Psychiatric Medications in Pregnancy and Lactation

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Objectives

- Educational
  - Discuss risks and benefits of psychotropic medications (in context of illness) with patients who are or may become pregnant or decide to breastfeed.

- Clinical
  - Keep Mom well.
  - Empower her to make a complex decision.

Overview

- Resources and guidance for risk-benefit based treatment planning
  - Medications & Illness
    - Risk highlights
    - Treatment principles
  - Patient oriented resources
  - Provider oriented resources
    - Data
    - Get questions answered
    - Make referrals
Identification and intervention - critical

- Up to 40% of women are identified with mental disorders in the perinatal period
  - 10-15% of women – depression in pregnancy
  - 50% continue into postpartum
  - Select populations – perinatal depression rates up to 30%
- Perinatal mental disorders are associated with negative consequences for mother, infant, and families

Bilszta et al. 2010; Einarson et al. 2001; Marcus et al. 2005; Flynn et al. 2006; Thombs et al. 2014

Perinatal Mental Healthcare

- Often undetected or untreated:
  - Less than 1/3 of women receive treatment for perinatal depression
- Women often (25 – 50%) discontinue psychotropic medication as a result of conception
  - Providers often support or advise this

Bilszta et al. 2010; Granien et al. 2010; Jolivet et al. 2007; Kung et al. 2006; Thombs et al. 2014

Risks and Benefits Discussion

- Risks of untreated illness
- Benefits of treatment
- Risks of medication
- Benefits (and risks) of breastfeeding
- Perception of risk
  - Personal history (treatment experience, severity)
  - Access to care
  - Worry about medication safety - #1

Kapelnik et al. (unpublished)
Decisions, Decisions
- Stop
- Stop and restart after 1st trimester
- Continue through pregnancy
- Lower dose
- Stop and restart if symptoms
- Stop and switch
- Some say reduce or discontinue in late pg
- Role of psychotherapy
- Role of other non-pharmacologic treatments
  - Light, Omega-3s,rotate, exercise, acupuncture, massage
- Don’t forget possible pre-conception taper!
- Pre-conception planning - ideal

Treatment principle
- Treat women like they could get pregnant at any time.
  - Document use of birth control
  - Encourage use of folic acid/PNV and positive health behaviors
  - Up to 80% of pregnancies unanticipated!
STOP meds - what happens?

- Relapse!
  - Women who maintained AD  Relapse rate = 26%
  - Women who discontinued AD  Relapse rate = 68%

- Or do they?

  - 2 prospective studies – HR 5.0 (above) and HR 0.88

- Some women at greater risk for relapse
  - 4+ episodes of depression, longer history (>5 years), younger age (<32)

Cohen et al. 2006; Yonkers et al. 2011

Treatment principles

- Individualized risks and benefits

- Account for severity in recommendations
  - Duration of illness
  - Number of episodes
  - Suicide attempts/violence history

Risks: Untreated Perinatal Depression

- Low birth weight/growth restriction, Shorter gestation
- Spontaneous abortion
- Pre-eclampsia/Pre-hypertension
- Gestational diabetes, fetal death, abnormal bleeding, failure to thrive
- Inadequate prenatal care
- Increased use of alcohol, drugs, and cigarettes
- Inconsistent use of birth control
- Less likely to engage in healthy parenting practices
- Behavior/Developmental effects
- Mental health problems – children, partners
- Suicide

Davalos et al. 2011; Davis et al., 2008; Bonari et al 2004; Kelly et al., 1999; Kelly et al., 2002; Gavin et al. 2011

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Covin et al. 2011; Chen et al., 2018; Enos et al. 2002; Nott et al., 1999; Raye et al. 2002; Smith et al. 2011
Provide understandable resources

Perception of risk: What we say and how we say it matters.

Patient Resources

- Provide handouts
  - OTIS – great option
- Provide list of websites for education and support
  - www.mothertobaby.org

Treatment principles

- Explicitly review with patient these goals:
  - Don’t expose to BOTH illness and medication
  - Use lowest effective dose
  - Use as few medications as possible
  - Use previously effective medication(s)
  - Consider alternatives
Guidelines: Reading the Research

- Did the study address:
  - Maternal health (age, weight, diabetes, etc.)
  - Maternal health behaviors (tobacco use, other substance use)
  - Maternal psychiatric illness
  - Medication administration issues

Antidepressants - SSRIs

- Risks: Increased risk of spontaneous abortion, preterm delivery, low birth weight

  - e.g. Does the study account for depression?
    - Wiener et al 2009: continuous SSRI exposure AND untreated depression associated with PTD
    - Untreated depression and depression associated factors - PTD, LBW with each
      - age, tobacco use

SSRIs & Malformations

- Studies generally indicate no specific pattern or substantial increase in structural malformations
- Criticized for noted methodologic limitations
- Significant findings most often for:
  - Cardiac malformations (septal defects, ventricular outflow tract defects)
    - Remain rare, low absolute risk
Paroxetine & Cardiac Defects
- Paroxetine – FDA warning (VSD)
  - Data remain mixed
- Avoid perinatal paroxetine (maybe)
  - Remember:
    - Use as few medications as possible
    - Use previously effective medication(s)
- Ultrasound
- Consider Fetal Echo

Persistent Pulmonary Hypertension
- 2006
  - OR = 6.1
  - Adjusted to 6-12/1000
- 2015
  - Adjusted for h/o depression - OR = 1.1 SSRI, 1.02 non-SSRI AD
- FDA revised warning:
  - Other factors associated with depression (diabetes, smoking, obesity, PTD, C-sxn) may account for the association

Neonatal Abstinence Syndrome (SSRIs/SNRIs)
- Symptoms include: tremors, feeding difficulties, irritability, increased muscle tone, increased crying, increased reflexes, sleep disruption, respiratory problems
- Occurs in 30% of neonates exposed to SSRIs in utero
- Monitor for 48 hours after birth, transient
- Possible dose-dependent relationship - with paroxetine
  - Use lowest effective dose
- Should we taper prior to delivery?
  - Generally not recommended due to relapse risk and lack of evidence supporting the practice
  - SSRI exposed infants and non-exposed 14 days prior to delivery
  - No difference in neonatal (neonatal adaptation) between groups
Mental & Motor Development, Autism - Antidepressants

- Limited data - existing studies – no definitive correlation between exposure and brain development
  - Maternal depression role

- A few studies suggest increased risk ASD:
  - Roughly – 1.5-2X increase with AD/SSRI
  - Again, role of depression/psychiatric illness?
    - Illness in pregnancy or severity – not assessed
    - When is – risk not seen or attenuated


SSRI/AD summary

- Lower birth weight +/- PTD
- Possibly select anomalies (cardiac)
- Possibly PPHN
- Chance of neonatal symptoms

Provider medication resources:
- FDA labels
  - http://www.womensmentalhealth.org
- http://www.infranrisk.com/
- http://www.reprotox.org/

Treatment principles

- Explicitly review with patient these goals:
  - Don’t expose to BOTH illness and medication
  - Use as few medications as possible
  - Use previously effective medication(s)
  - Use lowest effective dose
  - Consider alternatives
Sally H.

Pregnancy & Breastfeeding:

- Medications impact breastfeeding rates

Antidepressants

- Half life may be extended in infant (fluoxetine)
- Relative infant dose (RID <10%) useful – use your resources

  - No detectable levels in infant:
    - Nortriptyline
    - Paroxetine
  - Sertraline - RID 0.4-2.2%
  - Increased levels
    - Citalopram
    - Fluoxetine
  - TCAs may have advantages (nortriptyline)

Weissman 2004

FDA labels

http://www.womensmentalhealth.org/
Risks of untreated illness:
Perinatal Anxiety

- Untreated “stress” (GAD, Panic, PTSD, OCD)
  - Preterm labor, postterm delivery, cesarean delivery, preeclampsia
  - LBW, reduced breastfeeding
  - Hypertension in pregnancy, neonatal respiratory interventions/ventilator

Benzodiazepines

- Data mixed on oral clefts – recommend U/S
- Delivery outcomes – conflicting data PTD, LBW, possible increase C-section rates, shorter gestation, ventilatory support
- Neonatal effects
  - Sedation, decreased muscle tone (floppiness), and breathing problems
  - Withdrawal
- Lactation
  - Sedation, low energy, poor suckling
  - Use shorter acting RX
Approximately what % of perinatal women with BPAD relapse off medication?

A. 5%
B. 25%
C. 40%
D. 70%
Risk of Relapse of Bipolar Disorder in Perinatal Period

- 89 pregnant women with BPAD (I or II)
  - Continue medications - 37% relapse
  - Discontinue medications - 85% relapse
- 42 pregnant vs. 59 non-pregnant women with BPAD (I or II)
  - Greater risk with rapid discontinuation
  - Postpartum 70% recurred vs. 24%

Birth complications in bipolar disorder

- Increased risk of:
  - Placental abnormalities (placenta previa)
  - Antepartum hemorrhages
  - C-sxn, induction
  - Preterm delivery, SGA/LBW
  - STDs
  - Poor nutrition
- Drug toxic side effects (alcohol, drug, tobacco related)

Lithium in Pregnancy

- Ebstein’s anomaly and Lithium 1st trimester exposure
  - More recent estimate at 10-20 x general population
    - Baseline risk = 1:20,000 (0.005%)
    - Lithium risk = 1:1,000 (0.1%)
  - Risk is higher, overall absolute risk relatively small
- Polyhydramnios, polyuria, polydispsia
- Neonatal toxicity
  - “floppy baby”: cyanosis, hypertonicity
- Earlier delivery, lower APGAR scores, lower birth weight/LGA, NICU admits
- Neurobehavioral - no difference in mean or range global IQ scores
**Lithium and Lactation**

- Breast milk [Li] = 0-72% mother serum [Li] – RID 12-30%
  - Viguera 2005 – 10 pairs, 51% maternal serum, 9/10 no adverse events, 1/10 elevated TSH
  - Cyanosis, hypotonia, hypothermia
  - Dehydration, EKG changes
- Case reports (Bogen et al. 2012)
  - Feeding problems, hypotonia
- Generally not recommended, but consider benefits of breastfeeding
  - Monitoring indicated (Weight, Li, TSH, BUN/Cr q 6-8 wks or prn, monitor neurologic sx)

**Valproic Acid in Pregnancy & Lactation**

- Neural tube defects 1-9%
  - 3.6 – 25% (dose dependent)
- IUGR, Neonatal toxicity
- Autistic traits
- Neurobehavioral = Lower IQ
  - Dose-dependent (>1000 mg/day)
- Lactation
  - < 1% - 6% RID
  - Case report – thrombocytopenia, anemia
  - Monitor valproate level, liver enzymes, platelets

Meador et al 2009 & 2012; Elkjaer et al. 2018; Tomson et al. 2018

**Carbamazepine in Pregnancy & Lactation**

- NTD - 0.5% - 1%
- 4.5 – 7.2 % malformation rate (dose dependent)
- Craniofacial defects (11%)
- Fingernail hypoplasia (26%)
- Intrauterine growth retardation, Transient cholestatic hepatitis, Urinary tract abnormalities, Cardiovascular abnormalities
- Fetal Vitamin K deficiency
- Lactation
  - RID 4-6%
  - Case reports – hepatotoxicity
  - Monitor level, CBC, liver enzymes

Tomson et al. 2018; Tomson et al. 2004
Lamotrigine in Pregnancy & Lactation

- 2.5 – 4.3% malformation rate (dose dependent)
- Oral clefts 7.3/1000
- 10.4-fold increase compared to unexposed infants
- Meta-analysis:
  - No increased risk of malformations or other negative birth outcomes
- Not linked to poor school performance compared to unexposed

Lactation
- RID 9-18%
- Adverse event reported
- Monitor for rash, liver enzymes

Schizophrenia/Psychosis in Perinatal Period

- Postpartum Psychosis
  - Abuse, neglect, infanticide

- Schizophrenia risk of:
  - Preterm delivery, LBW/SGA, stillbirth
  - Placental abruption, congenital anomalies
  - Later emotional and behavioral problems (similar to affective illness)

- Relapse risk ~ 65%

References:
Antipsychotics – Pregnancy & Lactation

- Pregnancy outcomes
  - Gestational diabetes, CV malformations, Neonatal symptoms, birthweight effects, *infant hypoglycemia*
  - Confounding variables – hypertension, diabetes rates in patients with psychosis
  - FGAs may be preferred for metabolic reasons
- FDA Drug Labels February 2011
  - Risk for EPS
  - Risk for withdrawal

- Lactation
  - Olanzapine – most data – RID <2%

Mary J.

Guidelines: Documentation

- Document
  - "We discussed the risks, benefits, and alternatives to psychiatric medications, including ______, in pregnancy. We have also discussed the risks of untreated [mental illness] during pregnancy. Ms. X (and her partner) elect to __________."
Resources: Clinical & Education

- **Education for Patients & Providers**
  - [http://www.postpartum.net/](http://www.postpartum.net/)
  - [http://postpartumstress.com/](http://postpartumstress.com/)
  - [Http://www.beyondtheblues.info](http://www.beyondtheblues.info)
  - Iowa based resource
  - [https://the-periscope-project.org/](https://the-periscope-project.org/)
  - [https://www.mcpapformoms.org/](https://www.mcpapformoms.org/)

- **Perinatal/Reproductive Psychiatrists**
  - Seasons Center for Behavioral Health
  - Women’s Wellness & Counseling Service
  - Search social media
    - e.g. Facebook group: Reproductive Psychiatry-Women’s Mental Health

Again, always know where to look

- **FDA labels**
  - [www.perinatalmentalhealth.com](http://www.perinatalmentalhealth.com)
  - Join the listserv, attend MONA conferences
  - [http://www.perinatalmentalhealth.org](http://www.perinatalmentalhealth.org)
  - Join the listserv, follow on social media
  - formerly OTIS, great handouts
  - [http://www.reprotox.org/](http://www.reprotox.org/)

- **Apps**
  - [http://www.reprotox.org/](http://www.reprotox.org/)

Guidelines: build trust, improve decision making experience

- Provide best possible, most accurate information – **expert care**
- Acknowledge limitations
  - Data
  - Decision
- When available involve partners or other supports
- Acknowledge emotions
- Provide support and reassurance
Summary of guidelines/principles

- Treat women like they could get pregnant at any time.
- Individualize risks and benefits
- Account for severity in recommendations
- Don’t expose to BOTH illness and medication
- Use lowest effective dose – change gradually, monitor effectiveness
- Use as few medications as possible
- Use previously effective medication(s)