

Unique Aspects of Sleep in Women

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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

- **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

Zhang B et al (2006) Sleep 29:85-93

Hartz A et al (2013) Sleep Med 14(1):71-78

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!

1. J Dev Behav Pediatr. 22:226-233 2001
2. Dev Psychol. 48:1511-1528 2012
3. Sleep 33:1055-1060 2010

Sleep During Adolescence

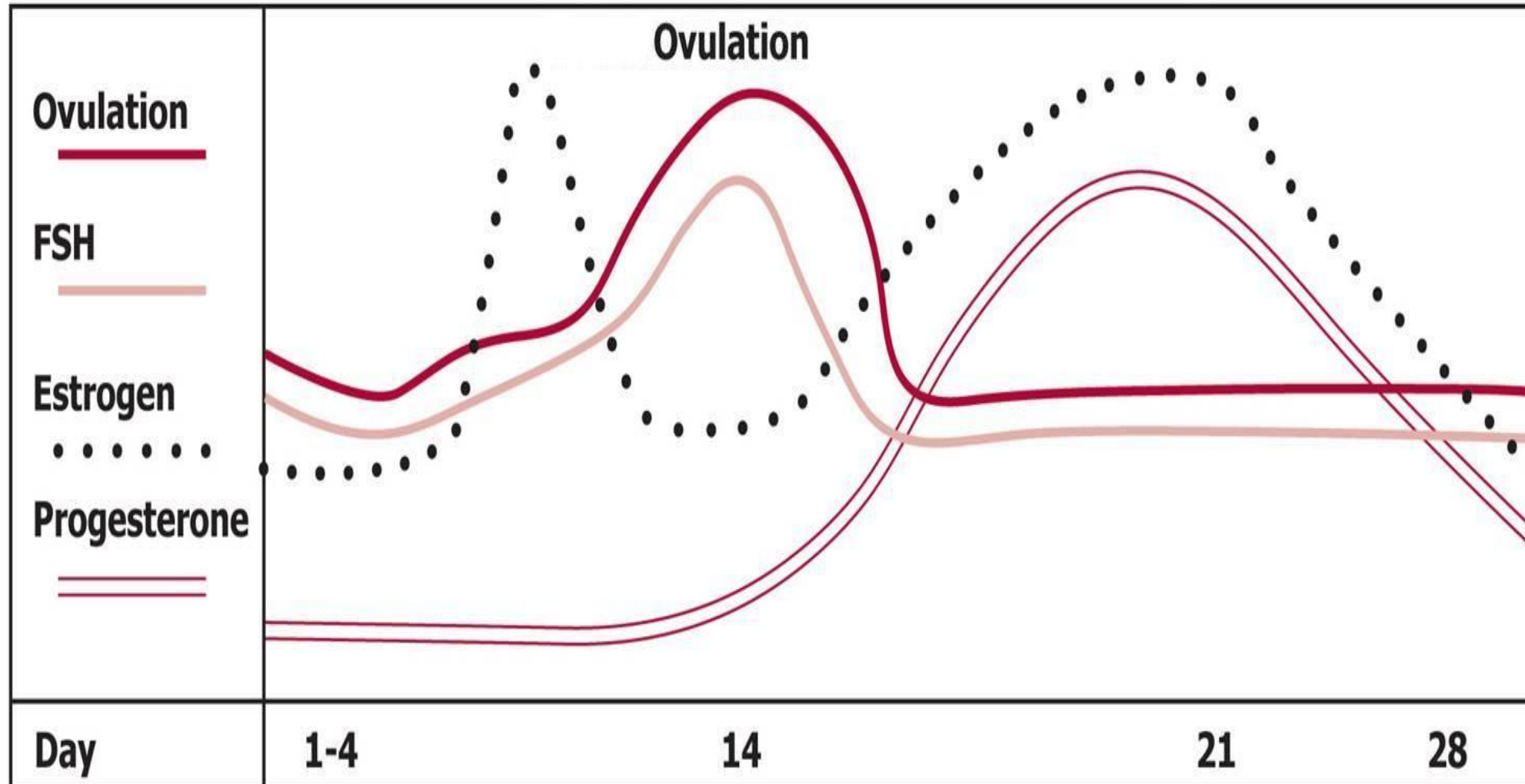
- Young women have shorter sleep latency and higher sleep efficiency compared to young men!
- **Onset of menses linked to increased risk of insomnia.**

1. Sleep. 21:871-881 1998

2. Pediatrics. 117:e247-56 2006

Sleep & Menstrual Cycle:

Human Reproductive Menstrual Cycle



- 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,

Common Complaints

- Insomnia or Excessive Daytime Sleepiness
- **Worst sleep efficiency in fourth week**
- **Recurrent emotional and physical symptoms** in association with the menstrual cycle

Sleep and the Menstrual Cycle. Health Psychology
1997;16:209-214

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.

Johnson SR (2004) Obstet Gynecol 104:845-859.

Premenstrual Dysmorphic Disorder:

- Severe Symptoms
- **Lower melatonin** levels in menstrual phase
- **Light therapy** a promising treatment by altering nocturnal melatonin secretion.

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

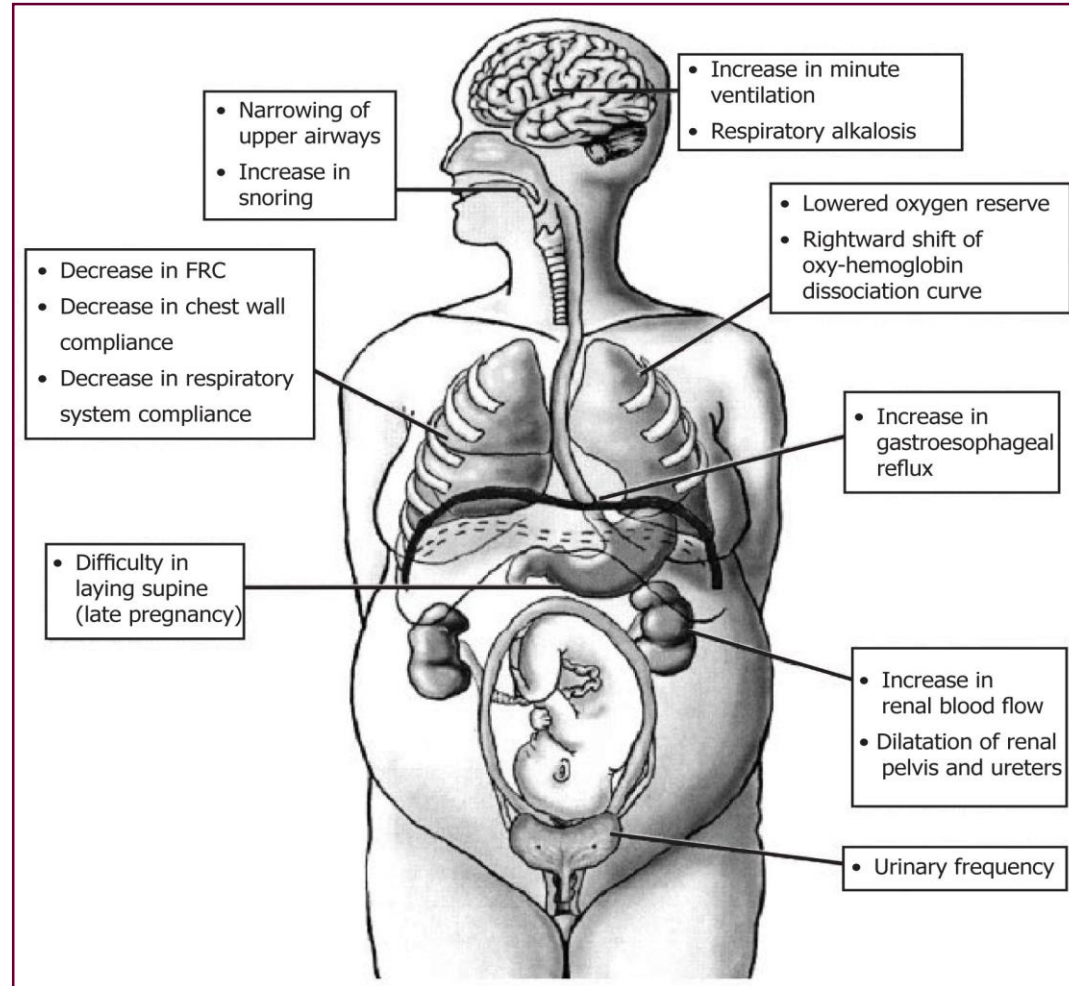
- Affects 4 to 12% women of reproductive age
- **30 times more likely to suffer from sleep apnea compared to controls**

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:



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**.

1. Sleep. 22:540-555 1999

2. Psychoneuroendocrinology. 33 (8):1124-1131 2008

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**

1. Eur J Neurosci. 27 (7):1780-1792 2008

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:

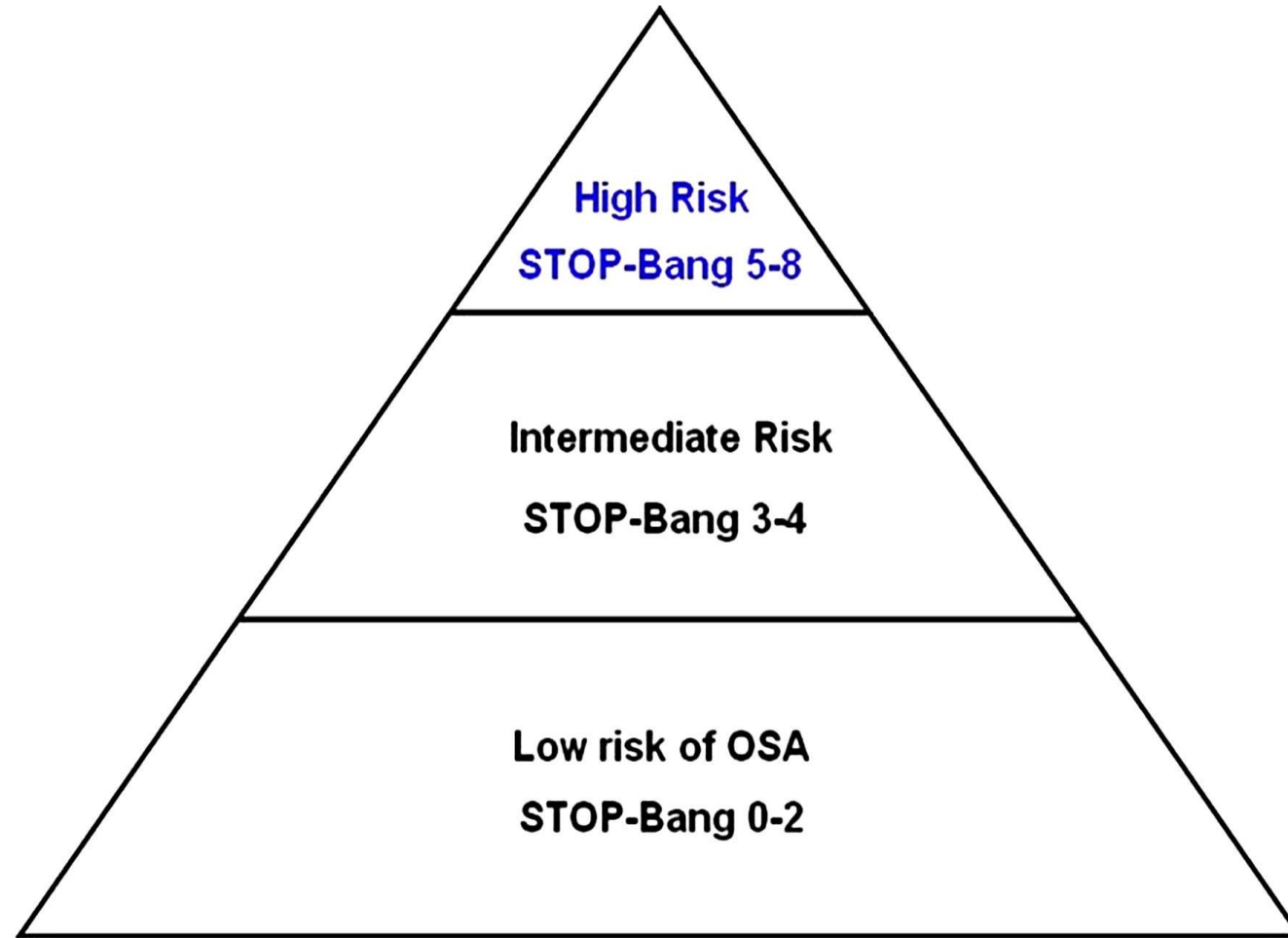
- Habitual snoring,
- Chronic hypertension,
- Baseline BMI ≥ 25 to 30, and
- Older maternal age

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**



- Most OSA screening tools have a sensitivity between 70% and 80%, with very low specificity.
- None of them worked very well in pregnant women.

Maresh 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**

1. Sleep. 36 (11):1625-1632 2012

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

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

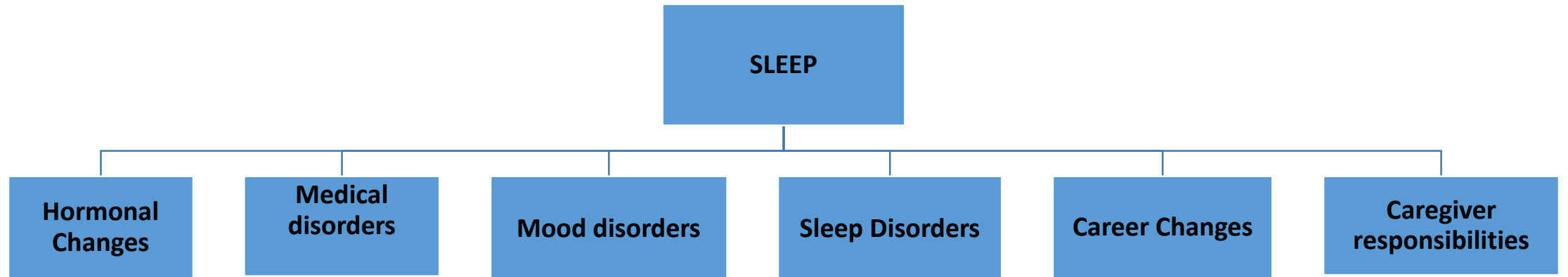
- **Painful muscle contractions in the foot or leg.**
- Sudden awakening is typical
- **Prevalence** of nocturnal leg cramps increases from 10% before pregnancy to 21% in the first trimester, 57% in the second trimester, and up to **75% in the third trimester**
- Vitamin B1 & B6 may be beneficial

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.

The menopausal transition. Am J Med. 118 (Suppl. 12B):8-13 2005

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.**

Gender difference in Sleep Apnea Presentation

	MEN	WOMEN
Snoring	*****	**
Daytime sleepiness	*****	**
Morning headaches	**	*****
Depressive features	**	*****
Apnea Frequency	*****	**
Hypopnea Frequency	**	*****

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

P Polo-Kantola, R Erkkola, H Helenius, et al.: When does estrogen replacement therapy improve sleep quality?. Am J Obstet Gynecol. 178:1002-1009 1998

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