Sleep Disorders in Pregnancy

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University of Pittsburgh
• No conflicts of interest
“If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process ever made.”

--Alan Rechtschaffen
What Controls Sleep?

1. How long you have been awake

2. Time of Day
How much sleep is normal?

AIM FOR 7-9 hours/night
SHORT SLEEP DURATIONS ARE COMMON

Prevalence of Short Sleep Duration (<7 hours) for Adults Aged >=18 Years, by County, United States 2014

Data Sources: CDC, Behavioral Risk Factor Surveillance System 2014, Census 2010, ACS 2010-2014

Date: 8/1/2016
Why is sleep important?

After one night ...

• Increased car accidents
• More emotional
• Memory deficits

Chronic sleep loss...

• ↑ cardiovascular disease
• ↑ obesity
• ↑ diabetes
<table>
<thead>
<tr>
<th>Chronic condition</th>
<th>Short sleep (&lt;7 hours)</th>
<th>Sufficient sleep (≥7 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart attack</td>
<td>4.8 (4.6–5.0)</td>
<td>3.4 (3.3–3.5)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>4.7 (4.5–4.9)</td>
<td>3.4 (3.3–3.5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.6 (3.4–3.8)</td>
<td>2.4 (2.3–2.5)</td>
</tr>
<tr>
<td>Asthma</td>
<td>16.5 (16.1–16.9)</td>
<td>11.8 (11.5–12.0)</td>
</tr>
<tr>
<td>COPD (chronic obstructive pulmonary disease)</td>
<td>8.6 (8.3–8.9)</td>
<td>4.7 (4.6–4.8)</td>
</tr>
<tr>
<td>Cancer</td>
<td>10.2 (10.0–10.5)</td>
<td>9.8 (9.7–10.0)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>28.8 (28.4–29.2)</td>
<td>20.5 (20.2–20.7)</td>
</tr>
<tr>
<td>Depression</td>
<td>22.9 (22.5–23.3)</td>
<td>14.6 (14.3–14.8)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3.3 (3.1–3.5)</td>
<td>2.2 (2.1–2.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11.1 (10.8–11.4)</td>
<td>8.6 (8.4–8.8)</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval.

Age-adjusted to the 2000 US standard population.

The prevalence of each condition is significantly higher (p<0.05) for persons reporting short sleep compared with those reporting sufficient sleep.
Sleep Protects Against The Common Cold

Chances of Catching a Cold When Exposed to the Virus (%)

- 17.2%
- 22.7%
- 30%
- 45.2%

Sleep Duration:
- > 7 hours
- 6.01 to 7 hours
- 5 to 6 hours
- < 5 hours

Source: Prather et al, 2015
Sleep Timing

- Circadian Rhythms
- Try to go to bed and wake up around the same time every day (within an hour)
- If your schedule allows it try to go to bed by 11 PM
Sleep Midpoint

11P-7A
12A-6A
1A-5A

11P-7A
9P-5A
10P-6A
1A-9A
QUALITY MATTERS

• Sleep needs to be adequate in duration/timing but QUALITY is also important

• Poor sleep quality may be due to
  – Getting up multiple times at night because of physical or environmental issues
  – Sleep disorders
    – Sleep apnea
    – Insomnia
    – Restless Legs Syndrome
Sleep Apea

- Apnea Hypopnea Index (AHI)
- SDB= AHI ≥ 5
  - Mild 5-14.9
  - Moderate ≥15-29.9
  - Severe ≥ 30
OSA and CV Disease

Cumulative Incidence of Hypertension in Participants Without OSA and Untreated Patients With OSA

## T2DM and OSA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Population</th>
<th>No OSA</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM</td>
<td>17.2</td>
<td>6.6</td>
<td>14.1</td>
<td>21.0</td>
<td>28.9</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diabetic medications</td>
<td>9.3</td>
<td>3.7</td>
<td>8.0</td>
<td>11.4</td>
<td>15.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.68 (0.98)</td>
<td>5.38 (0.72)</td>
<td>5.58 (0.83)</td>
<td>5.76 (0.96)</td>
<td>6.06 (1.22)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Data are expressed as percentage of cohort or mean (SD). HbA1c = glycosylated hemoglobin; T2DM = type 2 diabetes mellitus.
Sleep Fragmentation

- Sleep apnea: Intermittent hypoxia & Intrathoracic pressure swings

Short Sleep Duration

Circadian Disruption

- Sleep apnea: Intermittent hypoxia & Intrathoracic pressure swings

Sympathetic Activity

Activation-HPA axis

Cortisol

Leptin

Ghrelin

Oxidative Stress

Inflammation

Hypertension

Cardiac Disease

Diabetes
Principles and Practice of Sleep Medicine.
Facco, Francesca; Louis, Judette... Show all.; Knavert, Melissa Pauline; Izci Balserak, Bilgay. Published January 1, 2017. Pages 1540-1546.e4. © 2017.
SLEEP AND PREGNANCY
NuMoM2b Sleep Duration Study

Actiwatch (Philips Respironics)
Distribution of Sleep Duration at Visit 2

- <6
- 6 to <7
- 7 to <8
- 8 to <9
- SD >9
Short Sleep and Gestational Diabetes Risk

GDM risk by Sleep Duration Status

Sleep duration < 7 (n=218)
6.9%

Sleep duration ≥ 7 (n=564)
3.2%

Facco et al, 2015, SMFM Abstract # 256
Late Sleep Midpoint (> 5 AM) and Gestational Diabetes Risk

GDM risk by Sleep Duration Status

OR = 2.58 (1.24-5.36)

Late sleep midpoint (> 5A) (n=148) 8.1%

Sleep midpoint ≤ 5A (n=634) 3.3%

Facco et al, 2015, SMFM Abstract # 256
# TABLE 4
Association of sleep duration and timing with gestational diabetes

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<th>Sleep characteristic categories</th>
<th>Gestational diabetes n/N (%)</th>
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<td>Race/ethnicity, 4 categories N = 782</td>
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<td><strong>Sleep duration</strong></td>
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<td>&lt;7 h</td>
<td>15/218 (6.9)</td>
<td>2.24 (1.11–4.53)</td>
<td>2.26 (1.12–4.58)</td>
<td>2.12 (1.04–4.30)</td>
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<td><strong>Sleep midpoint</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>&gt;5 AM</td>
<td>12/148 (8.1)</td>
<td>2.58 (1.24–5.36)</td>
<td>3.87 (1.74–8.59)</td>
<td>2.41 (1.15–5.07)</td>
</tr>
<tr>
<td>≤5 AM</td>
<td>21/634 (3.3)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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</table>

**P value** = .0246

**P value** = .0232

**P value** = .0380

**P value** = .0220

**P value** = .0266

**P value** = .0586

**P value** = .0190

**OR** given to show association between gestational diabetes and sleep characteristic, without consideration of covariates and with separate adjustment for: age, BMI, race/ethnicity categories; white, non-Hispanic race/ethnicity; frequent snoring noted before pregnancy; and employment schedule (regular day shift, some form of shift work, unemployed). For race/ethnicity, Asian and other are collapsed.

*BMI*; body mass index; *CI*, confidence interval; *OR*, odds ratio.

Sleep-Disordered Breathing Substudy
SDB Prevalence in Nulliparous Women

AHI ≥ 5

3.6% in early pregnancy
8.3% in mid pregnancy

MILD

Snorers/Obese women had about a 20% prevalence of OSA in mid pregnancy assessment

MODERATE/SEVERE

5 ≥ AHI < 15

AHI ≥ 15
### Incidence of Gestational Diabetes

<table>
<thead>
<tr>
<th></th>
<th>EARLY PREGNANCY</th>
<th>MID-PREGNANCY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3.47 (1.95, 6.19)</td>
<td></td>
<td></td>
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<tr>
<td>2.79 (1.63, 4.77)</td>
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<td></td>
</tr>
</tbody>
</table>
Incidence of Preeclampsia

<table>
<thead>
<tr>
<th></th>
<th>No SDB</th>
<th>Yes SDB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Pregnancy</td>
<td>5.6%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Mid Pregnancy</td>
<td>5.0%</td>
<td>12.6%</td>
</tr>
</tbody>
</table>

Adjusted OR

<table>
<thead>
<tr>
<th></th>
<th>EARLY PREGNANCY</th>
<th>p-value</th>
<th>MID-PREGNANCY</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted OR</td>
<td>1.94 (1.07, 3.51)</td>
<td>0.03</td>
<td>1.95 (1.18, 3.23)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Sleep Health
A **Modifiable** Risk Factor for Adverse Pregnancy Outcomes?
Continuous Positive Airway Pressure

CPAP

• Sleep apnea is a potentially modifiable pregnancy risk factor
• Opportunity to study if OSA treatment with CPAP can reduce the frequency of hypertensive disorders of pregnancy
CPAP Trials in Non-Pregnant Cohorts

• Normalization of AHI
• Improved Sleep Quality
• Less daytime sleepiness, improved daytime functioning
• CV and metabolic health ????
Figure 2. Cumulative Incidence of Hypertension or Cardiovascular Events During Follow-up

Effect of CPAP on Blood Pressure in Patients With Obstructive Sleep Apnea and Resistant Hypertension

The HIPARCO Randomized Clinical Trial

Miguel-Angel Martínez-García, MD, PhD; Francisco Capote, MD, PhD; Francisco Campos-Rodríguez, MD, PhD; Patricia Lloberes, MD, PhD;

Change in diastolic blood pressure

Change in systolic blood pressure

Change in 24-h mean blood pressure
Effect of Continuous Positive Airway Pressure on Glycemic Control in Patients with Obstructive Sleep Apnea and Type 2 Diabetes. A Randomized Clinical Trial

Elisabet Martínez-Cerón 1,2, Beatriz Barquiel 3, Ana-Maria Bezos 4, Raquel Casitas 1,2, Raúl Galera 1,2, Cristina García-Beníto 5, Angel Hernanz 6, Alberto Alonso-Fernández 2, and Francisco García-Rio 1,2,8
SAVE TRIAL
Therapy with CPAP plus usual care, as compared with usual care alone, did not prevent cardiovascular events in patients with moderate-to-severe obstructive sleep apnea and established cardiovascular disease.

McEvoy et al. NEJM. 2016.
CPAP & Pregnancy

• CPAP and pregnancy data extremely limited
• Pregnancy is an ideal scenario in which to better understand the role of CPAP as a preventative strategy in reducing cardio-metabolic morbidity
Treatment of Sleep Disordered Breathing Reverses Low Fetal Activity Levels in Preeclampsia

Diane M. Blyton, PhD,1 Michael R. Skilton, PhD,2 Natalie Edwards, PhD,1,* Annemarie Hennessy, PhD,3 David S. Colermajer, PhD,1 and Colin E. Sullivan, PhD1

- 10 Preeclamptic Women
- Fetal Movement Sensor
  - White bars fetal movements
  - Grey bars fetal hiccups
Pre-eclampsia and nasal CPAP: Part 2. Hypertension during pregnancy, chronic snoring, and early nasal CPAP intervention

Dalva Poyares a,b, Christian Guillemainault b,c, Helena Hachul a, Luciane Fujita a, Shanon Takaoka b, Sergio Tufik a, Nelson Sass a

a Federal University of Sao Paulo Sleep Disorders Center, Brazil
b Stanford University Sleep Medicine Program, 801 Quarry Road, Suite 3301, Stanford, CA 94305, USA

- Pregnancy women with CHTN
- Early pregnancy intervention
- 7 CPAP, 9 Controls
- Better BP control
Reduced Nocturnal Cardiac Output Associated with Preeclampsia is Minimized with the Use of Nocturnal Nasal CPAP

Diane M. Blyton, MSc1,2; Colin E. Sullivan, PhD1; Natalie Edwards, PhD1

1The University of Sydney; 2Royal Prince Alfred Hospital, Sydney

- 24 severe pre-E
- Randomized
  - 12 CPAP, 12 no treatment
- 15 controls nulliparous
- Cardiac output reductions minimized and total peripheral resistance decreased with CPAP
MFMU SLEEP Trial

• RCT
• Nulliparous women who have a BMI $\geq 30$ and/or who snore will be identified and asked to perform a home sleep test to identify sleep apnea positive subjects (AHI $\geq 5$)
• OSA + women will be randomized
  – Auto-titrating CPAP
  – Sleep hygiene control (i.e., usual care)

• Primary hypothesis of this trial is that treatment of OSA with CPAP in pregnancy will result in a reduction in the rate of hypertensive disorders of pregnancy
Screen

• Rate of OSA much higher in women obese women and those with self reported snoring

• nuMoM2b 25% of women reported frequent snoring

• Snorers/Obease women had about a 20% prevalence of OSA in mid pregnancy assessment
Timing of Screen

• Balance
  – Optimize cost-effective screening (later in pregnancy)
  – Optimal treatment effect (earlier in pregnancy)

• 16w 0 d-20w 6 d gestation
Exclusion

• Age < 18
• Previously prescribed, current or planned therapy for sleep apnea
• Inability to sleep in a stable place with access to the CPAP machine at least 5 nights/week
• Current use prescribed sleeping pills for insomnia
• Current use of opiates
• Active drug use, alcohol use, unstable psychiatric condition
• Severe asthma requiring continuous oral steroid therapy for more than 14 days in past 6 months
• Conditions requiring oxygen supplementation
Exclusion

- Current use of antihypertensive medications to treat chronic hypertension
- Chronic renal disease with Cr > 1.3
- Antiphospholipid antibody syndrome
- Acute liver disease
- Thrombocytopenia < 100K
- Active vaginal bleeding more than spotting
- Known chromosomal/genetic/major malformation of the fetus
- Uterine malformations
- Participation in another interventional study that influences preE, GDM
- Delivery/care planned at a non-network site
Diagnose Sleep Apnea via Home Sleep Test (HST)
Severe Sleep Apnea & Hypoxemia Exclusions-Urgent Alerts

• If severe sleep apnea exclusion (AHI ≥ 30), nocturnal hypoxemia (02 sat ≤ 90% ≥ 10 % of recording time)
  – Anticipated less than 1%
CPAP vs. Sleep Hygiene Control

• Auto titrating-CPAP
  – Informational handout about healthy sleep
  – CPAP machine with appropriate mask, education about CPAP
  – Weekly follow-up

• Sleep Hygiene Control (i.e., usual care)
  – Informational handout
  – Sleep resources
  – Monthly follow-up
Compliance Monitoring for CPAP

- Compliance incentive
Primary Outcome

• Hypertensive disorders of pregnancy a composite of:
  – Gestational hypertension diagnosed before the onset of labor (antepartum)
  – Preeclampsia
  – Superimposed Preeclampsia
  – HELLP
  – Eclampsia
Secondary Outcomes

- Gestational diabetes by GTT criteria- GTT to be performed at or after 24 weeks gestation
- Preterm birth- < 34 weeks, <37 weeks, spontaneous, indicated
- Birthweight
Blood Analytes

• Mechanistic lab assays in the domains of:
  – Inflammation
  – Oxidative stress
  – Endothelial dysfunction
  – Angiogenesis
  – Hormonal mechanisms of energy regulation
Placental Collection

• Samples can be collected up to 72 hours after delivery as long as they have been stored in a 4 degree Celsius freezer between delivery and pickup.

• Samples will be stored for future histological analysis and analysis of stable proteins via immunohistochemistry.
Sample Size Assumptions

- 90% power to detect 30% reduction in reduction in the frequency of hypertensive disorders of pregnancy in women who get active-CPAP therapy
- nuMoM2b data -incidence of hypertensive disorders among women with OSA =20%
- 20% of women will use the device so infrequently over the course of the entire pregnancy that we would expect them to have an outcome frequency the same as in the control arm
- 1-2% cross over
Sample Size

• 1350 women/group (2700)

• Identify 1.33 women (BMI ≥ 30 and or snore) for every woman who agrees to the sleep test
  – 75% consent to sleep test

• Identify 1.25 women with a positive sleep test for every women who randomizes
  – 80% still eligible, and consent to randomization
Interventions to Improve Sleep

- Education
- Behavioral Interventions
Continuous Positive Airway Pressure
CPAP
CPAP & Pregnancy

• CPAP and pregnancy data extremely limited
• Pregnancy is an ideal scenario in which to better understand the role of CPAP as a preventative strategy in reducing cardio-metabolic morbidity
Questions?

YOU ONLY SLEEP 8 HOURS
Association Between Sleep Duration and Diabetes in Black and White Adults
NuMoM2b Sleep Duration Study

Actiwatch (Philips Respironics)
Distribution of Sleep Duration at Visit 2

- <6
- 6 to <7
- 7 to <8
- 8 to <9
- SD >9

Sleep Duration
Short Sleep and Gestational Diabetes Risk

GDM risk by Sleep Duration Status

Sleep duration < 7 (n=218) 6.9%
Sleep duration ≥ 7 (n=564) 3.2%

OR = 2.24 (1.1-4.53)

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*P value* = .0246

| Sleep midpoint                |                             |                                   |                             |                             |                             |                                    |
| >5 AM                         | 12/148 (8.1)                | 2.58 (1.24–5.36)                  | 3.87 (1.74–8.59)           | 2.41 (1.15–5.07)           | 2.61 (1.22–5.57)           | 2.62 (1.23–5.58)                   | 2.84 (1.16–6.99)                   | 3.71 (1.50–9.21)                   |
| ≤5 AM                         | 21/634 (3.3)                | 1.00                              | 1.00                        | 1.00                        | 1.00                        | 1.00                               | 1.00                               | 1.00                               |

*P value* = .0114

OR given to show association between gestational diabetes and sleep characteristic, without consideration of covariates and with separate adjustment for: age, BMI, race/ethnicity categories, white, non-Hispanic race/ethnicity, frequent snoring noted before pregnancy, and employment schedule (regular day shift, some form of shift work, unemployed). For race/ethnicity, Asian and other are collapsed.

BMI, body mass index; CI, confidence interval; OR, odds ratio.

Shorter sleep duration was associated with worse glucose control.

- 2-6 mg/dL increase in glucose observed per hour less of sleep.

Table 2. Relationships Between Continuous Sleep Exposures and Glucose

<table>
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<th>Glucose Outcome</th>
<th>Exposure</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
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<tbody>
<tr>
<td></td>
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<td>$\beta$</td>
<td>95% CI</td>
</tr>
<tr>
<td>Fasting</td>
<td>Sleep time</td>
<td>-2.52</td>
<td>-4.35 to -0.69</td>
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<tr>
<td>Breakfast</td>
<td>Sleep time</td>
<td>-3.72</td>
<td>-7.01 to -0.43</td>
</tr>
<tr>
<td>Lunch</td>
<td>Sleep time</td>
<td>-4.32</td>
<td>-8.16 to -0.48</td>
</tr>
<tr>
<td>Dinner</td>
<td>Sleep time</td>
<td>-5.97</td>
<td>-9.14 to -2.79</td>
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