Managing Mood Disorders During Pregnancy

Kimberly A. Yonkers, MD
Associate Professor, Departments of Psychiatry,
Obstetrics, Gynecology and Reproductive Sciences
And Instructor, Division of Epidemiology & Public Health
Director, Premenstrual Syndrome and Peripartum Research Program
Yale University School of Medicine
New Haven, Connecticut

Symptoms of Major Depression

- ***S*** **leep disturbance**
- ***A*****nhedonia/*****A*****gitation or psychomotor retardation**
- ***D*****epressed mood most of the day**
- ***F*****atigue or loss of energy**
- ***A*****ppetite disturbances**
- ***C*****oncentration difficulties**
- ***E*****steem diminished or guilt**
- ***S*****uicidal or recurrent thoughts of death**

Age-Specific Rates of MDD in the USA

Weissman MM. Presented at the APA; 1997; San Diego, CA.

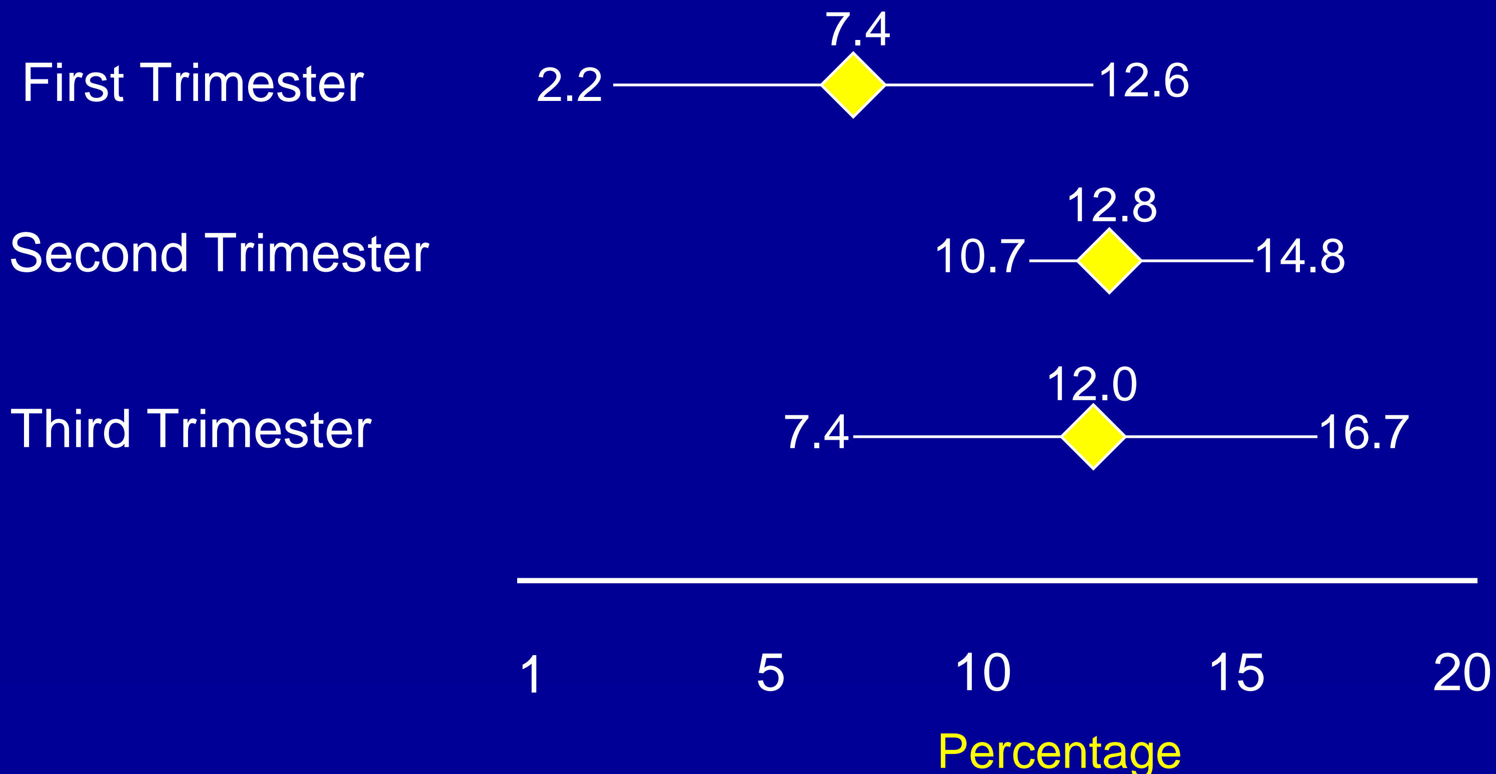
Leading Disability Causes Worldwide, 1990

• Unipolar major depression	• 10.7%
• Iron-deficiency anemia	• 4.7%
• Falls	• 4.6%
• Alcohol use	• 3.3%
• Chronic obstructive pulmonary disease	• 3.1%

Measured by DALY, one year of lost life

Global Burden of Disease, Lopez et al 1996

Prevalence Estimates of Depression By Trimester



Bennett HA, et al. *Obstet Gynecol* 2004;103:698-709.

Questions a pregnant woman may have about depression or its treatment

Can my illness influence my babies development and well-being?

Can antidepressant medication affect my baby?

Are my other health habits (diet, sleep, substance use) affecting my health or my babies well-being?

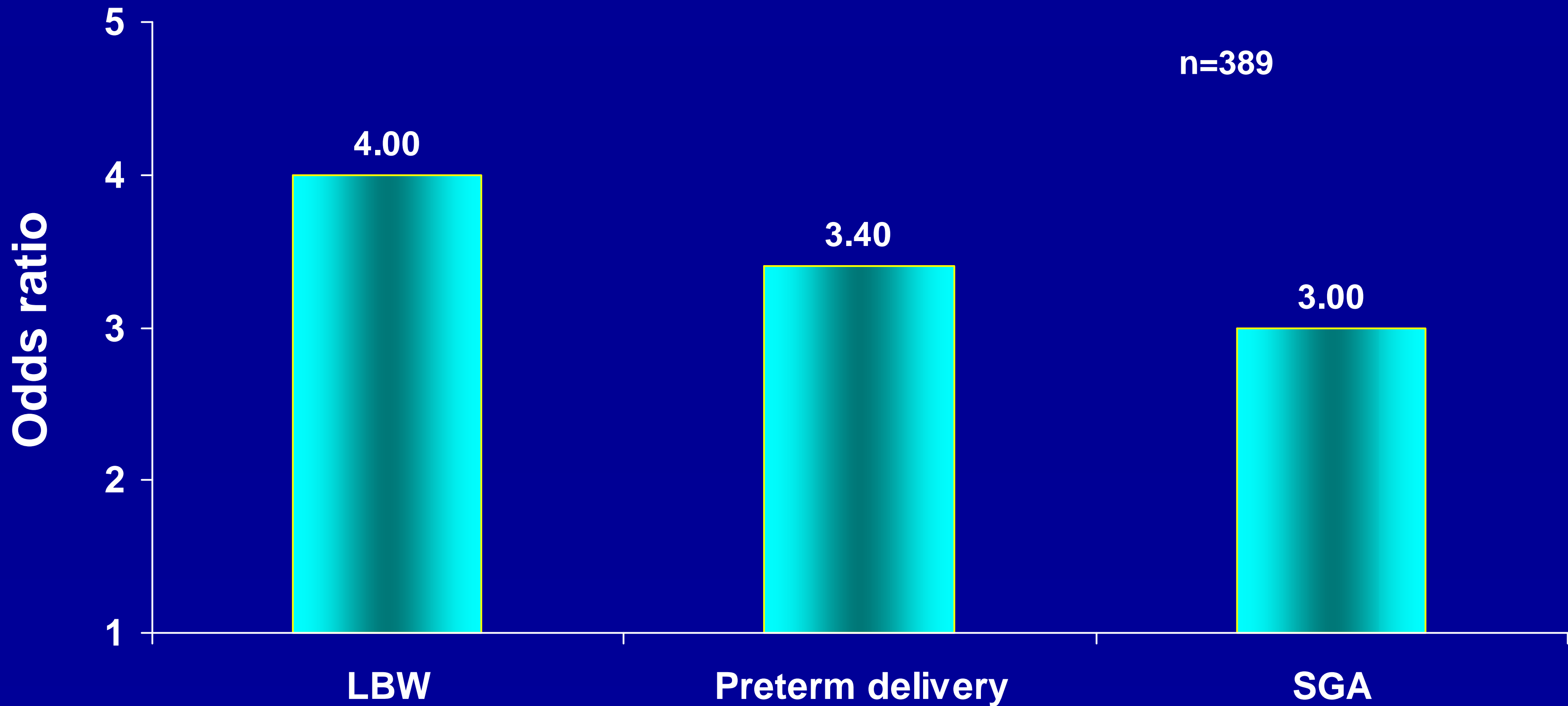
Does Depression Influence Pregnancy Outcomes?

Association of Depression and Pregnancy-Related Health Behaviors

- Depression is associated with cigarette smoking, drug abuse, and concurrent medication use
- Depressive symptoms may lead to poor weight gain, late or delayed prenatal care, and self-neglect

Kitamura et al, 1996, Zuckerman et al, 1989, Walker et al, 1999, Pritchard et al, 1994, Horrigan et al, 2000

Depression and Perinatal Outcomes



LBW=low birth weight <2,500 g; SGA=small for gestational age.
Steer RA, et al. *J Clin Epidemiol.* 1992;45:1093-1099.

Congenital Malformations in Association with Severe Stress

Group	n	Crude Frequency	Adjusted OR (95% CI)
Controls	20299	0.65	1.0
Exposed once	3395	1.15	1.5 (1.01-2.22)
Exposed twice	165	1.81	2.6 (0.8-8.42)
Exposed 2 Gestations	196	2.04	2.99 (1.06-8.43)

Hansen et al, Lancet, Vol 356, 875-880, 2000

Do Antidepressants Adversely Affect Birth Outcomes?

Other Medication Use in Women Prescribed SSRIs and the General Population of Pregnant Women

Use of Other Drugs Together with SSRIs during Early Pregnancy

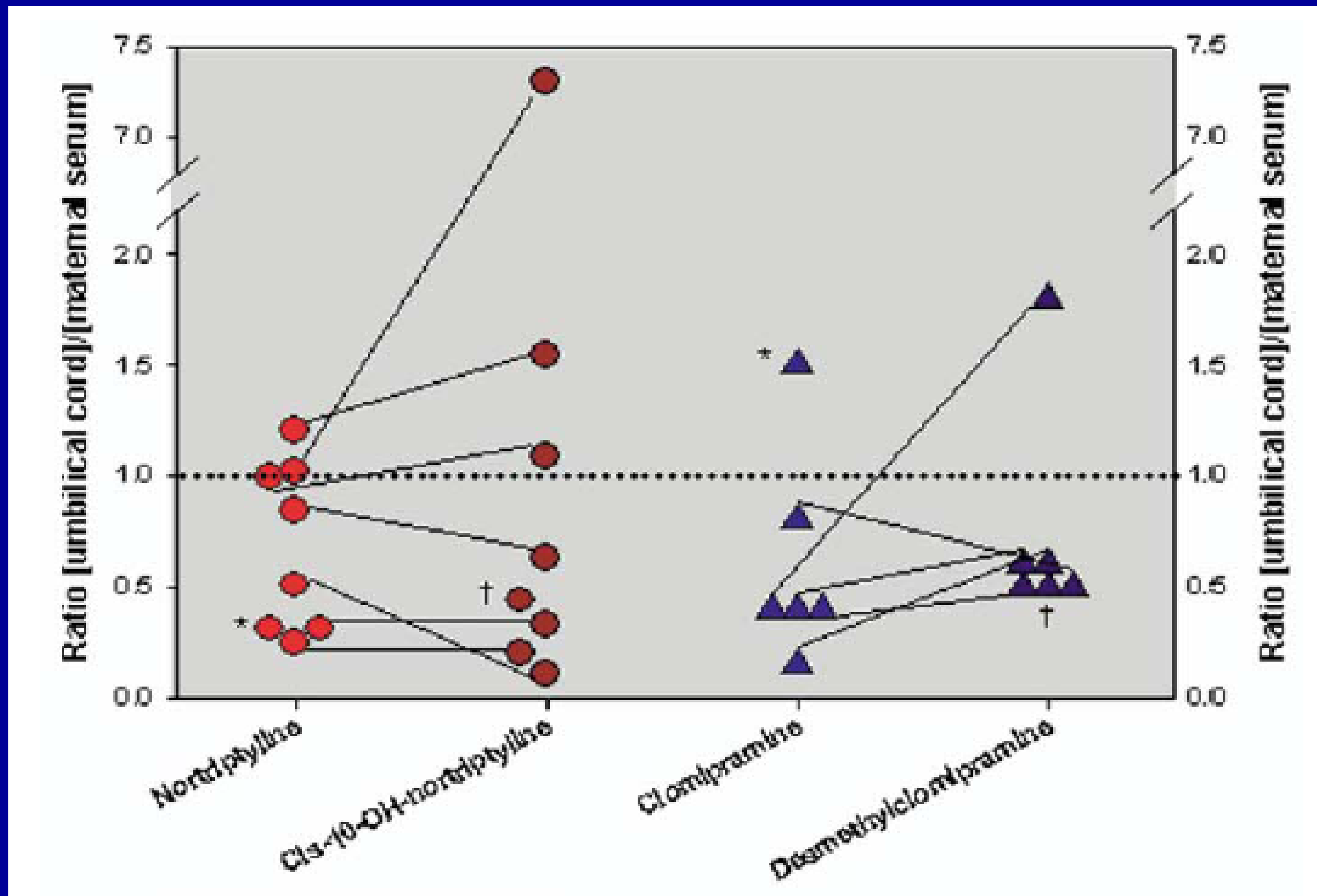
Drug group	Number of women		OR	95% CI
	SSRI	Population		
Drugs for stomach ulcer	191	6,527	3.20	2.77–3.68
Insulin	26	2,585	1.16	0.78–1.71
Multivitamins	158	19,118	0.77	0.65–0.90
Folic acid	178	21,268	0.78	0.67–0.91
Oral contraceptives	50	2,934	1.90	1.44–2.51
Progesterone/gestagens	9	3,444	0.33	0.18–0.61
Ovulation stimulation	9	2,146	0.66	0.34–1.27
Thyroid hormones	164	8,918	2.06	1.76–2.40
NSAID	194	14,734	1.25	1.08–1.44
Opioids	120	3,727	2.95	2.47–3.52
Minor analgesics	493	64,585	0.83	0.76–0.92
Drugs for migraine	51	2,381	2.50	1.90–3.29
Anticonvulsants	57	2,184	2.92	2.21–3.76
Neuroleptics	149	2,510	6.90	5.93–8.02
Sedatives	449	1,884	30.2	25.7–30.2
Hypnotics	374	1,983	18.4	16.8–20.1
Antiasthmatics	320	25,451	1.50	1.34–1.68
Cough medicine	20	4,032	0.59	0.38–0.91
Antihistamines for NVP	429	35,300	1.64	1.48–1.81
Other antihistamines	159	15,474	1.26	1.08–1.48

Kallen & Olausson, *Birth Defects Research, Vol 79, pp. 301-308, 2007*

Commonly Prescribed Tricyclic Antidepressants

• Amitriptyline	150-300 mgs
• Imipramine	100-250 mgs
• Nortriptyline	50-200 mgs
• Desipramine	150-300 mgs

Placental Passage of Tricyclic Antidepressants



Loughhead et al, Biological Psychiatry, 2006, Vol 59: pp. 287-290.

Antidepressants and Spontaneous Abortion

Class	Exposed	Non-Exposed	RR for Rate	95% CI
All (11)	12.4%	8.7%	1.45%	1.19,1.77
SSRI (6)	12.4%	8.4%	1.52%	1.17,1.98
TCA (3)	12.3%	10%	1.23%	0.84,1.78
DAA (2)	12.8%	7.7%	1.65%	1.02,2.69

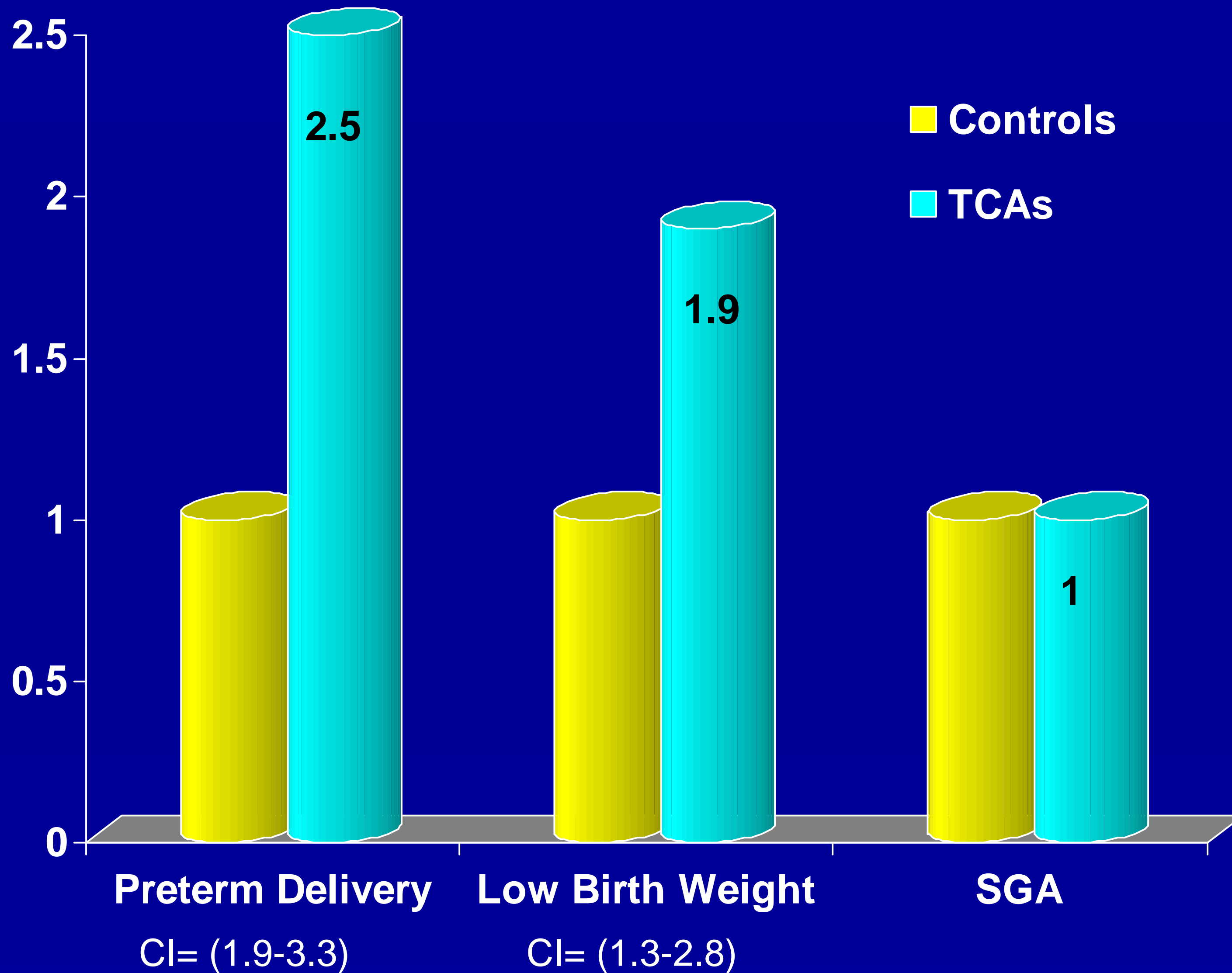
Hemels et al*, Annals of Pharmacotherapy,* Vol 39, pp 803-809, 2005

Tricycle Antidepressants in Pregnancy

- Tricyclic antidepressants do not have known teratogenic effects in the human
- There are reports of tachypnea, cyanosis and irritability among neonates exposed to tricyclic antidepressants in pregnancy

American Academy of Pediatrics, Committee on Drugs, 2000

The Effect of Tricyclic Antidepressants on Birth Outcomes

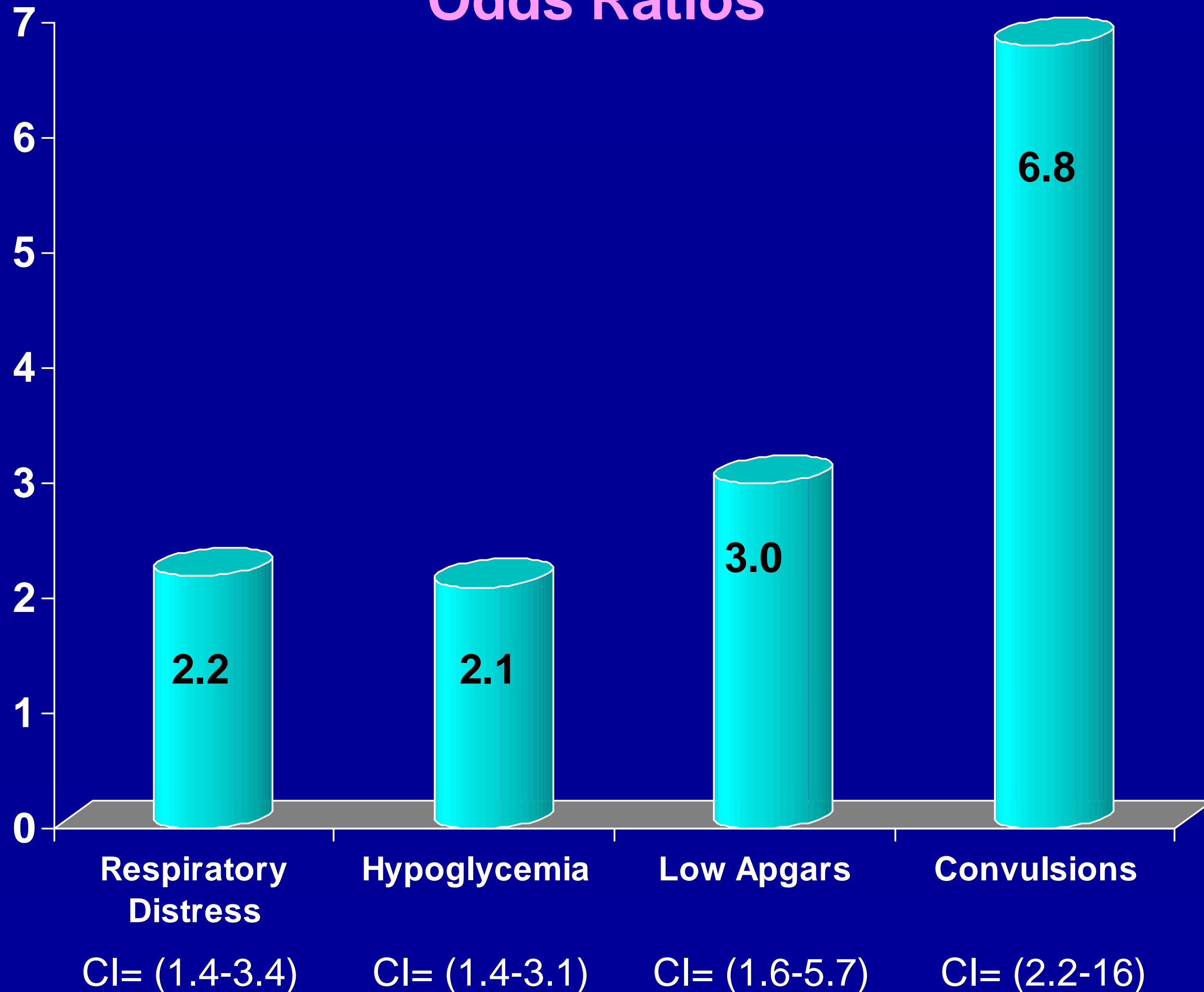


CI= (1.9-3.3)

CI= (1.3-2.8)

Kallen, Archives of Pediatric and Adolescent Medicine, 158, 312-316, 2004

The Effect of Tricyclic Antidepressants on Neonates



Kallen, Archives of Pediatric and Adolescent Medicine, 158, 312-316, 2004

Summary: The Effects of TCAs on Offspring Exposed In Utero

- TCAs are not associated with any particular malformation
- TCAs are associated with a number of perinatal effects including low birth weight, preterm delivery, jaundice, hypoglycemia, low APGAR scores and convulsions
- Whether these effects are due to the underlying illness or treatment is not known

Newer Antidepressants and Birth Outcomes

Generic name	Brand name	Usual dose
Bupropion	(Wellbutrin®)	150 mg
Citalopram	(Celexa®)	40 mg
Fluoxetine	(Prozac®)	20 mg
Fluvoxamine	(Luvox®)	50 mg
Mirtazapine	(Remeron®)	30 mg
Nefazadone	(Serzone®)	150 mg
Paroxetine	(Paxil®)	20 mg
Sertraline	(Zoloft®)	50 mg
Venlafaxine	(Effexor®)	75 mg

Are Newer Antidepressants Associated with Malformations?

Risk of ANY Malformation with Antidepressant Exposure

	# Exposed	% Malformation		P or RR
		Exposed	Not Exposed	
Kallen 2007	6481	4.7%	4.1%	RR=0.89
Malm 2005	1782	4.2%	3.5%	P= 0.6
Maschi 2007	200	1%	1%	NS
Wogelius 2006	1051	6.8%	3%	RR=1.84 (1.25,2.71)

Risk of Cardiac Malformations with Antidepressant Exposure

	# Exposed	% Malformation		P or RR
		Exposed	Not Exposed	
Kallen 2007*	6481	1.2%	1.3%	RR=0.97
Kallen 2007 (paroxetine)	815	2.1%	1.3%	RR=2.22 (1.29, 3.82)
Diav-Citrin (paroxetine)	1325	1.9%	0.6%	RR=3.46 (1.06,11.2
Wogelius 2006	1051	1.4%	1%	NS

*only significant finding was cystic kidney;

Risk of Malformations with SSRI Exposure: Case Cohort

- Alwan 2007 NEJM (9622 cases, 4092 controls): associations between any SSRI & anencephaly, craniosynostosis, omphalocele
- Louik 2007 NEJM (9849 cases, 5860 controls): associations between sertraline and omphalocele & septal defects; paroxetine and RV outflow obstructions
- Berard 2006 Birth Defects (101 cases, 1302 controls):ns; 24 cases of cardiac defects; were associated with paroxetine > 25 mgs

A Comparison of Serotonin Reuptake Inhibitors & Bupropion to All Antidepressants Using Two Prescription Databases: All Malformations

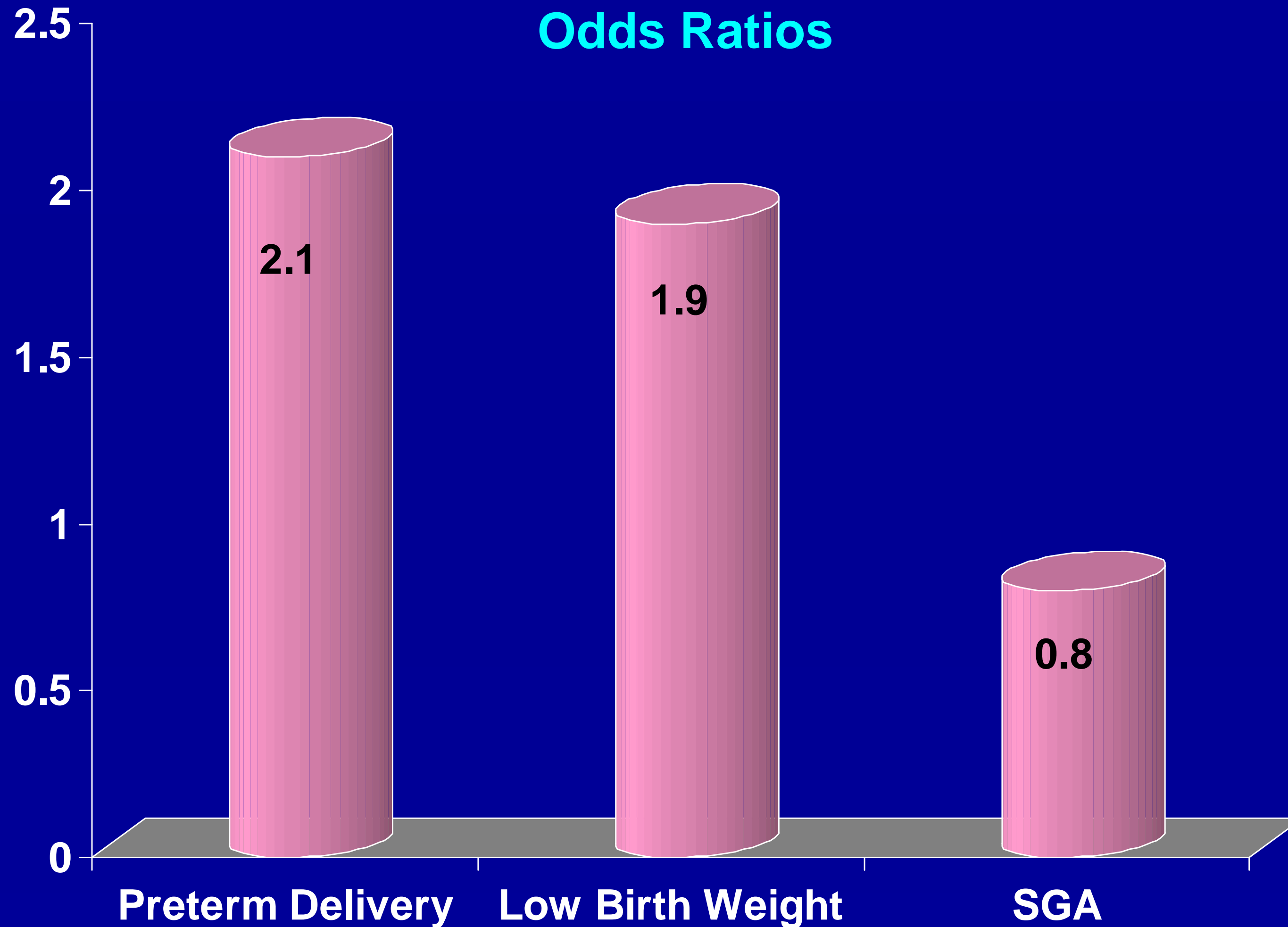
Medication	Prevalence Exposed	OR (95% CI)
Paroxetine	3.8	1.82 (1.17, 2.82)
Fluoxetine	2.1	0.84 (0.53, 1.33)
Sertraline	1.9	0.78 (0.46,1.34)
Citalopram	2.3	1.05 (0.48, 2.28)
Bupropion	1.9	0.75 (0.41, 1.38)

N=5956 infants; Source: GSK website clinical trial section, 3/2006; databases from United Health Care; women taking other teratogenic meds were excluded

Summary: Risk of Malformations with Newer Antidepresants

- Data regarding associations between newer antidepressants and malformations are inconsistent
- The strongest support is for an association between paroxetine and cardiac defects
- This may be dose related & most likely to cause ASDs and VSDs

Serotonin Reuptake Inhibitors and Perinatal Outcomes



Kallen, Archives of Pediatric and Adolescent Medicine, 158, 312-316, 2004

Persistent Pulmonary Hypertension in Offspring Exposed to Serotonin Reuptake Inhibitors in Utero

- Case control study
  - 377 mothers of infants with PPHtn
  - 836 matched controls
- Results
  - 14 infants with PPHtn took SRI after 20 weeks gestation
  - 6 control infants were SRI exposed
  - OR=6.1 (95% CI 2.2-16.8)
  - No increased in risk with exposure prior to 20 weeks or from exposure to antidepressants in general
  - Estimated absolute risk is 6-12 per thousand

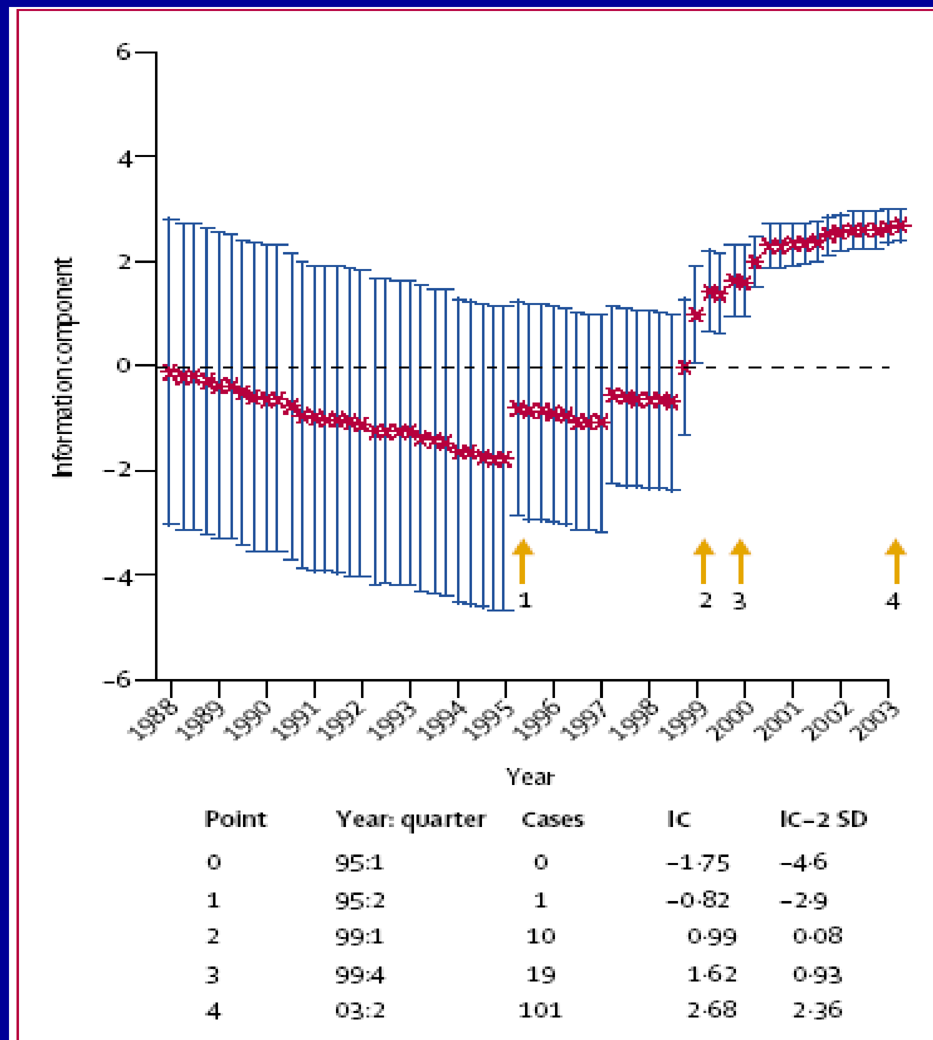
Chambers et al, NEJM, ,354, 579-588, 2006

Antidepressants Can Affect Newborns, Study Finds

- A new analysis of World Health Organization medical records has found that infants whose mothers take the drugs while pregnant may suffer withdrawal symptoms shortly after they are born. The study challenges the assurances that many doctors have long given pregnant women with depression that taking the drugs would not affect their babies.

http://www.nytimes.com/2005/02/03/health/04depresscnd.html
Sanz EJ, et al. *Lancet*. 2005;365:482-7.

Neonatal Withdrawal after Maternal SRI Use



Point	Year: quarter	Cases	IC	IC–2 SD
0	95:1	0	–1·75	–4·6
1	95:2	1	–0·82	–2·9
2	99:1	10	0·99	0·08
3	99:4	19	1·62	0·93
4	03:2	101	2·68	2·36

Information component is a log measure of association based upon Bayesian confidence Propogation neural network. This is used to identify ADRS that are more frequent than expected

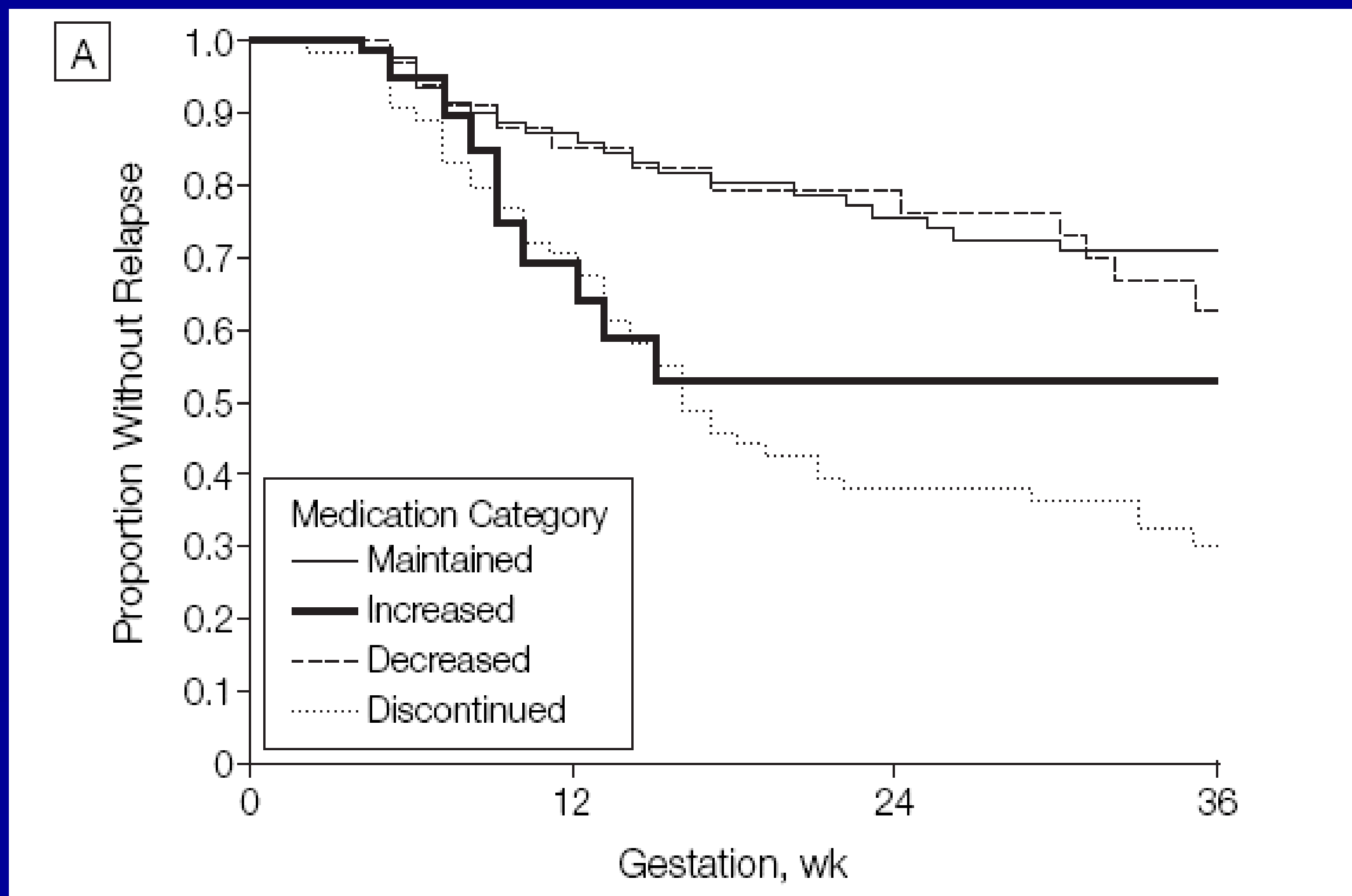
Sanz et al, Lancet, Vol 365; pp 482-487, 2005

Summary: Antidepressants and Perinatal Effects

- There is evidence to suggest associations between antidepressants and various perinatal effects
  - LBW and SGA as well as decreased birth size
  - PTD and shorter gestations
  - "Withdrawal" or "toxic" effects

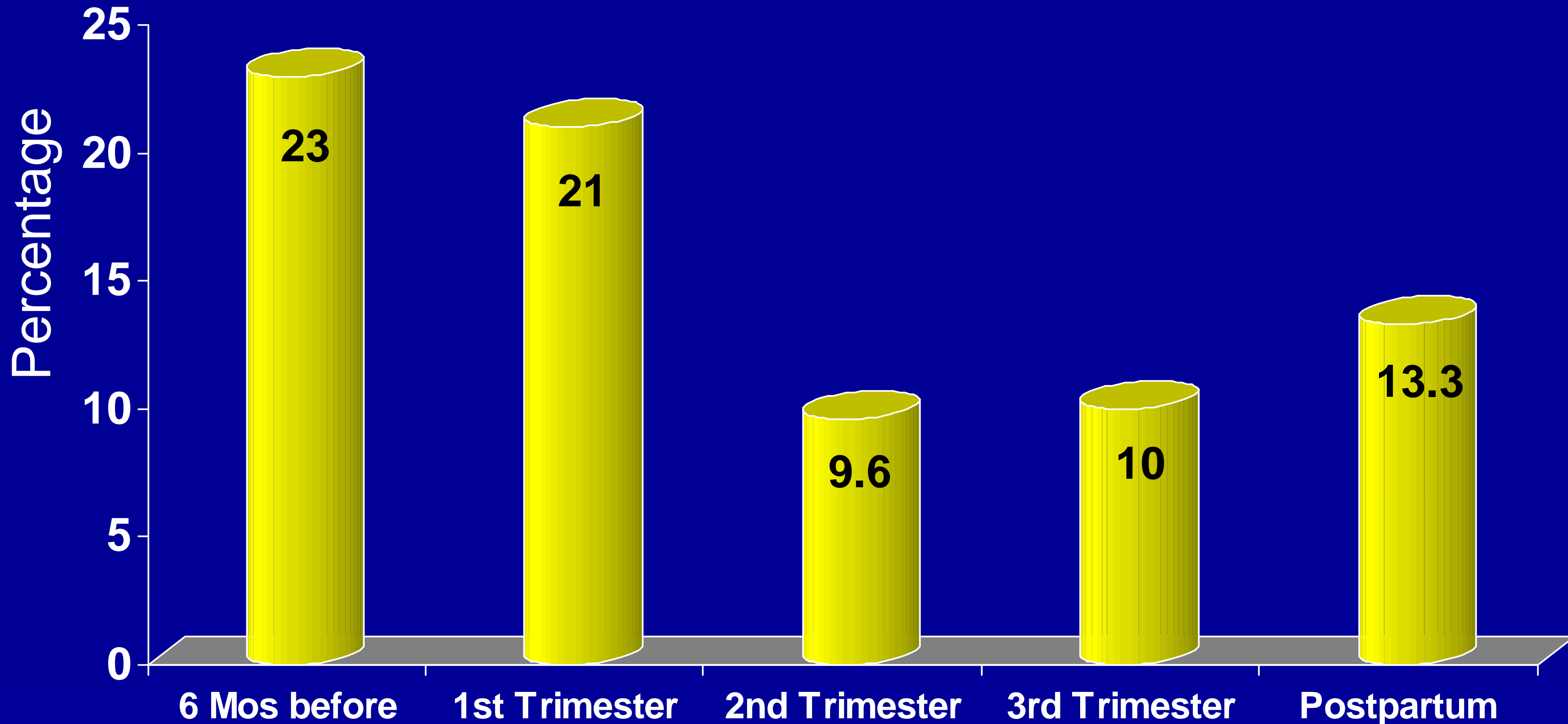
But some women may need medication…

Likelihood of Relapse in Women Recently In Episode of Major Depressive Disorder (n=201)

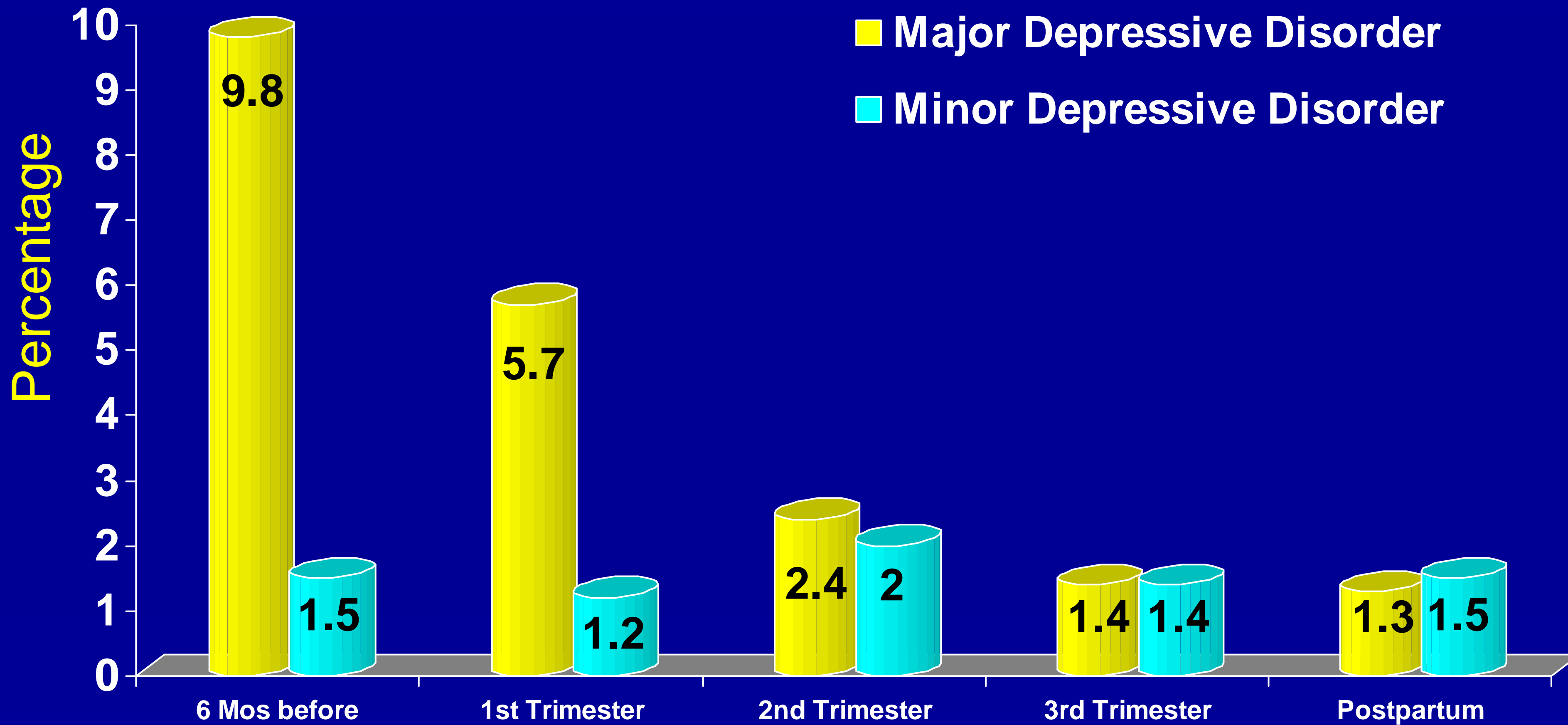


Cohen et al, JAMA, 2006, Vol 295, 499-507

Antidepressant Use Among Women Participating in the Yale Pink and Blue Study (n=2086)



Course of Depression in the Yale Pink and Blue Study (n=2086)



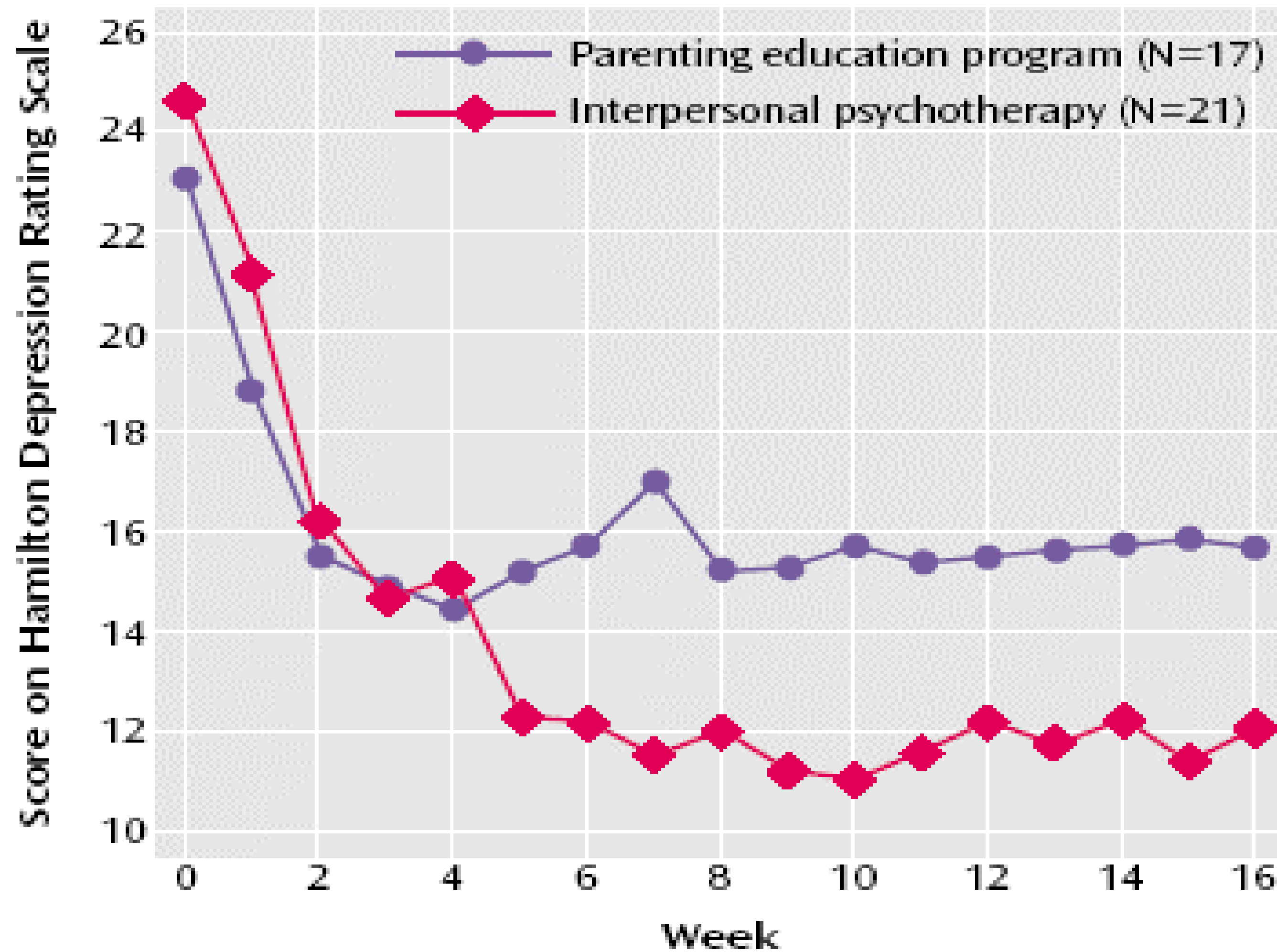
How Can I Carry a Pregnancy
When I am so Depressed?
Antidepressants Can Affect
My Newborn, Study Finds

Treating Unipolar Depression During Pregnancy

Encourage

- Regular prenatal care
- Smoking cessation
- Prenatal vitamins
- Higher folate doses (3-5 mgs) for women on anti-epileptic drugs
- Avoiding alcohol and other hazardous substances

Psychotherapy is effective for Depression During Pregnancy



Spinelli and Endicott, Am J Psychiatry, 2003; 160:555-562

Summary: Managing Depression During Pregnancy

- If appropriate use psychotherapy
- Empirically validated therapies should be recommended (cognitive-behavioral therapy or interpersonal psychotherapy)

Summary: Managing Depression During Pregnancy

- If psychotherapy alone is ineffective the risks of antidepressant treatment must be balanced with the morbidity associated with illness
- Avoid polypharmacy

THE YALE PINK
AND BLUE STUDY

For more information on Yale's study of depression and antidepressant treatment in pregnancy, please contact us at (203) 764-6621
or visit us at
www.Researchforher.com

The Perinatal Depression Provider Consultation Line

- A partnership of DPH, United Way of Connecticut/2-1-1, Yale School of Medicine's Perinatal Depression Research Program
- A non-crisis telephone line for providers with clinical inquiries about depression in pregnant and postpartum women
- Consultants provide information regarding symptoms of perinatal depression, treatment possibilities, and available community resources.

How Do I Access the Perinatal Depression Provider Consultation Line?

- Dial 2-1-1 and Press 2, then 4 off the menu tree

or

- Call Child Development Infoline directly at 1-800-505-7000

- Monday-Friday 8am-6pm (3/08-10/08)

Frequently Asked Questions

- ***Can I have my patient call?***

  The provider consultation line is a professional service for healthcare providers

- ***What can I expect when I call?***

  Infoline 2-1-1 staff will ask and answer initial questions and depending upon concerns will transfer call to Yale for further assistance. F/u call in 2 weeks

- ***Who should call?***

  Any physical or behavioral healthcare provider requesting clinical consultation about perinatal depression