Unique Aspects of Sleep in Women

Abid Bhat, MD MBA
Professor of Medicine &
Program Director, Sleep Medicine Fellowship Program,
University of Missouri Kansas City School of Medicine
Financial Disclosure

• None
Objectives:

1. Discuss unique aspects of sleep in women.

2. Discuss changes in sleep across different phases of life, including menstrual cycle, pregnancy and menopause.

3. Identify and treat common sleep disorders in women.
Limitation:

- Overall, insufficient data exists about sleep and sleep disorders in women.

Variability among Females:
- menstrual cycle: exact timing (need to confirm ovulation, rule out pregnancy, assess ovarian hormone concentrations)
- pregnancy: different effects by trimester
- menopause: vasomotor symptoms

American Academy of Sleep Medicine
Women and their sleep:

* 40% of women sleep well almost every night

* 46% reported sleep problems almost every night

* 84% of pregnant and post-partum women had sleep problems at least a few nights per week

National Sleep Foundation, 2007
• **Women of any age group more likely** than men **report dissatisfaction** with their sleep and daytime consequences.

• **Insomnia more common in women** and the disparity increases with age

Sleep in Infancy & Childhood:

• **Video:** Girls have a longer sleep period and more quiet sleep than boys!

• **Polysomnography:** Girls have less EEG arousals (better sleep efficiency) than boys!

2. Dev Psychol. 48:1511-1528 2012
3. Sleep 33:1055-1060 2010
Sleep During Adolescence

• Young women have shorter sleep latency and higher sleep efficiency compared to young men!

• Onset of menses linked to increased risk of insomnia.

Sleep & Menstrual Cycle:
Human Reproductive Menstrual Cycle

<table>
<thead>
<tr>
<th>Ovulation</th>
<th>FSH</th>
<th>Estrogen</th>
<th>Progesterone</th>
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Day | 1-4 | 14 | 21 | 28 |
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• Estrogen & progesterone influence sleep and circadian rhythm.

• Receptors for estrogen and progesterone present in many sleep-wake regulating nuclei in the CNS.

• Estradiol ↑EEG arousal in rodents through its inhibitory effect on sleep promoting neurons,

J Neurosci. 31:16107-16116 2011
Common Complaints

- Insomnia or Excessive Daytime Sleepiness

- Worst sleep efficiency in fourth week

- Recurrent emotional and physical symptoms in association with the menstrual cycle

Premenstrual Syndrome (PMS)

- Noted in 60% female.

- Irritability, mood swings, fatigue, depression, headaches, bloating and cramping.

- Frequent awakenings, non-restorative sleep, nightmares & excessive daytime sleepiness.

Premenstrual Dysmorphic Disorder:

• Severe Symptoms

• **Lower melatonin** levels in menstrual phase

• **Light therapy** a promising treatment by altering nocturnal melatonin secretion.

J Biol Rhythms. 12:47-64 1997
Menstrual-related Hypersomnia

• Sub-type of the Klein-Levin Syndrome (ICSD-3)
  ▪ Recurrent episodes of excessive sleepiness occur in association with the menstrual cycle.
  ▪ Relapsing severe hypersomnia with associated cognitive, psychiatric and behavioral disturbances
  ▪ Compulsive eating, hyper sexuality and depression associated

American Academy of Sleep Medicine
Menstrual Cycle & Shift Work!

• Female shift workers report *menstrual irregularities*

• Nurses working rotating shifts reported increased menstrual related complaints

• “More tension, nervousness, weakness and sickness at menstruation”
Polycystic Ovary Syndrome
• Affects 4 to 12% women of reproductive age

• 30 times more likely to suffer from sleep apnea compared to controls

1. J Clin Endocrinol Metab. 86:517-520 2001
2. J Clin Endocrinol Metab. 96:365-374 2011
Sleep During Pregnancy
• Disturbed sleep considered a normal part of pregnancy and therefore not warranting investigation or treatment!
Physiological Changes in Pregnancy:

- Narrowing of upper airways
- Increase in snoring
- Decrease in FRC
- Decrease in chest wall compliance
- Decrease in respiratory system compliance
- Difficulty in laying supine (late pregnancy)
- Increase in minute ventilation
- Respiratory alkalosis
- Lowered oxygen reserve
- Rightward shift of oxy-hemoglobin dissociation curve
- Increase in gastroesophageal reflux
- Increase in renal blood flow
- Dilatation of renal pelvis and ureters
- Urinary frequency
Sleep Loss and Adverse Pregnancy Outcomes

* Prenatal depression
* Gestational diabetes
* Pre-eclampsia
* Prolonged labor
* Increased Cesarean sections
* Abnormal fetal growth
* Preterm birth

Sleep in Pregnancy by Trimester

- **1st Trimester**
  - Excessive daytime sleepiness
  - Nausea & vomiting, frequent urination

- **2nd Trimester**
  - Sleep normalizes
  - Decreased nausea

- **3rd Trimester**
  - Decreased total sleep time
  - Increased insomnia / nocturnal awakenings
  - Increased daytime sleepiness

Effect of Progesterone

• **Soporific effect** may partly explain daytime sleepiness and fatigue in the first trimester, when progesterone is steadily rising.

• Animal and human studies have demonstrated that exogenous progesterone administration **shortens latency to sleep onset**.

Effect of Estrogen

• Estrogen has **excitatory effects** on the nervous system

• Selectively ↓ REM sleep.

• Estrogen also suppresses dopamine release into the blood circulation, which **may contribute to restless legs syndrome**

2. Relat Disord. 20 (7):716-722 2014
Treatment of Insomnia in Pregnancy
Non-pharmacological options

• Behavioral and cognitive therapies should be the initial treatment for women with pregnancy-related insomnia, after excluding primary sleep disorders.

• Cognitive-behavioral therapy for insomnia, improving sleep hygiene, using relaxation techniques.

• Lifestyle modifications such as regular exercise and avoidance of smoking and alcohol.
• 11% of pregnant women used a sleep aid and 1% used alcohol at some point in pregnancy to help them fall sleep!
Pharmacological Therapy

- **Diphenhydramine and Amitriptyline**: during pregnancy categorized as possible but unlikely to harm the fetus.

- **Non-Benzodiazepine agents** (Zolpidem): avoided or used with extreme caution in pregnancy.

- **Benzodiazepines**: Cleft palate and **floppy Baby syndrome**.
Pregnancy & Sleep Disordered Breathing
• Less than 3% of clinicians reported routinely asking patients about snoring. Yet 32% of women reported that they snored!
Respiratory Changes that increase the risk of sleep disordered breathing
• ↑ levels of estrogen and progesterone induce capillary engorgement, and mucosal **edema of the upper airway**.

• Hyperventilation with ↑sensitivity to CO₂ predisposed to obstructive/central **apnea events**
Respiratory changes that protect against sleep disordered breathing
• High circulating progesterone during pregnancy may protect the upper airway from obstruction by increasing upper airway dilator muscle (genioglossal) activity

• As pregnancy advances, women tend to spend less time in the supine position during sleep
Risk factors for Sleep Apnea in Pregnancy:

• Habitual snoring,

• Chronic hypertension,

• Baseline BMI ≥ 25 to 30, and

• Older maternal age
Screening tools for Sleep Apnea:

• Epworth sleepiness Scale.

• Berlin Questionnaire

• STOP-Bang Questionnaire
The STOP BANG Questionnaire

- **S** = **Snoring.** Do you snore loudly?
- **T** = **Tiredness.** Do you often feel tired, fatigued, or sleepy during daytime?
- **O** = **Observed apnea.** Has anyone observed you stop breathing during your sleep?
- **P** = **Pressure.** Do you have or are you being treated for high BP?
- **B** = **BMI > 35**
- **A** = **Age > 50 y**
- **N** = **Neck circumference > 40 cm**
- **G** = **Male** gender

High risk of OSA: ≥ 3 or more questions answered yes
Low risk of OSA: < 3 questions answered yes
• Most OSA screening tools have a sensitivity between 70% and 80%, with very low specificity.

• None of them worked very well in pregnant women.

Mahesh Nagappa, MD. International Anesthesia Research Society (abstract S-330)
Sleep Apnea and Hypertensive Disorders of Pregnancy
• A two-fold increase in the likelihood of preeclampsia in pregnancies complicated by sleep apnea

• Higher incidence of unplanned caesarian sections & fetal growth retardation

• CPAP safe to use during pregnancy

2. Sleep Breath. 18 (4):703-713 2014
Pregnancy and Restless Legs Syndrome
• Irresistible desire to move legs prior going to sleep.

• 15 to 25% of pregnant women in Western countries

• Prolactin has anti-dopaminergic activity

• Peaks in third trimester

• Iron and Folate deficiency, a possible trigger

Sleep Med Rev. 16 (4):297-307 2012
Treatment of RLS:

• Behavioral modification (avoid caffeine, anti-depressants and smoking)

• Iron supplementation

• Pharmacologic treatment (Ropinirole, Pramipaxole, Clonazepam) in last trimester (teratogenic effects)
Sleep-Related Leg Cramps
• Painful muscle contractions in the foot or leg.

• Sudden awakening is typical

• **Prevalence** of nocturnal leg cramps increases from 10% before pregnancy to 21% in the first trimester, 57% in the second trimester, and up to **75% in the third trimester**

• Vitamin B1 & B6 may be beneficial

Menopause & Sleep
• Permanent amenorrhea for a period of 12 months.

• Mean age in the US is 51 years.

• Peri-menopause: hormonal changes begin 7 to 10 years before the final menses.

Causes of Sleep Complaints in Menopause:

- Hormonal Changes
- Medical disorders
- Mood disorders
- Sleep Disorders
- Career Changes
- Caregiver responsibilities
• Hallmark symptoms include **hot flashes and sweating** (vasomotor symptoms)

• 75% of postmenopausal women and 40% of premenopausal women suffer from vasomotor symptoms.
• Usually lasts for 1 to 2 years.

• 25% report for up to 5 years and 9% may have it all their lifetime after menopause.
Common Complaints:

• Difficulty falling asleep and maintaining sleep.
• Early morning awakening
• Mood swings, palpitations and higher level of stress
• Vaginal dryness and urinary problems
RISK Factors for Hot Flashes:

- Obesity
- Smoking
- Reduced physical activity
- Lower socioeconomic status
- African-American Ethnicity
• Etiology is unknown.

• Hot Flashes are circadian with peak frequency in late evening

• Insomnia may be the exclusive climacteric symptom
Other Causes of Sweating:

- Physiologic (Menopause, emotional distress)

- Medications (Tamoxifen, Diltiazem, Levodopa)

- Diseases (Carcinoid syndrome, Hyperthyroidism, Systemic mastocytosis, VIPomas, Renal cell carcinoma)
Sleep Apnea and Menopause
- OSA less common in women until after menopause (~age 50) unless significantly obese

- Prevalence peaks at 65 years for women (vs. 55 years in men)

- **Post menopausal women 2.6 times more likely** than premenopausal women to have **sleep apnea**.
Gender difference in Sleep Apnea Presentation

<table>
<thead>
<tr>
<th></th>
<th>MEN</th>
<th>WOMEN</th>
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<tbody>
<tr>
<td>Snoring</td>
<td>*****</td>
<td>**</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
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<td>Morning headaches</td>
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<tr>
<td><strong>Depressive features</strong></td>
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<td>Apnea Frequency</td>
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<td>Hypopnea Frequency</td>
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Sleep 2002;25(4):412-9
Treating Hot Flashes
Non-Pharmacological interventions:

• Life style changes: Quit smoking, Limit Caffeine & alcohol intake

• Dress in layers, Ambient temperature in bedroom

• Meditation, Yoga, Mindfulness therapy
Pharmacologic Therapy for Menopause

• Hormone Replacement Therapy (HRT)

• Clonidine

• Gabapentin

• SSRI & SNRI (Paroxetine approved by the FDA)
• Paroxetine should be **avoided** in women taking Tamoxifen (blocks the metabolism)
Hormone Replacement Therapy (HRT) for Menopause:
- **HRT users report better quality of sleep than nonusers**

- Improved subjective sleep quality for 3 years after HRT

- **Mechanism:**
  - Estrogens likely acts on the Reticular Activating system
  - Progestin likely through GABA activity.

- **Risks associated with HRT**
  - Increased risk for breast cancer, stroke, heart disease and vascular dementia

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Bazedoxifene/Conjugated Estrogen

• Bazedoxifene, a selective estrogen receptor modulator.

• Combination available for treatment of hot flashes and osteoporosis prevention.

• Agonist effect on bone, antagonist effect on endometrium and neutral effects on breast tissue.

Other Options:

• Bio-identical Hormones
• Valerian
• Melatonin
• Flaxseed
Conclusion:

• Women’s sleep changes over the course of their life span.

• Women appear to have distinction in their sleep from men due to their physiological & hormonal differences.

• More research is needed to clarify the influence of the life cycle on sleep framework in women.
Questions