Preparing for Unplanned Pregnancies in Your Practice: 
What You Need to Know

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When Do Disorders Start?

- “Mental illnesses are the chronic diseases of the young”
- One-half of all diagnoses presented by age 14
- Three-quarters by age 24


What percent of pregnancies globally are unplanned annually?

1. 10%
2. 20%
3. 30%
4. 40% ✓
5. 50%


What percent of pregnancies in the United States are unplanned annually?

1. 10%
2. 20%
3. 30%
4. 40%
5. 50% ✓


Treating Women of Childbearing Potential

- 49% of pregnancies in the United States are unintended
- 80% of teen pregnancies unintended
- 82% of US women have had a child by age 40


Doctor, please call me back right away. I just found out I am pregnant and I don’t know what to do about my medication.
**Doctor, I am pregnant, what should I do?**

- Breathe
- Assess how the patient is doing and how she feels about the pregnancy
- Consider the contribution of each medication to her mental health
- Document all exposures during pregnancy
  - Medications, supplements, alcohol, marijuana, tobacco, illicit substances, over-the-counter medications

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**Context for Assessing Risk**

- Rate of major malformations: 3% to 4%
- Rate of premature delivery: 11% to 12%
- Rate of gestational diabetes: 2% to 7%
- Untreated psychiatric disorders carry risks for woman and baby
- Alcohol and tobacco use prevalent in patients with untreated psychiatric disorders
- Obesity increases obstetrical risks
- Older age increases risk

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**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
- Neonatal behavioral differences, such as irritability and decreased activity
- May lead to less adherence with prenatal care

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**Potential Physiological Risks**

- Fetal exposure to increased cortisol; higher anxiety symptom burden associated with higher maternal plasma and amniotic fluid cortisol levels, catecholamines
- May result in maternal vasoconstriction and limit oxygen and nutrient delivery to fetus
- Impact on long-term CNS development
  - Longitudinal cohort study, investigators demonstrated that children exposed in utero to perinatal anxiety are at increased risk for attentional problems at age 5 and 14

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**Risks of Untreated Bipolar Disorder during Pregnancy**

- > 330,000 women; included comparisons of women with bipolar disorder, with and without treatment
  - Bipolar disorder increases risk of
    - C-section
    - Small for gestational age
    - Prematurity
    - Congenital malformations
      - Without bipolar disorder: 2.0%; untreated 1.9%
      - 3.4% treated with a mood stabilizer (lithium or anticonvulsant)
**Schizophrenia: Pregnancy Considerations**

- Increased rates of obstetrical complications
  - Lower socioeconomic status
  - May delay recognition of pregnancy and onset of labor
  - Less likely to receive prenatal care
  - Higher rate of unplanned, unwanted pregnancies
  - Women who deny pregnancy due to delusions may be at particularly high risk of poor outcomes


**Schizophrenia: Obstetric Complications and Outcomes**

- Nilsson et al
  - Looked at 2096 births to 1438 mothers with schizophrenia; controls = 1,555,975 births in the general population of Sweden 1983–1997
  - Adjusted for socioeconomic status, cohabitation, smoking
  - Increased rates of
    - Perinatal death
    - Preterm labor
    - Low birth weight
    - Small for gestational age


**Risk of Relapse for Major Depression during Pregnancy**

- 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 years); more recurrent depression, earlier onset of depression


**Pregnancy and Postpartum: Risks of Discontinuing Medication**

- Retrospective and prospective data show mean rates of relapse during pregnancy between 55% to 70%
- Women who discontinue medication more likely to experience recurrences (85.5% vs 37%) and spend more time ill
- Particularly high rate of mood episodes postpartum (70%)
- Recurrence risk greater after rapid discontinuation (< 2 weeks) than gradual (2 to 4 weeks)
- Unplanned pregnancy associated with greater risk of recurrence


**Depression during Pregnancy: Medication**

**FDA Ratings**

- A: Studies in humans show no risk
- B: No evidence risk in humans; if no human data, animal data show no risk
- C: Risk cannot be ruled out
- D: Positive evidence of risk
- X: Contraindicated in pregnancy

The Pregnancy and Lactation Labeling Rule (PLLR) or “Final Rule”

- Subsections
  - Pregnancy
  - Lactation
  - Females and Males of Reproductive Potential
- Pregnancy Exposure Registry
  - Scientifically acceptable registry and contact info
- Risk Summary
  - Human, animal, pharmacologic data
  - Adverse developmental outcomes
  - Structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, alterations to growth
  - Background risks from the US population (ie, CDC data)
- Contact
  - Includes information about background rates of adverse events
    - Risks to be quantitatively compared to the risk for the same outcome in infants born to women not exposed to the drug, but who have the disease or condition for which the drug is indicated (ie, appropriate controls)

APA/ACOG Joint Recommendations

- Psychotherapy: First-line for mild to moderate MDD
- Lifestyle components: Nutrition, weight management, prenatal care, childbirth education; treatment for substance abuse
- Women trying to conceive who have 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 is 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


Can Nonrandomized Studies on the Safety of Antidepressants during Pregnancy Convincingly Beat Confounding, Chance, and Prior Beliefs?

- 7% to 13% of pregnant women in the United States use antidepressants
- Studies usually not controlled for by indication
- Usually do not control for depression during pregnancy
  - Some do, but not for severity
- Questions
  - Why do women who use antidepressants have an increased risk of reported perinatal outcomes?
  - Does depression play an etiologic role?
  - Do maternal behaviors that are caused by depression/anxiety increase risk?
  - Are there genetic or environmental associations that cause, both psychiatric disorders and adverse perinatal outcomes?
  - Or are antidepressants toxic in pregnancy?


Approaching the Data

- Outcomes of interest rare, eg, specific malformations
- Outcomes may differ by specific medication
- Findings suggest that risks are small to moderate
  - Need large databases
  - Large databases typically lack detail indication and severity
- Confounding
  - Depression and/or its severity among the group of interest and not among the control group
- A priori beliefs – interpretation
  - ie, 1.5-fold increase in risk could be evidence of safety or evidence of risk

Antidepressants and Pregnancy: Overview and Controversies

SSRI Use during Pregnancy

- Prevalence of SSRI use during pregnancy is 3% to 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 small
  - Recent case-control studies reveal inconsistent data regarding teratogenic risk of individual SSRIs
- Reproductive safety data on SSRI exceed what is known about most other medicines used in pregnancy

Risk of Cardiovascular Malformation following SSRI Exposure

- Recent analysis of 949,504 pregnant women enrolled in Medicaid
  - 3 months prior to pregnancy to 1 month following pregnancy
- 6.8% use of SSRIs during first trimester
- Risk for cardiac defects attenuated with increasing levels of adjustment for confounding

Are SSRIs Associated with an Increased Risk of Autism?

Studies have been inconsistent; Confounding variables
2 new papers in JAMA 2017

1) Canadian Study: Health administrative data sets; factored in large number of potential confounders and compared exposed children with unexposed siblings
   - 35,906 singleton births: After factoring in propensity scores for confounding, association not significant; association also not significant when exposed children were compared with unexposed siblings
2) Swedish Study: Controlled for pregnancy, maternal and paternal covariates, sibling comparisons, timing of exposure
   - Offspring born to 943,776 mothers
   - First trimester exposure associated with a small increased risk of preterm birth, but no increased risk of small for gestational age, autism spectrum disorder, or ADHD

SSRI = selective serotonin reuptake inhibitor


Antidepressants during Pregnancy: Later Pregnancy Considerations

- Established risk factors
  - Cesarean delivery, late preterm or postterm birth, large for gestational age, maternal black or Asian race, overweight/obesity, diabetes, asthma
  - Inconsistent results
    - One report showed increased risk by 6-fold (approximately 1%
    - Lower association seen (0.15%)
    - No association seen


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


Antidepressant Use Late in Pregnancy and Risk of PPHN

- Large Medicaid Database – 3.8 million pregnancies
  - 128,950 women (3.4%) filled at least 1 prescription for antidepressants last 90 days of pregnancy; 2.7% used an SSRI and 0.7% used a non-SSRI
  - Overall, 703 infants not exposed to antidepressants were diagnosed with PPHN (20.8; 95% CI, 20.4-21.3 per 10,000 births) compared with 322 infants exposed to SSRIs (31.5; 95% CI, 28.3-35.2 per 10,000 births), and 78 infants exposed to non-SSRIs (29.1; 95% CI, 23.3-36.4 per 10,000 births)

- Absolute Risks
  - With SSRI: 31.5/10,000 = 0.3%
  - No antidepressant: 20.8/10,000 = 0.2%
  - Associations between antidepressant use and PPHN were attenuated with increasing levels of confounding adjustment


Bupropion and Pregnancy

- Bupropion Pregnancy Registry, prospective birth outcome data
  - 3.6% (24/675) of the cohort experienced a congenital anomaly after first trimester exposure
  - There was no clear pattern of type of birth defects

- Small prospective study N = 136 women who used bupropion in the first trimester, there was no evidence of increased rates of malformations compared with 2 groups of women, those who used other antidepressants or and those who had known nonteratogenic exposures

- Small but increased risk of cardiovascular left outflow defects was reported in a retrospective case control study from a birth defect registry
  - The absolute risk was approximately 2 out of 1000 pregnancies


Are Antidepressants Associated with an Increased Risk of Spontaneous Abortion?

- Danish Medical Birth Registry and the Danish National Hospital Registry
  - 1,005,319 pregnancies: 114,721 (11.4%) ended in SA
  - 22,061 pregnancies exposed to antidepressants and 1843 with a diagnosis of depression with no antidepressant use, of which 2837 (12.9%) and 205 (11.1%) ended in SA, respectively

- No SSRIs was associated with SA

- Among women with a diagnosis of depression, the RR for SA after any antidepressant exposure was 1.00 (95% CI = 0.80–1.24)

- No SSRI was associated with SA

- In unadjusted analyses: Mirtazapine, venlafaxine, duloxetine associated with SA among women with depression—small Ns, lack of data re: severity

- Conclusion
  - Slightly increased risk of SA associated with the use of antidepressants
  - When comparing women with depression, antidepressants in general or individual SSRIs in particular were not associated with SA


Unadjusted RR for SA after Exposure to Specific Types of Antidepressants Compared to the Unexposed Cohort

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Unexposed Cohort RR</th>
<th>Unexposed Cohort 95% CI</th>
<th>Exposed Cohort RR</th>
<th>Exposed Cohort 95% CI</th>
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<td>Duloxetine</td>
<td>1.71</td>
<td>1.10–2.69</td>
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**CAM/Integrative Treatments**

- Omega-3 fatty acids—add-on
- Exercise—add-on
- Folate—add-on
- SAMe—?monotherapy (no specific study)
- St. John’s wort—similar to antidepressants but less known
- Acupuncture—monotherapy or add-on
- Bright light therapy—monotherapy or add-on
- Massage—add-on

**Lithium**

- Lithium: First-trimester risk of cardiovascular malformations
  - Ebstein’s anomaly: 0.1% to 0.2% (RR = 10–20)
  - RR for cardiac malformations is 1.2 to 7.7 and the risk for Ebstein’s anomaly rises from 1/20,000 to 1/1000
- Lithium
  - Complicates maternal GFR changes during pregnancy. Excreted more rapidly—may need to increase dose
  - After delivery, GFR decreases rapidly, should follow lithium levels during labor and delivery, adjust dose as needed

**Valproic Acid**

- WORST TERATOGEN KNOWN AMONG PSYCHOTROPICS
- Rate of major malformations: ≥ 10%
  - Neural tube defects, craniofacial, cardiovascular, and others
  - Risk of defects is substantial in very early pregnancy
  - Associated with increased risk for adverse cognitive and neurodevelopmental effects
  - Long-term follow-up (up to 3 years) suggests fetal exposure to valproate associated with lower IQ scores (not observed with lamotrigine)

**Lamotrigine in Pregnancy**

- No increased risk of major malformations
- Association with oral clefting NOT seen with larger numbers
  - Early data suggested it might be when numbers were smaller
  - Recent large study of registries did not find any association between oral clefts and lamotrigine
- Pregnancy increases lamotrigine clearance by > 50%
  - Returns to baseline after delivery
Atypical Antipsychotics in Pregnancy

- Large administrative Medicaid database
  - Nationwide sample of N = 1,360,101 pregnant women
  - After confounding adjustment, the RR was reduced to 1.05 (95% CI, 0.96–1.16) for atypical APs and 0.90 (95% CI, 0.62–1.31) for typical APs. The findings for cardiac malformations were similar
  - For the individual agents examined, a small increased risk in overall malformations (RR, 1.26; 95% CI, 1.02–1.56) and cardiac malformations (RR, 1.26; 95% CI, 0.68–2.45) was found for risperidone that was independent of measured confounders
- Pooled odds ratios of prospective studies
  - AP exposure associated with slightly increased risk of major malformations, heart defects, preterm delivery, small-for-gestational-age births, decreased birth weight
  - There was no significant difference in the risk of major malformations differences between typical (and atypical) AP medications


Benzodiazepines and Pregnancy

- Benzodiazepines are lipophilic and undergo rapid fetal transfer and uptake
- First trimester exposure: Inconsistent findings of association with cleft palate or other congenital abnormalities
- Late pregnancy exposure: Possible withdrawal, neonatal sedation, hypotonia, cyanosis
- Avoidance in the first trimester, avoidance of polypharmacy suggested


Aripiprazole and Quetiapine

- Exposed:
  - 312 live births with first trimester exposure to atypical antipsychotics
  - n = 4 major malformations confirmed
  - Risk: 1.3%
- Controls:
  - 177 control group live births
  - n = 1 major malformation confirmed
  - Risk: 0.6%
  - RR: 2.27 (95% CI: 0.26–20.15)


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

Women and Adult ADHD

- ADHD estimated to affect 4.4% of adults in the United States
- Increased risk of poorer general and mental health, substance abuse, impaired work performance, financial distress
- Growing appreciation that girls with ADHD have a substantial likelihood of continuing to have the disorder in adulthood
  - Biederman et al: Cohort of girls with longitudinal follow-up
  - Majority are still affected by ADHD over a decade later
  - Approximately one-third continuing to meet full criteria
  - Approximately another one-third meeting partial criteria
  - 10% experiencing impaired functioning


Primary Outcome: Major Malformations

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- Controls:
  - 177 control group live births
  - n = 1 major malformation confirmed
  - Risk: 0.6%
  - RR: 2.27 (95% CI: 0.26–20.15)
### What risk is most associated with stimulant use in pregnancy?

1. Neural tube defects
2. Cardiovascular malformations
3. Small for gestational age
4. Excessive maternal weight gain

### Stimulants in Pregnancy

- Stimulants often represent drugs of abuse rather than prescribed treatment
- Data suggest a potential impact upon fetal growth, rather than risk of teratogenicity
- Report of decreased body weight among pregnant animals exposed to methylphenidate
- First trimester methylphenidate exposure does not appear to increase the risk of congenital abnormalities beyond the rate in the general population

### Behavioral Teratogenicity

- Animal studies suggest that prenatal exposure to amphetamines is associated with changes in dopaminergic transmission and receptor expression, post-pubertal behavioral changes (decreased motor activity)
- Studies in humans are lacking, limited to stimulant use in the context of substance abuse
  - Children have generally not been found to have consistent impairment on standard cognitive tests and visual habituation, language development
  - In later childhood, heaviest maternal use of cocaine was associated with subtle deficits in executive function

### Treatment Considerations

- Variable risks of stopping medication
  - In general, stimulants have greater efficacy than non-stimulant medications
  - Importantly, some patients are at risk of motor vehicle accidents
  - Driving capability is a key functional outcome
    - Occupational or school functioning
  - Recommendations to reduce workload
    - Increase structure and organization at work or school
    - Employers may be able to offer accommodations
    - Psychotherapies to target functioning

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References: