Mood Disorders in Women of Child Bearing Age

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Multiple Choice Questions

- True or False: Do gender differences exist in prevalence, expression, comorbidity and course of the illnesses?
- What is the differential diagnosis of premenstrual dysphoric disorder? (circle all that apply)
    a) Premenstrual Syndrome (PMS)
    b) Depression
    c) Dysthymia
- True or False: SSRIs (Sertraline (20-50 mg/day), Citalopram (10-20 mg/day), Paroxetine (20-40 mg/day) are effective in treating depressive and anxiety symptoms of PMDD and reducing premenstrual dysphoria
- True or False: Pregnant women protected against relapse or new onset of major depression?
- What are the risk factors for postpartum depression?
    a) Past mood disorder
    b) Past postpartum disorder
    c) Depression during pregnancy
    d) Poor support system
    e) All of the above

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

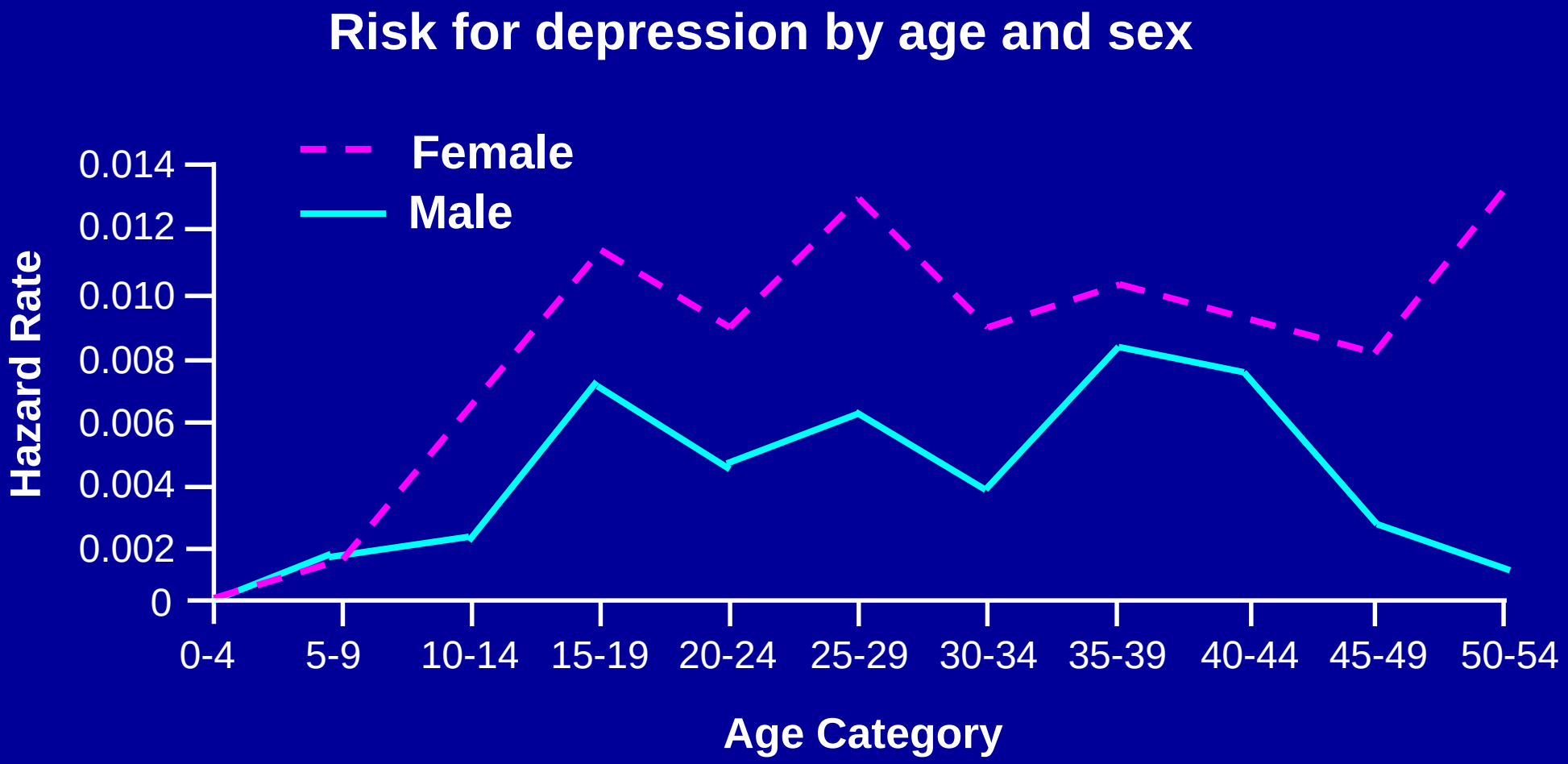
Overview

- 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.

Objectives

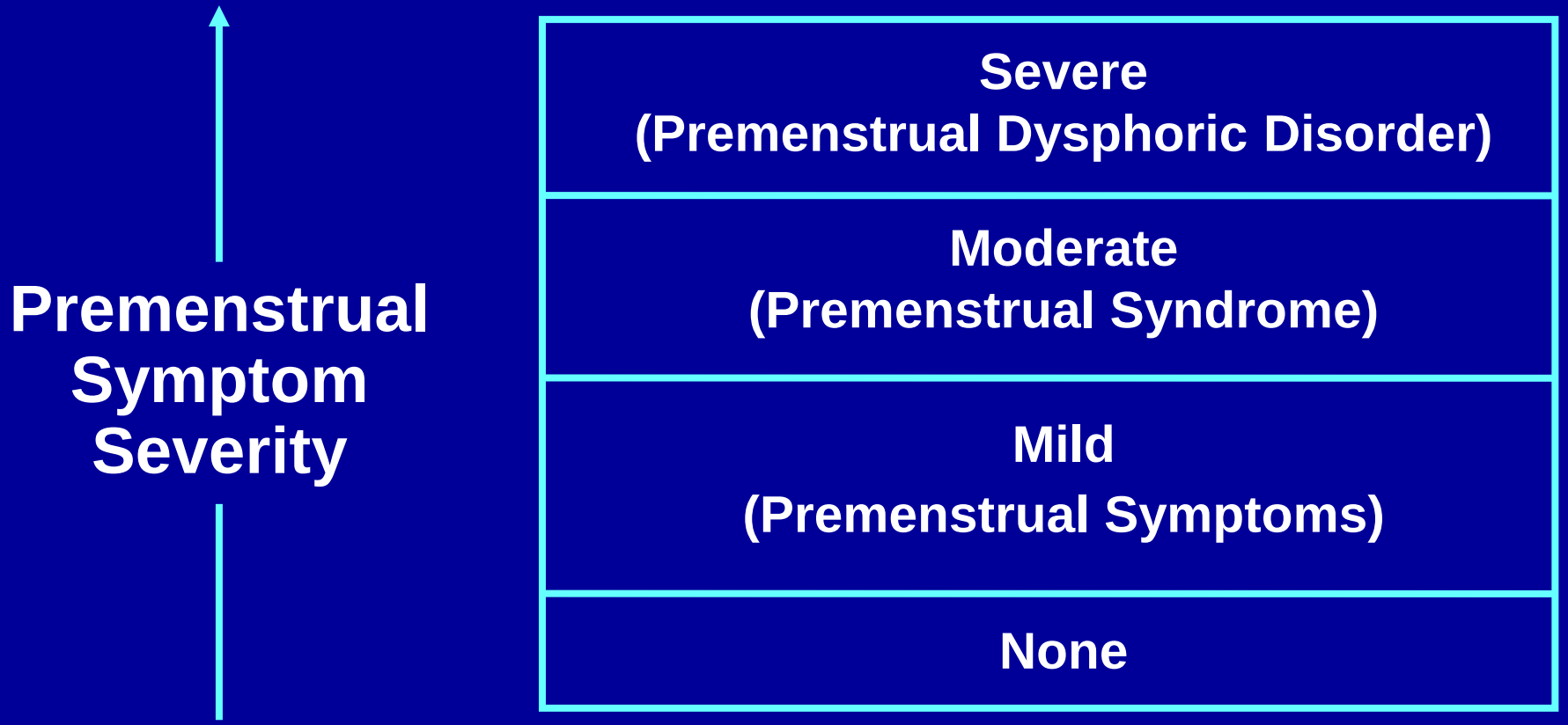
- To gain a better understanding of:
  - the relationship between reproductive function and mood.
  - how to effectively manage and treat depression in pregnancy and postpartum.
  - the risks associated with using psychotropic medications during pregnancy and while breastfeeding.

Affective Disorders in Women



Kessler R. *J Affect Disord.* 1993;29:85-96

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.

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)

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

Treatment With Selective Serotonin Reuptake Inhibitors (SSRIs)

- SSRIs effective in treating depressive and anxiety symptoms of PMDD
  - Fluoxetine (20-40 mg/day) relieves fatigue, irritability, poor concentration, low appetite, and lability
- SSRIs effective in treating depressive and anxiety symptoms of PMDD and reducing premenstrual dysphoria
  - Sertraline (50-100 mg/day)
  - Citalopram (10-20 mg/day)
  - Paroxetine (20-40 mg/day)

Rickels K, et al. *Cur Thes Res.* 1990;48:161-166.
Stone AB, et al. *J Clin Psychiatry.* 1991;52:290-293.
Yonkers K, et al. *JAMA.* 1997; 278:983-988.
Menkes DB, et al. *BMJ.* 1992;305:346-347.
Woods SH, et al. *Obstet Gynecol.*1992;80:339-344.
Yonkers K, et al. *J Clin Psychopharmacol.* 1996;16:3-8.

Relationship Between PMDD and Sex Steroids

- Recent studies on the TX 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.

Pregnancy and PMDD

- 50% of pregnancies are unplanned[1]
- Treatment of PMDD should take into account planning for and the possibility of pregnancy[2]

1. Henshaw S. *Family Plann Perspect.* 1998;30(1):24-29, 46.
2. Cohen L. *Depression and Anxiety.* 1998;8:18-26.

Major Depression During Pregnancy

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

Relapse of Major Depression During Pregnancy* (N=32)

Medication condition	Trimester relapsed I	Trimester relapsed II	Trimester relapsed III	Total relapsed	Total not relapsed
Discontinued (n=25)	60% (n=15)	8% (n=2)	0% (n=0)	68% (n=17)	32% (n=8)
Discontinuation Attempt/Change (n=7)	57% (n=4)	29% (n=2)	14% (n=1)	100% (n=7)	0% (n=0)
Total (N=32)	59% (n=19)	13% (n=4)	3% (n=1)	**75% (n=24)**	25% (n=8)

*Euthymic pregnant patients with histories of depression who discontinued or attempted antidepressant discontinuation or modification.

Cohen LS, et al, 2000 (submitted).

Psychotropic Drug Use in Pregnancy

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

Goal of Risk/Benefit Assessment

- To limit exposure to **either** illness or treatment, and help patient decide which exposure path poses the **least risk**

Impact of Untreated Depression in Pregnancy on Fetal Outcome

- Decreased appetite, lower than normal weight gain, increased use of cigarettes, alcohol, drugs
- Above behaviors associated with altered birth outcome
- Depression associated with preterm labor and low birth weight
- Congenital malformation: not known
- Neurobehavioral sequelae: not known

Zuckerman B, et al. *Am J Obstet Gynecol.* 1989;160:1107-1111.
Zuckerman B, et al. *Pediatr Clin North Am.* 1991;38:1387-1400.
Orr ST, Miller CA. *Epidemiol Rev.* 1995;17:165-171.
Steer RA, et al. *J Clin Epidemiol.* 1992;45:1093-1099.

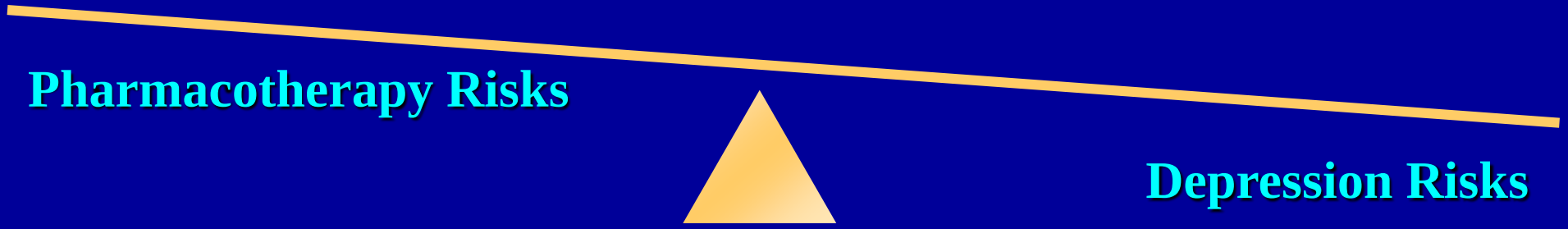
Risks Associated With Pharmacotherapy During Pregnancy

- Teratogenicity: gross evidence of organ dysgenesis (eg, Ebstein's anomaly with lithium)
  - Occurs 2-8 weeks after conception
- "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

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



New Antidepressants During Pregnancy (Cont'd)

- SSRIs
  - Sertraline (n=250+), paroxetine (n=265+), fluvoxamine (n=30+), Citalopram (n-410+)
- No higher rates of major malformations compared to nonexposed controls
- Medications in same family may have different reproductive safety profiles

Kulin NA, et al. *JAMA.* 1998;279:609-610.; Burt VK and Hendrick VC. Clin Manual of Women's Health. Am Psych Pub, 2005

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

Depression During Pregnancy: Treatment Implications

- To discontinue or maintain antidepressant treatment: consider maternal illness history, patient wishes, and available reproductive safety data
- Consider risk of relapse and risk of untreated disorder
- FDA recently issued a warning about paroxetine during pregnancy as research indicates use of paroxetine during pregnancy may increase cardiovascular anomalies in the fetus.

Steer, Orr, and Miller, *Epidemiologic Reviews.* 1995.
Cohen LS, et al. *APA.* 2000.

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.

Treatments for Postpartum Depression

- Psychotherapy
  - Interpersonal therapy (O'Hara et al. 2000)
  - Cognitive therapy (Appleby et al. 1997)
- Antidepressants
  - Fluoxetine (Appleby et al. 1997)
  - Sertraline (Stowe et al. 1997)
- 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.

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

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

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

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
- Consider infant serum levels

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

Treatment Strategies for Breast-feeding Women

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

Pregnancy and Bipolar Disorder: New Ideas

- Pregnancy traditionally considered protective against relapse
- New evidence shows that almost 50% of BP subjects who experienced pregnancy described severe emotional disturbances (1)
- Another study found that rates of recurrence of BP I and II were equal in pregnant and non-pregnant women (2)

1) Blehar MC et al, *Arch Gen Psychiatry*. 1988;45(3):289-92. Review
2) Viguera AC et al, *Am J Psychiatry*. 2002;159(12):2102-4.

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

Pregnancy, Delivery and Neonatal Complications in Women

- Jablensky et al (2005) ascertained the incidence of complications during pregnancy, labor, and delivery and the neonatal characteristics of infants born to women with schizophrenia, bipolar disorder, or major depression.
- Comprised of women with schizophrenia or major affective disorders who had given birth to 3,174 children during 1980–1992.

Jablensky et al. *Am J Psychiatry*. 2005;162(1):79-91

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.

BP Treatment during Pregnancy: Research Findings

- Teratogenic effects of lithium, valproate, and carbamazepine well documented
- Little data on anticonvulsant mood stabilizers and atypical antipsychotics
  - Preliminary study suggests no increased risk of teratogenicity using olanzapine antenatally (1)
- Lamotrigine associated with lower rates of malformations and is used often for women with epilepsy during reproductive years (2)

1) Goldstein et al, *J Clin Psychopharmacol* 2000;
2) Karceski et al, *Epilepsy Behav* 2001

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

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

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?

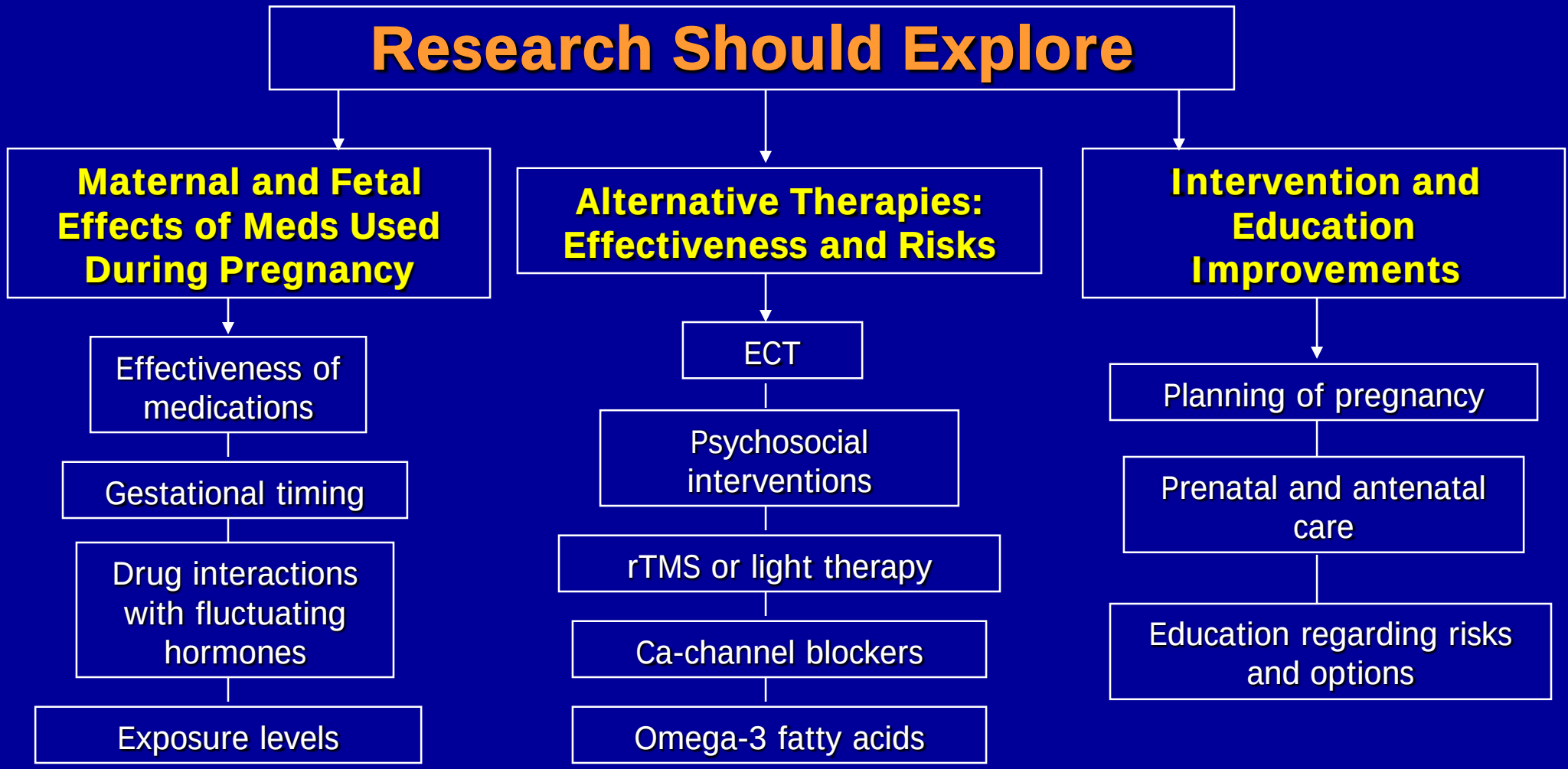
Monthly pediatric and maternal ***blood level monitoring***

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.

Breastfeeding and Psychotropics Conclusions

- Limited role for routine infant-serum monitoring
- Long-term impact of trace levels of medication unknown
- No antidepressant safer than another

Multiple Choice Questions

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