

Psychotropics in Pregnancy: Decision Making

Dr. Srikanth Reddy, MD

Assistant professor

Dept of Psychiatry

Outline

- Role of Psychiatrist in pregnancy
- Impact of psychiatric illness(es) on pregnancy outcome(s), both mother & fetus
- Clinical recommendations for prescribing psychiatric medications in Pregnancy
 - Antidepressants – Antipsychotics – Mood Stabilizers - Benzodiazepines
- Controversies & Limitations

Preamble

- Decision making in the treatment of pregnant women should be structured to include patient **education** regarding the natural history of her psychiatric disorder, the identification and review of **likely risks and benefits** associated both with the disorder and available somatic treatments, and frank discussion of available treatment options.

- Clinical decision making **must balance** the known and unknown risks of medication treatment with the known and unknown risks of untreated psychiatric illness.
- Open communication, provision of risk–benefit information to patients in a comprehensible format, and the ability to **listen to, reflect, and respect the patient’s concerns and value structure** are critical to optimizing treatment decisions and obtaining fully informed consent for treatment.

When pregnancy is discovered during an ongoing medication treatment **course, a risk–benefit analysis of medication continuation should be re-evaluated** in light of altered risks associated with treatment continuation and risk of illness recurrence during the peri-natal period.

Risks of Psychiatric Illness during Pregnancy

- **IMPACT ON MOTHER.**
- Untreated illness can lead to clinical deterioration with concomitant psychological distress, social and occupational dysfunction, financial hardship, **an inability to plan for and successfully cope with the impending life transition of motherhood**, and possible suicidal ideation and self-harm.

- With many psychiatric disorders, functional impairment results in **sleep disturbance, poor nutrition, lower use of prenatal vitamins, weight loss**, as well as increased risk of cigarette, alcohol, and drug use
- **Poor rates of prenatal care** can result in failure to detect **gestational anemia, diabetes and hypothyroidism**, which can have significant negative impact both on mother and fetus.

IMPACT ON OFFSPRING

- Severe prenatal maternal stress has been associated with congenital anomalies.
- Prenatal anxiety, pregnancy-specific anxiety, depression and maternal stress hormones have been associated with **preterm birth, increased rates of obstetrical interventions during labor and delivery, small-for-gestational age birth weight, impaired neonatal stress regulation, infant fearful temperament, adverse cognitive outcomes, and reduced gray matter brain volumes.**

- Mentally unwell mothers have increased likelihood of having **intrusive or withdrawn interactional styles with their infants** and may lack sensitivity and attunement to infant cues.
- These maternal behaviors have been associated with offspring **vulnerability for poor self-regulation, low self-esteem, insecure attachments, behavioral problems**, and delays in motor and cognitive development.

Pharmacological Treatments during Pregnancy

- Although **ethical considerations limit** performing randomized, prospective medication studies with pregnant women, improved methods for naturalistic studies (large samples, **propensity score matching**) and ongoing collection of observational data in registries have increased the information available to women facing perinatal treatment decisions.

- Pharmacotherapy is an important modality with illness unresponsive to alternative treatments.
- The psychiatrist plays an important role in an informed decision and in providing education to and fostering communication with the obstetrician and pediatrician.
- The medication to which a mother has responded in the past is often the best choice even in the absence of substantial data.

- For each psychotropic class, the available evidence is summarized in order of following domains:
- A) congenital teratogenicity
- B) late gestation effects
- C) neonatal withdrawal/toxicity
- D) developmental (neurobehavioral) teratogenicity, and lactation.

ANTI DEPRESSANTS

- **SEROTONIN REUPTAKE INHIBITORS** (SRI = SSRIs AND SNRIs). Across numerous studies of first trimester exposure, no SRI has reached the level of a confirmed teratogen.

Byatt N, et al. Antidepressant use in pregnancy: a critical review focused on risks and controversies. *Acta Psychiatr Scand.* 2013;127(2):94–114.S

- In several methodologically rigorous, large studies which used an untreated depressive control group as well as propensity score matching to control for depression severity and other confounders, **relative risk of cardiac malformation** as a whole or limited to septal defects with SRI use was not significantly greater than with no SRI use.

Huybrechts KF, et al. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med.* 2014;370(25):2397–2407.

- Several analyses in a large cohort found no increased risk attributable to SSRIs when depression status was controlled for.
- Ross LE, et al. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. *JAMA Psychiatry*. 2013;70(4):436–443.
- Additionally, SSRI use was not associated with any increased risk of stillbirth, neonatal death and post neonatal death in a second well controlled, large study.

Weissman MM, et al. Treatment of maternal depression in a medication clinical trial and its effect on children. *Am J Psychiatry*. 2015;172(5):450–459.

Neonatal Adaptation Syndrome

- It is reported to affect 30% of late pregnancy, SSRI-exposed newborns, and substantially more preterm infants are affected.
- Features include **respiratory difficulty, hypoglycemia, hypertonia, jitteriness, vomiting, seizures, and sleep disturbances.**
- The syndrome appears to be **time limited** with greatest incidence in the first 48 hours post birth, but potentially extending to 2 weeks post birth.

- A number of prospective studies have found **no impact** of SRIs or TCAs on **temperament, mood, arousability, activity level, distractibility, global intelligence quotient (IQ), or language** development in children followed to 7 years of age

Huybrechts KF, et al. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med.* 2014;370(25):2397–2407.

- **TRICYCLIC ANTIDEPRESSANTS:** The data **show no evidence of increased incidence of congenital malformations in fetuses** exposed to TCAs, although evidence is less extensive than that for the SRIs, and the majority of exposures have been to clomipramine.

- Children who were exposed to TCAs both in utero and through breast milk have been followed through preschool and compared with children who were not exposed to these drugs, and no developmental problems were found
- Ross LE, et al. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. *JAMA Psychiatry*. 2013;70(4):436–443.
- Due to increasing preferences for SRI treatment, fewer long-term studies are available following in utero TCA exposure.

FIRST-GENERATION ANTIPSYCHOTICS

- The greatest amount of data is available for FGAs.
- In a meta-analysis of nearly 75,000 births in women treated with low-potency antipsychotics (chlorpromazine), there was a 0.4 percent increased risk of malformations compared to the general population.

Wisner KL, et al. Antipsychotic treatment during pregnancy and lactation. *Adv Schizophr Clin Psychiatr.* 2007;3(2):48–55.

- Another systematic review found that the high-potency antipsychotic haloperidol was not associated with increased risks of malformation.

- Preterm birth and small-for-gestational age births may be more common with FGA relative to SGA exposure.
- Use of these agents in the second and third trimester is associated with increased rates of perinatal complications, **low birth weight and transient perinatal syndromes** (motor restlessness, tremor, hypertonicity, abnormal movements, difficulty with feeding, and possible neonatal jaundice and functional bowel obstruction).

Munk-Olsen T, et al . New parents and mental disorders: a population-based register study. *JAMA*. 2006;296:2582–2589

- Given the high risk to the mother and fetus or infant during a psychosis recurrence and the minimal risks described, continuation of treatment is recommended.

Sandman CA, et al . Exposure to prenatal psychobiological stress exerts programming influences on the mother and her fetus. *Neuroendocrinology*. 2012;95(1):7–21.

SECOND-GENERATION ANTIPSYCHOTICS

- While SGA as a class found conflicting results with no increase in major malformations in one but 2.1 to 2.7× rate of malformation in others 2 studies.
- Data from the first 195 analyzed registry participants in the National Pregnancy Registry for Atypical Antipsychotics cohort found no difference in malformation rates in SGA-exposed compared to controls.

Wisner KL, et al. Antipsychotic treatment during pregnancy and lactation. *Adv Schizophr Clin Psychiatr.* 2007;3(2):48–55.

- Low birth weight and higher NICU admissions were present for olanzapine-exposed infants.
- Via SGA-related increases in maternal weight gain, there is increased risk of neural tube defects in exposed infants, as well as increased risk of gestational diabetes, large-for-gestational age infants, and increased risk for c-section delivery.
- Clozapine may induce fatal agranulocytosis in adults so, caution should be demonstrated during use in pregnancy

- Larger studies are needed to replicate this finding and determine the longevity of the effect.
- There are no clear data yet available on long-term neurodevelopment of infants with in utero SGA exposure, except one small study which reported neurodevelopmental delays at 6 months, but resolved by 12 months

LITHIUM

- The scientific community has progressively reassessed the risk of Epstein cardiac anomaly following first trimester lithium exposure.
- While the risk was originally cited as 400-fold, this risk was later revised to 10 to 20-fold (0.5–1 per 1,000), and some argue the **risk may be still lower due to methodological limitations** in extant studies

- Neonatal signs of lithium toxicity have been described to include **muscle flaccidity, inhibition of normal neonatal reflexes, lethargy, cyanosis, and cardiovascular effects**, including atrial flutter, tricuspid regurgitation, and congestive heart failure.
- Careful monitoring of maternal lithium concentration in pregnancy is required because of the dramatic shifts in fluid volume during pregnancy.

lithium...continued..

- A higher GFR, coupled with the increased plasma volume, often leads to a **requirement for higher doses in the gravid woman to achieve comparable serum lithium** concentrations.
- Infants with higher lithium concentration at delivery had **low APGAR scores, longer hospital stays, more neuromuscular signs**; therefore, **withholding** maternal lithium therapy for 24 to 48 hours prior to delivery is a suggested strategy to lower these adverse outcomes.

Cohen LS, et al. A reevaluation of risk of in utero exposure to lithium.
JAMA. 1994;271:146–150

Mood Stabilizers/ ANTIPILEPTIC DRUGS (AED)

- First trimester use of Carbamazepine and Sodium Valproate with neural tube defects in 0.5 to 5 percent and major malformation in up to 16 percent of exposed offspring.

Meador KJ, et al . NEAD Study Group. In utero antiepileptic *r*drug exposure: fetal death and malformations. *Neurology*. 2006;67:407–412.s

- Reported malformation other than neural tube defects includes heart defects, urogenital defects, and oral clefts.

- Valproate mono- or polypharmacy conferred the greatest risk. Valproate was also associated with greater rates of fetal death compared to other AEDs.
- The recommendation is for women taking AEDs to take high dose folate (4 mg/day), which may mitigate against the risk of neural tube defects.

Meador KJ, et al . NEAD Study Group. In utero antiepileptic drug exposure: fetal death and malformations. *Neurology*. 2006;67:407–412.

- Lamotrigine has gained particular attention as a therapy for bipolar depression in women with bipolar disorder because of recent registry data finding no difference in rates of malformations compared to the general population.
- In patients using Phenytoin the risk of congenital malformations(Foetal hydantoin syndrome) is higher, but The risk to the foetus from uncontrolled seizures is greater than the risk from using Phenytoin.

Benzodiazepines

- ✓ May induce perinatal toxicity ; temperature dysregulation, apnea, lower APGAR scores, hypotonia, and poor feeding
- ✓ Use just before delivery associated with floppy baby syndrome
- ✓ Some studies suggest oral cleft palate defects; others are negative
- ✓ Consider tapering benzodiazepines before delivery
- ✓ Intermittent use is unlikely to induce withdrawal symptoms in the newborn

Non-somatic Treatments for Perinatal Mood Disorders.

- Non-pharmacological depression treatments, such as outpatient psychotherapy or mindfulness-based stress reduction, **can be advantageous for mild to moderately depressed or anxious mothers** by providing her with emotional support and instrumental skill development needed to facilitate coping through this life transition.

Sandman CA, et al . Exposure to prenatal psychobiological stress exerts programming influences on the mother and her fetus. *Neuroendocrinology*. 2012;95(1):7–21.

Take home message

- Encourage Pregnant patients to have Psychiatric referral
- All medication changes should be preferably done before pregnancy
- Psychiatrically stable Pregnancy should be our goal
- Use medication that something is known about

Continued...take home message

- Minimize the number of exposures for baby, but if the baby was exposed to medications, then, it may not make sense to discontinue the medications for breastfeeding
- Use team approach and communicate with family
- Be supportive if patient does not take your recommendations

THANK YOU