants with and 5860 infants without birth defects
- *Overall* SSRI use not associated with a significantly increased risk of omphalocele, craniosynostosis or heart defects
- Significant associations found between specific SSRIs and specific defects

Louik C, et al. *NEJM* 2007; 356:2675-2683

What Is Category Labeling?
Key to FDA Use-in-Pregnancy Ratings

Category	Interpretation
A	Controlled human studies have demonstrated no fetal risk
B	Animal studies indicate no fetal risk, but no human studies OR adverse effects in animals, but not in well-controlled human studies
C	No adequate human or animal studies OR adverse fetal effects in animal studies, but no available human data
D	Positive evidence of risk, but benefits outweigh risks
X	Contraindicated in pregnancy

Categories of Antidepressants

- SSRIs except Paroxetine: Category C
- Buproprion: Category C
- Venlafaxine: Category C
- Trazodone: Category C
- Nortriptyline and Imipramine: Category D

Prospective Studies of Antidepressants and Preterm Delivery

Author	Medication	Study Design	N	Results
Kulin et al, 1999	SSRIs	SSRIs vs. MC	267	No difference
Einarson et al, 2001	Venlafaxine	V vs. SSRI vs. NT V vs. NT	150/grp	No difference
Hendrick et al, 2003	SSRIs SSRI	No controls	147	6.5%
Suri et al, 2004	FLX	DEF vs. DE VS. ND	59	No difference
Chun-Fai-Chen,2005	Buproprion	B vs. NT B vs. OAD vs NT	136	No difference
Djuluk et al, 2006	Mirtazapine	M vs. OA vs. NT	104	10% M vs. NT 2% p=. 04

Antidepressants and Preterm Delivery: Results of Large Birth Registry Studies

Author	Registry	N	Results
Malm et al, 2005	Finnish Registry	1,782 SSRI	NS
Oberlander et al, 2006	Canadian Health Care Registry	1,451 S-ED 14,234 DE 92,192 NE	p=.001

Effects of Antenatal Depression and Antidepressant Treatment on Gestational Age at Birth and Risk of Preterm Birth

Prospective study of 93 women

- Group 1: Depressed with antidepressants
- Group 2: Depressed without antidepressants
- Group 3: Controls

Study controlled for risk factors for prematurity

Results: Antidepressant exposure associated with

1) Lower mean gestational age at birth
   (38.5 vs. 39.4 vs. 39.7 weeks)
2) Higher percentage of preterm deliveries
   (14.3% vs. 0% vs. 5.32%)
3) Higher percentage of special care nursery admits
   (20% vs. 9% vs. 0%)

Suri R. *Am J Psychiatry* 2007; 164: 1206-1213

Untreated Major Depression in Pregnancy

- Major Depression associated with an increased incidence of preterm delivery compared to nondepressed patients in a large registry study (Oberlander et al, 2006)
- Major Depression during pregnancy has been associated with adverse obstetrical outcomes in small prospective studies but results differ in larger prospective studies (Chung et al, 2001; Andersson et al, 2004)
- Major depression in pregnancy is clearly associated with an increased risk for postpartum depression

Relative Safety of Antidepressants in Pregnancy: *Neurobehavioral Sequelae*

Study	N	Med	Results
Misri et al. 1991	9	TCAs	No neurobehavioral sequelae up to age 8
Nulman et al. 1997	80 55 84	TCAs Fluoxetine Control	IQ, Bayley, McCarthy similar up to age 7
Casper et al, 2003	13 31	Control SSRIs	Lower Bayley psychomotor developmental indexes and motor quality in f/u (6-40 mo)

Casper et al. *J Pediatr.* 2003; 142: 402-408
Misri S, Sivertz K. *Int J Psychiatry.* 1991;157-171.
Nulman I, et al. *N Engl J Med.* 1997;336:258-262.

Persistent Pulmonary Hypertension of the Newborn

- Rare condition in the general population: estimated 1/1000 births
- Cause: Unknown
- Possible Causes:
  - Hypoxia and hypercarbia at birth (meconium aspiration, complicated deliveries)
  - Increased medial muscle thickness of pulmonary arteries
  - Vasoactive mediator abnormalities (nitrous oxide, leukotrienes, platelet activating factor)

Risk of Persistent Pulmonary Hypertension and SSRIs

Table 2. Use of SSRIs and Other Antidepressants during Pregnancy by Mothers of Infants with PPHN and Matched Controls.*

Variable	Definite PPHN (N=377)	Matched Controls (N=836)	Crude Matched Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)†	P Value‡
	no. (%)				
Maternal use of antidepressants					
Never during pregnancy	357 (94.7)	799 (95.6)	1.0	1.0	
Any time during pregnancy	20 (5.3)	37 (4.4)	1.3 (0.7–2.2)	1.4 (0.8–2.5)	0.30
SSRI	16 (4.2)	24 (2.9)	1.5 (0.8–2.9)	1.6 (0.8–3.2)	0.16
Other antidepressant	4 (1.1)	13 (1.6)	0.8 (0.3–2.4)	0.8 (0.2–2.7)	0.76
Maternal use of antidepressants					
Never during pregnancy	357 (94.7)	799 (95.6)	1.0	1.0	
Before wk 20	6 (1.6)	26 (3.1)	0.5 (0.2–1.3)	0.6 (0.2–1.5)	0.28
After wk 20	14 (3.7)	11 (1.3)	2.9 (1.3–6.5)	3.2 (1.3–7.4)	0.008
Maternal use of SSRIs					
Never during pregnancy	361 (95.8)	812 (97.1)	1.0	1.0	
Before wk 20	2 (0.5)	18 (2.2)	0.3 (0.1–1.1)	0.3 (0.1–1.2)	0.08
After wk 20§	14 (3.7)	6 (0.7)	5.1 (1.9–13.3)	6.1 (2.2–16.8)	0.001
Fluoxetine	3 (0.8)	4 (0.5)			
Sertraline	7 (1.9)	2 (0.2)			
Paroxetine	4 (1.1)	0			

Depression During Pregnancy: Treatment Implications

- To switch antidepressant before or during pregnancy
  - Pregravid: switch to safest treatment that affords efficacy
  - During pregnancy: avoid switching compounds without previous history of response
- To decrease or discontinue antidepressant prior to delivery
  - SSRIs and TCAs have been associated with neonatal complications, including lower Apgar scores and increased rates of admission to special care nurseries
  - Decision based on severity of depression, consultation with OBGYN/perinatologist

Casper, RC et al. J Pediatr. 2003; 142: 402-408; Center for Evaluation of Risks to Human Reproduction, 2004

Neonatal SSRI “Adaptation” Syndrome

- Clinical characteristics:
  - Respiratory distress
  - Autonomic instability
  - Poor feeding
  - Neurologic symptoms: tremor, myoclonus, seizures
- Neonatal adaptation syndrome occurs in 30% of neonates exposed to SSRIs in utero, leading to NICU and SCN admits
- Etiology controversial: SSRI withdrawal or serotonergic toxicity?
- Self limited, supportive treatment

Comparison of Finnegan Score Symptoms* in Neonates Exposed to SSRIs With Those in a Control Group

Table 2. Comparison of Finnegan Score Symptoms* in Neonates Exposed to SSRIs With Those in a Control Group

Symptom	SSRI-Exposed Infants (n = 60)	Control Infants (n = 60)
High-pitched cry	18	0
Sleep disturbance	21	2
Exaggerated Moro reflex	3	0
Tremor	37	11
Hypertonicity or myoclonus	14	1
Convulsions	2	0
Sweating	1	0
Fever	3	0
Autonomic nervous system†	4	2
Tachypnea	12	0
Gastrointestinal disturbance‡	34	2
Neonatal abstinence syndrome§	18	0

Abbreviation: SSRI, selective serotonin reuptake inhibitor.
*Data are given as number of patients. Some patients had more than 1 symptom.
†Yawning, sneezing, sniffles.
‡Exaggerated sucking, poor feeding, regurgitation, vomiting, loose stools.
§Defined as a Finnegan score of 4 or higher.

- 120 term newborns
- 60 exposed to SSRIs throughout pregnancy
- 30% “neonatal abstinence syndrome
- 8/18 rated severe (> 8 Symptoms) and 10/18 rated mild (4-7)

ARCHIVES OF PEDIATRICS & ADOLESCENT MEDICINE

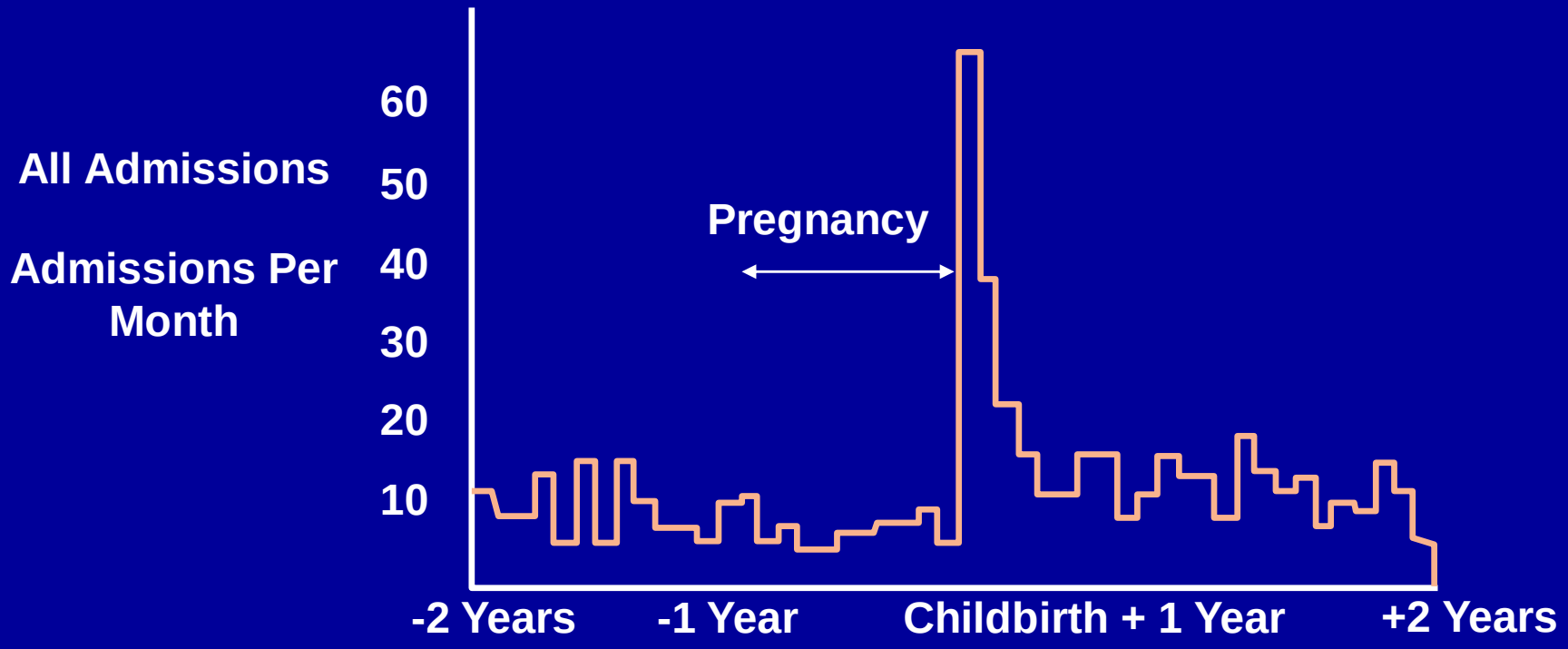
Levinson-Castiel, R. et al. Arch Pediatr Adolesc Med 2006;160:173-176.

Effects of SSRIs and Venlafaxine During Pregnancy in Term and Preterm Neonates

- Retrospective cohort study of 76 mothers treated with SSRIs of Venlafaxine during third trimester
- Results:
  - 100% of premature infants presented neonatal adaptiation symptoms compared to 69% of term infants
  - Median length of stay in hospital was almost 4 times longer for preterm compared to term infants (14.5 vs. 3.7 days)
  - 95% of premis demonstrated CNS symptoms (abnormal movements and agitation) vs. 30.9% of term (p=<.001)
  - 66.7% of premis demonstrated respiratory symptoms vs. 25.5% of term (p=<.001)

Ferreira et al., 2007 *Pediatrics 119*: 52-57

Postpartum Psychiatric Hospitalizations



Kendell RE, et al. *Br J Psychiatry*. 1987;150:662.

Postpartum Mood Disorders

Disorder	Incidence (%)	Treatment	Presentation
Postpartum blues	26 to 85	Support/reassurance	80% resolve by week 2; 20% evolve to PPD
Postpartum depression	10 to 20	Antidepressant & psychotherapy	Major depression often with obsessions
Postpartum psychosis	0.2	Hospitalization; antipsychotics; mood stabilizers; benzodiazepines; antidepressants; ECT	Early onset usually by day 3; mixed/rapid cycling; risk of infanticide

PPD = postpartum depression.

Bright DA. *Am Fam Physician*. 1994;50:595.
Suri RA, Burt VK. *J Pract Psychiatry Behav Health*. 1997;3:67.

Postpartum Depression

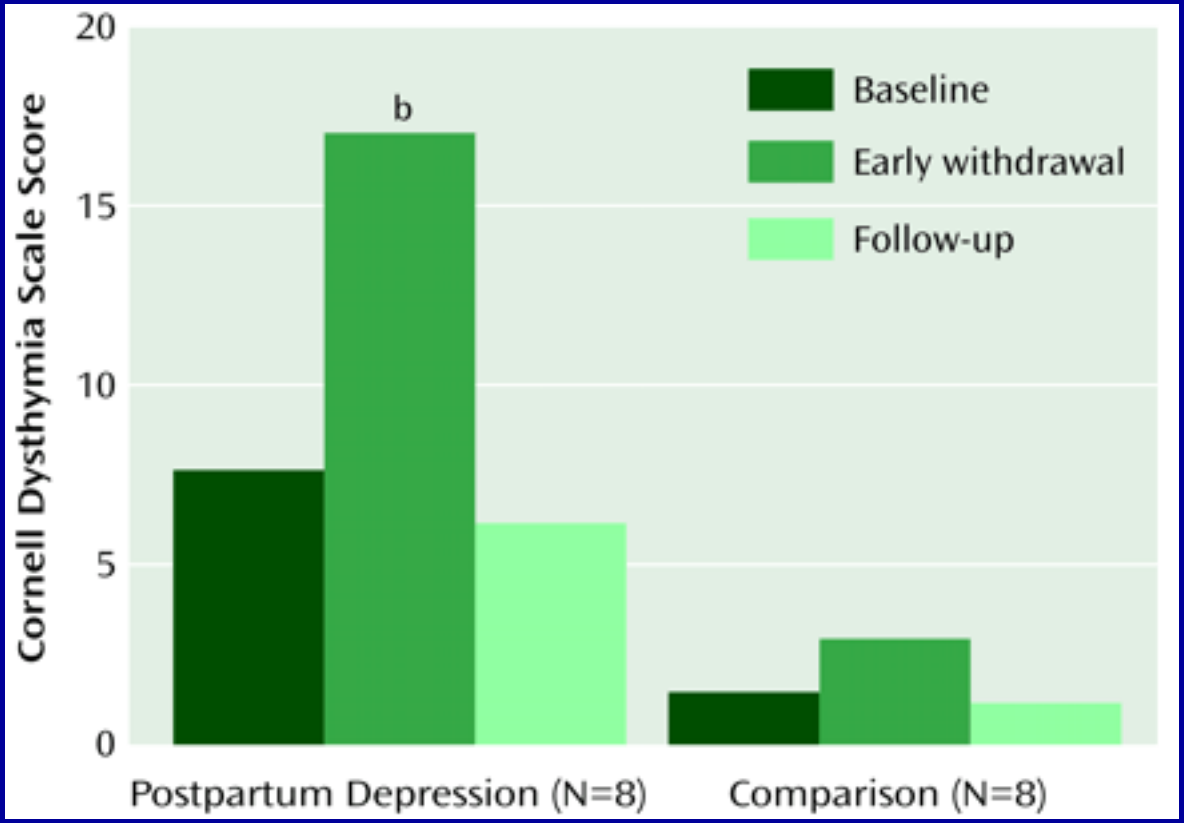
- Onset 1st month postpartum
- Often identified after 1st postpartum month
- ↑ Depression risk:
  - Past mood disorder
  - Past postpartum disorder
  - Depression during pregnancy
  - Poor support system

Cox JL, et al. *Br J Psychiatry*. 1993;163:27.
Suri RA, Burt VK. *J Pract Psychiatry Behav Health*. 1997;3:67.

Are There Differences Between Postpartum Depression and Non-Postpartum Depression

- Phenotypic Differences:
  - Postpartum depression appears to be associated with more anxiety, including obsessionality
  - Postpartum depression may have a different recurrence risk
  - Postpartum depression may cluster in families
  - Postpartum depression risk factors include history of affective instability at other times of hormonal change, such as history of PMDD and OCP mood symptoms

Effects of Gonadal Steroids in Women with a History of Postpartum Depression



Study Design:

16 week blinded study
8 women with h/o PPD only
8 w/no psychiatric history
1) GnRH agonist-->ovarian Suppression
2) Add back Estradiol 4-10 mg/d and progesterone 400-900 mg/d
3) Withdrawal of gonadal hormones

Results:

5/8 of women with h/o PPD had severe mood symptoms during hormone withdrawal phase vs. 0 women with no history

Bloch et al, ***Am J Psychiatry*****, 2000**

Can Postpartum Depression Be Prevented?

- Estimated risk for postpartum depression in a woman with a previous history of depression: unknown
- Estimated risk for *recurrence* of postpartum depression: 25%
- Limited research available for guiding treatment recommendations
- Postpartum antidepressant "prophylaxis" trials:
  - Nortriptyline no more effective than placebo in a RDB study (Wisner et al, 2001)
  - Sertraline more effective than placebo (7% vs. 50%) (Wisner et al, 2004) in RDB study

N-3 Fatty Acids in the Prevention and Treatment of Postpartum Depression

- n3FA levels have been found to be lower in patients suffering from major depression
- n3FA levels naturally decline during pregnancy as fetal requirements usually greater than maternal intake
- Epidemiological data support decreased rates of postpartum depression in countries with increased n3FA intake
- Several pilot studies suggest role for n3FA supplementation for both prevention and treatment of postpartum depression
- Dose ranges 1-4 gm EPA or DHA

Freeman MP. Prostaglandins, Leukot, Essential Fatty Acids 2006; 75: 291-7.

Treatments for Postpartum Depression

- Psychological Interventions:
  - Interpersonal therapy (O'Hara et al. 2000)
  - Cognitive therapy (Appleby et al. 1997)
  - Marital Therapy (?)
- Hormones
  - Estrogen (Gregoire et al. 1996)

O'Hara MW, et al. *Arch Gen Psychiatry.* 2000;57:1039-1045.
Appleby L, et al. *BMJ.* 1997;314:932-936.
Stowe ZN, et al. *Am J Psychiatry.* 1997;154:1255-1260.
Gregoire AJ, et al. *Lancet.* 1996;347:930-933.

Treatments for Postpartum Depression

Author	N	Med	Design	Results
Stowe et al.	26	Sertraline	8 week Open label	83%> 50% improvement 66% full remission
Suri et al.	6	Fluvoxamine	8 week Open label	67% full remission
Cohen et al.	15	Venlafaxine	8 week Open label	80% full remission
Nonacs et al	8	Buproprion SR	8 week Open label	75% > 50% improvement 47% full remission

Stowe et al. Sertraline in the treatment of women with postpartum depression. Depression 1995; 3: 49-55

Suri et al. Fluvoxamine for postpartum depression [letter] Am J Psychiatry 2001; 158: 1739-1740

Cohen et al. Venlafaxine in the treatment of postpartum depression. J Clin Psychiatry 2001; 62: 592-596.

Nonacs et al. Buproprion SR in the treatment of postpartum depression: a pilot study. Int J Neuropsychopharm 2005; 8(3): 445-449.

Randomized Controlled Trials in the Treatment of Postpartum Depression

Author	N	Design	Results
Appleby et al.	87	FLX and 1 CBT session FLX and 6 CBT sessions Placebo and 1 CBT session Placebo and 6 CBT sessions	All groups improved significantly FLX> placebo No greater improvement with CBT added to FLX
Misri et al.	35	Paroxetine only vs. Paroxetine and 12 CBT	Both groups improved significantly No greater improvement with CBT
Wisner et al.	109	DB trial of NTP vs. Sertraline	Both groups improved significantly No difference between groups on % response/remission, time to response

“Treatment Resistant” PPD

- No studies to inform treatment decisions
- Algorithm similar to major depression w/non-postpartum onset except consider breastfeeding issues with augmentation agents such as Lithium
- Always double check thyroid status
- Always evaluate family and marital dynamics--
  marital problems have been strongly associated with persistent PPD
- Strongly consider bipolar differential
- ECT

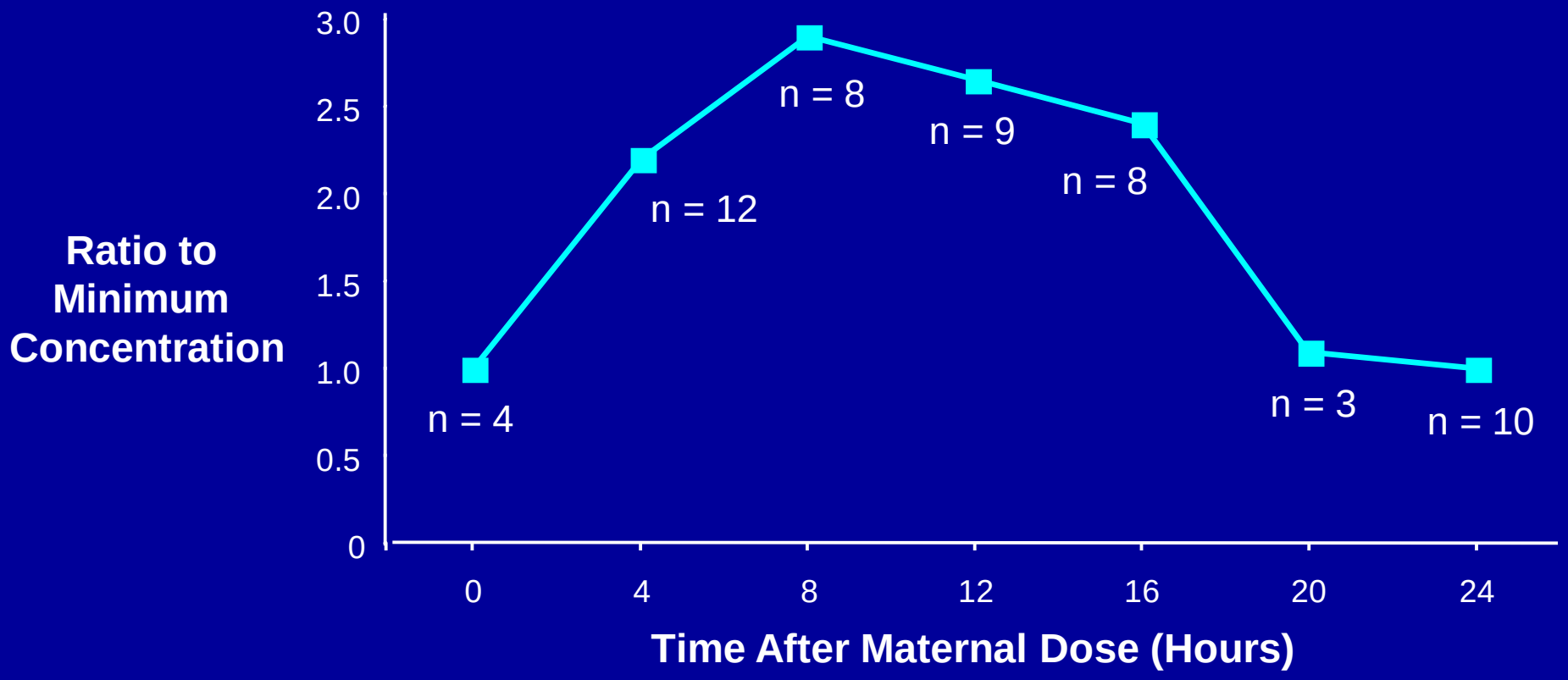
Breastfeeding and Psychotropic Drug Use

- All psychotropic medications found in breast milk
- Concentrations of medications in breast milk vary: milk/plasma ratio poor indicator of exposure
- Majority of clinical practice guided by case reports and clinical impression vs systematic data
- Neurodevelopmental follow-up data limited to case reports that examine children in first year of life

Wisner KL. *Am J Psychiatry*. 1996;153:1132-1137.

Llewellyn A, Stowe ZN. *J Clin Psychiatry*. 1998;59:41.

Sertraline in Breast Milk



Stowe ZN, et al. *Am J Psychiatry.* 1997;154:1255-1260.

Managing Postpartum Depression in Breast-Feeding Women

- Baseline assessment of infant
- Monitor infant clinical status
- Use lowest effective dose
- SSRIs appear to be safest and effective
  - Sertraline is preferred medication with several studies showing undetectable infant serum levels (including metabolite)
  - Avoid Fluoxetine because of higher infant serum concentrations and several case reports of increased irritability, poor feeding, agitation
- Consider infant serum levels, especially when clinical changes occur

Burt VK, et al. *Am J Psychiatry.* 2001. In press.

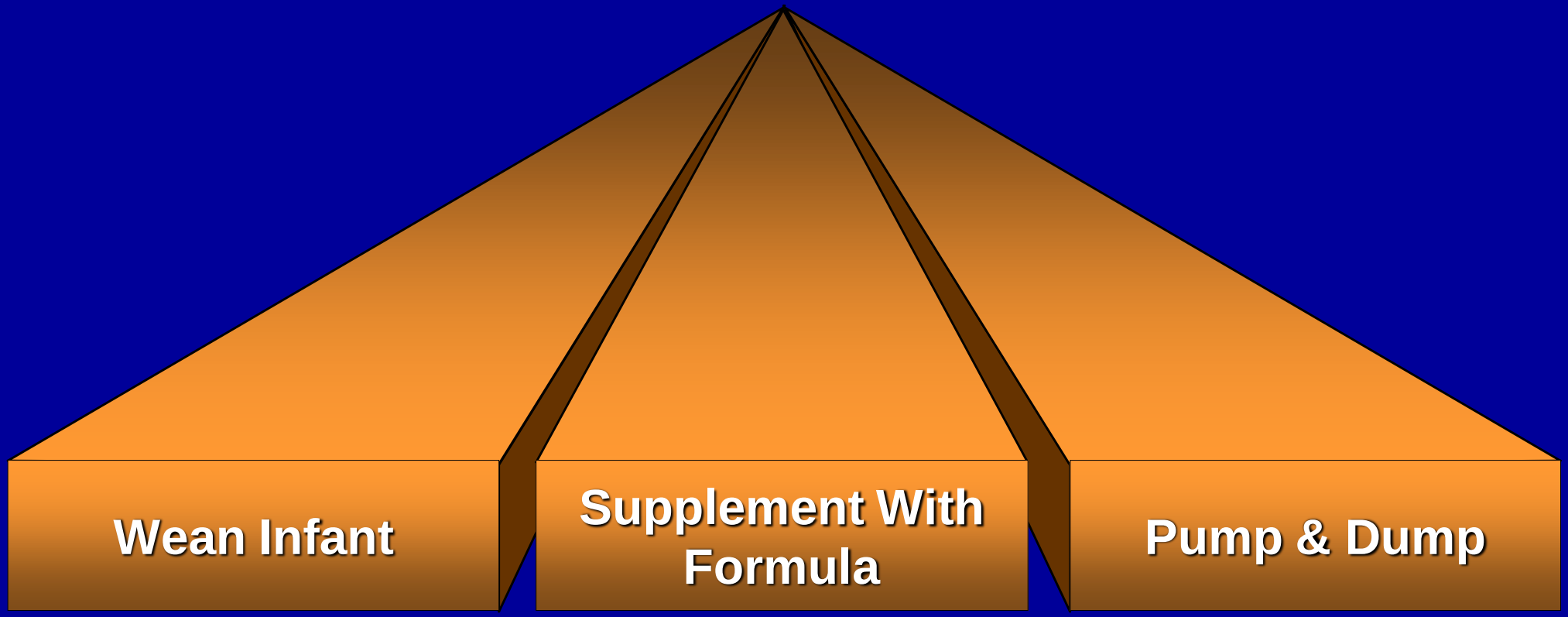
Premature Infants, Lactation and Antidepressants

- All studies investigating plasma concentrations in infants exposed to antidepressants through breastfeeding have included only term infants
- No studies of premature infants
- 1 case report of over-sedation, poor feeding in a 36 week premi exposed to Nefazadone in breastmilk
- Liver metabolic enzymes (CP450) immature until approximately 2 months of age

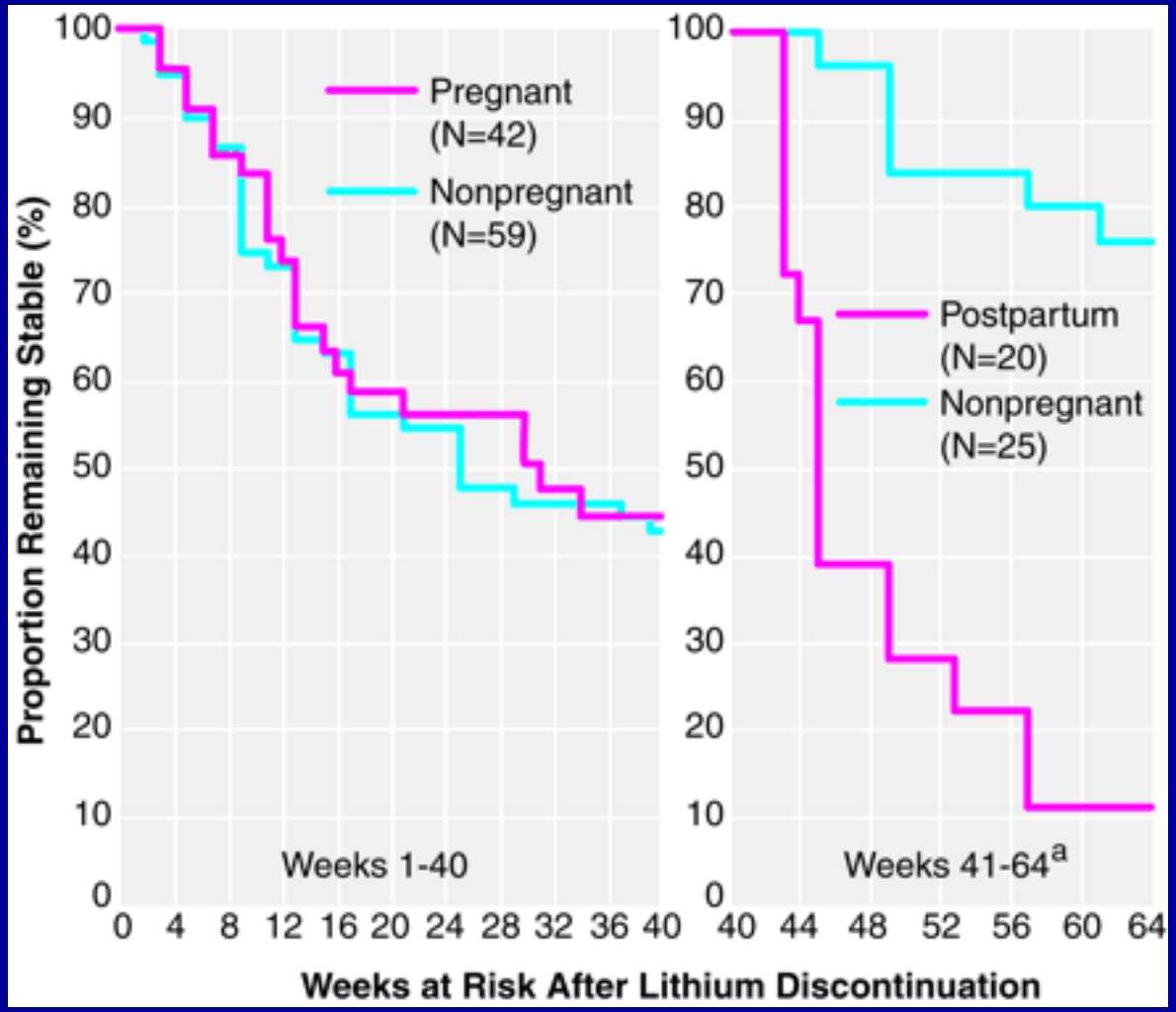
Treatment Strategies for Breast-feeding Women

- Nonpharmacological interventions
  - Psychotherapy (interpersonal, CBT)
  - Stress reduction modalities
- Psychopharmacological treatment
  - “Pump and Dump”

Breast-Feeding: Minimizing Infant Exposure



Risk of Recurrence In Bipolar Women During Pregnancy Off Lithium



Viguera et al, *Am J Psychiatry,* **2000**

Pregnancy and Bipolar Disorder: Postpartum Period

- Postpartum Psychosis: usually occurs within six weeks of childbirth, usually presents with delusions
- BP women have 100-fold higher risk than women without a psychiatric illness history of experiencing postpartum psychosis (1)
- 40% of the female BP subject population experienced postpartum mania or depression (2)
- Freeman et al (2002): 67% of 50 BP women with children experienced a postpartum mood episode within one month of delivery

1) Pariser SF, *Ann Clin Psychiatry* 1993
2) Jefferson et al, 1987

BP Treatment During and After Pregnancy

- No consensus on best time to reintroduce prophylaxis but some experts recommend commencing in the second or third trimester to minimize teratogenic risk
  - Only 2 out of 21 women given lithium in third trimester or after delivery had recurrence of their psychotic illness (1)
  - Only 1 of 14 of BP women relapsed in the acute puerperium if treating with prophylactic agents (2)
- Safety and effectiveness of newer medications and alternative treatments requires further investigation

1) Stewart DE et al, *Br J Psychiatry*. 1991;158:393-7.
2) Cohen LS et al, *Am J Psychiatry*.1995;152(11):1641-5.

Typical Treatment Options in Bipolar Depression

Mood Stabilizers	Antidepressants	Alternative Treatments
Lithium	Bupropion	Antipsychotics
Carbamazepine	SSRIs	Thyroid Hormone
Divalproex	Venlafaxine	Gabapentin
ECT	Nefazodone	Omega-3 Fatty Acids
Lamotrigine	Mitrtazapine	Phototherapy
	MAOIs	Sleep deprivation
	TCAs	Psychotherapy

Jefferson JW, Greist JH. Textbook of Psychiatry, Washington, DC, American Psychiatric Press, 1994; Post RM, et al *Neuropsychopharmacol* 1998; Worthington JJ III and Pollack MH, *Am J Psychiatry* 1996; Amsterdam J, *J Clin Psychopharmacol* 1998; Barbini B et al, *Psychiatry Res* 1998; Wirz-Justice A et al, *Biol Psychiatry* 1999; Stoll AL et al, *Arch Gen Psychiatry* 1999; Bowden CL, *J Clin Psychiatry* 1998.

Evaluations of Bipolar Treatment During Pregnancy

Lithium	Largest concerns are in higher rate of **cardiovascular abnormalities** and **lithium toxicity**; monitoring of lithium levels during delivery is standard.
Valproate	Human teratogen: **neural tube defects**, possible mental retardation effects, complications at delivery. Experts recommend switching meds before conception.
Carbamazepine	Human teratogen: **craniofacial defects, dev. delay, neural tube defects**, low birth weight. Avoid use during pregnancy if possible; suppl. with vitamin K.
Lamotrigine	Sparse research shows normal rates of defects. Concerns regarding hepatotoxicity and fetal metabolization of drug. Currently cleared for use during pregnancy.
1st gen AP	No increased rate of malformation; some short-lived **withdrawal** and extrapyramidal symptoms in infants. May want to switch patient to AP if deemed effective.
2nd gen AP	Limited data. Olazapine associated with **weight gain, IR, gestational diabetes, and preeclampsia**. Monitor weight, glucose, and blood pressure in patient.
Ca-Channel Blockers	Efficacy in BP treatment unproven, but data shows no adverse drug-related effects.
Benzodiazepines	Potential increased risk for **cleft lip or palate**, possible **dev. delay**. **Withdrawal** symptoms observed, neonatal **toxicity** should be monitored. High potency compounds may be preferable.
ECT	Few side effects and risks. Fetal cardiac monitoring should be used to detect arrhythmias. ECT parameters should be adjusted according to hormone levels. Additional concerns regarding anesthesiology during pregnancy.

AP = antipsychotic; IR = insulin resistance; ECT = electroconvulsive therapy.; Yonkers KA et al, *Am J Psychiatry* 2004

Teratogenicity Time Table

Days	Organ System	Associated Defects
10-32	CNS	Neural Tube
20-56	Cardiac	Ebsteins Anomaly
42-63	Lips and palate	Cleft lip and palate
24-56	Limbs	
60-140	Craniofacial	Craniofacial

Teratogenicity and Mood Stabilizers

- Lamotrigine (C)
  - Cleft lip/palate: 8.9/1000 vs. .5-2.1/1000 in general population (NAED Pregnancy Registry, 2006)
  - Rates of major malformations (cardiac, GU and GI, NTD) are dose related:

<100 mg/d	1.3%
100-200 mg/d	1.9%
>200 mg/day	5.4%

  - Rates of major malformations in general population estimated 1-2%

(UK Epilepsy and Pregnancy Register, 2006)

Teratogenicity and Mood Stabilizers

- Lithium
  - Ebstein's anomaly in general population 1/20,000
  - Reanalyzed rate in Lithium exposed infants is 1/1000 or 2/1000 (.1-.05%)
  - Counsel that risk is very low, but still 20-40 times the rate in general population

Yonkers et al. *American J Psychiatry*, 2004

Teratogenicity and Mood Stabilizers

Valproic Acid

Rates of major malformations 6-20.3%

Rates of neural tube defects 5-9%

Carbamazepine

Rates of major malformations 2.2-8.2%

Rates of craniofacial defects 11%

Yonkers et al. *American J Psychiatry*, 2004

Treatment with Lithium During Pregnancy

- Levels in umbilical cord blood=maternal blood levels
- Avoid toxicity at delivery by discontinuing the dose for approx. 48 hours
- Neonatal toxicity is directly related to maternal blood levels

Newport et al., *Am J Psychiatry*, 2005

Atypical Antipsychotic Use During Pregnancy

- Conventional, but not atypical, antipsychotics linked with hyperprolactinemia and amenorrhea
  - Exception: risperidone associated with increased prolactin levels[1]
- Animal studies show no teratogenic or embryotoxic effects
- All atypical APs linked to weight gain[2]

1) Volavka et al. *J Clin Psychiatry* 2004 2) Allison et al. *Am J Psychiatry* 1999

Atypical Antipsychotic Use During Pregnancy

- Study by McKenna et al. (2005):
  - 151 pregnant women on an atypical antipsychotic, age-matched with a control group
  - Followed through pregnancy and birth
  - No difference in rates of major malformations, complications during labor, rates of hospitalization during pregnancy, neonatal complications, diabetes, or hypertension
  - Higher rates of low birth weight among exposed women, although no difference in mean birth weight
  - Exposed women less likely to take vitamins during pregnancy
  - No differences *between* drugs emerged

McKenna et al. *J Clin Psychiatry* 2005

Pregnancy and Bipolar Disorder: Management Guidelines

Comprehensive ***prenatal counseling*** should begin at least three months *before* pregnancy

Treatment should be **avoided *if clinically feasible*** (particularly during the first trimester)

If treatment is pursued:

Use *minimally effective dose* and monitor maternal blood levels

Monotherapy is preferable

For patients treated with lithium, *monitor blood* for serum lithium, electrolyte, and thyroid levels

Burt VK and Rasgon NL, *Bipolar Disord* 2004

Preconception Counseling In Bipolar Patients

- Careful review of previous affective episodes--look for modifiable precipitants, including seasonal relationship, sleep disruptions, travel, medications
- Careful review of menstrual cycle history
- Careful review of family history: postpartum psychosis may cluster in families!
- Recommend folic acid 400 micrograms/day and 3-4 mg/day if continuing a mood stabilizer
- Recommend BBT +/- LH kit monitoring to confirm ovulation

- Goal: Minimum Time Off Mood Stabilizer !!

Pregnancy and Bipolar Disorder: Breastfeeding

- Data are lacking on safety of using medications while breastfeeding
  - Many drugs appear in low concentrations in breast milk
  - Long half lives of drugs may pose accumulation problems
  - Effects of drugs may be dangerous for infants during critical neural developmental periods

Burt VK and Rasgon NL, *Bipolar Disord.* 2004;6(1):2-13. Review
Yonkers KA, et al. Am J Psychiatry. 2004;161:608-620.

Management Guidelines for Breastfeeding

Treatment should be based on ***medication profiles***, ***mother's clinical state***, and ***past response to medications***

Mother, partner, and family doctor ***educated*** about potential ***risks*** of medication use as well as ***benefits*** of breastfeeding

If NO

Review healthy formula feeding practices and bonding alternatives

If YES

Polypharmacy should be avoided

Supplement with formula feeding to minimize exposure?

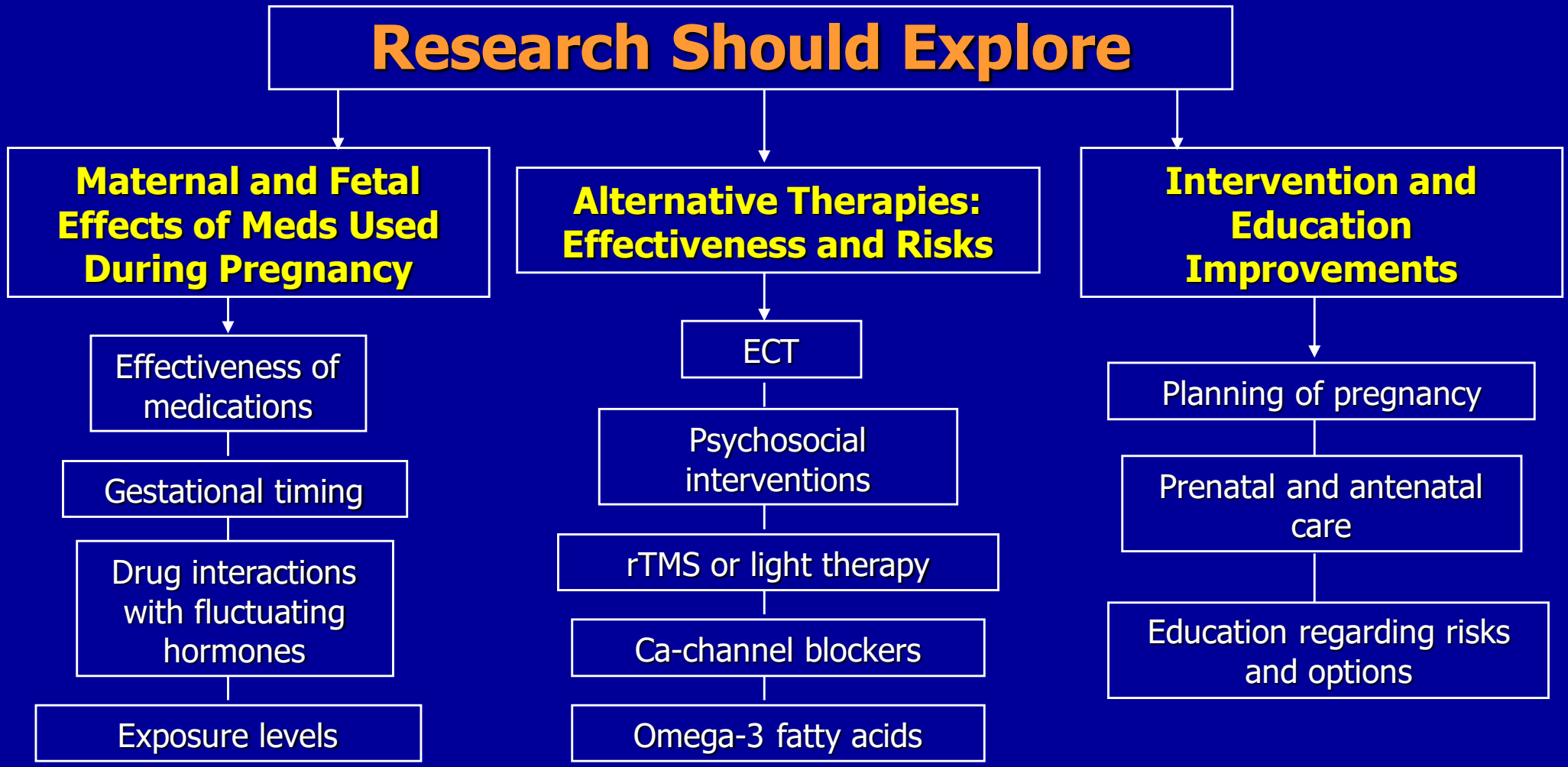
Monthly pediatric and maternal ***blood level monitoring***

Take medication directly after breastfeeding to ***minimize infant exposure***

Use ***lowest possible dose*** that is effective

Burt VK and Rasgon NL, *Bipolar Disord.* 2004;6(1):2-13. Review
Yonkers KA, et al. *Am J Psychiatry*. 2004;161:608-620.

Pregnancy and Bipolar Disorder: Future Directions



Burt VK and Rasgon NL, *Bipolar Disord.* 2004;6(1):2-13. Review
Yonkers KA, et al. Am J Psychiatry. 2004;161:608-620.

Post-Lecture Exam
Question 1

1. Which of the following are true regarding the known risks to antidepressant use in pregnancy?

a. SSRI neonatal adaptation syndrome in 20-30% of infants exposed in the last trimester of pregnancy

b. Paroxetine has been associated with congenital heart defects and is now category D

c. SSRIs may be associated with an increased risk for spontaneous abortion according to metanalysis

d. All of the above

Post-Lecture Exam
Question 2

2. Double blind placebo controlled studies of the treatment options for premenstrual dysphoric disorder include:

a. SSRIs all month

b. SSRIs luteal phase only

c. Yasmin oral birth control pill

d. All of the above

e. None of the above

Post-Lecture Exam
Question 3

3. Risks of congenital malformations with mood stabilizers in the treatment of bipolar women have been estimated to be the following:

a. Lamotrigine 1.3% at <100 mg day and 5.4% at > 200 mg day

b. 1-2% in Lithium exposed infants

c. 20-30% in valproic acid exposed infants

d. Atypical antipsychotics have been studied extensively and have been shown to be risk free, and are category A

Post-Lecture Exam
Question 4

4. Which of the following factors about postpartum depression are true?

a. Anxiety during pregnancy has been associated with postpartum depression

b. Postpartum depression is clearly linked to hormone changes postpartum in all women

c. Marital problems have been associated with treatment resistant postpartum depression

d. All SSRIs have been extensively studied and no metabolites have been found in infant serum in mother nursing pairs

Post-Lecture Exam
Question 5

5. Treatment options for postpartum depression include:

a. Interpersonal psychotherapy

b. Cognitive behavioral therapy

c. Antidepressant medication

d. Group psychotherapy

Answers to Pre and Post Lecture Exams

1. D
2. E
3. A
4. A and C
5. A, B, C, and D