Unipolar Depression

Special dosing considerations during the perinatal period and what to do with anti-depressant partial/non-response

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Disclosures

"Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose."

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General Consideration

- 50% of all pregnancies unplanned
- Caution about implicit bias
- 10.3% women in reproductive age on antidepressants
- 6.8% use anti-depressants in first trimester

- Ref: National Center for Health Statistics, National Health and Nutrition Examination Survey, 2015–2018,Finer et al 2014,Huybrechts et al 2014

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General Consideration

- Unease about prescribing medication during pregnancy
- Psychotropics cross placenta
- Observational studies only
- No RCT for pregnant women
- RCTs of antidepressants for perinatal depression have only been completed in post-partum women

Ref: Wisner et al AJP 2000,FDA,medication guide 2017

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Major Depressive Disorder

- Depressed mood
- Diminished interest or pleasure
- Weight loss
- Insomnia or hypersomnia
- Psycho-motor agitation or retardation
- Feeling or loss of energy
- Feeling of worthlessness or excessive guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death, SI

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Specifiers

- Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present. The intensity is distressing but manageable and result in minor impairment in social or occupational functioning
- Moderate: Number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for "mild" or "severe"
- Severe: Number of symptoms is substantially in excess of that required to make the diagnosis, intensity is distressing and unmanageable and markedly interferes with functioning.
- Psychotic symptoms: Delusions and or/ hallucinations

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Indications for Treatment

Ref: Team Health works for mom ,MCAP

	May not be indicated	Should be considered
Severity	Mild depression	Moderate to severe depression
Suicidal ideation	No	Yes
Function	Able to care for self /baby	Difficulty functioning
Course of illness	Responded to psychotherapy in past	Psychotic symptoms present
Access to care	Engaged in psychotherapy or non medication treatment	Limited access to alternative treatment
Co-morbid symptoms	No other co-morbid symptoms	Co-morbid anxiety disorders

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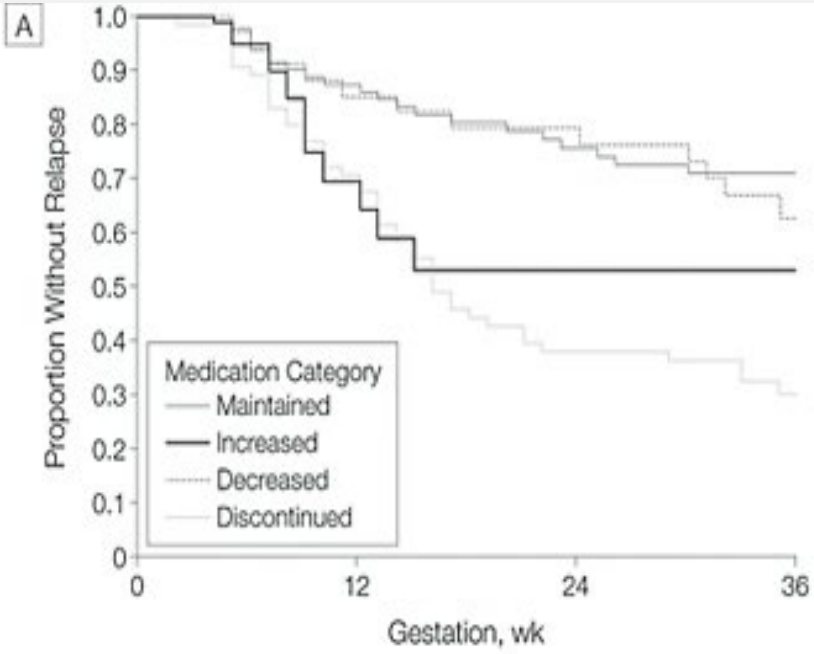
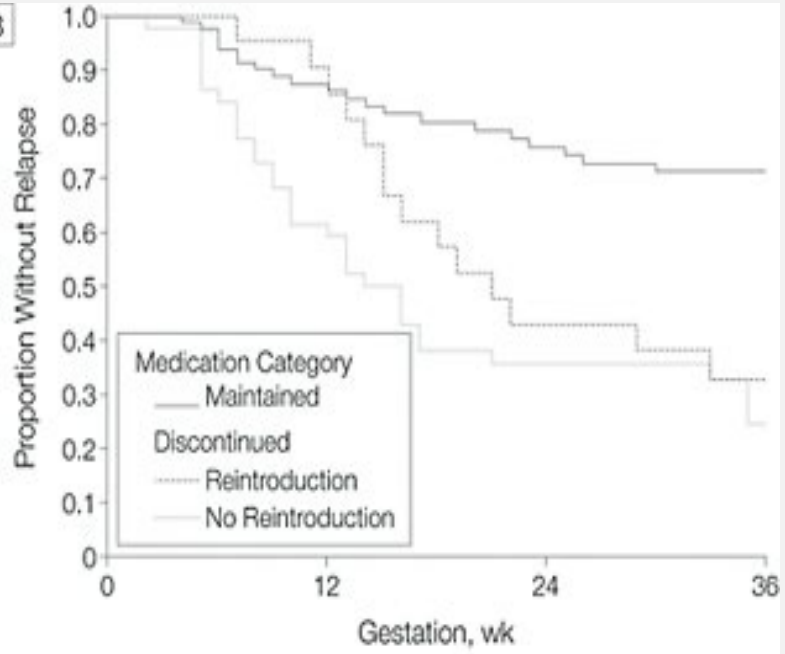
Risk of Stopping Anti-depressants

Ref:Cohen et al JAMA 2006



No. at Risk				
Maintained	82	63	49	28
Increased	20	13	9	4
Decreased	34	29	26	13
Discontinued	65	46	23	11



No. at Risk				
Maintained	82	63	49	28
Discontinued				
Reintroduction	21	19	9	3
No Reintroduction	44	27	14	8

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Treatment

- Start conversation early
- Moderate to severe depression
- Use lowest effective doses
- Consultations with experts
- Maximize non-medication alternatives
    - Maximize social supports
    - Psycho-education of patient and family members
    - CBT

Ref: Cohen et al 2006 ,DeVane et al 2006,Tracy et al 2005

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Preconception Counselling: Asymptomatic Patient

Asymptomatic patient with h/o of mild to moderate depression or perinatal depression, currently not on medication

- Assess for residual symptoms
- Period of stability at least 6 months
- Encourage patient to start therapy
- Monitor closely
- Plan to promptly start medication if symptoms emerge

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Preconception Counselling: Asymptomatic Patient

Asymptomatic patient with h/o severe depression, severe PPD, psychosis or SI.

- Assess for residual symptoms
- Period of stability at least 6 months
- Encourage linkage with psychotherapy
- Monitor closely
- Promptly start medication if symptoms (even mild) emerge
- Consider starting medication in third trimester or soon after birth of baby

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Preconception Counselling :Symptomatic Patient

- Mild symptoms, no h/o of depression, PPD: Psychotherapy and consider starting medication (patient comfort, psycho-social support)
- Mild symptoms with h/o of recurrent depression: Consider starting medication
- Moderate to severe symptoms: Psychotherapy and start treatment
- Patient should be stable for 6 months or more before conceiving

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Pregnant Patient: Symptomatic

- Mild symptoms no h/o : Psychotherapy and consider starting medication (patient comfort, psycho-social support)
- Mild symptoms with h/o of recurrent depression: Consider starting medication or optimizing current medications (switch or taper)
- Moderate to severe symptoms: Psychotherapy and start treatment
- Detailed h/o of medications trials and period of trial
- Consider starting medications that have been effective in past
- Consider medications that have been effective for family members

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Treatment with SSRI

- SSRI's are the first line of treatment for depression in perinatal period .
- Side-effects ,tolerability, past response to medication should dictate medication choice
- To limit exposure to fetus, one medication at therapeutic dose is preferable to multiple medications at sub-therapeutic dose
- Dose requirement may increase throughout pregnancy secondary change in blood volume, GFR and induction of cytochrome enzymes
- Insomnia is one of the most consistent risk factor for psychiatric decompensation and should be aggressively treated

Ref: Cohen et al 2006

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SSRI Use During Pregnancy

- "Data on reproductive safety of SSRI exceed what is known about most other medicines used in pregnancy "
- Increasing data on the pharmacologic treatment of depression during pregnancy
- Consistent conclusion that the absolute risk of SSRI exposure is small

Ref: *Louik C et 2007,Alwan et al 2007,Grigorladis et al 2013*

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Risk of Congenital Malformation

- There is no known consistent pattern of malformations with SSRI exposure
- Case-control studies reveal inconsistent data regarding teratogenic risk of individual SSRI
- No evidence of increased risk of congenital malformation
- No increase to small absolute risk increase of heart defects

Ref: Huybrechts et al 2014a,Wang et al 2015,Berard 2016

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Birth Outcomes

- Recent meta-analyses show no increased risk for miscarriages
- Small but significant risk of pre-term birth with anti-depressants even when controlling for depression(3-4 days)
- LBW or SGA: No significant risk, or if any very small and not clinically meaningful(<100 grams)

- Ref:Kjaersgaard et al 2013,Huang et al 2014,Wisner et al 2013

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Risk of PPHN

- FDA alert in 2006
- Lower risk in follow up studies
- Largest study (Ref: Huybrechts et al JAMA 2015) showed absolute risk of

  SSRI: 0.3%

  No antidepressants: 0.2%
- Other factors (race, BMI, C-section) may play a role
- Association is significantly reduced with adjustment of confounding factors
- Even if there is a risk, absolute risk is very low

Ref :Chambers 2006,Kallen 2008,Andrade et al 2009,Wichman 2007,Wilson et al 2010

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Poor Neonatal Adaptation

- Late trimester exposure to SSRI is associated with transient restlessness, increased muscle tone, jitteriness and tachypnea in 25-30% of infants
- Limitations: Not adequately controlled for maternal illness

  Inadequate blinding of exposure in neonates
- FDA requires labels for both SSRI and SNRI under “Use in specific population “section of drug labels

  Referred as “possibly a drug discontinuation syndrome “

  Clinical picture can be similar to serotonin syndrome
- Mild, self limited, no lasting repercussions
- Studies also indicate stopping anti-depressants in third trimester does not decrease risk for neonatal adaptation syndrome

Ref:Oberlander et al 2004,Moses-Kolko et al 2005,Deligiannidis et al 2014

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Tapering SSRI in Third Trimester

- “No data to support the practice of tapering SSRIs during the third trimester; furthermore, we must be aware of the risks associated with withdrawing antidepressant at a time when women are entering into a period of extremely high risk for affective illness “

Ref:Oberlander et al 2004,Moses-Kolko et al 2005,Deligiannidis et al 2014

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Risk of Autism Spectrum Disorder

- Alarm caused by initial studies (Rais et al 2014, Man et al 2015)
- Subsequent studies that have considered the confounds have found no increased risk
- Women with depression may have a higher risk of giving birth to children with autism
- Medication itself does not appear to confer additional risk

Ref :Mezzacappa et al 2017,Andrade et al 2017

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Long Term Neurobehavioral Effects

- Suri et al ., J clinical Psychiatry 2014
- 13 prospective studies have assessed neuro-behavioral infant outcome after in utero anti-depressant exposure
- N=721 children with antidepressant exposure and N=380 children without exposure
- Longest follow up is 4-5 years
- Majority do not suggest long term adverse effects neurobehavioral developments
- No significant difference in neurobehavioral development
- Generally encouraging but sample sizes are small
- Some reports of possible subtle effects on gross motor function and language development as well as potential for longer term consequences following poor neonatal adaptation
- Most studies do not assess for the severity of depressive symptoms in mothers

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Neurodevelopmental Implications

- No evidence of associated IQ deficits or long term behavioral problems
- Untreated depression in pregnancy and postpartum period associated with cognitive and behavioral problems.

Ref:Nulman et al 1997,Brown et al 2016,Capron et al 2015

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Which is the Best-Antidepressant in Perinatal Depression ?

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Medications: SSRI

Sertraline: Preferred medication

Start at 25 mg for 3-5 days then 50 mg, increase by 50 mg every 3-4 weeks up to 200 mg

Fluoxetine: well studied in pregnancy, RDI up to 14.6

Start at 20 mg, increase by 20 mg every 3-4 weeks up to 80 mg

Escitalopram: Limited data but no known risks

Start at 5 mg, increase by 5 mg every 3-4 weeks up to 20 mg

Citalopram: Relatively well studied, no known risks

Start at 20 mg, Max dose 40 mg

Risk of cardiac rhythm abnormalities above 40 mg

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Medications: SSRI

Paroxetine: Well studied ,some risk of cardiovascular defect, not supported by recent studies. Various other S/E limit use.

Start at 10 mg, increase by 10mg up to 60 mg.

Fluvoxamine: Limited data, no known teratogenicity. Increased risk of drug –drug interactions

Start at 25 mg, increase by 25-50 mg every 3-4 weeks up to 300mg

Vilazodone (Viibryd), Vortioxetine (Trintellix): No human data

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Medications: SSRI

Pharmacokinetics of pregnancy lead to plasma concentration decrease by end of pregnancy. Doses may need to be higher then FDA limits to achieve therapeutic effects

Common S/E

- GI S/E (nausea, heart burn, diarrhea, constipation)
- Headache, dizziness, vivid dreams
- Activation (restlessness, increased anxiety)
- Increase appetite/weight
- Sexual S/E

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Medications: SNRI

Less well studied then SSRI, more likely to cause withdrawal

Venlafaxine: Bulk of evidence shows no known teratogenicity

May increase diastolic BP, caution in patients with pre-eclampsia

Start XL formulation at 37.5 mg and titrate up to 225 mg

Desvenlafaxine: No systematic studies in human, closely related to venlafaxine, likely safe

Duloxetine: Bulk of evidence shows no risk

Start at 30 mg, increase 3-4 weeks to 120mg

Levomilnacipran: No human data

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Bupropion

- Limited data but bulk of evidence has not shown teratogenicity
- No risk of weight gain or sexual S/E
- Helpful for smoking cessation
- Some risk of reducing seizure threshold: Caution in pre-eclampsia
- Some risk of lowering milk supply
- Preferred XL formulation
- Start at 150 mg, max 450 mg

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Mirtazapine

- Limited human data
- No known teratogenicity
- Few sexual S/E
- Risk of metabolic syndrome
- Anti-emetic: Useful in hyperemesis gravidarum
- Start at 7.5 mg, titrate up to 45 mg

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Other Antidepressants

TCAs

- Generally considered safe during pregnancy and breast-feeding
- Amitriptyline and Nortriptyline have the most data
- Imipramine and Desipramine are other safe options
- Clomipramine: Limited human data shows possible risk of cardiac malformation
- Doxepin considered safe in pregnancy but not in breast feeding

MAOI: No human data

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Breastfeeding is a choice,

Lets treat it that way

Gayle Tzemach Lemmon Posted 05/11/2012

www.huffingtonpost.com

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Considerations during Lactation

- Relative infant dose of<10% acceptable in lactation
- Exposure through breast milk is less as compared to transplacental passage
- Practice of pumping and dumping is not advised
- Sleep deprivation increases risk of relapse for mother
- Collaborate with pediatrician
- Infant monitored for sedation, weight gain and developmental milestones

Ref:Burkey et al 2013

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Exposure to Antidepressant via Breastmilk

- Relative infant doses less than 10% of maternal dosage are acceptable per FDA;
- Antidepressant RIDs https://www.ncbi.nlm.nih.gov/books/NBK501922/
  - Bupropion 0.2-2.0
  - Citalopram 3-10
  - Desvenlafaxine 5.5-8.1
  - Doxepin: AVOID: reports of hypotonia, sedation, vomiting, suppressed respiratory rate, weight loss
  - Duloxetine <1
  - Escitalopram 5.2-7.9
  - Fluoxetine 0.6-14.6 (long half-life)
  - Fluvoxamine <2
  - Mirtazapine 0.5-3
  - Nortriptyline 0.87-3.71 (watch for dry mouth, constipation, urinary retention)- favored TCA in lactation
  - Paroxetine 1.2-2.8
  - Sertraline 0.4-3
  - Venlafaxine 6-9

Ref :Chad L et al 2013; Newton ER & Hale TW 2015

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Insomnia in Perinatal Period

- Pregnant women experience changes in sleep pattern
- Increased rate of pre-term and LBW
- Increased pain perception, increased rate of C/S
- Increased risk of perinatal depression and anxiety
- Review sleep hygiene
- CBT-I identified as evidence based treatment of choice
- Mindfulness based yoga intervention improve sleep quality

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Insomnia in Perinatal Period

- Doxylamine
- Melatonin: Concerns about circadian rhythm and reproductive function in fetus
- Diphenhydramine: Limited data, occasional use is acceptable
- Trazodone: Not likely to result in major congenital malformation, distributed in milk in small amounts
- Zolpidem: Risk for preterm, LBW. Risk for flaccidity and withdrawal, safe during lactation
- Amitriptyline (150 mg): May cause withdrawal, considered safe in lactation (WHO)
- Doxepin: Can consider in pregnancy, but avoid in breastfeeding(hypotonia, respiratory depression)
- Zaleplon: little pregnancy and lactation data
- Zopiclone or Eszopiclone : No increased risk of malformations(small studies), but withdrawal at birth, low excretion into breastmilk
- Ramelteon, Belsomra, Valerian root,CBD: No data

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Combination/Augmentation

- 50% reduction in symptoms is considered a response
- 1/3 of patients remit on first anti-depressant treatment
- After a year of treatment with a sequence of 4 antidepressants only 2/3 patients achieve remission
- TRD: No response after 2 adequate antidepressant trial
- 10% patients develop TRD in first year of treatment

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Partial/Non-Response

Inadequate dose

Titration or Compliance limited by S/E

Third trimester: May need dose above FDA max.

Psychosocial factors (unemployment, education level, social support, financial stressors, abuse, complicated pregnancy)

Effective medications in past or in family

Assess for residual symptoms: fatigue, motivation, concentration, insomnia, SI

Assess for co-morbid d/o: substance use, anxiety, psychotic symptoms, pain d/o

Assess for mania or hypomania

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Residual Symptoms Management

- Reduced positive affect: depressed mood, loss of happiness, interest, pleasure, loss of energy and enthusiasm, decreased self confidence: switch to Wellbutrin or SNRI or augment with Wellbutrin
- Increased negative affect: anxiety, guilt, fear, irritability: SNRI
- Fatigue /Motivation: Wellbutrin or SNRI
- Concentration: Wellbutrin/ SNRI/ Lithium/ Thyroid
- Appetite: Mirtazapine
- Insomnia : Mirtazapine
- SI: Lithium

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Co-Morbid Disorders

- Substance Use d/o
- Nicotine Dependence: Wellbutrin
- Anxiety d/o: Optimize SSRI
- Psychotic symptoms: Atypical antipsychotics
- Pain d/o: SNRI,TCA

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Brexanolone (Zulresso)

- Allopregnanolone /Neurosteroid
- Allosteric modulator of GABA receptors
- Schedule IV drug
- 7/10 patients receiving medication achieved remission after the 60 hours (placebo 1/11)
- Requires 60 hours of continuous infusion
- Mothers are required to stop breastfeeding
- Sedation and dizziness are common S/E

Ref: Kane et al 2017

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Thank You !

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