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Original article

Fetal growth restriction: From Polyvagal theory to developmental impairments?

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Abstract

Background: The Polyvagal theory argues that behavioral modulation is a fundamental neurodevelopmental process that depends on autonomic regulation.

Objective: The present study aimed to assess sleep architecture in newborns with fetal growth restriction (FGR) using polysomnography as an indicator of Polyvagal theory.

Methods: We studied polysomnography recordings from 68 preterm infants, 34 with FGR and 34 born with appropriate growth for gestational age (AGA), who were matched according to the corrected age for prematurity (CA). Total sleep time, arousals, the percentage of quiet sleep, active sleep, indeterminate sleep, and heart rate were compared between the groups. Linear multiple regression analyses were used to evaluate polysomnography data for the FGR and AGA groups.

Results: Average heart rate was significantly lower in most FGR groups compared with AGA groups, and small to large effect sizes were observed in several sleep responses when comparing these groups. In the lineal regression model the CA explains significantly the differences in heart rate, controlled by FGR ($p = .012$). Additionally, there was evidence that sleeping states show similar trends, that is, increases in quiet and indeterminate sleep, as well as decreases in active sleep when CA was controlled by FGR.

Conclusion: FGR probably intensifies the unfavorable effect of preterm birth in the responses evaluated by polysomnography. It seems that FGR is associated with alteration in sleep regulation and with differences in heart rate modulation, which may serve as a strategy to preserve energy and such differences likely underlie neurodevelopmental impairments in affected newborns.

Keywords: Fetal growth restriction; Sleep; Neurodevelopment; Polysomnography; Polyvagal theory; Neonatal

1. Introduction

Fetal growth restriction (FGR) occurs when a fetus does not reach his or her biological growth potential as a consequence to impaired placental function [1].

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FGR is optimally defined as the difference between physiological smallness for gestational age and pathological fetal size with signs of placental disease. In such patients, estimated fetal weight is less than the 3rd or 10th percentile, with abnormal Doppler findings in the umbilical artery [2].

Previous studies have demonstrated that FGR produces diverse complications and sequelae after birth. There is also evidence that FGR is associated with altered circadian rhythms. FGR fetuses exhibit impaired organization of behavioral sleep states [3]. FGR infants is also associated with low melatonin excretion in adult life [4]. In addition to poor sleep quality, children with FGR exhibit a greater amount of N2 sleep and a lower amount of N3 sleep [5,6].

Likewise, there is extensive evidence to suggest that FGR exerts effects on the central nervous system: such as alterations in cortical volume and structure, decreases in the total number of cells, myelination deficits, and impairments in brain connectivity. Thus, these structural alterations are known to lead to adverse neurodevelopmental outcomes [7]. Despite previous results, adverse outcomes are frequently subtle, and the primary aspect of behavior that causes impairments in cognitive and emotional development in infants with FGR remains to be fully elucidated.

Polyvagal theory may provide insight into this matter, as it has been postulated that the behavior regulation depends on autonomic regulation. Particular value is conferred to the vagus nerve for its contribution to the coordination of processes that allow survival, breathing, sucking, heart rate; it favors the dynamic feedback between the organs of the body and the nervous central system. Besides, the vagus nerve promotes an inhibitory mechanism that leads to successful transition of the fetus from a biological environment to social challenges that it will face during childhood [8–11]. Additionally, Porges (2011) proposed that interoception is the basic level of functioning that provides mechanisms for the regulation of behavioral states. Neonates offer an excellent opportunity for studying the relationships between interoception and regulation of functional states, since there is a strong relationship between autonomic activation and behavioral states. Because of their neural immaturity, the behaviors that differentiate active sleep from quiet sleep are more evident in newborns than in adults [11]. In contrast to those in adults, the pathways regulating peripheral motor activity in neonates are not depressed during active sleep [12].

Regulation of sleep/alertness represents the beginning of regulatory capabilities that underlie cognitive and emotional development [10,13]. Porges and Furman (2011) have proposed a model in which the development of the vagal system and its cortical-brainstem regulation allows newborns to regulate physiological states in response to environmental challenges, whereas it has been previously reported that newborns with FGR showed a disorganized transition between their alertness states [14].

However, to our knowledge, no studies have examined the effects of FGR on neonatal sleep using polysomnography. Therefore, to determine which aspects of neonatal behavior are associated with alterations in the behavioral systems of neonates with FGR, we aimed to compare sleep architecture between FGR and appropriate for gestational age (AGA) groups, using polysomnography as an index of Polyvagal theory.

2. Methods

2.1. Participants

The present study design was observational, comparative, and cross-sectional. The research was carried out at the Clinic of Sleeping Disorders of the National University of Mexico (UNAM), from January 2010 through December 2015. The FGR group included infants with a birthweight in the first percentile and corrected age for prematurity (CA) from 36 to 43 weeks, without neurological alterations and singleton products. Participants in the AGA group were selected according to the following inclusion criteria: birthweight in percentiles >10, CA from 36 to 43 weeks without neurological alterations singleton products. Exclusion criteria for both groups were as follows: five-minute Apgar score <7 and signs of severe hypoxia. Parents of newborns were invited to participate in this study, they were informed about the importance of their infants' participation, and they were asked to provide written informed consent in accordance with the Declaration of Helsinki. The Ethics and Research Committee at the Clinic approved the research protocol.

2.2. Procedures

Infants were sent by the Neonatal Intensive Care Unit at the Children's Hospital of the General Hospital of Mexico for a polysomnography study. Infants who fulfilled inclusion criteria were selected and classified according to their birthweight percentile, which was estimated in according with the methodology described in previous studies [15,16]. An amount of 2169 infants were assessed at the Hospital from 2010 to 2015. Out of the total aforementioned, 68 infants met the criteria. 34 infants comprised the FGR group and 34 the AGA group.

2.3. Polysomnography study

Polysomnography studies were carried out during a period of $\geq$ 120 min of sleep, so as to record such that

two or more awake/sleep periods. The head of the infant was cleaned, and silver electrodes were placed on the skull according to the International 10–20 system modified for infants. Electrode impedance was always <5 kilo-Ohms. Recordings were performed in a 24-channel digital polysomnographer (Phillips Respironics Inc., Koninklijke, VA) with 16 channels for electroencephalography (EEG). We used a bipolar EEG montage as follows: Fp1-C3, C3-O1, Fp1-T3, T3-O1, Fp2-C4, C4-O2, Fp2-T4, and T4-O2 derivations. Band-pass filters were set between 0.1 and 35 Hz. We used additional channels as follows: two channels for electrooculography (EOG) placed at the external eye angles, an additional channel for chin electromyography (EMG), one channel for nasal flow as measured using a thermistor, one channel for a D2 electrocardiography (EKG) recording, two channels for respiration belts in the thorax and at the abdominal circumference (pneumography), and one channel for a transcutaneous infrared sensor for oxygen saturation. A technician recorded any change in infant behavior during the recording session, according to criteria of behavioral states [17,18], and these infant behavior changes were recorded by video camera. The results of the polysomnography study were evaluated using epochs of 30 sec for identifying indeterminate sleep, active sleep, and quiet sleep following international guidelines used for infants [17,18]. EEG recordings were used to determine discontinuous, continuous, and trace alternate patterns. EMG recordings were used to search for the presence or absence of myogenic potentials. EOG activity was measured and qualified as the presence or absence of eye movements. EKG recordings were used to measure heart rate. Nasal flow and pneumatic impedance belts were used to search for respiratory irregularities.

2.4. Statistical analysis

The distribution of polysomnography measures was evaluated using the Shapiro–Wilk test of normality, which revealed that all measures except for heart rate exhibited a normal distribution. For this variable, a sampling simulation (bootstrapping), based on 1000 samples with bias correction, was added to the hypothesis tests. In this way, duration of total sleep time, number of arousals, percentage of quiet sleep, active sleep, and indeterminate sleep, and heart rate are reported with mean and standard deviation. Due to qualitative and quantitative changes during the development of neonatal sleep, each group exhibits different sleep features according to CA [19–20].

Comparisons of sleep features are not possible outside of two weeks. Therefore, the FGR and AGA groups were divided into four groups according to CA: 36 and 37 weeks, 38 and 39 weeks, 40 and 41 weeks, and 42 and 43 weeks. The groups were matched 1:1 according to CA, and differences in total sleep time, arousal, quiet sleep, active sleep, indeterminate sleep, and heart rate between each of the four groups were assessed using t-tests for sample-related analysis and calculating the effect size by Cohen´s d [21]. For qualitative variables, frequencies and percentages or medians and interquartile ranges were calculated. Comparisons between the FGR and AGA groups (in each age range) for these variables were performed using Chi-square and Wilcoxon tests, respectively. Linear multiple regression analyses were then performed using the enter method for each polysomnography variable, accounting for the following independent variables as a model: presence or absence of FGR and the four groups divided according to CA. These analyses were carried out with the objective of explaining the effect of each variable of the model on polysomnography variables. Analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) version 19, and the significance level was set at $p < .05$.

3. Results

3.1. Characteristics of newborns

The FGR and control groups each included 34 infants. The two groups were divided as follows: 36–37 CA: nine patients; 38–39 CA: 12 patients; 40–41 CA: seven patients; 42–43 CA: six patients. Differences in birthweight were found among all FGR and AGA groups. No significant differences in gender distribution or Apgar score were observed (see Table 1).

3.2. Differences in polysomnography findings between the FGR and AGA groups in each age category

Most comparisons revealed no significant differences. However, there were small to moderate effect sizes in the 36–37 CA group. In this age group, patients with FGR exhibited longer quiet sleep, shorter active sleep, and longer indeterminate sleep. In the 38–39 CA group, a moderate effect size was observed, indicating that heart rate was lower in the FGR group, with a trend towards a difference ($p = .070$). In the 40–41 CA group, effect sizes from small to large were observed in the FGR group, which exhibited greater arousal, shorter active sleep, shorter total sleep time, and longer indeterminate sleep. In contrast, a significant effect for total sleep time was observed in the 42–43 CA group. Indeed, total sleep time was longer in the FGR group, while heart rate was lower than that in the AGA group ($p = .012$). In this same age group, a moderate effect size was observed for arousal, while small effect sizes were observed for quiet sleep and indeterminate sleep (See Table 2).

Table 1
Neonatal characteristics of the groups.

Neonatal features	Groups by corrected age											
	36 and 37		*Stat.*	38 and 39		*Stat.*	40 and 41		*Stat.*	42 and 43		*Stat.*
	FGR ($n = 9$)	AGA ($n = 9$)		FGR ($n = 12$)	AGA ($n = 12$)		FGR ($n = 7$)	AGA ($n = 7$)		FGR ($n = 6$)	AGA ($n = 6$)	
Sex[a]												
Men	4 (44)	4 (44)	0.00	7 (58)	5 (42)	0.67	4 (57)	4 (57)	0.00	2 (33)	5 (83)	3.25
Woman	5 (56)	5 (56)	0.00	5 (42)	7 (58)	0.67	3 (43)	3 (43)	0.00	4 (67)	1 (17)	3.25
Birthweight (g)[b]	1543 (145)	1978 (434)	2.84*	1743 (276)	2058 (450)	2.06*	1599 (406)	2682 (457)	4.68***	1335 (454)	2713 (349)	5.89†
5 min Apgar score[c]	8 (8–9)	8 (8–9)	0.76	9 (8–9)	8 (7–9)	2.50	8 (8–9)	8 (7–9)	0.71	8 (7–9)	8 (8–9)	0.23
Gestational age at birth[b]	34.4 (0.8)	33.1 (1.9)	1.80	35.9 (1.6)	33.8 (2.0)	2.90**	36.2 (2.3)	37.3 (1.45)	1.03	34.6 (2.0)	37.2 (1.9)	2.29*

[a] Data are shown in frequency (percentage) and compared by Chi square.
[b] Data are shown in mean (standard deviation) and compared by *t*-test.
[c] Data are shown in median (interquartile range) and compared by U Mann-Whitney. FGR = Fetal growth restriction, AGA = Appropriate growth for gestational age, Stat. = Value of statistic.
* $p \leq 0.05$.
** $p \leq 0.01$.
*** $p \leq 0.001$.
† $p \leq 0.0001$.

Table 2
Differences between FGR and AGA groups in neonatal sleep architecture.

	Groups by corrected age															
	36 and 37		*t* or $IC_{95\%}$	*d*	38 and 39		*t* or $IC_{95\%}$	*d*	40 and 41		*t* or $IC_{95\%}$	*d*	42 and 43		*t* or $IC_{95\%}$	*d*
	FGR	AGA			FGR	AGA			FGR	AGA			FGR	AGA		
Total sleep time (min)	97.2 ± 17.0	94.7 ± 17.6	0.32	0.14	97.0 ± 18.8	96.8 ± 13.8	0.03	0.01	97.3 ± 13.4	104.9 ± 12.4	1.07	**−0.59**	107.9 ± 8.1	96.0 ± 11.8	2.11	**1.18**
Arousal (number)	23.6 ± 15.2	23.2 ± 14.9	0.05	0.03	21.8 ± 15.9	21.6 ± 12.3	0.03	0.01	20.4 ± 10.6	18.2 ± 10.8	0.40	**0.21**	18.6 ± 4.7	22.9 ± 13.2	0.65	**−0.43**
Quiet sleep (%)	64.1 ± 14.6	59.9 ± 11.1	0.71	**0.32**	58.0 ± 14.2	55.0 ± 17.5	0.36	0.19	60.5 ± 16.9	57.7 ± 21.3	0.22	0.15	56.7 ± 16.3	53.0 ± 10.7	0.36	**0.27**
Active sleep (%)	25.6 ± 13.7	33.4 ± 13.8	1.29	**−0.57**	34.1 ± 17.1	33.9 ± 15.1	0.02	0.01	33.3 ± 15.3	40.5 ± 21.6	0.57	**−0.38**	39.1 ± 17.2	41.7 ± 10.8	0.27	−0.18
Indeterminate sleep (%)	10.3 ± 8.4	6.7 ± 5.9	1.00	**0.50**	7.8 ± 6.4	7.6 ± 8.8	0.08	0.03	6.2 ± 7.0	1.7 ± 2.6	1.74	**0.85**	4.2 ± 3.2	5.3 ± 6.8	0.40	**−0.21**
Heart rate[a] (bpm)	129.4 ± 25.5	132.7 ± 14.2	0.30 −27.2, 17.0	−0.16	131.4 ± 12.4	138.6 ± 15.5	1.95 −14.8, −0.73	**−0.51**	136.6 ± 12.1	136.0 ± 6.7	0.11 −8.2, 9.7	0.06	138.6 ± 11.4	154.0 ± 13.2	3.77* −7.6, −23.2*	**−1.25**

The effect sizes > 0.20 are indicated in bold. Positive or negative values are indicators of effects: small, d = 0.20; medium, d = 0.5; large, d = 0.80; and very large, d ≥ 1.3.
Data are shown in mean ± standard deviation and compared by *t*-test and Cohen's d. FGR = Fetal growth restriction, AGA = Appropriate gestational age, IC = Confidence interval.
[a] For heart rate the confidence interval for the difference of means was obtained by bootstrapping.
* $p \leq 0.01$

3.3. FGR and prematurity effect

The regression model proposed was significant for the heart rate variable (F = 4. 76; p = .012), in which case, CA was the significant independent variable (p = .012) and the presence of FGR exhibited a trend towards a difference (p = .101); these variables explained 10% of the variance in heart rate. Similarly, the regression models proposed for active sleep (p = .083) and indeterminate sleep (p = .077) exhibited a similar trend, in which only CA was significative for active sleep (p = .048) and indeterminate sleep (p = .045), when CA was controlled for FGR (see Table 3).

4. Discussion

In the present study, using polysomnography, we aimed to determine whether changes in sleep architecture in infants with FGR underlie early alteration in neurodevelopment, as postulated by Polyvagal theory. Newborns with FGR exhibited alterations in heart rate, relative to those in the AGA group. In addition, all FGR age groups exhibited longer in quiet sleep and indeterminate sleep, as well as shorter in active sleep. These results suggest that FGR results in behavioral adaptation in newborns. As indicated by the effect sizes in FGR group and by the regression model, the probability of observing significant differences increased when the effects of FGR and CA (including prematurity) on heart rate, and some sleep states, were taken into account. Such findings indicate that other factors, besides prematurity should be taken into consideration, such as FGR. Notably, the present study included neonates with late FGR (i.e., after 34 gestational age at birth), where the effects of FGR on central nervous system development are subtle yet important. To the best of our knowledge, the present study is the first to have analyzed sleep in neonates with FGR via polysomnography. Our study is also novel in that infants were followed-up after hospital discharge, and in that we characterized 6 weeks of sleep development.

4.1. Sleep organization

Numerous studies have demonstrated that, regardless of medical illnesses after birth, preterm newborns and those with FGR exhibit changes in sleep organization, including decreases in active sleep and increases in quiet sleep and indeterminate sleep [22–25], in accordance with the findings of the present study. Such changes in sleep organization are critical, as reduced active sleep may significantly impact brain maturation. Active sleep provides endogenous stimulation needed to form long-term circuitry in the central nervous system in both fetuses and neonates [26]. While some studies reported no significant differences in active sleep or quiet sleep between FGR and AGA groups [27], these studies noted that one of the control groups included patients with neurological injuries, which may have also influenced the regulation of sleep states [19].

4.2. Heart rate

Heart rate variability is an ideal tool for assessing the autonomic nervous system. Lower average heart rate was observed in the FGR group, allowing us to infer that parasympathetic activity was prominent in this group, in accordance with the findings of previous studies [28]. Heart rate decreases also occur during quiet sleep [24], during which parasympathetic activity is prominent [23,24]. In addition to lower average heart rate, a tendency for increased quiet sleep was observed in the FGR group. These findings indicate that decreases in average heart rate may be caused by increased parasympathetic activity, as part of an energy-preservation strategy.

Sleep is controlled by two intimately related processes: a homeostatic process and a circadian pacemaker [29]. Alterations in sleep states related to specific autonomic control may be an early neurophysiological expression of altered neural plasticity. This plasticity represents an adaptive or maladaptive response to environmental stresses or disease states. All of these can be

Table 3
Regression model for each polysomnography measurement.

	Total sleep time	Arousal	Quiet sleep	Active sleep	Indeterminate sleep	Heart rate[a]	
	β (t)	*β (t)*	*β (t)*	*β (t)*	*β (t)*	*β (t)*	*IC95% β*
FGR (presence)	0.04 (0.36)	−0.01 (−0.05)	0.11 (0.93)	−0.13 (−1.07)	0.13 (1.07)	−0.19 (−1.66)	−12.92, 0.79
Groups by CA (>38)	0.16 (1.30)	−0.09 (−0.75)	−0.13 (−1.04)	0.24 (2.01)*	−0.24 (−2.04)*	0.30 (2.60)**	1.16, 8.04*
R^2 *ADJ*	−0.01	−0.02	0.01	0.04	0.05	0.10	
F	0.90	0.29	0.98	2.59	2.66	4.76	
p	0.410	0.752	0.381	0.083	0.077	0.012	

CA = corrected age for prematurity, FGR = fetal growth restriction. Data presented with standardized beta values (t value).
[a] For Heart rate, β (t) values are presented with confidence interval (IC) of β obtained by bootstrapping.
* $p \leq 0.05$
** $p \leq 0.01$.

further expressed as alterations in behavior and cognition [23]. Hence, changes in heart rate may reflect how FGR neonates ensure homeostasis prior to the introduction of environmental demands.

According to the Polyvagal theory of Porges, interoception refers to the capacity to detect and interpret sensory information and to regulate internal organs and motor output. Polyvagal theory argues that the cortex monitors visceral states, providing immediate neural commands in order to make instantaneous adjustments via dynamic shifts in vagal control of the heart that derives in state regulation. When the environment is safe and people in this environment are trustworthy, defense mechanisms are disabled, encouraging social engagement and positive attachment. The parasympathetic nervous system is proposed as the modulator of stress and the reactivity of the vagal brake. The aforementioned findings reflect the notion that visceral tone is regulated in response to environmental challenges [11,12].

Our results may indicate that FGR is associated with difficulties in the central regulation of autonomic function. Healthy neonates turn off the vagal brake to decrease or increase heart rate when shifting from a state of lower metabolic demand to a state of higher metabolic demand (i.e., from quiet sleep to active sleep) [12]. In the present study, patients in the FGR group exhibited decreased heart rate, which may reflect difficulties in adjusting to environmental challenges. Thus, in order to preserve energy, infants with FGR may maintain a low heart rate during sleeping states in which metabolic demands are lower.

4.3. Behavioral states

We hypothesized that autonomic dysfunction associated with FGR leads to difficulties in the regulation of behavioral states. The sleep-awake transition is a potential marker of mature neurodevelopment [30]. In the same way, a link has been shown between sleep regulation and executive function in infants and toddlers with normal development [31]. Additional research has indicated that, beginning in the fetal stages, patients with FGR have difficulties to well establish behavioral states [32] and presents a disorganized transition in their awake states [14]. In accordance with these findings, our results suggest that infants with FGR exhibit difficulties in regulating sleep states. These early characteristics may lead to alterations in other behavioral systems. The behavioral characteristics of FGR are frequently subtle in the neonatal stage, but they may mark the beginning of well-documented neurodevelopmental impairments in this population. Nonetheless, future longitudinal studies involving FGR cohorts should aim to verify this working hypothesis.

4.4. Limitations and strengths

As far as we know, there is not a study that has analyzed neonatal sleep of FGR by doing the following: polysomnography performing a follow-up on infants after hospital discharge and characterizing six weeks of sleep development. The results of this study should be interpreted in light of the limitations that a small sample size offers. A larger sample size would probably allow a stronger association of FGR over heart rate and sleep states changes. However, this group of 64 neonates, 34 FGR and 34 AGA, was recruited during six years. Additional research involving tertiary care centers with experience in FGR should be conducted. Furthermore, future studies should consider variables other than FGR (e.g., brain plasticity, stress due to the time spent in the Neonatal Intensive Care Unit), in order to identify early markers of neurological sequelae in infants with FGR.

5. Conclusions

During sleep, heart rate was lower in the FGR groups, which also exhibited increases in quiet sleep and indeterminate sleep, as well as decreases in active sleep. There was a significant effect of CA (that includes prematurity) on active sleep, indeterminate sleep and heart rate, as expected. Nevertheless, the presence of FGR could be associated with such variations with a subtle effect, so we could believe that both variables should be considered in order to explain such changes. These results suggest that infants with FGR have difficulty regulating sleeping states. These difficulties may reflect adaptation associated with FGR, which likely underlies neurodevelopmental impairments in this population.

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