Biomagnetism in perinatal medicine. Our experience in Greece

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Summary

This is a report on our experience in the application of biomagnetism in perinatal medicine. We provide a brief description of our research work in fetal magnetoencephalography and fetal magnetocardiography in normal, preeclamptic and IUGR pregnancies, together with hemodynamics of the umbilical cord and uterine arteries, providing a new approach to biomagnetism as a non invasive imaging modality in the investigation of perinatal complications.

Key words: fMEG; fMCG; Hemodynamics of umbilical cord/uterine arteries.

Introduction

It is commonly known that the vascular system of mother and placenta plays an important role in the intrauterine development of the fetus. The umbilical cord arteries of newborns delivered by mothers with preeclampsia contain more than twice the amount of collagen and markedly less elastin in comparison to the corresponding arteries of newborns delivered by healthy mothers. Pathologic uteroplacental vasculature causes decreased uteroplacental perfusion and may explain the reduced placental weights and the intrauterine growth retardation seen in most – but not all – cases of preeclampsia. Preeclampsia and intrauterine growth retardation (IUGR) are major causes of maternal and neonatal morbidity and mortality. Preeclampsia complicates 5%-7% of pregnancies in the USA, while IUGR affects 3%-7% of all pregnancies worldwide and is the second common cause of perinatal mortality – after preterm labor – in developed countries [1].

The wide application of fetal heart monitoring in obstetric practice has led to the increased recognition of fetal heart dysrhythmias. A variety of techniques have been employed for the assessment of heart rate disorders, but only the electrocardiogram (ECG) can properly characterize the abnormality. However, though ECG is the mainstay of cardiology, its usefulness in cardiology is of limited value. This is due primarily to the poor signal quality of fetal ECGs recorded from the maternal surface, which typically shows low amplitude and strong maternal interference [2]. M-mode echocardiography has been implemented in the diagnosis of fetal arrhythmias, but this method requires considerable expertise and good tracings are often difficult to obtain because of fetal movements. The duration of examination is often prolonged especially when the fetus is in an unfavorable position. Tracings obtained during early pregnancy are often unsatisfactory because of the small size of the fetal heart [3]. Furthermore, differential diagnosis of an arrhythmic event may be difficult because analysis of the signal morphology is not possible. Pulsed Doppler velocimetry of the fetal abdominal aorta and inferior vena cava provides an accurate diagnosis of the different types of congenital fetal arrhythmias. However, interpretation of the waveforms requires significant acquisition and the method has indications only in high-risk pregnancies due to the destructive cumulative biologic effect on fetal tissues [4].

Up to now it has not been possible to assess fetal brain function directly while the membranes are intact. Several indirect methods are in clinical use such as cardiotocography, biophysical profile, amniotic fluid examination, Doppler sonography, hormone analysis, and ultrasound investigations of fetal growth and fetal movements. Direct measurements of the brain's magnetic activity have important advantages over electroencephalographic (EEG) recordings [5]. Fetal magnetoencephalography (fMEG) provides higher temporal and spatial resolution than EEG because magnetic fields are not distorted by flow through the tissues [6]. As a consequence, significant fMEG activity can often be recorded in the absence of conventional EEG abnormalities [7].

In recent years SQUID biomagnetometry has proven to be most helpful in the study of hemodynamics of certain vessels by measuring the exceedingly weak magnetic fields emitted by circulating blood cells. The higher the concentration of blood cells in the tested area, the higher the biomagnetic fields produced and the higher the recorded measurements. This technique has been successfully used for studying fetal brain activity, fetal heart, and hemodynamics of the uterine and umbilical artery [8-21].

Methods

Biomagnetic recordings were obtained by a single channel second order gradiometer DC-SQUID (MODEL 601; Biomagnetic Technologies Inc., San Diego, USA) [8-21]. During the recording procedure the patient was relaxed lying on a wooden

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bed free of any metallic object so as to decrease the environmental noise and get better signal to noise ratio. Ultrasound scanner Doppler examination assessed the exact position of the target area prior to the procedure in order to be sure that the biomagnetic signals from nearby vessels were excluded. The recordings were performed after positioning the SQUID sensor 3 mm over assessed by the Doppler examination to allow the maximum magnetic flux to pass through the coil with little deviation from the vertical direction. Thirty-two consecutive measurements were taken and digitized by a 12-bit precision analogue-to-digital converter with a sampling frequency of 256 Hz. The duration of the above recordings is justified because the chosen time interval is enough to cancel out, on the average, all random events and to allow only persistent ones. The biomagnetic signals were band-pass filtered, with cut-off-frequencies of 0.1-100 Hz. The associated Nyquist frequency limit, with the above-mentioned sampling frequency, was 128 Hz, which was well above the constituent frequency components of interest in biomagnetic recordings and avoids aliasing artifacts. Conversion of the analog signals into digital recordings was accomplished by means of an AD converter on line with a computer. The average spectral densities from the 32 signals of magnetic field intensity were obtained using Fourier statistical analysis. The obstetricians were ignorant of the biomagnetic values [8-21].

Fetal magnetoencephalography

Kotini *et al.,* [8] investigated the fMEG in IUGR pregnancies. The study population comprised 28 preeclamptic (34-37 weeks' gestation) and 19 normal pregnancies (34-37 weeks' gestation). The preeclamptic group consisted of 11 cases with birth weight below the 10th percentile (1969 ± 129 g) and 17 cases above the 10th percentile (2496 ± 257 g). There were however five cases in the preeclamptic group (18%) which showed biomagnetic amplitudes with low values (birth weight > 10th percentile). Biomagnetic signals (waveforms) recorded from fetal brains were expressed in terms of magnetic power spectral amplitudes. The total corresponding spectral amplitudes in the frequency range 2-7 Hz were high (719 ± 69 Ft/ √Hz in neonates < 10th percentile and 537 ± 105 Ft/ √Hz in neonates > 10th percentile) in most (82%) preeclamptic pregnancies and low (382 ± 35 Ft/ √Hz) in most normal pregnancies (95%). The difference between normal and all preeclamptic pregnancies was highly significant (t-test: $p < 0.0001$). Comparing the two groups of preeclampsia we found also a highly significant difference (t-test: $p < 0.0001$).

Anastasiadis *et al.*, [9] investigated the fMEG in normal and preeclamptic pregnancies. Eleven pregnant women with preeclampsia and 21 normal pregnancies were included. All were at 37-40 weeks of pregnancy. Biomagnetic signals (waveforms), recorded from the fetal brains in the frequency range of 2-7 Hz, were expressed in terms of magnetic power spectral amplitudes. These were low (376.67 ± 28.66 Ft/ √Hz) in almost all normal pregnancies, and high (554.91 ± 149.56 Ft/ √Hz) in most pregnancies complicated with preeclampsia. These findings were of statistical significance (t-test, $p < 0.005$). There was no placenta lesion that was specific to preeclampsia, but certain lesions were more extensive than normal, including syncytial knots, infracts, cytotrophoblastic proliferation and thickening of the trophoblastic basement membrane. The most significant lesion in preeclamptic placentae was seen in the decidual vessels. There was acute atherosis of the decidual vessels with foamy macrophages, partially or completely obliterating the lumens. The lesion was prominent in eight out of 11 placentae from preeclamptic pregnancies and only one out of 21 women in the normal control series (t-test, $p < 0.005$).

Anninos *et al.* [10] investigated the fMEG obtained in normal and preeclamptic pregnancies using non-linear analysis. The study population included two groups aged 18-37 years old at 37-40 weeks of pregnancy. The first group consisted of 21 pregnant women with uneventful pregnancies while the second group comprised 11 women with pregnancies complicated by preeclampsia. By means of the application of non-linear analysis and dimensionality calculations they observed a clear saturation (7.2 ± 0.36) for the dimension of the fMEG from preeclamptic pregnancies and no saturation from normal pregnancies.

Anastasiadis *et al.* [11] investigated the fMEG mapping in normal and preeclamptic pregnancies. Ten pregnant women with preeclampsia and 11 healthy gravidae were included in the study. All were preterm at 28 to 37 weeks' gestation. Biomagnetic signals (waveforms), recorded from the fetal brains in the frequencies 2-7 Hz, were expressed in terms of magnetic power spectral amplitudes: these were low in almost all normal pregnancies, and high in most pregnancies complicated with preeclampsia. fMEG recordings were of high magnetic power spectral amplitudes in seven out of ten cases. The highest values were noted in association with severe preeclampsia. The three cases with relatively low fMEG recordings were of mild preeclampsia and of early gestational age (28-30 weeks). fMEG recordings of normal pregnancies were of low magnetic power spectral amplitudes. There was however a single case with fMEG recording exceeding 650 Ft/ √Hz. With this exception the ISO-SA maps lacked of dense "organized" concentrations of ISO-contour lines in the frequency band 2-7 Hz. The difference between the two study groups was statistically significant (Wilcoxon rank sum test $p = 0.001$). The pictorial representation of the results in the form of ISO-spectral amplitude (ISO-SA) mapping showed two different patterns: (a) ISO-contour lines 'organized' in dense concentration zones (preeclamptic pattern), (b) ISO-contour lines at random distribution without dense concentration zones (normal pattern).

Fetal magnetocardiography

Anastasiadis *et al.* [12] studied the differentiation of heart rate dynamics between normal (n = 19) and IUGR (n = 11) fetuses from 34 to 37 weeks of gestation. They quantified the chaotic dynamics of each heart rate time series obtained by fMCG using correlation dimension. The correlation dimension was significantly lower in IUGR than in normal fetuses (t-test, $p < 0.001$). The periodic dynamics were also obtained by fMCG and measured by power spectrum. The low-frequency components and therefore the periodicity of the low-frequency range were significantly higher in IUGR than in normal fetuses (t-test, $p < 0.001$).

Anastasiadis *et al.* [13] investigated the validity of fMCG in the diagnosis of fetal heart rate arrhythmias in normal pregnancies, as compared to the number of arrhythmias reported in other series, which were detected by use of other diagnostic techniques. They also evaluated the influence of ritodrine on the fetal heart rhythm in pregnancies treated for the risk of preterm labor by means of fMCG, in order to provide preliminary results that could be utilized in the future establishment of fMCG as a screening procedure in the diagnosis and management of fetal arrhythmias. They performed a prospective study on two subgroups of pregnant women: one of 84 women with normal healthy singleton pregnancies and one of 68 pregnant women treated with ritodrine for the risk of preterm labor. The

prevalence of fetal arrhythmias in the first subgroup was 3.5% (3/84), while in the second subgroup it was 16% (11/68). The incidence of fetal arrhythmias detected in the population of normal pregnancies was comparable to that reported in previous studies by use of other techniques.

Kotini *et al.* [14] investigated fMCG in 64 women, 21-30 years old, with single normal pregnancies and gestational ages 28-40 weeks. Spectral analysis was used to quantify heart rate variability and to identify the maturation of the autonomic nervous system. According to the results, there was an increase of the ratio LF/HF of the power spectrum, which reflects the maturation of the autonomous nervous system and also an increase in heart rate variability in the course of pregnancies, which was statistically significant (ANOVA, $p < 0.0005$) comparing the R-R intervals of the number of cases in the four groups of 28-30, 37-40, 31-33 and 37-40 weeks of gestation.

Kotini *et al.* [15] investigated fetal arrhythmias with the use of fMCG. The subjects involved in the study included 84 pregnant women, 19-41 years old (30.55 ± 7.18 Ft/ $\sqrt{Hz}$) with single normal uncomplicated pregnancies and gestational ages 25-32 weeks, and 68 pregnant women 23-42 years old (32.89 ± 5.28 Ft/ $\sqrt{Hz}$) treated with ritodrine for the risk of preterm labor with gestational ages 26-35 weeks. Fourteen fetuses were found with cardiac arrhythmia six cases with tachycardia, one with bradycardia and seven with supraventricular/ventricular (S/V) extrasystoles. Power spectra analysis of fMCG arrhythmic signals assesses the functional state of the autonomic nervous system. fMCG and power spectral analysis of the arrhythmic signals showed that there was no deviation in the physiological process of the fetal heart in cases of fetal arrhythmia.

Anastasiadis *et al.* [16] evaluated the power spectral analysis of fMCG in 64 pregnancies in order to investigate the power spectral amplitude distribution in the frequency range between 2 and 3 Hz. In all cases with normal and uncomplicated pregnancies, the data from the fetal heart and specifically the QRS complexes were identifiable and unaffected by any maternal cardiac activity, and furthermore the power spectral amplitudes, which varied between 120 and 350 fT/$\sqrt{Hz}$, were directly related to gestational age.

Biomagnetism of the umbilical cord

Kotini *et al.* [17] assessed the value of biomagnetic recordings of the umbilical artery over Doppler ultrasound screening in order to predict complications of impaired uteroplacental blood flow in fetuses with IUGR. The study population included 11 IUGR preeclamptic (34-37-weeks gestation; birth weight $1,969 \pm 129$ g) and 19 normal pregnancies (34-37-weeks gestation; birth weight $3,195 \pm 229$ g). Umbilical artery Doppler ultrasound waveform measurements were expressed in terms of pulsatility index (PI). Biomagnetic signals (waveforms) recorded from the IUGR umbilical arteries were expressed in terms of magnetic power spectral amplitudes. In all cases, the frequency band considered was 2 to 7 Hz. The spectral amplitudes were low (mean: 117 ± 24 fT/ $\sqrt{}$ Hz) in most (90.9%) IUGR pregnancies and high (mean: 224 ± 37 fT/ $\sqrt{}$ Hz) in most normal pregnancies (89.5%). There was a statistically significant difference between normal and IUGR pregnancies with respect to spectral amplitudes ($p < 0.0001$), Doppler PI ($p < 0.0005$), pH ($p < 0.0005$) and Apgar score ($p < 0.0005$). Multiple linear regression analysis revealed an influence of PI, pH and Apgar scores on the biomagnetic values (ANOVA: $p < 0.0005$).

Anninos *et al.* [18] investigated the hemodynamics of the fetoplacental circulation in normal and preeclamptic near-term pregnancies. Thirteen abnormal and 25 normal pregnancies were included in this study. The biomagnetic signals were analyzed using nonlinear analysis in order to differentiate these two types of pregnancies. The application of nonlinear analysis reveals a clear saturation dimension value for preeclamptic and no-saturation for normal pregnancies. These findings were statistically significant and were correlated with fetal heart rate monitoring, pH and Apgar score: high biomagnetic cases (140-300 fT/$\sqrt{Hz}$) were related with normal patterns, pH > 7.25 and Apgar > 7, while low biomagnetic recordings (50-110 fT/$\sqrt{Hz}$) were connected with abnormal patterns, pH < 7.25 and Apgar < 7.

Biomagnetism of the uterine artery

Anastasiadis *et al.* [19] elucidated the hemodynamics of the uterine artery in normal and abnormal pregnancies. Two hundred and three women (gestational age 28-42 weeks) were included in the study. Forty-three had preeclampsia and/or IUGR and 160 were normal. Uterine artery waveform measurements were evaluated by use of pulsatility index (PI) (normal value PI < 1.45). Biomagnetic signals of uterine arteries were recorded and analyzed with Fourier analysis. The biomagnetic signals were distributed according to spectral amplitudes as high (140-300 fT/ $\sqrt{Hz}$), low (50-110 fT/ $\sqrt{Hz}$) and borderline (111-139 fT/ $\sqrt{Hz}$). There was a statistically significant difference between normal and abnormal pregnancies concerning the waveform amplitudes ($p < 0.001$) and the PI index ($p < 0.001$). Specifically, they noticed high biomagnetic amplitudes in most normal pregnancies (92.5%) and low biomagnetic amplitudes in most preeclamptic cases (90.7%).

Anastasiadis *et al.* [20] investigated the hemodynamics of the uteroplacental circulation in normal and preeclamptic pregnancies. Twenty-two pregnancies complicated by preeclampsia and 49 normal pregnancies were included in this study. All were near term. Biomagnetic signals were recorded from the uterine arteries and after statistical Fourier analysis the findings were designated in terms of spectral amplitudes as high (140-300 fT/$\sqrt{Hz}$), low (50-110 fT/$\sqrt{Hz}$) and borderline (111-139 fT/$\sqrt{Hz}$). The uterine artery waveforms and the corresponding spectral densities were of high amplitudes in most (89.7%) normal pregnancies and of low amplitudes in most (81.8%) pregnancies complicated by preeclampsia ($p < 0.005$). These findings were of statistical significance and were correlated with fetal heart rate (FHR) monitoring, pH, Apgar score at 1 and 5 min and birth weight percentiles: high amplitude cases were related with normal FHR patterns, pH > 7.25, Apgar score > 7 and birth weight > 75th percentile, while low amplitude recordings were connected with abnormal FHR patterns, pH < 7.25, Apgar score < 7, and birth weight < 10th percentile (8 cases) and < 50th percentile (10 cases).

Anninos *et al.* [21] studied the hemodynamics of uteroplacental circulation in normal and preeclamptic pregnancies. Fifteen pregnancies complicated with preeclampsia and 37 normal pregnancies were included in this study. All women were near term. Applying nonlinear analysis to the biomagnetic activity recorded from the uterine arteries in preeclamptic pregnancies and using dimensionality calculations they observed a clear saturation value around 10 for the preeclamptic pregnancies and no-saturation for the normal pregnancies. These findings were statistically significant and were correlated with fetal heart rate monitoring, pH, and Apgar score at 1 and 5 min. High amplitude cases were related to normal fetal heart rate patterns, pH > 7.25, and Apgar score > 7 while low amplitude recordings were correlated with abnormal fetal heart rate patterns, pH < 7.25, and Apgar score < 7.

Discussion

IUGR is an important risk factor for adverse neurodevelopmental outcome in preterm and term infants [22-27]. The compromised intrauterine environment adversely affects both growth potential and brain development. It is reasonable to presume that there are common factors in the pathogenesis of growth failure and brain injury. The association of placental abnormalities and fetal brain injury has been primarily based on observations from autopsy series comparing placental and brain pathology of stillborn and early neonatal deaths [28, 29]. There have been significant correlations between placental lesions causing reduced uteroplacental blood flow and ischemic brain injury, suggesting that acute or chronic intrauterine hypoxia contributes to ischemic brain injury in infants who die. Fitzhardinge and Steven [30] prospectively followed-up a group of 96 IUGR infants and noted that 50% of males and 36% of females had poor school performance, defined as the necessity of special school or special classes. Overall, 25% had minimal cerebral dysfunction, defined as hyperactivity, a short attention span, learning difficulties, poor fine coordination and hyperreflexia. Histopathologic examination of placentas obtained from pregnancies complicated by preeclampsia or IUGR revealed a strong correlation of pathologic placental features with impaired blood flow in uteroplacental circulation as detected by Doppler ultrasound examination. Elevation of S/D ratios in Doppler waveform of the uterine arteries correlates with increased risk for preeclampsia and IUGR. It has been apparent from a number of studies that Doppler ultrasound has contributed greatly in the detection and management of high-risk pregnancies – such as the ones complicated by preeclampsia or IUGR – reducing perinatal morbidity and mortality by approximately 38%. However, despite the wide application of Doppler sonography in clinical practice in assessing fetuses at risk for antepartum compromise, the sensitivity of the method differentiates greatly in different studies. Maulik *et al.* [31] suggest that Doppler sonography cannot act as a screening method to predict fetal distress and poor perinatal outcome. Golzarian *et al.* [32] conducted an experimental study on biomagnetic recordings obtained before and after artificially induced intestinal ischemia. The study showed a strong correlation between reduced arterial blood flow and low biomagnetic amplitudes.

Several observational studies have explored cerebral redistribution (abnormal MCA Doppler US result and/or abnormal UA/MCA Doppler ratio) for the prediction of perinatal outcome in high-risk pregnancies [33-35]. However, it is difficult to compare the findings of these studies, since the definition of adverse perinatal outcomes varied. Diverse end points were used, including major outcomes such as perinatal death, neurologic complications and necrotizing enterocolitis, as well as minor outcomes such as cesarean section for fetal distress, acidosis and admission to the neonatal intensive care unit. Often, major outcomes were combined with minor outcomes as end points to achieve statistical power. Fetal brain activity can be detected with fMEG in normal and preeclamptic preterm pregnant women [8-11] and in early and late gestational age [5, 6]. The method provides certain advantages compared with conventional EEG due to its ability to record brain activity without direct contact with the head and the transparency of magnetic signals in passing through extracerebral fetal layers and the mother's abdomen. Therefore, it may provide a clinical tool for screening purposes in the antenatal surveillance of the fetal nervous system and especially in IUGR pregnancies for the prediction of perinatal outcome.

Fetal heart rate monitoring is generally performed with the cardiotocogram (CTG), the fetal electrocardiogram (fECG) or Doppler ultrasound. The CTG gives only the momentary heart rate with limited accuracy. The fECG produces electric waveforms, has low signal to noise ratio and interference by the large amplitude maternal ECG field. In addition, the amplitudes of the fetal heart diminish from 27 to 35 weeks of gestation because the vernix caseosa insulates the fetal skin. Doppler ultrasound can detect FHR with a high success rate but it provides less information than the fECG because it is not sufficiently accurate in assessing fetal heart rate and does not provide information on waveforms. An alternative technique for the detection of electrical events in the fetal heart is fMCG which offers significant advantages for assessing fetal rhythm. It shows higher signal to noise ratio, reduced maternal interference compared to fECG, and the electrically insulating properties of vernix caseosa have no apparent effect on it. Magnetic signals from the fetal heart are relatively unaffected by the poor conductivity of the surrounding tissues and the maternal heart and fall off rapidly with source to detector distance. A number of studies reported in the past refer to the advantages that fMCG presents compared to other diagnostic techniques such as M-mode echocardiography, two-dimensional imaging, pulsed Doppler and color flow Doppler [36-38]. All the above-mentioned studies confirm the diagnostic accuracy of fMCG, especially regarding functional heart disorders like cardiac arrhythmias, but, to our knowledge, there are only a limited number of reports in the literature evaluating the screening properties of the method.

In conclusion, our data suggest a potential usefulness of biomagnetometry as a secondary diagnostic test in high-risk pregnancies or as an adjuvant to Doppler ultrasound. In the presence of abnormal biomagnetic activity, intensified fetal surveillance should be considered mandatory on the basis of the likelihood of developing complications, and early intervention might be required.

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