TITLE PAGE

Journal:

Medical & Biological Engineering & Computing

Title of paper:

Uterine electromyography for discrimination of labor imminence in women with threatened preterm labor under tocolytic treatment

Author and addresses

J. Mas-Cabo[1], G. Prats-Boluda[1], A. Perales[2], J. Garcia-Casado[1], J. Alberola-Rubio[2], Y. Ye-Lin[1]

[1]Centro de Investigación e Innovación en Bioingeniería, Universitat Politècnica de València, Camino de Vera s/n Ed.7F, 46022 Valencia, Spain jmas@ci2b.upv.es, gprats@ci2b.upv.es, jgarciac@ci2b.upv.es, yiye@ci2b.upv.es

[2]Servicio de Obstetricia, H.U. P. La Fe, Valencia, Spain Perales_alf@gva.es, palberola.rubio@gmail.com,

Contact details of the corresponding author:

Name: Gema Prats Boluda

Phone:

Email: gprats@ci2b.upv.es

Total number of words in the manuscript: 5731

Number of words of the Abstract: 195

Number of Figures: 6

Number of Tables: 3

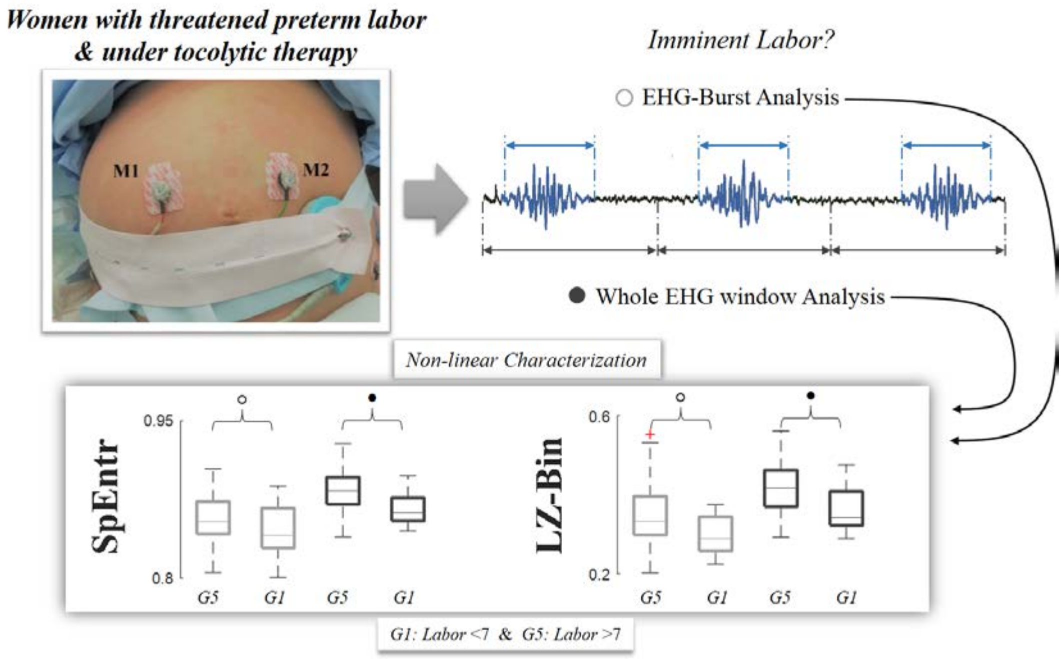
ABSTRACT

Current techniques used in clinical practice present serious limitations to detect imminent delivery in patients with threatened preterm labor being this an outstanding goal in obstetrics. Electrohysterogram (EHG) has emerged as an alternative technique, providing relevant information about labor onset when recorded in controlled checkups without tocolytic drugs. Those works are mainly focused on EHG-bursts analysis and to a lesser extent whole EHG windows analysis. No studies have compared the performance of both methods for labor prediction using the same database. We assessed the capability of EHG signals to discriminate the imminence (< 7 days) of labor in women with threatened preterm labor under tocolytic therapy, using both EHG-burst and whole EHG window analyses, by working out temporal, spectral and non-linear parameters. Only non-linear parameters distinguished those women who delivered in less than 7 days from the rest, for both EHG-burst (2 parameters) and whole EHG window analysis (4 parameters). Therefore, EHG provides relevant information about labor imminence even being recorded in women with threatened preterm labor under tocolytic therapy. Indeed, whole EHG window outperforms EHG-burst analysis promoting the development of real-time systems to predict imminent labor approaching the use of EHG in clinical praxis.

Keywords: Electrohysterogram, premature labor, tocolytic therapy, non-linear analysis.

GRAPHICAL ABSTRACT

The capability, for imminent labor prediction (labor <7 days), of EHG recordings carried out on preterm threatened patients and under tocolytic therapies is analyzed by using EHG-burst and whole EHG window analysis. Compared to temporal and spectral parameters, non-linear features had a better performance in the separation of women who delivered in less or more than 7 days



1. INTRODUCTION

Premature births are defined as childbirths occurring prior to week 37 of gestation and constitute a leading cause of neonatal mortality and morbidity, cognitive impairments, cardiovascular system complications and up to 40% of these survivors develop chronic lung disease [12, 26]. In developed countries, preterm birth rates, the major cause of mortality excluding congenital malformations [18], are about 12% of total births [12] and seem to be on the rise [11]. These situations entail a high cost for families and the health systems. Studies carried out in US have found that preterm births costs can be five times higher than those of term labor ones [26].

Different methods are traditionally used to diagnose preterm labor, some based on the measurement of the cervical length, dilatation and consistence of the cervix, such as the Bishop score [8]. However, all these techniques are limited when it comes to predicting preterm labor [8, 20]. A better method of diagnosing imminent labor is thus needed for women with threatened preterm labor (TPL) to minimize unnecessary hospitalizations, reduce healthcare costs and improve maternal and fetal well-being [4].

Uterine contractility is monitored during pregnancy to evaluate the threat of preterm labor. The most common technique for evaluating uterine contractility is by external tocodynamometry (TOCO) [13]. Nevertheless, TOCO presents some disadvantages and limitations such as the required re-positioning, its effectiveness depends on the subjectivity of the clinician and it do not provide any information on the efficiency of uterine contractions, which is essential information for detecting true preterm labor [16]. An alternative method of monitoring and analyzing uterine contractility is by external measurement of the uterine electrical activity [13]. This technique, also called electrohysterography (EHG), records non-invasively the electrical activity associated with the contraction of the myometrial cells of the uterus (EHG-bursts) [9, 13]. Literature report that EHG characteristics are ‘dynamic’, and they change throughout pregnancy [3, 5]. At early gestational ages the uterine electrical activity is scarce and poorly coordinated, however as labor approaches it becomes more and more intense and synchronized [5, 9]. Several studies have focused on using EHG parameters to identify ‘true’ labor contractions and ‘false’ labor contractions in term and preterm pregnancies from EHG recordings carried out in routine checkups, without any drug being administered to women [6, 24, 28, 29]. However, the applicability of this technique in clinical practice still remains unclear, since tocolytic agents are usually given at the first signs of threatened preterm labor, impairing uterine myoelectrical activity. Few studies have conducted on women with threatened preterm labor under tocolytic agents [28], thus not having analyzed EHG parameters (linear and non-linear) capability to predict labor horizon under this common clinical situation. Furthermore, factors that could limit the clinical application of EHG technique include the entangled acquisition systems ordinary used in the research field, whose use is not viable in clinical practice, and the need for identification of EHG-bursts, which is in contrast to the need of simplified protocols and automated segmentation processes in clinical environments. In this regard, almost all the studies in this field focus on the analysis of EHG-bursts [10, 21, 24]. The segmentation of EHG-burst is a process that depends on the experts' subjectivity and requires a long time [6], making this analysis unsuitable for real time diagnostic systems. Some authors propose whole EHG window analysis [7], which greatly simplifies the segmentation process and could make EHG analysis suitable for real time applications and so more attractive to clinicians. Even if the above-mentioned types of analysis have been reported by several authors in the literature, there is no work extant that compares the imminent labor prediction capacity of both methods.

Therefore, with the purpose of bringing closer the use of EHG to clinical praxis, the aim of the present work is to study the feasibility of EHG parameters (linear and non-linear) to discriminate, whether delivery will occur in more or less than 7 days from the EHG recording, in women with threatened preterm labor, under different stages of tocolytic treatment and using a simplified EHG recording system. The results provided by conventional EHG-burst analysis will be compared with those from whole EHG window analysis.

2. MATERIALS & METHODS

2.1. DATA ACQUISITION

Eighty eight EHG recording sessions with a duration between 30 and 60 minutes conducted on 51 patients with singleton pregnancies are included in this study. All the recordings were carried out at the "Hospital Universitario y Politécnico La Fe", in Valencia, whose Institutional Review Board approved this study, which adheres to the Declaration of Helsinki. All patients were informed about the nature of the study and the recording protocol and signed a written informed consent form. Women included were in gestational ages between 25 and 36 weeks and showing symptoms of preterm labor, such as cervical effacement or regular uterine dynamics. These situations entailed that most of the records (91 %) were carried out under the effect of tocolytic drugs.

The patients enrolled in the study were followed up until their labor ended, and those who presented risk of preterm labor but finally did not initiate labor spontaneously were excluded. The following obstetric data was collected: gestational age, previous gestations, abortions, parity, cervical length and if the EHG recording was performed without, during or after tocolytic treatment. Table 1 shows the obstetric data of the subjects involved in the study. Furthermore additional information about the Database obstetrical information is shown in Figure 1 in form of histograms.

Insert Table 1

Insert Figure 1

In order to study the capability to discriminate labor in less than 7 days in threatened preterm women under tocolytic treatment, the evolution of different EHG parameters as labor approaches was analyzed. Thus the recordings were divided into four groups, according to their time to delivery (TTD). G1 includes women who gave birth in less than 7 days after the recording session, G2 is composed of recordings from women who gave birth between 7 and 14 days after the recording session, and G3 and G4 are formed by recordings from women who delivered between 14 to 30 days, and more than 30 days, respectively. In order to study the utility of EHG parameters in distinguishing between patients who gave birth in less than or more than 7 days, an extra group G5 was considered, formed by all the patients who delivered in more than 7 days (G2 + G3 + G4) after the recording. Figure 2 graphically represents the distribution of all the registers included in the different groups and the time to delivery associated with each group.

Insert Figure 2

For each recording session, the abdominal surface was prepared to reduce skin-electrode impedance by an abrasive paste (Nuprep, Weaver and Company, USA). The EHG signal was registered by placing two disposable monopolar Ag/AgCl electrodes (3M red dot 2560, USA) symmetrically with respect to the median axis on the supraumbilical zone, the inter-electrode distance being 8 cm. Another two disposable electrodes were placed on each hip as reference and ground electrodes. This configuration was chosen to simplify the acquisition protocol, allowing simultaneous clinical recordings with other medical devices, such as TOCO and ultrasounds. Figure 3 shows the configuration of the disposable electrodes together with TOCO and ultrasound for fetal heart rate monitoring.

The signals picked up by the electrodes were conditioned by two custom-made amplifiers, which provide a 2059 V/V gain in the band 0.1 to 150 Hz. After amplification, the signals were digitalized with a 24 bit ADC at 500 Hz. Further information on this wireless signal recording module, developed ad hoc by this group can be found in the original paper [33]. From these two monopolar electrodes, a bipolar signal was obtained as the difference between M1 and M2, where M1 and M2 are the monopolar signals registered by the two disposable electrodes. The TOCO signal was simultaneously acquired using a Corometrics 170 from (GE Medical Systems, USA) and transmitted to the PC with a sampling frequency of 4 Hz.

Insert Figure 3

2.2. DATA ANALYSIS

EHG signals were digitally filtered in the range 0.1 to 4 Hz, since most of their spectral content distributes mainly in that range [24], by a 5^{th} order Butterworth bandpass digital filter. EHG signals were also resampled at 20 Hz.

As previously mentioned, the present work tackles both classical EHG-burst and whole EHG window analysis. EHG-burst were manually segmented by the following criteria: significant amplitude and frequency changes regarding the basal tone with durations greater than 40 s, and absence of motion artefacts and respiratory interference [28]. A total of 338 analyzable EHG-bursts were obtained. For the whole EHG window analysis, only segments corresponding to patient motion artifacts or fetal movements were detected by visual inspection and discarded (≈ 2824 minutes of analyzable EHG records). These segments were divided into analysis windows of 120 s with 50% overlap, in order to include representative sections of the recording at a reasonable computational cost. Preliminary studies were performed to determinate the optimal bandwidth for the whole EHG window analysis working out parameters in window sizes of: 1, 2 5 and 10 min of duration. Results were very similar for windows of 2, 5 and 10 min, selecting finally a size of 2 min in order to reduce the computational cost.

Figure 4A includes a diagram of how EHG parameters were calculated for the EHG-burst analysis, and Figure 4B shows the procedure to obtain the same EHG parameters in the whole EHG window analysis.

For both analyses (EHG-burst and whole EHG window), a set of temporal, spectral (obtained from Welch periodogram), and non-linear parameters (which measure time series complexity) were calculated (8 in total): peak to peak amplitude of the EHG signals, median frequency, dominant frequency, sample entropy (length of repeated templates: 2, tolerance: 0.15) [32], spectral entropy [35], time reversibility [15], multistate Lempel-Ziv index [2, 35] (including 6 states) and binary Lempel-Ziv index [2, 35]. As for temporal and spectral parameters, we computed others like RMS, median frequency, H/L ratio, deciles and Teager, which showed similar results to those obtained from App, MF and DF [27]. Therefore, so as to be concise only results for the last three parameters are shown in the present manuscript. Regarding non-linear parameters, sample and spectral entropy measure the complexity of a finite time series in time and spectral domain respectively, and they provide higher values for more "chaotic" signals [6, 32]. As for time reversibility estimates "how similar" a time series looks like when viewed in forward or reverse time [15]. Lempel-Ziv indexes evaluate signal complexity by counting the number of different patterns in a time series [2, 35]. Lempel-Ziv multistate approach was included in order to evaluate high frequency and low amplitude signal components [2]. After obtaining the EHG parameters from each EHG-burst and/or each analysis window, the median values of each EHG parameters were worked out for every recording session.

For each parameter, a Wilcoxon ranked test ($\alpha = 0.05$) was performed in order to assess whether its median values differ between different groups (G1, G2, G3, G4) and between G1 and G5 for both EHG-burst analysis and whole EHG window analysis. Moreover, a post hoc power analysis of each parameter and analysis (EHG-Burst and whole EHG window analysis) has been carried out to assess the clinical significance to differentiate between G1 and G5.

Insert Figure 4

3. RESULTS

Figure 5 shows 1000 s of EHG bipolar records from women with threatened preterm labor from the four groups considered: G1, G2, G3 and G4, which correspond to less than 7 days, 7 to 14 days, 14 to 30 and more than 30 days from the EHG recording to delivery, respectively. Several high amplitude EHG-bursts (≈ 250 –

300 μV) can be easily identified in the EHG recording of the patient from G1. It can be noticed how EHG-burst amplitude decreases as TTD increases: G2 (≈ 170 μV), G3 (≈ 150 μV) and G4 (≈ 100 μV).

Insert Figure 5

Tables 2 and 3 show the mean and standard deviation of the values of the parameters obtained from EHG records for the EHG-burst analysis and the whole EHG window analysis are shown in respectively. For easier visual analysis, in Figure 6 the median values of each parameter for both EHG-burst analysis and whole EHG window analysis are displayed according to the time to delivery. It also shows the significant differences obtained between the different groups for both analyses performed, represented by black and white dots in the upper part of each graph. If there is any significant difference between patients who delivered in less than 7 days (G1) and those who delivered in more (G5) it is also indicated in the lower part of them (blue braces).

Insert Table 2

Insert Table 3

Insert Figure 6

Regarding temporal and spectral parameters, an increase in the amplitude values (App) as labor approaches can be observed in Figure 6, being more evident in EHG-burst analysis than in whole EHG window analysis. Despite this, significant differences were only obtained for G3 vs. G4 (p: 0.028, EHG-burst analysis and p: 0.027, whole EHG window analysis). No clear tendency is exhibited for median frequency (MF) (see Figure 6) for either EHG-burst or whole window analysis. For this parameter significant differences were only obtained when comparing G3 vs. G4 for whole EHG window analysis. The dominant frequency (DF) exhibited a decreasing trend from G4 to G1 in EHG-burst analysis (G1: 0.349 ± 0.03 Hz, G4: 0.366 ± 0.04 Hz, Table 2) whereas in the whole EHG window analysis it barely changes (see Figure 6). However, no significant differences were found between women who delivered in less than seven days and those who gave birth in more than seven for both whole EHG window analysis and EHG-burst analysis.

Regarding the non-linear parameters, as can be seen in Figure 6, sample entropy present almost no changes as labor approaches, for both EHG-burst analysis and whole EHG window analysis and in none of the performed analyses shows significant differences between groups G1 and G5. By contrast, spectral entropy decreased remarkably and in the case of the whole EHG window analysis it presents a notable ability to distinguish between different groups (G1 vs. G4 (p = 0.001), G2 vs. G4 (p = 0.015), G3 vs. G4 (p = 0.039) and G1 vs. G5 (*p* = 0.009)). This parameter presents a post hoc power of 93.2% when differentiating between G1 vs G5. These are encouraging results since the spectral entropy has not been used previously to characterize EHG changes along gestation, and it could provide useful information about labor onset under whole EHG window analysis.

On the other hand in Figure 6, time reversibility seems to increase, for the whole EHG window analysis, in groups close to labor, compared to those further from delivery. For the whole EHG window analysis significant differences were found when comparing G1 and G5 (*p* = 0.037). However, this parameter presented a post hoc power of 5.4%, probably due to the high variability in its values. Finally, regardless of the status number (binary o multistate), Lempel-Ziv indexes present a similar trend to sample and spectral entropy, decreasing as labor approaches for both EHG-burst and whole EHG window analysis. The results obtained when comparing different groups are very similar in the two analyses, and statistically significant differences were obtained for both when comparing G1 vs. G4, G2 vs. G4, G3 vs. G4 and G1 vs. G5. Lz-Bin and Lz-Multi exhibited a post hoc power up to 90% for both analysis when differentiating G1 and G5.

In short, despite the fact that amplitude and spectral parameters present changing trends throughout gestation, they do not discriminate well between the groups for both EHG-burst and whole EHG window analysis. Furthermore, neither signal amplitude nor spectral parameter shows a statistically significant difference between G1 and G5. On the other hand, a remarkable trend can be observed for non-linear parameters when labor approaches (except for SampEntr), especially when applying the whole EHG window analysis. In order to discriminate threatened preterm women who delivered in less than 7 days from those who gave birth in more, statistically significant differences were found in 2 and 4 non-linear parameters for EHG-burst analysis (LZ-Bin and LZ-Multi) and whole EHG window analysis (SpEntr, Time Rev, LZ-Bin and LZ-Multi), respectively. Nevertheless post hoc power analysis indicated that Lz-Bin and Lz-Multi are able to discriminate between G1 and G5 groups in both EHG-Bursts and whole EHG Windows analysis and SpEntr when computed in whole EHG window analysis.

4. DISCUSSION

Imminent labor prediction in women with threatened preterm labor still remains as a major challenge in clinical praxis. Electrohysterography has proven to provide more accurate information about labor onset compared with the current clinical techniques. However, most studies were carried on woman far from labor without the effect of tocolytic therapies –regular checkups- and usually with entangled and complex acquisition protocols designed for research purposes. In this study, the capability for imminent labor prediction of EHG records carried out in women with threatened preterm labor, under common clinical conditions and using a simplified acquisition protocol was evaluated. EHG signals were mainly recorded in women under tocolytic therapies (30) or after tocolytic treatment (51), only 7 women were recorded previous tocolytics. This is because that EHG signals were recorded in threatened preterm women who were hospitalized and not at the hospital emergency rooms. Although more than one recording session was obtained from the same woman, only recordings corresponding to different situations (without, under and post tocolytic therapy) have been included in this study.

As for EHG characterization, temporal, spectral and non-linear parameters computed from both EHG-burst and whole EHG window analyses were worked out.

4.1 EHG Temporal parameters as labor approaches

Regarding temporal parameters, although our results showed an increase in both EHG-burst amplitude and whole EHG window amplitude as labor approaches, a significant difference was only obtained for G3 vs. G4 (labor between 14-30 days' *vs.* labor for more than 30 days), and no significant differences were obtained between patients who delivered in less than or more than 7 days, either in EHG-burst or whole EHG window analysis. These results suggest that amplitude related parameters are not reliable indicators for determining the proximity of delivery, which agrees with other authors who state that classical contraction parameters such as duration, amplitude as well as RMS and intensity were not capable of differentiating between the preterm and term delivery groups [17]. By contrast, other studies have found significant differences in RMS values between deliveries in less than and more than 14 days for whole EHG window analysis [25]. These differences could be mainly due to the different bandwidth used by the authors (1 – 1500 Hz) and may not be attributable to EHG activity. They also computed the RMS value only for EHG-burst signals and also considered a different time to delivery (TTD <14 vs TTD >14). Other factors related with the acquisition protocol and skin preparation can also affect the amplitude values of the EHG signals, making this parameter by itself unreliable for imminent labor prediction.

4.2 EHG Spectral parameters as labor approaches

Some authors highlight a shift of the spectral content towards high frequencies when delivery approaches [5, 28]. One of the most studied and useful uterine EMG measurements for predicting preterm labor is peak frequency, which increases in women who deliver prematurely [20, 24]. Lemancewicz et al found that the dominant frequency for whole EHG window analysis, estimated within the frequency range 0.24-4 Hz could be used for differentiating patients who delivered within 7 days from those delivered after 7 days [19]. Other studies suggest that median frequency could be used to discriminate term and preterm labors, for both whole EHG window analysis [6] and the EHG-burst analysis [17]. Nevertheless, no statistically significant differences were found in our results for either the frequency peak or mean frequency for distinguishing the G1 vs. G5 group (labor in less than 7 days' vs. more than 7 days'). Indeed, for the EHG-burst analysis only DF parameter showed significant differences when comparing G1 vs. G4 (p = 0.049), and in the whole EHG window analysis only MF in comparing G3 vs. G4 (p = 0.018) and DF when comparing G1 vs. G3 (p = 0.031) showed significant differences. These results could mainly be due to several factors. Firstly, previous studies have shown that the shifting of the spectral content toward higher frequencies is produced 24 h before delivery for term labors and 4 days before in preterm ones [22], and in our database, 7 of the 14 records included in the group TTD <7 were between 4 to 7 days before delivery. Indeed, studies on the evolution of EHG spectral parameters vs. TTD that use broad time horizons (several weeks before delivery) suggest their evolution is clearly non-linear. Furthermore a shift to lower frequency content 10 days before delivery was found for preterm patients [22] and other authors noted an increase of the signal energy in ranges [0.3 – 0.9] Hz and [1.2 – 1.5] Hz between 6-8.5 weeks before labor, then a decrease of about 4.5 to 5.5 weeks before labor and finally a further increase 0.5 to 1 week before delivery for term labor patients [23]. Secondly, almost all EHG records (≈ 91%) included in the present work were taken from patients who received tocolytic treatment. We consider that this real clinical condition could cause differences in the results when compared to other studies, since the ability of tocolytic drugs such as Nifedipine has been shown to affect the amplitude and spectral content of the EHG signals, resulting in smaller amplitude signals and in a significant decrease of PSD peak frequency [30].

4.3 EHG Non-linear parameters as labor approaches

With reference to SampEn, literature has reported controversial results: some authors state that SampEn calculated in the range [0.3 - 3] Hz for whole EHG window analysis presented a downward trend when labor is closer [6], other studies reported that for EHG-burst analysis no significant differences were obtained in sample entropy between preterm and term records [17]. Vrhovec et al revealed that SampEn showed a non-linear trend throughout pregnancy [31]. However, in the present work the SampEn did not show any remarkable trend. These controversial results may be related with different factors such as differences in recording protocols, analysis bandwidths or the inclusion criteria of the signal segments analyzed. In the present work, we have discarded EHG segments with evidences of motion artifacts or respiratory interference as they can affect non-linear parameters. Indeed SampEn has been proven to be sensitive to motion artifacts, sampling frequency, the length of the embedded vectors (m) and the tolerance (r) [1, 6, 34].

As for Lempel-Ziv index, Lemancewicz found significantly higher values in the range [0.24 - 4] Hz for TTD <7 days group against TTD >7 group [19]. Our results show that Lempel-Ziv in the range [0.1 - 4] Hz tend to decrease as labor approaches for both EHG-burst and whole EHG window analysis, which indicates that the EHG signal becomes more regular and deterministic. These differences with the Lemancewicz results may be due to specific computing details, such as different bandwidth, and size of analysis window and/or others related with inclusion or exclusion criteria of the EHG signals segments affected by motion artifacts or respiratory interference. Moreover post hoc power analysis reveals that both LZ-Bin and LZ-Multi are robust parameters to determine imminent labor regardless the type of analysis (EHG-Burst or whole EHG window analysis) and therefore they could be potentially used for designing preterm labor prediction systems.

For the time reversibility parameter, other authors found that Time Rev increases as labor approaches in term patients, reaching an AUC to distinguish labor contractions of 0.99 [15]. The same trends for both types of analysis are observed in the present study, although significant differences for TTD <7 days group against TTD >7 group were only obtained for whole EHG window analysis. However, our results reveals a high variability in Tr values, which results in a low post hoc power value (5.4%). Then we consider that Tr is not a robust parameter for predicting imminent labor in threatened preterm women under tocolytic therapies.

As far as we are concerned, the spectral entropy parameter has not been previously computed in EHG signals. It has been previously used in the literature to evaluate the organization of the spectral content in EEG signals picked up from patients during anesthesia [14]. In the present study, this parameter shows a downward trend as labor approaches, giving rise to a very promising result, especially in whole EHG window analysis to identify patients who give birth in less than 7 days.

4.4 EHG-burst or whole EHG window analysis

In general, whole EHG window outperforms EHG-burst analysis in terms of distinguishing (statically significant differences of EHG parameters) recordings from different TTD groups. Specifically, the results for whole EHG window analysis showed that all the tested non-linear parameters, except for SampEn, presented statistically significant differences for women who delivered before 7 days and those after 7 days. In contrast, when using EHG-burst analysis, only binary and multistate LZ parameters presented statistically significant differences. Therefore, the use of complexity parameters in whole EHG window analysis in patients under common clinical conditions could lead to a promising tool for predicting labor in less than 7 days. All these results show that the whole EHG window analysis is not only able to track the evolution of EHG as labor approaches, but it may have a better performance than EHG-burst analysis for predicting whether a patient with threatened preterm labor will deliver in more or less than 7 days. These are remarkable results, since whole EHG window analysis greatly simplifies the segmentation process as compared to traditional EHG-burst analysis which is usually tedious, subjective and offline. In this regard, the use of an automatic classifier able to discard patient motion artifacts, fetal movements and respiratory interference in combination with a whole EHG window analysis system would facilitate the use of EHG techniques in clinical practice.

5. CONCLUSIONS

This paper analyzes the feasibility of the EHG to discriminate those patients with threatened preterm labor who delivered in less than 7 days from those who delivered in more, under common clinical conditions, by calculating linear and non-linear parameters computed from both EHG-bursts and whole EHG window analyses. Although some temporal and spectral parameters showed an increasing trend as labor approaches in both EHG-burst and whole EHG window analysis, complexity parameters presented a better performance in distinguishing between the different time-to-delivery groups. For the EHG-burst analysis two non-linear parameters (LZ-Bin and LZ-Multi) presented significant differences ($p < 0.05$) between groups of women who delivered in <7 days vs.>7 days and four non-linear parameters for whole EHG window analysis (SpEntr, Time Rev, LZ-Bin and LZ-Multi). It point out that whole EHG window analysis could be used to predict preterm labor under common clinical conditions with better performance than the classical EHG-burst analysis. Since this method does not require EHG burst annotation, this together with automatic detector of mother and fetal motion artifact and respiration interference in EHG recording, could be used to develop a preterm labor prediction system in real time based on EHG and therefore may facilitate the translation of the EHG technique to clinical praxis.

Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

REFERENCES

1. Aboy M, Cuesta-Frau D, Austin D, Micó-Tormos P (2007) Characterization of sample entropy in the context of biomedical signal analysis. Annu Int Conf IEEE Eng Med Biol - Proc 5942–5945. doi: 10.1109/IEMBS.2007.4353701

2. Aboy M, Hornero R, Abásolo D, Álvarez D (2006) Interpretation of the Lempel-Ziv complexity measure in the context of biomedical signal analysis. IEEE Trans Biomed Eng 53:2282–2288. doi: 10.1109/TBME.2006.883696

3. Chkeir A, Fleury MJ, Karlsson B, et al (2013) Patterns of electrical activity synchronization in the pregnant rat uterus. Biomed 3:140–144. doi: 10.1016/j.biomed.2013.04.007

4. Crandon AJ (1979) Maternal anxiety and neonatal wellbeing. J Psychosom Res 23:113–115. doi: 10.1016/0022-3999(79)90015-1

5. Devedeux D, Marque C, Mansour S, et al (1993) Uterine electromyography: A critical review. Am J Obstet Gynecol 169:1636–1653. doi: 10.1016/0002-9378(93)90456-S

6. Fele-Žorž G, Kavšek G, Novak-Antolič Ž, Jager F (2008) A comparison of various linear and non-linear signal processing techniques to separate uterine EMG records of term and pre-term delivery groups. Med Biol Eng Comput 46:911–922. doi: 10.1007/s11517-008-0350-y

7. Fergus P, Cheung P, Hussain A, et al (2013) Prediction of Preterm Deliveries from EHG Signals Using Machine Learning. PLoS One. doi: 10.1371/journal.pone.0077154

8. Garfield RE, Maner WL (2006) Biophysical methods of prediction and prevention of preterm labor: uterine electromyography and cervical light-induced fluorescence – new obstetrical diagnostic techniques. In: Preterm Birth. pp 131–144

9. Garfield RE, Maner WL (2007) Physiology and electrical activity of uterine contractions. Semin Cell Dev Biol 18:289–295. doi: 10.1016/j.semcdb.2007.05.004

10. Garfield RE, Maner WL, MacKay LB, et al (2005) Comparing uterine electromyography activity of antepartum patients versus term labor patients. Am J Obstet Gynecol 193:23–29. doi: 10.1016/j.ajog.2005.01.050

11. Goldenberg RL, Culhane JF, Iams JD, Romero R (2008) Epidemiology and causes of preterm birth. Lancet 371:75–84. doi: 10.1016/S0140-6736(08)60074-4

12. Gynecologists AC of O and (2012) ACOG practice bulletin no. 127: Management of preterm labor. Obstet Gynecol 119:1308–1317. doi: 10.1097/AOG.0b013e31825af2f0

13. Hadar E, Biron-Shental T, Gavish O, et al (2015) A comparison between electrical uterine monitor, tocodynamometer and intra uterine pressure catheter for uterine activity in labor. J Matern Neonatal Med 28:1367–1374. doi: 10.3109/14767058.2014.954539

14. Hans P, Dewandre P, Brichant JF, Bonhomme V (2005) Comparative effects of ketamine on Bispectral Index and spectral entropy of the electroencephalogram under sevoflurane anaesthesia. Br J Anesth 94:336–340. doi: 10.1093/bja/aei047

15. Hassan M, Terrien J, Marque C, Karlsson B (2011) Comparison between approximate entropy, correntropy and time reversibility: Application to uterine electromyogram signals. Med Eng Phys 33:980–986. doi: 10.1016/j.medengphy.2011.03.010

16. Hassan M, Terrien J, Muszynski C, et al (2013) Better pregnancy monitoring using nonlinear correlation analysis of external uterine electromyography. IEEE Trans Biomed Eng 60:1160–1166. doi: 10.1109/TBME.2012.2229279

17. Horoba K, Jezewski J, Matonia A, et al (2016) Early predicting a risk of preterm labour by analysis of

antepartum electrohysterograhic signals. Biocybern Biomed Eng 36:574–583. doi: 10.1016/j.bbe.2016.06.004

18. Lawn JE, Wilczynska-Ketende K, Cousens SN (2006) Estimating the causes of 4 million neonatal deaths in the year 2000. Int J Epidemiol 35:706–718. doi: 10.1093/ije/dyl043

19. Lemancewicz A, Borowska M, Kuć P, et al (2016) Early diagnosis of threatened premature labor by electrohysterographic recordings - The use of digital signal processing. Biocybern Biomed Eng 36:302–307. doi: 10.1016/j.bbe.2015.11.005

20. M L, WL M, LR C (2012) Noninvasive Uterine Electromyography For Prediction of Preterm Delivery. Am J Obs Gynecol 204:1–20. doi: 10.1016/j.ajog.2010.09.024.Noninvasive

21. Maner WL, Garfield RE (2007) Identification of human term and preterm labor using artificial neural networks on uterine electromyography data. Ann Biomed Eng 35:465–473. doi: 10.1007/s10439-006-9248-8

22. Maner WL, Garfield RE, Maul H, et al (2003) Predicting Term and Preterm Delivery With Transabdominal Uterine Electromyography. Obstet Gynecol 101:1254–1260. doi: 10.1016/S0029-7844(03)00341-7

23. Marque C, Gondry J (1999) Use of the electrohysterogram signal for characterization of contractions during pregnancy. IEEE Trans Biomed Eng 46:1222–1229.

24. Maul H, Maner WL, Olson G, et al (2004) Non-invasive transabdominal uterine electromyography correlates with the strength of intrauterine pressure and is predictive of labor and delivery. J Matern Neonatal Med 15:297–301. doi: 10.1080/14767050410001695301

25. Most O, Langer O, Kerner R, et al (2008) Can myometrial electrical activity identify patients in preterm labor? Am J Obstet Gynecol 199:378. doi: 10.1016/j.ajog.2008.08.003

26. Petrou S (2005) The economic consequences of preterm birth duringthe first 10 years of life. BJOG An Int J Obstet Gynaecol 112:10–15. doi: 10.1111/j.1471-0528.2005.00577.x

27. Rabotti C, Sammali F, Kuijsters N, et al (2015) Analysis of uterine activity in nonpregnant women by electrohysterography: A feasibility study. In: Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS. pp 5916–5919

28. Schlembach D, Maner WL, Garfield RE, Maul H (2009) Monitoring the progress of pregnancy and labor using electromyography. Eur J Obstet Gynecol Reprod Biol 144:2–8. doi: 10.1016/j.ejogrb.2009.02.016

29. Sikora J, Matonia A, Czabański R, et al (2011) Recognition of premature threatening labour symptoms from bioelectrical uterine activity signals. Arch Perinat Med 17:97–103.

30. Vinken MPGC, Rabotti C, Mischi M, et al (2010) Nifedipine-induced changes in the electrohysterogram of preterm contractions: feasibility in clinical practice. Obstet Gynecol Int 2010:325635. doi: 10.1155/2010/325635

31. Vrhovec J, Lebar AM (2012) An Uterine Electromyographic Activity as a Measure of Labor Progression. Appl EMG Clin Sport Med 243–268. doi: 10.5772/25526

32. Vrhovec J, Macek-Lebar A, Rudel D (2007) Evaluating Uterine Electrohysterogram with Entropy. 11th Mediterr Conf Med Biomed Eng Comput 144–147. doi: 10.1007/978-3-540-73044-6_36

33. Ye-Lin Y, Bueno-Barrachina JM, Prats-boluda G, et al (2017) Wireless sensor node for non-invasive high precision electrocardiographic signal acquisition based on a multi-ring electrode. Measurement 97:195–202. doi: 10.1016/j.measurement.2016.11.009

34. Ye-Lin Y, Garcia-Casado J, Prats-Boluda G, et al (2014) Automatic identification of motion artifacts in EHG recording for robust analysis of uterine contractions. Comput Math Methods Med. doi: 10.1155/2014/470786

35. Zhang XS, Roy RJ, Jensen EW (2001) EEG complexity as a measure of depth of anesthesia for patients. IEEE Trans Biomed Eng 48:1424–1433. doi: 10.1109/10.966601

List of Figures

Fig. 1. Histograms of the obstetrical information collected from the included patients.

Fig. 2. Distribution of all included registers in the different groups according to their time to delivery in days.

Fig. 3. Electrode configuration for EHG acquisition, in combination with TOCO and ultrasound for fetal monitoring.

Fig. 4. Diagram of the methodology employed to obtain EHG parameters for both types of analysis performed, EHG-burst analysis (A) and whole EHG window analysis (B). Where V_i are the analysis windows for the whole EHG windows analysis with a fixed duration of 120 s.

Fig. 5. EHG recordings from women with threatened preterm labor for the different groups according to their TTD: G1 (A), G2 (B), G3 (C) and G4 (D).

Fig. 6. Evolution of median values of EHG parameters according to their time to delivery, EHG-burst parameters are represented in gray and whole EHG window analysis in dark lines. '○' means statistical significant difference ($p < 0.05$) were obtained for the parameter in the EHG-burst analysis and '●' represents statistically significant differences when parameters are worked out in the whole EHG window analysis. Blue braces indicate significant differences between G5 (TTD> 7) and G1 (TTD< 7) and the black ones indicate significant differences between the rest of the groups.

List of Tables

Table 1. Patients' Obstetrical information.

Table 2. Mean and standard deviation of EHG-burst parameters in each group.

Table 3. Mean and standard deviation of EHG complete record analysis parameters in each group.

Fig. 1. Histograms of the obstetrical information collected from the included patients.

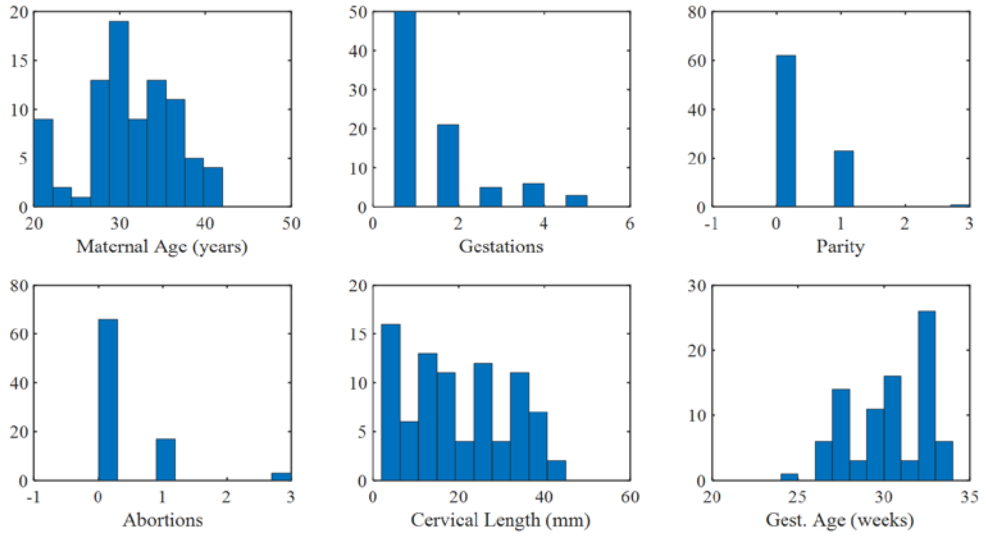


Fig. 2. Distribution of all included registers in the different groups according to their time to delivery in days.

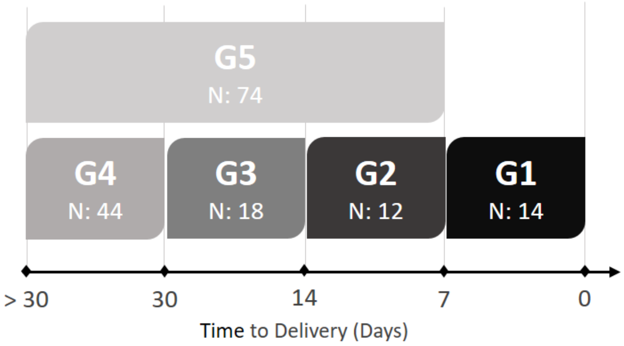


Fig. 3. Electrode configuration for EHG acquisition, in combination with TOCO and ultrasound for fetal monitoring.

Fig. 4. Diagram of the methodology employed to obtain EHG parameters for both types of analysis performed, EHG-burst analysis (A) and whole EHG window analysis (B). Where V_i are the analysis windows for the whole EHG windows analysis with a fixed duration of 120 s.

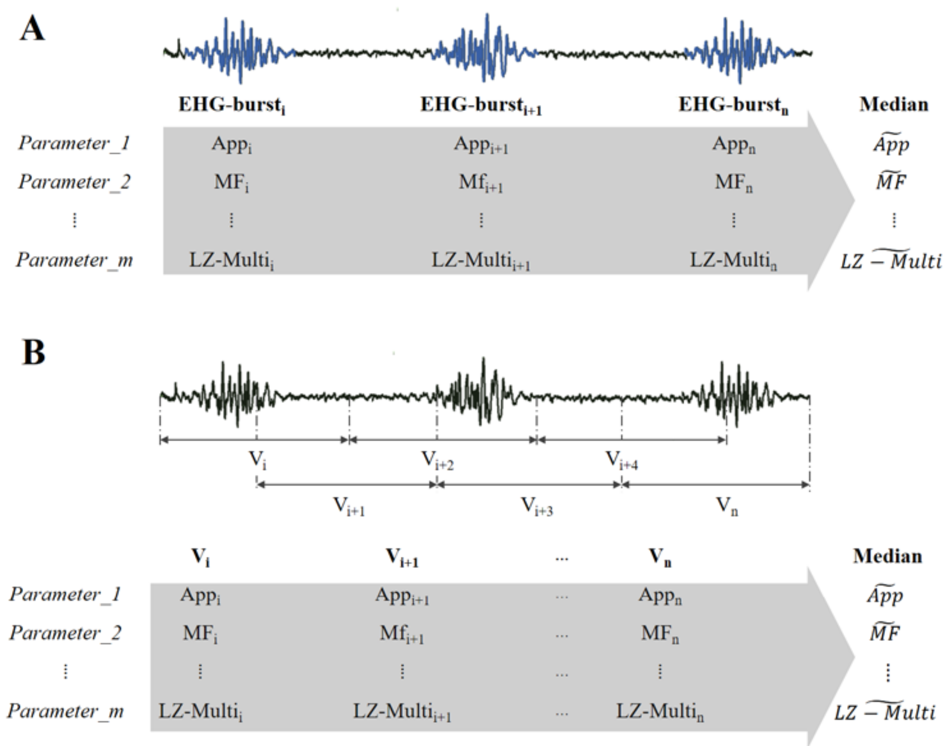


Fig. 5. EHG recordings from women with threatened preterm labor for the different groups according to their TTD: G1 (A), G2 (B), G3 (C) and G4 (D).

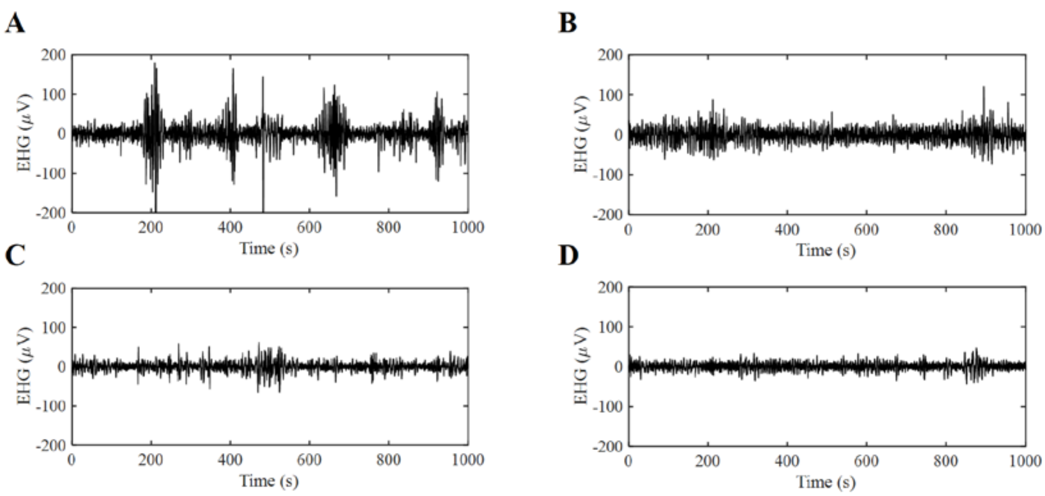


Fig. 6. Evolution of median values of EHG parameters according to their time to delivery, EHG-burst parameters are represented in gray and whole EHG window analysis in dark lines. '○' means statistical significant difference ($p < 0.05$) were obtained for the parameter in the EHG-burst analysis and '●' represents statistically significant differences when parameters are worked out in the whole EHG window analysis. Blue braces indicate significant differences between G5 (TTD> 7) and G1 (TTD< 7) and the black ones indicate significant differences between the rest of the groups.

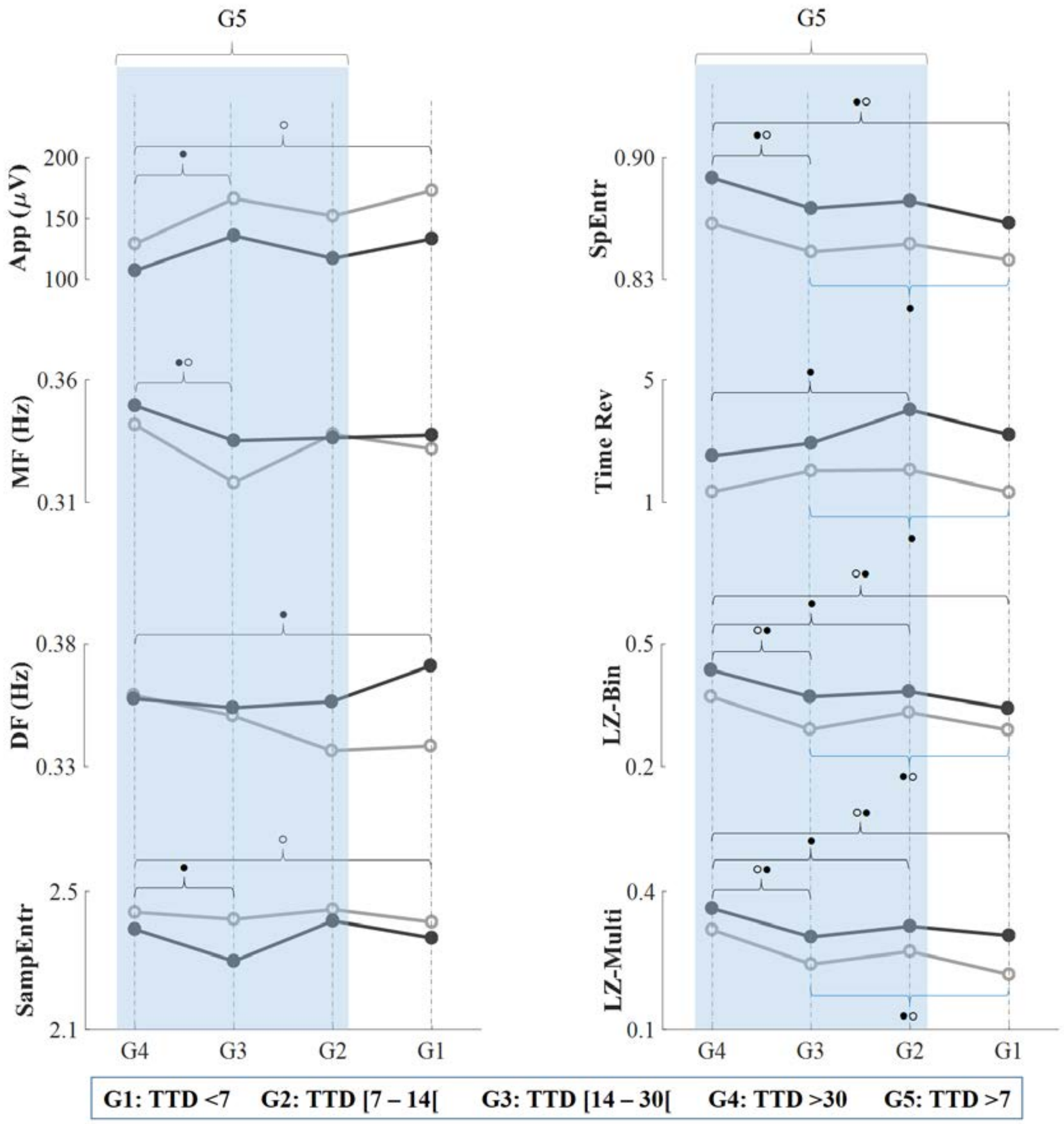


Table 1: Patients' Obstetrical information.

		G1 **<7 days**	**G2** **[7-14[**	**G3** **[14-30[**	**G4** **>30 days**	**G5** **>7 days**
Maternal Age (years)		30.9 ± 4.7	25.7 ± 4.9	33.6 ± 3.9	31.3 ± 5.4	26.7 ± 9.9
Gestations		2.0 ± 1.5	1.5 ± 1.1	1.7 ± 0.9	1.6 ± 0.7	1.62 ± 1.14
Parity		0.4 ± 0.9	0.3 ± 0.4	0.4 ± 0.5	0.3 ± 0.4	0.32 ± 0.62
Abortions		0.33 ± 0.89	0.27 ± 0.47	0.22 ± 0.43	0.28 ± 0.45	0.26 ± 0.41
Cervical Length (mm)		9.8 ± 6.5	13.1 ± 5.8	25.6 ± 10.6	21.9 ± 13.4	19.3 ± 14.6
Gest. Age (weeks)		32.0 ± 2.5	31.1 ± 2.2	32.3 ± 1.4	29.7 ± 2.1	31.8 ± 2.2
ATB (Tocolytic) Classification. Number of records	***Without***	1	0	0	6	6
	Under	4	5	6	15	26
	Post	9	7	12	23	42
	Total	14	12	18	44	74

Table 2. Mean and standard deviation of EHG-bursts' parameters in each group.

	G1	***G2***	***G3***	***G4***	***G5***
App (µV)	188.2 ± 95.6	159.3 ± 63.0	176.1 ± 57.6	136.1 ± 63.0	151.1 ± 63.1
MF (Hz)	0.312 ± 0.03	0.317 ± 0.02	0.305 ± 0.03	0.330 ± 0.04	0.318 ± 0.03
DF (Hz)	0.349 ± 0.03	0.344 ± 0.04	0.360 ± 0.03	0.366 ± 0.04	0.364 ± 0.04
SampEntr	2.32 ± 0.71	2.45 ± 0.03	2.32 ± 0.30	2.41 ± 0.15	2.39 ± 0.20
SpEntr	0.846 ± 0.027	0.854 ± 0.011	0.850 ± 0.030	0.862 ± 0.022	0.861 ± 0.02
Time Rev	2.17 ± 5.8	2.59 ± 1.05	2.25 ± 1.41	2.14 ± 2.56	2.28 ± 2.08
LZ-Bin	0.29 ± 0.05	0.32 ± 0.04	0.30 ± 0.07	0.38 ± 0.07	0.35 ± 0.07
LZ-Multi	0.22 ± 0.07	0.27 ± 0.03	0.25 ± 0.06	0.32 ± 0.07	0.29 ± 0.07

Table 3. Mean and standard deviation of EHG complete record analysis parameters in each group.

	G1	***G2***	***G3***	***G4***	***G5***
App (µV)	144.9 ± 74.5	129.5 ± 61.5	145.2 ± 47.1	128.1 ± 92.6	132.5 ± 78.9
MF (Hz)	0.322 ± 0.02	0.316 ± 0.02	0.331 ± 0.02	0.348 ± 0.02	0.332 ± 0.02
DF (Hz)	0.373 ± 0.03	0.359 ± 0.01	0.356 ± 0.01	0.367 ± 0.03	0.360 ± 0.02
SampEntr	2.17 ± 0.34	2.35 ± 0.2	2.14 ± 0.37	2.33 ± 0.17	2.28 ± 0.25
SpEntr	0.867 ± 0.016	0.875 ± 0.010	0.876 ± 0.025	0.891 ± 0.020	0.88 ± 0.02
Time Rev	3.44 ± 1.81	4.31 ± 1.10	3.20 ± 1.49	2.89 ± 1.55	3.62 ± 1.52
LZ-Bin	0.36 ± 0.05	0.38 ± 0.03	0.39 ± 0.07	0.44 ± 0.07	0.42 ± 0.07
LZ-Multi	0.30 ± 0.04	0.32 ± 0.02	0.31 ± 0.05	0.35 ± 0.05	0.34 ± 0.05

492

Brief biography

Mr. Javier Mas-Cabo

Received the Engineer degree in Industrial engineering & the MSc. in Biomedical Engineering, from the Universitat Politècnica de València, Spain, in 2014 and 2016.

Dr. Gema Prats-Boluda

MSc Industrial Engineering, PhD Electronic Technology, UPV 2001 and 2009. Associate professor and researcher at UPV. Her research is focused on sensors, instrumentation, processing and remote sensing of biosignals

Dr. Alfredo Perales

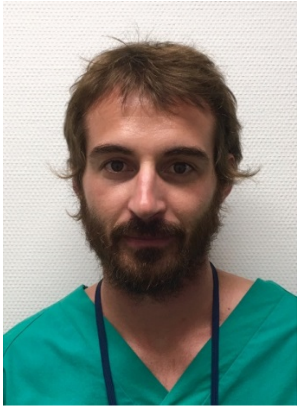
Professor of Obstetrics & Gynecology, Medical School University of Valencia. Chairman of Obstetric and Gynecology dept, UP Hospital La Fe. His research is focused on: Prematurity, Preeclampsia prediction, Intrauterine growth restriction and non invasive prenatal test.

Dr. Javier Garcia-Casado

MSc Industrial Engineering, PhD Electronic Technology, UPV 2001 and 2005. His research is focused on instrumentation and analysis of gastrointestinal, uterine and cardiac biomedical signals.

493

Dr. José Alberola Rubio



Mr. Jose Alberola-Rubio. Degree in Computer Science, Biomedical Engineering MSc, Medical PhD. Research interests: biomedical signals processing, electrophysiology, machine learning.

Dr. Yiyao Ye-Lin

Received her PhD from UPV in 2009. She currently works as professor for UPV. Her research interests include biomedical signal processing, pattern analysis, wireless sensor network, biomedical instrumentation.