Comparison of labour induction with misoprostol and dinoprostone and characterization of uterine response based on electrohysterogram

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Comparison of labour induction with misoprostol and dinoprostone and characterization of uterine response based on electrohysterogram

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Objective: To compare the uterine activity response between women administered dinoprostone (prostaglandin E2) and misoprostol (prostaglandin E1) for induction of labor (IOL) by analyzing not only the traditional obstetric data but also the parameters extracted from uterine electrohysterogram (EHG). Methods: Two cohorts were defined: misoprostol (25 mcg vaginal tablets; 251 women) and dinoprostone cohort (10 mg vaginal inserts; 249 women). All the mothers were induced by a medical indication of a Bishop Score <=6. Results: The misoprostol cohort was associated with a shorter time to achieve active labour (p=0.017) and vaginal delivery (p=0.009) and with a higher percentage of vaginal delivery in less than 24h in mothers with a very unfavourable cervix score (RR: 1.41, IC95% 1.17–1.69, p=0.002). Successful inductions with misoprostol showed EHG parameter values significantly higher than basal state for amplitude and pseudo Montevideo units (PMU) 60' after drug administration, while spectral parameters significantly increased after 150'. This response was not observed in failed inductions. In the successful dinoprostone group, the duration and number of contractions increased significantly after 120', PMU did so after 180', and no significant differences were found for spectral parameters, possibly due to the slower pharmacokinetics of this drug. Conclusion: Successfull inductions of labor by misoprostol are associated with earlier effective contractions than in labors induced by dinoprostone.

Keywords: Labor Induction; Cervical Ripening; drug effects; Surface Electromyography; signal interpretation

Introduction

Late-term pregnancies are those that extend beyond the 40 + 6 weeks of gestational age (GA), may last up to 41 + 6 weeks, and are associated with an increase in fetal and maternal morbidity and mortality [1]. The aim of IOL is to reduce maternal and foetal risks compared with expectant management of labour. IOL is used to initiate uterine contractions before the onset of spontaneous labour [2]. The IOL usage rate has increased in recent years and 22.8% of all births were induced in the United States in 2012 [3], converging from a rare event to a common procedure in the last decades [4]. IOL is indicated when the risks of continuing pregnancy overtake the benefits of waiting for the spontaneous onset of labour [5] and incites the artificial cervical ripening which boosts cervical dilatation [6]. Pharmacological agents such as prostaglandins (dinoprostone and misoprostol), which reduce the duration of labour and promote vaginal delivery [7], are commonly used for this purpose. The process of induction can last up to 24 or 48 hours and success is not guaranteed and can be ended by a cesarean section. These waits, sometimes unnecessary, can lead to greater maternal-fetal exhaustion and suffering as well as associated costs. In this sense, it would be of great interest to be able to characterize the uterine response to labor induction drugs and to infer the labor induction outcome for a better labor management in the first hours of IOL

Many clinical trials have compared the safety and efficacy of dinoprostone vaginal inserts with intravaginal misoprostol tablets [8,9]. Austin et al performed a metaanalysis from randomized trials to compare these cervical ripening agents, reporting that women administered misoprostol had a higher incidence of vaginal delivery over those administered dinoprostone, with similar incidences of uterine hyperstimulation, cesarean delivery and fetal tachsystole [7]. Hofmeyr et al (10)

reported that misoprostol needs less oxytocin and is associated with a lower rate of failure to achieve vaginal delivery within 24 hours. In contrast, Liu et al[10] considered that although misoprostol appears to be more efficient in inducing labour than dinoprostone regarding time to achive labor period, the latter is safer than misoprostol due to its lower rates of uterine tachysystole and hyperstimulation. As no clear tendencies can be concluded from these results, further studies are needed to evaluate the effectiveness of both products.

During IOL, the assessment of uterine activity is essential to determine the uterine response to the pharmacological agents, since an excess may endanger maternal and fetal well-being, e. g. increased uterine activity is related to a higher incidence of acidosis at birth [11]. Uterine activity (tone, frequency, intensity and duration of contractions) is typically monitored noninvasively with tocodynamometers (TOCO) [12]. However, this method does not provide sufficiently reliable information [13,14] since it is highly influenced by the sensor position and abdominal wall thickness [12]. The TOCO must therefore be constantly recalibrated and the sensor probe repositioned for proper monitoring of uterine activity [12].

Electrohysterography (EHG), the uterine electromyogram recorded on the abdominal surface, is an alternative technique for monitoring uterine activity. Previous studies have established that EHG performs better than TOCO in terms of detecting contraction [12,13,15] and it has been suggested that the intrauterine pressure can be estimated from EHG analysis [16,17]. Moreover, EHG parametrization can be used to characterise the electrophysiological contractions; e. g. differences in EHG parameters have been associated with labour vs non-labour conditions [14,18] or term vs preterm deliveries [19,20].

The present study was based on the hypothesis that dinoprostone or misoprostol administered in late term pregnancies provide different responses in terms of uterine activity. Our objective was not only to compare the traditional obstetrical data associated with IOL efficiency and maternal-fetal safety, which has been the cause of certain controversy, but also to evaluate the electrophysiological response in terms of the evolution of EHG parameters in expectant mothers treated with dinoprostone and misoprostol. This latter with the intention of exploring the possibility of predicting the success of the induction from the electrophysiological response in the first hours.

Materials and methods

An observational study was performed on expectant mothers admitted to the Hospital Universitario y Politécnico La Fe, in Valencia, Spain, for cervical ripening and induced labour by either misoprostol or dinoprostone vaginal inserts. The inclusion criteria were induction of labour in late-term gestation with singleton pregnancy, null parity, cephalic presentation, and unfavourable cervix (defined as Bishop score <= 6). Exclusion criteria were: active cardiac, renal, pulmonary or hepatic disease, severe preeclampsia, placenta previa, premature rupture of membranes and vaginal bleeding during pregnancy, previous cesarean section, and suspected fetal compromise (growth restriction oligohydramnios, known fetal anomalies, etc.).

In order to determine the number of women to enrol in the study, a non-equality test was designed (contrast of usual hypothesis) in which a confidence interval for the difference was estimated. It was established an error type 1 (α) of 0.05, an error type 2 (β) of 0.2, so as to achieve a statistical power ($1 - \beta$) of 80% and it is considered a clinically relevant difference (Δ) of 15 %. Therefore, the estimated sample size was 165 per drug (misoprostol and dinosprostone). Nonetheless, given the possibility of

continuing to make records and in order to give more robustness to the study, the database was expanded to approximately 250 women per branch.

The induction method for the dinoprostone cohort was dinoprostone 10 mg (Propess, Ferring S.A.U) inserted into the posterior vaginal fornix with removal after at least 12 h. No additional doses of dinoprostone were given. The misoprostol cohort received a 25 mcg tablet (Misofar, Laboratorios BIAL, S.A) inserted in the posterior vaginal fornix. If required, an additional 25 mcg tablet could be administered every 4 h up to a maximum of 4 doses, at the obstetrician's discretion.

The mothers were transferred to the labour ward if a regular contraction pattern was observed or active labour was diagnosed. IOL was considered successful when the active phase of labour was reached, i.e. when woman experience regular uterine dynamic with 3-5 contraction every 10 minutes, 4 cm of cervical dilatation and cervical effacement [21]. Therefore, labour induction was considered failed when women did not achieve active phase of labour. The women were thus subdivided into the following groups: GMS (misoprostol-success), GMF (misoprostol-failure), GDS (dinoprostone-success) and GDF (dinoprostone-failure). The collected obstetric data included maternal age, gestational age, estimated fetal weight, and preinduction Bishop score. The outcomes used to assess labour induction in both groups were: the need to use oxytocin, success and time to active period, success and time to vaginal delivery, time to achieve regular uterine activity and cesarean section rate. Maternal-fetal safety included uterine hyperstimulation rate, incidence of meconium-stained amniotic fluid and neonatal outcomes.

Continuous cardiotocograph recordings were made with a Corometrics 250cx commercial maternal monitor (General Electric Healthcare) from at least 30 min prior to drug administration and during the entire IOL process. Additionally, when EHG

recording devices and qualified staff were available, EHG recordings were taken in a women subgroup to further characterize uterine response to drugs, comprising 30 minutes of basal activity (without drug) until 4 hours after drug administration. For each EHG recording session the woman's abdominal surface was exfoliated with gel (Nuprep, Weaver and Company, USA). A bipolar signal was captured from two Ag/AgCl disposable electrodes (Kendal, USA) supraumbilical at each side of the medial line with 8cm of inter-electrode distance corresponding to EHG monopolar records (M1, M2). Reference and ground electrodes were placed on each of the woman's hips. The electrodes were connected to commercial biosignal amplifiers (Grass 15LT+4 Grass 15A94; Grass Instruments, West Warwick, RI) in which the signals were amplified and filtered between [0.1, 30] Hz to be subsequently acquired at a sampling frequency of 1000 Hz. To eliminate low- and high-frequency interference and noise, the signals were also bandpass filtered between 0.2 – 1 Hz with a 5th order Butterworth filter and subsequently down-sampled at 20 Hz.

All the EHG-bursts present in the EHG recordings were manually segmented according to the following rules: i) the bursts had to synchronise with the contractions detected in the simultaneous uterine pressure record, ii) entail a significant increase in EHG amplitude and/or frequency in comparison to rest activity, and iii) last for a minimum duration of 30 seconds with no evidence of artefacts during contraction [22].

In order to characterize the electrophysiological state of the uterus, the parameters of EHG-bursts were extracted from the temporal and spectral domain. In the former, the following parameters were computed: duration (s), peak-to-peak amplitude (μV), number of contractions (NCT), and pseudo-Montevideo units (PMU). PMU was calculated as the total energy of contractions present in the EHG within a 30 min interval. Since it has been proven that there is a shift of spectral content towards high

frequencies as labour approaches [20,23,24], the following spectral parameters were extracted from the power spectral density of the EHG-bursts estimated by the periodogram method: mean frequency in the range 0.2-1Hz (MF) and the ratio between the energy content in high (0.34-1 Hz) and low (0.2-0.34Hz) frequency (HL ratio). The median of the values of the parameters obtained from contractions present in 30 min analysis windows were computed, and mean and standard deviation were then calculated for all the women in each group.

Statistical Analysis

A statistical analysis was performed using the Chi-square test, paired t-test and Wilcoxon or Mann–Whitney test, where appropriate, using SPSS v22 (SPSS, Chicago, USA). A P value < 0.05 was considered significant.

Ethical Approval

Approval was granted by the local medical ethical board (code: DINOMISO, approved 30th of June, 2015) and written informed consent was obtained from each of the volunteers. The study adhered to the Declaration of Helsinki's guidelines.

Results

Table 1 shows the main demographic characteristics of the study population; 500 expectant mothers were included in the study: 249 in the dinoprostone cohort and 251 in the misoporostol cohort. No statistical differences were found between the cohorts in the population study as regards mean maternal age, gestational age, fetal weight estimation and Bishop Score before IOL.

Table 2 shows the IOL characteristics for the total population. Similar rates of vaginal deliveries were obtained in both cohorts (74% and 75%). However, the

misoprostol cohort was associated with shorter time in achieving vaginal delivery: 18.69± 8.57 h versus 21.21 ± 9.87 h than the dinoprostone cohort (p=0.009). The former group showed a higher percentage of vaginal deliveries in less than 24h (75%) vs 56% in the latter group (Risk ratio (RR): 1.33 95%CI 1.15 – 1.55, p=0.0002). To assess the efficacy of labour induction related with the Bishop Score in vaginal deliveries (excluding cesarean deliveries), we divided the Bishop Score before IOL data into two groups (Table 3). For women included in the very unfavourable group (Bishop score 0-3), those induced with misoprostol were associated with more vaginal deliveries in less than 24h (72%, 110 out of 152) than those administered dinoprostone (51%, 76 of 150) (RR: 1.41, IC95% 1.17 – 1.69 p=0.002).

Regarding uterine contractions, the interval between administration of the drug until regular uterine dynamics appeared was shorter for the misoprostol than the dinoprostone cohort, 312.45 ± 196.11 vs 349.53 ± 174.64 minutes (p=0.03), see Table 2. Although similar numbers of women achieved active labour in both cohorts (88% and 87%), the misoprostol group achieved it earlier than the dinoprostone group:15.45 ± 8.02h vs 17.38 ± 8.83 h (p=0.017). Additionally, 43.03% of the mothers in the misoprostol group required augmentation with oxytocin, compared with 55.02 % in the dinoprostone group (p=0.01). No statistical differences were found between the groups regarding the parameters that assess maternal and fetal safety from the onset of IOL until active labour.

A total of 66 women with singleton pregnancies were included in the EHG study, of whom 33 received misoprostol and 33 dinoprostone. The characteristics and success rate of labour induction and the comparisons with the original cohorts are summarized in supplementary information (see Table S1). Only vaginal delivery before

24h or after 24 h using misoprostol showed statistical differences with the original cohort shown in Table 2 (p=0.01).

Figure 1A shows a TOCO and a simultaneous EHG recording from a woman who reached active labour in the misoprostol cohort. Comparing the EHG-bursts present at basal activity and those acquired in the last hour of recording, the later EHG-bursts were higher in frequency and amplitude and of shorter duration. In contrast, only duration (and amplitude to a lesser extent) of the EHG-bursts exhibited a clear change as labour progressed in the dinoprostone cohort, as can be seen in Figure 1B.

The temporal evolution of the computed parameters in both the misoprostol and dinoprostone cohorts are shown in Figure 2; detailed mean and standard deviation values of the parameters are provided in supplementary information (Table S2). In the misoprostol cohort, the EHG-burst duration before administration was 81.7 ± 17.6 s and decreased progressively to values of 66.5 ± 13.7 s at the end of the recording session for GMS. EHG-burst duration was also seen to drop in the failure group (GMF), resulting in a smaller reduction, from 82.63 ± 20.74 s to 73.83 ± 19.86 s. The success group presented a higher increment in their values than the failure group for peak-to-peak amplitude as well as spectral parameters (MF and H/L ratio). The pseudo-Montevideo units also showed a progressive rise in value for GMS that was not seen in the GMF.

Similarly, clear trends of successful induction (GDS) were seen in the dinoprostone cohort in parameter duration, peak-to-peak amplitude, PMU and number of contractions. EHG-burst duration was reduced throughout the recording session with values at basal activity of 83.7 ± 19.2s and72.9 ± 29.0 at the end of the recording session. In contrast, peak-to-peak amplitude values increased, while none of the spectral parameters showed clear trends. PMU values were greater in the success group (GDS)

than in the failure group (GDF) in most of the analysis windows and an upward trend was observed in successful inductions throughout the recording session.

Comparing both success groups (GMS vs. GDS) it can be clearly appreciated that duration and peak-to-peak amplitude evolved along similar lines, showing decreasing and increasing tendencies respectively. Regarding the spectral parameters, well established trends were seen in the misoprostol group and significant differences with dinoprostone were found 4 hours after vaginal administration for MF and H/L ratio. In MF an evidently increasing trend is seen for misoprostol, while dinosptrone values remain almost constant. Similar behaviour can be observed in the evolution of the H/L ratio (see Figure 2). Finally, both PMU and NCT parameters showed increasing trends in both successful groups, with higher values for dinoprostone than for misprostol.

To assess the evolution of the statistical significance of each parameter in each group in order to characterize the uterine response to drug administration, we compared the parameter values in every analysis window with those of basal activity in each group. The parameters with statistical significance in each group are given in Table 4. First, with one exception (GMF, 150'), no significant differences were found in the failure groups (GDF and GMF). In the success groups, more EHG parameters in the misoprostol group presented statistical differences ($p<0.05$) with basal recording in comparison to the dinoprostone group. PMU and amplitude increased significantly in the former group as early as 60 minutes and the statistical differences remained until the end of the recording. NCT and spectral parameters (MF and H/L) also increased significantly throughout the recording session, showing statistical differences with basal activity after 90 and 150 minutes, respectively. In the dinoprostone group, NCT and

duration rose and fell significantly, respectively, after 120 minutes until the end of the recording. PMU increased significantly after 180 m until the end of the recording.

Discussion

Fetal and maternal risks have been found to increase in post-term pregnancies, and several studies have related the increase of maternal and neonatal morbidity with more than 41 weeks of gestation [25,26]. The question of whether inducing labour in late-term pregnancies improves the outcome according to whether misoprostol 25 mcg or dinoprostone 10 mg is administered remains unclear, as does their electrophysiological influence on uterine dynamics. In this observational study, we assessed the efficiency, safety and electrophysiological characteristics of pharmacologically induced labour by dinoprostone and misoprostol in late-term pregnancies.

Regarding the efficiency and safety of IOL, our results show that mothers administered misoprostol have better rates of vaginal delivery in less than 24h after drug administration (RR: 1.33 95%CI 1.15 – 1.55, p=0.0002), achieve regular uterine contractions and active labour in significantly shorter times than those administered dinoprostone, and require less oxytocin augmentation (p=0.01). These results agree with previous randomized controlled trials [7,27]. Additionally, misoprostol achieves significantly higher rates of vaginal delivery for the very unfavourable cervix group (RR: 1.41, IC95% 1.17 – 1.69 p=0.002). Both drugs have similar safety profiles, the cesarean rate does not show significant differences, and the neonatal outcomes were similar for both cohorts. These results are in agreement with some previous studies [7,27], but not with those that argue that the use of misoprostol may lead to increased episodes of tachysystole and hyperstimulation [10]

Parameters were extracted from the EHG-burst to assess the electrophysiological characteristics of the contractions. The results show that parameter peak-to-peak

amplitude was significantly higher than basal activity in succes groups and that the differences started earlier in misoprostol success group than in dinoprostone success group (60 vs. 180 minutes). Only GMS showed a noticeable shift toward higher frequencies throughout the recording session. This is consistent with studies that analyzed the electrical activity of the human uterus during pregnancy and labour at term [20], obtaining significantly higher peak frequency for women delivering <24h from the recording than those that delivered >24h (0.4768± 0.0144 Hz vs 0.4042±0.0185 Hz). These results suggest that misoprostol provides effective contractions earlier, which are related not only to higher amplitudes but also to higher frequencies of EHG-bursts, as suggested by Garfield et al [23], who indicated that effective contractions require multiple and higher frequency of action potential spikes of uterine cells. In the misoprostol group, the changes in uterine electrophysiological state can be appreciated in the well-established statistical differences (maintained until the end of the EHG recording) identified in most of the parameters 90 minutes after labour induction. Furthermore, PMU was significantly higher at 60 minutes after labour induction, which agrees with the findings of other studies [28], which also reported that regular uterine contractions appeared after 1-2 h and uterine activity increased throughout the recording session. The time required to achieve significant changes in EHG characteristics is consistent with pharmacokinetic studies [29] in which peak plasma concentration is reached between 75 and 80 minutes after 400 µg vaginal administration, then decreasing slowly with detectable levels of the drug even after 6 h.

In the dinoprostone group, only duration and NCT parameters changed significantly from the basal state after 2 h of drug administration for succesful inductions (GDS). No significant and maintained changes in peak-to-peak amplitude or spectral parameters were seen in the first 4 hours of induction in this group. Other

studies found that uterine EMG activity significantly increases between 2-8 h after dinoprostone administration [30]. Although there was no statistical difference in the temporal evolution of peak-to-peak amplitude, this parameter started a noticeable increase 60 minutes after drug administration. This result is consistent with Yount et al's pharmacokinetic study [31] in which peak plasma level was reached about 1-2 hours after vaginal dinoprostone administration. The fact that no changes were observed in the spectral parameters in the GDS group could therefore be due to the relatively slow dynamics of the drug and to a short analysis window (4 h). In this respect, it would be desirable to extend the recording time (up to 8 h) to better analyze the uterine electrophysiological response of this group.

The results of the present study indicate that the misoprostol success and failure groups had a different electrophysiological response to the induction drug. Although a larger database would be required to corroborate these results, they suggest that EHG recordings could be used for early prediction of induction success.

In conclusion, the present study not only compared obstetrical outcomes but also the uterine electrophisiological response of expectant mothers treated with 25 μg of misoprostol (doses repeated up to 4 times) and those vaginally administered 10 mg of dinoprostone. Successful labour induction by misoprostol is associated with earlier effective contractions than when induced by dinoprostone. We also found that the evolution of the EHG-burst parameters are in line with the pharmacokinetics of each drug and was more evident in misoprostol. In successful inductions by misoprostol, myoelectrical uterine activity presented a significant shift towards higher frequencies associated with a greater excitability of muscular cells. Different patterns were obtained for successful and failed IOLs with both drugs. The results suggest that EHG provides relevant information on the electrophysiological state of the uterus during labour

induction, and indicate the possibility of designing a system able to predict labour outcomes. This would provide improved maternal-fetal well-being as well as reduced hospital costs, as it has been found that cesarean sections performed after prolonged failed inductions require longer hospitalization and greater attention to both mother and child [32]. Results also show that EHG monitoring could provide further insight into the best dosage and method of IOL drug administration.

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Conflicts of interest

This research has received funding from Bial S.A. a company that may be affected by the research reported in the enclosed paper.

References

1. Bleicher I, Vitner D, Iofe A, et al. When should pregnancies that extended beyond term be induced? *. J. Matern. Neonatal Med. 2017;30:219–223.
2. Wing DA. Principles of labor induction. [Internet]. Available from: http://www.uptodate.com/home.
3. Martin JA, Hamilton BE, Osterman MJK, et al. Births: final data for 2012. Natl. Vital Stat. Rep. 2013;62:1–68.
4. Glantz JC. Obstetric variation, intervention, and outcomes: doing more but

accomplishing less. Birth. 2012;39:286–290.

5. Henderson J, Redshaw M. Women's experience of induction of labor: a mixed methods study. Acta Obstet. Gynecol. Scand. 2013;92:1159–1167.

6. Dögl M, Vanky E, Heimstad R. Changes in induction methods have not influenced cesarean section rates among women with induced labor. Acta Obstet. Gynecol. Scand. 2016;95:112–115.

7. Austin SC, Sanchez-Ramos L, Adair CD. Labor induction with intravaginal misoprostol compared with the dinoprostone vaginal insert: a systematic review and metaanalysis. Am. J. Obstet. Gynecol. 2010;202:624.e1-9.

8. Nadia Bennett K, Park H, Cioffi J, et al. A comparison of obstetrical outcomes and costs between misoprostol and dinoprostone for induction of labor. J. Matern. Neonatal Med. 2016;29:3732–3736.

9. Wang L, Zheng J, Wang W, et al. Efficacy and safety of misoprostol compared with the dinoprostone for labor induction at term: a meta-analysis. J. Matern. Fetal. Neonatal Med. 2015;7058:1–11.

10. Liu A, Lv J, Hu Y, et al. Efficacy and safety of intravaginal misoprostol versus intracervical dinoprostone for labor induction at term: A systematic review and meta-analysis. J. Obstet. Gynaecol. Res. 2014;40:897–906.

11. Mussi S, Incerti M, Plevani C, et al. Effect of oxytocin during labor on neonatal acidemia. J. Matern. Neonatal Med. J. J. Matern. Neonatal Med. J Matern Fetal Neonatal Med. 2016;29:3098–3103.

12. Euliano TY, Nguyen MT, Darmanjian S, et al. Monitoring uterine activity during labor: A comparison of 3 methods. Am. J. Obstet. Gynecol. 2013;208:66.e1-66.e6.

13. Alberola-Rubio J, Prats-Boluda G, Ye-Lin Y, et al. Comparison of non-invasive electrohysterographic recording techniques for monitoring uterine dynamics. Med. Eng. Phys. 2013;35:1736–1743.

14. Schlembach D, Maner WL, Garfield RE, et al. Monitoring the progress of pregnancy and labor using electromyography. Eur. J. Obstet. Gynecol. Reprod. Biol. 2009;144:S33–S39.

15. Hadar E, Biron-Shental T, Gavish O, et al. A comparison between electrical uterine monitor, tocodynamometer and intra uterine pressure catheter for uterine activity in labor. J. Matern. Neonatal Med. J Matern Fetal Neonatal Med. 2015;28:1367–1374.

16. Euliano T, Skowronski M, Marossero D, et al. Prediction of intrauterine pressure waveform from transabdominal electrohysterography. J. Matern. Neonatal Med. 2006;19:803–808.

17. Rabotti C, Mischi M, van Laar JOEH, et al. Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals. Physiol. Meas. 2008;29:829–841.

18. Ye-Lin Y, Prats-Boluda G, Alberola-Rubio J, et al. Prediction of labor using non-invasive laplacian EHG recordings. 2013 35th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE; 2013. p. 7428–7431.

19. Lucovnik M, Kuon RJ, Chambliss LR, et al. Use of uterine electromyography to diagnose term and preterm labor. Acta Obstet. Gynecol. Scand. 2011;90:150–157.

20. Maner WL, Garfield RE, Maul H, et al. Predicting term and preterm delivery with transabdominal uterine electromyography. Obstet. Gynecol. 2003;101:1254–1260.

21. World Health Organization. Recommendations for augmentation of labour. 2014. Available online at: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/augmentation-labour/en/.

22. Ye-Lin Y, Garcia-Casado J, Prats-Boluda G, et al. Automatic Identification of Motion Artifacts in EHG Recording for Robust Analysis of Uterine Contractions. Comput. Math. Methods Med. 2014;2014:119–145.

23. Garfield RE, Maner WL. Physiology and electrical activity of uterine contractions. Semin. Cell Dev. Biol. 2007;18:289–295.

24. Leman H, Marque C, Gondry J. Use of the electrohysterogram signal for characterization of contractions during pregnancy. IEEE Trans. Biomed. Eng. 1999;46:1222–1229.

25. Halloran DR, Cheng YW, Wall TC, et al. Effect Of Maternal Weight On Postterm Delivery. J Perinatol. 2012;32:85–90.

26. Adhikari M, Gouws E, Velaphi SC, et al. Meconium aspiration syndrome: importance of the monitoring of labor. J. Perinatol. 1998;18:55–60.

27. Vogel JP, Gülmezoglu AMM, Hofmeyr GJ, et al. Global Perspectives on Elective Induction of Labor. Clin. Obstet. Gynecol. 2014;57:331–342.

28. Aronsson A, Bygdeman M, Gemzell-Danielsson K. Effects of misoprostol on uterine contractility following different routes of administration.

29. Shan Tang O, Schweer H, Seyberth HW, et al. Pharmacokinetics of different routes of administration of misoprostol. Hum. Reprod. 2002;17:332–336.

30. Aviram A, Melamed N, Hadar E, et al. Effect of Prostaglandin E2 on Myometrial Electrical Activity in Women Undergoing Induction of Labor. J Perinatol. 2014;31:413–418.

31. Yount SM, Lassiter N. The Pharmacology of Prostaglandins for Induction of Labor. J. Midwifery Women's Heal. 2013;58:133–144.

32. Nicholson G, Cyr PL. Cost Of Failed Labor Induction: A Us Hospital Perspective. Value Heal. 2013;16:A75.

Figure Captions

Figure 1. Example of TOCO and simultaneous EHG recordings of women that reached active labour after IOL with A) misoprostol, B) dinoprostone

Figure 2. Temporal evolution of EHG parameters in 30min windows. Drug was administered after 30 minutes of basal recording (marked with a black line). Statistical difference between GMS and GDS is marked with a grey circle on the time axis. GMS: group of misoprostol success; GMF: group of misoprostol failure; GDS: group of dinoprostone success; GMF: group of dinoprostone failure.

Table 1. Demographic characteristics of the study population

	MISOPROSTOL COHORT	DINOPROSTONE COHORT	P-VALUE
Maternal age (years)	31.53 ± 5.27	32.37 ± 5.10	0.07
Gestational age (weeks)	41 ± 0.17	41 ± 0.43	0.08
Estimated fetal weight (gr)	3343.56 ± 305.80	3342.51 ± 310.92	0.96
Bishop Score before induction	2.16 ± 1.21	2.29 ± 1.25	0.23
0-1	78 (31.07%)	69 (27.71%)	0.47
2-3	134 (53.39%)	137 (55.02%)	0.78
4-5	39 (15.34%)	43 (17.27%)	0.64

Table 2. Characteristics of induction of labour (p-values<0.05 in bold)

	MISOPROSTOL COHORT	DINOPROSTONE COHORT	P-VALUE
Oxytocin augmentation	110 (43%)	137 (55 %)	0.01
Vaginal delivery	185 (74%)	188 (75%)	0.64
>24 hours	46 (25%)	82 (44%)	**0.001**
≤24 hours	139 (75%)	106 (56%)	
Time to vaginal delivery (hours)	18.69 ± 8.57	21.21 ± 9.87	**0.009**
Active labour period	222 (88%)	217 (87%)	0.76
Time to active labour period (hours)	15.45 ± 8.02	17.38 ± 8.83	**0.017**
Time from active labour until complete dilation (hours)	3.27 ± 2.02	3.33 ±2.09	0.78
Time to regular uterine activity (minutes)	312.4 ± 196.1	349.5 ± 174.6	**0.03**
Arterial pH	7.24 ± 0.07	7.25 ± 0.07	0.22
Vein pH	7.29 ± 0.09	7.30 ± 0.06	0.24
Cesarean section	66(23%)	61(24%)	0.64
Tachysystole	7 (2.79%)	14(5.62%)	0.18
Uterine hyper-stimulations	2 (0.79%)	5 (2.0%)	0.99
Meconium	47 (18.7%)	28 (11.2%)	0.07

Table 3. Vaginal delivery occurrence before 24 h for very unfavourable cervix (Bishop Score before inductions ≤3)

COHORT	RATIO	RISK RATIO	P-VALUE
Misoprostol	0.72	1.41 [1.17 – 1.69]	0.0002
Dinoprostone	0.51		

Table 4. Statistical significance ($p<0.05$) of EHG parameters in 30' windows after drug administration compared to basal state. *GMS: group of misoprostol success; GMF: group of misoprostol failure; GDS: group of dinoprostone success; GDF: group of dinoprostone failure.*

1: duration, 2: peak to peak amplitude, 3: mean frequency, 4: H/L ratio, 5: PMU and 6: NCT

Group	30'	60'	90'	120'	150'	180'	210'	240'
GMS								
GMF								
GDS								
GDF								

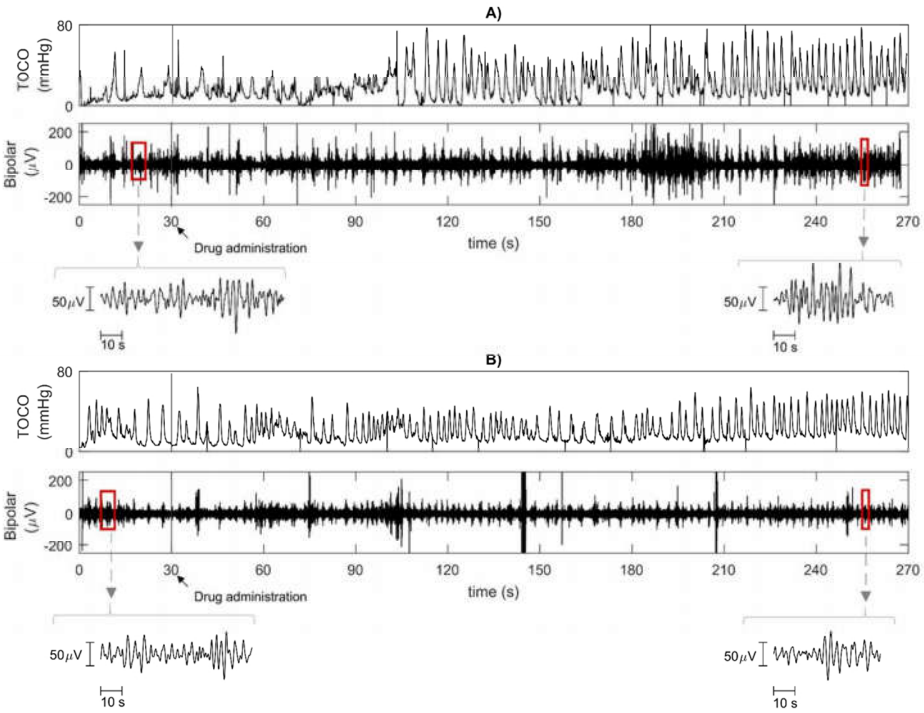

Figure 1. Example of TOCO and simultaneous EHG recordings of women that reached active labour after IOL with A) misoprostol, B) dinoprostone

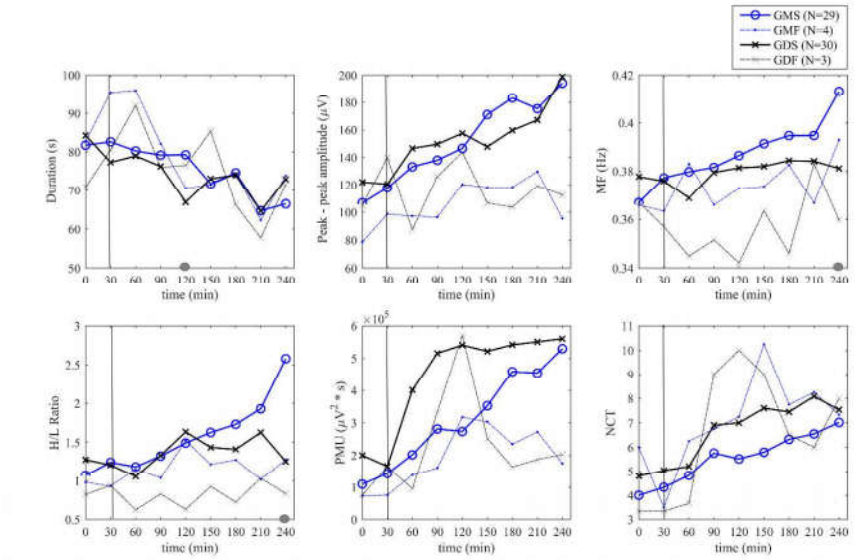

Figure 2. Temporal evolution of EHG parameters in 30min windows. Drug was administered after 30 minutes of basal recording (marked with a black line). Statistical difference between GMS and GDS is marked with a grey circle on the time axis. GMS: group of misoprostol success; GMF: group of misoprostol failure; GDS: group of dinoprostone success; GMF: group of dinoprostone failure.

Table S1: Characteristics of induction of labour for EHG cohorts. P-values are those of tests on statistical differences between each parameter from cohorts shown in Table 2 and those of EHG cohorts for misoprostol and dinoprostone.

	MISOPROSTOL COHORT (EHG)	P-VAL.	DINOPROSTONE COHORT (EHG)	P-VAL.
Oxytocin augmentation	14(42%)	0.87	18(54%)	0.95
Vaginal delivery	22(67%)		22(67%)	
>24 hours	11(50%)	**0.01**	8(36%)	0.49
≤24 hours	11(50%)		14(64%)	
Time to vaginal delivery (hours)	20.23 ±10.21	0.53	16.84 ± 8.75	0.14
Active labor period	29(87%)	0.92	26(78%)	0.23
Time to active labor period (hours)	17.20 ± 9.48	0.39	15.90 ± 9.55	0.41
Time from active labor until complete dilatation (hours)	3.60 ± 1.73	0.27	2.60 ± 1.13	0.58
Time to regular uterine activity (minutes)	320.78 ± 185.59	0.92	287.31± 192.08	0.13
Arterial pH	7.25 ±0.06	0.52	7.24 ±0.67	0.50
Vein pH	7.25 ± 0.06	0.72	7.30 ± 0.06	0.67
Cesarean section	11(33%)	0.39	11(34%)	0.22
Tachysystole	2(6%)	0.31	4(3.0%)	0.18
Uterine hyper-stimulations	1(3.0%)	0.23	1(3.0%)	0.70
Meconium	9(27%)	0.25	4(12%)	0.78

Comparison of labour induction with misoprostol and dinoprostone and characterization of uterine response based on electrohysterogram

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Comparison of labour induction with misoprostol and dinoprostone and characterization of uterine response based on electrohysterogram

Objective: To compare the uterine activity response between women administered dinoprostone (prostaglandin E2) and misoprostol (prostaglandin E1) for induction of labor (IOL) by analyzing not only the traditional obstetric data but also the parameters extracted from uterine electrohysterogram (EHG). Methods: Two cohorts were defined: misoprostol (25 mcg vaginal tablets; 251 women) and dinoprostone cohort (10 mg vaginal inserts; 249 women). All the mothers were induced by a medical indication of a Bishop Score <=6. Results: The misoprostol cohort was associated with a shorter time to achieve active labour (p=0.017) and vaginal delivery (p=0.009) and with a higher percentage of vaginal delivery in less than 24h in mothers with a very unfavourable cervix score (RR: 1.41, IC95% 1.17–1.69, p=0.002). Successful inductions with misoprostol showed EHG parameter values significantly higher than basal state for amplitude and pseudo Montevideo units (PMU) 60' after drug administration, while spectral parameters significantly increased after 150'. This response was not observed in failed inductions. In the successful dinoprostone group, the duration and number of contractions increased significantly after 120', PMU did so after 180', and no significant differences were found for spectral parameters, possibly due to the slower pharmacokinetics of this drug. Conclusion: Successfull inductions of labor by misoprostol are associated with earlier effective contractions than in labors induced by dinoprostone.

Keywords: Labor Induction; Cervical Ripening; drug effects; Surface Electromyography; signal interpretation

Introduction

Late-term pregnancies are those that extend beyond the 40 + 6 weeks of gestational age (GA), may last up to 41 + 6 weeks, and are associated with an increase in fetal and maternal morbidity and mortality [1]. The aim of IOL is to reduce maternal and foetal risks compared with expectant management of labour. IOL is used to initiate uterine contractions before the onset of spontaneous labour [2]. The IOL usage rate has increased in recent years and 22.8% of all births were induced in the United States in 2012 [3], converging from a rare event to a common procedure in the last decades [4]. IOL is indicated when the risks of continuing pregnancy overtake the benefits of waiting for the spontaneous onset of labour [5] and incites the artificial cervical ripening which boosts cervical dilatation [6]. Pharmacological agents such as prostaglandins (dinoprostone and misoprostol), which reduce the duration of labour and promote vaginal delivery [7], are commonly used for this purpose. The process of induction can last up to 24 or 48 hours and success is not guaranteed and can be ended by a cesarean section. These waits, sometimes unnecessary, can lead to greater maternal-fetal exhaustion and suffering as well as associated costs. In this sense, it would be of great interest to be able to characterize the uterine response to labor induction drugs and to infer the labor induction outcome for a better labor management in the first hours of IOL.

Many clinical trials have compared the safety and efficacy of dinoprostone vaginal inserts with intravaginal misoprostol tablets [8,9]. Austin et al performed a metaanalysis from randomized trials to compare these cervical ripening agents, reporting that women administered misoprostol had a higher incidence of vaginal delivery over those administered dinoprostone, with similar incidences of uterine hyperstimulation, cesarean delivery and fetal tachsystole [7]. Hofmeyr et al (10)

reported that misoprostol needs less oxytocin and is associated with a lower rate of failure to achieve vaginal delivery within 24 hours. In contrast, Liu et al[10] considered that although misoprostol appears to be more efficient in inducing labour than dinoprostone regarding time to achive labor period, the latter is safer than misoprostol due to its lower rates of uterine tachysystole and hyperstimulation. As no clear tendencies can be concluded from these results, further studies are needed to evaluate the effectiveness of both products.

During IOL, the assessment of uterine activity is essential to determine the uterine response to the pharmacological agents, since an excess may endanger maternal and fetal well-being, e. g. increased uterine activity is related to a higher incidence of acidosis at birth [11]. Uterine activity (tone, frequency, intensity and duration of contractions) is typically monitored noninvasively with tocodynamometers (TOCO) [12]. However, this method does not provide sufficiently reliable information [13,14] since it is highly influenced by the sensor position and abdominal wall thickness [12]. The TOCO must therefore be constantly recalibrated and the sensor probe repositioned for proper monitoring of uterine activity [12].

Electrohysterography (EHG), the uterine electromyogram recorded on the abdominal surface, is an alternative technique for monitoring uterine activity. Previous studies have established that EHG performs better than TOCO in terms of detecting contraction [12,13,15] and it has been suggested that the intrauterine pressure can be estimated from EHG analysis [16,17]. Moreover, EHG parametrization can be used to characterise the electrophysiological contractions; e. g. differences in EHG parameters have been associated with labour vs non-labour conditions [14,18] or term vs preterm deliveries [19,20].

The present study was based on the hypothesis that dinoprostone or misoprostol administered in late term pregnancies provide different responses in terms of uterine activity. Our objective was not only to compare the traditional obstetrical data associated with IOL efficiency and maternal-fetal safety, which has been the cause of certain controversy, but also to evaluate the electrophysiological response in terms of the evolution of EHG parameters in expectant mothers treated with dinoprostone and misoprostol. This latter with the intention of exploring the possibility of predicting the success of the induction from the electrophysiological response in the first hours.

Materials and methods

An observational study was performed on expectant mothers admitted to the Hospital Universitario y Politécnico La Fe, in Valencia, Spain, for cervical ripening and induced labour by either misoprostol or dinoprostone vaginal inserts. The inclusion criteria were induction of labour in late-term gestation with singleton pregnancy, null parity, cephalic presentation, and unfavourable cervix (defined as Bishop score <= 6). Exclusion criteria were: active cardiac, renal, pulmonary or hepatic disease, severe preeclampsia, placenta previa, premature rupture of membranes and vaginal bleeding during pregnancy, previous cesarean section, and suspected fetal compromise (growth restriction oligohydramnios, known fetal anomalies, etc.).

In order to determine the number of women to enrol in the study, a non-equality test was designed (contrast of usual hypothesis) in which a confidence interval for the difference was estimated. It was established an error type 1 (α) of 0.05, an error type 2 (β) of 0.2, so as to achieve a statistical power ($1 - \beta$) of 80% and it is considered a clinically relevant difference (Δ) of 15 %. Therefore, the estimated sample size was 165 per drug (misoprostol and dinosprostone). Nonetheless, given the possibility of

continuing to make records and in order to give more robustness to the study, the database was expanded to approximately 250 women per branch.

The induction method for the dinoprostone cohort was dinoprostone 10 mg (Propess, Ferring S.A.U) inserted into the posterior vaginal fornix with removal after at least 12 h. No additional doses of dinoprostone were given. The misoprostol cohort received a 25 mcg tablet (Misofar, Laboratorios BIAL, S.A) inserted in the posterior vaginal fornix. If required, an additional 25 mcg tablet could be administered every 4 h up to a maximum of 4 doses, at the obstetrician's discretion.

The mothers were transferred to the labour ward if a regular contraction pattern was observed or active labour was diagnosed. IOL was considered successful when the active phase of labour was reached, i.e. when woman experience regular uterine dynamic with 3-5 contraction every 10 minutes, 4 cm of cervical dilatation and cervical effacement [21]. Therefore, labour induction was considered failed when women did not achieve active phase of labour. The women were thus subdivided into the following groups: GMS (misoprostol-success), GMF (misoprostol-failure), GDS (dinoprostone-success) and GDF (dinoprostone-failure). The collected obstetric data included maternal age, gestational age, estimated fetal weight, and preinduction Bishop score. The outcomes used to assess labour induction in both groups were: the need to use oxytocin, success and time to active period, success and time to vaginal delivery, time to achieve regular uterine activity and cesarean section rate. Maternal-fetal safety included uterine hyperstimulation rate, incidence of meconium-stained amniotic fluid and neonatal outcomes.

Continuous cardiotocograph recordings were made with a Corometrics 250cx commercial maternal monitor (General Electric Healthcare) from at least 30 min prior to drug administration and during the entire IOL process. Additionally, when EHG

recording devices and qualified staff were available, EHG recordings were taken in a women subgroup to further characterize uterine response to drugs, comprising 30 minutes of basal activity (without drug) until 4 hours after drug administration. For each EHG recording session the woman's abdominal surface was exfoliated with gel (Nuprep, Weaver and Company, USA). A bipolar signal was captured from two Ag/AgCl disposable electrodes (Kendal, USA) supraumbilical at each side of the medial line with 8cm of inter-electrode distance corresponding to EHG monopolar records (M1, M2). Reference and ground electrodes were placed on each of the woman's hips. The electrodes were connected to commercial biosignal amplifiers (Grass 15LT+4 Grass 15A94; Grass Instruments, West Warwick, RI) in which the signals were amplified and filtered between [0.1, 30] Hz to be subsequently acquired at a sampling frequency of 1000 Hz. To eliminate low- and high-frequency interference and noise, the signals were also bandpass filtered between 0.2 – 1 Hz with a 5th order Butterworth filter and subsequently down-sampled at 20 Hz.

All the EHG-bursts present in the EHG recordings were manually segmented according to the following rules: i) the bursts had to synchronise with the contractions detected in the simultaneous uterine pressure record, ii) entail a significant increase in EHG amplitude and/or frequency in comparison to rest activity, and iii) last for a minimum duration of 30 seconds with no evidence of artefacts during contraction [22].

In order to characterize the electrophysiological state of the uterus, the parameters of EHG-bursts were extracted from the temporal and spectral domain. In the former, the following parameters were computed: duration (s), peak-to-peak amplitude (μV), number of contractions (NCT), and pseudo-Montevideo units (PMU). PMU was calculated as the total energy of contractions present in the EHG within a 30 min interval. Since it has been proven that there is a shift of spectral content towards high

frequencies as labour approaches [20,23,24], the following spectral parameters were extracted from the power spectral density of the EHG-bursts estimated by the periodogram method: mean frequency in the range 0.2-1Hz (MF) and the ratio between the energy content in high (0.34-1 Hz) and low (0.2-0.34Hz) frequency (HL ratio). The median of the values of the parameters obtained from contractions present in 30 min analysis windows were computed, and mean and standard deviation were then calculated for all the women in each group.

Statistical Analysis

A statistical analysis was performed using the Chi-square test, paired t-test and Wilcoxon or Mann–Whitney test, where appropriate, using SPSS v22 (SPSS, Chicago, USA). A P value < 0.05 was considered significant.

Ethical Approval

Approval was granted by the local medical ethical board (code: DINOMISO, approved 30th of June, 2015) and written informed consent was obtained from each of the volunteers. The study adhered to the Declaration of Helsinki's guidelines.

Results

Table 1 shows the main demographic characteristics of the study population; 500 expectant mothers were included in the study: 249 in the dinoprostone cohort and 251 in the misoporostol cohort. No statistical differences were found between the cohorts in the population study as regards mean maternal age, gestational age, fetal weight estimation and Bishop Score before IOL.

Table 2 shows the IOL characteristics for the total population. Similar rates of vaginal deliveries were obtained in both cohorts (74% and 75%). However, the

misoprostol cohort was associated with shorter time in achieving vaginal delivery: 18.69± 8.57 h versus 21.21 ± 9.87 h than the dinoprostone cohort (p=0.009). The former group showed a higher percentage of vaginal deliveries in less than 24h (75%) vs 56% in the latter group (Risk ratio (RR): 1.33 95%CI 1.15 – 1.55, p=0.0002). To assess the efficacy of labour induction related with the Bishop Score in vaginal deliveries (excluding cesarean deliveries), we divided the Bishop Score before IOL data into two groups (Table 3). For women included in the very unfavourable group (Bishop score 0-3), those induced with misoprostol were associated with more vaginal deliveries in less than 24h (72%, 110 out of 152) than those administered dinoprostone (51%, 76 of 150) (RR: 1.41, IC95% 1.17 – 1.69 p=0.002).

Regarding uterine contractions, the interval between administration of the drug until regular uterine dynamics appeared was shorter for the misoprostol than the dinoprostone cohort, 312.45 ± 196.11 vs 349.53 ± 174.64 minutes (p=0.03), see Table 2. Although similar numbers of women achieved active labour in both cohorts (88% and 87%), the misoprostol group achieved it earlier than the dinoprostone group:15.45 ± 8.02h vs 17.38 ± 8.83 h (p=0.017). Additionally, 43.03% of the mothers in the misoprostol group required augmentation with oxytocin, compared with 55.02 % in the dinoprostone group (p=0.01). No statistical differences were found between the groups regarding the parameters that assess maternal and fetal safety from the onset of IOL until active labour.

A total of 66 women with singleton pregnancies were included in the EHG study, of whom 33 received misoprostol and 33 dinoprostone. The characteristics and success rate of labour induction and the comparisons with the original cohorts are summarized in supplementary information (see Table S1). Only vaginal delivery before

24h or after 24 h using misoprostol showed statistical differences with the original cohort shown in Table 2 (p=0.01).

Figure 1A shows a TOCO and a simultaneous EHG recording from a woman who reached active labour in the misoprostol cohort. Comparing the EHG-bursts present at basal activity and those acquired in the last hour of recording, the later EHG-bursts were higher in frequency and amplitude and of shorter duration. In contrast, only duration (and amplitude to a lesser extent) of the EHG-bursts exhibited a clear change as labour progressed in the dinoprostone cohort, as can be seen in Figure 1B.

The temporal evolution of the computed parameters in both the misoprostol and dinoprostone cohorts are shown in Figure 2; detailed mean and standard deviation values of the parameters are provided in supplementary information (Table S2). In the misoprostol cohort, the EHG-burst duration before administration was 81.7 ± 17.6 s and decreased progressively to values of 66.5 ± 13.7 s at the end of the recording session for GMS. EHG-burst duration was also seen to drop in the failure group (GMF), resulting in a smaller reduction, from 82.63 ± 20.74 s to 73.83 ± 19.86 s. The success group presented a higher increment in their values than the failure group for peak-to-peak amplitude as well as spectral parameters (MF and H/L ratio). The pseudo-Montevideo units also showed a progressive rise in value for GMS that was not seen in the GMF.

Similarly, clear trends of successful induction (GDS) were seen in the dinoprostone cohort in parameter duration, peak-to-peak amplitude, PMU and number of contractions. EHG-burst duration was reduced throughout the recording session with values at basal activity of 83.7 ± 19.2s and72.9 ± 29.0 at the end of the recording session. In contrast, peak-to-peak amplitude values increased, while none of the spectral parameters showed clear trends. PMU values were greater in the success group (GDS)

than in the failure group (GDF) in most of the analysis windows and an upward trend was observed in successful inductions throughout the recording session.

Comparing both success groups (GMS vs. GDS) it can be clearly appreciated that duration and peak-to-peak amplitude evolved along similar lines, showing decreasing and increasing tendencies respectively. Regarding the spectral parameters, well established trends were seen in the misoprostol group and significant differences with dinoprostone were found 4 hours after vaginal administration for MF and H/L ratio. In MF an evidently increasing trend is seen for misoprostol, while dinosptrone values remain almost constant. Similar behaviour can be observed in the evolution of the H/L ratio (see Figure 2). Finally, both PMU and NCT parameters showed increasing trends in both successful groups, with higher values for dinoprostone than for misprostol.

To assess the evolution of the statistical significance of each parameter in each group in order to characterize the uterine response to drug administration, we compared the parameter values in every analysis window with those of basal activity in each group. The parameters with statistical significance in each group are given in Table 4. First, with one exception (GMF, 150'), no significant differences were found in the failure groups (GDF and GMF). In the success groups, more EHG parameters in the misoprostol group presented statistical differences ($p<0.05$) with basal recording in comparison to the dinoprostone group. PMU and amplitude increased significantly in the former group as early as 60 minutes and the statistical differences remained until the end of the recording. NCT and spectral parameters (MF and H/L) also increased significantly throughout the recording session, showing statistical differences with basal activity after 90 and 150 minutes, respectively. In the dinoprostone group, NCT and

duration rose and fell significantly, respectively, after 120 minutes until the end of the recording. PMU increased significantly after 180 m until the end of the recording.

Discussion

Fetal and maternal risks have been found to increase in post-term pregnancies, and several studies have related the increase of maternal and neonatal morbidity with more than 41 weeks of gestation [25,26]. The question of whether inducing labour in late-term pregnancies improves the outcome according to whether misoprostol 25 mcg or dinoprostone 10 mg is administered remains unclear, as does their electrophysiological influence on uterine dynamics. In this observational study, we assessed the efficiency, safety and electrophysiological characteristics of pharmacologically induced labour by dinoprostone and misoprostol in late-term pregnancies.

Regarding the efficiency and safety of IOL, our results show that mothers administered misoprostol have better rates of vaginal delivery in less than 24h after drug administration (RR: 1.33 95%CI 1.15 – 1.55, p=0.0002), achieve regular uterine contractions and active labour in significantly shorter times than those administered dinoprostone, and require less oxytocin augmentation (p=0.01). These results agree with previous randomized controlled trials [7,27]. Additionally, misoprostol achieves significantly higher rates of vaginal delivery for the very unfavourable cervix group (RR: 1.41, IC95% 1.17 – 1.69 p=0.002). Both drugs have similar safety profiles, the cesarean rate does not show significant differences, and the neonatal outcomes were similar for both cohorts. These results are in agreement with some previous studies [7,27], but not with those that argue that the use of misoprostol may lead to increased episodes of tachysystole and hyperstimulation [10]

Parameters were extracted from the EHG-burst to assess the electrophysiological characteristics of the contractions. The results show that parameter peak-to-peak

amplitude was significantly higher than basal activity in succes groups and that the differences started earlier in misoprostol success group than in dinoprostone success group (60 vs. 180 minutes). Only GMS showed a noticeable shift toward higher frequencies throughout the recording session. This is consistent with studies that analyzed the electrical activity of the human uterus during pregnancy and labour at term [20], obtaining significantly higher peak frequency for women delivering <24h from the recording than those that delivered >24h (0.4768± 0.0144 Hz vs 0.4042±0.0185 Hz). These results suggest that misoprostol provides effective contractions earlier, which are related not only to higher amplitudes but also to higher frequencies of EHG-bursts, as suggested by Garfield et al [23], who indicated that effective contractions require multiple and higher frequency of action potential spikes of uterine cells. In the misoprostol group, the changes in uterine electrophysiological state can be appreciated in the well-established statistical differences (maintained until the end of the EHG recording) identified in most of the parameters 90 minutes after labour induction. Furthermore, PMU was significantly higher at 60 minutes after labour induction, which agrees with the findings of other studies [28], which also reported that regular uterine contractions appeared after 1-2 h and uterine activity increased throughout the recording session. The time required to achieve significant changes in EHG characteristics is consistent with pharmacokinetic studies [29] in which peak plasma concentration is reached between 75 and 80 minutes after 400 µg vaginal administration, then decreasing slowly with detectable levels of the drug even after 6 h.

In the dinoprostone group, only duration and NCT parameters changed significantly from the basal state after 2 h of drug administration for succesful inductions (GDS). No significant and maintained changes in peak-to-peak amplitude or spectral parameters were seen in the first 4 hours of induction in this group. Other

studies found that uterine EMG activity significantly increases between 2-8 h after dinoprostone administration [30]. Although there was no statistical difference in the temporal evolution of peak-to-peak amplitude, this parameter started a noticeable increase 60 minutes after drug administration. This result is consistent with Yount et al's pharmacokinetic study [31] in which peak plasma level was reached about 1-2 hours after vaginal dinoprostone administration. The fact that no changes were observed in the spectral parameters in the GDS group could therefore be due to the relatively slow dynamics of the drug and to a short analysis window (4 h). In this respect, it would be desirable to extend the recording time (up to 8 h) to better analyze the uterine electrophysiological response of this group.

The results of the present study indicate that the misoprostol success and failure groups had a different electrophysiological response to the induction drug. Although a larger database would be required to corroborate these results, they suggest that EHG recordings could be used for early prediction of induction success.

In conclusion, the present study not only compared obstetrical outcomes but also the uterine electrophisiological response of expectant mothers treated with 25 µg of misoprostol (doses repeated up to 4 times) and those vaginally administered 10 mg of dinoprostone. Successful labour induction by misoprostol is associated with earlier effective contractions than when induced by dinoprostone. We also found that the evolution of the EHG-burst parameters are in line with the pharmacokinetics of each drug and was more evident in misoprostol. In successful inductions by misoprostol, myoelectrical uterine activity presented a significant shift towards higher frequencies associated with a greater excitability of muscular cells. Different patterns were obtained for successful and failed IOLs with both drugs. The results suggest that EHG provides relevant information on the electrophysiological state of the uterus during labour

induction, and indicate the possibility of designing a system able to predict labour outcomes. This would provide improved maternal-fetal well-being as well as reduced hospital costs, as it has been found that cesarean sections performed after prolonged failed inductions require longer hospitalization and greater attention to both mother and child [32]. Results also show that EHG monitoring could provide further insight into the best dosage and method of IOL drug administration.

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Conflicts of interest

This research has received funding from Bial S.A. a company that may be affected by the research reported in the enclosed paper.

References

1. Bleicher I, Vitner D, Iofe A, et al. When should pregnancies that extended beyond term be induced? *. J. Matern. Neonatal Med. 2017;30:219–223.
2. Wing DA. Principles of labor induction. [Internet]. Available from: http://www.uptodate.com/home.
3. Martin JA, Hamilton BE, Osterman MJK, et al. Births: final data for 2012. Natl. Vital Stat. Rep. 2013;62:1–68.
4. Glantz JC. Obstetric variation, intervention, and outcomes: doing more but

accomplishing less. Birth. 2012;39:286–290.

5. Henderson J, Redshaw M. Women's experience of induction of labor: a mixed methods study. Acta Obstet. Gynecol. Scand. 2013;92:1159–1167.

6. Dögl M, Vanky E, Heimstad R. Changes in induction methods have not influenced cesarean section rates among women with induced labor. Acta Obstet. Gynecol. Scand. 2016;95:112–115.

7. Austin SC, Sanchez-Ramos L, Adair CD. Labor induction with intravaginal misoprostol compared with the dinoprostone vaginal insert: a systematic review and metaanalysis. Am. J. Obstet. Gynecol. 2010;202:624.e1-9.

8. Nadia Bennett K, Park H, Cioffi J, et al. A comparison of obstetrical outcomes and costs between misoprostol and dinoprostone for induction of labor. J. Matern. Neonatal Med. 2016;29:3732–3736.

9. Wang L, Zheng J, Wang W, et al. Efficacy and safety of misoprostol compared with the dinoprostone for labor induction at term: a meta-analysis. J. Matern. Fetal. Neonatal Med. 2015;7058:1–11.

10. Liu A, Lv J, Hu Y, et al. Efficacy and safety of intravaginal misoprostol versus intracervical dinoprostone for labor induction at term: A systematic review and meta-analysis. J. Obstet. Gynaecol. Res. 2014;40:897–906.

11. Mussi S, Incerti M, Plevani C, et al. Effect of oxytocin during labor on neonatal acidemia. J. Matern. Neonatal Med. J. J. Matern. Neonatal Med. J Matern Fetal Neonatal Med. 2016;29:3098–3103.

12. Euliano TY, Nguyen MT, Darmanjian S, et al. Monitoring uterine activity during labor: A comparison of 3 methods. Am. J. Obstet. Gynecol. 2013;208:66.e1-66.e6.

13. Alberola-Rubio J, Prats-Boluda G, Ye-Lin Y, et al. Comparison of non-invasive electrohysterographic recording techniques for monitoring uterine dynamics. Med. Eng. Phys. 2013;35:1736–1743.

14. Schlembach D, Maner WL, Garfield RE, et al. Monitoring the progress of pregnancy and labor using electromyography. Eur. J. Obstet. Gynecol. Reprod. Biol. 2009;144:S33–S39.

15. Hadar E, Biron-Shental T, Gavish O, et al. A comparison between electrical uterine monitor, tocodynamometer and intra uterine pressure catheter for uterine activity in labor. J. Matern. Neonatal Med. J Matern Fetal Neonatal Med. 2015;28:1367–1374.

16. Euliano T, Skowronski M, Marossero D, et al. Prediction of intrauterine pressure waveform from transabdominal electrohysterography. J. Matern. Neonatal Med. 2006;19:803–808.

17. Rabotti C, Mischi M, van Laar JOEH, et al. Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals. Physiol. Meas. 2008;29:829–841.

18. Ye-Lin Y, Prats-Boluda G, Alberola-Rubio J, et al. Prediction of labor using non-invasive laplacian EHG recordings. 2013 35th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE; 2013. p. 7428–7431.

19. Lucovnik M, Kuon RJ, Chambliss LR, et al. Use of uterine electromyography to diagnose term and preterm labor. Acta Obstet. Gynecol. Scand. 2011;90:150–157.

20. Maner WL, Garfield RE, Maul H, et al. Predicting term and preterm delivery with transabdominal uterine electromyography. Obstet. Gynecol. 2003;101:1254–1260.

21. World Health Organization. Recommendations for augmentation of labour. 2014. Available online at: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/augmentation-labour/en/.

22. Ye-Lin Y, Garcia-Casado J, Prats-Boluda G, et al. Automatic Identification of Motion Artifacts in EHG Recording for Robust Analysis of Uterine Contractions. Comput. Math. Methods Med. 2014;2014:119–145.

23. Garfield RE, Maner WL. Physiology and electrical activity of uterine contractions. Semin. Cell Dev. Biol. 2007;18:289–295.

24. Leman H, Marque C, Gondry J. Use of the electrohysterogram signal for characterization of contractions during pregnancy. IEEE Trans. Biomed. Eng. 1999;46:1222–1229.

25. Halloran DR, Cheng YW, Wall TC, et al. Effect Of Maternal Weight On Postterm Delivery. J Perinatol. 2012;32:85–90.

26. Adhikari M, Gouws E, Velaphi SC, et al. Meconium aspiration syndrome: importance of the monitoring of labor. J. Perinatol. 1998;18:55–60.

27. Vogel JP, Gülmezoglu AMM, Hofmeyr GJ, et al. Global Perspectives on Elective Induction of Labor. Clin. Obstet. Gynecol. 2014;57:331–342.

28. Aronsson A, Bygdeman M, Gemzell-Danielsson K. Effects of misoprostol on uterine contractility following different routes of administration.

29. Shan Tang O, Schweer H, Seyberth HW, et al. Pharmacokinetics of different routes of administration of misoprostol. Hum. Reprod. 2002;17:332–336.

30. Aviram A, Melamed N, Hadar E, et al. Effect of Prostaglandin E2 on Myometrial Electrical Activity in Women Undergoing Induction of Labor. J Perinatol. 2014;31:413–418.

31. Yount SM, Lassiter N. The Pharmacology of Prostaglandins for Induction of Labor. J. Midwifery Women's Heal. 2013;58:133–144.

32. Nicholson G, Cyr PL. Cost Of Failed Labor Induction: A Us Hospital Perspective. Value Heal. 2013;16:A75.

Figure Captions

Figure 1. Example of TOCO and simultaneous EHG recordings of women that reached active labour after IOL with A) misoprostol, B) dinoprostone

Figure 2. Temporal evolution of EHG parameters in 30min windows. Drug was administered after 30 minutes of basal recording (marked with a black line). Statistical difference between GMS and GDS is marked with a grey circle on the time axis. GMS: group of misoprostol success; GMF: group of misoprostol failure; GDS: group of dinoprostone success; GMF: group of dinoprostone failure.