Characterization of Uterine Response to Misoprostol based on Electrohysterogram

C. Benalcazar Parra[1], R. Monfort-Orti[2], Y. Ye-Lin[1], J. Alberola-Rubio[2], A. Perales Marin[2], J. Mas-Cabo[1], J. Garcia-Casado[1] and G. Prats-Boluda[1]

[1]*Centro de Investigación e Innovación en Bioingeniería, Universidad Politécnica de Valencia, Valencia, Spain*

[2]*Obstetric service, Hospital Universitario y Politécnico La Fe de Valencia, Valencia, Spain*

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Abstract: When the maternal and fetal risks of prolonging gestation are higher than the benefits, labor induction is performed in order to stimulate uterine contractions and to facilitate cervical ripening. Nevertheless, not all cases end up in successful induction leading to an increase in the rate of caesarean sections. The aim of this study was to study the electrophysiological uterine response to misoprostol drug by obtaining and analyzing the evolution of temporal and spectral parameters from uterine electromyogram (electrohysterogram, EHG) records picked up during the first 4 hours of labor induction. Successful inductions showed a progressive increase in amplitude and a frequency shift in spectral content towards higher frequencies approximately 120 min after the initiation of labor induction; such response was not seen in failed inductions. In conclusion, the electrophysiological response caused by effect of misoprostol in pregnant women has been characterized by EHG parameters which showed patterns in their evolution that were different for successful and failed labor inductions. EHG recording and analysis could serve as a very helpful tool to predict the success of labor induction and hence reduce risks and facilitate labor management in this frequent clinical situation.

1 INTRODUCTION

Labor induction is a common practice in obstetrics accounting for 20% of all births (Martin, 2010). It is indicated when the maternal and fetal risks of prolonging gestation are higher than the benefits. It is performed in order to stimulate uterine contractions and to facilitate cervical ripening. However almost 20% of all inductions are associated to caesarean deliveries (Seyb, 1999). Successful induction has been defined as woman achieving active stage of labor within 48 h, although other studies as Gudex et al (Gudex, 1993) define it as vaginal delivery at any moment after the induction of labor. A key factor to reduce the maternal and fetal distress, time and hospital costs is to know whether a woman will reach active stage of labor or not within a few hours of the onset of labor induction.

Assessment of cervical condition is important to estimate successful of labor induction. The common method to assess cervical status and to predict labor induction is by Bishop score (Bishop, 1964). Despite Bishop score is widely used by clinicians, some studies have reported that this score is subjective and with poor reproducibility (Faltin-Traub, 2004). Other studies as Watson et al (Watson, 1996) and Crane et al (Crane, 2004) have proven that the information of cervical length, maternal age, height, weight, parity, and birth weight could be used for predicting labor induction success. Despite all these efforts, no reliable models are available for predicting success of labor induction in the clinical setting.

The characterization of uterus electrophysiological condition may provide additional information for predicting labor induction success. In this respect, electrohysterogram (EHG), which is the recording of the uterine electrical activity on abdominal surface, has been proven to be a promising technique to assess not only the uterine dynamics but also the uterus electrophysiological condition (Garfield, 2007; Schlembach, 2009; Euliano, 2013). To date, no efforts have been made in predicting labor induction success by using EHG records. So as to explore the possibility of predicting labor induction success during the first 4 hours with

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the help of EHG information, the aim of this work was to study the electrophysiological uterine response to labor induction drug (misoprostol) by obtaining and analyzing the evolution of temporal and spectral parameters of EHG.

2 MATERIAL AND METHODS

2.1 Recording Protocol

The study adheres to the Declaration of Helsinki and was approved by the ethics committee of the hospital. All subjects were informed of the nature of the study and signed an informed consent form. Recording sessions were carried out in healthy women with singleton pregnancies who were determined to undergo labor induction at Hospital Universitario y Politécnico La Fe de Valencia. All women underwent labor induction with vaginal insertion of 25 µg of Misoprostol (Misofar, BIAL, Coronado, Portugal) with repeated doses every four hours up to three administrations. The induction was considered successful when woman reaches active stage of labor. Women were divided into successful (GS) and failed induction (GF) groups according to such criterion.

For surface myoelectrical recording, the skin was carefully prepared using an abrasive paste in order to reduce the contact impedance. Subsequently four monopolar Ag/AgCl electrodes were placed on abdominal surface as shown in figure 1: 2 electrodes supraumbilical at each side of the medial line with 8 cm of inter-electrode distance corresponding to EHG monopolar records (M1, M2), 1 reference electrode in the right hip and 1 ground electrode in the left hip. The recorded abdominal signals were amplified and band-pass filtered (0.1-30 Hz) using a commercial biosignal amplifier (Grass 15LT+4 Grass 15A94; Grass Instruments, West Warwick, RI) and digitalized at a sampling rate of 1000 Hz. Simultaneous tocographic signal (TOCO) was obtained by placing a pressure sensor on the abdominal surface and conditioned using monitor Corometrix 250cx series (GE HealthCare, General Electric Company, USA) which sends the data to a personal computer at a sampling rate of 4 Hz. Both signals were stored for subsequent analysis. Each recording session comprises: 30 minutes of basal activity (without drug) and 4 hours after the onset of labor induction. Finally the following obstetrical data were also collected: maternal age, gestational age, body mass index (BMI), gestations, parity, Bishop score, fetal weight and time to delivery from the initiation of the labor induction.

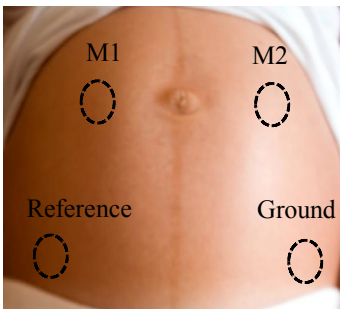

Figure 1: Configuration of surface electrodes for obtaining monopolar EHG recordings (M1, M2).

2.2 Signal Preprocessing and Analysis

Since EHG signal distributes its energy between 0.1 Hz and 4 Hz, a pre-processing step was required. First, monopolar signals were band-pass filtered between 0.1 and 4 Hz in order to remove undesired components. Then signals were down sampled to a sampling rate of 20 Hz to reduce the amount of data and computational cost. Finally, bipolar EHG signal were obtained digitally to reduce common mode interferences as follows:

$$Bip = M2 - M1 \quad (1)$$

Since counting the number of uterine contractions in a period time is traditionally used to study the progress of labor, first of all the number of contractions detected by conventional method (TOCO) and EHG was valued. TOCO contractions were considered when detecting a significant rise in amplitude (>20mmHg) and a minimum duration of 30s. EHG bursts associated to uterine contraction were manually segmented from bipolar signal using the following criteria: burst had to correspond to significant increase in amplitude and/or frequency in comparison to basal activity, present a minimum duration of 30 seconds, and no artifact evidence should have been observed during contraction.

Next, in order to characterize the EHG bursts, a set of temporal and spectral parameters were obtained in the range of (0.2-1Hz) since important information is contained in this range (Garfield, 2007) (Marque, 1986):

- Duration (s)
- Peak to peak amplitude (µV)
- Mean frequency: MF (Hz)
- Dominant frequency in 2 frequency ranges: DF1 (0.2-1 Hz) and DF2 (0.34-1 Hz)
- Ratio between the energy content in high (0.34-1 Hz) and low frequency ranges (0.2-0.34 Hz): H/L ratio

So as to analyze the uterine electrophysiological response to labor induction drugs, the median values of parameters computed from EHG-bursts in windows of 30 minutes were worked out for each patient. Then, for each parameter and window of analysis, the mean and standard deviation were calculated over all the patients of each group (GS, GF).

3 RESULTS

For a total of 14 patients, 79.6% ended in successful induction. The obstetrics and clinical parameters of the study groups are summarized in Table 1. Women in both groups, GS and GF groups, were comparable in terms of maternal age (31.9 ± 3.62 vs. 32±2) and bishop scores (1.36±1.03 vs. 1.33±1.53). Time to delivery was slightly shorter for women ending in successful inductions than for those who did not (22.98 ± 10.8 h vs. 26.62 ± 9.81 h) and newborn weight was also shorter for GS group (3381 ± 484 g vs. 3541.67 ± 9.81 h).

Table 1: Obstetrical and clinical parameters of patients induced with misoprostol. Mean (std).

Variable	Success N=11	Failure N=3
Maternal age (years)	31.9 ± 3.62	32 ± 2
Gestational age (days)	287.64 ± 1.96	287.0 ± 0
BMI (kg/m2)	30.88 ± 6.15	31.13 ± 1.36
Gestations	1.27 ± 0.47	1 ± 0
Parity	0.18 ± 0.40	0 ± 0
Bishop score	1.36 ± 1.03	1,33 ± 1,53
Newborn weight (g)	3381 ± 484	3541.67 ± 271
Time to delivery (h)	22.98 ± 10.8	26.62 ± 9.81

Figure 2 shows the total number of contractions detected by TOCO records and EHG records. For all

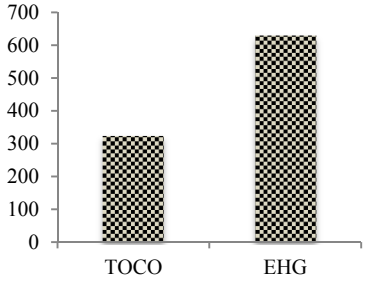

Figure 2: Contractions detected by TOCO and EHG records.

recording session, the total number of detected contractions in EHG records was almost double than in TOCO records (627 vs. 324).

Figure 3 shows an EHG recording from a woman who reached active stage of labor. When comparing the EHG-burst obtained during the last hour and basal activity, the EHG-burst amplitude was significantly greater, contraction duration was shortened, and the biopotentials oscillation was faster suggesting the appearance of high frequency components in EHG-burst.

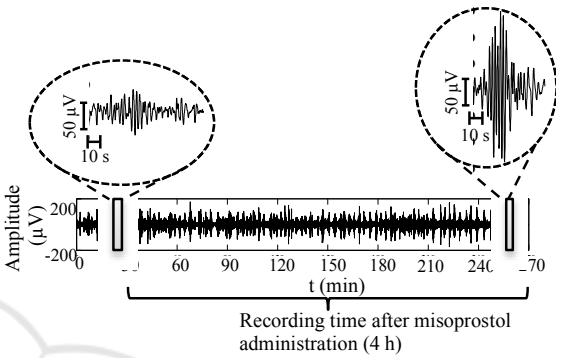

Figure 3: Morphological changes in EHG burst of a patient of the study (successful induction).

Means and standard deviations of the computed parameters in each analysis window of 30 minutes for GS and GF are shown in table 2 and evolution of mean values are depicted in figure 4. For GS group, EHG-burst duration tends to decrease, with values of 88.6±23.6 seconds at basal state (prior to drug administration) to values of 61.6±13.0 seconds at the last analysis window. By contrast, no clear trends were observed in this parameter for GF group.

In regard to EHG-bursts amplitude, GS group presented higher uterine contraction intensity than GF group even in the basal state. In addition GS group experiment a growing trend with values of 124.1±39.8 µV at basal state up to 167.8±58.9 µV at the last analysis window. By contrast, the EHG-burst amplitude changes were less noticeable in GF group (from 83.4±15.1 µV to 102.9±11.2 µV).

Concerning to the spectral parameters, as it can be seen in figure 4, mean frequency, DF1, DF2 and H/L ratio parameters undergo an increasing trend for GS group, showing a shift of the EHG-burst spectral content towards higher frequencies (Fast wave high). In GS patients, this shift is clearly revealed in the H/L ratio (1.1±0.6 basal state vs. 2.8±2.0 4 hours after labor induction onset), which measures the energy ratio in between the high and low frequency bands. Although similar H/L ratio values are obtained for both GS and GF groups, this parameter

did not show a clear trend after labor induction onset in the GF group, resulting in a considerably lower value than GS group at hour 4.

4 DISCUSSION

Labor induction has become a common practice in obstetrics. The number of labor inductions has increased significantly in recent years. Studies explain that this rise is due to an increase in medically indicated induction as well as an increase in elective induction (Grobman, 2007). Despite this, not all inductions have successful outcomes, resulting in an increase in the rate of caesarean section. It is important to know whether a woman will reach or not a successful induction so that clinicians may be able to better plan deliveries, preventing maternal and fetal stress which can appear in long induction processes.

In this study, it was analyzed the response of misoprostol drug used for preinduction cervical ripening not only with traditional obstetrical indicators, but also with parameters that characterize the resulting myoelectrical activity of the uterus. Our data shows that 25 μg of Misoprostol with repeated dose up to three administrations has similar efficacy in terms of success rate in comparison with other authors (Mayer, 2016). Accordingly to Mayer et al, success inductions with 200 μg of misoprostol occurred in 77.3% of the cases and our results shows a 79.6% of success inductions.

In addition, for patients involved in the study, the time between induction and delivery for success group was 22.98 ± 10.8 h. Although this result does not match with those of other authors (Papanikolaou et al, 2004) who obtain a shorter value of time to delivery 11.9 h, this could be explained because of the different dose employed for labor induction. Instead of 25μg of misoprostol, they used a 50μg dose with repeated doses up to three times.

On the other hand, our results show that EHG records have better performance in detecting uterine contractions than TOCO records (627 vs. 324). Given that nowadays the number of contractions is a basic parameter to assess labor progress, this technique could provide a better assessment in this sense. This is also consistent with other studies that have seen the limitations concerning to the use of TOCO records for monitoring uterine dynamics in other conditions (Euliano, 2009).

Concerning to the characteristics of the EHG, the results of this work indicate that patients from GS and GF experiment a different electrophysiological response to the induction drug. Failure group, except for contraction duration, did not show any clear trend. In contrast, in success group a gradual increase is evident in values of EHG-burst amplitude as well as spectral parameters. These results suggest that misoprostol, as an agent for the stimulation of uterine activity, acts favoring the increase of cell junctions (gap junction); thus increasing the total number of active cells during EHG-burst (Garfield, 2007) and so the presence of more intense contractions and an increased ratio of the cells' excitability. In comparison with basal state, significant changes in EHG characteristics begin to show as early as about 90-120 minutes after misoprostol administration. These results coincide with other authors who have analyzed the effect of misoprostol on uterine contractility (Arronson et al, 2004). This study reported that the first effect of misoprostol is an increment in uterine tonus. Then after 1-2 h, the tonus began to decrease and is replaced by regular uterine contractions being the uterine activity, measured in Montevideo units, significantly greater after 2 h of misoprostol administration. Moreover the time required to manifest the changes in EHG characteristics when inducing with misoprostol is coherent with the pharmacokinetic studies (Tang, 2002). In such study it was found that plasma concentration of misoprostol gradually increases after 400μg of vaginal administration and peak plasma concentration is reached between 75 and 80 minutes. After that, plasma concentration slowly decreases and undetectable levels of drug are seen even after 6 h.

Furthermore, other authors have analyzed the evolution of the EMG activity up to 12 hours after administration of dinoprostone which is another commonly drug used for labor induction (Aviram et al, 2014). They found that uterine EMG activity, defined as mean electrical activity of the uterine muscle over a period of 10 minutes, did not change significantly during the first two hours, and then increased between 2 and 8 hours after dinoprostone administration. Another study that analyzed the EMG activity during labor induction with oxytocin and dinoprostone (Toth, 2005), found statistically significant difference in the uterine activity index between successful and unsuccessful labor induction after 210 minutes of labor induction onset In comparison with our results, the uterus response to misoprostol is faster than the response to dinoprostone shown in those other studies. Other authors have used DF2 parameter of EHG to analyze

Table 2: Mean and standard deviation of parameters in each 30 minutes period. S: Successful induction F: Failure induction.

Parameter		0'	30'	60'	90'	120'	150'	180'	210'	240'
Duration (s)	S	88.6±23.6	87.5±25.2	76.3±16.7	87.9±25.4	76.7±20.9	70.0±13.6	69.6±16.1	60.8±6.7	61.6±13.0
	F	88.5±20.9	97.3±11.0	95.8±33.3	83.7±27.0	89.7±45.9	75±2.8	85.8±23.7	64.0±7.0	90.8±49.6
Amplitude (μV)	S	124.1±39.8	124.3±33.9	135.8±46.9	141.6±37.9	130.4±35.2	155.2±52.7	162.1±83.1	152.6±65.3	167.8±58.9
	F	83.4±15.1	96.1±11.7	93.0±31.7	86.2±20.6	96.2±16.9	92.2±12	84.7±13.5	101.6±13.1	102.9±11.2
MF (Hz)	S	0.37±0.03	0.38±0.02	0.39±0.03	0.38±0.04	0.40±0.03	0.40±0.04	0.40±0.04	0.40±0.05	0.42±0.04
	F	0.37±0.02	0.36±0.02	0.39±0.02	0.36±0.02	0.37±0.02	0.36±0.03	0.38±0.02	0.37±0.01	0.39±0.02
DF1 (Hz)	S	0.31±0.04	0.29±0.05	0.33±0.08	0.32±0.06	0.34±0.10	0.37±0.08	0.37±0.10	0.36±0.11	0.39±0.08
	F	0.30±0.04	0.31±0.04	0.32±0.06	0.29±0.03	0.30±0.04	0.29±0.02	0.29±0.02	0.29±0.03	0.31±0.01
DF2 (Hz)	S	0.41±0.03	0.41±0.04	0.43±0.05	0.41±0.04	0.43±0.05	0.43±0.06	0.44±0.05	0.44±0.06	0.45±0.05
	F	0.40±0.03	0.40±0.03	0.41±0.05	0.40±0.05	0.40±0.02	0.41±0.03	0.42±0.20	0.44±0.03	0.40±0.02
H/L	S	1.1±0.6	1.3±0.6	1.4±0.6	1.4±0.8	1.7±1.2	1.9±1.2	2.0±1.3	2.2±1.6	2.8±2.0
	F	1.0±0.3	0.9±0.3	1.4±0.5	0.9±0.3	1.4±0.9	0.9±0.4	1.2±0.4	0.9±0.4	1.2±0.5

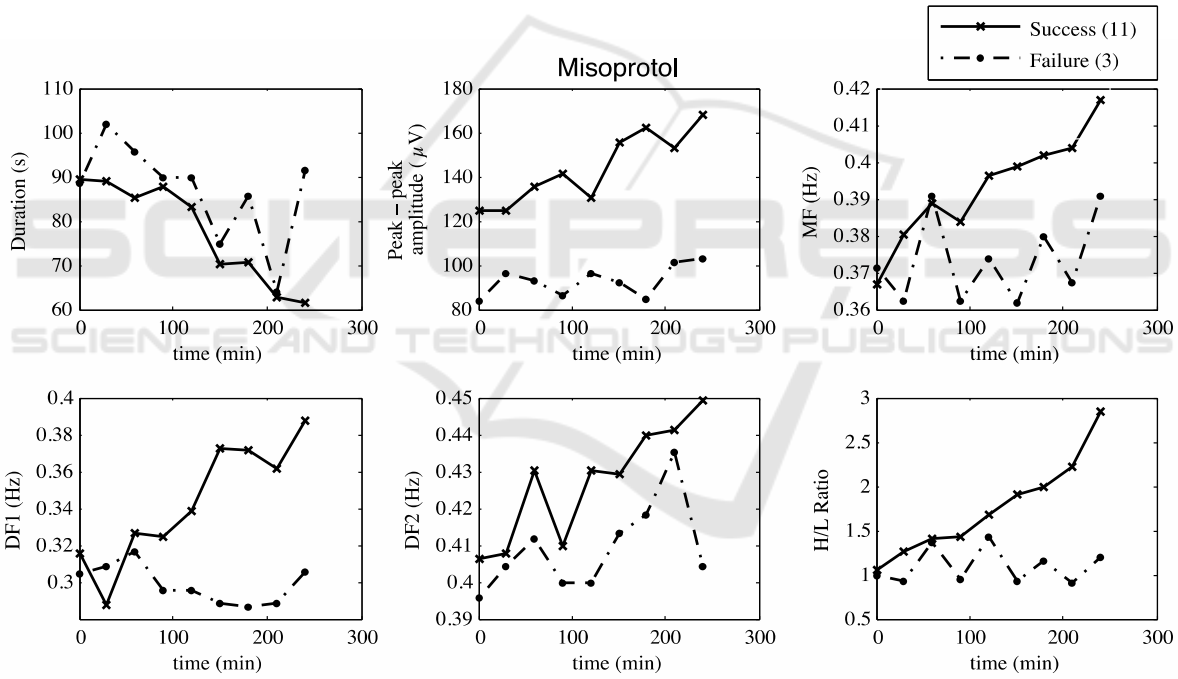

Figure 4: Temporal evolution of the EHG-burst parameters for women induced with misoprostol.

the effect of nifedipine which is tocolytic agent to decrease uterine activity (Vinken, 2010). Our work confirms the utility of spectral parameters to characterize the electrophysiological response of the uterus to drugs, and points to the possibility of predicting the success of labor induction by analyzing the EHG in the first 4 hours. For this final aim, a more comprehensive database and the use of machine learning methods would be needed.

5 CONCLUSION

To conclude, 25 μg of misoprostol with repeated doses up to 3 administrations showed good performance for labor induction. EHG can provide relevant information about the electrophysiological state in labor induction, In contrast to failed inductions, a successful labor induction is associated to remarkable changes in the characteristics of the

EHG signal (burst amplitude increase and energy shift towards higher frequencies) after 120 minutes of vaginal drug administration. These results point that EHG analysis could help to predict the outcome of labor induction.

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REFERENCES

Martin J A, Hamilton B E, Ventura S J. et al. Births: final data for 2010. Natl Vital Stat Rep. 2012;61:1–72.

Seyb ST. Risk of cesarean delivery with elective induction of labor at term in nulliparous women. Obstet Gynecol 1999, 94:600–607

Gudex G. Induction of labour with prostaglandin E2 a prospective audit. NJ Med J 1993; 106: 78–80.

Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol 1964;24:266–8

Faltin-Traub EF, Boulvain M, Faltin DL, Extermann P, Irion O. Reliability of the Bishop score labour induction at term. Eur J Obstet and Gynecol Reprod Biol 2004; 112: 178–181

Watson WS, Stevens D, Welter S, Day D. Factor predicting successful labor induction. Obstet Gynecol 1996; 88: 990–992.

Crane JM. Predictors of successful labor induction with oral or vaginal misoprostol. J Matern Fetal Neonat Med 2004;15: 319–323.

Garfield R, Maner W, "Physiology and electrical activity of uterine contractions," Semin. Cell Dev. Biol., vol. 18, no. 3, pp. 289-295, June 2007

A. Aronsson, M. Bygdeman, and K. Gemzell□Danielsson, "Effects of misoprostol on uterine contractility following different routes of administration," Hum. Reprod., vol. 19, no. 1, pp. 81–84, Jan. 2004

Schlembach D, Maner WL, Garfield RE, Maul H. Monitoring the progress of pregnancy and labor using electromyography. European Journal of Obstetrics, Gynecology, and Reproductive Biology 2009; 144(Suppl 1): S33–9.

Euliano TY, et al. Monitoring uterine activity during labor: A comparison of 3 methods. Am J Obstet Gynecol. 2013;208(1):66.e1–66.e6.

Marque C, Duchene JM, Leclercq S, Panczer GS, Chaumont J. Uterine EHG processing for obstetrical monitoring. IEEE Trans. Biomed. Eng. 1986; 33(12): 1182-7

Grobman, William A. Elective Induction: When? Ever? Clinical obstetrics and gynecology (0009-9201). 50 (2), p. 537.

Mayer R, Oppelt P, Shebl O, Allerstofer, C, Weiss C. Initial clinical experience with a misoprostol vaginal insert in comparison with a dinoprostone insert for inducing labor. Euro. Jour. of Obst. and Gyneco. and Reprod. Biol. , Volume 200 , 89 – 93.

Papanikolaou E, Plachouras N, Drougia A, Andronikou S, Vlachou C, Stefos T, Paraskevaidis E, Zikopoulos K. Comparison of Misoprostol and Dinoprostone for elective induction of labour in nulliparous women at full term: A randomized prospective study. Reproductive Biology and Endocrinology 2004, 2:70.

Vinken M, Rabotti C, Mischi M, van Laar J, Oei S. Nifedipine-induced changes in the electrohysterogram of preterm contractions: feasibility in clinical practice. Obstet Gynecol, vol 2010, 2010, pp 1-8.

Tang OS, Schweer H, Seyberth HW, Lee SW and Ho PC (2002) Pharmacokinetics of different routes of administration of misoprostol. Hum Reprod 17,332-336.

Aviram A, Melamed N, Hadar E, Raban O, Hiersch L, Yogev Y, et al. Effect of Prostaglandin E2 on Myometrial Electrical Activity in Women Undergoing Induction of Labor. J Perinatol. 2014;31:413–8.

Toth T. Transcutaneous electromyography of uterus in prediction of labor outcome induced by oxytocine and prostaglandine shape. Gynaecologia et perinatologia: journal for gynaecology, perinatology, reproductive medicine and ultrasonic diagnostic, vol 14 no 2, 2005.