A PRIMER ON CAMS FOR PERIPARTUM DEPRESSION
Learning Objective

• Explain the therapeutic and safety profiles of complementary and alternative medicines (CAMs) that may be used for peripartum depression
Epidemiology of Peripartum Depression

- ~14-23% of women suffer with depression at some point during their pregnancy
  - 10% general population
  - 25% among physician mothers

- Underdiagnosed
  - Overlapping symptoms with pregnancy (e.g., fatigue, sleep disturbance) or postpartum symptoms (e.g., "baby blues")
  - Lack of symptom reporting

- Only 10% of women with prenatal depression receive conventional treatment
  - Lack of diagnosis
  - Fears of harm to the fetus
  - Stigma

- Less than 50% of physicians receive treatment

- The American College of Gynecology and Obstetrics recommends screening for depression at least once during the peripartum period
  - The Edinburg Postnatal Depression scale (EPDS) has been validated for use during both the prenatal and postnatal periods

Consequences of Untreated Depression During Pregnancy

- Miscarriage
- Inadequate maternal weight gain
- Poor self-care
- Substance use
- Preeclampsia
- Postpartum depression
- Cesarean delivery

- Impaired fetoplacental function
- Preterm birth
- Low birth weight
- Small for gestational age
- Fetal distress
- Neonatal care unit admittance
- Impaired cognitive and emotional development

Untreated depression during pregnancy

Untreated postnatal depression

Decreased gray matter volume in offspring at age 2 months

Child attention problems

Conventional Antidepressant Therapies for Prenatal Depression

- First-line therapies include non-pharmacological, psychotherapeutic approaches
  - May be ineffective
  - Limited access (e.g., women from rural areas)
  - Long duration to therapeutic benefit (up to 12 weeks)

- Antidepressant pharmacotherapies
  - SSRIs, SNRIs, TCAs
  - Have been rigorously tested in clinical trials of depression during pregnancy
  - Most studies and meta-analyses indicate safety for use during pregnancy
  - Some low risk of:
    - Premature delivery, low birth weight, major fetal malformations, neonatal behavioral syndrome, and persistent pulmonary hypertension
  - 66% of women find the idea of taking a psychotropic medication during pregnancy unacceptable

- TMS – limited but encouraging data support safety and efficacy

Complementary and Alternative Medicines (CAMs)

- Herbal remedies/supplements (such as folate, St. John’s Wort)
- Mind/body practices (such as yoga, meditation, prayer, massage, acupuncture, and exercise)
- As many as 50% of women turn to CAMs during pregnancy
  - For relief from depression, anxiety, urinary tract infections, nausea, induction of labor
- Less than 40% of women disclose to their clinician that they are using CAMs
- Many women consider CAMs (including herbal remedies/supplements) to be “natural” and therefore “safe”

Among Nurse Midwives

41.5% have received some formal training on CAM use during pregnancy

Most feel that their training in use of CAMs is inadequate

73.2% recommend CAM therapy, including herbal supplementation

Potential Issues With CAMs

• CAMs, especially herbal remedies, have not been tested in rigorous clinical trials for their safety and efficacy in prenatal depression (unlike conventional antidepressants)
• Herbal remedies/supplements are not FDA-regulated
  • May contain contaminants (arsenic, lead, mercury, bacteria)
  • Varying degrees of active ingredients
• When utilized as alternatives to conventional antidepressants, may leave depression undertreated
• Potential for interactions with conventional medications
• May be contraindicated during pregnancy

Folate

• Vitamin B complex found in leafy greens like spinach
• Required for normal cell growth and replication, nucleic acid synthesis, DNA repair, and modulation of homocysteine
• Maternal folate deficiency is linked to:
  • Erroneous embryonic neural tube development
  • Major depressive disorder, schizophrenia, and bipolar disorder
  • Less likely to respond to SSRI pharmacotherapy
• Several countries, including the United States, require folic acid (a synthetic form of folate) supplementation in grain products
• Recommended 0.4-1 mg/day of folic acid intake in women of reproductive age
• Little evidence to suggest efficacy of folate monotherapy for depression; however, may be useful as an adjunct to antidepressant pharmacotherapy

Folate Metabolism

Normal homocysteine levels

Normal synaptic plasticity and neuronal signal transmission

Normal neurotransmitter production

Normal silencing of gene expression
Methylenetetrahydrofolate Reductase (MTHFR)

- MTHFR is required for folate metabolism to L-methylfolate
- C677T and A1298C polymorphisms
  - Result in reduced MTHFR enzyme activity
  - Linked with major depressive disorder, schizophrenia, and bipolar disorder

L-methylfolate

- L-methylfolate (MTHF) supplementation bypasses MTHFR metabolism of folate
  - Not affected by MTHFR polymorphisms
- 15 mg/day of L-methylfolate augmentation of SSRI shows significant reduction in Hamilton Depression Rating Scale (HAMD) scores
- Enlyte (L-methylfolate, folinic acid, folic acid) has FDA authorization to be promoted for depression due to folate deficiency
- Further studies are needed to evaluate safety and efficacy in prenatal depression

S-adenosylmethionine (SAMe)

• SAMe is a major methyl donor in the CNS

• Involved in DNA methylation, neurotransmitter synthesis, and synaptic plasticity

• Several studies indicate SAMe is as effective as tricyclic antidepressants (TCAs) for treating depression

• Efficacy and safety in prenatal depression have not been adequately addressed to recommend its use during pregnancy

Omega-3 Fatty Acids

- Eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA)
  - Found naturally in fish
  - Help maintain membrane fluidity and structure
  - Aid in metabolism of neurotransmitters
  - Anti-inflammatory
  - May be necessary for normal neural tube development

- Consumption thought to be low in Western civilizations, especially relative to omega-6 fatty acids (found in processed foods containing vegetable oil)

- Some data indicating efficacy as adjunctive to antidepressant therapy in the treatment of depression during pregnancy

- Recommended that pregnant women consume sufficient levels of EPA+DHA by consuming 8-12 ounces of seafood weekly

- Confounded by FDA advisories against mercury contamination in fish

- May be contraindicated in patients taking anticoagulants

Saint John’s Wort (SJW)

- *Hypericum perforatum*
- Flowering shrub native to Europe
- Most commonly utilized herbal CAM for depression in the general population
- Some studies indicating 300-1200 mg/day of 5% extract may be effective for mild to moderate (but not severe) depression
- Primary bioactive substances are hypericin and hyperforin
  - Decrease serotonin receptor density
  - Decrease production of cortisol
  - Inhibit reuptake of serotonin, norepinephrine, dopamine and acetylcholine

Potential Issues With SJW Use During Pregnancy

• Few rigorous trials on the safety and efficacy of SJW for prenatal depression
  • Some human and animal studies suggest no major fetal consequences
  • Other studies have found increased risk of colic, drowsiness, lethargy, and low birth weight associated with SJW use during pregnancy

• As an herbal remedy; not FDA regulated for purity

• Strong inducer of the liver enzyme cytochrome P450 3A4 (CYP3A4)
  • CYP3A4 is involved in metabolism of many conventional medications, including SSRIs
  • May impair effectiveness of medications metabolized by CYP3A4
  • At this time, SJW is not recommended as a monotherapy or adjunct therapy in the treatment of prenatal depression

Bright Light Therapy

• Hypothesized to correct altered circadian rhythms, a condition that has been linked to depression
• 7000-10,000 lux for 30 min within the first 10 minutes of waking
• Effective for both MDD and seasonal affective disorder
• Results for efficacy in prenatal depression are mixed
• To date, studies have shown no clinically meaningful side effects to the fetus and no birth complications
• Care should be exercised in patients with bipolar disorder as there is some evidence for induction of mania

Exercise

• Attractive adjunctive treatment for depression due to:
  • Low cost
  • Availability
  • Wide range of overall health benefits

• Numerous studies in the general population report benefits of exercise to symptoms of depression
  • Hypothetically due to impact on both neuroendocrine and neurotransmitter functions

• May be more effective for prenatal depression during early and middle stages rather than later stages

• The American College of Obstetricians and Gynecologists (ACOG) recommends 30 minutes of moderate exercise on most days in pregnant women (unless otherwise contraindicated)

Yoga

• Combines physical postures with breathing and relaxation techniques
• Involves physical exercise (which is recommended by ACOG)
• Reported to decrease symptoms of depression and anxiety during pregnancy
• One study found increased birthweight and gestational age associated with prenatal yoga
• Studies have shown little to no safety concerns for prenatal depression
• May be best suited as adjunctive to conventional antidepressant therapy, especially in more severe cases of prenatal depression

Acupuncture

- Involves placement of fine needles at specific points in the body
- Hypothetically restores blocked energy flow
- Mixed data regarding efficacy in treating depression and anxiety during pregnancy
- Little in terms of safety data
- Some acupuncture points may stimulate the uterus, causing premature labor and delivery
Massage

• Mixed data suggesting that prenatal massage may reduce symptoms of depression and anxiety
• Massage delivered by a partner or professional may be equally effective
• Massage may hypothetically modulate the hypothalamic-pituitary-adrenal (HPA) axis via increased vagal activity and upregulation of glucocorticoid receptors
• Although prenatal massage appears relatively safe, there are not enough rigorous data on efficacy to recommend as an alternative to conventional antidepressant therapy

Summary

- Many women with depression turn to the use of CAMs as treatments they consider “natural” and therefore “safe” during pregnancy

- Relative to conventional antidepressants, CAM therapies have not been rigorously tested and show mixed data for efficacy and safety

- Although their efficacy for treating prenatal depression is not yet clear, certain CAMs (such as folate and exercise) are recommended during pregnancy as adjunctive to conventional antidepressant therapies

- It is essential that clinicians are informed by their patients regarding the use of CAMs so that CAM-drug interactions and potentially contraindicated treatments can be avoided – this will likely require inquiry by the clinician