

The Role of Maternal Sleep in Stillbirth

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Why study sleep?

The Importance of Sleep

"If you are an average person, 36% of your life will be spent...entirely asleep... what that [time] is telling us, is that sleep-at some level-is **important**."

—Russel G. Foster, FRS,
University of Oxford

That's
months per year

4.32

or

32 years of your 90 year life



Jim McIngvale

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!

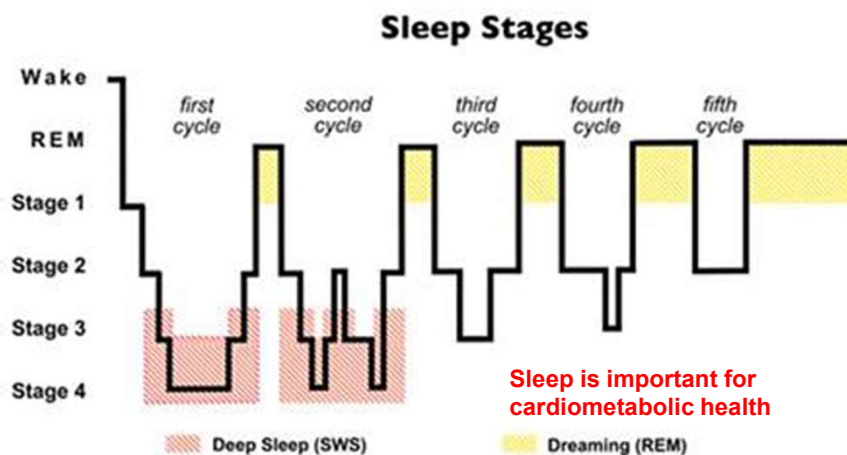


Sleep consumes 1/3 of human existence; unhealthy sleep can severely impair the other 2/3.

The Sleep Cycle

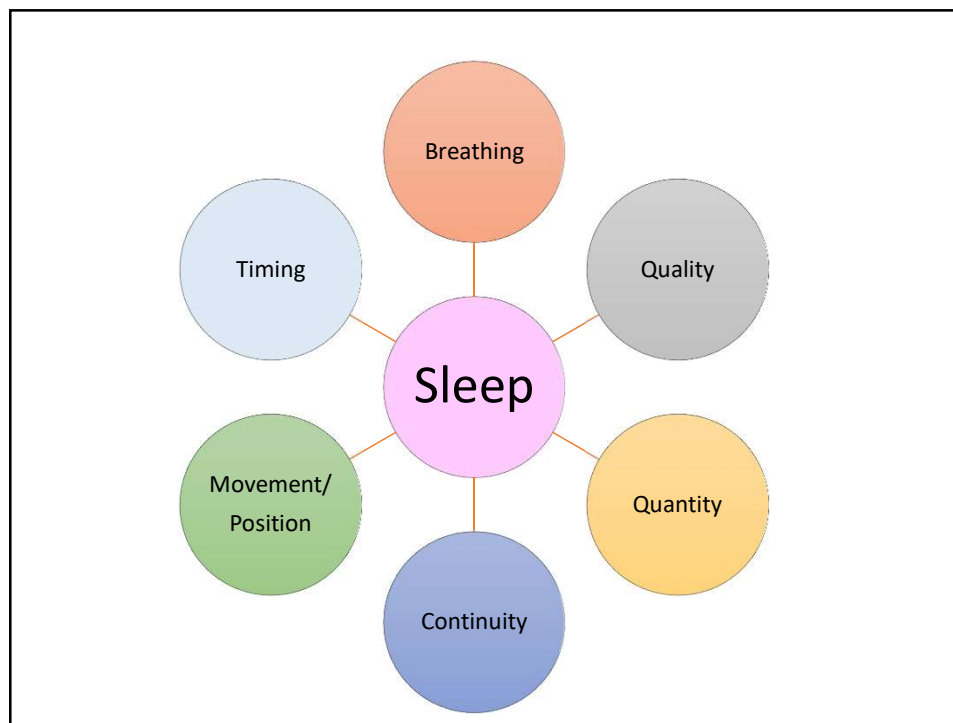
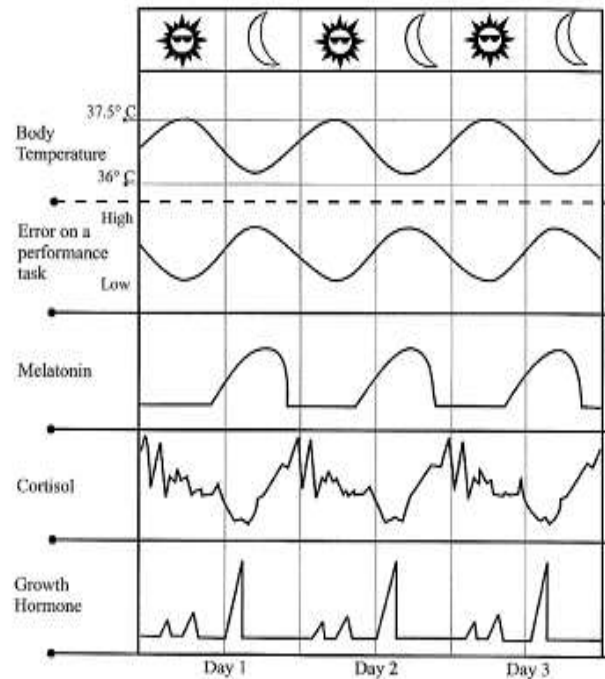
Alternating states of sleep across the night:

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



During the Sleep Cycle:

- Body temperature lowers
- Hormone levels rise and fall



What does sleep have to do with stillbirth?



Stillbirth

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

Vicki Flenady, Laura Koopmans, Philippa Middleton, J Frederik Freen, Gordon C Smith, Kristen Gibbons, Michael Coory, Adrienne Gordon, David Ellwood, Harold David McIntyre, Ruth Fretts, Majid Ezzati

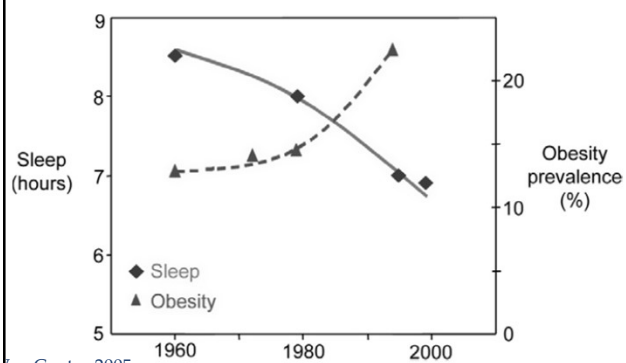
THE LANCET 2011

- 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:



van Cauter 2005



Lack of sleep alters appetite hormones.....

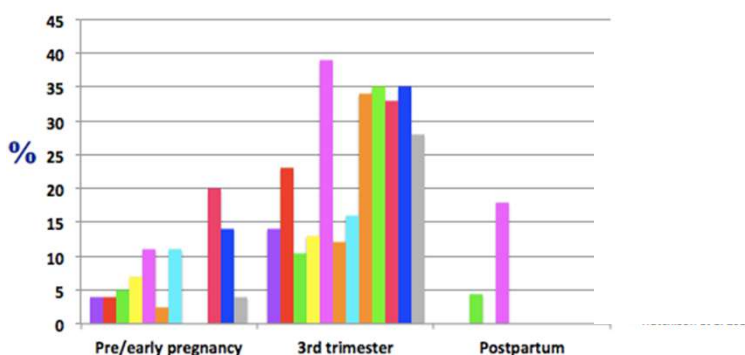
- leptin ("fullness hormone")



- ghrelin ("hunger hormone")



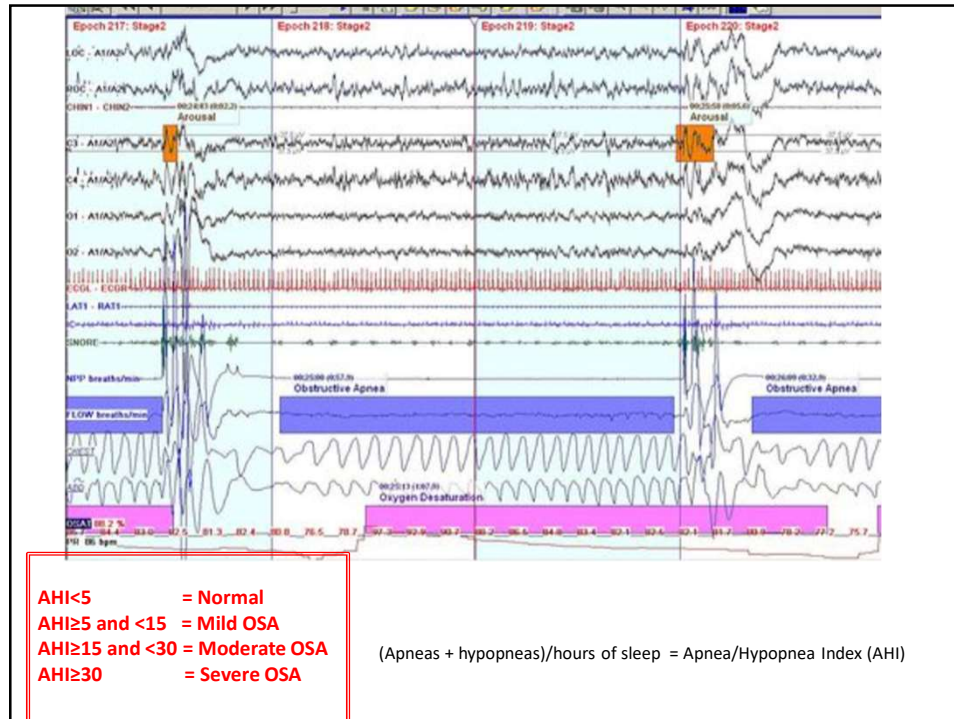
Sleep-Disordered Breathing and Hypertension



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**



OSA AND SEVERE MATERNAL-INFANT MORBIDITY/MORTALITY IN THE USA

<http://dx.doi.org/10.5665/sleep.3644>

Obstructive Sleep Apnea and Severe Maternal-Infant Morbidity/Mortality in the United States, 1998-2009

Judette M. Louis, MD, MPH¹; Mulubhan F. Mogos, PhD²; Jason L. Salemi, MPH²; Susan Redline, MD, MPH³; Hamisu M. Salihu, MD, PhD^{1,2}

of 24%. After controlling for obesity and other potential confounders, OSA was associated with increased odds of pregnancy-related morbidities including preeclampsia (OR, 2.5; 95% CI, 2.2-2.9), eclampsia (OR, 5.4; 95% CI, 3.3-8.9), cardiomyopathy (OR, 9.0; 95% CI, 7.5-10.9), and pulmonary embolism (OR, 4.5; 95% CI, 2.3-8.9). Women with OSA experienced a more than fivefold increased odds of in-hospital mortality (95% CI, 2.4-11.5). The adverse effects of OSA on selected outcomes were exacerbated by obesity.

Conclusions: Obstructive sleep apnea is associated with severe maternal morbidity, cardiovascular morbidity, and in-hospital death. Targeted interventions may improve pregnancy outcomes in this group.

**Nulliparous Pregnancy Outcomes Study
Monitoring Mothers-to-be**

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)

Treatment with positive airway pressure:

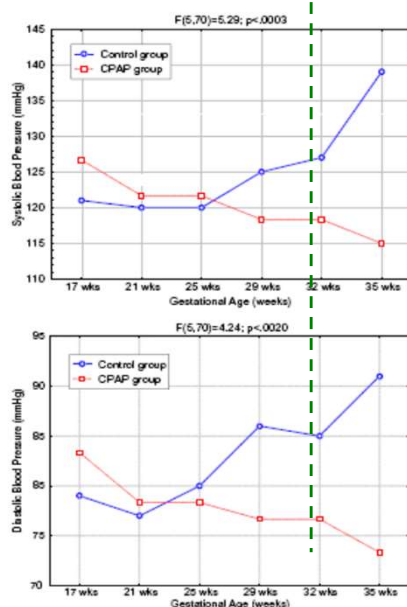


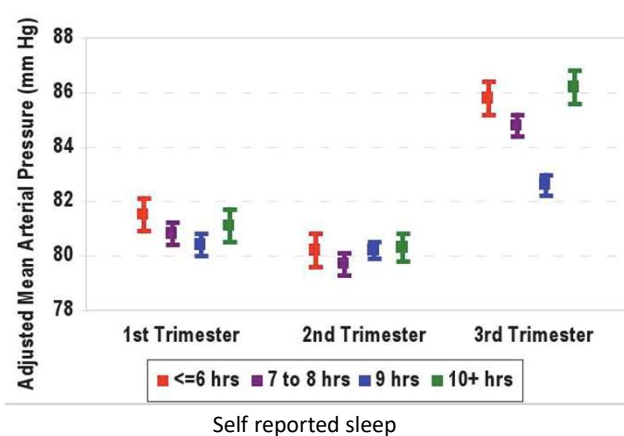
Fig. 1. Longitudinal blood pressure measurements.

Alpha-methyl dopa dose increased in controls;
constant or decreased in CPAP



Poyares et al 2008

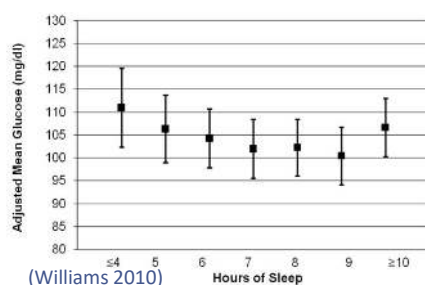
Sleep Duration and Hypertension:



Williams 2010

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:



aRR for GDM in those sleeping <4hrs is 5.6 (95%CI 1.3-23.7)

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](#)

Meta-analysis of 9,795 pregnant women:

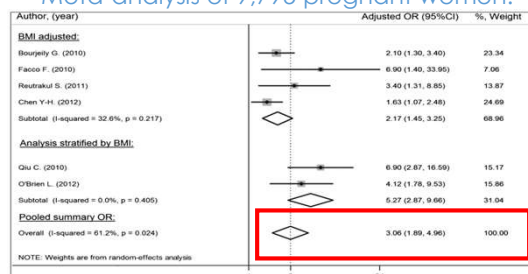


Figure 3
Stratified analysis: Forest plots showing studies' adjusted ORs of the association between SDB and GDM and the pooled summary OR (n = 6).

[Luque-Fernandez, 2013](#)

Sleep and Placental Abruption:

THE JOURNAL OF
**MATERNAL-FETAL
& NEONATAL
MEDICINE**

<http://informahealthcare.com/jmf>
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informa
healthcare

ORIGINAL ARTICLE

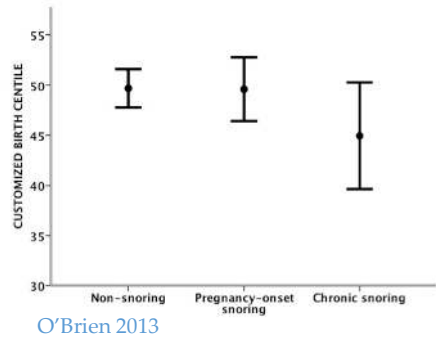
Maternal sleep duration and complaints of vital exhaustion during pregnancy is associated with placental abruption

Chunfang Qiu¹, Sixto E. Sanchez^{2,3}, Bizu Gelaye⁴, Daniel A. Enquobahrie^{1,5}, Cande V. Ananth^{6,7}, and Michelle A. Williams⁴

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)

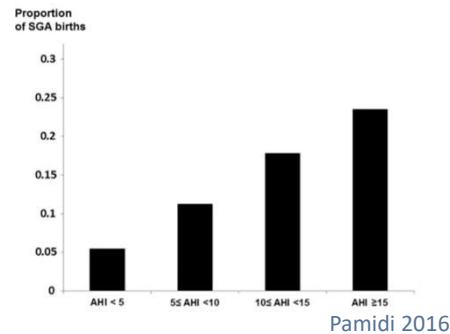
Fetal growth in women with sleep-disordered breathing:



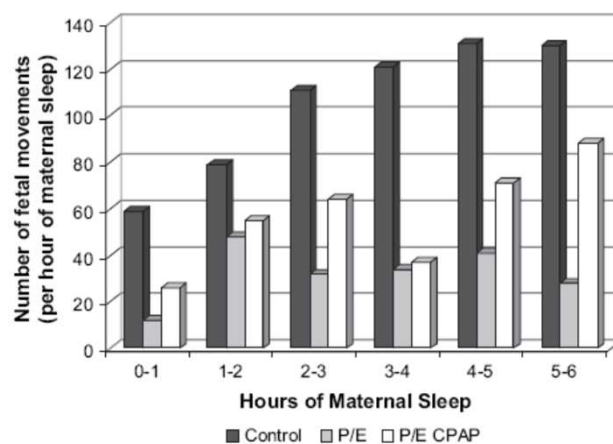
Pooled aOR of SDB Sx (6 studies):
aOR of 1.6 (1.1-2.2) for FGR

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

Warland, Dorrian, Morrison, O'Brien 2018



Hypertension, Sleep-Disordered Breathing and Fetal Movements



? Due to impaired
cardiac output and
increased
peripheral vascular
resistance



Uteroplacental
hypoperfusion and
fetal hypoxemia



Fetal growth in women with sleep-disordered breathing:

	OSA (n=14)	Control (n=27)	
Perinatal Outcome			
Gestation at delivery (weeks)	38.7(1.0)	39.4 (1.3)	0.06
Birthweight (grams)	3378(472)	3567(501)	0.25
Birthweight centile	47 (29)	54 (30)	0.49
Impaired fetal growth (Birthweight <10 th centile or fall in customised centile >33% between 32 weeks and term)	6 (43%)	3 (11%)	0.04
Birthweight <10 th centile	2 (14%)	3 (11%)	1
Fall in customised centile >33% between 32 weeks and term	4 (29%)	0 (0%)	<0.01

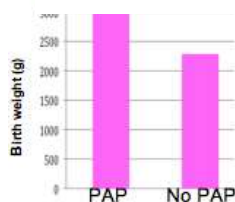
(Fung et al 2013)

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**

Kneitel, Treadwell & O'Brien 2018

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

Posted on 11 August 2017 - 03:49am
Last updated on 11 August 2017 - 07:40am



Sleep Disorders Linked to Preterm Birth in Large California Study

Insomnia, Sleep Apnea Nearly Double the Risk of a Preterm Delivery Before 34 Weeks

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, Dorrian, Morrison, O'Brien 2018

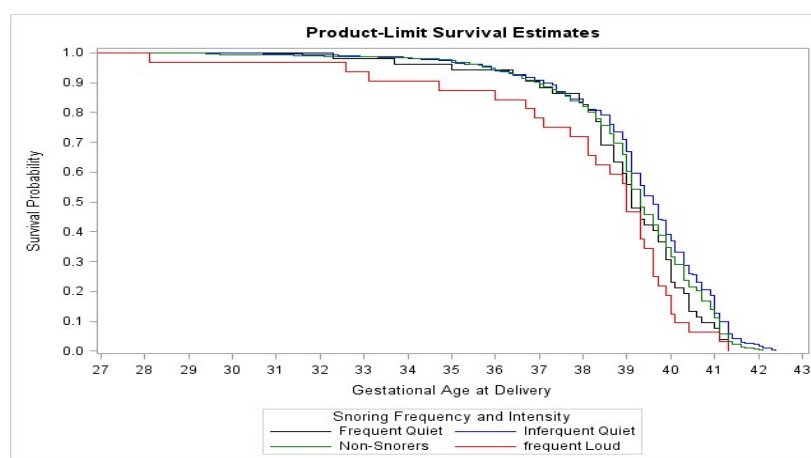
aOR 1.3 (1.0–1.7) for insomnia and PTB <37/40 and aOR 1.7 (1.1-2.6) for PTB <34/40
aOR 1.5 (1.2–1.8) for OSA and PTB <37/40 and aOR 4.1 (2.2-8.3) for PTB <34/40

Felder 2017

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

Blair 2015

SDB and Time to Delivery



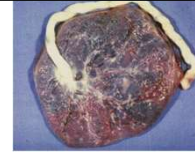
In n=954 non-hypertensive, non-diabetic women, there was an increased hazard ratio for earlier delivery in chronic loud frequent snorers vs. controls: HR 1.60, (95% CI 1.04, 2.45)

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

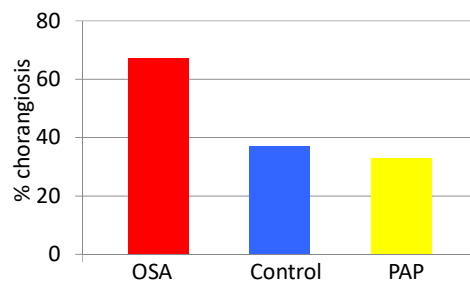
Markers of tissue hypoxia as well as markers of angiogenesis are more common in OSA compared to controls



(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:

	AHI<5 (n=23)	AHI>5 (n=14)	AHI>15 (n=6)	AHI>30 (n=4)
Feto-placental weight ratio	6.3±1.5	6.1±1.3	5.8±1.0	5.3±0.3



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

All due to pre-eclampsia

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

Case 3

PE047:

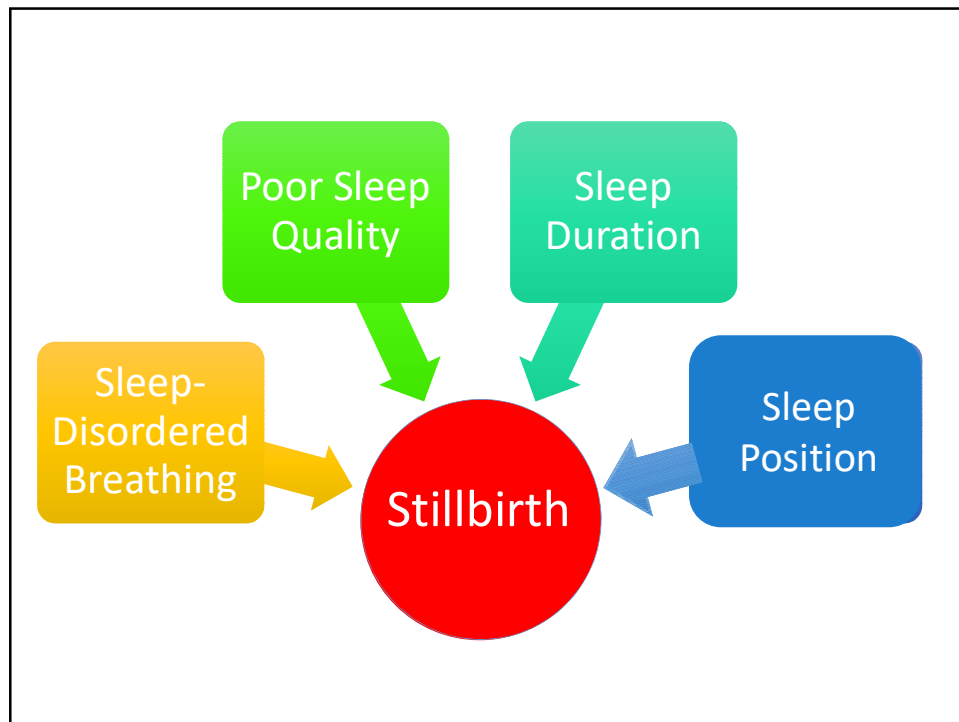
34yo African American, GHTN, BMI 42 G1 P0
 BPs at enrollment (35 weeks) >150/80mmHg despite escalating
 meds over previous 3 weeks

- 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:

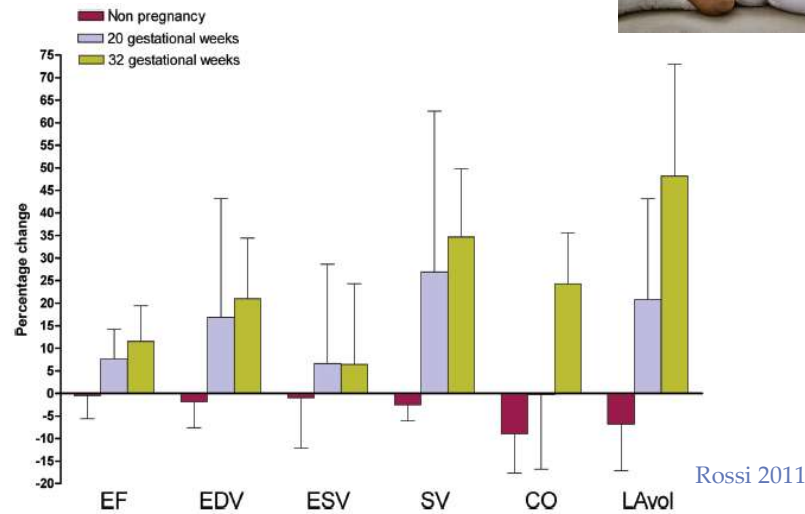


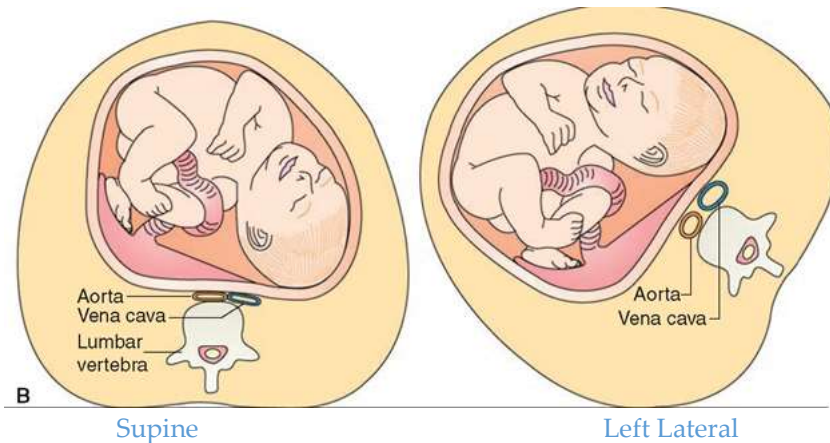
Figure 2 Percentage differences of hemodynamic parameters of left side of the heart. EF (ejection fraction: %), EDV (end-diastolic volume: ml), ESV (end-systolic volume: ml), SV (stroke volume: ml), CO (cardiac output: L/min), LAVol (left atrium volume: ml) Percentage difference from supine to left lateral position is calculated with the following formula: $X (\%) = \frac{(X_{lateral} - X_{supine})}{X_{supine}} \times 100$ where X is a cardiac parameter.

Gravid uterus compresses the inferior vena cava resulting in:

↓ venous return
 ↓ ejection fraction
 ↓ cardiac output

} impaired uterine perfusion

“Maternal supine hypotensive syndrome”



<http://what-when-how.com/nursing/normal-pregnancy-maternal-and-newborn-nursing-part-4/>

Lateral Tilt for procedures

Maternal position during caesarean section for preventing maternal and neonatal complications (Review)

Cluver C, Novikova N, Hofmeyr GJ, Hall DR



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

Stacey 2011, Owusu & O'Brien 2013, Gordon 2015, Heazell 2017, McCowan 2017



INDIVIDUAL PARTICIPANT DATA META-ANALYSIS				
<p>IPD 851 stillbirth cases & 2257 pregnant controls</p>				
	Stillbirth Case N=851	Pregnant Control N=2257	OR (95% CI)	aOR (95%)
Going-to-sleep position last 2 weeks				Cases 826 Controls 1953
Left side	359 (42.19)	1074 (47.59)	1	1
Supine/Back	67 (7.87)	73 (3.23)	2.89 (2.01 to 4.14)	2.63 (1.72 to 4.04)
Right side	221 (25.97)	624 (27.65)	1.1 (0.9 to 1.34)	1.04 (0.83 to 1.31)
Tummy	3 (0.35)	8 (0.35)	1.15 (0.3 to 4.45)	0.63 (0.12 to 3.25)
Variable side	102 (11.99)	265 (11.74)	0.92 (0.69 to 1.23)	0.97 (0.7 to 1.35)
Propped up	20 (2.35)	46 (2.04)	1.28 (0.74 to 2.23)	1.3 (0.68 to 2.49)
No recall	79 (9.28)	167 (7.40)	1.4 (1.03 to 1.91)	2.26 (1.48 to 3.46)

Other sleep practices related to stillbirth:



The STARS Study

Variable	Stillbirth (n=153)	Controls (n=480)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Sleep Duration last month				
≤6 hours	15 (9.8%)	47 (9.8%)	1.05 (0.56-1.97)	1.11 (0.57-2.16)
6.5-8.5 hours	86 (56.2%)	283 (59.0%)	1.00 Reference	1.00 Reference
≥9 hours	45 (29.4%)	79 (16.5%)	1.87 (1.21-2.91)	1.75 (1.10-2.79)
Awakenings last month:				
≤1 awakening	23 (15.0%)	61 (12.7%)	1.06 (0.63-1.79)	1.13 (0.65-1.97)
≥2 awakenings	121 (79.1%)	341 (71.0%)	1.00 Reference	1.00 Reference
Get up last month:				
≤1 time up	47 (30.7%)	129 (26.9%)	1.00 (0.67-1.51)	1.16 (0.75-1.79)
≥2 time up	98 (64.1%)	270 (56.3%)	1.00 Reference	1.00 Reference
Restless last month:				
None or little restless	52 (34.0%)	97 (20.2%)	1.71 (1.02-2.88)	1.73 (1.03-2.99)
Average restless	52 (20.9%)	102 (21.3%)	1.00 Reference	1.00 Reference
More than average or very restless	62 (40.5%)	201 (41.9%)	0.98 (0.60-1.60)	0.91 (0.54-1.53)
Sleep Quality last month:				
Good/Very Good	48 (31.4%)	89 (18.5%)	1.69 (1.04-2.75)	1.64 (0.98-2.75)
Average	50 (32.7%)	134 (27.9%)	1.00 Reference	1.00 Reference
Poor/Very Poor	47 (30.7%)	193 (40.2%)	0.65 (0.41-1.03)	0.65 (0.40-1.06)
Awakenings last night:				
≤1 awakening	41 (26.8%)	63 (13.1%)	2.16 (1.37-3.41)	2.03 (1.24-3.34)
≥2 awakenings	94 (61.4%)	312 (65.0%)	1.00 Reference	1.00 Reference

O'Brien et al 2018

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 durations ~~are~~ 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). [Warland 2008](#)



Fetal behavioural states in maternal positions –% time



	1F	2F	4F
Left	11.3	79.1	9.6
Right	22.0	71.7	6.3
Semi-recumbent	16.7	81.9	1.5
Supine	34.4	63.4	2.3
Chi-Sq: 32.2 (p<0.0001)			



46% of all 4F occurred in left-lateral
41% of all 1F occurred in supine position

In the supine position:

- fetal heart rate variability reduced
- Fetal behavior change from active to quiescence (low oxygen consuming state).




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

Stone 2016

PrenaBelt Trials

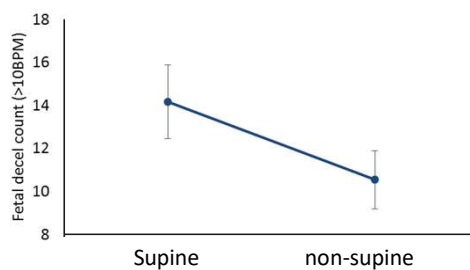
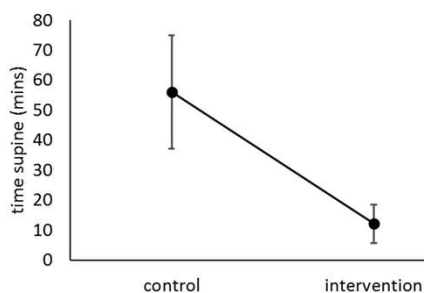


Location	Halifax, Canada 	Adelaide, AU 	Accra, Ghana 
Design	Double-blind, sham-controlled, randomized, crossover	Unblinded, non-intervention control, randomized, crossover	Double-blind, sham-controlled, randomized
Intervention	PrenaBelt, sham-PrenaBelt	PrenaBelt, nothing	PrenaBelt, sham-PrenaBelt
Duration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

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.



Warland, ...Kember.. & O'Brien 2018



Sleep Position Intervention

The Ghana Prenabelt Trial



First longitudinal intervention trial for supine sleep



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%)



Coleman, Kember,& O'Brien 2019



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 !



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www.starlegacyfoundation.org