Comparison of the Electrophysiological Myoelectrical Activity Evolution in Induction of Labor with Pharmacological and Mechanical Methods

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Keywords: Electrohysterography, Induction of Labour, Foley, Dinoprostone, EHG-Biomarker.

Abstract: Induction of labour (IOL) refers to triggering the contractions onset, either by pharmacological (PIOL) or mechanical methods (MIOL), and is indicated when maternal and foetal well-being is compromised. There is great uncertainty regarding the success of IOL regardless of the method. In current clinical practice, it is based on assessment of cervical status by Bishop's score and degree of uterine activity by tocography. However, Bishop's score has been shown to be subjective and poorly reproducible and tocography requires constant repositioning and is severely affected by obesity. Meanwhile, electrohysterography (EHG) has surpassed traditional clinical measures in monitoring PIOL progress and predicting its outcome. Although there is no evidence of uterine myoelectric activity response of MIOL. Therefore, this work aimed to identify EHG-biomarkers to help to determine possible differences in myoelectric response between PIOL and MIOL success. For this purpose, the uterine response during the first 5h after Dinoprostone (PIOL) administration and Foley catheter (MIOL) insertion was compared by EHG. For PIOL, a significantly lower time to achieve active phase of labor and delivery, together with faster myoelectric response was found: slightly higher contraction force, significantly higher Mean Frequency and lower Spectral Entropy after 2.5h. Between-group differences were especially marked in Spectral Entropy (90-150 and 210-300min). Overall, this pioneering work has demonstrated the feasibility of EHG for the characterisation of evolution also in MIOL. Furthermore, the results suggest that EHG biomarkers may be useful in the IOL method comparison, although they should be cross-checked with expanded databases and further investigations.

1 INTRODUCTION

Induction of labour (IOL) refers to the process of artificially stimulating the uterus to initiate labour by pharmacological or mechanical agents when continuation of gestation compromises maternal-fetal well-being (Reshme, Samal, Padmaja, Shalini, & Radhika, 2022). Indications for IOL include elective induction at 40 weeks, prolonged pregnancy, pregnancy-induced hypertension or diabetes, oligohydramnios, intrauterine growth restriction and Rh isoimmunisation (Liu et al., 2019; Reshme et al., 2022).

The global incidence of IOL tripled between 1990 and 2019, going from 9.5% in 1990 to 29.4% in 2019 in the United States (Martin, Hamilton, Osterman, & Driscoll, 2021), while the worldwide prevalence is estimated by the WHO at 25% (World Health

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Diaz-Martinez, A., Ye-Lin, Y., Monfort-Ortiz, R., Garcia-Casado, J., Rey-Ferreira, I., Nieto-del-Amor, F., Diago-Almela, V., Martinez-de-Juan, J. and Prats-Boluda, G.
Comparison of the Electrophysiological Myoelectrical Activity Evolution in Induction of Labor with Pharmacological and Mechanical Methods.
DOI: 10.5220/0011664700003414
In *Proceedings of the 16th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2023) - Volume 4: BIOSIGNALS*, pages 66-73
ISBN: 978-989-758-631-6; ISSN: 2184-4305

Organization, 2018). Out of the three and a half million newborn registered in 2021 only in the USA, between twenty thousand and forty thousand will end the IOL process as failed, which in the broadest sense is defined as the non-achievement of vaginal delivery (Ayala & Rouse, 2022; Hamilton, Martin, & Osterman, 2022). This entails an elevated risk of maternal and perinatal complications, including higher rates of obstetric intervention, cesarean delivery, chorioamnionitis, admission to the neonatal intensive care unit, and increased blood loss (Ayala & Rouse, 2022). If the IOL is unsuccessful, the protocol is to perform a cesarean section which can cost up to $7,595 (1.3 times a standard cesarean section) in the USA (Nicholson & Cyr, 2013). Not only does it have a major impact on maternal and neonatal health, but IOL also overburdens delivery rooms and affects health care costs, costing more than $2 billion annually in the USA (Kaimal et al., 2011). Given the volume of IOLs performed each year, the development of a robust and reliable system to aid in procedural decision making would be a key factor in enabling clinicians to better plan and manage deliveries, prevent maternal and fetal complications, and optimize hospital resources.

IOL methods can be broadly divided into pharmacological (PIOL) and mechanical (MIOL) (Liu et al., 2019). The former involve the administration of prostaglandins, orally or vaginally, to stimulate the onset of contractions. Among the most commonly employed options, the use of E2 (PGE2-Dinoprostone) is distinguished by its slow-release vaginal application, which allows clinicians to respond quickly in case a complication arises (Geethanjali & Palli, 2022; Reshme et al., 2022). Whereas the latter consist of the use of balloon devices and hygroscopic dilators that, applying pressure to the internal face of the cervix so as to increase endogenous prostaglandin secretion. c Of these, the Foley catheter stands out for its low cost, simplicity, reversibility and lack of serious side effects. In comparison with PIOL, IOL with amniotic balloons requires a subsequent oxytocin augmentation procedure in many cases, which is associated with a significant rate of dysfunctional deliveries and caesarean sections (Geethanjali & Palli, 2022; Salim et al., 2011). Despite of this, the literature suggests that mechanical methods have similar efficacy, incur fewer adverse events (such as uterine tachycardia) and have lower costs compared to pharmacological agents (Jozwiak et al., 2012).

On the other hand, in order to assess IOL evolution in current clinical practice, the most commonly used method consists of the assessment of cervical status and uterine dynamics, as measured by Bishop Score (BS) and tocography respectively (Euliano et al., 2013; Geethanjali & Palli, 2022). Despite being widely employed, BS has been shown to be subjective and has poor reproducibility, making it a poor predictor of IOL outcome (Marconi, 2019). In terms of contraction detection, it should be noted that electrohysterography (EHG) is a promising research technique that has been shown to outperform tocography in both pregnancy and childbirth (Mas-Cabo et al., 2020; Song et al., 2021; J. Xu, Chen, Lou, Shen, & Pumir, 2022), especially in the growing population of obese patients (Krogh et al., 2022; Mas-Cabo et al., 2020). EHG consists of recording uterine myoelectric activity generated by billions of myometrial cells on the abdominal surface. Its energy is distributed over a bandwidth ranging from 0.1 to 4 Hz (Devedeux, Marque, Mansour, Germain, & Duchêne, 1993). EHG-bursts are composed by the slow wave (SW) -which has a period equal to the duration of the contraction and whose bandwidth overlaps with the baseline being difficult to analyse and extract reliable information from it (Nieto-Del-Amor et al., 2021)- and by the fast wave (FW), which can be further divided into two components (Devedeux et al., 1993; Terrien, Marque, & Karlsson, 2007): the Fast Wave Low (FWL) which ranges from 0.13 to 0.26 Hz and is associated with the propagation of the contraction, and the Fast Wave High (FWH) which ranges from 0.26 to 0.88 Hz and is related to the excitability of the uterine cells (Benalcazar-Parra et al., 2018; Mas-Cabo et al., 2020). Although the frequency content of FWH is thought to extend up to 3-4 Hz (Fele-Žorž, Kavšek, Novak-Antolič, & Jager, 2008), a high proportion of studies focus down to 1Hz perhaps as a consequence of maternal cardiac interference (1.38-1.5 Hz) (J. Xu et al., 2022).

Considering the aforementioned, the aim of the present work is therefore to characterize and compare the uterine electrophysiological response to IOL by Dinoprostone and by Foley catheter during the first 5 hours of induction by electrohysterography and its associated EHG-Biomarkers of women who achieve Active Period of Labour (APL). Given the large increase in the rate of inductions in recent years, improving the understanding of the myoelectric response to pharmacological and mechanical inductions is becoming increasingly relevant to clinical practice. Not only to guide clinical practices, but also to delve deeper into the underlying physiological mechanism and thus promote a better understanding of the optimal methods for IOL in each case.

2 MATERIALS AND METHODS

2.1 Study Design

A prospective observational cohort study was conducted in pregnant women admitted for cervical ripening at the Hospital Universitario y Politécnico La Fe (Valencia, Spain). Either they were candidates for pharmacological induction with Dinoprostone (10mg, Propess, Ferring SAU) or mechanical induction with a Foley catheter (Folysil, Coloplast). Both methods were withdrawn after 12 hours. In case the catheter fell out on its own during the MIOL procedure it ended earlier. In this study only IOLs that reached the active period of labor were considered. Fetal macrosomia, multiple pregnancies, advanced maternal age (>45 years), severe preeclampsia, placenta previa, premature rupture of membranes, vaginal bleeding during pregnancy and active cardiac, renal, pulmonary or hepatic disease; were exclusion factors for this study due to bias. This work adhered to the guidelines of the Declaration of Helsinki and was approved by the hospital's Institutional Review Board (Registration Number 2018/0530). Patients were informed of the nature of the study and gave written informed consent.

The following clinical information was included: maternal age, body mass index (BMI), number of previous pregnancies, parity, gestational age at delivery, initial BS, increase in BS during IOL (12 h after insertion), time to achieve APL, time to delivery and completion of vaginal delivery. The chi-square test was used to detect statistically significant differences in nominal variables between groups. Ordinal variables were compared using the Wilcoxon rank sum test. Continuous variables were compared with Student's t test or the Wilcoxon rank sum test, depending on whether they were considered normal or not by the Shapiro-Wilk test.

2.2 Signal Acquisition

For EHG recording, the abdominal surface was exfoliated using abrasive gel (Nuprep, Weaver and Company, Aurora, CO, USA) and cleaned with isopropyl alcohol to reduce skin-electrode impedance. Four single-use Ag/AgCl electrodes (Red Dot 2660-5, 3M, St. Paul, MN, USA) were then placed as shown in Figure 1. Two electrodes (M1 and M2) were placed symmetrically with respect to the mid-axis at a distance of 6 cm from each other. The other two electrodes were placed on each hip to provide reference and ground biopotentials.

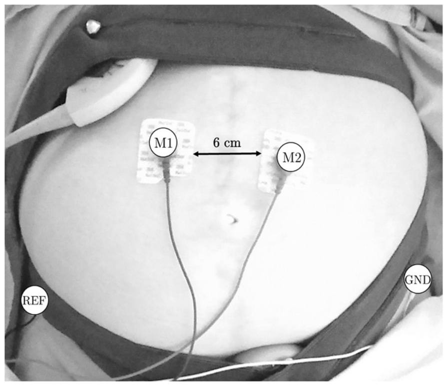

Figure 1: Electrodes positioning for uterine myoelectrical recording. M1: monopolar electrode 1. M2: monopolar electrode 2. REF: Reference electrode. GND: Ground electrode.

Both monopolar signals were conditioned with a custom-made wireless recording module, which provided a gain of 2059 V/V in the 0.1-150 Hz bandwidth and digitized with a 24-bit analog-to-digital converter at 500 Hz (Ye-Lin, Bueno-Barrachina, Prats-boluda, Rodriguez de Sanabria, & Garcia-Casado, 2017). The recording starts 30 minutes before the start of the IOL and ends 5 hours later. Unlike other research settings where up to 16 electrodes are placed (Muszynski et al., 2018; Y. Xu, Hao, & Zheng, 2020), this simplified protocol was chosen because it does not compromise routine clinical practice or add additional complexity to the highly stressful situation faced by women due to the imminence of labor (Benalcazar-Parra et al., 2018).

Digitalized monopolar EHG signals were filtered between 0.1-4 Hz (5th order zero-phase Butterworth bandpass filter) and then downsampled to 20 Hz to maintain a balance between temporal resolution and computational cost (Diaz-Martinez et al., 2021; Mas-Cabo et al., 2020). A bipolar signal was then computed as its difference (M2-M1) to reduce common-mode interference and increase signal quality (Mas-Cabo et al., 2020; J. Xu et al., 2022). Finally, two experts identified the onset and end of the EHG bursts, which were related to uterine contractions. They were associated with substantial changes in amplitude and frequency with respect to the reference tone with durations longer than 40 seconds and without respiratory interference or motion artefacts (Diaz-Martinez et al., 2021; Mas-Cabo et al., 2020; J. Xu et al., 2022).

2.3 EHG Parametrisation

In order to characterize uterine contractions, a set of temporal, spectral and nonlinear parameters were calculated from the EHG-Bursts. The Root Mean Square (RMS) calculated at 0.1-4 Hz was included as a measure of amplitude related to uterine contraction intensity (Diaz-Martinez et al., 2021; Mas-Cabo et al., 2020). As labor progresses, contractions are more frequent and of greater intensity, which is equivalent to a higher signal amplitude (Diaz-Martinez et al., 2021; J. Xu et al., 2022). The RMS is therefore expected to show an upward trend throughout the IOL. In addition, the Mean Frequency (MNF) was calculated in order to characterise the expected shift in spectral content towards higher frequencies due to enhanced cell excitability as parturition approaches. It was calculated at 0.2-1 Hz (Horoba et al., 2016; Mas-Cabo et al., 2020) to minimise the influence of cardiac interference and baseline fluctuation (J. Xu et al., 2022). Successful IOL is associated with an increase in MNF (Diaz-Martinez et al., 2021). Finally, Spectral Entropy (SpEn) (Diaz-Martinez et al., 2021; J. Xu et al., 2022) and Higuchi Fractal Dimension (HFD) (Diaz-Martinez et al., 2021; Kesić & Spasić, 2016) were computed as non-linearity parameters. It was done in the FWH bandwidth to provide a robust characterisation of the EHG (Mas-Cabo et al., 2020; J. Xu et al., 2022). It is due to the fact that as delivery approaches, myoelectric activity also tends to become more organised and predictable, resulting in a downward trend of non-linearity parameters (Benalcazar-Parra et al., 2018; Diaz-Martinez et al., 2021).

EHG parameters were calculated for each section identified as contraction during the first five hours of induction. Then, in order to reduce the effect of intrinsic variability of uterine contractility, uterine contractility was analysed at 30-minute time (from now on, analysis window) (Benalcazar-Parra et al., 2018; Diaz-Martinez et al., 2021). There were 11 windows per recording: 1 in the baseline condition (before drug administration or probe placement) and 10 to assess the response during the first five hours of IOL. Median values of the EHG-burst parameters were calculated for each 30-minute window in order to obtain a single representative value per analysis window for each recording session. Then, the mean of each parameter in each 30-minute window was calculated for each group (MIOL and PIOL).

Finally, statistically significant differences in uterine myoelectric response between MIOLs and PIOLs were analysed. For this purpose, significant changes from baseline activity of EHG parameters throughout the recording session were determined for each window of analysis and for each induction method using the Wilcoxon signed-rank test (α=0.05). The same statistical test was employed to evaluate the differences between induction methods, comparing each parameter in each window of analysis between the methods.

3 RESULTS

A total of 73 patients were recruited, of which 52 were induced by pharmacological methods and the remaining 21 by mechanical methods. Their obstetric and delivery variables are summarised in Table 1. Significant differences have been found for parity, gestational age at delivery, time to reach the active period of labour and time to delivery between MIOL and PIOL.

Table 1: Obstetric data and outcomes of labour induction of women enrolled in the study, mean ± standard deviation or number of cases. BMI: Body Mass Index. GAD: Gestational Age at Delivery in weeks. BS: Bishop Score. APL: Active Period of Labour. p: Wilcoxon Rank-sum or t-student test p-value (in bold: statistically significant difference, p<0.05).

Variable		MIOL	PIOL	p
Mat. age (years)	μ±σ	32.2±5.5	34.0±5.6	0.241
BMI (kg/m2)	μ±σ	24.6±4.2	26.05±7.5	0.124
Gestations	μ±σ	2.1±0.7	2.0±1.4	0.212
Parity	μ±σ	0.1±0.4	0.6±0.7	**0.009**
GAD (weeks)	μ±σ	39.4±1.5	40.7±0.5	**<0.005**
Initial BS	μ±σ	3.1±1.2	2.6±2.6	0.427
ΔBS	μ±σ	2.1±1.8	3.3±4.6	0.967
Time to APL (h)	μ±σ	25.9±6.9	16.4±9.1	**<0.005**
Time to Del. (h)	μ±σ	29.2±6.0	20.8±12.1	**<0.005**
Vag. Ending	N	19/21	46/52	0.806

The uterine myoelectric activity parameters in response to the IOL is represented in Figure 2 for the MIOL (blue) and PIOL (red) groups. An increasing trend is described for the RMS in both groups, although it is slightly more accentuated for PIOL. No differences were found with respect to baseline or between IOL methods.

The MNF shows a more pronounced upward trend again for the PIOL group, in which case differences with respect to baseline are identified at 150 and maintained from 210 to 300. By contrast, the MIOL shows no significant evolution. Differences between groups are found at 150 and 210-300.

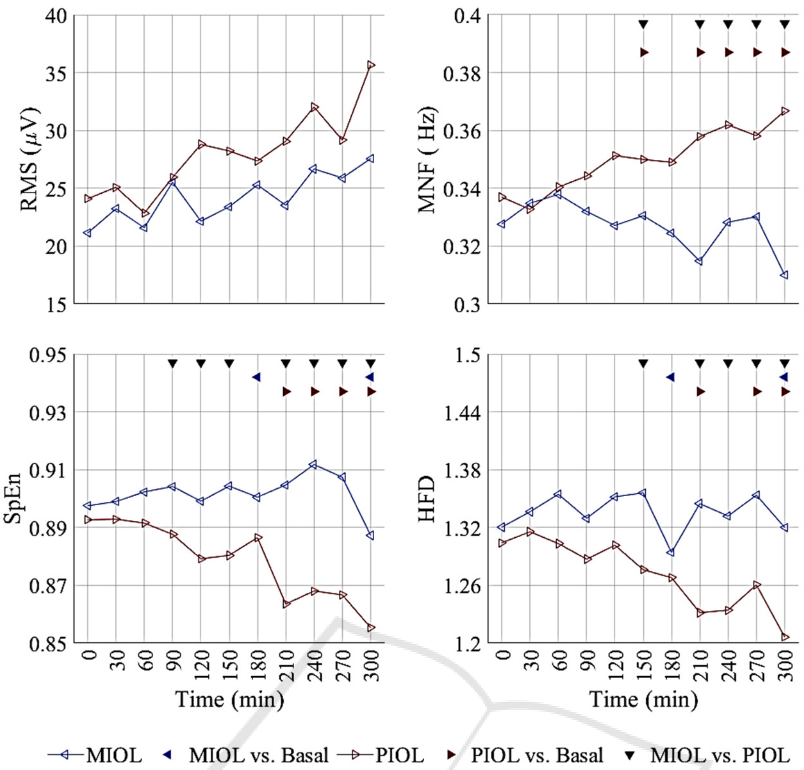

Figure 2: Temporal evolution of temporal, spectral and non-linear parameters for mechanical (MIOL) and Pharmacological Induction of Labour (PIOL) groups. Statistical differences between groups are indicated by black downward-pointing triangles and with respect to basal activity by blue leftward (MIOL) and red rightward (PIOL) triangles.

As for the non-linearity parameters, the trends are also more noticeable for PIOL. For both parameters, difference with respect to baseline were identified for PIOL from 210 and for MIOL only at 180 and 300. By contrast, MIOL did not show any trend during the first 5 hours. When comparing MIOL and PIOL groups, significant differences were found for SpEn from 90 except for 180, and for HFD from 150.

4 DISCUSSION

In this work we have analysed and compared the difference in uterine myoelectric response between the induction methods of Dinoprostone and Foley catheter. As far as we are concerned, this is the first study to report this type of EHG-biomarker in the comparison between IOL methods. These initial results in this line of research will need to be corroborated with expanded databases and future studies, such as the comparison of MIOL successes and failures. We believe that the EHG-biomarker information proposed could lead to the design of robust and generalizable systems for predicting the success of labour induction.

Regarding obstetric variables, differences were found in parity and gestational age at delivery. This can be explained because after a previous caesarean section, IOL is associated with a higher risk of uterine dehiscence, uterine rupture and repeat caesarean section compared to women with spontaneous onset of labour. Mechanical methods are suggested to this group because they are associated to lower risk of hyperstimulation and uterine rupture (Kruit, Wilkman, Tekay, & Rahkonen, 2017). Thus, at equal gestations, there are fewer vaginal deliveries in the MIOL group. Despite this, we believe that the differences found in myoelectric activity are not due to the difference in gestational age, as it is considered that in both groups the uterus are sufficiently mature, in addition to the fact that no significant differences are found at the basal analysis window. We therefore attribute the differences found to the IOL method

It should be added that previous studies in the PIOL field have suggested that the differences that might be due to the number of previous deliveries are minimal, especially in RMS, MNF, SpEn and HFD (Diaz-Martinez et al., 2021). On the other hand, the lower gestational age in the MIOL group is again due to protocol indications, as the use of the Foley catheter was used in case of the fetal growth restrictions, which requires induction at 37 weeks, with a favourable safety profile compared to Dinoprostone (Villalain et al., 2019).

Finally, the time from the induction onset to the active period of labor was significantly shorter for PIOL. Our results are consistent with Wang's meta-analysis (Wang, Hong, Liu, Duan, & Yin, 2015) of up to 731 women induced with controlled-release Dinoprostone and 722 with Foley, which suggests that PIOL results in a reduction in time to delivery and oxytocin use. Lastly, our results seem consistent with other studies in terms of BS modification, as in Pennell's study (Pennell et al., 2009), we found no significant changes between induction methods.

Of note, while the uterine electrophysiological response to PIOL has been researched previously (Benalcazar-Parra et al., 2018; Diaz-Martinez et al., 2021), studies on myoelectric uterine response to MIOL are limited and primarily focused on obstetric output. MIOL is known to be associated with a decreased risk of uterine hyperstimulation. This could be consistent with the lower contraction strength obtained in the present work, although no differences were found in the first 5 hours of IOL. In addition, MIOL has been associated with a higher oxytocin requirement than PIOL (Reshme et al., 2022; Wang et al., 2015), suggesting that cells are less excitable after this procedure. This is consistent with our results, as MIOL MNF shows no difference from baseline, while PIOL MNF does.

On the other hand, non-linearity results obtained suggest lower complexity in the case of PIOL uterine activity, a trait associated with shorter time to delivery. The literature points out that the use of prostaglandins is associated with an acceleration of gap junction formation, which in turn leads to more coordinated uterine contractions (Rayburn, 2002). In addition, Pennell (Pennell et al., 2009) described by Kaplan-Meier curves a higher proportion of deliveries in PIOL compared to MIOL before 10 hours from the start of the IOL process, which is consistent with our results.

5 CONCLUSIONS

In this work, the EHG technique and its associated EHG-biomarkers have demonstrated their feasibility to characterise the evolution of uterine dynamics also during the MIOL process. They have been shown to provide new relevant information on cellular excitability and the coordination of contractile activity that could not be perceived with the traditional tocography technique. Our results suggest that PIOL triggers a faster uterine myoelectric response than MIOL, with contractions of higher amplitude, a significantly higher MNF after 2.5h of IOL onset and a higher degree of regularity and less complexity, with also statistically significant differences for both groups also after about 2.5h from the start of induction.

Therefore, this accurate and quantitative assessment of the IOL process based on EHG could lead to more reliable IOL success prediction systems and help to improve maternal-fetal wellbeing. In addition to helping to better understand the electrophysiological response in the IOL environment.

ACKNOWLEDGEMENTS

This work was supported by the Spanish Ministry of Economy and Competitiveness and the European Regional Development Fund (MCIU/AEI/FEDER, UE RTI2018-094449-A-I00-AR and PID2021-124038OB-I00).

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