

PSYCHIATRIC COMPLICATIONS OF PREGNANCY

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OVERVIEW

- MISINFORMATION FROM DOCTORS ...
BUY A DRESS, YOU'LL FEEL BETTER
- MUCH NEEDS TO BE LEARNED
YET MUCH IS NOW KNOWN
- COMMON
YET GENERALLY UNTREATED

COMPLEX ISSUE

■ EVALUATION AND TREATMENT PLANNING FOCUC ON

- MOTHER
- FETUS / NEWBORN / CHILD
- FAMILY / SUPPORT SYSTEM

RISK : BENEFIT RATIO

- RISKS AND BENEFITS OF TREATMENT
 - CONSIDER THE MOTHER AND OFFSPRING
- RISKS AND BENEFITS OF NON-TREATMENT MUST ALSO
 - CONSIDER THE MOTHER AND OFFSPRING

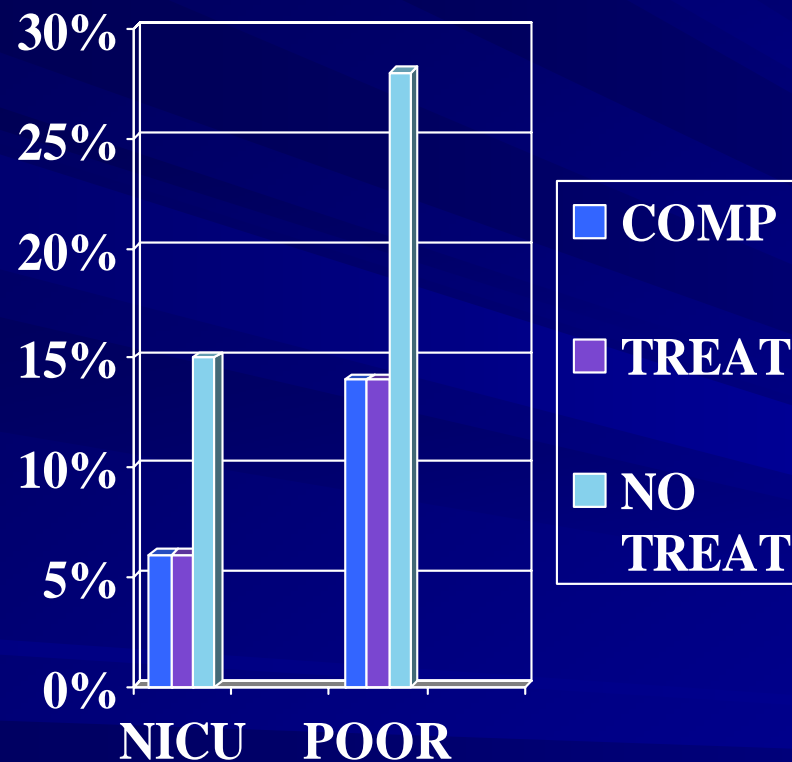
WE'VE COME A LONG WAY

PREVENTION AND TREATMENT
ARE EFFECTIVE

RESOURCES ARE EXPANDING

PPD IS OUT OF THE CLOSET

IMPACT ON NEONATES OF UNTREATED ANXIETY OR DEPRESSION



■ VIGUERA & COHEN

■ 540 OB RECORDS

■ RETROSPECTIVE

■ POOR OUTCOME:

– APGAR < 5

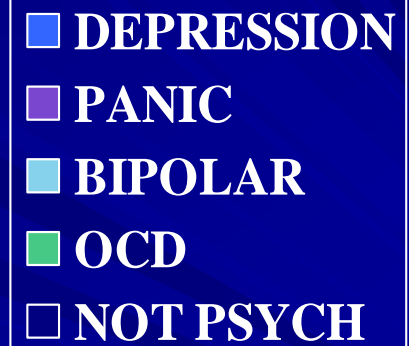
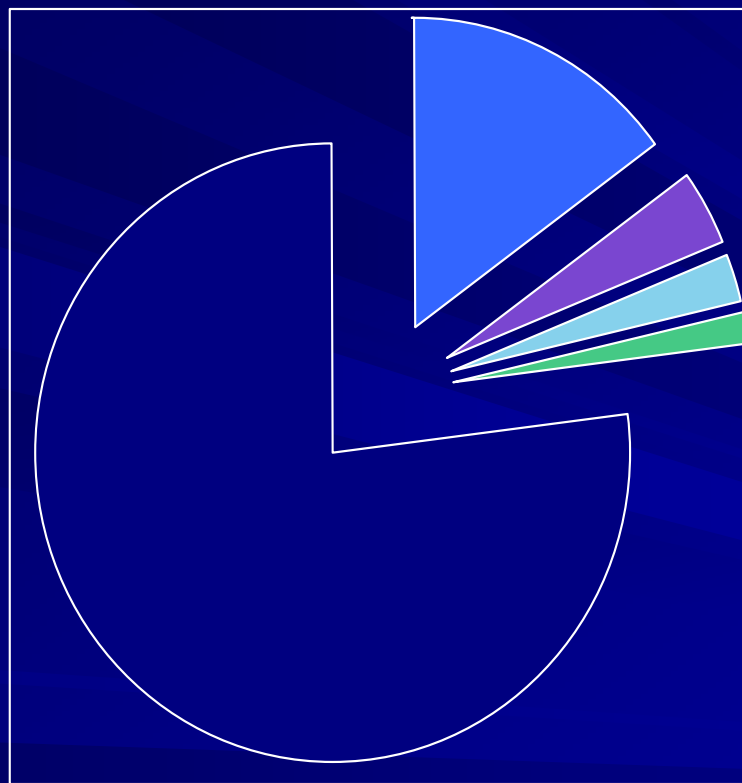
– WT < 2500 gm

– GEST < 37 wk

– NICU

– DEATH

POSTPARTUM PSYCHIATRIC ILLNESS



INCIDENCE OF POSTPARTUM DEPRESSION

■ MDE

- General Population 15 %
- Prior MDE 30 – 40 %
- Prior PPD 60 – 70 %

Risk Rates for PP Recurrence

Depression	60 – 70 %
Panic	100 %
Bipolar	90 – 100 %
OCD	100 %

Natural Course of Postpartum Depression

- WITHOUT TREATMENT, ONE YEAR
AFTER DIAGNOSIS,
- 40% REMAINED MARKEDLY ILL.

PRIMARY RISK FACTORS

- PRIOR EPISODE OF DEPRESSION
- FAMILY HISTORY OF DEPRESSION
- TEEN MOTHER
- BINGE DRINKING / NICOTINE USE DURING PREGNANCY
- PHYSICAL ABUSE DURING PREGNANCY

OTHER PREDICTIVE FACTORS

■ PERCEIVED HIGH LEVEL OF STRESS

- INSOMNIA
- FATIGUE
- SENSORY AROUSAL
- DIFFICULT INFANT TEMPERAMENT
- CHILDCARE DEMANDS

SYMPTOM INTENSITY INCREASES WITH

- LOW CONFIDENCE IN PARENTING SKILLS
- CHANGES IN EMOTIONAL RELATIONSHIPS
- ISOLATION
- IDENTITY TRANSFORMATION
- SIGNIFICANT ANXIETY DURING PREGNANCY

PSYCHIATRIC SYMPTOMS DURING PREGNANCY

- FATIGUE

- INSOMNIA

- ANXIETY

PSYCHIATRIC SYMPTOMS DURING POSTPARTUM

- HYPER AROUSAL, ANXIETY
- MAGNIFIED HEARING SENSITIVITY
- STARTLE RESPONSE
- FAST HEART RATE
- SHALLOW, RAPID BREATHING
- “SCARY THOUGHTS ABOUT THE BABY”

OTHER COMMON PSYCHIATRIC SYMPTOMS DURING POSTPARTUM

FATIGUE, LOSS OF CAPACITY TO SLEEP
POOR SHORT TERM MEMORY
REDUCED MENTAL FOCUS
POOR CONCENTRATION
EXCESSIVE OR UNEXPLAINED
TEARFULNESS

ESSENTIALS OF TREATMENT

- RECOGNITION AND DIAGNOSIS
- EDUCATION OF PATIENT AND FAMILY
- MEDICINE, AS APPROPRIATE
- NIGHT SLEEP, TWO BLOCKS OF
FOURS EACH
- 4 PM BREAK FOR ONE HOUR

FOUR SCREENING QUESTIONS FOR MOTHERS

- DO YOU HAVE TROUBLE SLEEPING,
EVEN WHEN YOU GET THE
OPPORTUNITY?
- HAVE YOU BEEN FEELING
OVERWHELMED?
- ARE YOU ENJOYING YOUR BABY?
- ARE YOU WORRYING OR CRYING A
LOT?

Maternal Depression and Infant Salivary Cortisol

■ Prospective Study

19 Case Dyads, 6 months postpartum

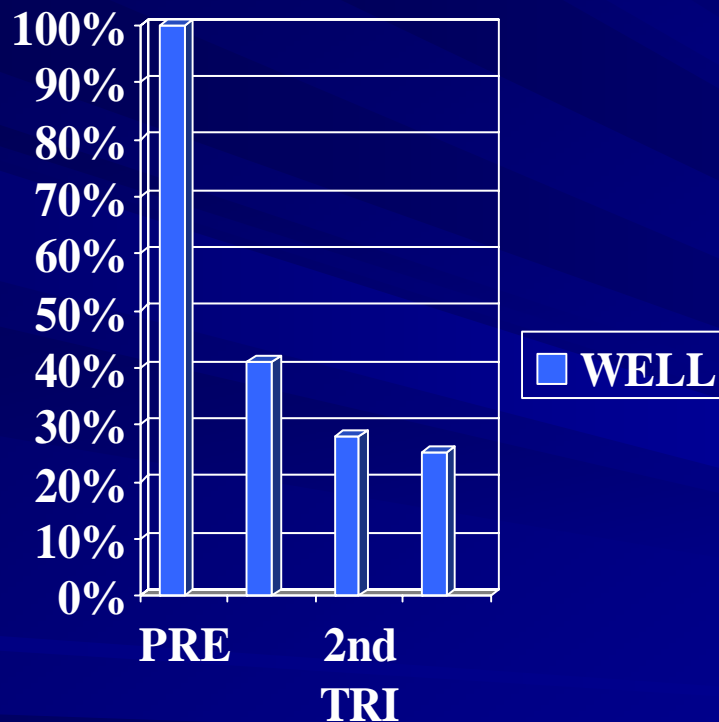
11 Control Dyads

	Cortisol	
Baseline	No Difference	
Stressed	Hyper reactive	$p = 0.002$

EDUCATION OF FAMILY

- MOTHER FEELS SHAME, GUILT, HELPLESSNESS AND HOPELESSNESS
- HUSBAND FEARS 'HE WILL NEVER GET HIS WIFE BACK.'
- EXPECTATIONS OF EACH OTHER NEED TO BE CLARIFIED AND REALISTIC
- PHYSICAL AND EMOTIONAL SUPPORT FROM OTHERS IS NEEDED

RELAPSE OF DEPRESSION AFTER DISCONTINUATION



- EUTHYMIC ON MEDICINE AT START OF PREGNANCY
- MEDICINE STOPPED WHEN PREGNANT
- COHEN 1999

Omega-3 Fatty Acid and Postpartum Depression

- 23 countries N = 14,532 subjects
- Fish consumption has a direct correlation with the concentration of omega-3 fatty acid in breast milk; and an inverse correlation with postpartum depression
- South Africa 8# 24%
- USA 48# 11%
- Singapore 81# 0.5%
- Caution: mercury and pesticides
 - Oct 2001 J Affective Disorders

Prophylactic Estrogen in Recurrent Postpartum Affective Disorder

- Hx Puerperal Psychosis N = 7
- Hx Puerperal MDE N = 4
- Negative Hx for nonpuerperal affective disorder
- Postpartum Recurrence Rate 1 / 11 (9%)

Sichel Biol Psychiatry 1995

TRICYCLIC ANTIDEPRESSANTS

- NO TERATOGENESIS
- TRICYCLICS THAT ARE COMPATIBLE WITH BREASTFEEDING INCLUDE:
 - NORTRIPTYLINE
 - DESIPRAMINE
 - IMIPRAMINE
 - AMITRYPTILINE
 - BUT, NOT DOXEPINE (long T 1/2; accumulates to low, but detectable amounts)

Antidepressants and Birth Defects

■ No increased risk for major birth defects

– Prozac	2500	3%
– Paxil	92	0%
– Effexor	125	2%
– Zoloft	187	2%

However, Prozac vs Control: Increased
Minor Malformations 15 % vs 6 %

Fluoxetine and Pregnancy Prospective Study N = 228 (254 controls)

	Control	Fluoxetine	p
% Loss	10.5	9.1	NS
Major	5.5	4.0	NS
3 Minor	15.5	6.5	0.03

C Chambers 1996

Fluoxetine and Complications

Prospective Study

A : 101 Only 1st and 2nd Trimester Exposure

B : 73 Only 3rd Trimester Exposure

Relative Risk

Event	A	B
Premature	1	4.8
NICU	1	2.6
Poor Adapt	1	8.7

SSRI and PREGNANCY OUTCOME

■ N = 267	CONTROL = 267	
■ PAROXETINE, SERTRALINE, FLUVOXAMINE		
■ MAJOR DEFECT	4.1%	3.8%
■ BIRTH WEIGHT	3439 gm	3445 gm
■ MISCARRIAGE	NS	
■ STILL BIRTH	NS	
■ PREMATURITY	NS	

Kulin JAMA 1998

Neonatal Withdrawal Syndrome and SSRI's

- Report of 5 cases with 3rd trimester exposure:
- Paroxetine N = 3 10 to 40 mg/day
- Citalopram N = 1 30 mg/day
- Fluoxetine N = 1 20 mg/day
- Irritability, constant crying, shivering, increased tonus, eating and sleeping difficulties and convulsions. 4 of 5 treated with chlorpromazine.
- Onset a few days after birth, duration up to one month
Nordeng Acta Paediatr 2001

SSRI DOSE CHANGES DURING PREGNANCY

- NATURALISTIC STUDY N = 34
 - SSRI MONOTHERAPY
 - PRIOR TO 28 WK GESTATION
 - DOSE CHANGES RELATED TO BDI
-
- 22 / 34 (65%) required a dose
increase at 27 (+/- 7) wks gestation

Response Patterns in Postpartum and Non-Postpartum Depression

PPD	N = 26
Other Depression	N = 25

3 Week Response (CGI of 1 or 2)

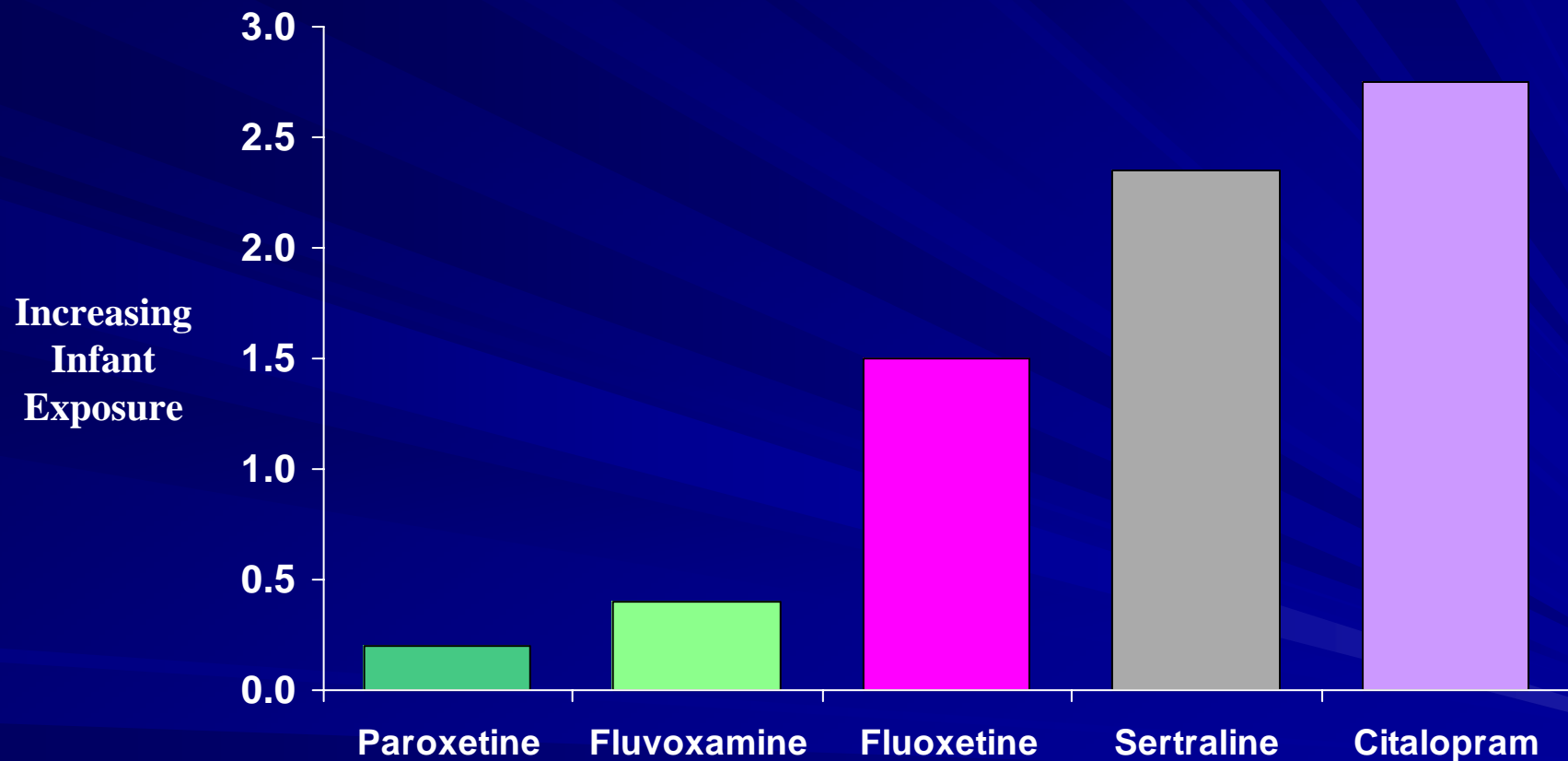
PPD	36%
Non PPD	75%

Hendrick Depress Anxiety 2000

Venlafaxine and PPD

- N = 15 (within first 3 months Postpartum)
- Prospective, Flexible-dose, Open Study
- Mean Dose 162.5 mg / day
- Remission in 12 / 15 (80%)
 - HAM-D score \leq 7
 - Or CGI score \leq 2
 - Cohen J Clin Psychiatry 2001

Milk/Plasma Ratios In Mothers Treated With SSRIs



Jensen et al. *Ther Drug Monit.* 1997;19:236.

Suri et al. *Medscape Women's Health.* 1998;3:1.

Fluoxetine and Breastfeeding

- N = 19 mother – infant dyads (inc 1 twin)
- Dose = 10 – 60 mg / day
including 3rd trimester for all but 2 dyads
- Fluoxetine 6 / 19 (30%) 1 – 84 ng/ml
- Norfluoxetine 17 / 19 (85%) 1 – 265 ng/ml

– Hendrick, Stowe Biol Psychiatry 2001

CHILDHOOD IMPACT OF UNTREATED POSTNATAL ANXIETY OR DEPRESSION

KINDERGARTEN BLINDED TEACHERS

GIRLS PROSOCIAL

BOYS DISRUPTIVE

BOTH RESTRICTED IMAGINATIVE PLAY

– Sinclair D Doctoral Thesis (UBC – 1997)

BREASTFEEDING AND ANTIDEPRESSANTS

■ SSRI'S : Sample N>100

– PAXIL Not Detected to 0.1 ng/ml

– ZOLOFT Occ Detected to 2.0 ng/ml

– Misri J Clin Psychiatry 2000

– Stowe Am J Psychiatry 1997

Breastfeeding and Other Antidepressants

■ Small Sample Reports

- a) WELLBUTRIN (N=1) ND (limit unknown)
- b) LUVOX (N=4) ND to 2.5 ng/ml
- c) CELEXA (N=7) +D to 13 ng/ml
- d) EFFEXOR (N=6) +D to 38 mcg/ml

a Hendrick Br J Psychiatry 2001

b Rampono Br J Clin Pharmacol 2000

c Schmidt Biol Psychiatry 2000

d Ilett Br J Clin Pharmacol 2002

PREEXISTING PANIC DISORDER AND PREGNANCY

N	Worse	No Change	Improved	
22			64%	VILLEPONTEAUX 1992
38	20%			COHEN 1994
45		49%		WISNER 1996
67	33 %	23%	43%	NORTHCOTT 1994
215	38%		41%	Hertzberg 1999

PREEXISTING PANIC AND POSTPARTUM

■ N	WORSE	NO CHANGE	BETTER		
40	35%	58%	7%	COHEN	1994
■ 67	63%			NORTHCOTT	1994
■ 45		49%		WISNER	1996
■ 215	38%			HERTZBERG	1999

POSTPARTUM PANIC AND THIRD TRIMESTER BZD

NATURALISTIC STUDY (N = 40) OF
PREEXISTING PANIC AND POSTPARTUM
EXACERBATION

THIRD TRIMESTER PHARMACOTHERAPY
REDUCED POSTPARTUM WORSENING
 $P < 0.0001$

COHEN 1994

Neonatal Outcome and Clonazepam in Pregnancy

N = 38 with HX of Panic Disorder

No Occurrence of:

- Orofacial Anomalies
- Neonatal Apnea
- BZD Withdrawal Syndrome
- Temperature or other Autonomic Dysregulation

One case each of Hypotonia and Respiratory Distress
when also exposed to imipramine, among two infants
born to the same mother

Weinstock Psychother Psychosom 2001

BZD and Congenital Abnormalities

- Matched case-control teratologic study

■ Sample	N	BZD Exposure
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■ No Defects	38,151	75 (0.20%)
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■ Defects	22,865	57 (0.25%)
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Neurodevelopment and Prenatal BZD Exposure

- Prospective Study of 17 children at 6, 10 and 18 months of age, with psychotropic fetal exposure to only BZD. Control = 29 without exposure.
- Retarded Gross Motor at 6 and 10 months, nearly normal at 18 months
- Impaired Fine Motor at each data point (Delayed Pincer Grasp) Laegreid Neuropediatrics 1992



ANXIOLYTICS

■ CLONAZEPINE

- 1 OF 14 STUDIES LINKED CLEFT ABNORMALITIES IN UP TO 7/1,000 COMPARED TO 6/10,000 IN GENERAL POPULATION
- LONG $T_{1/2}$, LOW SEDATION
- 0.25 TO 1 mg hs IS VERY EFFECTIVE FOR PANIC, ANXIETY AND INSOMNIA
- COMPATIBLE WITH BREASTFEEDING

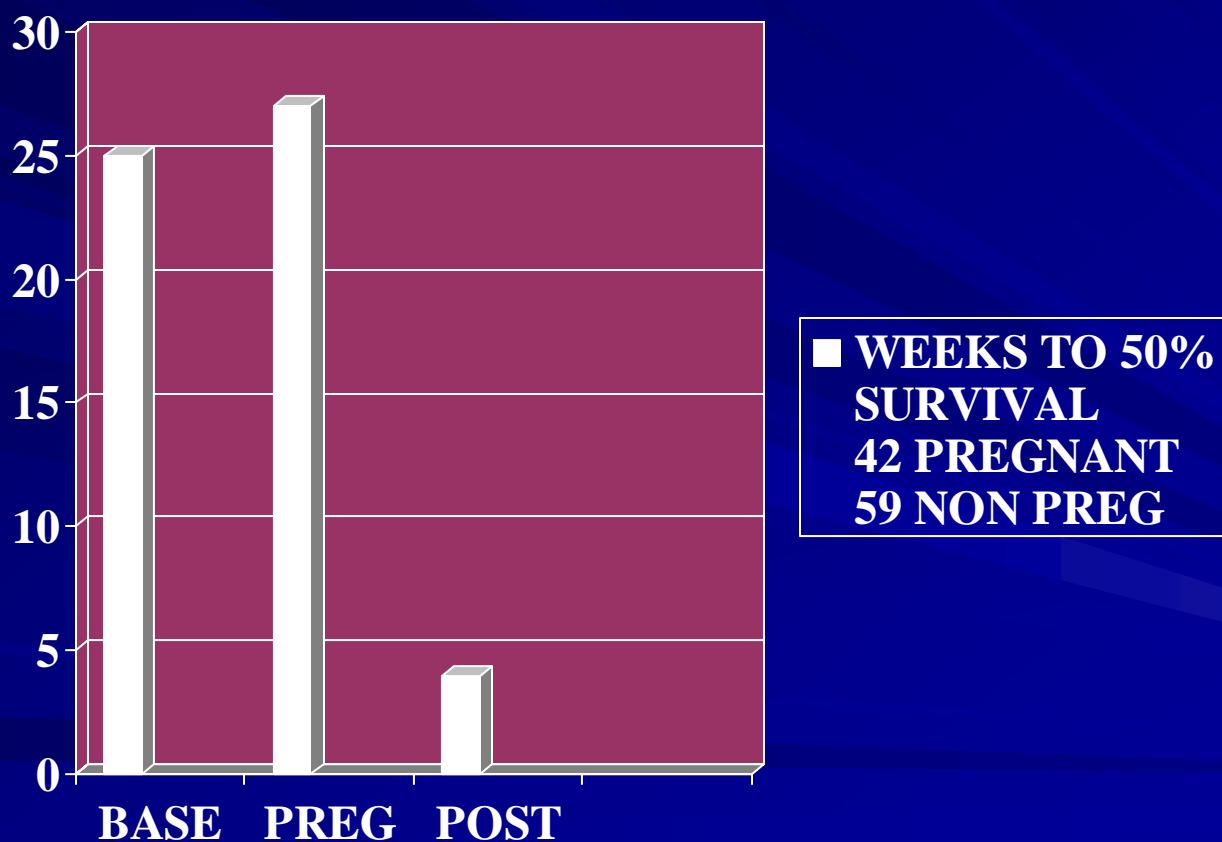
SLEEP AIDES

■ IF BREASTFEEDING

- CLONAZEPAM 0.25 - 1 mg hs
- LORAZEPAM 0.25 - 1 mg hs
- TRAZODONE 12.5 - 75 mg hs

- Milk / plasma ratio of 0.142 (+/- 0.045) in 6 women
 - Verbeeck br J Clin Pharmacol 1986

LITHIUM DISCONTINUATION IN PREGNANCY VS CONTROL WEEKS TO RELAPSE VIGUERA AmJPsychiatry 2000



Estradiol and Postpartum Psychosis

- Open Pilot Study N = 10
- Active Symptoms mean BPRS 78
- Baseline Estradiol 49.5 pmol/L
- 17 beta-estradiol 1 mg tid – qid to establish estradiol concentration of follicular phase
- During week one, BPRS decreased to 18.8, $p < 0.001$ Ahokas J Clin Psychiatry 2000

LITHIUM and CARDIAC DEVELOPMENT

4 Case-control Studies of Ebstein's Anomaly

N = 25, 34, 59 and 89 (total = 207)

No occurrences of lithium exposure

Ebstein's Anomaly Rates

1/2,000 ON LITHIUM (ESTIMATE)

1/20,000 GENERAL POPULATION

CARDIAC ULTRASOUND AT 20 WEEKS

Cohen JAMA 1994

BIPOLAR PROPHYLAXIS IN POSTPARTUM

- N = 27
- OPEN DESIGN
- FOLLOWED 3 MONTHS POSTPARTUM
- RELAPSE RATES

WITH PROPHYLAXIS	1 OF 14
NO PROPHYLAXIS	8 OF 13

Cohen Am J Psychiatry 1995

1st TRIMESTER LITHIUM and MAJOR MALFORMATIONS

- PROSPECTIVE N = 138 exposed
- LITHIUM 2.8%
- CONTROL 2.4%
- 1 CASE OF Ebstein's Anomaly in exposed
- GESTATIONAL AGE n.s.
- HIGHER BIRTHWEIGHT 3383 vs 3475
 - p = 0.02 Jacobson Lancet 1992

ANTICONVULSANTS AND BIRTH DEFECTS

- OFFSPRING OF EPILEPTIC MOTHERS HAVE 15 FOLD HIGHER SPINA BIFIDA
 - WITH CARBAMAZEPIN: 0.5 - 1%
 - WITH VALPROIC ACID: 1 - 5%
- DOCUMENT BIRTH CONTROL AND DISCUSSION OF FETAL RISKS
- MAY BE USED 10 WEEKS AFTER CONCEPTION
- COMPATIBLE WITH BREASTFEEDING ?

Lamotrigine Monotherapy

1st Trimester Exposure

Prospective UK Registry 9/92 – 3/02 (Morrow JI)

7 / 260 = 2.7% No Clustering of Defects	Defects	No Defects
Live Birth	6	253
Lost Pregnancy	1	23

Lamotrigine Monotherapy

1st Trimester Exposure

GlaxoSmithKline Prospective Registry through 3 / 2002

$4 / 200 = 2\%$ No Clustering	Defects	No Defects
Live Birth	4	196
Lost Pregnancy	0	15 Induced AB 8 Spontaneous 1 Fetal Death

OBSESSIVE COMPULSIVE DISORDER (OCD)

- NEARLY ALL PREMORBID OCD WILL RELAPSE POSTPARTUM, WITHOUT TREATMENT
- OCD OFTEN BEGINS IN THE THIRD OR 'FOURTH' TRIMESTER
- ALL POSTPARTUM PSYCHIATRIC DISORDERS INCLUDE 'SCARY THOUGHTS ABOUT THE BABY.'

OLANZEPINE and HUMAN PLACENTA

- 'NORMAL-TERM PLACENTA PERFUSED SINGLE COTYLEDON SYSTEM'
- 5 – 14 % OF LABELLED OLANZEPINE CROSSES FROM THE MATERNAL TO THE FETAL COMPARTMENTS IN 4 HOURS

■ Schenker Clin Exp Pharmacol Physiol 1999

Olanzapine-exposed Pregnancies

- N = 23 Lilly Worldwide P S Database
- Spontaneous abortion 13%
- Stillbirth 5%
- Major Defects 0%
- Prematurity 5%

SUPPORTIVE RESOURCES FOR THE MOTHER

- DEPRESSION AFTER DELIVERY
 - NON-PROFIT
 - FREE SERVICES
 - SUPPORT GROUPS
 - QUARTERLY NEWSLETTER
 - HOTLINE 206 283-9278