

Perinatal Mood Disorders

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Perinatal and Reproductive Psychiatry

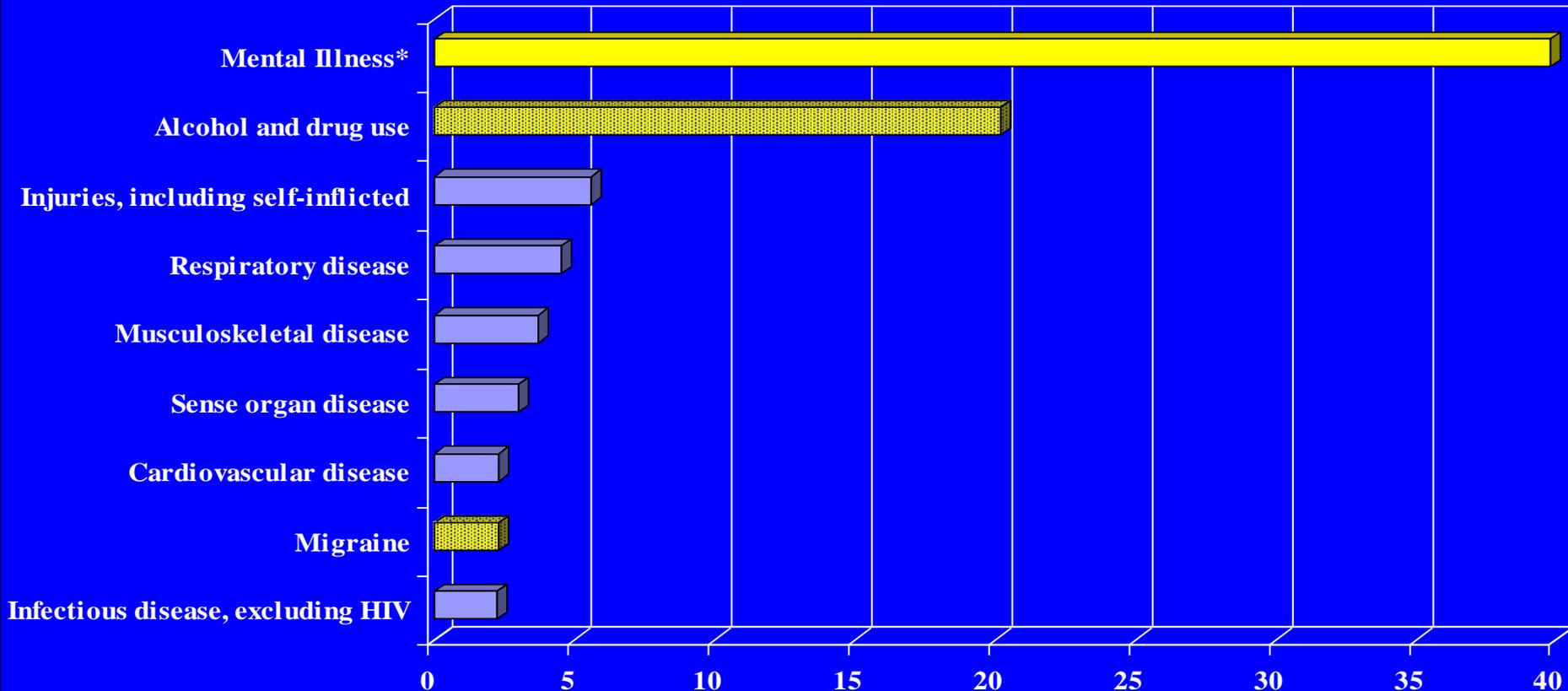
Massachusetts General Hospital

M. Freeman, Disclosure (past 12 months)

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Causes of Disability by Illness Category

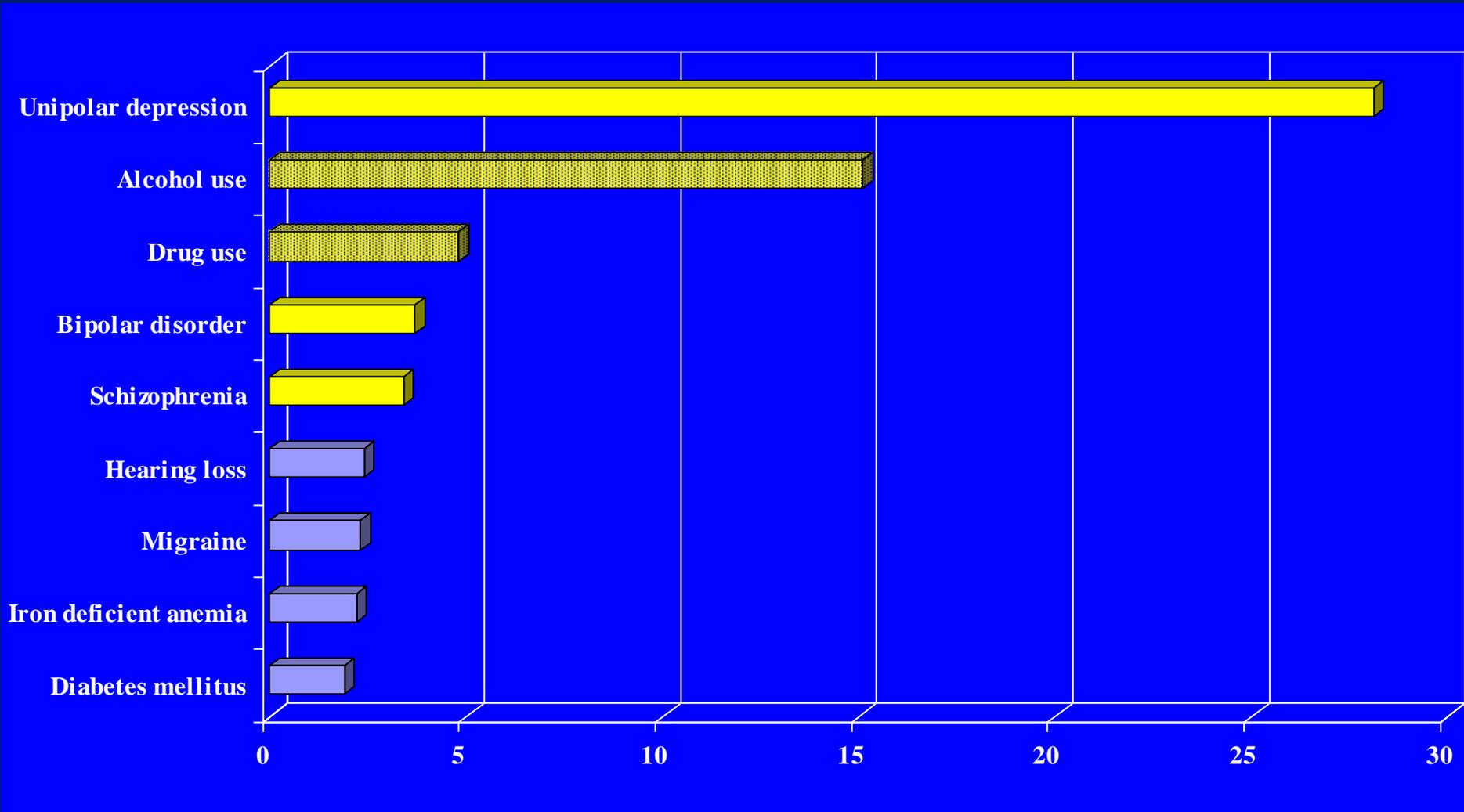
United States and Canada, 15-44 years old



Causes of Disability by Specific Illness

United States and Canada

15-44 years old



Risks of Untreated Antenatal Depression

Possible complications:

- May negatively affect maternal weight gain
- May increase the risk of low birth weight, prematurity, and small for gestational age (SGA)
- Neonatal behavioral differences, such as irritability and decreased activity
- May lead to less compliance with prenatal care
 - Wisner et al., 1999; Wisner et al., 2009; Mulder et al., 2002; Yonkers et al, APA/ACOG guidelines, Obstetric & Gynecology, 2009

APA/ACOG Joint Recommendations

- **Psychotherapy: first line for mild - moderate MDD**
- Lifestyle components - nutrition, weight management, prenatal care, childbirth education; Treatment for substance abuse
- Document all exposures dating back to conception
- **Women trying to conceive - histories of MDD:**
 - Encourage period of euthymia
 - Sustained remission - may consider tapering and discontinuing.
 - More recently depressed or with symptoms: consider remaining on medication, optimizing medication
- **Pregnant women with severe MDD: medication first-line**
- **Pregnant women on antidepressants during pregnancy:** take into account patient preferences, previous course of illness
- Medication selection should be based on known safety information

Antidepressants and Pregnancy: Overview and Controversies



MGH Center for Women's Mental Health
Reproductive Psychiatry Resource and Information Center

Home About Specialty Areas Library Blog Clinical and Research Program Newsletter Resources

Women's Mental Health Across the Life Cycle

PDS and PMDD Psychiatric Disorders During Pregnancy Breastfeeding and Psychiatric Medication Postpartum Psychiatric Disorders Fertility and Mental Health Menopausal Symptoms

Welcome
Welcome to the Massachusetts General Hospital Center for Women's Mental Health, a perinatal and reproductive psychiatry information center.

We are excited about the launch of our new website and encourage you to spend some time on the site. Not only have we changed the "look" of our site, we have updated the content in our Specialty Area pages and libraries, and have made our site easier to navigate.

This website provides a range of current information including discussion of new research findings in women's mental health and how such investigations inform day-to-day clinical practice. Despite the growing number of studies being conducted in women's health, the clinical implications of such work are frequently controversial, leaving patients with questions regarding the most appropriate path to follow. Providing these resources to patients and their doctors so that individual clinical decisions can be made in a thoughtful and collaborative fashion dovetails with the mission of our Center.

Latest News from our Blog

22nd Annual Postpartum Support International Conference
Published: April 27th, 2008
The 22nd Annual Postpartum Support International (PSI) Conference will be held in Houston, TX from June 4 through June 7, 2008. The theme of this year's conference is ... (read more)

Depression in New Fathers Leads to Behavioral Problems in Their Children
Published: April 13th, 2008
While many studies have highlighted the prevalence of depression in new mothers and have demonstrated that postpartum depression (PPD) in the mother may affect a child's cognitive, social, and emotional ... (read more)

www.womensmentalhealth.org

SSRI use during pregnancy

- Prevalence of SSRI use during pregnancy is 3-7%
- Recent findings and more data inform the pharmacologic treatment of depression during pregnancy
 - Consistent conclusions that the *absolute* risk of SSRI exposure in pregnancy is small¹⁻³
 - Recent case-control studies reveal inconsistent data regarding teratogenic risk of individual SSRIs⁴⁻¹⁰
- Reproductive safety data on SSRI exceed what is known about most other medicines used in pregnancy

¹ Louik C, et al. *N Engl J Med* 2007; ² Einarson TR, Einarson A. *Pharmacoepidemiol Drug Saf* 2005; ³ Einarson A, et al. *Am J Psychiatry* 2008; ⁴ Alwan S, et al. *N Engl J Med* 2007; ⁵ Greene MF. *N Engl J Med* 2007;

⁶ Hallberg P, Sjoblom V. *J Clin Psychopharmacol* 2005; ⁷Wogelius P, et al. *Epidemiology* 2006;

⁸ www.gsk.ca/english/docs-pdf/PAXIL_PregnancyDHCPL_E-V4.pdf Dear Healthcare Professional (3/17/08);

⁹ www.fda.gov/medwatch/safety/2005/Paxil_dearhcp_letter.pdf Dear Healthcare Professional (3/17/08)

¹⁰ Pederson et al., *BMJ*, 2009

Long term data

- Limited conclusive data: TCAs and SSRIs
- Fluoxetine
 - Two studies demonstrating absence of neurobehavioral differences with TCAs versus fluoxetine in exposed vs nonexposed children

TCA = tricyclic antidepressant.

Nulman I, et al. *N Engl J Med*. 1997;336:258-262. Nulman I, et al. *Am J Psychiatry*. 2002;159:1889-1895. Oberlander TF, et al. *J Clin Psychiatry*. 2004;65:230-237. Oberlander TF, et al. *Arch Pediatr Adolesc Med*. 2007;161:22-29. Misri S, et al. *Am J Psychiatry*. 2006;163:1026-1032.

Paroxetine: Pregnancy

- Paroxetine –
 - new language on prescribing information, concerning increased risk of cardiovascular malformation with 1st trimester use (U.S. FDA, 2005)- not peer reviewed;
 - FDA labeling change from C to D- not based on more than one data set, not based on systematic scientific data
- Two independent systematic meta-analyses of published and unpublished data sets do NOT show increased rate of malformations (Einarson et al., AJP 2008; Gentile, JCP 2009)

Antidepressants During Pregnancy: Later Pregnancy Considerations

- Persistent pulmonary hypertension of the newborn (PPHN)
 - Lung abnormality in newborns
 - 1-2 out of 1000 live births
 - Abnormal persistence of high pulmonary vascular resistance at birth disrupts normal transition from fetal to newborn blood flow in lungs, shunting of the blood away from lungs and lack of oxygen; fatal in 10-20%
- Established risk factors:
 - cesarean delivery; late preterm or postterm birth; large for gestational age; maternal black or Asian race, overweight/obesity, diabetes, asthma

Antidepressants During Pregnancy: Later Pregnancy Considerations

- Risk of persistent pulmonary hypertension of newborn (PPHN) with SSRIs?
- INCONSISTENT
 - One report showed increased risk by 6-fold (Chambers 2006; approximately 1%)
 - Lower association seen with Källén and Olausson, 2008 (0.15%)
 - No association seen by Andrade et al., 2009; Wichman et al., 2007; Wilson et al., 2010

Antidepressants During Pregnancy: Later Pregnancy Considerations

- Reports of suspected neonatal syndrome: “withdrawal” or “toxicity,” complications after in utero exposure to SSRIs; low birth weight; prematurity
- Overall studies do not adequately control for maternal mental health condition, adequate blinding of exposure in neonatal assessments
- Tapering does not appear to decrease occurrence when confounders assessed

Suri et al., 2007; Moses Kolko et al., 2005; Jordan et al., 2008; Oberlander et al., 2006; Suri et al., 2007; Warburton et al., 2010

Risk of Relapse for Major Depression (MDD) During Pregnancy

- Cohen et al., JAMA, Jan 2006
 - Prospective study of MDD during pregnancy N=201;
 - euthymic prior to pregnancy, currently/recently using antidepressants; patients decided to continue/discontinue medication (not randomized)
 - **43% relapsed during pregnancy**
 - 26% of those who continued medication
 - **68% of those who discontinued medication**
 - Predictors of Relapse
 - Unmarried; Younger (<32 y); More recurrent depression, earlier onset of depression

Depression, Antidepressants During Pregnancy

- The literature regarding risks of antidepressants in pregnancy is constantly changing, complicated to interpret risks and personalize the risk/benefit decisions
- Pregnancy definitely does not protect against relapse of major depression, and the rates of relapse are unacceptably high, even with antidepressant continuation
- APA/ACOG guidelines suggest psychotherapy as first line, although many women will need other interventions such as medication

Postpartum Depression

- **Prevalence: 10-20%**
- **Anxiety is common**
- Risks of untreated maternal depression
- Risks of medication exposure via breastmilk



Nonacs and Cohen, 1998

Negative Effects of Maternal Depression on the Child

- Insecure attachment
- Behavioral problems
- Cognitive function
- Increased risk of abuse, neglect
- Childhood psychiatric diagnoses & symptoms
- Compliance with preventative measures
- Thoughts of harming infant

Civic & Holt, 2000; Cicchetti et al., 1988; Feldman et al., 1999; Murray et al., 1999; Murray et al., 1996; Sharp et al., 1995; Kotch et al., 1999; Cadzow et al., 1999; Jennings et al., 1999; McLennan & Kotelchuck, 2000; Weissman et al., 2006.

Breastfeeding

Benefits to the baby: Motor skills, Language development, Higher cognitive scores; Lower risks of otitis media, atopic dermatitis, type 2 diabetes, obesity, Crohn's Disease, asthma, Hodgkin's Disease

Benefits to the mother: Decreased postpartum blood loss, lower risk of ovarian cancer, premenopausal breast cancer, supports bonding with baby for some women



Vestergaard et al., 1999, Anderson et al., 1999; Labbok, 1999; Ip et al., AHRQ, 2007; Centers for Disease Control and Prevention (CDC), 2007

Treatment Recommendations: Perinatal Depression

- Moderate to severe depression
 - Consider role of antidepressants; discuss risks and benefits with mother
- Use lowest effective doses
- Consultation with experts
- Maximize non-medication alternatives



Antidepressant Trials for the Treatment of PPD

Study	Design and Size	Medication studied
Appleby et al., 1997	Placebo-controlled, N=87	fluoxetine
Yonkers et al, 2008	placebo controlled, N=70	Paroxetine
Wisner et al., 2006	RCT, N=109	Sertraline vs. Nortriptyline
Misri et al., 2004	N=35, all received parox, half randomized to CBT also	Paroxetine
Stowe et al., 1995	Open-label; N=21	Sertraline
Cohen et al., 1997	Open-label; N=19	Venlafaxine
Suri et al., 2001	Open-label; N=6	Fluvoxamine
Nonacs et al., 2005	Open-label; N=8	bupropion

Antidepressant Treatment During Breastfeeding

Most studies of infant exposure to antidepressants show low levels of drug in breast milk and infant serum

Weissman et al., 2004; Burt et al., 2001

Few case reports of adverse effects:

Doxepin: infant had clinical effects of vomiting, sedation (Frey et al., 1999)

Fluoxetine: Case report of high infant blood levels, colicky symptoms (Lester et al., 1993)

- In women who took Fluox during pregnancy, followed postpartum while nursing: slower infant growth in non-randomized study (Chambers et al., 1999)

Citalopram: sleep trouble in infant (Schmidt et al., 2000)

Nefazodone: Case report: drowsiness, lethargy, inability to maintain body temp in a premature baby (Yapp et al., 2000)

Bupropion: possible seizure in an infant (Chaudron et al, 2004)

Breastfeeding and Antidepressants

Fluoxetine	<p>Due to long half life, may be more likely to be found at detectable levels in infant serum, especially at higher doses.</p> <ul style="list-style-type: none"> Reasonable for use if a woman has had a good previous response to it and reasonable to consider if used during pregnancy.
Sertraline	<ul style="list-style-type: none"> Consistent reports of low levels of exposure, relatively large amount of study
Citalopram, escitalopram	<ul style="list-style-type: none"> Less systematic study of mom-baby pairs compared with sertraline and paroxetine, observed low levels of exposure to infant via breastfeeding
Paroxetine	<ul style="list-style-type: none"> Consistent reports of low levels of exposure, relatively large amount of study Use limited by commonly experienced withdrawal symptoms, maybe more sedating than other SSRIs
Bupropion	<ul style="list-style-type: none"> Paucity of systematic study; a few case reports in older infants that demonstrate low levels of exposure via breastfeeding May be advantageous in smokers Reasonable for use if women have had good previous response One case report of possible infant seizure
Venlafaxine, Desmethyl venlafaxine	<ul style="list-style-type: none"> Higher levels of desmethylvenlafaxine found in breastmilk than venlafaxine No adverse events reported
Tricyclic Antidepressants	<ul style="list-style-type: none"> Considered reasonable for breastfeeding if use clinically warranted; few adverse affects in babies and generally low levels of exposure reported
Mirtazapine, nefazodone, MAOIs, duloxetine	<ul style="list-style-type: none"> Systematic human lacking in the context of breastfeeding

Perinatal Depression

- Non-medication treatments
 - **Psychotherapy** (Spinelli, 1997; Dennis et al., 2004; APA/ACOG guidelines, Yonkers et al 2009)
 - **ECT** (Miller, 1994)
 - Complementary and Alternative Medicine (CAM treatments) (Integrative Medicine)

Bipolar Disorder in Pregnancy and Postpartum

Pregnancy & Postpartum: Risks of Discontinuing Medication

Viguera, et al. 2000:

- Retrospective comparison of recurrence rates, pregnant (N=42) vs. nonpregnant women (N=59) with bipolar disorder
- Rates of recurrence after discontinuation of medication
 - Similar for pregnant and nonpregnant women, except more depressive episodes in pregnant women (**overall recurrence rate = 55%**)
 - **Women at increased risk of recurrence postpartum (70% vs. 24%; 2.9 x more likely to have recurrence than nonpregnant women after same time course)**
 - **Recurrence risk greater after rapid discontinuation (≤ 2 wks) than gradual (2-4 wks)**

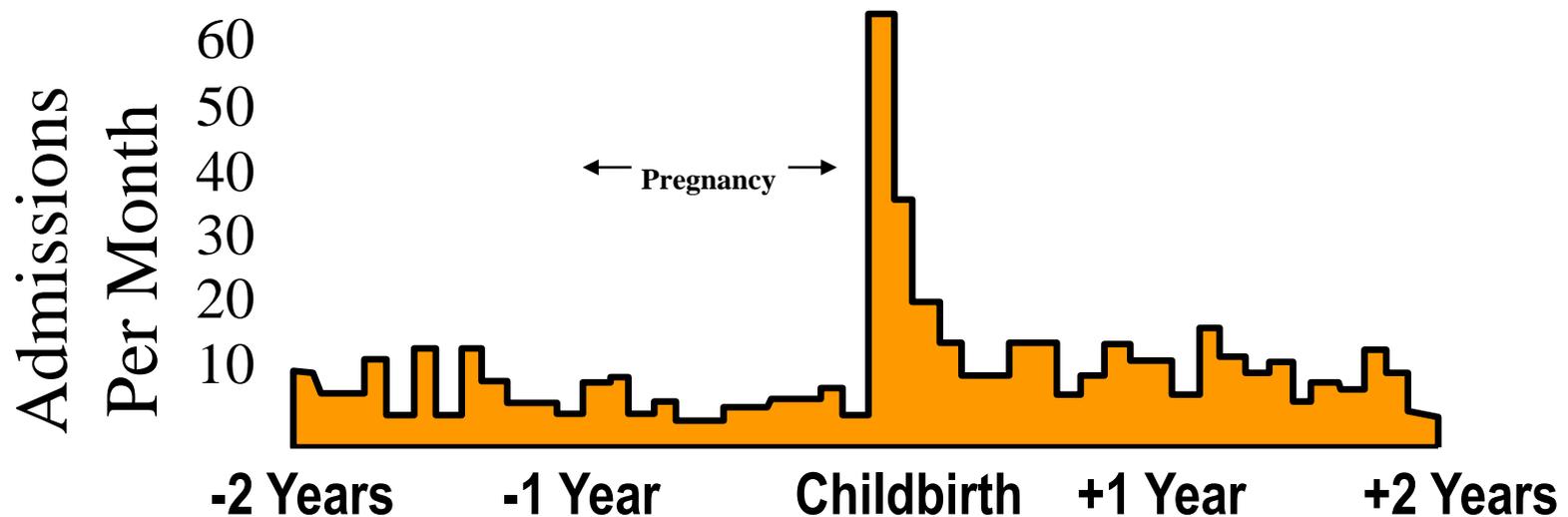
Viguera, et al. 2000

Bipolar Disorder: Course During Pregnancy

Viguera, et al. 2007

- 89 pregnant women with bipolar I or II followed through pregnancy
 - Enrolled by 24 weeks gestation, euthymic for at least 1 month prior to conception, either continued or discontinued mood stabilizers for the pregnancy
- 70.8% relapsed into a mood episode during pregnancy
- Women who discontinued medication were more likely to experience recurrences (85.5% vs. 37%) and spend more time ill
- Rapid mood stabilizer discontinuation associated with higher risk of recurrence (RR=1.4, p=0.008)
- Unplanned pregnancy associated with greater risk of recurrence (RR=1.5, p=0.006)

Risk of Psychiatric Hospitalization During Pregnancy and Postpartum



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

Highest risk of hospitalization for new mothers 10-19 days postpartum, increased outpt contacts 1st three months

-Munk-Olsen et al., *JAMA*, 2006

Postpartum Psychosis

Postpartum Psychosis

- 1 to 2 per 1000 pregnancies
- Rapid, dramatic onset within first 2 weeks
- **High risk of harm to self and infant**
- **Suspect Bipolar disorder:**
 - Underlying diagnosis: affective psychosis (bipolar disorder or schizoaffective disorder)
 - Family and genetic studies, index episode follow-up

Nonacs and Cohen, 1998; Jones & Craddock, 2001; Spinelli, AJP, April 2009

Diagnosis?

- Majority have bipolar disorder or schizoaffective disorder (72-80%)
- Schizophrenia (12%)
- More likely to be related to an affective disorder than not
- Risk factors:
 - history of postpartum psychosis,
 - previous psychosis,
 - bipolar disorder,
 - previous psychiatric hospitalizations

Postpartum Psychosis

- Psychiatric emergency
- Estimated that 4% of women with postpartum psychosis commit infanticide
 - Actual rates of infanticide are difficult to estimate, as infanticide may be under-reported

(Spinelli, AJP 2004; Spinelli, AJP 2009)

Risk Factor	% that developed postpartum psychosis
Hospitalization for psychotic episode during the pregnancy	44%
Hospitalization for a past psychotic episode prior to the pregnancy	14.5%
Any previous psychiatric hospitalization	9.2%
Previous hospitalization for bipolar mood episode	2.0%
Baseline population risk	0.07%

Acute Treatment

- Inpatient psychiatric hospitalization to ensure the safety of mother and baby
- Rule out medical conditions that might precipitate: screening for drugs of abuse, comprehensive metabolic panels, thyroid function tests, calcium, B12, and folate
- Primary pharmacotherapy should include a mood stabilizer and an antipsychotic medication, with medications for anxiety, insomnia, and agitation as needed

Acute Treatment

- Length of stay depends on clinical condition
- Many women will need to stop breastfeeding if they were doing so prior to hospitalization, may consider pumping milk
 - Sleep deprivation may contribute to worsening clinical status
 - Paucity of information regarding many medications used for acute postpartum psychosis

Treatment After Discharge

- Little data to inform length of care
 - 6-12 months of pharmacotherapy
 - psychotherapy and close monitoring
- Treatment planning for adequate sleep, support, help in meeting the needs of caring for a baby
- Close monitoring is required for safety
 - Psychoeducation of family and friends

Mood Stabilizers in Pregnancy

- **Lithium: 1st trimester - risk of cardiovascular malformations**
 - Ebstein's anomaly: 0.1%-0.2 (RR 10-20)
 - Risk ratio for cardiac malformations is 1.2-7.7 and the risk for Ebstein's anomaly rises from 1/20,000 to 1/1000
- **Lithium**
 - Complicated by maternal glomerular filtration rate (GFR) changes during pregnancy- Excreted more rapidly -- may need to increase dose
 - After delivery, GFR decreases rapidly, should follow Li levels during labor and delivery, adjust dose as needed

Yonkers, et al. 2004; Newport, et al. 2005

Anticonvulsants in Pregnancy

Risk of neural tube defects:

Valproate (1-5%)

Carbamazepine (0.5-1%)

Valproate:

Data Associated with increased risk for adverse cognitive and neurodevelopmental effects compared with other anticonvulsants

Long-term follow up to 3 years- suggests fetal exposure to valproate associated with lower IQ scores (not observed with lamotrigine)

Yonkers, et al. 2004; Newport, et al. 2005; Meador et al., 2009

IQ Scores of Children at 3 Years of Age According to In Utero Exposure to Antiepileptic Drugs

Variable	Carbamazepine (N= 73)	Lamotrigine (N= 84)	Phenytoin (N= 48)	Valproate (N= 53)
Mean IQ (95% CI)†	98 (95–102)	101 (98–104)	99 (94–104)	92 (88–97)
Mean difference in IQ from valproate group (95% CI)‡	6 (0.6–12.0)	9 (3.1–14.6)	7 (0.2–14.0)	
P value§	0.04	0.009	0.04	

* The results are based on regression models for the intention-to-treat population (309 children). See Table 1 in the Supplementary Appendix for full results of the regression models. IQ at 3 years of age was imputed for 77 of the original 309 children born alive who were not assessed at that age (1 of these children died from severe heart malformation, 6 were enrolled in the NEAD study from the United Kingdom study after they had reached 3 years of age, 31 withdrew before 3 years of age, and 39 did not present for testing).

† Least-squares means from the primary analysis are given after adjustment for maternal IQ and age, antiepileptic-drug dose, infant's gestational age at birth, and maternal preconception use of folate.

‡ Although the confidence intervals for carbamazepine and phenytoin overlap with the confidence interval for valproate, the confidence intervals for the differences between carbamazepine and valproate and between phenytoin and valproate do not include zero.

§ P values are for the comparison with the valproate group. P values from tests of the null hypothesis of no difference from the valproate-group mean were adjusted for multiple comparisons.²³

Lamotrigine in Pregnancy

- Pregnancy increases lamotrigine clearance by >50%
 - Returns to baseline after delivery
- Association with oral clefting
 - North American Antiepileptic Drug Pregnancy Registry; 5 of 564; 1st trimester exposures rate of 8.9 per 1,000; compared with 0.37 in general population
 - recent large study of registries did not find any association between oral clefts and lamotrigine
- First trimester birth defects more likely with anticonvulsant polypharmacy (International Lamotrigine Pregnancy Registry)
 - 3/168 (1.8%) with monotherapy; 5/50 (10%) lamotrigine + valproate

Myllynen, et al. 2003; Tran, et al. 2002; Dolk et al., 2008

GlaxoSmithKline “Dear Healthcare Professional Letter” June 2006

Atypical Antipsychotics in Pregnancy

- Prospective study after first trimester exposure to olanzapine (N=60), risperidone (N=49), quetiapine (N=36), clozapine (N=6); comparison with controls
- Exposed women: higher rates unplanned pregnancy, did not take vitamins/folate, smoking, less education; high rates of polypharmacy and various diagnoses
- Rates of malformations did not differ between group exposed to atypicals and control group (0.9% vs. 1.5%)
- No significant difference between labor complications or neonatal complications

National Pregnancy Registry for Atypical Antipsychotics

Research Study at the Massachusetts
General Hospital
Center for Women's Mental Health

To determine the safety of atypical
antipsychotics in pregnancy for
women and their babies

Participation will involve **3** brief phone
interviews over approximately **8** months

Call Toll-Free:
1-866-961-2388



Pregnancy: Testing

- Ultrasound - Level II
 - Cardiac (18-20 wks)
 - Spina bifida (18-20 wks)
- Fetal echocardiography

Jacobson, et al. 1992

Postpartum Treatment

- **Prescribe Sleep!**
 - Sleep deprivation – similar to antidepressants regarding risk of induction of mania/hypomania (10%)
- **Prescribe Support!**
 - Good social support associated with quicker recovery, less symptomatic; better prophylaxis against episodes

Mood Stabilizers & Breastfeeding

- **Lithium and Breastfeeding: Recent report**

- N=10 mother-baby pairs;

- Mother's stable, lithium monotherapy 600-1200 mg q day
- Babies' serum levels 0.09-0.3 meq/L (average 0.16)
- Transient increases in elevated infant TSH, BUN, Cr

- **Recommendations** –consider when

- 1) Bipolar disorder in mother that is stable
- 2) Lithium monotherapy (or simple regimen)
- 3) Adherence to infant monitoring

Monitoring Li level, TSH, BUN, Cr immediately postpartum, 4-6 weeks of age, and then every 8-12 weeks

- 4) Healthy infant
- 5) Collaborative pediatrician

Viguera, et al. 2007 (Feb)

Avoiding Pregnancy

Ask About Birth Control Methods and Document

Interactions with Oral Contraceptives Pills (OCPs)

– **May Decrease Efficacy of OCPs:**

- Carbamazepine
- Oxcarbazepine
- Topiramate
- St John's Wort
- Modafinil, armodafil

– **Oral contraceptives may decrease lamotrigine levels**

Perinatal Mood Disorders: Summary

- Women at high risk of depression and other disorders
- Women, children, and families are impacted
- Effective, safe, accessible, and acceptable treatments are needed
- Treatment considerations involve risks of medications, risks of the untreated disorder
- Unknowns: Collaborative treatment decisions, patient preferences highly prioritized