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Characterization of the effects of Atosiban on uterine electromyograms recorded in women with threatened preterm labor.

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ABSTRACT

Although research studies using electrohysterography on women without tocolytic therapy have shown its potential for preterm birth diagnosis, tocolytics are usually administered in emergency rooms at the first sign of threatened preterm labor (TPL). Information on the uterine response during tocolytic treatment could prove useful for the development of tools able to predict true preterm deliveries under normal clinical conditions. The aim of this study was thus to analyze the effects of Atosiban on Electrohysterogram (EHG) parameters and to compare its effects on women who delivered preterm (WDP) and at term (WDT). Electrohysterograms recorded in different Atosiban therapy stages (before, during and after drug administration) on 40 WDT and 27 WDP were analyzed by computing linear, and non-linear EHG parameters. Results reveal that Atosiban does not greatly affect the EHG signal amplitude, but does modify its spectral content and reduces the energy associated with the fast wave high component in both WDP and WDT, with a faster response in the latter. EHG signal complexity remained constant in WDT, while it increased in WDP until it reached similar values to WDT during Atosiban treatment. The spectral and complexity parameters were able to separate ($p < 0.05$) WDT and WDP prior to and during tocolytic treatment and before and after treatment, respectively. The results pave the way for developing better and more reliable medical decision support systems based on EHG for preterm delivery prediction in TPL women in clinical scenarios.

Keywords: Electrohysterogram, Atosiban, excitability, complexity, preterm labor.

1. INTRODUCTION

1.1. Preterm labor and tocolytic treatment

The World Health Organization defines preterm labor (PL) as all births that take place before the end of the 37th week, or 259 days, of gestation (1). In developed countries the preterm delivery rate is around 10% of total births (2,3) and has risen in most industrialized countries (3). 75% of perinatal mortality is associated with preterm labor, while the survivors have an increased risk of cardiovascular, respiratory, and neurodevelopmental complications and will require monitoring by specialists in the first years of their lives (3,4). All the complications associated with PL entail higher social and economic costs in terms of intensive care and long-term monitoring than term births. Studies carried out in the USA have shown that preterm births can cost up to five times more than term births (4).

While the methods currently used to diagnose PL in clinical practice, such as Bishop Score, fetal fibronectin, cervical length and tocodynamometry are inaccurate and/or subjective (5–7), early detection of spontaneous PL is vital in order to prevent or mitigate the negative consequences of preterm deliveries on newly born infants. Antenatal corticosteroids, which have been shown to reduce neonatal mortality and the multiple complications associated with preterm deliveries, are the best option in such cases (8). However antenatal corticosteroids require at least 48 hours to take effect and lasts up to 7 days, so that one of the aims of tocolytic therapy is to maintain the pregnancy as long as the effects of antenatal corticosteroids last. These drugs also impair microorganisms from the vagina entering the amniotic cavity and help to reduce the risk of infection (9).

A variety of tocolytic drugs with different action mechanisms are now used in clinical practice to prevent PL, such as betamimetics, calcium channel blockers, oxytocin receptors, among others (9). During pregnancy uterine activity is mainly regulated by the balance between progesterone and oxytocin (10). Specifically, oxytocin molecules have proven to be a key factor in the progression or induction of labor, being capable of increasing uterine activity in humans (10,11). In this sense,

Atosiban is a synthetic peptide (desamino-oxytocin analog) that has been shown to be a competitive oxytocin and vasopressin antagonist (11,12). Atosiban, widely used in Europe (9,12), blocks the oxytocin receptors of myometrial cells, inhibiting the release of Ca^{2+} ions into the cytoplasm (9). These $^{+}$ ions play an important role in smooth-muscle cell contractions, as the depolarization phase is mainly due to inward currents of Ca^{2+} and Na^{+} ions (10,13,14). Since Atosiban blocks the oxytocin receptors impairing the entrance of Ca^{2+} ions, it reduces cell excitability, as reported in some *in vitro* studies on human myometrial cells (12).). A reduced excitability involves that myometrial cells will contract less frequently, in lower number and less synchronized (12,15,16). Other studies on humans have also reported reduced uterine activity associated with Atosiban (12,16).

1.2. Electrohysterogram in preterm labor diagnosis

Electrohysterography is a noninvasive tool to characterize the electrophysiological state of the uterus and provide information on labor onset (6,17,18). Uterine myoelectrical activity (electrohysterogram, EHG) is recorded through electrodes on the maternal abdomen (19,20). These recordings can differentiate between the basal tone, associated with the resting state of the uterus, and the EHG-bursts, which represent the electrical activity associated with the contractions of myometrial cells. EHG-bursts have two main components: the fast wave low (FWL) in the [0.13 - 0.26] Hz range associated with EHG propagation, and the fast wave high (FWH), which contains the high frequency content of the EHG signal [0.36 – 0.88] Hz, and has been said to be directly related to myometrial cell excitability (19,21).

Most authors make use of parameters extracted from the EHG for predicting PL, with good classification results, including values of: 0.94 (22), 0.98 (23) and 0.96 (24) for the area under the ROC curves, among others. However, despite their reputed high accuracy, EHG recording protocols and analysis tools are still restricted to the research field (25,26). There are several reasons for this: clinicians are not familiar with the technique and its interpretation, there is no standard regarding

electrode position and configuration, and the recording protocols and devices need to be simplified and made more compact. Another relevant factor is that EHG recordings have always been carried out on women during regular check-ups under physiological conditions (20,26), whilst in clinical practice tocolytic therapies are usually administered at the first signs of TPL.

1.3. Electrohysterogram during tocolytic treatment

Tocolytic drugs are indicated to impair uterine myoelectrical activity. Some authors have found fewer uterine contraction when measured by ultrasound (27), while others have reported a reduction of between 57 - 65 % in uterine activity estimated by external tocodynamometry (11). However, considering only the number of contractions per minute is not enough to evaluate the uterine response to tocolytics or for predicting PL. Some studies describe how different tocolytic agents can affect EHG recordings and analyses (15,16,28), but only analyzed the patients twice: prior to tocolytic drug administration and immediately after the treatment. In addition, no distinction was made between the truly preterm mothers (WDP) and those who finally delivered at term (WDT), thus masking possible differences in their tocolytic response. These limitations are vitally important since tocolytic treatments usually take around 48h. This time lapse is relevant, since detecting false alarms in the early stages of tocolytic administration could save health systems huge amounts of money by avoiding unnecessary hospitalizations and would also improve attention to the truly preterm mothers. Information on the response of WDT and WDP groups to tocolytic drugs could thus be a key factor in developing tools able to predict true preterm deliveries in clinical practice.

In this context, the aim of this work was to characterize and compare the effects of Atosiban on EHG signals recorded in mothers with TPL who truly delivered preterm and those who finally delivered at term.

2. MATERIALS & METHODS

2.1. Subjects and EHG recordings

A total of 146 EHG 30 – 200 min recordings from 86 pregnant women admitted to the "*Hospital Universitario y Politécnico la Fe*" (Valencia, Spain) showing symptoms of TPL were included in this study, which was approved by the Hospital Institutional Review Board and adhered to the Declaration of Helsinki. All the participants were informed of the characteristics of the study and the recording protocol prior to giving their written informed consent. All the subjects presented preterm labor symptoms such as cervical effacement or regular uterine dynamics on admission. Gestational ages ranged between 25 – 36 weeks. Recordings were made under normal clinical conditions i.e. most of the subjects were under the effect of tocolytic therapies. Few of the subjects could be recorded prior to Atosiban administration since tocolytic therapy is mostly administered in the emergency room and maternal-fetal welfare is given priority. Some of the subjects had been remitted from other health centers in which they already received the first dose of Atosiban.

Atosiban was administered by means of an intravenous bolus injection (6.75 mg) for 1 min, followed by 18 mg/h for 3 h and a final maintenance dosage of 6 mg/h for 45 h. The patients were grouped into five different stages according to the time lapse between the EHG recording and the start of Atosiban therapy: S0 (before therapy, <0 h), S1 (1 – 24 h), S2 (24 – 48 h), S3 (48 – 72 h) and S4 (>72 h).

All the patients were followed up until delivery. Excluding criteria were: non spontaneous labor initiation (21/146), preterm membrane rupture (10/146) and multiple gestations (5/146). 110 of 146 EHG recordings from 67 patients were included in the EHG analysis. In all cases Atosiban achieved short-term success, i.e. none of the patients delivered <48h after initiation of the therapy, although 27/67 women delivered preterm (WDP group) and 40/67 delivered at term (WDT group). Figure 1 shows the EHG recording cohorts, separating term and preterm deliveries in each therapy stage. Further obstetrical information on the subjects is shown in Table 1, including maternal age, gestational age, previous gestations and cervical length.

The abdominal skin was carefully prepared to reduce skin-electrode impedance prior to recording by Nuprep abrasive paste. Two disposable monopolar Ag/AgCl electrodes (3M red dot 2560) were symmetrically positioned with respect to the median axis over the umbilicus, with a distance of 8 cm between electrodes (See Figure 2). Two disposable electrodes were also placed on the subjects' hips as reference and ground electrodes. This configuration was chosen to simplify the acquisition protocol and to allow simultaneous clinical recordings by other devices, such as TOCO or ultrasound monitor, as shown in Figure 2. A custom-made wireless recording module was used to acquire the bioelectrical signals, providing a 2059 V/V gain in the 0.1 to 150 Hz band and digitalizing the monopolar signals by a 24 bit ADC at 500 Hz (29).

2.2. EHG signals analysis

Since most of the EHG spectral content distributes between 0.1 to 4 Hz range (18) monopolar EHG signals (M1 and M2, see Figure 2) were digitally filtered in that range (zero-phase 5^{th} order Butterworth band-pass filter), and then downsampled at 20 Hz so as to maintain the trade-off between temporal resolution and computational cost. Once the monopolar signals were conditioned, a bipolar signal was calculated as their difference to reduce common-mode interferences and increase signal quality (30).

In this work whole EHG window analysis was used to characterize the EHG signals rather than EHG burst analysis because - it greatly simplifies the segmentation process; - previous results reveal that this kind of analysis outperforms EHG-burst one in providing information about labor horizon (31); this kind of analysis would be easier to implement on real time systems that provide bedside results.

The EHG segments were divided into 120 s windows with a 50% overlap. This selection was based on a previous work that compared different window length (1 min, 2 min, 5 min and 10 min) to differentiate EHG signal of patients who finally delivered in less than 7 days from those who delivered in more, attempting to maintain a trade-off between computational cost and the amount of discarded data (31).

The EHG parameters were calculated in each window. The median value of all the analysis windows of the EHG recordings was then calculated to obtain a single representative value of each parameter and recording. Figure 3 contains an explanatory diagram of the entire analysis.

A set of EHG parameters was selected to determine the effects of Atosiban on uterine myoelectrical activity in the WDT and WDP groups, including temporal, spectral and non-linear features: peak to peak amplitude (18), H/L ratio and Lempel-Ziv complexity (32). Peak to peak amplitude, directly related to the intensity of uterine contractions, is one the most widely used parameters for EHG characterization (18). As the spectral parameters can also be used to evaluate cell excitability (21), a high to low energy ratio parameter (H/L Ratio) was calculated to consider this aspect. The H/L Ratio represents the relation between the FWH energy computed in (0.34-1 Hz) with respect to the FWL energy computed in (0.2-0.34 Hz) so as to minimize the influence of cardiac interference and baseline fluctuation and is defined as:

$$H/_L\ Ratio = \frac{\sum_{0.34}^{1} PSD}{\sum_{0.2}^{0.34} PSD} \quad (1)$$

Non-linear parameters have been widely used in EHG studies to characterize the electrophysiological state of the uterus and obtain information on the labor time horizon (33). In a previous study, various non-linear parameters have been used to characterize EHG signals recorded from women with threatened preterm labor (under tocolytic treatment): sample entropy, spectral entropy, Time reversibility and Lempel-Ziv complexity (31). We found that Lempel-Ziv was the most reliable parameter for discriminating women who delivered <7 days from the others (31). So as to compute the Lempel-Ziv complexity, the signal is firstly converted into a binary sequence, by using the median value as threshold, given its robustness to outlier values (32). The resulting sequence is scanned from left to right, increasing the complexity counter by one unit every time a new subsequence is encountered. Higher Lempel-Ziv values involve more complex patterns close to randomness, and in contrast low values are related with more organized or less complex signals (32,34). In this work,

Lempel-Ziv complexity was computed in the whole EHG bandwidth (0.1- 4 Hz) since it has been proven in a previous study (31) to better discriminate patients who finally delivery at term from the preterm ones when compared with other analyzed bandwidths: 0.34-4 Hz, 0.34-1 Hz.

A two-sided comparison by the Wilcoxon statistical test ($\alpha = 0.05$) was performed to assess the differences between the EHG parameters. The WDT and WDP recordings were first compared in each Atosiban administration stage (S0, S1, S2, S3 and S4), and then those from all the Atosiban stages of the same group were also compared. No significant differences were found for any obstetrical feature when those included in Table 1 were compared in the same way.

3. RESULTS

Figure 4 shows the evolution of the EHG parameters during early Atosiban administration, corresponding to the transition from stage S0 to stage S1, for a preterm and term delivery. It can be seen that the EHG amplitude is always higher for the former than the latter, there is no conclusive amplitude trend for either case and in both cases the H/L Ratio decreased during Atosiban administration. WDT had a steeper H/L Ratio drop response in the first 15 minutes, followed by a monotonical decrease and a smaller slope (similar to that of WDT) during the 18 mg/h Atosiban treatment. WDP had higher H/L ratio values than WDT during the entire recording and also higher initial Lempel-Ziv complexity values, this latter indicating a less coordinated and organized EHG signal. WDT did not seem to be greatly affected by the tocolytic therapy in this case, although WDP showed a remarkable increase in the Lempel-Ziv index during the first 15-20 minutes of Atosiban administration, after which the values and trend became similar to those of WDT.

Figure 5 shows a longitudinal study of three EHG recordings with their associated power spectrum densities (PSD) and Lempel-Ziv values of two single patients (WDP & WDT) at different stages of Atosiban administration. In both cases the signal´s amplitude has no large variations between stages S0, S2 and S4 stages. High frequency components (0.34 - 1 Hz) can be appreciated in the signal PSDs

200 of stage S0 recordings i.e. before Atosiban administration in both WDP and WDT. In S2 there are
201 fewer high frequency components. Note that the recording of the WDP was performed 42 h after the
202 tocolytic treatment for the preterm labor patient. That is, in this particular case the recording was
203 performed close to stage S3 which may explain the visually significant drop of the high frequency
204 spectral content. In stage S4, i.e. recordings taken more than 72h after Atosiban administration, when
205 the effects of the drug are weaker, the high frequency components can be seen again. WDP Lempel-
206 Ziv complexity has a low value in S0, which is associated with the more organized and coordinated
207 signals close to labor. After administering Atosiban the Lempel-Ziv complexity greatly increases its
208 value in S2. In S4 it still has a similar complexity level. WDT signal complexity already shows a higher
209 initial complexity value during stage S0 and so is not greatly affected by the tocolytic.

210 Figure 6 contains the violin-plots and median values (squares) of each EHG parameter in the different
211 Atosiban stages for both term and preterm groups. In contrast to Figures 4 and 5, which give the
212 Atosiban response of individual patients, Figure 6 includes information on the global response of all
213 the WDT and WDP to Atosiban during the different stages. Significant differences between the term
214 and preterm groups in the same stage are indicated in the tables above the violins, while the significant
215 differences between the stages for the same WDP or WDT group are given above and below the
216 violins, respectively. Both term and preterm groups show a similar signal amplitude evolution. This
217 dropped slightly in S1, rapidly increased in S2 and S3 and fell again after 72h of drug administration
218 (S4). No significant differences were found between the term vs preterm groups in any drug stage.

219 The median values of the H/L Ratio for the preterm group were higher than those of the term group in
220 all the stages and were statistically significant for S0, S1 and S2. These differences are noteworthy
221 since they could be used to differentiate WDT and WDP before and during Atosiban treatment. The
222 median values of the H/L ratio also show different trends. The WDT H/L ratio suddenly fell to its
223 minimum value in S1 (first 24h of tocolytic therapy) while the median WDP value was even higher in
224 S1 than S0 and fell to its minimum value in stage S3. This response can also be appreciated in the

significant differences among the stages ($p < 0.05$). S0 was significantly different to S1 and S2 for WDT (rapid response) but not for WDP. In this latter group, the sustained significant differences were 'delayed' in S1 vs S2, S3 and S4, suggesting WDT had a faster response to the tocolytic drug than WDP. This was also seen in the individual case shown in Figure 4, where the WDP took longer to reduce the H/L Ratio values than the WDT. After 72h of drug administration the H/L ratio increased in both groups, indicating a similar total duration of the effects of Atosiban.

EHG signal complexity showed significantly higher values for WDT than WDP in S0. The higher EHG signal complexity or signal disorder may suggest that the uterine status of these patients indicates a longer time to delivery. This result agrees with the individual response shown in Figures 4 and 5, where the WDP (close to labor) showed lower Lempel-Ziv values than WDT before Atosiban administration. Again, this could be of great interest to discriminate between term and preterm deliveries. The Lempel-Ziv also showed different trends in the two groups studied. The WDT median Lempel-Ziv values were not greatly affected during drug administration, presenting no significant differences between any stages. The WDP Lempel-Ziv increased significantly in the first 24h after Atosiban administration. Significant differences with S0 values were maintained until 72h after administration. Similar values were obtained after this increase (S1-S3) for both WDP and WDT, probably associated with the successful avoidance of imminent delivery. After 72h of therapy the WDP Lempel-Ziv parameter fell significantly (S4 in comparison with S3, S2 and S1) and reached a similar median value to S0, seeming to point to the end of the drug's effect on the preterm labor cases.

4. DISCUSSION

Obstetrics urgently needs to be able to predict whether women with TPL in normal clinical conditions will have true preterm deliveries. Most EHG studies on predicting preterm labor are carried out during regular check-ups and have not considered the influence of tocolytic therapies. Precise information on the effects of these therapies on electrohysterographic signals could lead to more reliable labor

prediction systems, improve maternal-fetal wellbeing and avoid unnecessary hospitalizations. In the present study temporal, spectral and non-linear parameters were used to evaluate the effect of Atosiban on uterine myoelectrical activity on WDT and WDP groups, unlike previous studies that analyzed patients only before and after tocolytic drug administration (≈ 48h) (9,16,28). This study included a detailed analysis of the effect of the tocolytic agent in different stages of the treatment, separating term from preterm patients to obtain information on the physiological response to Atosiban, which could permit a more accurate interpretation of the EHG signal in a clinical context. It also paves the path for the development of specific expert systems based on EHG signals that consider the Atosiban stage that would permit more reliable preterm labor prediction.

Similar EHG signal amplitude, trends and values were obtained for WDP and WDT during Atosiban treatment. Amplitude stayed almost constant during the first 24h of therapy, increased between 24 and 72h and then decreased for both term and preterm groups. Kandil et al (15) recorded EHG in the same pregnant women before and after treatment with hexoprenaline sulphate and found reduced EHG signal amplitude, burst duration and frequency of occurrence in women in which tocolysis was effective in prolonging pregnancy by at least 48 h. The women who failed to respond to tocolysis (labor in less than 48h) had neither reduced EHG amplitude nor burst duration after the treatment. In the present work tocolysis was effective in all the women studied, which according to Kandil's results would mean reduced signal amplitude during therapy. As the present work was a cross-sectional study and there was wide variation in the amplitude values, the significance of this parameter is limited. Amplitude strongly depends on the recording conditions and individual factors such as skin impedance and the thickness of the fat layer (35,36), so that it is reasonable to expect masked trends and overlapping distributions when grouping different subjects. In this sense, some non-invasive measures, such as the BMI, may provide indirect information about fat layer that could be used for amplitude normalization. However, BMI could be inaccurate or non-representative of the fat content in pregnant women because the weight is greatly influenced by the fetus development. Therefore, EHG amplitude

values are not usually normalized. Instead of using amplitude normalization techniques, most authors prefer to use other features for characterizing the EHG signal, such as spectral or non-linear parameters, which have proven to be less sensitive to bioelectrical recording amplitude.

In the spectral content distribution of uterine myoelectrical signals a marked trend towards lower frequencies was found during Atosiban therapy. This is probably due to the fact that Atosiban actively reduces cell excitability by blocking oxytocin receptors (11,12). This blocking turns into a decrease of the high frequency content (FWH energy) and thus a drop of the H/L Ratio. These results are in agreement with the reduced EHG peak frequency reported by Vinken et al in women treated with Nifedipine. They found lower PSD peak frequency values for signals recorded within 15 min after administration of Nifedipine than those obtained before the drug treatment (28). They also reported higher peak frequency values in patients recorded within 24h after starting Nifedipine (S1 in the present study) against those recorded 24h after finishing the tocolytic treatment (S4 here). In the present work, EHG was recorded in a wider range of treatment stages and this shift towards lower frequency content was seen to be 'delayed' in the WDP group. This delay in the reduction of high frequency EHG components in preterm women could be directly related to the number of oxytocin receptors expressed by myometrial cells. It is reasonable to expect more receptors in WDP than WDT myometrial cells, since labor is closer (see time to delivery in Table 1) (10,12), which means that Atosiban takes longer to block all the oxytocin receptors and inhibit cell excitation. Should this different trend be confirmed in a larger database, it would support the potential diagnostic value of monitoring this EHG parameter during the first few hours of tocolytic treatment.

Vinken et al (28) also report a higher average PSD peak EHG frequency recorded 24h after treatment in patients who delivered < 7 days than for >7 days from Nifedipine therapy initiation. This group classification could not be performed in the present work due to a database imbalance. Nevertheless, the higher median H/L Ratio values during all stages of the WDP group (median TTD 10.5 days) compared to WDT group (median TTD 49 days) are in agreement with those reported in (28). It should

also be noted that these differences are reduced after tocolytic therapy (S3 & S4), so that the stage in which the recording takes place could be of great importance for decision support systems when predicting preterm labor.

As far as we know, there are no previous studies which evaluate the effect of Atosiban on the EHG by non-linear parameters. In this work, the regularity of the uterine myoelectrical signal was assessed by computing the Lempel-Ziv parameter. High Lempel-Ziv values involve more complex patterns closer to randomness, and by contrast, low values are related with more organized signals (34,37). Our hypothesis is that EHG signal complexity (LZ value) is associated to the uterine cells' connectivity, which is required to generate synchronized myoelectric activity to expel the fetus during labor. The more synchronized and propagated action potentials (high connectivity between muscular cells) the more organized EHG signals (26,32,38). In this sense, prior to Atosiban administration, the WDP signal complexity was significantly lower than that of WDT, indicating that Lempel-Ziv could be useful in predicting preterm labor in TPL patients not administered Atosiban. Our results showed that no significant changes in LZ parameter were observed in WDT group after drug administration. Women in this group are far from delivery and connectivity between uterine cells is poor; therefore drug administration does not alter this characteristic nor the associated EHG feature (LZ). Whereas in WDP group, lower LZ values before Atosiban administration than in WDT reflect enhanced uterine cells interconnection that could lead to labor in a shorter period of time. During the tocolytic treatment, the amount of propagated action potentials is decreased due to the inhibitory effect of contractile activity of Atosiban, given rise to a more random EHG signal and higher LZ values. This occurs shortly after the first bolus of high concentration of Atosiban (S1), suggesting a faster effect in comparison to what happened with cell excitability and H/L ratio. LZ parameter may not be useful in discriminating between term and preterm deliveries when recordings are made during Atosiban therapy. Twenty-four hours after the end of therapy (72h after initiation), the propagated action potentials were reestablished in preterm labor group, that is, the failure of Atosiban in the longer term could be inferred from the

significantly lower Lempel-Ziv values in the WDP group at this stage. This contrasts with the H/L Ratio, which was able to separate WDT from WDP during the early stages of drug administration, but not in the final stages after the tocolytic treatment.

Finally, it can be said that no significant differences were found between the groups or stages in any of the obstetrical features shown in Table 1 (except those related to time to delivery). The different groups present homogeneous composition from an obstetrical point of view and thus results of EHG features are not biased due to differences in the gestational age at the moment of the recording or any other obstetrical feature. Differences in EHG parameters are then expected to be associated to uterine electrophysiological condition and its response to Atosiban.

Despite the reduced size of our actual database, we tested different classifiers based on logistic regression in order to distinguish between WDT and WDP in each of the different Atosiban stages, and a global classifier which included all the recordings of the database without taking into account in which Atosiban stage the EHG recordings were performed. Preliminary results (not shown) point that best classification performance is obtained for recordings prior to Atosiban administration, followed by stage 1. The worst performance was obtained with the global classifier which does not take into account the Atosiban stage. These results highlight the need to consider the tocolytic treatment stage for contextualizing the EHG signal and features in order to develop reliable medical decision support systems for predicting preterm deliveries in women with threatened preterm labor.

We are actively working to increase the number of TPL patients in different tocolytic stages and extrapolate the conclusions obtained to a global population to further the development of reliable PL prediction tools in normal clinical scenarios.

5. CONCLUSIONS

This paper describes an evaluation of the effects of administering Atosiban on uterine myoelectrical activity in women with TPL, distinguishing between term and preterm deliveries.

Reduced spectral content was found in the fast wave bandwidth in all the women during Atosiban therapy. This therapy took longer to reduce cell excitability in women who delivered preterm, since myometrial cells express more oxytocin receptors in these patients than in those further away from labor. The women who delivered preterm also showed lower signal complexity than those at term before Atosiban and 24h after the end of the therapy. Atosiban was also found to equalize signal complexity in all the women during tocolytic therapy.

The spectral content and the signal complexity level were revealed as potential indicators for separating truly preterm from term deliveries. The different responses to Atosiban of the WDT and WDP groups reported here indicate that the stage in which the recording takes place may have a strong influence on the development and discrimination capability of PL predictive tools, as the perspectives are potentially better in recordings prior to the administration of tocolytics. However, this is uncommon in clinical practice. During the first 48h of treatment, spectral parameters could still be potentially useful to separate term and preterm deliveries. Complexity parameters may not be quite so useful in these tocolytic treatment stages; conversely, 72h after therapy initiation, the complexity parameters could work better than spectral ones to discriminate WDP from WDT. In this sense, the study revealed that WDP showed lower signal complexity than WDT before Atosiban (S0) and 72h after the initiation of Atosiban administration (S4).

When longitudinal measurements can be performed on the same patient, special attention must be paid to this time lapse in order to reduce hospital admissions and avoid repetition of pharmacological doses.

In-depth knowledge of how the recorded EHG is affected by tocolytic therapies will pave the way for improved and more reliable medical decision support systems for predicting preterm deliveries in women with threatened preterm labor.

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Table 1. Obstetrical features of the women in the different stages: Median (Interquartile range).

*In most patients Cervical Length was measured prior to the administration of Atosiban (not when EHG record was performed), since it indicates TPL.

Legend: Wilcoxon statistical tests were performed on the different groups (term and preterm) in all stages (S0, S1, S2, S3 and S4) and on the different stages in each group for all obstetrical features. No significant differences were obtained for any feature during the different stages, except when comparing the time to delivery and the gestational age at the moment of the delivery between WDP and WDT.

Fig. 1: EHG recording cohort in the different stages.

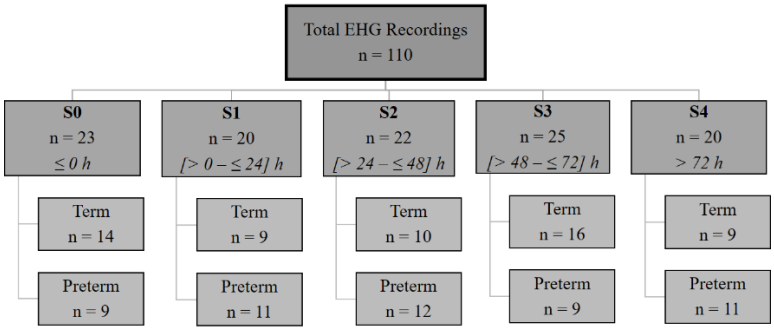


Fig. 2: Signal recording: EHG monopolar channels (M1, M2), ultrasound (US) and tocodynamometry (TOCO).

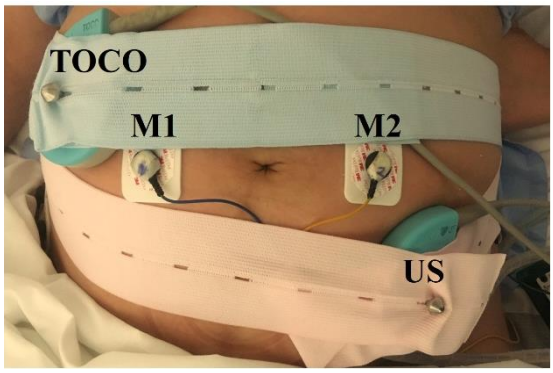


Fig. 3: Diagram of the whole EHG window analysis methodology. The length of each window was fixed to 120 s with a 50% overlap.

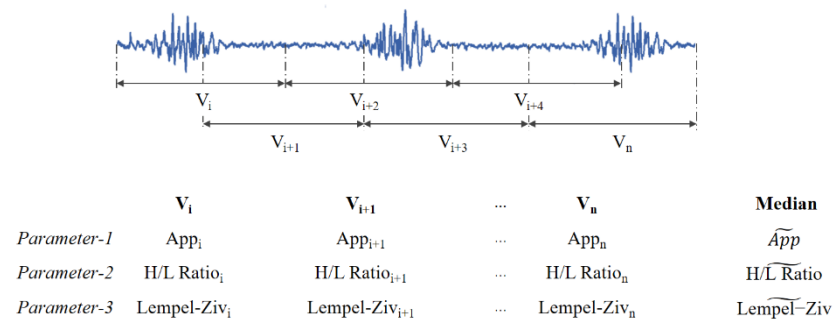
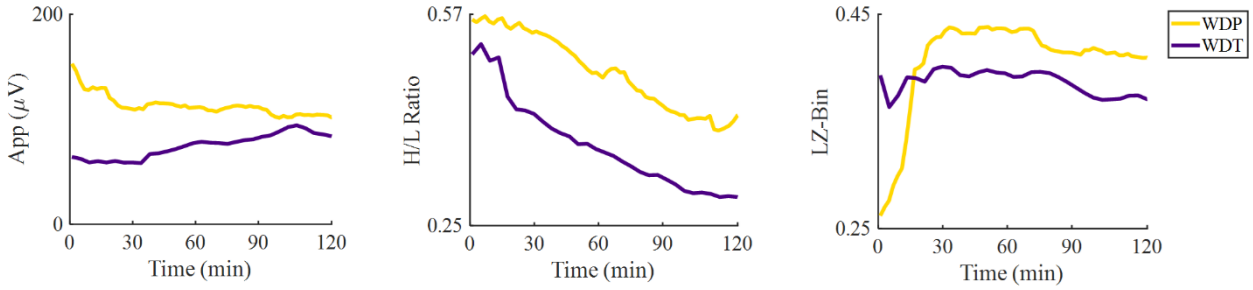


Fig. 4: Evolution of EHG parameters during first hours of Atosiban administration for two different TPL patients, one preterm (yellow) and one term (purple).



Legend: The beginning of Atosiban treatment in the first minutes of the recording. LZ-Bin correspond to the Lempel-Ziv complexity computed by converting the signal into a binary sequence

Fig. 5: EHG recordings carried from two patients, one preterm and one term, their associated PSDs and Lempel-Ziv complexity values in three different stages: S0, S2 and S4 (The elapsed time between Atosiban administration and the EHG recording is indicated by the value in brackets under each stage). Note that PSDs and Lempel-Ziv values are associated to the whole EHG recordings. Shaded region of the PSDs is the Fast Wave High (FWH) bandwidth.

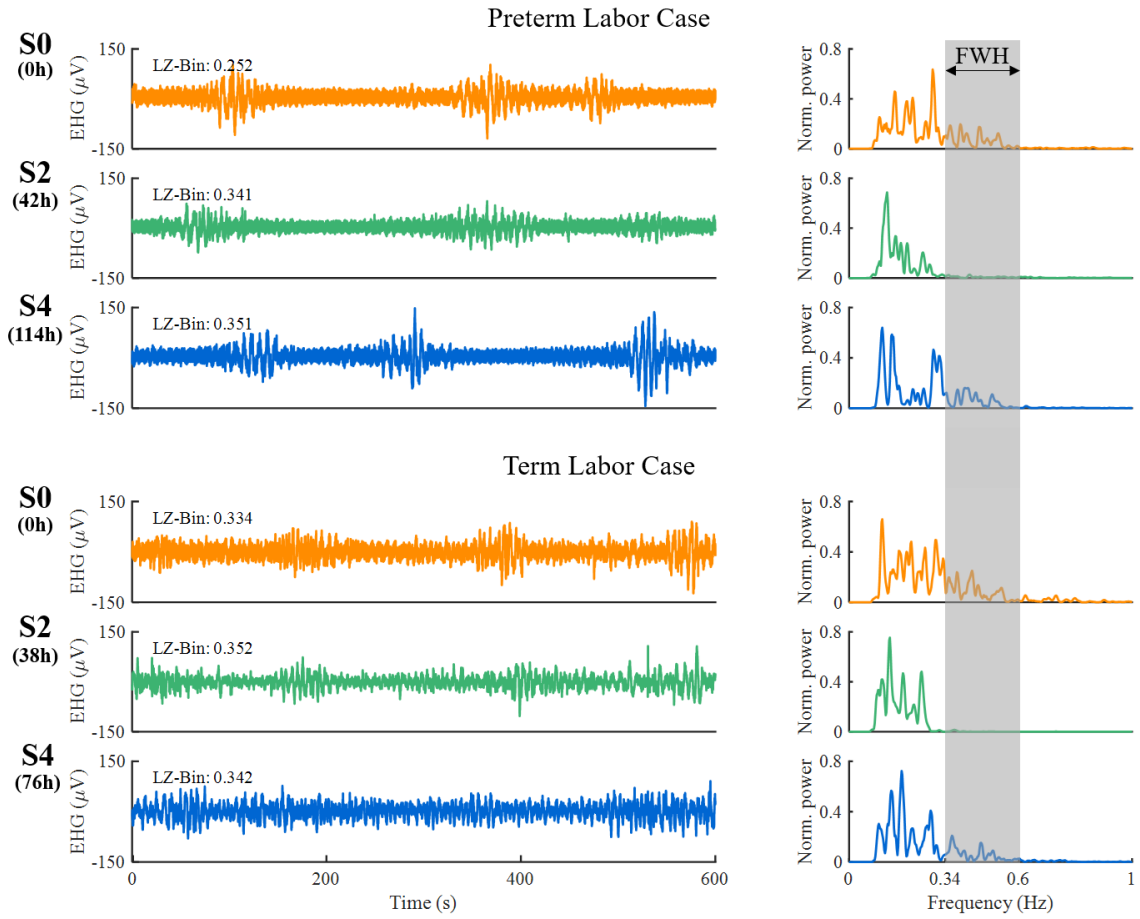
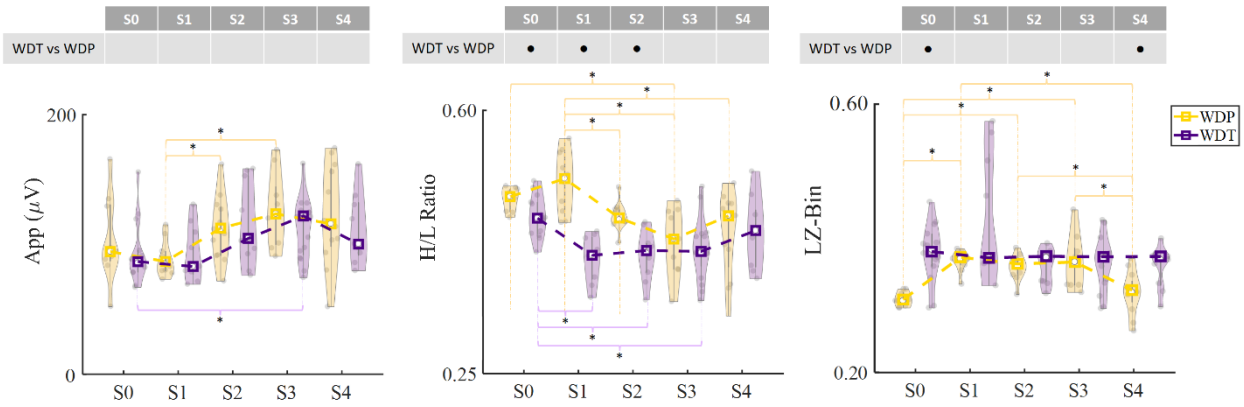


Fig.6: Median value of EHG parameters in the different Atosiban stages, for term (purple) and preterm (yellow) patients. The different stages according to the time lapse between the EHG recording and the initiation of Atosiban therapy are: S0 (before, <0 h), S1 (>0 – 24h), S2 (24 – 48h), S3 (48 -72h) and S4 (>72 h).



Legend: Significant differences between term and preterm groups for all Atosiban administration stages are indicated in the tables (●), and the differences between stages for the same group: WDP or WDT is shown above and below the violins, respectively (*). LZ-Bin correspond to the Lempel-Ziv complexity computed by converting the signal into a binary sequence

536 **Table 1.** Obstetrical features of the women in the different stages: Median (Interquartile range).

	Preterm				
	S0	S1	S2	S3	S4
Maternal Age (years)	29 (7.0)	32 (14.2)	31 (8.0)	34 (13.5)	34 (10.5)
Gestations	1 (1.00)	2 (1.75)	1 (2.00)	1 (1.50)	1 (0.50)
Cervical Length (mm)	11 (18.0)	13 (7.5)	15.5 (10.5)	16 (11.0)	18 (24.5)
Gestational age at Delivery (weeks)	34.0 (1)	34.0 (3.5)	33.0 (1.5)	33 (2.5)	34 (2)
Time to Delivery (Days)	12.5 (28.5)	27 (25)	13.5 (12)	12 (16)	13 (10.5)
Gestational age at Recording (weeks)	33 (3.0)	29 (4.5)	31.5 (3.5)	31 (3.2)	32 (3.0)
	Term				
Maternal Age (years)	36 (15.0)	33 (10.0)	33 (5.0)	34 (6.0)	34 (4.7)
Gestations	2 (1.0)	2 (2.0)	1.5 (2.0)	1.5 (2.0)	1 (0.5)
Cervical Length* (mm)	14 (18)	20 (19)	22 (17)	27.5 (11)	23 (11)
Gestational age at Delivery (weeks)	38.0 (2.0)	38.5 (2)	40.0 (3.0)	39.0 (3.0)	38.0 (1.5)
Time to Delivery (Days)	56.5 (23)	53.5 (27.5)	48 (26)	52 (33)	41 (25)
Gestational age at recording (weeks)	29.5 (4.0)	30.0 (7.0)	32.5 (5.0)	31.5 (5.5)	31.0 (2.2)

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*In most patients Cervical Length was measured prior to the administration of Atosiban (not when EHG record was performed), since it indicates TPL.

Legend: Wilcoxon statistical tests were performed on the different groups (term and preterm) in all stages (S0, S1, S2, S3 and S4) and on the different stages in each group for all obstetrical features. No significant differences were obtained for any feature during the different stages, except when comparing the time to delivery and the gestational age at the moment of the delivery between WDP and WDT.