PSYCHIATRIC COMPLICATIONS OF PREGNANCY

REX GENTRY, MD
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 PLANING FOCUS 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

- DEPRESSION
- PANIC
- BIPOLAR
- OCD
- NOT PSYCH
INCIDENCE OF POSTPARTUM DEPRESSION

MDE

- General Population 15 %
- Prior MDE 30 – 40 %
- Prior PPD 60 – 70 %
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Risk Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>60 – 70 %</td>
</tr>
<tr>
<td>Panic</td>
<td>100 %</td>
</tr>
<tr>
<td>Bipolar</td>
<td>90 – 100 %</td>
</tr>
<tr>
<td>OCD</td>
<td>100 %</td>
</tr>
</tbody>
</table>
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

Graph showing the percentage of individuals well before and after discontinuing treatment.
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
  - AMITRYPTILLINE
  - 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)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Fluoxetine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Loss</td>
<td>10.5</td>
<td>9.1</td>
<td>NS</td>
</tr>
<tr>
<td>Major</td>
<td>5.5</td>
<td>4.0</td>
<td>NS</td>
</tr>
<tr>
<td>3 Minor</td>
<td>15.5</td>
<td>6.5</td>
<td>0.03</td>
</tr>
</tbody>
</table>

C Chambers 1996
Fluoxetine and Complications
Prospective Study

A : 101  Only 1\textsuperscript{st} and 2\textsuperscript{nd} Trimester Exposure
B : 73  Only 3\textsuperscript{rd} Trimester Exposure

Relative Risk

<table>
<thead>
<tr>
<th>Event</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature</td>
<td>1</td>
<td>4.8</td>
</tr>
<tr>
<td>NICU</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Poor Adapt</td>
<td>1</td>
<td>8.7</td>
</tr>
<tr>
<td>Outcome</td>
<td>Paroxetine, Sertraline</td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Major Defect</td>
<td>4.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Birth Weight</td>
<td>3439 gm</td>
<td>3445 gm</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Still Birth</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Prematurity</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

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 ≤ 7
  - Or CGI score ≤ 2
    - Cohen J Clin Psychiatry 2001
Milk/Plasma Ratios In Mothers Treated With SSRIs


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

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 Pharmacl 2000
c  Schmidt Biol Psychiatry 2000
d  Ilett Br J Clin Pharmacol 2002
## PREEXISTING PANIC DISORDER AND PREGNANCY

<table>
<thead>
<tr>
<th>N</th>
<th>Worse</th>
<th>No Change</th>
<th>Improved</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td></td>
<td></td>
<td>64%</td>
<td>VILLEPONTEAUX 1992</td>
</tr>
<tr>
<td>38</td>
<td>20%</td>
<td></td>
<td></td>
<td>COHEN 1994</td>
</tr>
<tr>
<td>45</td>
<td></td>
<td>49%</td>
<td></td>
<td>WISNER 1996</td>
</tr>
<tr>
<td>67</td>
<td>33%</td>
<td>23%</td>
<td>43%</td>
<td>NORTHCOTT 1994</td>
</tr>
<tr>
<td>215</td>
<td>38%</td>
<td></td>
<td>41%</td>
<td>Hertzberg 1999</td>
</tr>
</tbody>
</table>
**PREEXISTING PANIC AND POSTPARTUM**

<table>
<thead>
<tr>
<th>N</th>
<th>WORSE</th>
<th>NO CHANGE</th>
<th>BETTER</th>
<th>Study/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>35%</td>
<td>58%</td>
<td>7%</td>
<td>COHEN 1994</td>
</tr>
<tr>
<td>67</td>
<td>63%</td>
<td></td>
<td></td>
<td>NORTHCOTT 1994</td>
</tr>
<tr>
<td>45</td>
<td></td>
<td>49%</td>
<td></td>
<td>WISNER 1996</td>
</tr>
<tr>
<td>215</td>
<td>38%</td>
<td></td>
<td></td>
<td>HERTZBERG 1999</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Sample</th>
<th>N</th>
<th>BZD Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Defects</td>
<td>38,151</td>
<td>75 (0.20%)</td>
</tr>
<tr>
<td>Defects</td>
<td>22,865</td>
<td>57 (0.25%)</td>
</tr>
</tbody>
</table>
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

WEEKS TO 50% SURVIVAL
42 PREGNANT
59 NON PREG
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)

<table>
<thead>
<tr>
<th></th>
<th>Defects</th>
<th>No Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>7 / 260 = 2.7%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Clustering of</td>
<td>Defects</td>
<td>No Defects</td>
</tr>
<tr>
<td>Defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live Birth</td>
<td>6</td>
<td>253</td>
</tr>
<tr>
<td>Lost Pregnancy</td>
<td>1</td>
<td>23</td>
</tr>
</tbody>
</table>
# Lamotrigine Monotherapy

## 1st Trimester Exposure

GlaxoSmithKline Prospective Registry through 3 / 2002

<table>
<thead>
<tr>
<th></th>
<th>Defects</th>
<th>No Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Birth</td>
<td>4</td>
<td>196</td>
</tr>
<tr>
<td>Lost Pregnancy</td>
<td>0</td>
<td>15 Induced AB, 8 Spontaneous, 1 Fetal Death</td>
</tr>
</tbody>
</table>

4 / 200 = 2% No Clustering
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
Olanzepine-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