Unique Aspects of Sleep in Women

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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
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
• 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*.

References:

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 $\geq 25$ 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
Fig. 1

Sleep Medicine Clinics 2013 8, 65-72

DOI: (10.1016/j.jsmc.2012.11.004)

- High Risk
  STOP-Bang 5-8

- Intermediate Risk
  STOP-Bang 3-4

- Low risk of OSA
  STOP-Bang 0-2
• 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

*Int J Gynaecol Obstet. 95 (1):48-49 2006*
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:
• 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.

Am J Respir Crit Care Med. 167:1181-1185 2003
# 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>
<td>*****</td>
<td>**</td>
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<tr>
<td><strong>Morning headaches</strong></td>
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<td>********</td>
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<tr>
<td><strong>Depressive features</strong></td>
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<td>********</td>
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<tr>
<td>Apnea Frequency</td>
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<tr>
<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