The Role of Maternal Sleep in Stillbirth

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Why study sleep?
Why is Sleep Important?

Key to health, performance, safety and quality of life

Necessary as the water we drink, the air we breathe and the food we eat

Sleep is NOT the absence of wakefulness
- Active, complex, and highly regulated
- Involves different areas of the brain
- Duration and timing are important
- Essential for life
- We all need it!

Sleep consumes 1/3 of human existence; unhealthy sleep can severely impair the other 2/3.

The Sleep Cycle

Alternating states of sleep across the night:
- NREM: Non-Rapid Eye Movement; Stages 1-3; 75% of the night
- REM: Rapid Eye Movement; Dreams occur; 25% of the night

Sleep is important for cardiometabolic health
During the Sleep Cycle:

- Body temperature lowers
- Hormone levels rise and fall

During the Sleep Cycle:

- Breathing
- Timing
- Movement/Position
- Continuity
- Quality
- Quantity

During the Sleep Cycle:

- Body Temperature
- Melatonin
- Cortisol
- Growth Hormone

During the Sleep Cycle:

- Day 1
- Day 2
- Day 3
What does sleep have to do with stillbirth?

Stillbirth

Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis

- maternal weight
- maternal hypertension
- maternal diabetes
- placental abruption
- small size for gestational age
- maternal smoking
- maternal age
- primiparity

A role for sleep in all of these

Maternal sleep is an important contributor to pregnancy outcomes......
Sleep and Maternal Weight:

Lack of sleep alters appetite hormones.....
- leptin ("fullness hormone")
- ghrelin ("hunger hormone")

Habitual snoring affects about 35% of pregnant women by the 3rd trimester and up to 85% of those with pre-eclampsia

OSA affects about;
- 8-10% of pregnant women
- 15-25% of women BMI ≥ 30
- 60% of women BMI ≥ 40
- 50% of women with Pre-eclampsia
Apneas + hypopneas)/hours of sleep = Apnea/Hypopnea Index (AHI)

AHI<5 = Normal
AHI≥5 and <15 = Mild OSA
AHI≥15 and <30 = Moderate OSA
AHI≥30 = Severe OSA

Recent multicenter trial of approx n=3000 nulliparous women found aOR of 1.94 (95% CI 1.07–3.51) for pre-eclampsia in women with OSA

(Facco et al 2017)
Alpha-methyl dopa dose increased in controls; constant or decreased in CPAP

Treatment with positive airway pressure:

Sleep Duration and Hypertension:

Very short sleep (<5h) associated with a 9.5-fold increased odds of pre-eclampsia (95%CI 1.8 to 49.4)
Sleep and Maternal Glucose/Gestational Diabetes:

- Sleep <7 hrs associated with GDM  
  aOR 2.2 (95%CI 1.1-4.5)  
  Facco 2017

- Short sleep duration is inversely correlated with 1-hr 50g load OGTT:
  - Each hour of reduced sleep associated with 4% increase in glucose levels in pregnancy  
  Reutrakul 2011

Sleep and Placental Abruption:

- Compared to “normal” sleep duration (7-8 hours), extreme durations were associated with increased odds of placental abruption:
  - Short sleep (≤6 h) was associated with an odds ratio of 2.0 (95% CI 1.1-3.7)
  - Long sleep (≥9 h) was associated with an odds ratio of 2.1 (95% CI 1.1-4.1)
Fetal growth in women with sleep-disordered breathing:

Pooled aOR of SDB Sx (6 studies):
aOR of 1.6 (1.1-2.2) for FGR

Warland, Dorrian, Morrison, O’Brien 2018

Pooled aOR of OSA Dx (5 studies):
aOR of 1.4 (1.1-1.9) for FGR

Hypertension, Sleep-Disordered Breathing and Fetal Movements

Due to impaired cardiac output and increased peripheral vascular resistance

Uteroplacental hypoperfusion and fetal hypoxemia

Edwards & Sullivan 2008
Fetal growth in women with sleep-disordered breathing:

<table>
<thead>
<tr>
<th>Perinatal Outcome</th>
<th>OSA (n=14)</th>
<th>Control (n=27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation at delivery (weeks)</td>
<td>39.0 (1.0)</td>
<td>39.4 (1.0)</td>
<td>0.60</td>
</tr>
<tr>
<td>Birthweight (grams)</td>
<td>3378 (472)</td>
<td>3567 (501)</td>
<td>0.15</td>
</tr>
<tr>
<td>Birthweight centile</td>
<td>47 (20)</td>
<td>54 (30)</td>
<td>0.49</td>
</tr>
<tr>
<td>Impaired fetal growth (Birthweight &lt; 10th centile or fall in 3rd trimester)</td>
<td>6 (43%)</td>
<td>3 (11%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Birthweight &lt; 10th centile</td>
<td>2 (14%)</td>
<td>3 (11%)</td>
<td>1</td>
</tr>
<tr>
<td>Fall in centile &lt; 33% between 32 weeks and term</td>
<td>4 (29%)</td>
<td>0 (0%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Serial measures of fetal growth in n=54 controls, n=34 untreated OSA, n=14 treated OSA:
- Fetal growth problems defined as birth weight <10th centile, or a slowing of fetal growth by >30% during the last trimester.
- In a logistic regression model, after accounting for co-morbid hypertension, diabetes, anti-hypertensive and anti-diabetic medications, maternal age, and smoking, untreated OSA was associated with a 3-fold increased odds of fetal growth problems (OR 3.0, 95%CI 1.1-8.3, p=0.03).
- There were no differences in fetal growth trajectories between non-OSA and treated OSA

Infant Outcomes with Positive Airway Pressure

APAP in pregnancy is associated with improved birth weight: Infants born to women who used APAP during pregnancy, compared to infants born to women who did not use APAP, have larger birth weight (3036±833g vs. 2485±1050g, p=0.08) even after accounting for duration of APAP use

APAP is associated with longer gestation. Women who used APAP continued their pregnancies for a mean of 2.5 weeks longer than non-users (37.7±2.8 weeks vs. 35.1±4.1 weeks, p=0.03).

This is a clinically significant duration that may have long-term impact on infant health.

Anecdotally women on APAP report:
- improved BP control
- feeling better
- more fetal movement

O’Brien unpublished
Preterm Birth:

Pregnancy: Sleep disorders increase the risk of premature birth

- Pooled aOR of SDB Sx (4 studies): aOR of 1.5 (1.0-2.0) for PTB
- Pooled aOR of OSA Dx (6 studies): aOR of 1.6 (1.2-2.2) for PTB
- Pooled aOR of short sleep (5 studies): aOR of 1.4 (1.0-2.1) for PTB
- Pooled aOR of poor sleep quality (4 studies): aOR of 2.0 (1.3-2.9) for PTB

Warland, Dorian, Morrison, O’Brien 2018

Felder 2017

aOR 1.3 (1.0–1.7) for insomnia and PTB <37/40 and aOR 1.7 (1.1-2.6) for PTB <34/40
aOR 1.5 (1.2–1.8) for OSA and PTB <37/40 and aOR 4.1 (2.2-8.3) for PTB <34/40

African American women with poor sleep quality have much higher odds of PTB than Caucasian women

Blair 2015

SDB and Time to Delivery

In n=954 non-hypertensive, non-diabetic women, there was an increased hazard ratio for earlier delivery in chronic loud frequent snorers vs. controls: HR 1.60, (95% CI 1.04, 2.45)

These women delivered approximately 6 days earlier;
25% were considered “early term” (37+0 – 38+6 weeks)

Dunietz…Schisterman…O’Brien 2018
OSA and the Placenta

Markers of tissue hypoxia as well as markers of angiogenesis are more common in OSA compared to controls (Ravishankar 2015, Bourjeily 2015)

The feto-placental weight ratio, a common metric of the balance between fetal and placental growth, is reduced as the severity of OSA increases:

<table>
<thead>
<tr>
<th></th>
<th>AHI&lt;5 (n=23)</th>
<th>AHI&gt;5 (n=14)</th>
<th>AHI&gt;15 (n=6)</th>
<th>AHI&gt;30 (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feto-placental weight ratio</td>
<td>6.3±1.5</td>
<td>6.1±1.3</td>
<td>5.8±1.0</td>
<td>5.3±0.3</td>
</tr>
</tbody>
</table>

Chorangiosis, an increase in the number of vessels in the chorionic villi, likely a result of a hypoxic stimulus as nRBC’s were also elevated (O’Brien, unpublished)

Case 1

32yo Caucasian, BMI 24   G4 P1
Fetal demise #1 at 20/40
Fetal demise #2 at 19/40
Premature delivery at 27/40 - NICU

Enrolled on trial at 21/40   AHI=1 (no sleep apnea)
Did not develop pre-eclampsia
Delivered healthy male infant at 36+2 weighing 6lb 1oz

Interestingly, unlike her previous placenta which showed typical histological changes, the placenta was normal except for one small infarct. Was this due to positive airway pressure?
**Case 2**

30yr, AA, BMI 64, HTN, multiple fetal losses (G4 P0)
BPs at enrollment >140/80mmHg on meds
Found to have OSA on study PSG (AHI=28)
While on auto-PAP BPs 110-120/64-84mmHg (still on meds)

Delivered 39 week male
infant weighing 9lb 15oz

Subsequent pregnancy did not use her auto-PAP.....
.... presented at 28 weeks with a fetal demise

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**Case 3**

PE047:

34yo African American, GHTN, BMI 42 G1 P0
BPs at enrollment (35 weeks) >150/80mmHg despite escalating meds over previous 3 weeks
- Morning after baseline sleep study, subject in triage with non-reactive FHR, reduced FM, and severe maternal desats (nadir SpO2 70%)
- Obstetrics plan to deliver that day (35/40)
- Study team paged; decision made to start auto-PAP immediately

**Subsequently found to have severe OSA on sleep study (AHI=117)**

On APAP:
- FHR became reactive
- Maternal SpO2 normal
- Discharged and continued pregnancy for another 2 weeks
- Delivered healthy 6lb 3oz female infant
Why is maternal position important?

Increase in wake cardiovascular parameters from supine to left:

Rossi 2011
Gravid uterus compresses the inferior vena cava resulting in:
- venous return
- ejection fraction
- cardiac output

\[ \text{impaired uterine perfusion} \]

"Maternal supine hypotensive syndrome"

Lateral Tilt for procedures

Care is taken to avoid supine maternal position for a 30-60 min procedure BUT there is potential for many hours spent supine during sleep in the last 12 weeks of pregnancy.
Sleep Position and Stillbirth

Several case-control studies and a cross-sectional study all demonstrate an association between maternal self-report of supine sleep and late stillbirth

Other sleep practices related to stillbirth:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stillbirth (n=153)</th>
<th>Controls (n=480)</th>
<th>Unadjusted OR (95%CI)</th>
<th>Adjusted OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Duration last month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 hours</td>
<td>86 (56.9%)</td>
<td>393 (50.8%)</td>
<td>1.05 (0.96-1.17)</td>
<td>1.05 (0.95-1.17)</td>
</tr>
<tr>
<td>9 hours</td>
<td>45 (29.4%)</td>
<td>79 (16.5%)</td>
<td>1.87 (1.15-2.91)</td>
<td>1.75 (1.10-2.79)</td>
</tr>
<tr>
<td>AWAKENINGS LAST MONTH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01 awakening</td>
<td>23 (15.0%)</td>
<td>61 (12.7%)</td>
<td>1.06 (0.63-1.79)</td>
<td>1.14 (0.65-1.97)</td>
</tr>
<tr>
<td>02 awakenings</td>
<td>121 (79.1%)</td>
<td>341 (71.0%)</td>
<td>1.00 Reference</td>
<td>1.00 Reference</td>
</tr>
<tr>
<td>GET UP LAST MONTH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01 time up</td>
<td>47 (30.7%)</td>
<td>129 (26.9%)</td>
<td>1.10 (0.67-1.81)</td>
<td>1.16 (0.75-1.79)</td>
</tr>
<tr>
<td>02 time up</td>
<td>30 (19.4%)</td>
<td>270 (56.3%)</td>
<td>1.00 Reference</td>
<td>1.00 Reference</td>
</tr>
<tr>
<td>RESTLESSNESS LAST MONTH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or little restless</td>
<td>52 (34.0%)</td>
<td>97 (20.2%)</td>
<td>1.71 (1.02-2.80)</td>
<td>1.73 (1.03-2.90)</td>
</tr>
<tr>
<td>More than average or very restless</td>
<td>62 (40.5%)</td>
<td>261 (41.9%)</td>
<td>0.98 (0.60-1.60)</td>
<td>0.91 (0.54-1.53)</td>
</tr>
<tr>
<td>SLEEP QUALITY LAST MONTH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good/Very Good</td>
<td>68 (41.4%)</td>
<td>89 (18.5%)</td>
<td>1.69 (1.02-2.75)</td>
<td>1.64 (0.98-2.75)</td>
</tr>
<tr>
<td>Average</td>
<td>90 (22.9%)</td>
<td>134 (27.9%)</td>
<td>1.00 Reference</td>
<td>1.00 Reference</td>
</tr>
<tr>
<td>Poor/Very Poor</td>
<td>47 (30.7%)</td>
<td>193 (40.2%)</td>
<td>0.65 (0.41-1.03)</td>
<td>0.74 (0.40-1.06)</td>
</tr>
<tr>
<td>AWAKENINGs LAST NIGHT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01 awakening</td>
<td>41 (26.8%)</td>
<td>63 (13.1%)</td>
<td>2.16 (1.37-3.41)</td>
<td>2.03 (1.26-3.24)</td>
</tr>
<tr>
<td>02 awakenings</td>
<td>94 (51.4%)</td>
<td>312 (63.9%)</td>
<td>1.00 Reference</td>
<td>1.00 Reference</td>
</tr>
</tbody>
</table>

What does this mean?

Perhaps long periods of undisturbed sleep such as long sleep duration and not waking more than once, independent of other risk factors are associated with late fetal demise?

- Prolonged sleep can compensate for poor sleep quality
- Long sleep duration associated with sedentary lifestyle/SES
- Long sleep durations associated with depression/anxiety

What about blood pressure?
- BP drops during sleep and reaches its lowest point in deep sleep
- Arousals and awakenings associated with sympathetic surge; transiently increase BP
- Could awakenings serve to maintain BP and avoid long periods with relatively low BP?

Maternal hypotension has been associated with fetal growth restriction, preterm birth, and stillbirth

- Friedman 1978, Ng 1992, Steer 2004
- aOR for stillbirth in women with at least three mean arterial pressure values ≤83mmHg was 1.8 (95%CI 1.1 -3.0).
In the presence of a stressor (uteroplacental perfusion or hypoxia), shift to a low oxygen consuming state would be a protective reaction.

Maternal supine position may be disadvantageous for fetal wellbeing and in compromised pregnancies may be a sufficient stressor to contribute to fetal demise.

**In the supine position:**
- fetal heart rate variability reduced
- Fetal behavior change from active to quiescence (low oxygen consuming state).

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**PrenaBelt Trials**

<table>
<thead>
<tr>
<th>Location</th>
<th>Halifax, Canada</th>
<th>Adelaide, AU</th>
<th>Accra, Ghana</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Double-blind, sham-controlled, randomized, crossover</td>
<td>Unblinded, non-intervention control, randomized, crossover</td>
<td>Double-blind, sham-controlled, randomized</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>PrenaBelt, sham-PrenaBelt</td>
<td>PrenaBelt, nothing</td>
<td>PrenaBelt, sham-PrenaBelt</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>2 nights</td>
<td>2 nights</td>
<td>12 weeks</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Sleep lab</td>
<td>Home</td>
<td>Home</td>
</tr>
<tr>
<td><strong>Sample</strong></td>
<td>Healthy, 3rd trimester</td>
<td></td>
<td>200</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>23</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td><strong>Discontinue</strong></td>
<td>3 DO</td>
<td>4 EX</td>
<td>19 DO/LTFU + 19 EX = 38</td>
</tr>
<tr>
<td><strong>1° Outcome</strong></td>
<td>Body position</td>
<td>Body position</td>
<td>Birth weight</td>
</tr>
<tr>
<td><strong>2° Outcomes</strong></td>
<td>Sleep quality &amp; quantity, user feedback, resps, BPS validation</td>
<td>fetal HR, SR, sleep quality, sleep quantity, resps, BPS validation</td>
<td>Compliance, body position, user feedback, pregnancy outcomes</td>
</tr>
</tbody>
</table>

Kember, Warland & O’Brien
Sleep Position Intervention

Use of a positional therapy device in n=25 third trimester women; randomized to wear device on either night 1 or night 2.

<table>
<thead>
<tr>
<th>Time supine (min)</th>
<th>Fetal heart rate (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>Intervention</td>
</tr>
<tr>
<td>Supine</td>
<td>non-supine</td>
</tr>
</tbody>
</table>

N=200 pregnant women randomized to positional intervention or sham

Goal: to reduce low birth weight and stillbirth
Sleep Position Intervention
The Ghana Prenabelt Trial

- Difficulty with adherence to wearing device:
  - Women use the device about 50% of the time

- But.....in women randomized to active device:
  - Supine sleep reduced by about 30 mins
  - Reduction from 33% of night spent supine to 25%

- Higher mean birth weight (3191g vs. 3081g)
  - Lower proportion of growth restriction (15% vs. 24%)

Maternal sleep has an important role in maternal cardio-metabolic health and fetal wellbeing:
- Gestational hypertension/pre-eclampsia
- Gestational diabetes
- Fetal growth problems
- Preterm birth
- Stillbirth

Interventions to optimize sleep in pregnancy may offer significant benefit to mothers and babies
Thank you!