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Maternal sleep behaviours preceding fetal heart rate events on cardiotocography

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First author profile

Dr Danielle Wilson is a postdoctoral research fellow at the Institute for Breathing and Sleep, Austin Health and the Department of Obstetrics and Gynaecology at the University of Melbourne, Mercy Hospital for Women. She recently completed her PhD looking at the prevalence and impact of sleep-disordered breathing in hypertensive disorders of pregnancy, and aspires to extend her research program into sleep behaviours and sleep disorders during pregnancy and the role they play in maternal and fetal wellbeing.

Key points summary

- Maternal sleep behaviours including supine position and sleep-disordered breathing are potential contributors to stillbirth but much of this work is based on self-reported data.
- Using time-synchronised polysomnography and cardiotocography, we found that nocturnal fetal heart rate decelerations were more likely to be preceded by a change in body position compared to epochs containing normal fetal heart rate, particularly in hypertensive pregnancies with or without fetal growth restriction.
- There was no temporal relationship between maternal sleeping position, snoring or apnoeic events and an abnormal fetal heart rate overnight.

- We conclude that most fetuses can tolerate sleep-related stressors with no evidence of fetal heart rate changes indicating compromised wellbeing.
- Further work needs to identify how sleep behaviours contribute to stillbirth risk and how these intersect with underlying maternal and fetal conditions.

Abstract

In Australia, a significant proportion of stillbirths remain unexplained. Recent research has highlighted nocturnal maternal behaviours as potentially modifiable contributors. This study determined whether sleep-related behaviours including sleep position and sleep-disordered breathing adversely affect fetuses overnight, in both uncomplicated pregnancies and those at increased risk due to hypertensive disorders or fetal growth restriction (FGR). All participants underwent polysomnography with time-synchronised fetal heart rate (FHR) monitoring (cardiotocography - CTG) in late pregnancy. CTGs were analysed for abnormal FHR events, including decelerations and reduced variability, by two blinded observers and exported into the sleep study to temporally align FHR events to sleep behaviours. For each FHR event, 10 control epochs with normal FHR were randomly selected within the same participant. Conditional logistic regression assessed the relationships between FHR events and sleep behaviours. From 116 participants, 52 had a total of 129 FHR events overnight; namely prolonged decelerations and prolonged periods of reduced variability. Significantly more FHR events were observed in women with FGR and/or a hypertensive disorder compared to uncomplicated pregnancies ($p=.006$). FHR events were twice as likely to be preceded by a change in body position within the five minutes prior, compared to control epochs ($p=.007$), particularly in hypertensive pregnancies both with and without FGR. Overall, FHR events were not temporally related to supine body position, respiratory events or snoring. Our results indicate that most fetuses tolerate sleep-related stressors, but further research is needed to identify the interplay of maternal and fetal conditions putting the fetus at risk overnight.

Keywords: polysomnography, pregnancy, sleep position, sleep-disordered breathing, fetal heart rate decelerations

Introduction

The prevalence rate of late stillbirth (> 28 weeks gestation) in many high resource countries has remained unchanged for decades (Cousens *et al.*, 2011), with a significant proportion of these remaining unexplained even after complete investigation. Night-time and sleep may be a period of heightened vulnerability for the fetus, with over 50% of women perceiving that their stillborn baby had passed during the night (Gordon *et al.*, 2015; Warland *et al.*, 2015). Given this- and that approximately one-third of time is spent sleeping- sleep-related behaviours have recently been investigated as potentially modifiable contributors to stillbirth.

A recent meta-analysis showed that the risk of stillbirth was increased in women who reported "going to sleep" in the supine position compared to the left side (aOR 2.63), suggesting that about 6% of late term stillbirths may be attributable to supine sleep position (Cronin *et al.*, 2019). A proposed mechanism is that the enlarged uterus compresses the inferior vena cava, resulting in a fall in cardiac output and uteroplacental blood supply when supine (Jeffreys *et al.*, 2006; Humphries *et al.*, 2019).

Sleep-disordered breathing (SDB) also occurs more commonly when supine. SDB encompasses a spectrum of disorders ranging from snoring to partial or complete obstruction of the upper airway repeatedly during sleep, resulting in sleep disruption and hypoxaemia. SDB during pregnancy has been related to adverse fetal outcomes including preterm birth, fetal growth restriction (FGR) and neonatal intensive care unit admission (Brown *et al.*, 2018; Warland *et al.*, 2018b; Liu *et al.*, 2019), but as yet no strong links have been established between SDB and stillbirth (Louis *et al.*, 2014; Bin *et al.*, 2016; Spence *et al.*, 2017).

The triple risk model for late stillbirth (Warland & Mitchell, 2014) proposes that unexplained stillbirth occurs when three risk factors interrelate – maternal, placental/fetal and a stressor. Known maternal risk factors for stillbirth include age, obesity and maternal disease such as hypertension, whereas fetal and placental factors include (FGR) and placental insufficiency (Flenady *et al.*, 2011). The influence of potential stressors such as supine sleep position or SDB may be subtle and inconsequential on their own, but may be significant contributors for a vulnerable fetus, due to placental disease or maternal conditions (Warland & Mitchell, 2014).

Fetal heart rate (FHR) analysis with cardiotocography (CTG) is commonly used as a non-invasive assessment of adequate fetal oxygenation both antenatally and in labour (Parer & Nageotte, 2004). Indications for using CTG antenatally include the assessment of fetal wellbeing in high risk pregnancies such as FGR and maternal hypertensive disorders. In these high risk pregnancies, abnormal CTGs may be seen where there are reduced fetal oxygen reserves or reduced placental function (Grivell *et al.*, 2015).We propose that sleep-related stressors such as supine position and SDB may result in abnormal CTG features including prolonged FHR decelerations (which reflect a fetal response to hypoxia) or reduced baseline variability in the FHR, where there is disturbance of sympathetic and parasympathetic input from the cardio-regulatory centre in response to hypoxia (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2017b).

We have used data collected from two prospective studies (Wilson *et al.*, 2020; Skrzypek *et al.*, 2021) to enable large-scale analysis of objectively-measured maternal sleep behaviour during pregnancy and its impact on FHR events captured with CTG. We hypothesise that sleep behaviours, particularly supine body position and SDB, are temporally related to FHR changes overnight among women in late pregnancy, particularly those with hypertensive disorders of pregnancy (HDP) or fetal growth restriction (FGR).

Methods

Participants

These data are a secondary analysis of two prospective case-control studies with similar protocols but different patient groups, investigating the impact of SDB during pregnancy on fetal health, between 2012 and 2018 (Wilson *et al.*, 2020; Skrzypek *et al.*, 2021). Specifically, the cases in these studies had a hypertensive disorder of pregnancy which included gestational hypertension, preeclampsia or chronic hypertension (Tranquilli *et al.*, 2014) or fetal growth restriction which met the Delphi consensus criteria (likely to be caused by placental insufficiency, based on estimated fetal weight or abdominal circumference <3rd centile, or estimated fetal weight or abdominal circumference <10th centile with abnormal fetoplacental Dopplers on ultrasound (Gordijn *et al.*, 2016). Women with pregnancies complicated by suspected aneuploidy, structural anomaly or fetal infection were excluded. Healthy control participants in these two studies were 1:1 gestation (completed sleep study within ± 4 weeks of gestational age) and BMI (within ± 4kg/m^2) matched to either a hypertensive or FGR case and had no evidence of HDP or FGR. All participants were recruited from antenatal outpatient clinics or as inpatients, and multiple pregnancy and those less than 18 years old were excluded.

Ethical Approval

The Human Research Ethics Committees at Austin Health and Mercy Hospital for Women approved the studies. The inclusion of participants into this study conformed to the standards set by the *Declaration of Helsinki*, except for registration in a database, and written informed consent was voluntarily provided by all participants.

Procedures

Basic demographic and obstetric data were collected at recruitment to the study. This included maternal age, parity, gestation, pre-pregnancy BMI and relevant comorbidities such as gestational diabetes (Nankervis *et al.*, 2014). Birth outcomes were collected following delivery and included gestational age at delivery, birthweight centile (customised for maternal BMI, ethnicity, parity, fetal sex and gestation) and Apgar scores at 1 and 5 minutes.

All participants underwent an overnight sleep study (polysomnography - PSG) with time-synchronised fetal heart rate (FHR) monitoring in the third trimester of pregnancy. Overnight PSG was conducted in the Austin Health sleep laboratory using the Compumedics E series (Abbotsford, Victoria, Australia), or if preferred, unattended in the participant's home with the Somté (Compumedics) portable sleep-monitoring device. Inpatients were studied using the portable device. Signals recorded included electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), arterial oxygen saturation, thoracic and abdominal respiratory effort via inductance plethysmography, nasal airflow measured via nasal cannula, oronasal thermistor, leg movements, snoring and body position at the level of the chest. Sleep and respiratory events were scored as per the American Academy of Sleep Medicine (AASM) criteria (Berry *et al.*, 2016) with respiratory events categorised as apnoeas (a decrease in airflow of ≥ 90% from baseline for ≥ 10 sec); hypopnoeas (decrease in airflow ≥ 30% from baseline for ≥ 10 sec and followed by either an oxygen desaturation of ≥ 3% or an EEG cortical arousal); and respiratory event related arousals (RERAs; a sequence of breaths lasting ≥ 10 sec characterised by increasing respiratory effort or by flattening of the inspiratory portion of the nasal pressure waveform leading to an arousal from sleep). The number of apnoeas and/or hypopnoeas and/or RERAs per hour of sleep was calculated as the respiratory disturbance index (RDI), with an RDI ≥ 5 indicating presence of SDB. The oxygen desaturation index was defined as the number of arterial oxygen desaturations of ≥ 3% from baseline, per hour of sleep (ODI3). BMI at the time of the sleep study was also recorded.

Cardiotocography (CTG) was performed to measure the fetal heart rate using the Monica AN24 (Monica Healthcare Ltd.) and was time-synchronised to the PSG recording. The Monica AN24 is a non-invasive monitor requiring the placement of 5 adhesive electrodes onto the maternal abdomen to monitor fetal ECG, maternal ECG and uterine EMG to measure uterine contractions and maternal movement.

Data Analysis

CTG analysis

The CTGs were deidentified and assessed by two obstetricians (AF, HS) for any of five abnormal FHR events potentially signifying fetal distress (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2019). These events were chosen *a priori* and included:

- Event 1. A deceleration lasting between 60-90 seconds with a >15 beats per minute fall below the baseline.
- Event 2. A deceleration lasting for >90 seconds and <5 min with a >15 beats per minute fall below the baseline (a prolonged deceleration).
- Event 3. the presence of ≥2 late decelerations (uniform repetitive decreases in the fetal heart rate with slow onset mid to end of a contraction and nadir >20 seconds after the peak of the contraction) in a 20 minute section of CTG.
- Event 4. the presence of ≥2 complicated variable decelerations (a decrease in the fetal heart rate with rapid onset and recovery accompanied by one of the following features - a rise in baseline, reduced baseline variability, slow return to the baseline, large amplitude (by 60 beats per minutes or dropping to 60 beats per minute) and or long duration (>60 seconds) or presence of post deceleration overshoot) in a 20 minute section of CTG.
- Event 5. baseline variability of ≤5 beats per minute for >20 minutes (prolonged reduced variability).

FHR changes with a low likelihood of association with fetal compromise were excluded. This included isolated decelerations (<15 beats per minute fall from baseline) which were of short duration (<60 seconds), and uncomplicated variable decelerations (where there were none of the above mentioned accompanying pathological features). Baseline variability was assessed by estimating the difference in beats per minute, between the highest peak and the lowest trough of the fluctuations above and below the baseline in one-minute segments (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2019). Concordant FHR events between the two obstetricians were included and discordant events were reviewed a second time by both obstetricians to determine whether they met criteria for inclusion.

The CTGs were analysed for rate of successful FHR tracing during the maternal sleep period. The criteria for CTGs to be included in analysis was an overall CTG recording of >25% of the sleep recording period, and ii) sufficient continuous FHR without loss of contact to allow comparison of fetal events to normal FHR trace for control purposes (see sleep study analysis). After the CTG recordings were assessed, they were exported into the sleep study recording in order to temporally align FHR events to sleep behaviours (Fig 1).

Sleep study analysis

Once the CTG was exported to the sleep study, each FHR event was located and the corresponding sleep behaviours at the exact time of the start of the FHR event were noted, including sleep stage (wake, N1/2 ("light sleep"), N3 ("deep sleep"), or rapid-eye-movement (REM) sleep), body position (supine, left, right, prone), snoring (present or absent), and time (hrs) from sleep onset. Sleep onset was defined as the first 30-second epoch of any stage of sleep (Berry *et al.*, 2016). For the 5 minutes preceding the FHR event, the number of respiratory events (apnoeas, hypopnoeas or RERA's) were counted, whether the participant had changed body position (from left, right, supine or prone to a different position), and whether there was a significant body movement with cortical arousal (without a change in body position).

Within each participant where FHR events were identified, each FHR event was matched to 10 control 30-sec epochs selected at random, and the sleep behaviours at the start of that epoch and in the preceding 5 minutes were noted, as above. Control epochs were selected using a random number generator, inputting all available epoch numbers for each PSG/CTG recording. Control epochs required 5 preceding minutes of continuous FHR with no missing data, to ensure the trace was normal. A normal antenatal CTG trace will demonstrate a baseline fetal heart rate of 110-160 bpm, normal baseline variability of 6-25 bpm, reactivity (FHR accelerations) and no decelerations (Ayres-de-Campos *et al.*, 2015). FHR event epochs and control epochs were matched by sleep stage (wake, N1/2, N3 or REM) given that respiratory events are typically most severe during REM sleep (Mokhlesi & Punjabi, 2012)). In this way, if an FHR event occurred during REM sleep when respiratory events are likely, it will only be matched with other control epochs during REM sleep. Therefore, control epochs were selected based on the random number generator until 10 epochs within the matching sleep stage with no missing data were identified for each FHR event.

Study Design Summary

The design for the current study with respect to the primary analysis of whether sleep behaviours were temporally related to fetal heart rate changes overnight among women in late pregnancy, was a within-participants analysis comparing sleep characteristics overnight during periods of FHR events to sleep characteristics during epochs without FHR events. Due to the within-participants design, only those with FHR events could be included in the primary analysis.

The secondary analyses focus on comparing FHR events in those with complicated versus uncomplicated pregnancies, with a further between-participants comparison between pregnant women who did have or did not have FHR events overnight utilising data from all participants in the study.

Statistical Analysis

All statistical analyses were performed with Stata (StataCorp LP, College Station, TX, USA). The data that support the findings of this study are openly available in Figshare at http://doi.org/10.6084/m9.figshare.14544687(Wilson *et al.*, 2021). Means with standard deviations (*M ± SD)* were utilized for descriptive analysis of normally distributed variables or median and interquartile range (*Mdn (IQR)*) for non-normally distributed variables. A two-sided p value of less than 0.05 was considered to indicate statistical significance.

Within the participants who had FHR events, conditional logistic regression was performed to assess the univariate relationship between FHR event (vs. control epochs) as the outcome variable, and maternal sleep behaviours as explanatory variables. The grouping variable was the 1:10 matching of each FHR event to 10 control epochs *within the same participant.* Due to the extreme positive skew of number of respiratory events within each 5 min epoch, this was collapsed into an ordinal variable of 0 respiratory events, 1-2 respiratory events and 3+ respiratory events. Stepwise conditional logistic regression modelling was then performed with FHR event as the dependent variable, and explanatory variables with an α of less than 0.20 on univariate analysis were included.

As the FHR and control epochs were matched for sleep stage, a regression to investigate any relationship between FHR events and sleep stage could not be performed. Instead, the rate of FHR events per hour in each sleep stage was compared using a Friedman Test with Wilcoxon signed-rank tests with Bonferroni adjustment for post hoc comparisons.

To compare the incidence of FHR events in uncomplicated versus FGR and HDP pregnancies, a Kruskal-Wallis H test was performed. Interaction terms were entered into the conditional logistic regression models to investigate the impact of maternal and fetal factors (HDP and FGR) on the relationships between sleep behaviours and FHR events.

Comparison of demographic and sleep variables between participants who had FHR events and those who did not was performed using Fisher's exact test of independence for categorical variables, independent-samples t-tests for normally distributed continuous variables and Mann-Whitney U tests for non-normally distributed continuous variables.

Results

Participants

A total of 161 women participated across both studies and the data from 116 participants was sufficient for inclusion in this analysis (see Figure 2 for consort diagram). The median rate of successful CTG recording for the sample was 6h 31m (IQR 5h 12m, 7h 25m) or 95.1% (IQR 82.5, 99.7) of the maternal sleep period. At the time of the sleep study, the average age of the participants was 32.9 (4.8) years with an average gestational age of 32.6 (3.3) weeks, an average BMI of 33.7kg/m^2 (7.1) and 68 (58.6%) were nulliparous. Thirty-six (30.3%) of the women had an HDP, 15 (12.9%) had FGR, 13 (11.2%) had both an HDP and FGR, and there were 52 (44.8%) normotensive well-grown control pregnancies. There was one fetal death in utero two weeks after the sleep study, and one neonatal death in the neonatal intensive care unit; both participants were normotensive with severe FGR. Thirty-five (30.2%) studies were performed within the sleep laboratory, with the remaining 81 performed with ambulatory PSG.

Nocturnal Fetal Heart Rate Events

From 116 participants, only 52 women had FHR events during their sleep study. A total of 129 FHR events were identified. The number of events per participant ranged from 1 to 9, with a median of 2.0 (1.0, 3.0). From these, 78 events (60%) were decelerations lasting 60-90 sec (Event 1), 24 events (19%) were prolonged decelerations of >90 sec (Event 2), and 27 events (21%) were prolonged reduced variability (Event 5). No late decelerations (Event 3) or complicated variable decelerations (Event 4) were observed. Due to the 1:10 case control matching of FHR events to control epochs within each participant, a total of 1,290 control epochs were also randomly identified.

Sleep-related Precedents to Fetal Heart Rate Events

FHR events were not associated with any single body position, but were significantly more likely to be preceded by a *change* in body position in the five minutes prior, compared to control epochs (OR 2.00 (1.20, 3.31), $p = 0.007$; Table 1). Twenty-two percent (28) of FHR events were preceded by a change in body position, compared to only 14% (178) of the control epochs. Table 2 describes the direction the mother changed her body position into before the FHR event compared to body position changes noted prior to normal CTG, with FHR events most often occurring after a change to a supine or right lateral position ($p = .063$). Of the 28 FHR events following a change in body position, 17 (61%) were decelerations of 60-90 sec, 9 (32%) were prolonged reduced variability and 2 (7%) were prolonged decelerations of > 90 sec.

Table 1. Frequency of sleep-related behaviours in fetal heart rate event epochs versus control epochs and univariate relationships with fetal heart rate events

Predictor	FHR Event (n = 129)	Control Epoch (n = 1,290)	OR (95% CI)	p
Body Position				
Left (Ref)	39 (30.2%)	438 (34.0%)	1.0	
Supine	46 (35.7%)	459 (35.6%)	1.19 (0.69, 2.06)	.534
Right	36 (27.9%)	320 (24.8%)	1.33 (0.79, 2.23)	.289
Prone	8 (6.2%)	73 (5.7%)	1.60 (0.38, 6.72)	.518
Resp events per 5 min				
0 (Ref)	93 (72.1%)	974 (75.5%)	1.0	
1-2	25 (19.4%)	207 (16.1%)	1.31 (0.79, 2.17)	.290
3+	11 (8.5%)	109 (8.5%)	1.13 (0.45, 2.83)	.789
Snoring*	23 (19.0%)	282 (23.1%)	0.58 (0.28, 1.19)	.139
Position Change	28 (21.7%)	178 (13.8%)	2.00 (1.20, 3.31)	.007
Movement with Arousal	43 (33.3%)	401 (31.1%)	1.14 (0.74, 1.75)	.556
Hrs from sleep onset	3.5 (2.7)	3.7 (2.8)	0.96 (0.88, 1.05)	.366

Note. Body position measured at the time of the fetal heart rate event. Respiratory events, snoring, position change and movement with arousal measured during five minutes prior to fetal heart rate event.

*snoring not assessable when flow signal absent on home studies (8 FHR events and 70 control epochs). FHR = fetal heart rate, OR = odds ratio, CI = confidence interval, resp = respiratory.

Table 2. Direction that maternal body position changed into before FHR events versus control epochs

	FHR Event (n = 28)	Control Epoch (n = 178)	p
Left	4 (14.3%)	72 (40.4%)	.063
Supine	13 (46.4%)	54 (30.3%)	
Right	9 (32.1%)	44 (24.7%)	
Prone	2 (7.1%)	8 (4.5%)	

Note. p value based on Pearson chi-squared test. FHR = fetal heart rate

There were no univariate relationships between FHR events and body position at the same time, respiratory events, snoring, and body movement with arousal in the preceding five minutes, or time from sleep onset (Table 1). Interestingly, supine positioning overnight was common in these women with a median of 25.5% (7.2, 40.0) of total sleep time spent lying on the back.

A stepwise selection model including explanatory variables with an α of less than 0.20 on univariate analysis was performed, and confirmed that an FHR event was more than twice as likely to occur within five minutes of a change in body position, whereas snoring did not contribute to the model (Table 3).

Table 3. Sleep-related behaviours associated with fetal heart rate events on cardiotocography on conditional stepwise logistic regression modelling

Variable	B (SE)	aOR (*95% CI*)	p
Position Change	0.73 (0.26)	2.08 (1.24, 3.47)	.005
Snoring	-0.51 (0.38)	0.60 (0.29, 1.26)	.177

Note. aOR = adjusted odds ratio. Overall model includes position change and snoring, χ^2 (2) = 9.59, p = .0083.

Of the 129 FHR events identified, the majority occurred during light "N1/2" sleep (44.2%) and overnight wake periods (30.2%), with fewer events during deep "N3" sleep (14.0%) and REM sleep (11.6%). The number of FHR events per hour was significantly different across sleep stages (χ^2(3) = 15.23, p = .002, Fig 3). Specifically, the rate of FHR events per hour was higher in N1/2 sleep compared to N3 sleep (z = 2.889, p = .0039).

Sleep-related Precedents to Fetal Heart Rate Events in Pregnancies Complicated by Maternal and Fetal Factors

Of the 52 participants who had FHR events overnight, 21 of the pregnancies were uncomplicated (controls), 11 of them were FGR, 10 of them had an HDP, and 10 had both FGR and an HDP (FGR/HDP). On average, significantly more nocturnal FHR events were observed in each woman in the FGR (*Mdn (IQR)* = 3.0 (2.0, 4.0)), HDP (2.5 (1.0, 4.3)) and FGR/HDP group (3.5 (1.8, 5.0)) compared to the control group (1.0 (1.0, 2.0), p = .006).

FHR events following a change in body position were much more likely to occur in the HDP and FGR/HDP groups, but not in the control and FGR groups (Table 4). No interactions were observed between maternal and fetal complications and body position, SDB, snoring, movement with arousal and time from sleep onset, meaning there was no relationship between any of these sleep behaviours and FHR events within any of the pregnancy complication groups.

Table 4. Interactions between body position change and maternal/fetal condition in the association with nocturnal fetal heart rate events

	FHR Event	Control Epoch	OR (95% CI)	p
Controls (n=21)	4 (12.9%)	30 (9.7%)	1.47 (0.43, 5.01)	.538
FGR (n=11)	5 (13.2%)	52 (13.7%)	0.95 (0.33, 2.71)	.924
HDP (n=10)	11 (42.3%)	70 (26.9%)	2.68 (0.99, 7.23)	.052
FGR & HDP (n=10)	8 (23.5%)	26 (7.7%)	3.80 (1.53, 9.43)	.004

Note. Body Position Change odds ratios expressed as Yes vs No (reference group). FHR = fetal heart rate, OR = odds ratio, FGR = fetal growth restriction, HDP = hypertensive disorder of pregnancy.

Comparison between Participants with and without Fetal Heart Rate Events Overnight

Table 5 details differences in demographics, sleep indices and fetal outcomes between the 52 women who did and the 64 women who did not have FHR events during the night of the study. Women with FHR events had their sleep study at an earlier gestation and were more likely to be nulliparous compared to those without FHR events. Compared to healthy control pregnancies, those with FGR and FGR with a hypertensive disorder were more likely to have FHR events during sleep. A larger proportion of supine sleep was seen in those with FHR events compared to those without, however this was related to more supine sleep amongst the participants with FGR (FGR = 32.9% (24.8, 50.2) vs. well-grown = 20.4% (4.8, 32.2), p = .0025) who were more prone to FHR events. There was also a trade-off between a higher proportion of N3 "deep" sleep for less N1/2 "light" sleep in the FHR event group. There was no difference in BMI, GDM, total sleep time, sleep efficiency, or RDI between the groups (Table 5).

After controlling for comorbidities of FGR, the presence of any hypertensive disorder of pregnancy and GDM, the fetuses with nocturnal FHR events were more likely to be delivered earlier and have lower Apgar scores at 5 mins compared to fetuses without FHR events.

Table 5. Comparison between participants with and without fetal heart rate events.

	Participants with FHR events (n = 52)	Participants with no Events (n = 64)	p
Demographics			
Age (years)	32.3 (5.4)	33.4 (4.2)	.222
BMI first visit (kg/m^2)	29.2 (8.0)	31.0 (6.9)	.193
BMI at PSG (kg/m^2)	32.6 (7.8)	34.6 (6.4)	.126
Gestation at PSG (weeks)	31.1 (3.6)	33.8 (2.6)	<.0001
Nulliparous	39 (75.0%)	29 (45.3%)	.001
Healthy controls	21 (44.8%)	31 (59.6%)	.45
HDP	10 (27.8%)2	26 (72.2%)	.26[#]
PE	(50.0%)	2 (50.0%)	1.0[#]
GH	7 (35.0%)	13 (65.0%)	.790[#]
Chronic HTN	1 (8.3%)	11 (91.7%)	.045[#]
FGR	11 (73.3%)	4 (26.7%)	.039[#]
FGR and HDP	10 (76.9%)	3 (23.1%)	.029[#]
GDM	6 (12.8%)	9 (14.3%)	1.000
Sleep Variables			
Total Sleep Time (min)	381.5 (83.1)	385.1 (76.6)	.807
Sleep Efficiency (%)	77.9 (12.5)	79.9 (10.6)	.349
N1/2 (%)	49.4 (10.4)	55.6 (12.9)	.0066
N3 (%)	34.0 (10.8)	28.3 (13.1)	.0118
REM (%)	16.5 (6.3)	16.2 (5.8)	.776
%TST Supine	30.5 (16.4, 46.4)	18.7 (3.1, 33.4)	.0712[a]
SDB (RDI > 5)	23 (44.2%)	28 (43.8%)	1.000
RDI	4.6 (3.1, 7.7)	3.8 (2.0, 7.8)	.445
ODI3	1.4 (0.3, 2.5)	0.6 (0.0, 3.8)	.594
SpO2 nadir (%)	90.0 (88.0, 91.5)	91.0 (88.0, 93.0)	.328
Fetal Outcomes[b]			
Delivery Gestation (weeks)	37.0 (0.3)	37.8 (0.2)	.011
Birthweight Centile	31.6 (4.0)	42.3 (3.5)	.0524

Apgar 1 min	7.7 (0.3)	8.1 (0.2)	.318
Apgar 5 min	8.6 (0.1)	9.1 (0.1)	.0097

Note. Values given as M (SD), Mdn (IQR) or n (%). HDP, FGR and GDM present at time of sleep/CTG study. GDM unknown for six participants. FHR = fetal heart rate events, BMI = body mass index kg/m^2, PSG = polysomnography, HDP = hypertensive disorder of pregnancy, PE = preeclampsia, GH = gestational hypertension, HTN = hypertension, FGR = fetal growth restriction, GDM = gestational diabetes mellitus, N1/2 = light sleep, N3 = deep sleep, REM = rapid eye movement sleep, %TST = percentage of total sleep time, SDB = sleep-disordered breathing, RDI = respiratory disturbance index, ODI3 = oxygen desaturation index of ≥3% per hour, SpO2 nadir = lowest oxygen saturation during sleep.

[#] chi square p value compared to healthy control group only

[a] p= .36 after adjustment for relationship between FGR and %TST supine sleep.

[b] fetal outcomes given as M (SE) and p value adjusted for FGR, HDP and GDM on ANCOVA.

Discussion

Main Findings

This is among the first and largest study to investigate the relationship between fetal wellbeing during maternal sleep using CTG and objectively measured sleep position and sleep-disordered breathing. We found that abnormal FHR events (decelerations and prolonged reduced variability) were more likely to occur at night in pregnancies complicated by hypertension, fetal growth restriction or both, compared to uncomplicated pregnancies. Further, we identified that clinically significant decelerations and prolonged reduced variability, were significantly more likely to be preceded by a change in body position in the five minutes prior compared to "normal" FHR epochs. This effect was particularly seen in women with a hypertensive disorder of pregnancy, with or without concurrent fetal growth restriction. Supine sleep and mild SDB were common in late pregnancy, however supine sleep, respiratory events and snoring were not associated with fetal heart rate changes.

Interpretation

While high risk pregnancies such as those complicated by hypertensive disorders or fetal growth restriction are more likely to have CTG abnormalities during monitoring while awake (Montan & Ingemarsson, 1989; Esposito *et al.*, 2019), we are not aware of any other studies looking at the frequency, and precipitants of, CTG abnormalities during maternal sleep. Here we report that FHR decelerations and reduced variability occur more commonly overnight in high risk pregnancies, and are more likely to occur following change of maternal position during sleep. These findings are important, giving the rapidly growing literature on the impact of sleep- and sleep position- on stillbirth risk. While fetal heart rate decelerations that occur in the antenatal period are less studied than those during labour (Lear *et al.*, 2020), prolonged decelerations can occur in response to any sustained interruption of fetal oxygenation. This may occur antenatally during episodes of maternal hypoxia or maternal hypotension, both of which may be more common during sleep. Maternal hypoxia associated with sleep-disordered breathing, and aorto-caval compression causing supine hypotension are plausible contributors to the increase in abnormal fetal heart rate events occurring overnight in high risk pregnancies. The prolonged decelerations and episodes of reduced variability following change in maternal position could relate to either sleep-related respiratory events or maternal cardiovascular changes. Upper airway obstruction is more likely to occur while supine. Further, maternal supine hypotension occurs due to compression of the inferior vena cava and abdominal aorta resulting in reduced maternal stroke volume, cardiac output (Humphries *et al.*, 2017), and uteroplacental perfusion. Our results demonstrated that FHR events often occurred following maternal repositioning to a supine or right lateral position, where the enlarged uterus can exert greater compression on the inferior vena cava and abdominal aorta and more significantly alter cardiac autonomic nervous activity, compared to the left lateral position (Kuo *et al.*, 1997). Cord compression may also be a contributor to the prolonged decelerations seen following a change in maternal position, which may be exacerbated among compromised fetuses with reduced amniotic fluid volume (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2017a).

In this study we were particularly concerned not to compromise the analysis with the inclusion of antenatal events likely to be considered innocuous (e.g. short, isolated, uncomplicated variable decelerations related to transient cord compression) and not associated with increased risk of hypoxia. We confined the antenatal fetal heart events to those known to be associated with increased risk of hypoxia. Prolonged decelerations indicate a reduction of umbilical blood flow, or reduced fetal oxygen supply. In response to hypoxia, the fetal chemoreflex is triggered (Giussani, 2016), resulting in increased parasympathetic outflow via the vagus nerve to slow the fetus's heart rate and reduce myocardial oxygen consumption. Increased sympathetic outflow triggers peripheral vasoconstriction to redirect blood flow to critical organs and support arterial pressure (Lear *et al.*, 2018a). With complete cord occlusion, the increase in fetal total peripheral resistance and hypertension triggers the baroreflex-mediated fetal heart rate deceleration. After the first few seconds of this baroreflex response, the peripheral chemoreflex becomes the dominant mediator once cerebral oxygen changes are detected by the peripheral chemoreceptors in the carotid bodies (Lear *et al.*, 2020).

Normal baseline variability in the fetus is generated when the sympathetic and parasympathetic system are in balance with one another. While the maintenance of FHR variability is complex, it is likely due to numerous sporadic inputs from various areas of the cerebral cortex and lower centres to the cardiac integratory centres in the medulla oblongata, which are then transmitted down the vagus nerve. In the presence of cerebral hypoxia and acidosis, these inputs decrease and variability decreases (Parer & Nageotte, 2004). One of the most common causes of reduced baseline variability is an episode of deep fetal sleep (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2017b). For this reason, we proposed that reduced variability should be prolonged, beyond the usual fetal sleep phase. The lengthy periods of reduced variability following a change in maternal body position in this study could be due to a state of fetal quiescence, where a mild change in fetal oxygen tension may be sufficient to trigger a change into- or a prolongation of- this lower oxygen consuming state (Stone *et al.*, 2017b).

In uncomplicated pregnancies, isolated decelerations such as those witnessed in our healthy control group are not uncommon on an antenatal FHR trace (Murray, 2017) and usually represent the fetus mounting successful adaptions against adverse conditions (Lear *et al.*, 2018b). It is unlikely that these fetuses will develop inadequate oxygenation as a result of isolated mild variable decelerations (Parer & Nageotte, 2004). Despite this, we actually showed that after controlling for pregnancy complications, the presence of nocturnal FHR decelerations was associated with an earlier delivery gestation and lower 5-minute Apgar scores, opening a future avenue for investigation.

FHR decelerations and reduced variability at night were more common among women with HDP and/or FGR, which possibly reflects underlying placental insufficiency with decreased oxygen delivery and consumption (Zhu *et al.*, 2016), reduced amniotic fluid volume (predisposing to cord compression) or both (Hofmeyr & Gülmezoglu, 2002; Reeves & Galan, 2012). These fetuses may have lower reserves to deal with relatively mild nocturnal events, particularly cord compression following position change. FHR decelerations and reduced variability following maternal position change were limited to the pregnancies complicated by a hypertensive disorder, including preeclampsia with a growth restricted fetus. Fetal and placental reserves are a critical factor in determining how a fetus copes with a transient hypoxic stress. Poor placental development in PE pregnancies can lead to reduced placental size with reduced area available for gas exchange, and excessive vasoconstriction may result in a reduced diameter of the uterine arteries, reducing uterine artery blood flow (George & Granger, 2011; Powe *et al.*, 2011). These pregnancies may thus be particularly susceptible to changes in blood flow associated with change in maternal body position, due to their background impaired placental oxygen exchange (Zhu *et al.*, 2016). That FHR events occurred more commonly among women with HDP and/ or FGR is perhaps unsurprising, but the relationship of FHR decelerations and prolonged reduced variability with change in maternal position- rather than supine sleep- was a novel and unexpected finding.

Despite the women in this study spending a quarter of the night in the supine position, we were surprised to find that supine sleep position was not temporally associated with adverse FHR changes, for neither healthy nor complicated pregnancies. There have been relationships reported between self-reported supine "sleep onset" during the later stages of pregnancy and fetal wellbeing, including reduced birthweight, fetal cerebral redistribution and stillbirth (Anderson *et al.*, 2019; Cronin *et al.*, 2019; Robertson *et al.*, 2020). There is biological plausibility for the supine position causing detrimental effects including aorto-caval compression resulting in decreased cardiac output (Humphries *et al.*, 2019) and impaired utero-placental blood flow (Jeffreys *et al.*, 2006). Most recently, functional MRI techniques have demonstrated that lying supine- as compared to left lateral- resulted in a 24% reduction in total internal iliac arterial blood flow to the uterus, with a 6.2% reduction in oxygen movement across the placenta (Couper *et al.*, 2021). During supine wakefulness, surrogate markers of fetal hypoxia on Doppler flow measurements have been reported (Khatib *et al.*, 2014). However, Ibrahim et al (2015) found no changes in FHR patterns after moving heavily pregnant women between the supine and lateral positions. Experimentally, in fetal sheep, oxygen consumption has been shown to remain normal until uterine artery blood flow drops below 50% (Wilkening & Meschia, 1983), so it may be that a significant degree of hypoxaemia is required before overt signs of fetal distress are observed on a nocturnal CTG. Very few studies have looked at the impact of maternal body position on fetal wellbeing objectively during sleep, with Stone et al. (2017a) and Warland et al. (2018a) finding that supine sleep was associated with fetal quiescence and fetal heart rate decelerations, suggesting the fetus is adapting its behavioural state in response to mild hypoxic stress.

There could be a few reasons for the discrepancy with the limited previous studies during maternal sleep. Firstly, we looked at distinct and clinically-determined episodes of deceleration and prolonged reduced variability which may represent fetal responses to mild hypoxic insults, whereas Stone et al. (2017a) focused on a more fine-scale analysis of fetal behavioural states including heart rate variability as a measure of cardiac autonomic control. Secondly, the maternal autonomic nervous system may compensate for cardiovascular changes associated with supine body positioning, also explaining why FHR decelerations occurred after maternal position was first altered. Increased peripheral vasoconstriction when supine can help maintain blood flow to the uterus through collateral channels, providing an alternate route to the inferior vena cava (Humphries *et al.*, 2017). Increased heart rate during supine rest (Kuo *et al.*, 1997; Lanni *et al.*, 2002; Humphries *et al.*, 2020) suggests that sympathetic activity is elevated in an attempt to normalize cardiac output in the supine position. While asleep, pregnant women may also compensate for reductions in sympathetic tone and blood pressure by increasing heart rate and peripheral vascular resistance when supine (Ishkova *et al.*, 2020). It may be that the initial impact of maternal body position change on cardiovascular parameters is observable in the FHR which then stabilizes as the new position is maintained.

The relationship between maternal SDB and fetal heart rate has previously been explored, with mixed results (Joel-Cohen & Schoenfeld, 1978; Roush & Bell, 2004; Olivarez *et al.*, 2010; Fung *et al.*, 2013; Wilson *et al.*, 2020). However, these studies have looked at SDB severity globally, rather than the temporal relationship between respiratory event and subsequent oxygen desaturation and fetal response, which is a strength of this study. Unlike a recently published study by Pitts et al. (2021) which found that over 80% of FHR decelerations occurred within 30 seconds of a respiratory event, we found that only a quarter of FHR events were associated with SDB and demonstrated no relationship between time periods containing apneic events or snoring and FHR decelerations or reduced HR variability. Disparities in our results may be due to the sleep monitoring device used or different definitions for FHR decelerations, though depth of FHR deceleration in beats per minute was not stated by Pitts et al. (2021).

There is no evidence for an association between stillbirth and either self-reported snoring or objectively measured SDB based on large cohorts using hospital ICD codes (Louis *et al.*, 2014; Bin *et al.*, 2016; Spence *et al.*, 2017; Cronin *et al.*, 2020). We demonstrated that even in sleep epochs where severe SDB was present, the fetus was equally likely to display a healthy versus abnormal heart rate pattern. All FHR changes were on the mild end of the spectrum, with the two most 'severe' types of FHR decelerations not observed at all (multiple late decelerations and complicated variable decelerations). In the face of transient maternal hypoxaemia, the fetus is well protected by a combination of adaptive behaviours to ensure that the supply of oxygen meets its metabolic demands. These adaptions include an increased basal blood flow to most tissues, the left-shifted and steeper fetal haemoglobin oxygen dissociation curve allowing a high amount of oxygen to be bound and then unbound to the fetal tissues at lower oxygen tensions, and the capacity to hinder oxygen-consuming processes such as moving and breathing (Giussani, 2016; Lear *et al.*, 2018b). Furthermore, redistribution of cardiac output ensures an adequate supply of oxygenated blood to tissues most at risk of damage, such as the fetal brain and heart (Martin, 2008). The lack of late decelerations or complicated variable decelerations witnessed in our study implies that the fetal environment was not hypoxic enough to push these fetuses beyond their capacity to successfully adapt.

Information regarding FHR and variability over the course of the night and within each maternal sleep stage is scarce. We found that FHR decelerations and periods of reduced variability were more likely to occur during periods of light sleep compared to deep sleep, but women with these FHR events had less light sleep but more deep sleep than women without adverse FHR changes overnight. Conversely, DiPietro et al. (2021) showed that while maternal heart rate varied across sleep stages, fetal heart rate did not. Both short (McCowan *et al.*, 2017; Heazell *et al.*, 2018) and prolonged sleep length (O'Brien *et al.*, 2019) have been associated with late stillbirth. Accordingly, we investigated whether FHR changes were related to sleep duration and found there was no relationship with time from sleep onset and likelihood of CTG abnormalities.

Strengths and Limitations

This study is among the first to look closely at the temporal relationship between multiple objectively measured maternal sleep behaviours and adverse FHR events documented on time synchronized CTG. The within-subjects study design allowed us to compare periods containing decelerations and reduced baseline variability to normal fetal heart rate within each pregnancy without confounding by external factors. We had a substantial sample size with an average CTG success rate of over 6.5 hours per participant. As others have demonstrated (Lucchini *et al.*, 2020), objective measurement of sleep and fetal heart in pregnancy can be difficult and we had to exclude 45 participants from our analysis due to insufficient CTG data.

Studies highlighting a relationship between supine sleep and stillbirth risk are limited by a focus on the sleep onset period, retrospective recall and lack of maternal body position validation. We documented actual sleep position and subsequent fetal response throughout the night. We were surprised to find that FHR decelerations and prolonged reduced variability was more likely to be associated with maternal body position change than supine sleep. This underscores that more data are urgently needed to understand which transient events during sleep confer increased fetal risk, and to untangle how these intersect in the 'triple risk' model for late pregnancy stillbirth (Warland & Mitchell, 2014). Late stillbirth is thankfully a rare event, so the development of more sophisticated devices to measure sleep, fetal health and cardiovascular function may provide a clearer picture, aiding our understanding of contributory and protective mechanisms of sleep events and stillbirth risk. This will help determine whether public health messages about settling to sleep on the side- and interventions to assist side sleeping- can feasibly modify stillbirth risk.

Interpretation of the CTG in an antenatal setting can be challenging, but the pathophysiological adaptations and responses of the fetus seen intrapartum can be extrapolated to the antenatal setting to provide a 'real-time' assessment of fetal well-being to hypoxic challenges (Judd *et al.*, 2020). Given the limitations in assessing human placental function non-invasively, recent studies have demonstrated the feasibility of using MRI to measure blood flow and oxygen content in the uterine and umbilical vessels to calculate oxygen delivery and uteroplacental oxygen consumption (Saini *et al.*, 2020; Saini *et al.*, 2021). While these innovative techniques may be able to better quantify the impact of maternal positioning on fetal wellbeing, the difficulty lies in applying these techniques to a maternal sleep state where cardiovascular and respiratory function is altered.

Lastly, our study may have been limited by the pooled cohort which included healthy control pregnancies along with high risk pregnancies. However, this mixed cohort allowed us to investigate how nocturnal FHR tracing may differ across pregnancy groups.

Conclusion

This study found an increased risk of FHR events, namely decelerations and prolonged reduced variability, following a change in body position during maternal sleep, for women with a pregnancy complicated by an HDP with or without FGR. Supine sleep and SDB were not associated with fetal compromise. Our results indicate that most fetuses tolerate sleep-related stressors without significant sequelae. Further research is needed to identify the interplay of maternal and fetal conditions- as well as sleep events- putting the fetus at increased risk of adverse outcomes at night.

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Data Availability Statement

The data that support the findings of this study are openly available in Figshare at figshare.com, DOI: 10.6084/m9.figshare.14544687.

Competing Interests

Mark Howard receives research support from the Resmed Foundation, Philips Respironics and the Cooperative Research Centre (CRC) for Alertness, Safety and Productivity. Maree Barnes receives research support from AirLiquide Healthcare. This article is not related to either relationship. Danielle Wilson, Susan Walker, Alison Fung, Gabrielle Pell and Hannah Skrzypek declare they have no conflict of interest.

Author Contributions

The data for this study was collected at the Austin Health Sleep Laboratory or at the Mercy Hospital for Women. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work. All persons designated as authors quality for authorship, and all those who qualify for authorship are listed.

DW was involved in the study design, data collection, data analysis, interpretation of results and preparation of the manuscript.

SW, MH were involved in the study design, interpretation of results and preparation of the manuscript.

MB was involved in the study design and preparation of the manuscript.

GP was involved in the data collection and the preparation of the manuscript.

AF was involved in the study design, data analysis and preparation of the manuscript.

HS was involved in data analysis and preparation of the manuscript.

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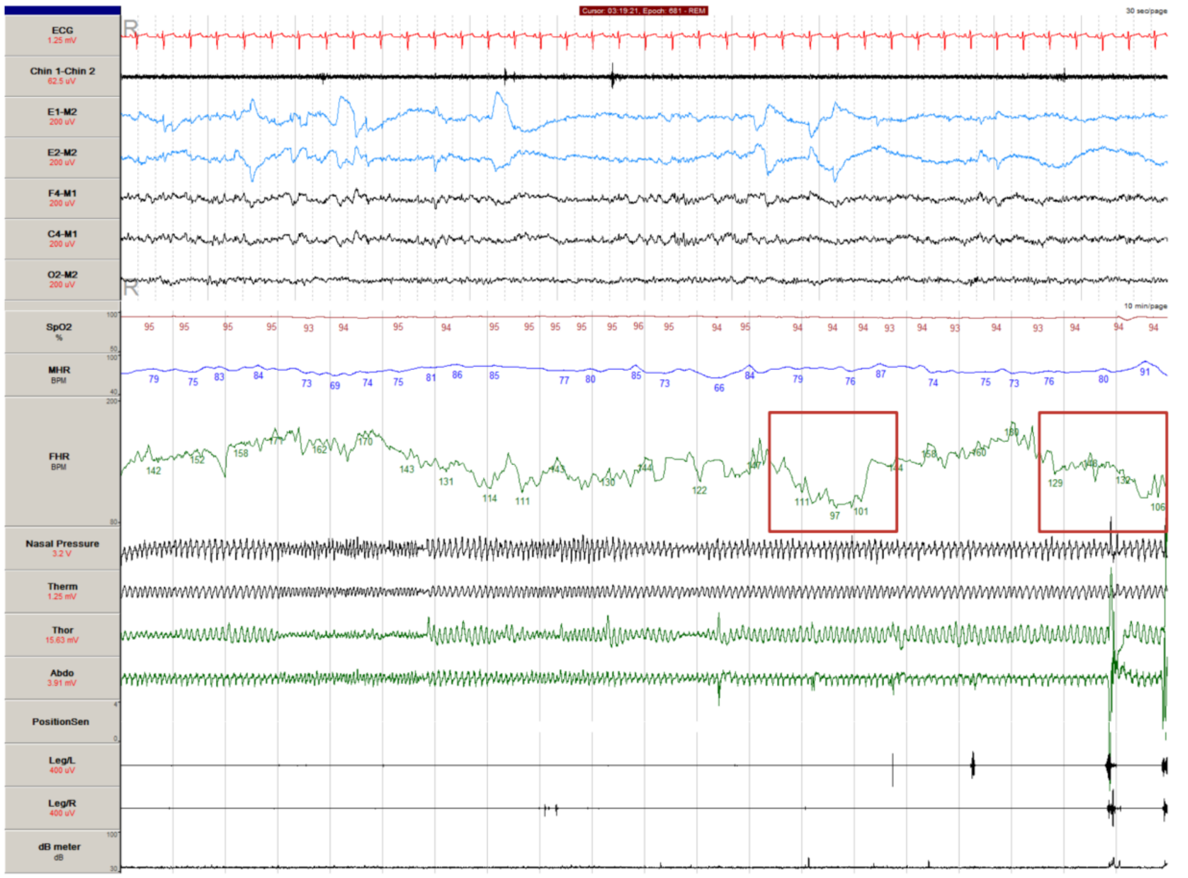

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Fig 1. Polysomnogram with time synchronized cardiotocography exported into the recording during REM sleep. The two boxes highlight fetal heart rate decelerations lasting between 60-90 seconds with a >15 beats per minute fall below the baseline. The top panel shows a 30 second epoch with the signals used to determine sleep stage (Chin 1 – Chin 2 = electromyogram, E1 and E2 = left and right electrooculogram, F4, C4 and O2 = frontal, central and occipital electroencephalogram) as well as electrocardiogram (ECG). The bottom panel shows a 10 minute window (with 30 second intervals) with the signals SpO2 (arterial oxygen saturation), MHR (maternal heart rate), FHR (fetal heart rate), therm (thermocouple), nasal pressure, thor (thoracic respiratory effort), abdo (abdominal respiratory effort), position, Leg L and Leg R and dB meter (to measure snoring).

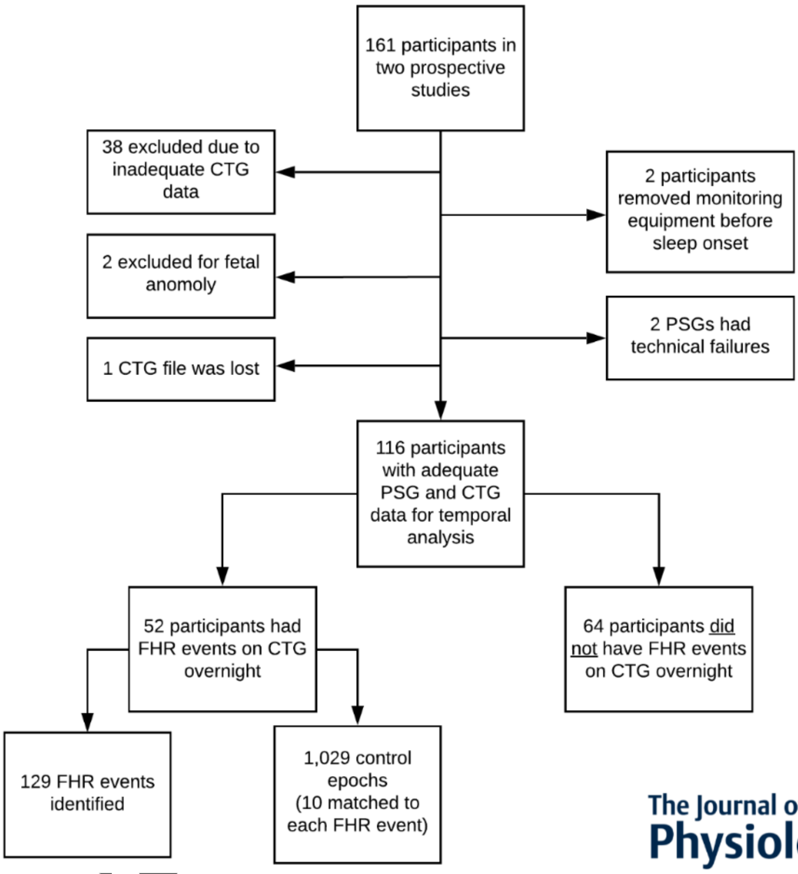


Fig 2. Consort diagram of the flow of participants through data analysis. Cardiotocograms (CTGs) were excluded for analysis if the fetal heart rate trace was present for < 25% of the sleep recording period, or there was insufficient continuous fetal heart rate trace without loss of contact to allow comparison of fetal heart rate events to normal trace for control purposes. PSG = polysomnogram, FHR = fetal heart rate.

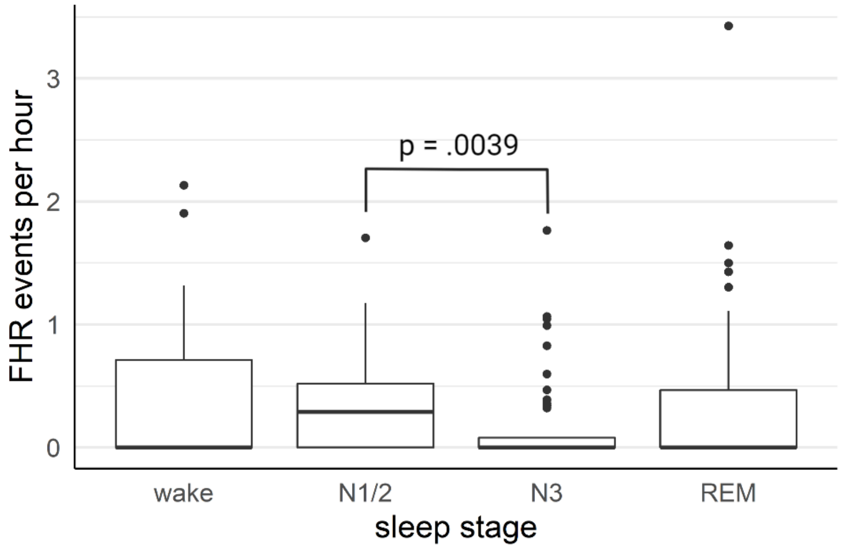
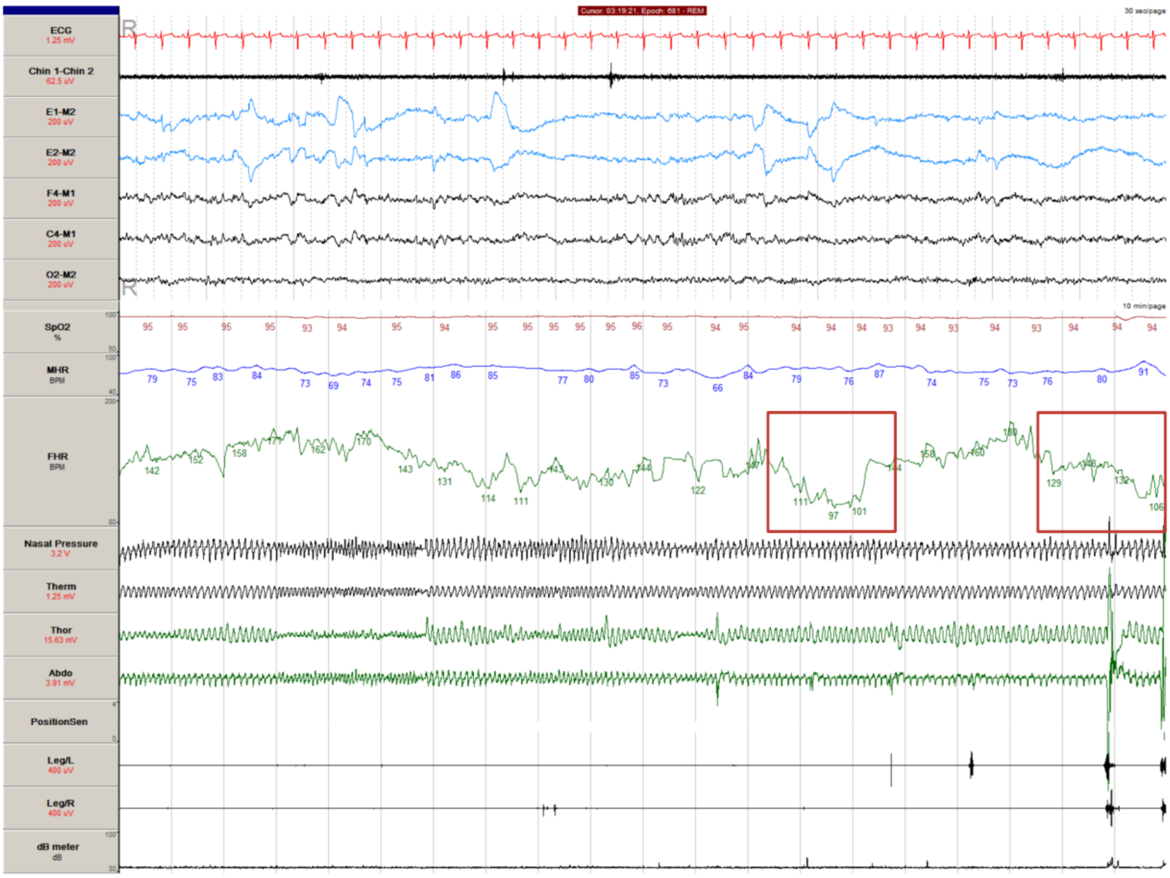


Fig 3. Number of fetal heart rate (FHR) events per hour in each sleep stage across the 52 participants with FHR events present. The rate of FHR events per hour was higher in N1/2 sleep compared to N3 sleep. REM = rapid eye movement sleep. Note. Due to low number of FHR events, median value for wake, N3 and REM is 0.



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