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PSYCHIATRIC MEDICATIONS & PREGNANCY

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DISCLOSURE

- I have no financial relationship with any companies related to this talk.

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THE PROBLEM (some of it)

- Pregnant women with psychiatric illness have higher rates of adverse pregnancy outcomes.
- "Mental Health conditions" account for @ 23% of pregnancy-related deaths in the U.S.(CDC; 9/22)
  - Suicide, overdose, other substance-related
- Fetuses/children exposed to peripartum depression have higher cortisol levels.
- Untreated antepartum depression is one of the strongest predictors of post partum depression

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PSYCHIATRIC DISORDERS

- Depression
- Bipolar Disorder
- Anxiety
- Psychotic Disorders
- ADHD
- PTSD

- Insomnia

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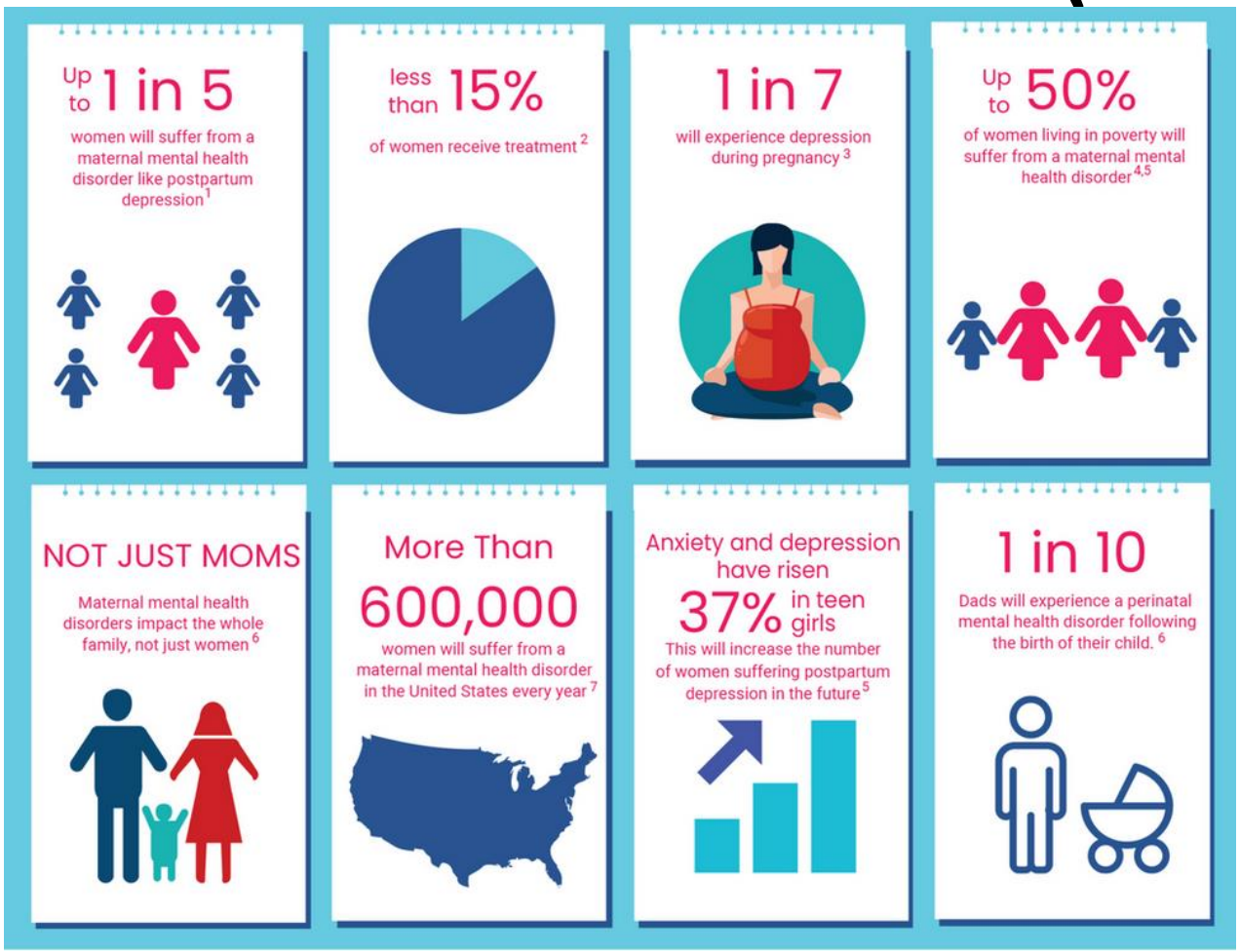
THE PROBLEM (more of it)



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Risks of untreated psychiatric illness during pregnancy

1. Unhealthy behaviors: changes in sleep, eating, activity; substance use
2. Dangerous and/or suicidal behavior
3. Preterm birth (conflicting evidence)
4. Low birth weight
5. Higher levels of cortisol in newborn
6. Higher risk of postpartum depression and psychosis, which lead to developmental effects

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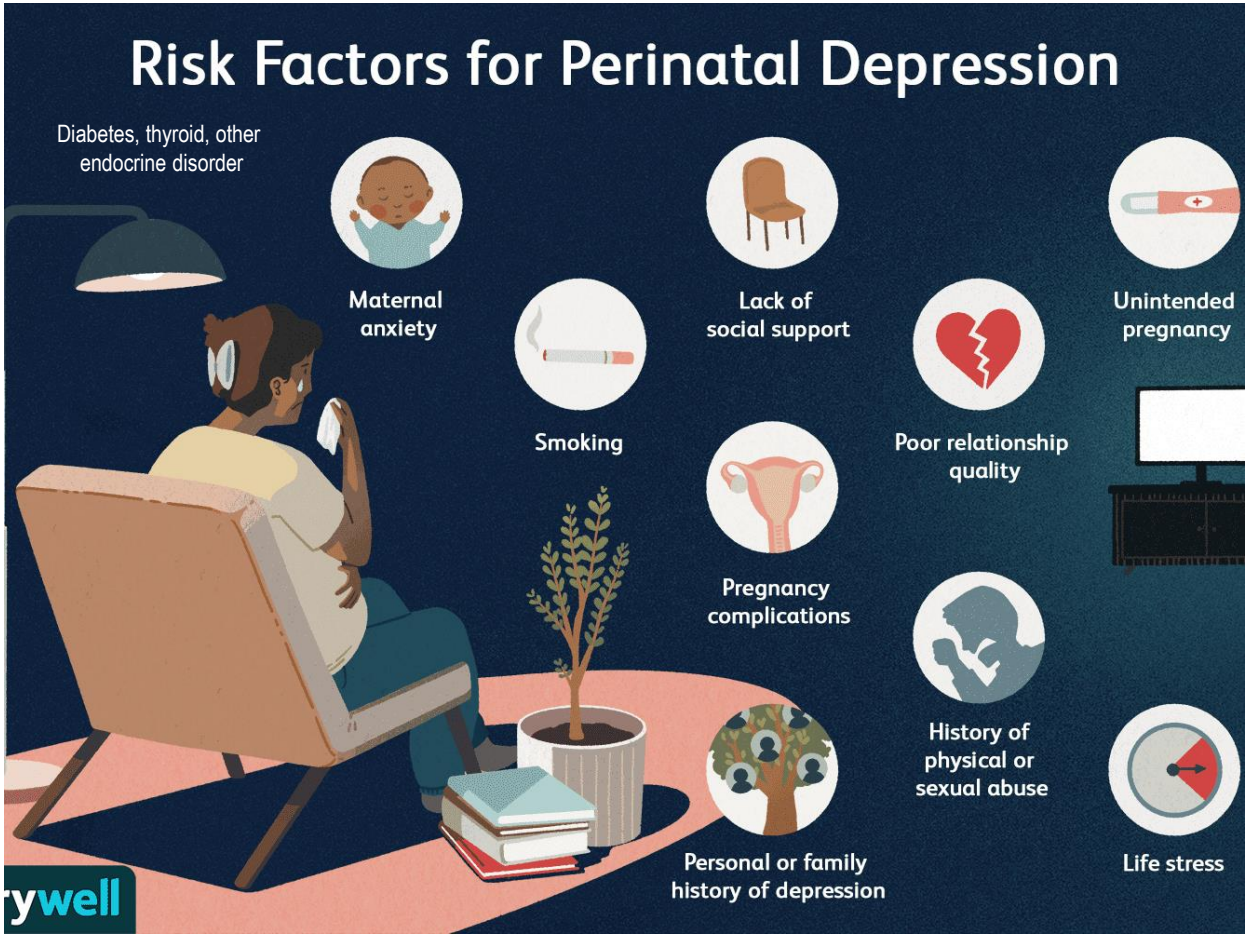
PERINATAL DEPRESSION



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POSTPARTUM DEPRESSION

- Increased infantile colic
- Impaired maternal-infant bonding
- Less adequate infant safety
- Less healthy child development practices
- Negative impact on infant development
  - IQ, language, behavior
- Suicide
  - Up to 20% of post partum deaths
  - One of the leading causes of peripartum mortality
- Infanticide

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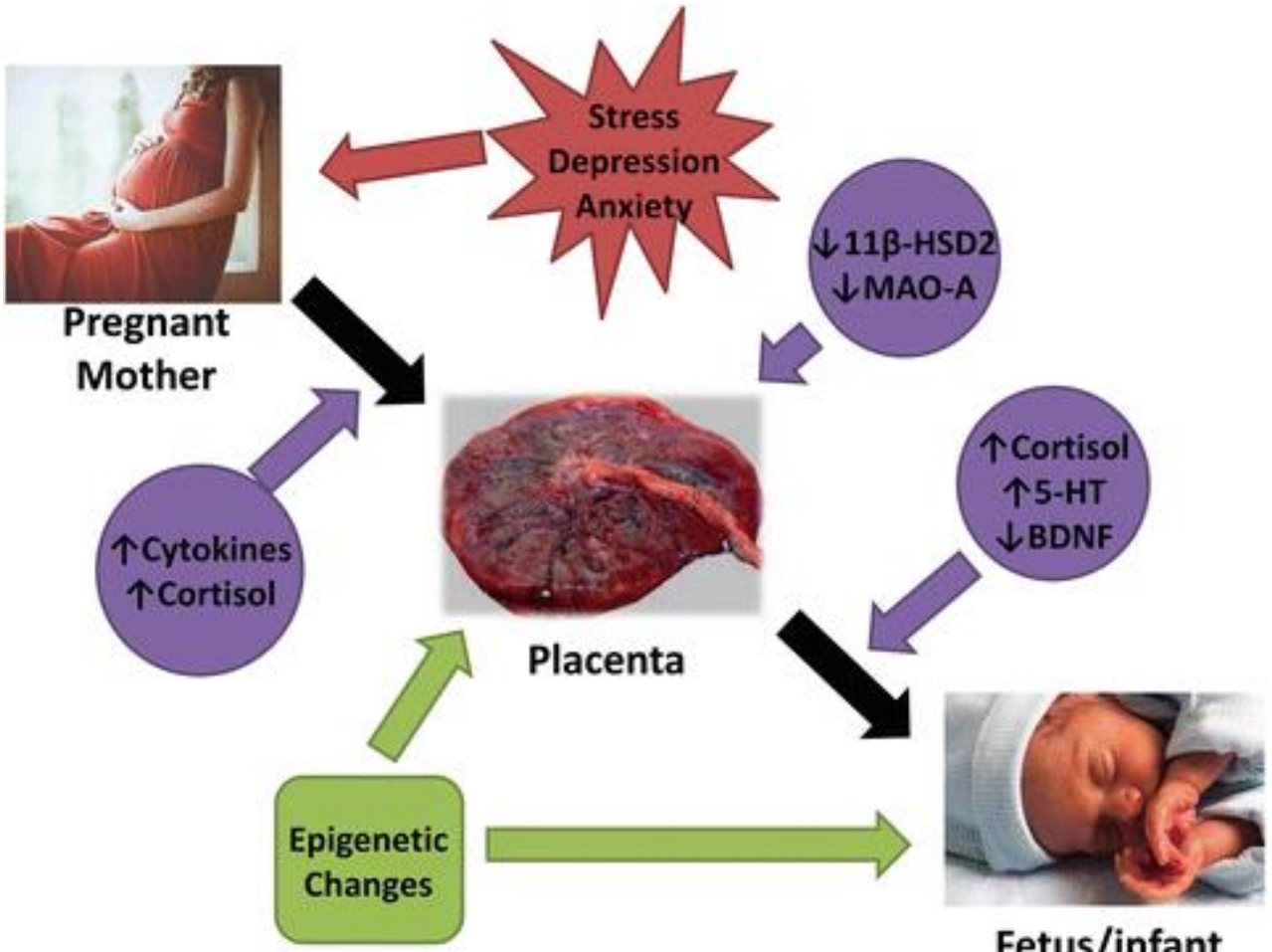
STRESS & DEPRESSION



11β-HSD2: 11 β-Hydroxysteroid dehydrogenase type 2
MAO-A: Monoamine Oxidase A
5-HT: Serotonin
BDNF: Brain-derived Neurotrophic Factor

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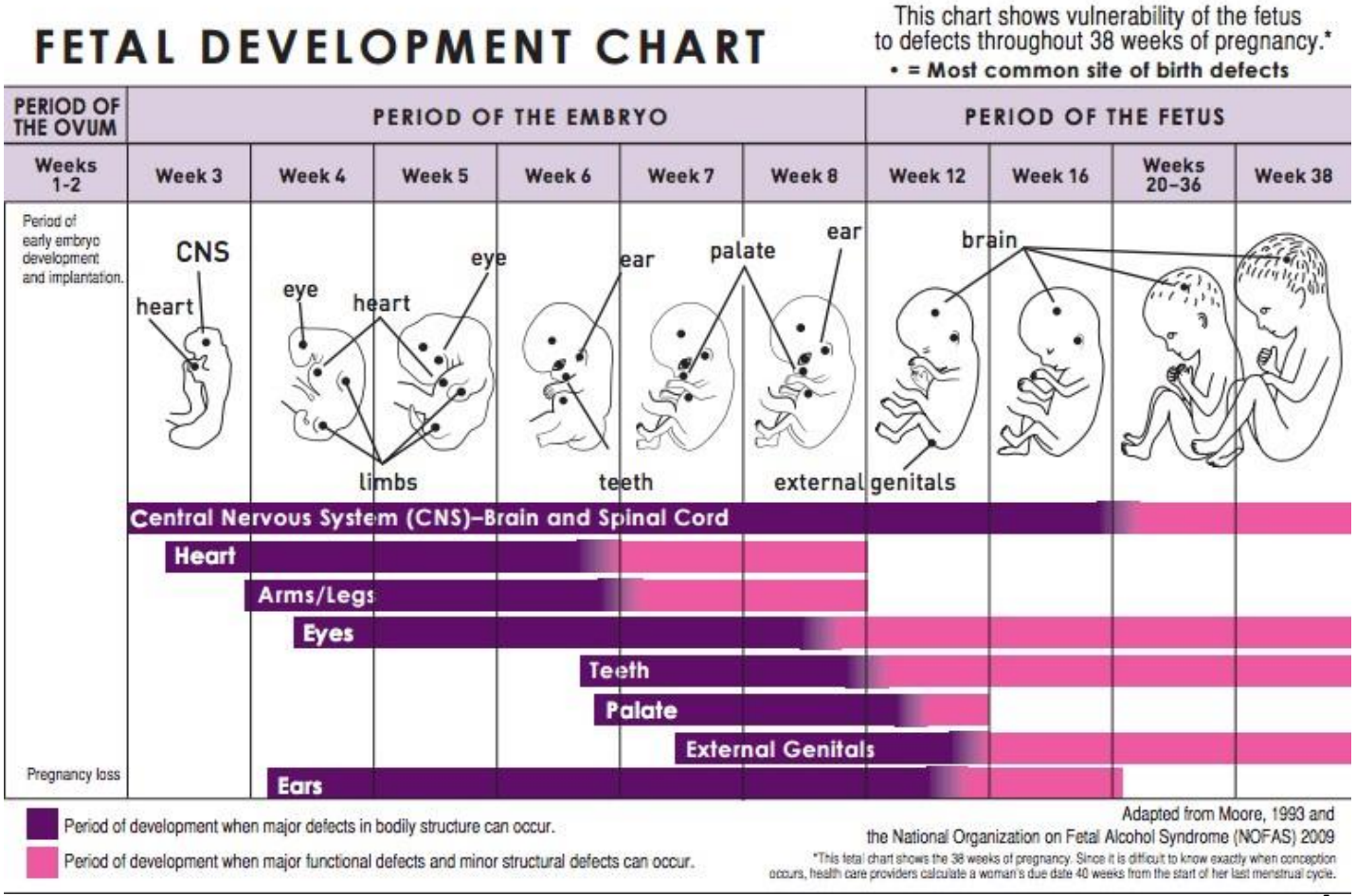
FETAL DEVELOPMENT



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THE PROBLEM (another one)

- 45% of pregnancies in developed countries are unplanned
- 75% of teen pregnancies are unplanned

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SCREENING FOR PSYCHIATRIC DISORDERS

- U.S. Preventative Services Task Force(2016):
  - Screening for depression including perinatal
- ACOG
  - Screening for psychiatric illness , including depression and anxiety at perinatal & postpartum visits
- Women's Preventative Services Initiative
  - Screening all adolescents & women for anxiety including pregnant and postpartum women
- e.g. Edinburgh Postnatal Depression Scale, PHQ-9, Mood Disorder Questionnaire

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RISKS OF STOPPING PSYCH MEDS FOR PREGANANCY

- High relapse rates
  - Major Depression
    - 60-70%
  - Bipolar Disorder
    - 80-100% (vs 30-37% who stay on medication)

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FDA PREGNANCY CATEGORIES & LABELLING

- 2014- FDA Pregnancy & Lactation Labelling Rule
- Starting 2015, all new products with labelling that summarizes current research
- Older products being phased in over time
  - Former FDA Pregnancy Categories still apply for these
  - A, B, C, D, X
    - Confusing system
    - Most new medications were placed in B until more human data available

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PRIMARY GOAL OF TREATMENT IN PREGNANCY

MINIMIZE THE NUMBER OF EXPOSURES!!!

- Medications
- Psychiatric illness

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Practical advice for designing a psychiatric medication plan for pregnancy

1. Make a plan before pregnancy
2. FDA category B is not necessarily safer than categories C and D
3. Use medications that we know more about: older is usually better
4. Don't undertreat—keep the patient well
5. Minimize the number of medications and the number of exposures
6. Active psychiatric illness counts as an exposure
7. Communication with family and providers is key
8. During pregnancy, it rarely makes sense to switch medications unless the patient is not tolerating or responding to the medication

LIMITATIONS OF THE LITERATURE

- Lack of controlled studies
- VERY difficult to control for confounding conditions associated w/ psychiatric illness
  - e.g. diabetes, obesity, smoking, drug use, etc.
- Many studies don't control for active illness
  - especially those on medication and with sxs
- Very few studies look at impact of pregnancy on dosing (or vice versa)
- Many studies misrepresent true "meaningfulness"

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PSYCHIATRIC MEDICATIONS

- Antidepressants
  - SSRIs
  - SNRIs
  - Tricyclics
- Lithium
- Anticonvulsants
- Antipsychotics
- Benzodiazepines
- Stimulants
- Sleep medications
- Other

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ANTIDEPRESSANTS

- Not associated w major organ malformations
  - Most data w/ SSRIs
  - Some w/bupropion and TCAs
- Cardiac defects
  - Older research showed association w/ SSRIs
    - Compared pts w MDD on SSRI to pts w/o MDD
  - Newer studies do not show an association
    - Compared pts w MDD on SSRI to pts w MDD not on SSRI
    - More evidence that **paroxetine (Paxil)** may cause defect

ANTIDEPRESSANTS

- Persistent Pulmonary Hypertension (PPHN)
  - Failure of pulmonary vasculature to decrease resistance at birth
  - 10%-20% mortality
  - Association w/ SSRIs reported (2006)
  - > 10 studies since
  - Very small increase in risk
    - @ 1% of exposed newborns
  - *Other risk factors for PPHN (obesity, tobacco, C-section) more common w MDD

ANTIDEPRESSANTS

- Preterm Birth/Low Birth Weight
  - Some increased risk but untreated MDD associated w/ increased risk
- Spontaneous Abortion
  - Modest increased risk (OR 1.4-1.6)
    - Very poor control for psychiatric illness & association
- Autism
  - No increased risk when psychiatric illness is controlled for

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SSRI EXPOSURE

TABLE. Studies of infant outcomes adjusted for psychiatric illness and severity of illness

Outcome of interest	Unadjusted odds ratio for exposure to SSRIs	Adjusted for psychiatric illness	Adjusted for severity of illness and/or other confounders
Cardiac defects[21]	1.25 (1.13-1.38)[a]	1.12 (1.00-1.26)	1.06 (0.93-1.22)
Preterm birth[16]	1.44 (1.34-1.56)[a]	1.61 (1.26-2.05)[a]	1.53 (1.40-1.66)[a]
Persistent pulmonary hypertension[23]	1.51 (1.35-1.69)[a]	1.36 (1.18-1.57)[a]	1.10 (0.94-1.29)
Autism: pooled case control[26]	1.7 (1.3-2.3)[a]	1.4 (1.0-2.0)	NA
Autism: pooled cohort[26]	1.8 (1.3-2.6)[a]	1.5 (0.9-2.7)	NA

[a] Odds ratios that are considered statistically significant.

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ANTIDEPRESSANTS

- Poor Neonatal Adaptation Syndrome (PNAS)
  - Poorly defined
    - Respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, constant crying
  - Most mild and self-limited
  - @ 1/3 of exposed newborns have mild sxs
  - Unclear if a withdrawal syndrome or toxicity
    - 1st report of neonatal "withdrawal" from antidepressant- 1973
  - FDA class (SSRIs; SNRIs) labeling (2004)
    - 3rd trimester exposure may be associated w/ PNAS

KETAMINE

- NMDA Glutamate antagonist
- FDA approved for treatment-resistant depression
- Minimal human data in pregnancy
- Animal studies
  - Some evidence for neurotoxicity
    - Especially prefrontal cortex
  - Also evidence for neuroprotection

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BREXANOLONE

- Synthetic version of allopregnanolone
  - A natural neurosteroid (progesterone metabolite)
- Not currently given during pregnancy or lactation
- Infused IV over 60 hours
- Often given on OB/GYN unit

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ELECTROCONVULSIVE THERAPY (ECT)

- For treatment-refractory depression or w/ severe sxs (eg SI, psychosis, mania, catatonia)
- No significant difference in
  - preterm labor or miscarriage
- Not teratogenic
  - Succinylcholine- typically used; not teratogenic
- "ECT should be considered a safe and effective treatment option for refractory or life-threatening depression in pregnancy." (APA & ACOG)

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TRANSCRANIAL MAGNETIC STIMULATION (rTMS)

- FDA approved for Tx of depression in 2008
- Stimulates areas of brain w/ electric pulse
- Often 5 sessions (@ 1hr) per week for 4-6 weeks
- Very safe w/ minimal side effects (occasional headache)
- No negative effects on pregnancy or fetus
- Follow-up study (1.5-5 years old):
  - No differences in cognitive or motor development compared to mothers w/ untreated depression in pregnancy

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DEEP BRAIN STIMULATION (DBS)

- For Movement Disorders (e.g. Parkinson's Disease), OCD, Tourette's syndrome
- Little information in pregnancy
- No apparent risk to fetus

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NON-PHARMACOLOGIC TREATMENTS

- Psychotherapy
  - especially CBT
- Yoga
- Other relaxation techniques
- Acupuncture
- Bright Light Therapy
- "Natural remedies" (Dietary supplements?)

LITHIUM

- 1st trimester exposure associated with Epstein Anomaly
  - Congenital heart defect
  - < 1% of exposed babies
- Other perinatal toxicity- case reports
  - Hypotonia, cyanosis, goiter, diabetes
- Long-term outcomes
  - F/U at age 5- no cognitive/behavioral issues
- Breastfeeding:
  - Low levels in milk
  - Can be problematic if baby dehydrated

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ANTICONVULSANTS

- Valproic Acid (Depakoate)
  - Up to 10% effects w 1st trimester exposure
  - Neural tube defects*, craniofacial abnormalities, cardiac defects, cleft palate, ↓ brain volume, hypospadias
- Carbamazepine (Tegretol)
  - Increase risk of spina bifida, other neural tube defects*, facial abnormalities, skeletal abnormalities, hypospadias
  - May increase risk of neonatal hemorrhage
- Lamotrigine (Lamictal)
  - No increased risk of congenital defects

* high dose folate during pregnancy may help prevent

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ANTIPSYCHOTICS

- Overall safe for use in pregnancy
- Studies show use in 1st trimester not assoc w/ ⬆ congenital malformations or cardiac defects
  - Possible slight increase for risperidone
- Studies show the psychiatric illness accounts for majority of risk to infant
- Lowest placental transfer for:
  - quetiapine (Seroquel), risperidone (Risperdal) haloperidol (Haldol), olanzapine (Zyprexa)

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ANTIPSYCHOTICS

- Normal metabolic changes in pregnancy may increase risk of gestational diabetes in conjunction w/ antipsychotics
- Many associated w/ maternal weight gain, ⬆infant birth weight, ⬆gestational diabetes
  - Very hard to control for comorbidities

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ANTIPSYCHOTICS

- Long-term risks unclear- very few studies
- FDA drug safety communication(2011)
  - potential risk for abnormal movements & withdrawal
    - restlessness, dystonia, hypertonia, tremor
- Several studies show no effect on cognition, IQ, test scores*, behavior in exposed children
  - 5 year-olds and 2nd - 8th graders

*math & language scores

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BENZODIAZEPINES

- Very messy data- much from 1970s
- Reports of various effects:
  - Temperature dysregulation, apnea, lower Apgar scores, hypotonia, poor feeding
- Early studies showed ⬆ risk of cleft palate
  - More recent studies show risk is low
- Possible slight ⬆ risk for ectopic pregnancy if taking prior to conception
- Combined w SSRI may ⬆ risk of congenital heart defect and PNAS

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OTHER ANXIOLYTICS

- SSRIs- as previous
- Buspirine (Buspar)
  - Very little evidence in humans
  - No ⬆ teratogenesis in animals
- Hydoxyzine (Vistaril)
  - Increasingly used to treat anxiety
  - Safety in pregnancy unclear
    - Possible ⬆ heart defects during 1st trimester
- Gabapentin (Neurontin)
  - Not approved for anxiety
  - No ⬆ risk of congenital malformations
  - Possible ⬆ pre-term birth & lower birth weight

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STIMULANTS

- Amphetamine (Adderall)/Methylphenidate (Ritalin; Concerta; Quillivant; Aptensio)
- Very few data
- No evidence of ⬆organ malformation
- Possible ⬆ risk of spontaneous abortion
- Long-term effects on cognition/behavior not known

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OTHER ADHD MEDICINES

- Atomoxetine (Straterra)
  - Little data in humans
  - No evidence of ⬆ birth defects
- Viloxazine (Qelbree)
  - Little data in humans
  - Possible toxicity in animal studies
- Clonidine (Catapress)
  - May lead to decreased heart rate in fetus
  - No evidence of teratogenicity
- Guanfacine (Tenex)
  - Little data in humans
  - No evidence of teratogenicity

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SLEEP AIDS

- Zolpidem (Ambien)
  - No ⬆ congenital abnormalities
  - Possible ⬆ risk of lower birth weight, preterm delivery, small for gestational age
- Zaleplon (Sonata)
  - No data in pregnancy
- Eszopiclone (Lunesta)
  - Few data in pregnancy; does not appear to be teratogenic
- Benzodiazepines
  - Temazepam (Restoril), Flurazepam (Dalmane), Triazolam (Halcion), etc
  - Concerns as above for anxiety
- Trazodone
  - Limited data- appears safe in pregnancy

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SLEEP AIDS-NEWER

- Suvorexant (Belsomra), Lemborexant (Dayvigo), Dairdorexant (Quviviq)
  - Dual Orexin Receptor Antagonists (DORAs)
  - Orexin involved with arousal & wakefulness
    - Produced in hypothalamus
    - May be involved in fertility
    - May be produced in placenta
  - Limited data in humans
- Ramelteon (Rozerem)and Tasimelteon (Hetlioz)
  - Melatonin agonists
  - Limited data in humans; some negative effects in animals
  - Increase prolactin

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SLEEP AIDS-MELATONIN

- A hormone produced in pineal gland
- May have a role in fertility & implantation
- Naturally increases during pregnancy
- Often decreased with severe preeclampsia
- Produced by the placenta
- May help establish circadian rhythm in fetus
- Classified as a dietary supplement in U.S.
  - Not regulated by FDA the way medications are

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OTCs & SUPPLEMENTS

- Diphenhydramine (Benadryl, Sominex, Tylenol PM)
- Doxylamine (Unisom)

- L-tryptophan
  - Efficacy unclear
  - Can interfere with other medications
- Magnesium
  - May help sleep and other pregnancy complications
- Valerian root
  - Minimal data in pregnancy
- Chamomile, Lavender, Lemon balm

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NON-PHARMACOLOGIC TREATMENTS

- **Try to address specific cause**
- Sleep Hygiene & Education
- Cognitive Behavioral Therapies (CBT-I)
- Acupuncture
- Yoga
- Aromatherapy?
- Warm baths?

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PERINATAL PRESCRIBING

RULE 1

All changes to drugs should be carried out before pregnancy if possible

This minimizes the number of exposures to the baby and promotes mood stability for the mother

RULE 2

Ideally the patient should be stable psychiatrically for at least 3 months before trying to get pregnant

This is not always practical but should provide some evidence and reassurance that the patient's mood is stable before pregnancy begins

RULE 3

Use drugs that we know something about: fewer data are available for recently approved drugs

If a drug has been available for several years there is at least some evidence that it is unlikely to be associated with major organ malformations, for example

RULE 4

Minimize the number of exposures for the baby

Try to minimize the number of drugs used but consider exposure to psychiatric illness an exposure.

Changing drugs once a woman is pregnant increases the number of exposures.

One common scenario is for a woman on a newer psychotropic drug to become pregnant and be switched to an older drug that has more evidence for safety. This plan increases the exposures for the baby—first to the newer drug and secondly to the older drug.

In addition, it is highly likely that the mother would relapse after switching, and exposure to the psychiatric disorder would constitute a third exposure for the child

RULE 5

Use a team approach

This includes family and other doctors involved in the patient's care.

To provide good care for mother and child it is essential to educate the family about the risks and benefits of treatment and no treatment, as well as signs and symptoms of relapse.

Similarly, communicating directly with the obstetrician and the pediatrician will minimize miscommunication and differences of opinion, and maximize the patient's treatment outcomes

RULE 6

Be supportive if the patient goes against your recommendations

There are many reasons why a woman might choose to go against her psychiatric treatment provider's advice, particularly regarding drug use during pregnancy.

It is important that the treatment provider continues to support the patient despite such disagreements.

Again, a team approach will often help avoid disagreements, and providing as much information as possible on the risks of untreated psychiatric disorders during pregnancy can also be helpful

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- Assistance with addiction and behavioral health resources and referrals
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- MACS TeleECHO™ Clinics: collaborative medical education through didactic presentations and case-based learning