Sleep Disorders in Women from Pregnancy to Menopause
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Women’s Sleep is Different

Women

- Have unique endocrine physiology that can disrupt sleep
- More likely than men to report poor sleep but take twice as long for apnea Dx
- Are more likely to experience daytime sleepiness
- Are three times more likely to suffer insomnia
- Experience more depression and anxiety that disrupts sleep
- 20% shift work and 20% SWSD
Common Sleep Disorders in Women

- Sleep and the Menstrual Cycle
  - pregnancy and menopause

- Obstructive Sleep Apnea
  - Differences in Women

Insomnia, Meds & Sleep Deprivation
40% middle age <5 hours sleep
Risk MI 2.98 (>9 hr risk 1.4)

- More often in women
  - Migraines
  - Multiple sclerosis
  - Polycystic Ovaries,
  - Malignancy related

Meisinger Sleep 30;9:
Night Shift Workers-Nurses Health Study

- 20% circadian rhythm disorder
- Breast cancer, ovarian cancer and perhaps endometrial cancer increased, possibly cardiovascular disease

- Suprachiasmatic nucleus drives circadian pacemaker with period about 24 hours and is reset by light
- Melatonin released from pineal is inhibited by nocturnal light
  - Oncostatic in experimental tumor cells and rodents
- Nurses work 1-14 years night or 15-29 years at least 3 nights/month rotating
- Risk greater in long duration workers
During the Sleep Cycle

- Core body temperature
- Growth hormone
- Cortisol
- Melatonin
- Sleep stage

Body temperature lowers
Hormone levels rise and fall
Menstruation and Sleep

Hormonal changes unique to women can cause more than half the sleep problems women experience. (NSF)

- **Progesterone:**
  - Promote sleep and increases NREM sleep while decreasing wakefulness

- **Estrogen:**
  - Enhances REM sleep and regulates flow of other hormones secreted during sleep

- Perimenstrual - bloating, breast tenderness, sleep disruption, daytime lethargy more in luteal phase

- Diclofenac 150 mg treated pain and restored sleep architecture in 10 patients
Menstrual Cycle

Fig. 1. Female sex hormone concentrations across the menstrual cycle (Schmidt-Matthiesen, 1992, modified).
Menstruation

- Rectal temp higher in luteal than follicular phase
- Stage 2 and spindle frequency parallel temperature increasing towards luteal phase
- REM sleep is the inverse, decreases by end of cycle

Driver and Baker, 1998
Hormonal Cycles

- GH and PL rises with sleep onset and N3
- ACTH and TSH follow circadian cycles
- LH, FSH depend on menstrual cycle

- GnRH first rises in sleep at puberty
  - Disrupted sleep as in OSA interferes with normal pubertal development in girls but not in boys, decreased gonadotropin levels
    - (RDI >1 with 3% desat)
    - Tanner breast development 1 stage behind

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Insomnia-National Sleep foundation Poll 2007

- 25 minute telephone survey 1003 women age 18-64 sleep duration 6 hours 41 min

Women responders reporting

Only a few good night sleep/month

- 24% child bearing age
- 40% pregnant women
- 55% post partum
- 25% peri menopausal and 30% post menopause

Post partum 84% insomnia

- 47% no help with childcare at night
- 20% drove drowsy with child
- 42% rare to “never” good night sleep
- 19% post partum blues
Cost of Poor Sleep

- Prescription Sleep MEDS
  - $3 billion in 9 months of 2006
  - $362 million on ads

- Calming night soaps, pillow sprays and body wash

- Dreamwater & sleep aromatherapy

- Spas employ sleep specialist

- PLUS

- $100 Billion annually
  - lost productivity, medical expense, sick leave, property and environmental damage
Sleep Disorder (Sedative-Hypnotic) Drug Information

The U.S. Food and Drug Administration (FDA) has requested that all manufacturers of sedative-hypnotic drug products, a class of drugs used to induce and/or maintain sleep, strengthen their product labeling to include stronger language concerning potential risks. These risks include severe allergic reactions and complex sleep-related behaviors, which may include sleep-driving. Sleep driving is defined as driving while not fully awake after ingestion of a sedative-hypnotic product, with no memory of the event.

Also included in the updated label are the dosing recommendations previously stated in FDA’s January 2013 Drug Safety Communication: The recommended initial dose of certain immediate-release zolpidem products (Ambien and Edluar) is 5 mg for women and either 5 mg or 10 mg for men. The recommended initial dose of zolpidem extended-release (Ambien CR) is 6.25 mg for women and either 6.25 or 12.5 mg for men.
FDA Risks of AM IMPAIRMENT 2011

- approximately 39 million prescriptions for zolpidem in 9 million patients 2011
- 63% of patients female

- Extended release products 11%

- Zolpidem levels >50ng/ml may impair driving to a degree that risks MVA

- ZOLPIDEM 10 mg at bed

- 15% OF 250 WOMEN TESTED HAVE CONCENTRATION >50 NG/ML 8 HOURS POST DOSE AND 3 >90 NG/ML

- 12.5 mg slow release preparation 33% women had zolpidem blood concentration >50ng/ml after 8 hours
Kennedy testifies she accidentally took sleeping pill before car crash, arrest

WHITE PLAINS, N.Y. — Kerry Kennedy testified at her drugged-driving trial Wednesday that she never sensed she was becoming impaired after accidentally taking a sleeping pill and has no memory of swerving into a tractor-trailer on a suburban New York highway.

"If I realized I was impaired I would have pulled over," said Kennedy, ex-wife of Governor Andrew Cuomo and daughter of the late senator Robert F. Kennedy.

She was arrested in July 2012 after her car hit the truck near her home outside New York City. She drove to the next exit, where she was found slumped over the steering wheel and failed sobriety tests.

The prosecution argues that even if she took the sleeping pill accidentally, Kennedy violated the law by failing to pull over when it took effect.

Taking the stand on the third day of her trial in White Plains, Kennedy said she remembers the first part of her drive that day but has no memory of the interval between when she got on the highway and when she stopped at the exit. She said she was confused when a man knocked on the window of her Lexus.

"He said, 'Have you been in an accident?'" Kennedy said.

"And I said, 'No,' because as far as I was concerned I hadn't been in an accident."

Kennedy, 54, testified earlier Wednesday that she accidentally took a sleeping pill that morning.

"I thought I was taking Synthroid, my thyroid medication," she said. But because blood tests revealed a small amount of the sleeping drug zolpidem, "I must have taken the sleeping medication by mistake."

Kennedy said she has taken the thyroid medication every day since 1991 and takes the sleeping pills to adjust to time changes when she travels. She said the sleeping pills were on a counter, near the thyroid pills, on the morning of the accident because she was planning a trip.

ASSOCIATED PRESS
Insomnia Therapy

➢ CBT with meds in early phase most effective, then taper med
  ● Stimulus control, relaxation, education and sleep restriction

➢ Insomnia may be sign of
  ● Depression, anxiety, PTSD
  ● Sleep apnea
  ● Restless legs
  ● Chronic pain, fibromyalgia
  ● Night episodes or eating
Obstructive Sleep Apnea

Women omitted from early studies thought 60:1 actual 3:1
OSA Risk factors Women

- **Menopause**
- In a Canadian population OSA increased from 21 to 47% after menopause despite BMI 30

- Weight gain and neck size increases risk

- **Diabetes** higher in women with OSA (control BMI age)

- **Hypothyroid** disease may increase sleep apnea
Sleep and Stroke

- Women 50-79-Womens health Initiative
  - Sleep > 9 hours 70% more risk CVA
  - Sleep <6 hours 14% more risk CVA
- Long sleep more illness and death

- Snoring risk factor for stroke in 110 snorers without OSA; measure carotid atherosclerosis
  - 20% mild snorers
  - 32% moderate snorers
  - 64% heavy snorers
- Adjust age, sex, smoking hypertension
Gender differences in OSA

- 289 people match age, AHI, BMI-
  - Women more depression, hypothyroid, insomnia (UARS)
  - 2.7 X more anxiolytics & antidepressants

- 93% women with mod – severe OSA not diagnosed

- Most costly - 25% consumed 65% services
  - Hyperlipidemia, CVD, arthropathy, asthma

- Women BMI >40 poorest health status used 1.4 times more health care
  - Specific AHI and 02 sat not affect utilization

- Women more non specific complaints,
UARS

- Women with UARS AHI <5 in 334 patient
- Tiredness or fatigue
- 43% premenopausal group abnormal menses, amenorrhea, dysmenorrhea
- 40% depression

- Disorder common female and often present with depression
Swift™ LT for Her

First fit with her in mind

The Swift™ LT for Her is the first mask designed specifically for women, combining the revolutionary design of the Swift LT with personalized features for women’s unique preferences:

- **Light touch:** No forehead support and weighs only 2.3 oz (67 g), sealing softly and securely to ensure a comfortable night’s sleep.
- **Easy fit:** Rotating barrel allows her to customize her best seal, while the simple design makes it easy to fit and clean.
- **Soft and stable:** 50% smaller mask frame width, making it perfect for side sleeping.
- **Whisper-quiet comfort:** Quietest nasal pillows system on the market (71% quieter than the Mirage Swift™ II—25 dBA*).
- **Innovative headgear design:** Adjustable backstrap can be worn over or under the hair to accommodate a wide range of hair styles in a soft, feminine print and light blue color.

*Testing per ISO 3744:1994 Acoustics determination of sound power levels of noise using pressure at 10 cm H₂O. Quoted percentage comparisons are calculated by converting sound power values from a logarithmic scale to a linear scale.
Hormone Replacement for OSA?

- Incidence sleep apnea women approaches men after menopause

- Short term (50 d) hormone replacement (estrogen and progesterone) in 15 post-menopausal women does not seem to improve sleep apnea symptoms. (Cistulli 1994)

- Contrastingly, a Swedish study looked at 5 women (4 postmenopausal, 1 peri-menopausal) given estradiol and trimgeston for 6 weeks. Reduction in RDI was 75% (AHI mean 14.9 to 3.6). (Wesstrom 2005)
Polycystic Ovarian Syndrome

- Ovaries produce too much testosterone
- Low FSH and poor follicle development
- Associated with:
  - Hirsuitism
  - Obesity (larger waist-hip ratio)
  - Fertility problems / Amenorrhea
  - Metabolic syndrome-insulin resistance

- OSA
  - 44% (AHI > 5 and EDS) [Average RDI 40]
  - 5.5% age and BMI matched controls (Fogel et al., 2001)

- Relationship to OSA may be related to insulin resistance (Vgonmtzas et al, 2001)
Pregnancy
Normal Pregnancy

- 1998 NSF poll – almost 80% of women reported more disturbed sleep during pregnancy
  - Increased urination
  - Tiredness starts early
  - Pelvic pressure
  - Insomnia—sleep maintenance-1 hour less
  - Lower back pain
  - Restless sleep
  - Leg Cramps
  - Frightening Dreams
Changes in Sleep During Pregnancy

**First Trimester**
Difficulty sleeping through the night; Daytime sleepiness; increased urination, nausea, and progesterone up

**Second Trimester**
Improved sleep and energy; Possible snoring, heartburn, and frightening dreams, RLS fetal movement

**Third Trimester**
Difficulty sleeping, increased urination, snoring, back pain, more restless legs, pressure diaphragm
Pregnancy Related Sleep Apnea

- Snoring or Sleep Disordered Breathing

- 30% of women experience snore or SDB
- Role in headaches, and daytime fatigue
- Rising estrogen affects mucosa
  - nasal obstruction, may cause rhinitis
- Progesterone increases CO2 sensitivity
  - Respiratory stimulant
- Snoring more but AHI not >5
Pre-eclampsia

- 5-10% pregnancies
- Hypertension after 20 weeks with proteinuria
- Risk mother and fetus
- High rate mild SB with inspiratory flow limitation
- CPAP improves CV parameters
Pre-eclampsia and Sleep Apnea

- A single night of autoPAP decreased blood pressure and uric acid in severe eclampsia AHI <5.

- Second study—High association of sleep apnea and gestational hypertension 38% AHI >5
  - BP not drop acutely-1 night
  - RDI not improve
  - Inflammatory markers not improve

- Suspect Eclampsia=increased airway resistance

- Possible pathogenetic role OSA in pre eclampsia
Pre eclampsia and SDB

- Normal fetus active in sleep and more towards AM
- Pre eclampsia less movement as night progresses
- Least movement in REM
- Fetal movement improved with CPAP
- SDB - worsen high peripheral vascular resistance, decreased cardiac output, uterine and placental blood flow
Pregnancy-associated Sleep Disorder

- Characterized by the occurrence of either insomnia or excessive sleepiness that develops in the course of a pregnancy

- Biphasic: Begins with sleepiness, ends with insomnia
  - Rarely nightmares, sleep terrors, post-partum psychosis
  - Associated with irritability, apathy, and moodiness
  - On MSLT, can have latency < 10 min.
Restless Legs Syndrome (RLS)

- Irresistible urge to move legs
- Relieved by movement
- Induced by immobility
- Evening preponderance
- 80% have PLMS
Restless Legs Syndrome

- 18% of women experience RLS
- Approximately 20% -40% of pregnant women experience RLS
- RLS can cause insomnia that may be misdiagnosed as depression
- RLS is very common in elderly women
  and men serum iron
Gestational Restless Legs Syndrome 25%

- Month 7 & 8
- Anemia, Fe deficiency 325 mg. Fe sulfate plus 100 mg Vitamin C,
- MG 350 mg
- Check your iron and folate levels
- Prolactin elevated (antidopaminergic)
- Therapy-Hydrocodone
- Exercise, yoga stretch
Post Partum

- **Sleep disruption**
  - Early pain, worries, anemia
  - Post partum distress at 3-5 days
  - Drop in progesterone
  - Post partum depression begins 2-4 weeks
  - Sleep problems and decreased vigilance post partum
  - Nightmares – infant lost in bed, act out search

- **Sleep interruption**
  - Oxytocin secreted in REM influenced by infant cries
  - In stage 1 sleep mother more easily woken by cry of her own baby
  - Breast feed more wake-ups, but also more N3
Sleep Tips for Mom

- Make your own sleep a priority
- Nap when your baby naps
- Co-sleeping was 6% in 1990
  - Now 22% first month & 13% at 6 months
- Florida up to 46% first 6 months
  - Japan until age 7
- Start to instill positive sleep habits in baby
- Breast feeding moms in first month 30 min more sleep with equal fragmentation
Menopause

http://www.aperfectworld.org/cartoons/menopause.png
Menopause = Disrupted Sleep
25-50% of women

- Vasomotor symptoms associate with arousal and disrupt sleep architecture
- Increased depression, somatic symptoms
- Progesterone
  - sedative stimulate GABA receptor
  - respiratory stimulant
  - apnea protection in pregnancy
- Estrogen
  - Increase REM cycle, affect NE, 5HT, Ach.
  - Decrease sleep latency and WASO
  - Temperature regulation, hot flash (catechols, LH up)
  - Regulates time of lowest body temp, pushing later and shallower
  - May have antidepressant effect (5HT agonist, increase NE, GABA agonist)
Menopause 2

- **Cortisol**
  - Estrogen affects cortisol with higher level earlier in sleep
  - Estrogen regulates AM cortisol and may stabilize night sleep

- **Melatonin**
  - Suppresses estrus in animals with seasonal reproduction
  - Males regress testicular tissue (high)
  - Keeps humans asleep in dark
  - Tamoxifen, oopherectomy, decreases melatonin
  - Estrogen may have reciprocal melatonin support function

- **Testosterone**
  - Minor effect on sleep but exogenous worsen sleep apnea,
Hot Flashes / Night Sweats
75% women

- Study of Women’s Health Across the Nation (Kravitz 2003)
  - Multiethnic study of 12,603 women
  - 38% of women reported difficulty sleeping within 2 weeks of the survey
  - The highest rate was in the late perimenopausal (45%) and surgically postmenopausal groups (48%)

- Hot flashes are relieved by estrogen in 90% of pts (if willing to take it)

http://www.redhotflush.co.uk/
Hormone Replacement for Sleep

- Double blind, crossover study of 63 post-menopausal women (Polo-Kantola 1998)
  - Improvement in sleep quality
  - Including vasomotor, somatic (tachycardia) and mood symptoms

- Contrasting study (Purdie 1995)
  - No effects of HRT on PSG sleep in 33 women
Other Therapies

- **Micronized progesterone**
  - may have less effect on vessels
  - improve WASO and sleep efficiency

- **Herbals**
  - black cohosh moderate effect, soy isoflavones (phytoestrogen) red clover, vit E, dong quai

- **Clonidine** 34-44% decrease symptom

- **Gabapentin** 300-900 mg reduce sx 66%

- **SSRI** fluoxetine, venlafaxine
28-63% of post-menopausal women report experiencing insomnia

PSG of 76 women 40-59
- Only differences between pre menopause and peri/post was longer REM latency in latter
- Women with hot flashes tended to have lower sleep efficiencies

Small study of women (5 pt and 5 controls) with vasomotor sx
- In women with hot flashes the symptoms coincided with the wake up.
Sleep and the Caregiver

Women frequently lose sleep when caring for an ill family member.
Sleep and the Caregiver

- 84% of caregivers for Alzheimer’s patients are women age 65
- Caregivers often have to coordinate medical care and personal care for patients
- Caregivers must make sure they receive adequate sleep. If sleep deprived, caregivers should seek help and research other available resources
Narcolepsy

- Cross-sectional study 109 pt (68 W)
- Primary narcolepsy
  - similar symptoms, sleep habits, medications, comorbidities
- Men 16 years to Dx
- Women 28 years to Dx
- More women undiagnosed at any point after symptom onset
- Epworth score similar
- MSLT sleep latency women 5.4 min vs 7.4 men

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Sleep in Multiple Sclerosis

- Sleep problems common but varied
- Propose brainstem pathology
  - RLS some evidence
  - central apnea less clear
- Plaques hypothalamus may cause narcolepsy
  - both HLA DR2
- 2 patients absent hypocretin no cataplexy
- Previous report 9/10 pt cataplexy (no csf)
- Neuromyelitis optica acute hypersomnolence and absent hypocretin
  - lesions hypothalamus
  - improved with MS therapy
Sleep Disorders in Women Are

- Dangerous
- Common
- Diagnosable
- Treatable
- Overlooked

- Third Pillar
  - DIET, EXERCISE, SLEEP