Author/s:
Skrzypek, H;Wilson, DL;Fung, AM;Pell, G;Barnes, M;Sommers, L;Rochford, P;Howard, ME;Walker, SP

Title:
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Date:
2022-12-01

Citation:
Skrzypek, H., Wilson, D. L., Fung, A. M., Pell, G., Barnes, M., Sommers, L., Rochford, P., Howard, M. E. & Walker, S. P. (2022). Fetal heart rate events during sleep, and the impact of sleep disordered breathing, in pregnancies complicated by preterm fetal growth restriction: An exploratory observational case–control study. BJOG an International Journal of Obstetrics and Gynaecology, 129 (13), pp.2185-2194. https://doi.org/10.1111/1471-0528.17192.

Skrzypek Hannah (Orcid ID: 0000-0002-4786-002X)

1. **Title page**

Fetal heart rate events during sleep, and the impact of sleep disordered breathing, in pregnancies complicated by preterm fetal growth restriction: an exploratory observational case control study.

Dr. Hannah SKRZYPEK*, MBBS, FRANZCOG, MRepMed, DDU, CMFM[1], Dr. Danielle L WILSON*, BSc, MSc, PhD[2,3], Dr. Alison M FUNG, MBBS, FRANZCOG, DDU, CMFM [1], Ms. Gabrielle PELL, RN, RM[2], Dr. Maree BARNES, MBBS[3], Ms. Lucy SOMMERS BAppSc (Hons.)[3], Mr. Peter ROCHFORD, BSc GradDip[3], A/Prof. Mark E HOWARD*, MBBS, FRACP, GDEB, PhD[3,4], Prof. Susan P WALKER*, MBBS, MD, FRANZCOG, DDU, CMFM[1,2].

*equal contribution

[1] Mercy Perinatal, Mercy Hospital for Women, Heidelberg, Victoria, Australia

[2] Department of Obstetrics and Gynaecology, University of Melbourne, Parkville, Victoria, Australia

[3] Institute for Breathing and Sleep, Austin Health, Heidelberg, Victoria, Australia.

[4] Department of Medicine, University of Melbourne, Parkville, Victoria, Australia

Shortened running title: CTG during sleep in fetal growth restriction

Corresponding Author: Dr Hannah Skrzypek hskrzypek@mercy.com.au; +61384584444; 163 Studley Rd Heidelberg, VIC, 3084, Australia

2. Abstract

Objectives

To evaluate fetal heart rate (FHR) patterns during sleep in pregnancies complicated by preterm fetal growth restriction (FGR) as defined by Delphi consensus criteria[1]. To determine whether co-existing sleep-disordered breathing (SDB) impacts on acute FHR events or perinatal outcome.

Design

Observational case control study

Setting and population

Women with preterm FGR and gestation matched well grown controls (estimated fetal weight above the 10th percentile with normal Doppler studies); tertiary maternity hospital, Australia.

Methods

A polysomnogram, a test used to measure sleep patterns and diagnose sleep disorders, and concurrent cardiotocography (CTG), was analysed for respiratory events and FHR changes.

Main outcome measures

Frequency of FHR events overnight in FGR cases versus controls and in those with or without SDB.

Results

Twenty-nine patients with preterm FGR and 29 controls (median estimated fetal weight 1st vs. 60th percentile, p<0.001) underwent polysomnography with concurrent CTG at a mean gestation of 30.2 weeks. The median number of FHR events per night was higher among FGR cases compared to controls (3.0 events [interquartile range 1.0, 4.0] vs 1.0 [0, 1.0]; p<0.001). Women with pregnancies complicated by preterm FGR were more likely than controls to be nulliparous, receive antihypertensive medications, be supine at sleep onset, and to sleep supine (32.9% of total sleep time vs 18.3%, p=0.03). SDB was common in both FGR and control pregnancies (48% vs 38%, respectively, p=0.55) but was generally mild and not associated with an increase in overnight FHR events or adverse perinatal outcome.

Conclusions

Acute FHR events overnight are more common in pregnancies complicated by preterm FGR compared to pregnancies with normal fetal growth. Mild SDB was common in late pregnancy and well tolerated, even by fetuses with preterm FGR.

Funding

NHMRC project grant 1065854; Norman Beischer Medical Research Foundation; Mercy Health. Funding sources had no role in conducting this research.

Keywords: CTG, pregnancy, polysomnography, sleep apnoea, sleep-disordered breathing, stillbirth, supine

Tweetable abstract: Mild sleep-disordered breathing seems well tolerated even by highly vulnerable fetuses.

3. Main body of text

Introduction

The potential vulnerability of the fetus overnight has been highlighted by the accumulating literature linking maternal sleep behavior and stillbirth.[2, 3] If maternal sleep represents a period of increased risk for the fetus, it is important to understand the pathophysiological mechanisms so that targeted interventions could be offered. The mechanisms for adverse fetal sequelae related to maternal sleep factors are poorly understood but sleep duration, sleep position, sleep quality and sleep-disordered breathing (SDB) may contribute.[4]

The possibility that SDB may contribute to adverse pregnancy complications is particularly worthy of investigation, given that a safe and effective intervention is already available, in the form of Continuous Positive Airway Pressure (CPAP). SDB occurs when the upper airway collapses repeatedly during sleep, resulting in snoring, airway obstruction and episodic maternal hypoxia. Previous work suggests that recurrent maternal hypoxic events during sleep are well tolerated by fetuses with normal placental function, but may be poorly tolerated among fetuses affected by fetal growth restriction (FGR) due to placental insufficiency.[5] This supports the 'triple risk' model for stillbirth proposed by Warland and Mitchell[6], where an intersection occurs between an underlying maternal and fetal/ placental risk factor, and an acute stressor to cause stillbirth. Applying this model, SDB could be an important mechanism linking acute events during sleep to stillbirth risk, particularly among FGR fetuses who have the greatest background risk[7,8].

We undertook continuous fetal heart rate (FHR) monitoring overnight to determine whether preterm growth restricted fetuses were more likely to have significant acute FHR events during maternal sleep than gestation matched appropriately grown controls. Concurrently, a sleep study was undertaken to assess whether co-existing SDB had any impact on the likelihood of these FHR events, or adverse perinatal outcome.

Methods

Study Design

We performed an observational case control study at Mercy Hospital for Women (Australia), an academic obstetric teaching hospital; and at a co-located sleep unit at Austin Health. The Human Research Ethics Committee approved the study and written informed consent was obtained from all participants. The study was supported by the National Health and Medical Research Council project grant 1065854, the Norman Beischer Medical Research Foundation, and Mercy Health which included external peer review. The funding sources had no role in conducting the research.

Study Participants

Cases were women with singleton pregnancies between 23+5 and 34+6 weeks' gestation complicated by FGR. Only cases where FGR met the Delphi consensus criteria [1] (i.e. FGR likely to be caused by placental insufficiency) were included. Women with pregnancies complicated by suspected aneuploidy, structural anomaly or fetal infection were excluded. Controls were women with singleton pregnancies with no evidence of FGR, matched 1:1 to cases for body mass index (BMI) at first antenatal visit (within ±4 kg/m^2) and gestational age (± 4 weeks).

Data collection and analysis

Sleep Assessment Measures

Basic demographic and obstetric data were collected at recruitment. Both cases and controls underwent an overnight sleep study (polysomnography; PSG) either in the sleep laboratory using Compumedics E series (Abbotsford, Victoria, Australia) or unattended in the participant's home using the Somte Compumedics portable sleep monitoring device, as per the American Academy of Sleep Medicine clinical practice guidelines.[9] Each control participant underwent a sleep study within ±4 weeks of gestational age of the matched FGR case. Participants were not specifically educated about side sleep in pregnancy as this study predated public health messaging regarding side sleep and stillbirth risk. Signals measured included electroencephalogram, left and right electrooculogram, and submental electromyogram for sleep staging, along with electrocardiogram. Body position was determined by a sensor at chest level. Respiration was monitored via thoracic and abdominal respiratory bands, a pulse oximeter (to measure blood-oxygen levels), a decibel meter (to detect snoring) and a nasal catheter and oronasal thermistor (to monitor nasal and oral airflow).

Polysomnography recordings were sleep-staged and respiratory-scored as per the American Academy of Sleep Medicine criteria[10] by an experienced sleep technologist who was blinded to FGR status. Respiratory events were 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 (a sequence of breaths lasting ≥10 sec characterised by increasing respiratory effort leading to an arousal from sleep).

The number of apnoeas and/or hypopnoeas and/or respiratory event related arousals per hour of sleep was calculated as the respiratory disturbance index (RDI). SDB was defined as an RDI of ≥ 5 events per hour. An RDI of between 5 and 14.9 is defined as mild SDB.[11] All participants diagnosed with mild SDB were offered clinical follow up with a sleep physician (not involved in the study), whereas those with severe disease, an RDI ≥ 15 or clinically significant symptoms (e.g. falling asleep while driving), were given urgent follow up within two weeks of the PSG and commenced on CPAP treatment if indicated and acceptable to the participant. Participants who were commenced on CPAP were included in the descriptive data of original sleep and CTG measures, as these recordings preceded their diagnosis. However, to eliminate any effect of intervention bias on outcomes, we subsequently excluded them from neonatal outcome analyses.

Fetal assessment measures

Multiparameter ultrasound assessment was performed in all cases and controls at recruitment, including fetal growth parameters, umbilical artery (UA) Doppler examination, middle cerebral artery Doppler examination and amniotic fluid index. Continuous FHR monitoring (cardiotocography – CTG) was performed using the Monica AN24 (Monica Healthcare Ltd., Nottingham, UK) and was time-synchronised to the polysomnogram. The Monica AN24 is a non-invasive monitor requiring the placement of 5 adhesive electrodes onto the maternal abdomen. The leads are connected to a small portable unit where the data is stored until the recording is completed. Once removed from the participant, the acquired signals are then converted into a digital format, processed and downloaded for review. Investigators and clinicians were blinded to the results of the overnight CTG.

The management of each FGR case was as per her usual care provider. The study team had no involvement in the ongoing management and monitoring of the FGR. Importantly, the treating team were blinded to all overnight CTGs so this could not provoke delivery and iatrogenic preterm birth which could bias neonatal outcomes. However, as a safety precaution, a 'usual care' unblinded CTG was conducted the morning after the sleep study (either as part of, or in addition to, usual surveillance) to ensure there was no new event in these high-risk fetuses that warranted intervention.

The CTGs were initially analysed for rate of successful FHR tracing during the overnight sleep period to give a value between 0 and 100%, with at least one hour of continuous successful FHR trace during confirmed maternal sleep necessary for inclusion. The CTGs were later assessed by two obstetricians, blinded to group allocation and sleep study results, for any of the following FHR events during sleep and awake periods overnight. These were chosen *a priori* and included:

1) Event 1: a deceleration lasting between 60-90 seconds with a >15 beats per minute fall below the baseline.
2) Event 2: a deceleration lasting for >90 seconds and <5 min with a >15 beats per minute fall below the baseline (a prolonged deceleration).[12]

3) Event 3: the presence of ≥2 late decelerations (uniform repetitive decreases in the FHR with slow onset mid to end of a contraction and nadir >20 seconds after the peak of the contraction[12]) in a 20 minute section of CTG.
4) Event 4: the presence of ≥2 complicated variable decelerations (a decrease in the FHR with rapid onset and recovery most commonly occurring with a uterine contraction 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[12]) in a 20 minute section of CTG.
5) 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. These included 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). Once the two obstetricians had independently assessed each CTG recording, FHR events were compared and an agreed list of events generated after re-review of CTG events where there were scoring differences.

Following delivery, birth and neonatal data were collected from medical records. This included gestation at delivery, birthweight, mode of delivery, Apgar scores at 1 minute and 5 minutes, and admission to the neonatal intensive care unit or special care nursery. Ultrasound estimated fetal weights (EFW) and birthweight were customized using the

GROW software V8.0.4,[13] which generates a 'term optimal weight' based on an optimized fetal weight standard. We adjusted for non-pathological factors affecting birthweight, namely gestational age, maternal height, weight, parity, and fetal/infant sex.

Sample size calculation

The primary outcome was the difference in prevalence of FHR events during the overnight sleep period between FGR cases and controls. We had minimal data on which to base a sample size, but our previous study had suggested <5% of healthy pregnancies had overnight FHR events[4] with several significant events in a severely growth restricted fetus. Assuming a 5% risk of events in non FGR fetuses, and a 25% risk in FGR fetuses (which was an empirical estimate given our previous data) in this exploratory study, we had 70% power with a 2-sided significance set at 0.05 with 28 patients in each group. We recruited above this target given the anticipated drop out, and to ensure we could optimise validity of findings by careful matching for relevant maternal characteristics.

Statistical Analysis

All statistical analyses were performed with Stata 16.0 (StataCorp LP, College Station, TX, USA). For descriptive analysis, means with standard deviations (*M±SD)* were used for normally distributed data or medians and interquartile ranges (*Mdn (IQR)*) for non-normally distributed continuous variables. A two-sided p-value of <0.05 was considered significant. Nevertheless, we recognise the limitations of applying such strict conventional criteria in a small exploratory study, and the potential for Type 2 error.

FHR data were analysed by the number of participants displaying each type of defined event, the total number of events per participant, and the rate of events per hour of CTG recorded overnight. Comparisons between the 1:1 case-control matched FGR and control groups for the FHR events and the neonatal outcomes were completed using McNemar's chi-square test for categorical variables, paired sample t-tests for normally-distributed continuous variables and Wilcoxon signed rank tests for non-normally distributed continuous variables. Multiple regression was performed to assess relationships between FGR and hourly rates of FHR events (log transformed) whilst controlling for potential confounders. Comparisons between groups based on SDB status (RDI ≥5) were performed using Fisher's exact test of independence, independent-samples t-tests and Mann-Whitney U tests as appropriate.

Results

Ninety-seven women consented to participate in the study. Figure S1 (supporting information) demonstrates the participant flow diagram. Out of the 79 patients who underwent a sleep study and overnight CTG, 2 participants were excluded due to technical errors, 2 participants removed the monitoring equipment prior to sleep onset, and 12 participants (10 cases and 2 controls) had insufficient CTG recordings to proceed with interpretation. Four controls were subsequently excluded from the analysis as their matched case had insufficient CTG data and one participant was excluded after a fetal anomaly was diagnosed after delivery. Data from 29 women with FGR and 29 matched controls were suitable for CTG analysis. After undergoing the sleep study, two participants

(1 FGR, 1 control) diagnosed with severe SDB commenced treatment and were excluded from the neonatal outcome analysis.

The demographic data, ultrasound findings at recruitment and delivery outcomes of the FGR and control groups are described in Table 1. Twenty-three of the 29 growth restricted fetuses had an EFW <3rd percentile and the remainder had an EFW 3-10th percentile with an abnormal UA Doppler waveform. Overall 18/29 (62%) of the growth restricted fetuses had an abnormal UA Doppler waveform. Women in the FGR group were more likely to be nulliparous and taking antihypertensive medications. The presence of gestational diabetes mellitus and BMI were similar between the groups. As expected, the median EFW percentile for cases was lower than controls at the time of the study (1st vs 60th centile, respectively, p <0.001). Given the severity of the growth restriction, it was unsurprising that cases were delivered earlier than controls (32.1 vs 39.4 weeks' gestation, p<0.001), had lower birthweights (1379g vs 3481g, p<0.001), more often required caesarean section birth (89.3% vs 35.7%, p<0.001) and were more commonly admitted to the special care nursery (85.7% vs 3.6%, p<0.001).

FHR events during sleep in FGR and control pregnancies

The sleep study with time synchronized CTG monitoring was performed at a similar mean gestational age (FGR = 29.7 (2.9) vs controls 30.7 (2.9) p=0.22). We were able to obtain prolonged overnight CTG readings for most participants, with an average monitoring duration of 6-7 hours. CTG success overnight was greater among controls compared to cases (Table 2).

Following assessment of all CTGs, only three of the five fetal heart event types were seen overnight. These were events type 1 (deceleration), 2 (prolonged deceleration) and 5 (prolonged reduced heart rate variability), all of which were more common in pregnancies complicated by FGR. FGR pregnancies were more likely to have 'any FHR event' overnight than controls (79.3% vs 51.7%, p=0.06), but the sample size in this exploratory study meant this just failed to achieve statistical significance. FHR events were more likely to be recurrent, with participants in the FGR group having approximately three times the total number of FHR events overnight (p<0.001), and per hour (p<0.001) (Table 2). These findings were unaltered when stratified by fetal sex (data not shown).

When compared to controls, fetuses with preterm FGR group were more likely to have a prolonged deceleration (11/29 (38%) vs 2/29 (7%), p=0.01) and prolonged periods of reduced variability (12/29 (41%) vs 0/29 (0%), p<0.001). There were no differences between the two groups in event type 1, a deceleration lasting between 60-90 seconds with a >15 beats per minute fall below the baseline (18/29 (62%) vs 14/29 (48%), p=0.34; Table 2).

Since the FGR group was more likely to be nulliparous, taking antihypertensive medication and sleep in the supine position (Tables 1 and S3), a multivariate regression was undertaken to control for these factors (Table S1, supporting information). The overall model significantly predicted number of FHR events per hour (log transformed), $F(4, 53) = 4.92$, $p=0.002$, $R^2 = 0.27$, with FGR the only significant predictor (p=0.007) whereas nulliparity, antihypertensive use and percentage of sleep time in the supine position were not significant (p=0.28, p=0.36 and p=0.94 respectively, Table S1 supporting information). The relationship between FGR and reduced variability remained significant even after adjustment for antihypertensive use, although antihypertensive use was a stronger predictor of reduced variability (log transformed; β=0.47, p<0.001) than FGR (β=0.26, p=0.03, Table S2 supporting information).

Sleep events in FGR and control pregnancies

The sleep measures between the FGR and control groups are reported in Table S3 (supporting information). Mild SDB was common, but did not differ between cases and controls (48% and 38%, respectively p=0.55). There were no differences in the RDI, total sleep time, sleep efficiency, arousal index and percentage of sleep time with oxygen saturation ≤90%. Notably, women with FGR were more likely to be supine at sleep onset and there was a significant difference in the percentage of total sleep time spent supine, with women in the FGR group sleeping on their backs for a third of the night on average compared to less than a fifth for controls (32.9% (23.0, 49.9) vs 18.3% (6.4, 31.5), p=0.03). There was, however, no relationship between the number of fetal events per hour (log transformed) and the percentage of supine sleep (square root transformed) overnight ($F(1,56)=1.22$, $p=0.28$, $R^2=0.02$).

Pregnancy outcomes for FGR and control pregnancies in those with and without SDB

SDB was not associated with an increased frequency of FHR events or neonatal outcomes (Figure 1 and Table 3). There were no differences in either the incidence of FHR events or events per hour between the FGR and control groups according to SDB status (Figure 1). Women with SDB were also no more likely to have a caesarean delivery, lower birthweight infant, lower Apgar scores or neonatal admission (Table 3), whether their pregnancy was complicated by FGR or not.

Temporal relationship between SDB and FHR events in FGR and control pregnancies

20.2% (21/104) of FHR events had one or more apnoeas or hypopnoeas in the five minutes prior. The proportion of FHR events preceded by these respiratory events was similar across event types (deceleration 19%, prolonged deceleration 17%, prolonged period of reduced variability 26%). The FGR group were no more likely to experience FHR events following these respiratory events compared to the control group (19.8% vs 21.7%, p=0.78).

Discussion

Main Findings

This study reports a comprehensive evaluation of FHR patterns among highly vulnerable fetuses during the maternal sleep period. We report that FHR events most likely to indicate significant compromise are more common overnight among fetuses with preterm FGR than gestation matched controls. We did not find that SDB was more common among women with FGR, nor did women with SDB have more acute FHR events or worse neonatal outcomes. One in five FHR events occurred following the respiratory events of apnoea or hypopnoea but this was no different between cases and controls. Compared to the control group, women with preterm FGR spent more time in supine sleep, but supine sleep was not associated with the number of FHR events.

Interpretation

This study uniquely undertook continuous FHR monitoring during maternal sleep in fetuses affected by preterm fetal growth restriction and gestation matched well grown controls.

Growth restricted fetuses were more likely to have prolonged decelerations and periods of prolonged reduced CTG variability. The increased presence of prolonged decelerations in the FGR group perhaps suggests a decreased ability to cope with an acute stressor during sleep, while the prolonged periods of reduced variability may reflect that FGR fetuses spend more time quiescent to preserve energy in the face of suboptimal placental function. Preterm FGR fetuses have higher rates of stillbirth and neonatal morbidity and mortality.[14] The increased number of acute FHR changes seen in these fetuses overnight supports that night and sleep may be a time of particular vulnerability in the face of reduced placental reserve.[15] The feasibility of remote CTG monitoring to improve surveillance in high risk pregnancies is gaining interest although few studies have employed overnight recordings. [16, 17] The TRUFFLE study demonstrated that intermittent CTG monitoring plays an important role in the surveillance and delivery of preterm growth restricted fetuses, particularly where short term variability can be assessed using computerized CTG.[18] Whether such findings can be translated to outpatient surveillance, including prolonged overnight monitoring, remains to be clarified.

We did not find that SDB was more common in women with preterm FGR, nor that SDB significantly contributed to an increase in acute FHR events or neonatal outcomes among these women. Previous work has highlighted the risks of SDB on perinatal outcomes. A recent meta-analysis found that women with SDB were more likely to have a low birth weight baby (<2500g) and were at higher risk of stillbirth or perinatal death (unadjusted OR 2.02 95% CI 1.25-3.28).[19] The women with SDB in this meta-analysis were older and had a higher BMI than those who did not. Some of the included studies used questionnaire-based assessment of SDB which would have reduced reliability,[20] and others failed to adjust for potential maternal confounding co-morbidities associated with placental dysfunction such as obesity, diabetes and hypertension. The large population-based retrospective analyses relied on hospital coding for SDB diagnosis and therefore likely included only severe cases. Mild SDB, as seen in our study, is common. It is possible that more severe disease may be required to adversely affect placental function. While SDB treatment may help mitigate perinatal outcomes associated with more severe disease, our study does not support a role for screening and treating mild SDB to improve outcomes in preterm FGR.

We report that women carrying growth restricted fetuses spent more of their sleep supine, an intriguing finding given the interest in supine sleep in pregnancy and its association with late stillbirth risk. A recent meta-analysis found that maternal supine 'going to sleep' position during the last two weeks of pregnancy was independently associated with late stillbirth risk (adjusted OR 2.63),[2] with the reduction in cardiac output associated with aortocaval compression in the supine position[21] proposed as a key mechanism. Growth restricted fetuses may be particularly at risk. Small fetuses (birthweight <10th centile) had an odds ratio for late stillbirth of 15.66 if their mothers recalled sleeping in a supine position versus 3.98 if not.[2] Despite this, we found that the proportion of time spent in the supine position overnight was not related to the number of FHR events. Women with growth restricted fetuses spending more time sleeping supine may be a chance finding, or it may be that these women with a smaller uterine size may simply be more able to comfortably sleep on their back. This finding warrants further prospective study.

Fetuses affected by preterm FGR may be more vulnerable overnight. The mechanism for acute FHR changes in these fetuses warrants further investigation. We did not find that SDB was more common in preterm FGR, nor did SDB impact on FHR events or neonatal outcomes. The FGR group had a similar number of FHR events preceded temporally by a respiratory event. Pitts et al. found in a cohort of third trimester women that 90% of prolonged decelerations were within 30 seconds of a respiratory event.[22] In contrast to our study where only 1 in 5 events were temporally related, SDB was more severe and present in 57.5% of participants. More severe SDB may be important, as may the circulatory changes associated with maternal position given the trend towards supine sleep in the mothers with FGR. This is the focus of our ongoing work.

Strengths and limitations

The strengths of our study include the case-control design in which preterm FGR cases were selected by standardized criteria and matched to controls for gestation and BMI. We undertook a comprehensive and objective analysis of sleep in relation to time-synchronized CTG, in order to evaluate the relationship of sleep behaviours with fetal events and neonatal outcomes. In contrast to previous studies which have largely relied on self-reported 'going to sleep' position,[23-25] our sleep position data were objective and not subject to recall bias. We acknowledge the challenges of inter-observer variability with subjective CTG interpretation, so adopted strict and standardized definitions for FHR events. The use of a structured guideline with standardised definitions of fetal heart rate events has been shown to reduce interobserver variability in CTG interpretation, with closest agreement seen reported for variable decelerations, late decelerations, repetitive decelerations and for prolonged decelerations: ie. events 1-4 of our study[26]. Our descriptions matched the classification provided in our national guideline[12], and our reviewing obstetricians have been assessed as Level III (highest level possible) practitioners in CTG interpretation.

An obvious limitation was the small sample size in this study and hence the limited generalizability, and potential for type 2 errors. This means both positive and negative findings in this exploratory study need to be interpreted with caution pending confirmatory research. It is possible that CTG abnormalities occur more frequently in preterm growth restricted fetuses both during awake and sleeping periods at night. Unfortunately, loss of contact due to maternal movement when settling to sleep meant we had insufficient duration of 'awake at night' CTG recordings to make this comparison.

We were inadequately powered to specifically evaluate any additional impact of SDB in preterm FGR given that we found mild SDB to be common in both groups. Preterm severe FGR is uncommon, and it is challenging to recruit high risk women to a study with intensive monitoring requirements and who frequently need delivery expedited prior to study completion. Preterm growth restricted fetuses were also more difficult to monitor overnight with more cases than controls excluded from analysis because of insufficient CTG recordings. This notwithstanding, the number recruited was higher than in studies of FHR monitoring during sleep in healthy populations,[27, 28] and we included only high quality data with an average of >6hrs of nocturnal CTG per participant. Finally, we were obliged to remove from outcome analysis the two participants whose SDB was of such severity that it warranted intervention during pregnancy. Although unlikely, this may have impacted on our negative findings regarding SDB and pregnancy outcome through 'treatment paradox', where expected associations with adverse outcome are not seen due to the effect of intervention.

Conclusion

In this exploratory observational study, we report that FGR fetuses have more frequent acute FHR events overnight than gestation matched well grown controls. The presence of SDB did not influence the number of acute FHR events overnight in the FGR or control group but the SDB in this study was notably mild. Our work suggests that nighttime may be a high-risk time for vulnerable fetuses, but the mechanisms linking sleep to fetal wellbeing need to be further explored.

4. Acknowledgements

The authors thank the staff at Perinatal Medicine and the research midwives at the Mercy Hospital for Women and the Department of Respiratory and Sleep Medicine at Austin Health. Thank you to Ms. Pavlina Toman (Austin Health) for polysomnogram analysis, and Prof. Stephen Tong (Mercy Perinatal) for his feedback on the manuscript. We are grateful to all study participants.

5. Disclosure of 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. The remaining authors report no conflict of interest.

6. Contribution to Authorship

Hannah Skrzypek: Methodology, Formal analysis, Investigation, Writing – Original Draft, Writing – Review & Editing

Danielle Wilson: Formal analysis, Investigation, Writing – Review & Editing

Alison Fung: Conceptualisation, Methodology, Formal analysis, Investigation, Writing – Review & Editing

Gabrielle Pell: Investigation, Project Administration, Writing – Review & Editing

Maree Barnes: Conceptualisation, Writing – Review & Editing

Lucy Sommers: Investigation, Formal Analysis, Writing – Review & Editing

Peter Rochford: Software, Formal Analysis, Writing – Review & Editing

Mark Howard: Conceptualisation, Methodology, Supervision, Writing – Review & Editing, Funding Acquisition.

Susan Walker: Conceptualisation, Methodology, Investigation, Supervision, Writing – Review & Editing, Funding Acquisition.

7. Details of Ethics Approval

The Mercy Hospital for Women Human Research Ethics Committee approved the study on the 24th of December 2012, project number 12/63.

8. Funding

The study was supported by NHMRC project grant 1065854 (SW, MH), the Norman Beischer Medical Research Foundation (DW and SW), and Mercy Health (SW). The funding sources had no role in conducting this research.

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This article has a Video Abstract presented by Dr Hannah Skrzypek.

10. Tables and Figures Caption List

a) in print tables and figures

b) tables and figures in supporting information

Table 1. Demographics, Ultrasound Findings at the time of Polysomnography and Delivery Outcomes

	FGR (n = 29)	Control (n = 29)	p
Age (years)	31.6 ± 5.9	31.6 ± 4.0	.98
Nulliparous	24 (82.8%)	17 (58.6%)	.02
Gestational Diabetes	3 (10.3%)	2 (6.9%)	>0.99
BMI first appt (kg/m²)	27.5 ± 8.0	27.8 ± 7.2	.32
BMI at PSG (kg/m²)	30.6 ± 7.6	31.5 ± 7.0	.25
Antihypertensives at PSG	10 (34.5%)	0 (0.0%)	.001
FGR gestation diagnosed (weeks)	27.1 ± 3.9	-	
US gestation (weeks)	28.4 ± 3.3	29.7 ± 3.4	.04
EFW (grams)	944.1 ± 435.3	1661.5 ± 679.6	<.001
EFW customized percentile	1.0 (0.1, 3.7)	60.2 (42.7, 84.5)	<.001
EFW <3rd percentile	23 (79.3%)		
EFW 3-10th with UAPI >95 centile or A/REDF	6 (20.7%)		
Abnormal UA Doppler	18 (62.1%)		
	FGR (n = 28*)	**Control (n = 28*)**	**p**
Delivery Gestation (weeks)	32.1 ± 3.4	39.4 ± 1.0	<.001
Caesarean birth	25 (89.3%)	10 (35.7%)	<.001
Emergency Caesarean birth	10 (35.7%)	6 (21.4%)	.13
Birthweight (grams)	1379.9 ± 697.5	3481.2 ± 471.8	<.001
Birthweight customized percentile	0.4 (0.0, 4.5)	54.3 (20.9, 73.8)	<.001
Apgar 1 min ≤ 7	15 (53.6%)	2 (7.1%)	.002
Apgar 5 min ≤ 7	8 (28.6%)	1 (3.6%)	.02
NICU	15 (53.6%)	0 (0.0%)	<.001
SCN	9 (32.1%)	1 (3.6%)	.005

Note. Values given as M ± SD, Mdn (IQR) or n (%). BMI measured at the first antenatal appointment was taken at a mean of 13.7 ± 4.5 weeks gestation. FGR = fetal growth restriction, BMI = body mass index kg/m², PSG = polysomnography, US = ultrasound, EFW = estimated fetal weight, AC = abdominal circumference, UA = umbilical artery, PI = pulsatility index, A/REDF = absent or reversed end diastolic flow, NICU = neonatal intensive care unit, SCN = special care nursery. *excluding two participants commenced on continuous positive airway pressure (CPAP) treatment (1xFGR, 1x control unmatched).

Table 2. Cardiotocography Variables for the Fetal Growth Restriction and Control Groups

	FGR (n = 29)	Controls (n = 29)	p
CTG tracing success# (hours)	6.1 (3.6, 7.8)	7.3 (6.3, 8.0)	.005
CTG tracing success# (%)	83.3 (44.0, 96.4)	96.0 (89.0, 100.0)	.007
Any event			
n (%)	23 (79.3%)	15 (51.7%)	.06
Total events/night	3.0 (1.0, 4.0)	1.0 (0.0, 1.0)	<.001
Total events per hour	0.5 (0.1, 0.7)	0.1 (0.0, 0.2)	<.001
Event Type			
1. Deceleration n (%)	18 (62.1%)	14 (48.3%)	.34
2. Prolonged deceleration n (%)	11 (37.9%)	2 (6.9%)	.01
3. Late decelerations n (%)	0 (0.0%)	0 (0.0%)	-
4. Complicated variable decelerations n (%)	0 (0.0%)	0 (0.0%)	-
5. Prolonged reduced variability n (%)	12 (41.3%)	0 (0.0%)	<.001

Note. Values given Mdn (IQR) or n (%). FGR = fetal growth restriction, CTG = cardiotocography. # CTG tracing success defined as the rate of successful fetal heart rate tracing achieved.

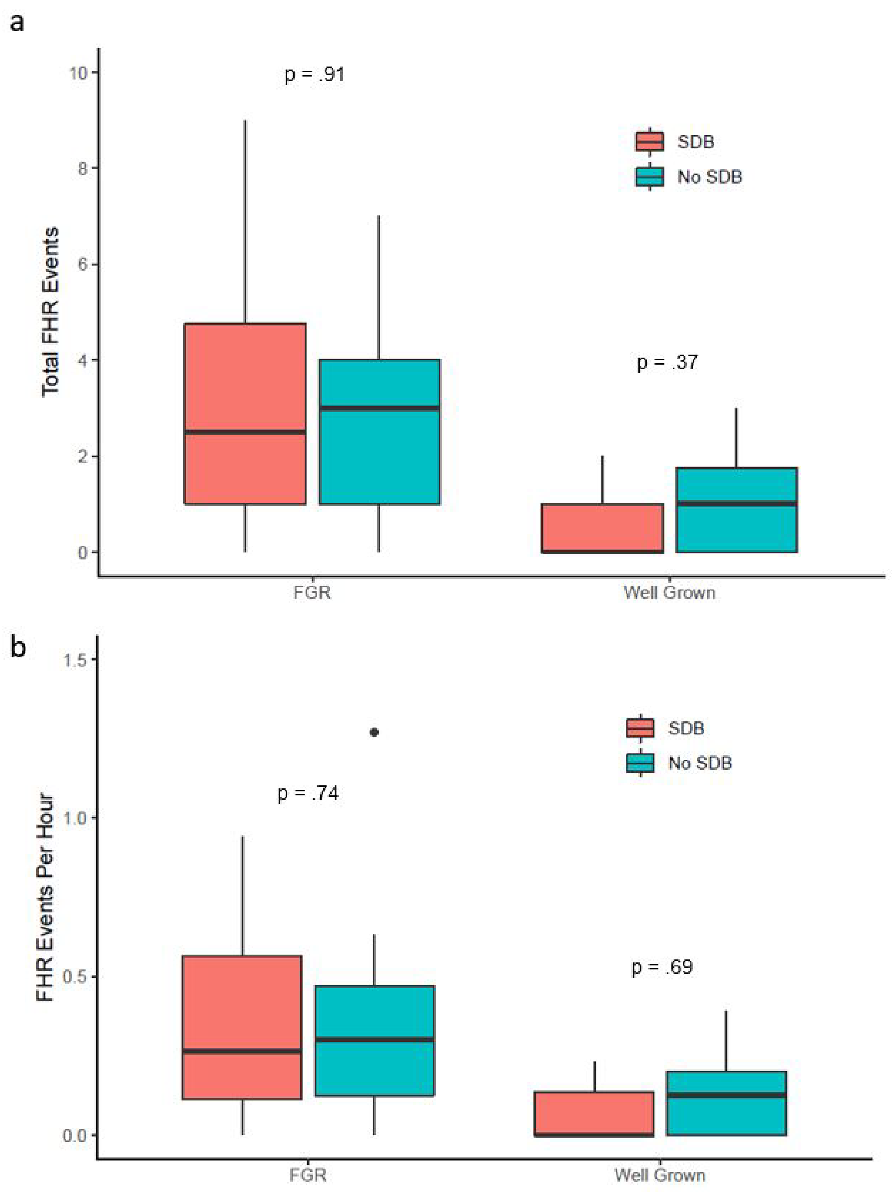
Table 3. Neonatal Outcomes for the Fetal Growth Restriction and Control Group by Sleep-Disordered Breathing Status

	FGR (n = 28*)			Controls (n = 28*)		
	SDB (n = 13*)	No SDB (n = 15)	p	SDB (n = 10*)	No SDB (n = 18)	p
Delivery Gestation (weeks)	31.6 ± 2.9	32.6 ± 3.9	.49	39.1 ± 0.7	39.5 ± 1.1	.32
Caesarean	12 (92.3%)	13 (86.7%)	1.0	5 (50.0%)	5 (27.8%)	.41
Emergency Caesarean	5 (38.5%)	5 (33.3%)	1.0	4 (40.0%)	2 (11.1%)	.15
Birthweight (grams)	1262.9 ± 559.8	1481.3 ± 803.6	.42	3430.4 ± 388.5	3391.1 ± 484.7	.83
Birthweight customized percentile	0.1 (0.0, 0.8)	1.1 (0.0, 8.4)	.25	48.4 (27.3, 73.9)	54.3 (13.7, 73.6)	.85
Apgar 1 min ≤ 7	6 (46.2%)	9 (60.0%)	.71	1 (10.0%)	1 (5.6%)	1.0
Apgar 5 min ≤ 7	5 (38.5%)	3 (20.0%)	.41	1 (10.0%)	0 (0.0%)	.36
NICU admission	8 (61.5%)	7 (46.7%)	.48	0 (0%)	0 (0%)	-
SCN admission	4 (30.8%)	5 (33.3%)	1.0	1 (10.0%)	0 (0%)	.36

Note. Values given as Mdn (IQR) or n (%). FGR = fetal growth restriction, SDB = sleep-disordered breathing, NICU = neonatal intensive care unit, SCN = special care nursery.

*excluding two participants commenced on continuous positive airway pressure (CPAP) treatment (1xFGR and 1x control)

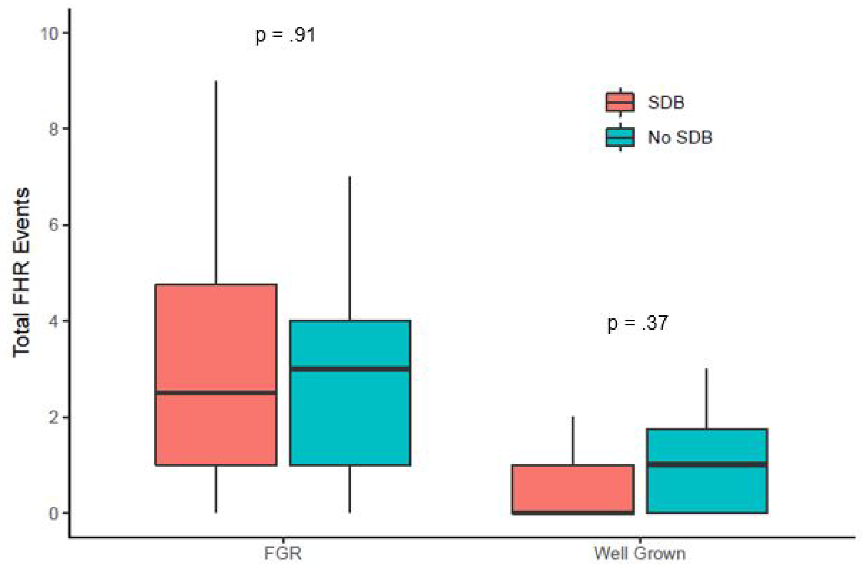
Figure 1 Boxplot displaying a) total fetal heart rate events and b) fetal heart rate events per hour for the fetal growth restriction and well grown control group by sleep-disordered breathing status.



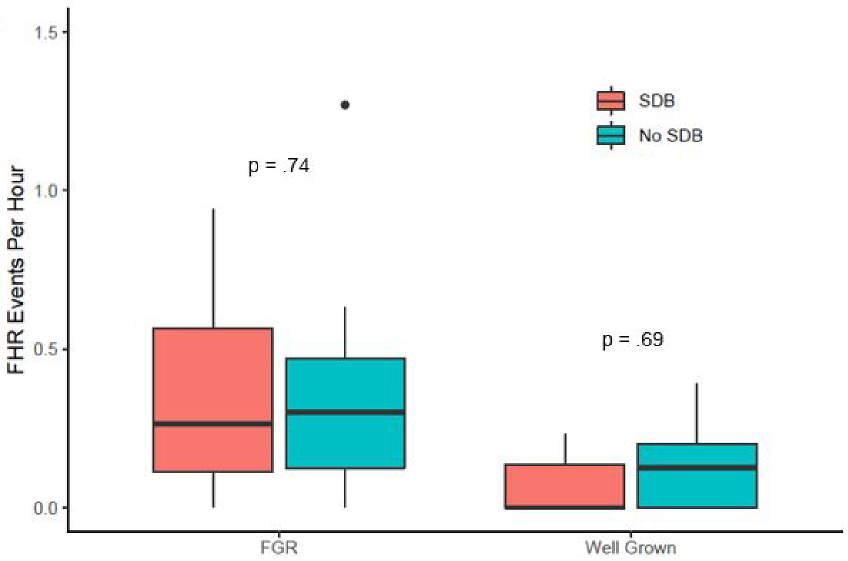
Average respiratory disturbance index for the FGR group with SDB was 7.1 (5.5, 9.8) and 8.7 (7.4, 10.5) for the control group with SDB (p=0.20). FHR = fetal heart rate, FGR = fetal growth restriction, SDB = sleep-disordered breathing.

Figure 1 Boxplot displaying a) total fetal heart rate events and b) fetal heart rate events per hour for the fetal growth restriction and well grown control group by sleep-disordered breathing status.

a



b



Average respiratory disturbance index for the FGR group with SDB was 7.1 (5.5, 9.8) and 8.7 (7.4, 10.5) for the control group with SDB (p=0.20). FHR = fetal heart rate, FGR = fetal growth restriction, SDB = sleep-disordered breathing.