Nonlinearity of Electrohysterographic Signals is Diminished in Active Preterm Labor

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Abstract. Electrohysterogram or uterine electromyogram (EHG) is a non-invasive record that has been shown to provide information about uterine electrical dynamics in labor. This study aimed to compare the irregularity and nonlinearity of uterine electrical dynamics at term and preterm labor using entropy-based methods. We analyzed a dataset of EHG recordings corresponding to parturient women who attended the Maternal-Perinatal Hospital "Mónica Pretelini Sáenz," Toluca, Mexico. Participants were classified as women in active labor at term (T = 30) and preterm labor (PT = 18). The raw EHG signals were analyzed using nonlinear entropy-based methods such as Multiscale Sample Entropy (MSE) and Phase Entropy (PhEn); MSE was evaluated in a range $s = 1 - 20$ and PhEn for $j = 2 - 40$.

Additionally, nonlinearity tests were performed on the EHG data by applying a surrogate analysis. The main statistical differences were found in the lower scales of s and j for MSE and PhEn, respectively. Interestingly, nonlinearity was significantly diminished in the preterm group than in the term group. We concluded that reduced nonlinearity of EHG dynamics might indicate lower regulation in control systems that generate uterine action potentials in preterm labor. A clinical approach for assessing uterine activity in preterm labor may be established using nonlinear analysis of EHG.

Keywords: EHG · Nonlinearity · Surrogate analysis · Uterine EMG · Preterm labor

1 Introduction

Premature births are the most common cause of perinatal illness and death, accounting for between 5% and 18% of all births [1]. From 1995 to 2000, a multi-state research found that preterm children born at 32–36 weeks of pregnancy manifested a nearly two-fold higher incidence of congenital abnormalities than their term peers [2].

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Electrohysterography, or uterine electromyography, is an approach that captures the uterine electrical activity resulting from the repolarization and depolarization of myometrial smooth muscle cells. This technique aims to provide information on uterine activity during pregnancy or childbirth. It measures the action potentials changes with electrodes placed in the maternal abdomen associated with the uterine contraction (electrohysterogram or EHG) [3].

Fele-zorz et al. [4] evaluated linear and nonlinear signal processing methods for the classification of term and preterm labor. It was shown that nonlinear signal processing techniques, such as sample entropy, had a superior accuracy to linear signal processing techniques, such as the root mean square (RMS). According to some authors, nonlinear features are a potential up-and-coming tool for differentiating physiological contractions during gestation and labor [5]. Entropy-based techniques, such as the Multiscale Sample Entropy (MSE), have been employed in research to investigate the irregularity of the EHG signal produced by parturient and nonparturient women. The results indicated that the MSE approach could differentiate between physiological conditions [6].

Recently, Reyes-Lagos et al. applied MSE and Phase Entropy (PhEn) analysis in EHG electrophysiological signals of parturient and nonparturient women. They conclude that uterine electrical dynamics in labor and nonlabor conditions maintain a high tendency to nonlinearity; however, nonlinearity is higher in nonlabor than in labor [7]. Notably, if a preterm birth is diagnosed early, it is possible to provide proper treatment for the pregnant mother. Thus, the assessment of the irregularity and nonlinearity of EHG signals could be used for the early prediction of premature births.

This study aimed to compare the irregularity and nonlinearity of uterine electrical dynamics at term and preterm labor using entropy-based methods. We hypothesize that entropy-based methods (MSE and PhEn) allow the identification of changes in nonlinear dynamics of uterine electrical dynamics between term and preterm labor.

2 Methods

The database of parturient women attended in the Maternal-Perinatal Hospital "Mónica Pretelini Sáenz" at Toluca, Mexico, was used in this study. The database contains 10 min of transabdominal signals from two groups of women, the first group from women in preterm active labor (PT = 18, women with less than or equal to 37 weeks of gestation), and the second group from women in active labor at term (T = 30, with more than 38 weeks of gestation). The data were recorded with the maternal-fetal device Monica AN24 (Monica Healthcare System, Nottingham, United Kingdom), with a sampling rate of 900 Hz.

We obtained the raw EHG signals from the transabdominal recordings utilizing the Monica DK computer package (Monica Healthcare, Nottingham, United Kingdom). The Monica DK was used to filter the trans-abdominal signals with a bandwidth of 0.2 Hz to 1 Hz, which is the EHG's prominent spectral band [8]. The electrohysterogram time series were resampled at 20 Hz to lower the computational complexity of the data processing.

Notably, we used the whole EHG signals in this study, not just manually chosen contractions bursts. The discrimination between term and preterm labor seems easier using entire EHG signals since no manual intervention is required.

The MSE and PhEn algorithms were used to process the whole 10 min of EHG data. Both entropy-based measures were proposed to measure the level of irregularity or unpredictability of a time series at different scales [9, 10]. For MSE, the value r was set to 0.15 and m to 2. The following coarse-grained sequences (s) are used in the MSE algorithm:

$$s_j{}^{(s)} = \frac{1}{s} \sum_{i=(k-1)s+1}^{ks} x_i, \; 1 \leq y_k \leq \frac{N}{s} \tag{1}$$

where s denotes the scale factor and *N/s* is the length of each coarse-grained signal for $1 \leq k \leq N/s$. The initial time series are the coarse-grained time series with the scale $s =$ 1. Additionally, y_k is a data point in the created time series, and x_i is a data point in the initial time series. For $s = 1 - 20$, the MSE curve was originated using 10-min EHG signals.

The Shannon entropy estimation from the distribution *p(j)* generates the PhEn, as illustrated in Eq. (2):

$$PhEn_j = \frac{-1}{\log(j)} \sum_{i=1}^{j} p(j)\log p(j) \tag{2}$$

PhEn assesses the rate of the signals' regularity or the degree of the distribution's compressibility in a second-order difference plot (SODP).

MSE and PhEn were chosen as the discriminating statistic for the surrogate test utilized to detect nonlinearity. Using surrogate data analyses on our initial EHG signals for T and PT, the null hypothesis that the inherent process of the EHG belongs to a stationary linear Gaussian process or uncorrelated noise was investigated. We generated 200 phase-randomized surrogates to conduct these experiments for each original PT or T time series by applying an Iterative Amplitude Adjusted Fourier Transform (iAAFT) with 100 iterations.

The MSE and PhEn were calculated for each of the iAAFT surrogates. As a result, for all T and PT signals, the linear dynamics null hypothesis was evaluated separately at any s or j. If the MSE or PhEn at the specific or s or j of the initial EHG signals was less than the 5th percentile of the distribution of MSE or PhEn values calculated in the complete surrogate set, the linear dynamics null hypothesis was rejected. As a result, the initial signals at that specific s or j were considered nonlinear [11].

The Fisher LSD test was then used to adjust for multiple data comparisons. Data were reported as mean ± SD to visualize homogenous data. A chi-squared test compared the percentage of nonlinear series generated from the T and PT surrogate time series at various j and s values. The significance level for all computations was set at $\alpha = 0.05$.

3 Results

Statistical differences in the irregularity of the EHG time series ($p < 0.05$) between T and PT were found for the three values of the scales analyzed with MSE, $1 < s < 3$

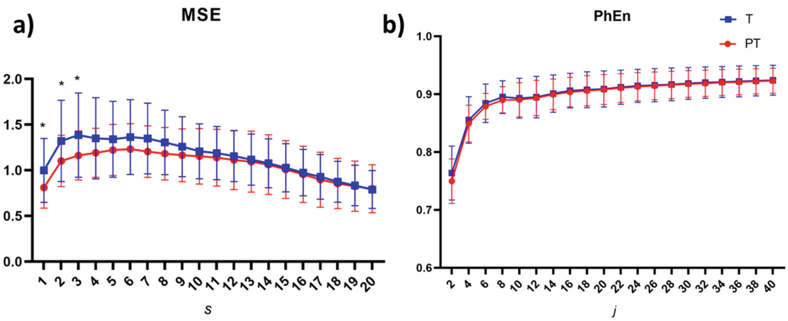

Fig. 1. a) Mean ± SD of Multiscale Sample Entropy (MSE, y-axis) with a scale range of $1 < s < 20$ (x-axis), performed to 10-min of electrohysterography records (EHG) for two groups of pregnant women: active labor at term (T, blue line, n = 30) and preterm labor (PT, red line, n = 18). b) mean values of Phase Entropy (PhEn, y-axis), with a scale range of $2 < j < 40$ (x-axis) applied to the EHG of the same groups of participants (T and PT). * $p < 0.05$ indicate significant differences between T and PT, according to Fisher's posthoc LSD test.

(Fig. 1a). On the contrary, Fig. 1b shows no significant differences between the means values of both groups in the PhEn parameter.

MSE scales, $4 < s < 6$ showed significant differences in nonlinearity by chi-squared analysis considering a 95% confidence interval, reporting the following p values for each scale: $s = 4$ ($p = 0.0343$); $s = 5$ ($p = 0.0016$) and $s = 6$ ($p = 0.0056$). Notably, after applying the chi-squared test, PhEn did not show any significant difference in nonlinearity (data not shown). In contrast, MSE has significant differences for three scales in nonlinearity, producing it a more suitable method for detecting nonlinear characteristics in the EHG under such study conditions. According to these results, MSE should be computed for $s = 1 - 6$ to detect significant changes in the irregularity and nonlinearity of electrohysterographic signals, respectively.

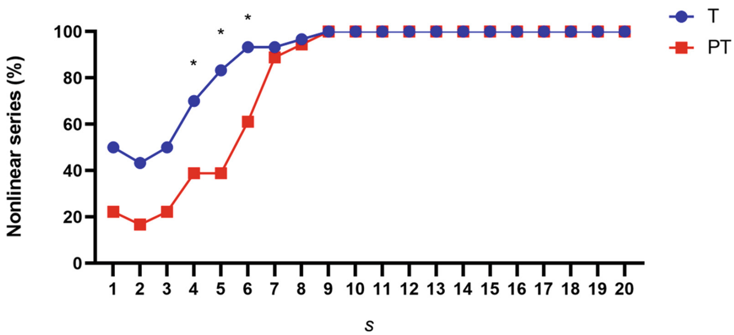

Fig. 2. Percentage of nonlinear series found by the Iterative Amplitude Adjusted Fourier Transform (iAAFT) surrogate analysis applied to Multiscale Sample Entropy (MSE) is shown; the x-axis depicts the scale s. The results correspond to women with preterm active labor (T, blue line) and preterm (PT, red line). * $p < 0.05$ indicate significant differences between T and PT according to the chi-squared test.

4 Discussion

We found that uterine electrical activity of term active labor exhibited higher irregularity (indicated by MSE, Fig. 1a) than preterm labor. Additionally, the percentage of nonlinear series was also higher in term active labor than in preterm labor (Fig. 2). Our results suggest that the uterine electrical activity during active childbirth at term is a nonlinear physiological process that emerges from gap junctions in the myometrium, coordinated by metabolic and bioelectrical events [5]. Such complex behavior could be linked to electrophysiological activity, hormonal responses, inflammation, and other processes involved in the labor onset [12]. In addition, increased MSE at term labor could indicate a considerable presence of uterine electrical fluctuations, resulting in a higher irregularity value and effectiveness of uterine activity during term labor. Interestingly, previous studies have reported that women who suffered cesarean section manifested decreased irregularity of uterine activity compared to women who experienced vaginal delivery [13].

This study compared a control group (T) and a pathological (PT) and revealed that the pathological group manifested decreased nonlinearity using MSE as a relevant nonlinear feature. This finding is consistent with previous studies that used nonlinear analysis methods such as MSE and PhEn [7]. In this sense, nonlinearity seems to be a strong characteristic of contractions measured during labor, and novel nonlinear features should be used to enhance EHG characterization.

Nonlinear assessment has great potential in studying uterine dynamics in pregnancy and labor. Particularly our findings offer a helpful method for distinguishing between preterm and term labor. The changes found in the nonlinearity and irregularity of the EHG between the studied groups contribute to a better knowledge of the electrophysiological mechanisms of the onset of preterm labor. Early identification of preterm births by assessing the nonlinearity of EHG and clinical characteristics of parturient women could help to make clinical decisions related to the administration of tocolytics, suppressing premature labor by inducing uterine quiescence or myometrial relaxation of the uterus [14].

Future work will incorporate the percentage of nonlinearity of different entropy-based methods as input features of machine learning models to discriminate between preterm and term labor.

5 Conclusion

The nonlinearity of uterine electrical activity during active childbirth at term seems to be linked to non-pathological physiological processes. At term labor, the mechanisms involved in controlling uterine contractions are likely to be more complex and effective, resulting in an electrohysterographic signal with higher nonlinearity and irregular behavior. In contrast, the nonlinearity of electrohysterographic signals was diminished in active preterm labor. We speculate that lower nonlinearity of uterine electrical fluctuations in preterm labor could be associated with a decreased participation of the control mechanisms involved in the generation of uterine action potentials, producing non-efficient contractions. A clinical approach for assessing uterine activity in preterm labor may be established using nonlinear analysis of EHG as the first stage.

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