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Spectral Power Differences in the Brain Activity of Growth-Restricted and Normal Fetuses

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Abstract

Using non-invasive fetal magnetoencephalography (fMEG), we investigated spontaneous brain activity in 28 fetuses diagnosed with intrauterine growth restriction (IUGR) and compared the results to 47 normal-growth fetuses. The fetal gestational age ranged from 28 to 39 weeks with post-natal recordings obtained on 17 of the IUGR fetuses. Power spectrum was computed and was divided into four frequency bands. A significant difference in the relative spectral power in delta, theta and beta bands ($P < 0.01$) was observed only in the 28–32 week gestation age group with alpha band showing a similar trend ($P = 0.054$). This observation suggests that growth restriction may have a more pronounced effect on the fetal brain in early gestation. Larger population studies could reveal the potential value of fMEG as an additional surveillance tool for growth-restricted fetuses.

Introduction

A compromised intrauterine environment adversely affects fetal growth and brain development. Badawi et al reported that neonatal encephalopathy can be attributed to antepartum events [1,2]. Since then there have been other reports that highlight the importance of events in the perinatal period that can play a major role in neonatal encephalopathy [3,4]. Irrespective of these differences, the general association of neonatal encephalopathy and antepartum fetal growth restriction has been observed in these studies [1,2, 4]. Studies of high-risk newborns with IUGR have reported that they have an increasing incidence of learning deficiency later in life [5–7]. Most randomized trials and observational studies in this population have shown that delivery at early gestational age (GA) (prior to 34 weeks) remains a major contributor to adverse perinatal outcome and fetal surveillance with delayed delivery seems to yield the best neonatal outcome.

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With technological advances it is now possible to non-invasively record fetal brain activity using MEG, a magnetic homologue of electroencephalography (EEG) [8,9]. In comparison to EEG, the advantage of MEG is that the magnetic fields can be detected outside the boundary of the skin without making direct contact with the body, and they are not distorted by tissue layers. Based on the non-invasive and passive nature of this technology, it is suitable to study the maturation of the fetal brain. In past few years we have shown the feasibility of recording fetal spontaneous brain activity [8], tracked the maturational changes of MEG patterns in healthy fetuses [9] and have explored the correlation between fetal MEG and behavioral states [10].

In the current study, we examined the spontaneous brain activity of growth-restricted fetuses starting as early as 28 weeks of gestation. We hypothesized that the MEG characteristics of spontaneous brain activity of growth-restricted fetuses will be different from those of normally developing fetuses. Kiefer et al. have reported longer latencies in IUGR fetuses, suggesting a delayed maturation in auditory evoked responses [11]. Apart from one study [12] that examined fetal brain activity in preeclamptic pregnancies with gestation ages limited to 34–37 weeks and in a narrow bandwidth of 2–7 Hz with a single-channel MEG system, there have been no other studies that have quantified the spontaneous fetal brain activity in growth-restricted fetuses across the third trimester.

Materials and Methods

The measurements in this study were performed using a non-invasive 151-channel SQUID (Superconducting Quantum Interference Device) fMEG system called SARA (SQUID Array for Reproductive Assessment). SARA was specifically designed to study different aspects of maternal and fetal physiology [13,14]. The sensors in the SARA system are arranged in a concave array. The mother simply sits and leans forward against the smooth surface of the array, allowing the SQUID sensors to receive signals from the entire maternal abdomen. To reduce the effects of environmental noise, SARA is installed in a magnetically shielded room (Vakuumschmelze, Germany).

A total of 47 low-risk fetuses and 28 IUGR fetuses were examined. 34 low-risk and 17 growth-restricted fetuses also had postnatal measurements. The fetal GAs ranged from 28 to 39 weeks. Fetuses that had any genetic disorder or malformations were not recruited in the study. The study protocol was approved by Institutional Review Board and a signed consent for participation was obtained from each mother. An ultrasound examination (GE Voluson 730) was performed prior to the MEG recording to document general fetal position, head localization, and biometric measurements for fetal weight estimation. The condition of IUGR was diagnosed by UAMS obstetricians in the clinical setting. Serial measurements for growth (head circumference, biparietal diameter, femur length) were performed after the diagnosis, usually every 1–2 weeks. Doppler flow measurements were performed as clinically indicated by the growth measurements. Biophysical Profile measurements were also performed by ultrasound as clinically indicated.

For our research protocol, the following ultrasound measurements were performed at each visit: fetal biparietal diameter, head circumference, and abdominal circumference. A fetal weight was generated along with its percentile according to Hadlock's [15] ultrasound database table in the GE ultrasound machine. IUGR fetuses were defined as having estimated weights below the 10th percentile for GA by ultrasound measurement according to Hadlock's table [15]. If the MEG study visit coincided with a clinic ultrasound measurement, that value was used for expediency. Table 1 shows serial measurements of the IUGR fetuses including the head circumference along with US estimated GA, actual GA at

the time of the study, GA at delivery and, the US GA and growth percentile when first diagnosed in clinic.

The MEG data were recorded in a continuous mode at a sampling rate of 312 Hz with a bandwidth of 0–100 Hz. Interfering maternal and fetal heart-signal components were removed by applying a spatial-filter-based null-projection algorithm. The data from each sensor were partitioned into disjoint time windows of 2 seconds and the power spectrum in each window was computed as the Fourier transform of the autocorrelation function. The power spectral estimate was defined as the average of the spectra over all the time windows. Then the estimated spectrum was averaged over all the sensors. Any interference from the power-line was removed by using a notch filter. The resulting spectrum from each recording was divided into different bands, namely, delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–25 Hz). In each band, relative power (RP) was defined as the ratio of the average power in that band to the average power in the range from 0.5–50 Hz.

The GAs were divided into three-week intervals of 28–30 wk, 31–33 wk, 34–36 wk and 37–39 wk. The postnatal measurements from both the groups ranged in post-menstrual age (PMA) from 36–44 weeks defined as GA at birth plus chronological age. In our study, the fetuses that were determined prenatally to be IUGRs during gestation turned out after birth to be either small for gestational age (SGA) or appropriate for gestational age (AGA) as determined by the Ponderal Index (PI) (weight-to-length ratio) [16]. In the post natal analysis, we grouped the fetal determined IUGRs as follows: Group 1: Fetal IUGR + SGA at birth; Group 2: Fetal IUGR + AGA at birth; Group 3: Fetal low-risk Normal + AGA at birth. The classification of the neonates was purely based on PI after birth. SGA here was used to indicate that the neonate is below a reference range for size or weight for a given age, whereas fetal IUGR referred to pathological processes that prevent the fetus from achieving its growth potential.

In each spectral band, the prenatal and postnatal RP values were separately analyzed via mixed-models ANOVA using the Mixed Procedure from SAS version 9.2 (The SAS Institute, Cary, NC). Post-hoc analysis of prenatal data focused primarily on IUGR-versus-low-risk differences in each three-week GA interval, whereas post-hoc analysis of postnatal data consisted of pair-wise comparisons among the three groups defined above. The unequal-variance t-test was used to compare postnatal values to prenatal values at 37–39 weeks within the same risk group. All statistical comparisons employed an $\alpha=0.05$ significance level despite the multiple comparisons, in order not to inflate Type II error in this discovery-oriented observational study.

Results

Analysis was performed on 214 recordings (158 normal and 56 IUGR) that were obtained from a total of 75 fetuses. Chi-square tests of homogeneous proportions yielded $P=0.84$ for recordings and $P=0.93$ for fetuses, both indicating that the proportion of IUGR did not vary significantly between GA intervals. When the groups and GAs were combined, the mixed-models ANOVAs revealed that RP had overall averages $\pm$ standard errors of 3.83 ± 0.070 in the delta band, 0.573 ± 0.015 in the theta band, 0.460 ± 0.015 in the alpha band, and 0.432 ± 0.013 in the beta band, showing that average RP was highest in the lowest-frequency delta band, and fell monotonically in the bands at successively higher frequencies. The high power concentration in the delta band is consistent with spectral results of EEG recordings from premature and term newborns [17].

Figure 1 shows the RP means plus/minus 95% margins of error for each combination of growth status and GA interval. In all four bands the GA interval from 28 to 30 weeks

showed the largest difference between IUGR and normal, amounting to 18%, 25%, 22%, and 32% of the overall averages in the delta, theta, alpha, and beta bands, respectively. Table 2 provides the actual IUGR-minus-normal differences and P values in each GA interval, and shows that the delta, theta and beta bands achieve high significance ($P<0.01$) only in the 28-to-30-week window, and that the alpha band trends towards statistical significance ($P=0.054$) only during this window.

Post-natal measurements (Figure 1) in the Group 1, Group 2, and Group 3 showed a significant decrease in delta and a significant increase in alpha, beta and theta bands as compared to the prenatal measurements. This observation is consistent with the fact that, as neurological maturation advances, there is a shift away from the delta band towards higher frequencies [17]. Furthermore, we observed a significant postnatal difference in the alpha band between the Group 3 and Group 1 ($P=0.016$). A higher alpha power is noted in the latter group.

Discussion

In summary, non-invasive fMEG provides an opportunity to study the neurological maturation of the fetus across gestation. The observation that the IUGR fetus shows a significant difference in the relative power only in the early part of third trimester (28–31 weeks), when compared to fetuses exhibiting normal growth, indicates that growth restriction may have a more pronounced effect on the fetal brain in early gestation. The fact that there was no significant difference in the later GA's may point towards possible accelerated neurological development to catch up with the maturation of low-risk fetuses. This observation appeared to continue at least through the early neonatal period among the IUGR fetuses that were also classified as small for GA at birth, where the alpha band showed a significantly higher relative power. Further studies on a large population could reveal the potential value of spontaneous fetal MEG brain activity as an additional surveillance tool that can aid in management of fetal growth restriction.

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Figure 1.

Relative Power vs Intrauterine Growth Status. Vertical and horizontal axes respectively show RP and GA; the latter is divided into 3-week intervals. Error bars at interval midpoints denote means (95% confidence limits) of RP. Fetal Groups: Fetal IUGR (Red); Fetal Low-Risk: (Black) In post-natal analysis the groups are divided into: Group 1: Fetal IUGR + SGA at birth (Red); Group 2: Fetal IUGR + AGA at birth (Light Red) and Group 3: Fetal Low-Risk + AGA at birth (black).

Table 1

IUGR serial growth measurements

ID	US GA and growth % when first diagnosed in clinic	Actual (by LMP or early US) GA at each study	Head Circumference each visit (cm) with corresponding US GA estimate	Actual GA at delivery
hr34	28w3d -6%	29w6d, 30w5d; 31w5d, 33w2d; 32w6d	25.1 (27w0d), 26.39(28w3d); 26.15(28w1d); 26.54(28w4d)	34w5d
hr36	28w3d <3%	32w6d; 34w3d	26(28w0d); 29.25(31w6d)	35w1d
hr40	33w2d <10%	36w1d; 41w0d	31.22(34w3d); 33.71 (38w0d)	40w6d
hr41	27w6d <3%	30w3d; 32w5d; 34w4d	25.52(27w3d); 26.64(28w5d); 28.46(30w6d)	34w4d
hr45	28w3d 8%	29w1d; 29w5d	24.38(28w2d); 24.36(28w4d)	36w5d
hr50	30w5d 3%	33w0d	30.31 (32w3d)	36w1d
hr52	23w6d <3%	28w3d	24.67(26w4d)	28w6d
hr72	34w0d 7%	34w1d	30.41 (33w3d)	35w3d
hr62	34w2d: 9%	36w3d; 37w2d	31.33(34w 4d); 31.17(34w3d)	38w5d
hr66	34w0d <3%	37w0d; 38w5d	32.26(36w0d); 32.64(36w3d)	39w5d
hr77	27w0d <3%	29w3d; 30w6d; 32w3d; 32w5d	26.74(28w6d);27.72(30w0d);NM [*] ;29.45(32w1d)	33w5d
hr78	32w2d 8%	35w0d; 35wk3d;	NM [*] ;30.8(33w6d)	36w0d
hr79	31w1d 3%	34w5d; 35w0d	30.15(33w0d);NM [*]	37w2d
hr82	33w6d 9.3%	35w0d; 35w6d; 37w0d; 38w0d	31.16(34w6d);NM [*] ;32.09(35w5d);32.32(36w0d)	38w2d
hr88	32w6d 10%,	32w6d; 33w3d; 34w0d; 34w5d	NM [*] ;29.32(32w0d); 30.33(33w5d); 28.96(31w4d)	35w0d
hr100	33w2d <3%	33w-2d	28.1(30w5d)	33w2d
pat101	26w3d 8%	29w2d; 30w4d	NM [*] ;26.3(28w4d)	31w2d
hr104	29w1d <3%	33w0d; 33w5d; 34w5d	27.8(30w1d); 27.94(30w1d)	35w0d
hr110	31w1d 9%	32w2d; 33w2d	29.31 (32w0d);NM [*]	33w5d
hr126	25w0d 8%;	37w1d; 38w2d	31.57(35w0d); 31.33(34w5d)	40w5d
hr128	30w1d <3%	33w5d; 35w2d; 36w3d	26.61 (29w0d); 27.86(30w3d); 27.75(30w3d)	37w3d
hr129	25w2d 10%	28w4d	24.5(26w4d)	29w3d
Hr130	23w2d 7%	32w4d	30.12(33w3d)	39w6d
hr139	28w6d <3%	32w0d	28.61 (31 w4d)	33w3d
hr141	30w1d 9%	32w3d; 33w4d	27.48(30w0d); 28.62(31w2d)	34w5d
hr143	30w6d<3%	32w1d; 33w1d; 36w1d; 37w1d	28.9(31 w6d); 30.07(33w2d); 30.09(34w3d); 31.59(35w3d)	37w4d
hr154	31w4d <3%	35w0d	28.71 (31 w4d)	37w6d
hr155	30w5d <3%	32w6d	28.3(31 w0d)	38w4d

NM^{*} no growth measurement performed

Table 2

Effect of Growth Status on RP, by Spectral Band and GA Interval.

Spectral Band	GA* Interval	IUGR-Normal: Difference $\pm$ SE [†]	$t^{\ddagger}$	$P^{\ddagger}$
Delta	28–30	0.6864 $\pm$ 0.2518	2.73	0.0078
	31–33	0.1861 $\pm$ 0.1884	0.99	0.3259
	34–36	−0.1261 $\pm$ 0.1934	−0.65	0.5163
	37–39	−0.2115 $\pm$ 0.2766	−0.76	0.4467
Theta	28–30	−0.1412 $\pm$ 0.0523	−2.70	0.0084
	31–33	−0.0165 $\pm$ 0.0393	−0.42	0.6761
	34–36	0.0411 $\pm$ 0.0404	1.02	0.3116
	37–39	0.0495 $\pm$ 0.0574	0.86	0.3909
Alpha	28–30	−0.1018 $\pm$ 0.0521	−1.95	0.0544
	31–33	−0.0093 $\pm$ 0.0393	−0.24	0.8124
	34–36	0.0693 $\pm$ 0.0405	1.71	0.0905
	37–39	0.0749 $\pm$ 0.0573	1.31	0.1945
Beta	28–30	−0.1379 $\pm$ 0.0493	−2.79	0.0064
	31–33	−0.0485 $\pm$ 0.0367	−1.32	0.1902
	34–36	0.0009 $\pm$ 0.0376	0.03	0.9796
	37–39	0.0240 $\pm$ 0.0542	0.44	0.6586

* Gestational Age in weeks, grouped as shown into three-week intervals.

[†] Estimated difference in RP (relative power) $\pm$ standard error of the estimate.[‡] t -statistic and associated P value from ANOVA post-hoc comparisons of IUGR to Normal in each GA interval. All t -statistics have degrees of freedom (DF) = 61.