Sleep Disorders in Women: Gender Matters

Katie Sharkey, MD, PhD, FAASM

Alpert Medical School of Brown University
Departments of Medicine and Psychiatry & Human Behavior
Alpert Medical School - Brown University - Rhode Island Hospital

Twitter: @katie_sharkey
Conflict of Interest Disclosure

1. I do not have any relationships with any entities producing, marketing, reselling, or distributing health care goods or services consumed by, or used on, patients, OR

X 2. I have the following relationships with entities producing, marketing, reselling, or distributing health care goods or services consumed by, or used on, patients.

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Harmony Biosciences research support</td>
</tr>
<tr>
<td>Consultant</td>
<td>Verily</td>
</tr>
<tr>
<td>Speakers’ Bureaus</td>
<td></td>
</tr>
<tr>
<td>Financial support</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Up-to-Date Royalties</td>
</tr>
</tbody>
</table>

X 3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

X 4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

1. 
2. 
Sleep Network

- Susan Redline, MD, MPH, Harvard Medical School (Network Chair)
- Jessica A. Mong, PhD, University of Maryland (Network Co-Chair)
- Hrayr Attarian, MD, Northwestern University
- Fiona Baker, PhD, SRI International
- Meir Kryger, MD, FRCPC, Yale University
- Andrew D. Krystal, MD, Duke University
- Judette Louis, MD, MPH, University of South Florida
- Jodi Mindell, PhD, Saint Joseph’s University
- Amita Sehgal, PhD, University of Pennsylvania
- Katherine M. Sharkey, MD, PhD, Brown University
- Ken P. Wright, Jr., PhD, University of Colorado, Boulder
- Phyllis C. Zee, MD, PhD, Northwestern University

Program Directors:
Rebecca Nebel, PhD & Monica Mallampalli, PhD
How do reproductive hormones and sleep interact to influence health?
Hormonal Studies

- Animal Studies
  - Hormones administered to ovariectomized or orchiectomized animals
- “Replacement” studies
  - In surgical or natural menopause
- Observational studies
  - Different menstrual phases, pre- vs. post-menopause, pregnancy
Estrogen - animals

- **Increases in behavioral arousal** including exploratory and wheel-running activity
- Decreased NREM and REM sleep in rodents
- Molecular mechanisms are being elucidated
  - e.g. decreased adenosine receptor expression in the ventrolateral preoptic nucleus

Estrogen - replacement

- 16 hypogonadal women; 31-65 yrs; menopausal 2-22 years; 10/16 experiencing hot flashes
- crossover design; 0.625 mg conjugated estrogen administered x 4 weeks with PSG at the end of 4 weeks
- Decreased sleep latency
- Increased REM time and percent

Progesterone

- $\text{GABA}_A$ receptor agonist with sleep-promoting effects
- Increases NREM sleep
- ? decreased vigilance and fatigue
- Raises core body temperature 0.3-0.5°C
Menstrual Cycle

- Follicular: low progesterone, estrogen rises to mid-cycle peak
- Midcycle FSH/LH surge
- Luteal: elevated estrogen & progesterone (P > E)
- Menstruation: abrupt drop in estrogen and progesterone
Menstrual Cycle – subjective sleep

• Manber and Bootzin (1997): 32 women, mean age = 38 yrs, kept sleep diaries x 2 months

• In late luteal phase compared to mid-follicular:
  • Worse subjective sleep quality
  • Longer sleep onset latency
  • Increased nocturnal awakenings/decreased sleep efficiency

• Replicated by Baker and Driver (2004) who also showed poorer subjective sleep quality in first 4 days of menstruation
Menstrual Cycle – objective sleep

• SWS and SWA do not differ across cycle
• REM sleep
  • Decrease REM% in late luteal phase
  • Effect of core temperature increase?
• Stage 2 sleep:
  • Higher Stage 2% in late luteal

Menstrual Cycle – objective sleep

- 27 women, mean age 26.9 ± 6.6 yrs with monthly menses
- Hormone levels measured at 2 time points during a single menstrual cycle:
  - follicular phase
  - peri-ovulatory to mid-luteal phase
- Home polysomnography (PSG) was recorded on the day of the peri-ovulatory/mid-luteal-phase blood draw

Menstrual Cycle – objective sleep

Prolactin

- Prolactin increases slow wave sleep
- Breastfeeding women demonstrate more slow wave sleep compared to controls and bottle feeding women

Adolescence
Menarche

• Carskadon et al. (1993) showed delay in sleep times associated with pubertal development in girls
• Fatigue is more common in adolescent girls than boys and 1/3 of teen girls report fatigue as a premenstrual symptom
• Noll (2006) showed relationship to sexual abuse
• Related to comorbid psychiatric illness?
Menarche

• 1014 adolescents (510 girls); 13 to 16 years of age
• DSM-IV diagnosis of insomnia = difficulty initiating or maintaining sleep or nonrestorative sleep, \( \geq 4 \) x/week, for \( \geq 1 \) month and results in significant distress or impaired function.
• Lifetime prevalence of insomnia = 10.7%.
• 88% of adolescents with insomnia history reported current insomnia.
• Median age of onset of insomnia was 11 yrs.
• 52.8% of adolescents with insomnia had a comorbid psychiatric disorder

Menarche

• Onset of menses was associated with a 2.75-fold increased risk for insomnia.

• Maturational development was not associated with insomnia in boys.

Pregnancy
Sleep Changes during Pregnancy

• Subjective complaints are common
  • 15-20% in 1st T and 66-90% in 3rd T
• Hertz, 1992, n=12 in 3rd T vs. controls
  • Decreased Sleep Efficiency
  • Decreased REM %
  • Increased Stage 1%
• Driver & Shapiro, 1992, n=5 studied prospectively
  • Increased WASO
  • Increased SWS from 1st T to 3rd T
• Brunner, 1994, n=9 studied prospectively
  • Increased WASO
  • Decreased REM %
Sleep Changes during Pregnancy

• Discomfort (Back pain, leg cramps)
• Waking for urination
• “Hormonal Influences”
  • Estrogen $\uparrow$ - more sleep disruption?
  • Progesterone $\uparrow$ - GABA-ergic, increases fatigue, body temperature and respiration during sleep
  • Prolactin $\uparrow$ - increased SWS
Disturbed sleep at the end of pregnancy is associated with worse obstetric outcomes

• Lee & Gay, 2004, n=131
  • Women with WASO > 15% had longer labor and were 5.2 x more likely to have a caesarean section

• Beebe & Lee, 2007
  • Decreased TST associated with higher pain scores
  • Increased WASO associated with higher affective response to pain
Sleep Changes from Pregnancy to the Postpartum Period

• Hertz, 1992, n=12 in 3rd T vs. controls
  • 7 women followed 3-5 months PP showed return to baseline sleep efficiency

• Actigraphy Studies
  • Gay, 2004
    • Decreased TST of 41 minutes from 3rd T to 1st month PP
  • McGovern, 2007
    • Sleep improves relative to 1st month pp but does not return to baseline
Changes in Sleep Timing and Circadian Rhythms in the Perinatal Period

• Wolfson et al., 2003, n=38 first-time mothers
  • 3rdT to 1\textsuperscript{st} month PP \(\rightarrow\) 52 minute delay
  • 1\textsuperscript{st} month PP to 4-12 months PP \(\rightarrow\) 72 minute advance

• Sharkey et al., 2013, n=32 high-risk mothers
  
  $36.6\% \rightarrow$ no shift
  $26.6\% \rightarrow$ phase advance
  $36.6\% \rightarrow$ phase delay
Changes in Sleep Timing and Circadian Rhythms in the Perinatal Period

Sleep Disordered Breathing in Pregnancy

• 25% of women report regular snoring by the end of pregnancy
  • ↑ ventilatory drive, metabolic rate
  • ↓ FRC, residual volume
  • changes upper airway
• Snoring/UARS associated with PIH, pre-eclampsia, adverse fetal outcomes (SGA)
  • 43% snorers vs 22% non-snorers with perinatal complications
• Risk factors for OSA during pregnancy:
  • higher baseline BMI
  • greater increase neck circumference

Restless Legs Syndrome Syndrome & PLMD in Pregnancy

- Restless Legs Syndrome/ Periodic Limb Movement Disorder: may be associated with
  - Iron-deficiency anemia
  - Gestational diabetes
  - Uremia
  - Dopamine blockage by prolactin
  - symptoms usually subside postpartum
- 15-20% women develop RLS in third trimester
Restless Legs Syndrome in Pregnancy

- 10 pregnant women with RLS; 9 controls
- Patients had higher estradiol levels during pregnancy
- Pts also had more PLMS at both times; sleep stages did not differ during pregnancy; controls had higher sleep efficiency and more REM sleep postpartum compared to controls

Polycystic Ovary Syndrome
Polycystic Ovary Syndrome

- Oligoovulation/anovulation
- Elevated circulating androgens
- Clinical Signs of androgen excess
- Polycystic ovaries on ultrasound
- Variable gonadotropin abnormalities
- Insulin Resistance
- Impaired glucose tolerance
- Type 2 Diabetes
Polycystic Ovary Syndrome

- Tasali et al. (2008): 52 women with PCOS and 21 age/BMI matched controls
- PSG and glucose tolerance test
- 56% of PCOS women had OSA vs. 19% controls
- PCOS women with OSA had more insulin resistance than PCOS women without OSA
- Appears to be linear relationship between prevalence of impaired glucose tolerance and severity of OSA
Menopause
Perimenopausal Women

• 2007 Sleep in America Poll by National Sleep Foundation “Sleep in Women”
• 25-min telephone survey of 1,003 American women aged 18 - 64 living in the continental US
• Data collected between 9/12/06 and 10/28/06
• Margin of error: +/- 3% at the 95% confidence level
• 59% of perimenopausal women have insomnia a few nights per week
• 43% report symptoms of a sleep disorders such as snoring, sleep apnea, or RLS
• 20% experience night sweats and hot flashes

*NSF Poll 2007
Sleep and Menopause

- 40-57% of menopausal women report difficulty falling asleep or maintaining sleep
- Up to 88% of perimenopausal women with hot flashes report insomnia
- PSG studies in this population have a poor correlation with subjective complaints
  - Wisconsin Cohort Study (Young, 2003): postmenopausal women had longer TST and more SWS than premenopausal women
  - Freedman & Roehrs (2007): 102 women, ages 44-56 yrs, who reported disturbed sleep; 53% had sleep d/o
    - PSG sleep efficiency most closely related to AHI/PLMD/arousals
    - PSQI predicted by anxiety and hot flashes
Sleep in Midlife Women

• Troxel (2009): SWAN study - 2148 women, ages 42-52
  • Marital happiness was associated with fewer sleep disturbances in Caucasian and African-American women controlling for age, ethnicity, medication use, symptoms of depression/anxiety, overall social support, and presence of children in the home

• Joffe et al. (2009): VMS – 103 women (51 depressed), ages; actigraphy x 2 days
  • Depressed women had shorter SPT, shorter TST, longer sleep latency, and lower sleep efficiency
  • No difference in number of awakenings or WASO
  • Depressed women had higher PSQI scores (12 vs 8.3) c/w Buysse et al. (2008)
Gender Matters in Sleep Apnea

• ~17% of women have sleep apnea, but 90% go undiagnosed

• Dursunoglu et al. (2009): 20 consecutive women studied in Turkish sleep lab compared with 71 men
  • Average age = 50 yrs in both sexes
  • Symptoms: Morning HA, dry mouth, hypothyroidism, and depression more common in women than men
  • History: hypothyroidism, and depression more common in women than men
  • AHIs: 17.9 ± 17.7 in women; 29.1 ± 22.7 in men
  • No difference in age, ESS, BMI, snoring, blood pressure
Gender Matters in Sleep Apnea

**NIGHTTIME CLUES**
- Frequent or loud snoring, gasping, or snorting sounds
- Difficulty falling asleep, frequent awakenings
- Restless sleep, changes in dreaming
- Frequent bathroom visits at night
- Nighttime heartburn

*some of which could be observed by a bed partner or roommate

**DAYTIME CLUES**
- Feeling depressed, anxious, irritable, or impatient
- Feeling tired, drained, or lacking energy
- Feeling sleepy or falling asleep at the wrong time or place
- Forgetfulness, foggy or fuzzy thinking, trouble with focus and concentration
- Accident proneness
Gender Matters in Sleep Apnea

• Home Sleep Tests (HSTs); may give “false negative” readings → rates range from 10% to over 20%

• Since respiratory disturbances in women are frequently associated with arousals rather than oxygen desaturations, HSTs often underestimate sleep apnea in women.

• A negative HST should be followed by PSG if the clinical suspicion for sleep apnea is high

• In women, the common co-occurrence of insomnia and sleep apnea may increase the likelihood of a false negative HST
Gender Matters in Insomnia

- Insomnia is 40–70% more common in women compared to men and higher rates occur with age.
- The rate of metabolism of some hypnotic medications is slower in women than men.
  - FDA recommends using a zolpidem dosage for women that is half the recommended dosage for men.\(^1\)
  - Gender differences have also been observed in CBT-I.\(^2\)
- Affective disorders, pain syndromes → more common in women & can interfere with sleep.

Gender Matters in RLS

- RLS is 2X as prevalent in women compared to men
  - Mostly due to increased incidence during pregnancy
  - Incidence estimated at 12–26%\(^1\)
  - Women with gestational RLS (gRLS) have 4X ↑ risk of RLS later in life and 3X risk of gRLS in future pregnancies

- gRLS associated with preterm birth, small for gestational age infants, and pregnancy-related hypertensive disorders.

- Ferritin level should be increased to >75 mcg/L in women with gestational restless legs syndrome to help manage symptoms.

- Restless legs syndrome is often misdiagnosed as leg cramps, peripheral neuropathy, or anxiety.

Gender Matters in Parasomnias

• Sleep related eating disorder is 1.5-4X more common in women
  • can be caused by commonly prescribed sedative hypnotics
  • women may be prescribed these sedative hypnotics more often because they have more insomnia

• REM sleep behavior disorder is under-recognized in women because their dreams have less violent content and their dream enactment is less physical.

Gender Matters - Conclusions

- Sex hormones influence rest/activity and sleep/wake behavior in animals
  - Molecular basis are consistent with our current understanding of neuroanatomical and neurochemical mechanisms
  - Relationship to human neurophysiology to be determined

- Sleep apnea, insomnia, and movement disorders may present differently and require different treatments in women vs. men
Gender Matters - Conclusions

• Times of hormonal transition are marked by sleep changes and difficulties in women
  • Menarche ➔ 2.75x increased risk of insomnia
  • Pregnancy ➔ sleep disruption in 3rd T and PP month 1
    ➔ RLS symptoms related to elevated estrogen
    ➔ psychosocial issues play a role
  • PCOS ➔ increased incidence of OSA
    ➔ severity of OSA correlates with insulin resistance and abnormal glucose metabolism
  • Menopause ➔ increased incidence of sleep disorders
    ➔ sleep disorders present differently in women
    ➔ psychosocial factors play a role
Sleep Network

- Susan Redline, MD, MPH, Harvard Medical School (Network Chair)
- Jessica A. Mong, PhD, University of Maryland (Network Co-Chair)
- Hrayr Attarian, MD, Northwestern University
- Fiona Baker, PhD, SRI International
- Meir Kryger, MD, FRCPC, Yale University
- Andrew D. Krystal, MD, Duke University
- Judette Louis, MD, MPH, University of South Florida
- Jodi Mindell, PhD, Saint Joseph’s University
- Amita Sehgal, PhD, University of Pennsylvania
- Katherine M. Sharkey, MD, PhD, Brown University
- Ken P. Wright, Jr., PhD, University of Colorado, Boulder
- Phyllis C. Zee, MD, PhD, Northwestern University

Program Directors:
Rebecca Nebel, PhD & Monica Mallampalli, PhD