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Original Article

Overdistention Accelerates Electrophysiological Changes in Uterine Muscle Towards Labour in Multiple Gestations

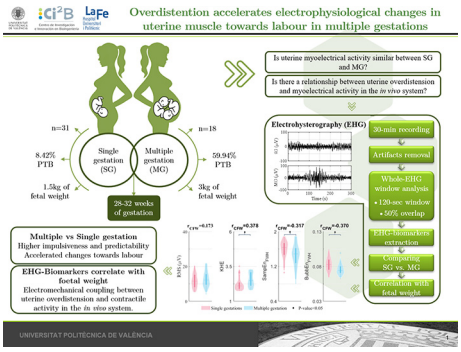
Alba Diaz-Martinez [a], Gema Prats-Boluda [a], Rogelio Monfort-Ortiz [b], Javier Garcia-Casado [a], Alba Roca-Prats [b], Enrique Tormo-Crespo [b], Félix Nieto-del-Amor [a], Vicente-José Diago-Almela [b], Yiyao Ye-Lin [a,*]

[a] Centro de Investigación e Innovación en Bioingeniería, Universitat Politècnica de València, Joint Research Laboratory in Biomedical Engineering between Beijing University of Tecgnology and the Universitat Politècnica de València, 46022 Valencia, Spain
[b] Servicio de Obstetricia, Hospital Universitario y Politécnico de La Fe, 46026 Valencia, Spain

HIGHLIGHTS

- EHG features in multiple pregnancy differ from singleton ones in third trimester.
- Multiple pregnancies show greater impulsivity and predictability than singletons.
- Uterine overdistension may cause accelerated biophysical process toward labour.
- Overdistension should be considered as a risk factor for preterm birth prediction.

GRAPHICAL ABSTRACT



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ABSTRACT

Background for the research: Premature birth and its associated complications are one of the biggest global health problems, since there is currently no effective screening method in clinical practice to accurately identify the true Preterm Birth (PTB) from the false threatened ones. Despite the high prevalence of PTB in multiple gestation (MG) women which amounted up to 60%, in the literature there is any work about their uterine myoelectric activities in vivo system. Electrohysterography (EHG) has been emerged as an alternative technique for predicting PTB in single gestation (SG) women.

Purpose: The aim of this study was to characterize and compare the uterine myoelectrical activity in vivo system of SG and MG women in regular check-ups, to provide the basis for early detection and prevention of preterm labour in MG.

Basic procedures: A prospective observational cohort study was conducted on 31 SG and 18 MG women between the 28th and 32th WoG who underwent regular check-ups in the Polytechnic and University Hospital La Fe (Valencia, Spain). The 30-minute bipolar recording was filtered in the 0.1-4 Hz bandwidth and downsampled to 20 Hz. Signal analysis was performed in 120-second moving windows with 50% overlap, after removing artefacts by a double- blind expert process. A set of 8 temporal, spectral and non-linear parameters were calculated: root mean square (RMS), kurtosis of the Hilbert envelope (KHE), median frequency (MDF), H/L ratio, and sample entropy (SampEn) and bubble entropy (BubbEn) calculated in the whole bandwidth (WBW) and the fast wave high (FWH). The 10th, 50th and 90th

* Corresponding author.
E-mail addresses: adiaz@ci2b.upv.es (A. Diaz-Martinez), gprats@ci2b.upv.es (G. Prats-Boluda), monfort_isaort@gva.es (R. Monfort-Ortiz), jgarciac@ci2b.upv.es (J. Garcia-Casado), roca_alb@gva.es (A. Roca-Prats), tormo_enr@gva.es (E. Tormo-Crespo), feniede@ci2b.upv.es (F. Nieto-del-Amor), diago_vicalm@gva.es (V.-J. Diago-Almela), yiye@ci2b.upv.es (Y. Ye-Lin).

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percentiles of all windows analysed were calculated to obtain representative values of the recordings. For each parameter and percentile, statistically significant differences between the SG and MG groups and their statistical power (SP) were analysed to determine both the existence of an effect and substantive significance, respectively.

Main findings: In comparison to SG, MG EHG exhibited significant higher impulsiveness and higher predictability than SG which was reflected in the KHE ($SP_{10} = 85.2$, $p_{10} < 0.001$) and entropy measures (SampEn FWH: $SP_{50} = 62.0$, $p_{50} = 0.0.016$; $SP_{90} = 52.5$, $p_{90} = 0.059$. BubbEn FWH: $SP_{50} = 75.2$, $p_{50} < 0.001$; $SP_{90} = 60.3$, $p_{90} = 0.002$), suggesting an accelerated evolution of uterine electrophysiological condition. In addition, several EHG parameters were found to significantly correlate with foetal weight such as amplitude (RMS: $r_{90} = 0.311$, $p_{90} = 0.006$), signal impulsiveness (KHE: $r_{10} = 0.311$, $p_{10} = 0.006$) and entropy measures (SampEn FWH: $r_{50} = -0.317$, $p_{50} = 0.005^*$; $r_{90} = -0.279$, $p_{90} = 0.013^*$. BubbEn FWH: $r_{50} = -0.370$, $p_{50} = 0.001^*$; $r_{90} = -0.313$, $p_{90} = 0.005^*$), suggesting an electromechanical coupling between uterine overdistension and contractile activity in vivo system.

Principal conclusions: In comparison to SG women, MG showed higher impulsiveness and predictability in early third gestational trimester, as reflected in KHE, SampEn and BubbEn, respectively. We found similar cell excitability between SG and MG women far from delivery. In addition, we confirmed the relationship between uterine overdistension and surface myoelectric activity, revealing the electromechanical coupling pathway in uterine smooth muscle. Therefore, contextualized EHG-biomarkers would provide valuable information for early detection of PTB risk, which would allow clinicians better PTB management through personalised therapeutic interventions.

1. Introduction

1.1. Preterm birth

Preterm birth (PTB), defined as all births before 37 complete weeks of gestation (WoG) or less than 259 days from the first day of the woman's last menstrual period is a leading cause of perinatal mortality and caused 2.3 million deaths in children under 5 years of age worldwide in 2019 [1]. Survival is associated with an increased risk of visual, neurodevelopment and cognitive impairment, cerebral palsy or prolonged hospital admissions for respiratory, metabolic or infectious morbidities [1,2]. Not only does PTB cause significant psychological and financial hardship for the families involved, but it also entails a high long-term economic burden for healthcare systems [2]. The average cost associated with a PTB amounts to €8,565 in the first-year, which is 5.4-fold more than a full-term birth. However, deliveries before 34 WoG can involve costs of up to €74,009 [2].

Despite the significant progress of modern medicine in the pregnancy care, PTBs are still on the rise [3,4]. In the United States, they rose from 9.63% in 2015 [3] to 10.48% in 2021 [4]. This upward trend has been broadly associated with an increase of maternal age. In Europe and the United States childbearing age increased by 14% between 1980 and 2021 due to socio-cultural changes [3,4]. Remarkably, the birth rate for women between 35 and 39 years has increased by 30.5% in the last two decades, and by 48% for women over 40 years of age [5]. Fertility and fecundability progressively decline after 32 and 37 years of age, respectively, as a result of a reduction in the quality and number of oocytes [6]. Due to this, assisted reproductive technologies (ART) are becoming increasingly popular [7].

The extensive use of ART has raised the rate of multiple gestation (MG) [6]. In fact, the occurrence of MG after ART hovers around 20% worldwide, ranging from <10% in several Nordic countries [7] to 30% in the USA [8], well above the 1-2% in natural conceptions [7]. ART has been associated with an increased risk of perinatal mortality and morbidity in both MG and single gestations (SG) compared to their naturally conceived counterparts [7,9]. The incidence of PTB is notably up to six times higher in MGs [7], leading to higher obstetric concern for this risk group. In comparison to SG, with a PTB rate of 8.42% in 2020, the prevalence of PTB in MG amounted to 59.94%. In fact, MGs are also associated with a higher rate of early PTB (19.19% vs 2.11%) [8]. The risks of stillbirth and neonatal deaths, perinatal complications and somatic pathologies, physical and neuropsychological developmental disorders, formation of congenital malformations and disability are therefore aggravated, especially in the case of MG [10].

Treatments for the prevention of PTB in SG, such as tocolytic therapy, progesterone and cervical cerclage, appear to be ineffective in MGs [11], which may suggest that MG have distinct pathways that promote uterine contractility and thus trigger PTB [12]. If so, this critical factor should be included for designing preterm labour prediction system based on EHG, which is ignored up to now [13–15]. Uterine overdistension has been associated with significant inflammatory cytokines and prostaglandin increases in a non-human primate model, indicating that mechanical stress-induced inflammation is an early warning sign of PTB [16] However, there is no evidence to support a link between uterine contractility and uterine distension in the *in vivo* human system.

1.2. Current predictive techniques in clinical practice

Early detection is the key factor in PTB prevention. At present, the most common techniques to determine its risk are monitoring uterine dynamics by tocodynamometer, assessing cervical length (CL) and biochemical markers such as foetal fibronectin [17], although these methods have been found to be subjective or inaccurate in predicting PTB [17–19]. Firstly, tocodynamometry requires constant transducer repositioning and is strongly influenced by the tightness of the binding, maternal-foetal movement and maternal obesity [18]. Secondly, although CL measurement is the most cost-effective method used in hospital practice [17], the results can be considerably biased by the examiner's experience [19]. Finally, the foetal fibronectin test has also been proposed as a screening method for patients at PTB risk. The clinical value of the CL and fibronectin tests lies mainly in their high negative predictive values, while their positive predictive values are lower and do not identify the patients who will actually deliver preterm [17,19]. As a result, there is currently no screening method in clinical practice to accurately identify women at real risk of PTB in order to provide a patient-oriented strategy to continue pregnancy as long as possible, thus minimising the negative consequences and ruling out

women with false PTB threats to avoid unnecessary interventions and reduce hospital costs [17].

Electrohysterography (EHG) has emerged as an alternative technique for preventing PTB due to its high sensitivity [13–15,20]. In fact, it has been shown to outperform traditional tocodynamometry in monitoring uterine dynamics [18,21] as well as being barely influenced by obese patients [20]. The EHG technique involves recording the intermittent action potential bursts associated with uterine contractions and basal activity when the uterus is at rest [20,22]. Traditionally EHG analysis has focused on the fast wave component, which is subdivided into two other components: fast wave low and fast wave high (FWH). Previous studies have shown that the peak frequency of the former ranges between 0.13 and 0.26 Hz and is mainly related to signal propagability [23], while the latter is associated with cell excitability and mainly distributes its energy between 0.34 and 4 Hz [20,24].

In early gestation, electrical physiological activity is low and uncoordinated [24,25]. As pregnancy progresses, the factors causing uterine quiescence are down-regulated and electrical coupling increases, allowing the functional syncytium including the entire uterus to form [20,24,26]. Simultaneously, there is an increase in cellular excitability due to changes in the transduction mechanisms and in the synthesis of various proteins [9]. These changes are responsible for generating a more intense and synchronised signal as gestation progresses [22], ultimately leading to high-intensity contractions capable of expelling the foetus at delivery [16,20,22]. The above-described changes are reflected in the EHG as an increased amplitude and shift of spectral content towards higher frequencies, constituting one of the most reliable distinguishing hallmarks of PTB [20,22]. The EHG signal has also been shown to become more predictable as pregnancy progresses, with lower signal complexity [22]. Literature suggested that EHG contains relevant information about electrophysiological uterine changes throughout pregnancy, suggesting its potential utility for predicting preterm labour [13–15,27]. However, these studies have focused on analysing EHG in SG, with MG being an exclusion criterion [18,22,28]. To our knowledge, there are at present no descriptive studies in the literature on the characterisation of EHG in the MG *in vivo* system. The aim of this study was therefore to characterize and compare the uterine myoelectrical activity in vivo system of SG and MG women attending regular check-ups, to determine the existence of the accelerated biophysical process in MG women, which also provides the basis to early identify preterm labour risk and warning signs for better prevention for this specific group with higher premature risk and major maternal-neonatal impact. We also sought to determine the relationship between uterine overdistension and EHG characteristics of the *in vivo* system.

2. Materials and methods

2.1. Study design

There is no EHG database currently available that includes recordings in MG, being this latter usually considered as exclusion criteria in several EHG studies [18,22,28]. Moreover, to minimize bias associated with differences in protocols and with the subjectivity of the examiners, in terms of skin preparation, we opted to generate our own database and conduct a prospective observational cohort study on 31 SG and 18 MG women between the 28th and 32nd WoG who underwent regular check-ups in the Polytechnic and University Hospital La Fe (Valencia, Spain). Uterine electrophysiology was taken into account to establish the inclusion criteria for gestational age. Notably, myoelectric activity in women attending regular check-ups is scarce, especially before 26 WoG for both SG and MG [29,30]. Moreover, fetal weight significantly increases from the beginning of the third trimester, while some preparatory changes for delivery occur (such as the formation of the lower segment of the uterus in 32th WoG) [31]. In addition, the percentage of MGs who deliver prematurely increases drastically after the 32nd WoG, which may bias the comparison if a higher gestational age is included [8].

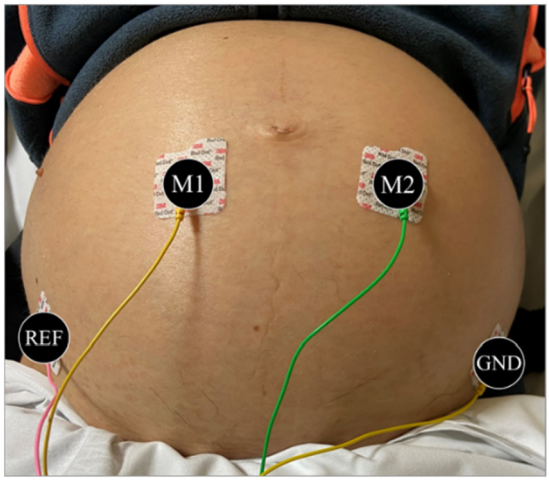

Fig. 1. Electrode positions for uterine myoelectrical recording. M1: monopolar electrode 1. M2: monopolar electrode 2. REF: Reference electrode. GND: Ground electrode.

Foetal macrosomia, large advanced maternal age (>45 years), severe preeclampsia, placenta praevia, premature membrane rupture, vaginal bleeding during pregnancy, triplet gestation or higher, suspected foetal compromise (growth restriction, oligohydramnios, known foetal anomalies, etc.) and active cardiac, renal, pulmonary or hepatic disease were factors for exclusion from the study due to their bias.

This study adhered to the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of the hospital (register number 2022-205-1). Patients were informed about the nature of the study and gave their written informed consent.

2.2. Clinical data

The clinical data collected during the study were: maternal age, maternal body mass index, number of previous gestations and deliveries, CL at the time of the recording, gestational age at recording and delivery, newborn foetal weight, prematurity of the birth and type of delivery ending. We estimated the calculated foetal weight (CFW) at recording by the foetal percentile of birth weight using the reverse of the traditional Hadlock formulation [32].

The chi-square test was used to determine statistically significant differences between the groups ($\alpha = 0.05$) in dichotomous variables (prematurity of the birth and vaginal delivery). As the remaining variables were continuous, they were compared with the Student's t-test or the Wilcoxon rank sum test, according to the normality of the data distribution in the Shapiro-Wilk test ($\alpha = 0.05$).

2.3. EHG signal acquisition

For each 30-minute recording the abdominal surface was prepared by a gentle exfoliation with abrasive gel (Nuprep, Weaver and Company, Aurora, CO, USA) and cleaned with isopropyl alcohol to reduce skin-electrode impedance. Four disposable Ag/AgCl electrodes (Red Dot 2660–5, 3M, St. Paul, MN, USA) were then placed as shown in Fig. 1. Since the uterine volume increases as pregnancy progresses, deforming the abdominal surface [31], anatomical references have been taken to reduce the electrode placement

bias. Electrodes M1 and M2 were symmetrically positioned with respect to the median axis at a distance of 8 cm from each other, midway between the pubic symphysis and the uterine fundus with the highest bulk of uterine muscle giving rise to the highest signal-noise ratio [28]. The relatively high inter-electrode distance was set to reduce the blurring effect of the volume conduction. The other two electrodes were placed on each iliac crest to provide reference and ground biopotentials. Both monopolar signals were conditioned by a custom-made biopotential amplifier, providing a 2059 V/V gain in the 0.1–150 Hz bandwidth and digitized by a 24-bit analogue-to-digital converter at 500 Hz [33].

2.4. EHG signal analysis

Since the spectral EHG content is mainly distributed between 0.1-4 Hz [20], the monopolar EHG signals were bandpass filtered in this bandwidth (5th order Butterworth bandpass filter of zero phase) and then downsampled at 20 Hz to maintain the trade-off between temporal resolution and computational cost while avoiding aliasing [22]. Similar to other previous works, the digital filter was selected to attenuate rejection band to a negligible level with minimal alteration in passband. A bipolar signal was then calculated as the difference between monopolar signals (M2-M1) to reduce common-mode interferences and increase the signal-to-noise ratio [18].

Due to the fact that SG women are still far from delivery, the EHG-bursts associated with uterine contractions can cause subtle changes from baseline activity and make it extremely challenging to identify their onset and duration, leading to a great deal of uncertainty in the results [22,34]. However, previous studies have revealed the feasibility of whole window analysis to characterize EHG signals [22,35]. This method considerably simplifies signal pre-processing as it only requires the exclusion of non-physiological segments (motion artefacts or respiratory interference), thus facilitating its implementation in real-time applications. In this work, two experts identified the physiological segments in the EHG recordings using a double-blind process.

Taking into account the relative slow dynamic of uterine myoelectric activity, we divided the recording into moving window with a 50% overlap to compute the EHG parameters in which the signal is supposed to be stationary [35]. With this approach, a trade-off between the analysis window length for the accuracy of the measure and the stationary assumption has to be made [36]. Di Marco et al. found that 5-min motion and labour contraction-free EHG can be considered as weak-sense stationarity signal [37]. By contrast, Esgalhado et al. who attempted to detect automatically uterine contraction in EHG recordings used a smoothing window length of 70 seconds to minimize the non-stationarity bias [38]. In this work, we set the window length to 120 seconds which has been shown to successfully discriminate between preterm and term delivery [35,39], being a compromise between computational cost and preserving the representative segment of the recordings [35].

A set of 8 temporal, spectral and non-linear parameters were calculated for each EHG analysis window. The root mean square (RMS) [34] and Hilbert envelope kurtosis (KHE) [40] worked out in the whole bandwidth (WBW) characterised the intensity and impulsiveness of uterine myoelectrical activity, respectively [22]. For the spectral parametrization, the median frequency (MDF) [34] was calculated in 0.2-1 Hz to minimize the influence of cardiac interference (>1 Hz) and baseline fluctuation [22]. The H/L Ratio was also obtained as the ratio between the energy content in high (0.34–1 Hz) and the low (0.2-0.34 Hz) frequency bands [20,22]. Since the physiological changes in SGs may occur later in pregnancy, MG women can be expected to exhibit higher values for both temporal and spectral parameters [9]. On the other hand, it has been shown that signal predictability increases and the complexity of the EHG signals decreases in SG women as delivery approaches. In this work we computed sample entropy (SampEn) [22,34] and bubble entropy (BubbEn) [39] in both FWH and WBW to quantify signal predictability [20,22,34]. The MG group, which is assumed to have an accelerated biophysical process, can be expected to show lower values for the non-linear parameters.

Afterward, we obtained N values for the N analysis window for each parameter and recording session. Due to the slow dynamic of EHG electrophysiological changes throughout pregnancy, we omitted the slight variation of uterine myoelectric activity in 30-minute recording so that we can use the commonly used pseudo-stationary approach to quantify the EHG signal [34,35,41]. In this work, we calculated the 10th, 50th (median), and 90th percentiles of all the analysed windows to obtain representative values for the records to capture the basal activity and EHG bursts characteristics [22]. Due to the low occurrence of uterine contraction events in EHG recordings, 10th and 90th percentile of those EHG parameters that exhibit higher value for uterine contraction than basal activity (amplitude, spectral parameter) may better corresponds to the basal activity and EHG bursts characteristics respectively. As for those EHG parameters with lower value for uterine contraction than basal activity (non-linear parameters linked with signal predictability and organization degree), which usually exhibit a decreasing trend as labour approaches, 10th and 90th percentiles may be associated with EHG bursts characteristics and basal activity respectively.

In this work, we analysed both statistically significant differences between the SG and MG groups and their statistical power to determine both the existence of effect and substantive significance, respectively for each the parameter and percentile. The Wilcoxon rank sum test ($\alpha = 0.05$) was used to perform the statistical analysis. To determine the relationship between the increase in uterine volume and the acceleration of the biophysical process, we computed Spearman's correlation (non-normal distribution) between each EHG parameter and CFW along with their p-value to determine their relationship with uterine overdistension in the *in vivo* system. The statistical significance correlation with the CFW were also obtained for CL.

3. Results

Of the total number of 78 recordings, 51 were SG and the remaining 27 MG. Table 1 summarises the obstetric characteristics of both groups. As expected, the MG group had a higher prevalence of PTB than SG, as reflected in their significantly lower gestational age at delivery and higher PTB rate. In comparison, the MGs showed significantly lower CL at the time of recording, as well as a higher number of previous gestations and CFW at the recording time and at birth. The SG vaginal delivery rate was significantly higher than in the MG. No significant differences were found between the groups in maternal age, body mass index and parity.

Fig. 2 gives a representative example of the EHG recordings from SG (upper) and MG (lower) women at 31st WoG. Only one contractile event can be clearly identified by a subtle change from baseline activity at around 100 seconds in the SG recording, while two contractile events with greater amplitude and frequency components can be distinctly seen (around 100 and 800 seconds) in the MG recording.

Fig. 3 depicts the distribution of the 10th, 50th and 90th percentiles of the EHG parameters for the SG and MG groups. The statistical power of the comparisons is shown in Table 2.

The MG group had a similar RMS to SG for the 10th and 50th percentiles, while the 90th percentile was slightly higher than SG, although without significant differences. KHE had significantly

Table 1
Obstetric characteristics of the study population. P-values are marked by (*) if there is a statistically significant difference ($\alpha < 0.05$) between the single gestation (SG) and multiple gestation (MG) groups.

Variable		SG	MG	P-value
Maternal age (years)	$\mu \pm \sigma$	34.0±4.7	36.2±6.2	0.144
Maternal Body Mass Index	$\mu \pm \sigma$	28.3±5.1	28.4±4.1	0.911
Gestations	$\mu \pm \sigma$	2.0±1.2	3.1±2.0	0.006*
Parity	$\mu \pm \sigma$	0.5±0.7	0.8±1.4	0.252
Cervical length (mm)	$\mu \pm \sigma$	39.4±7.5	32.6±11.5	0.004*
Gestational Age at Recording (days)	$\mu \pm \sigma$	209.2±13.6	215.5±12.8	0.103
Gestational Age at Delivery (days)	$\mu \pm \sigma$	277.7±9.6	250.6±10.3	<0.001*
Calculated Foetal Weight sum (g)	$\mu \pm \sigma$	1504.8±395.9	2979.4±778.6	<0.001*
Newborn Fetal Weight sum (g)	$\mu \pm \sigma$	3379.1±429.5	4499.8±804.6	<0.001*
Preterm Birth	N	4/51	25/27	<0.001*
Vaginal Delivery	N	32/51	3/27	<0.001*

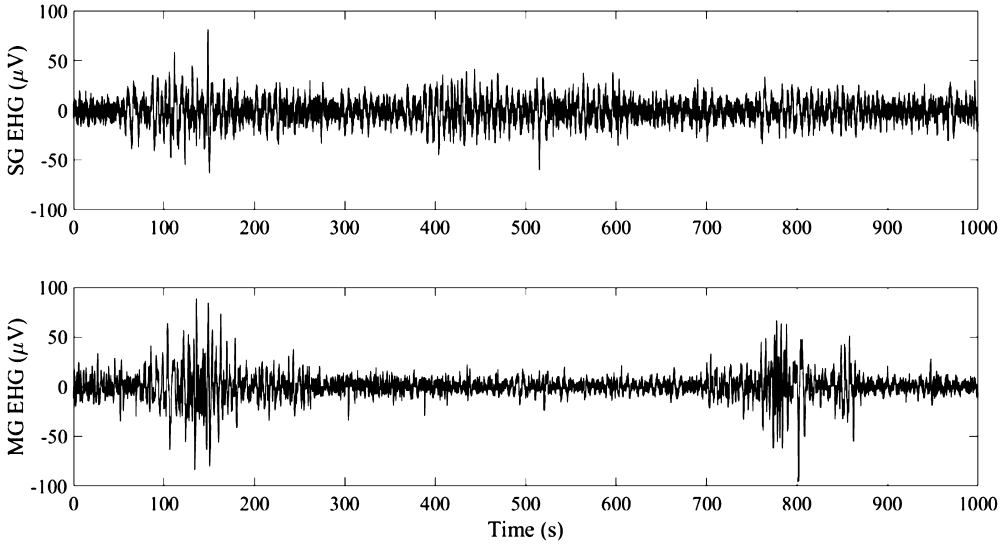

Fig. 2. Electrohysterographic (EHG) recordings from Single (SG) and Multiple Gestations (MG) performed during the 31st gestational week.

Table 2
Statistical power (%) of the comparisons between the SG and MG groups. RMS: Root Mean Square. KHE: Kurtosis of the Hilbert Envelope. MDF: Medium Frequency. SampEn: Sample Entropy. BubbEn: Bubble Entropy. WBW: Whole Bandwidth. FWH: Fast Wave High. CL: Cervical Length.

Variable	Percentile		
	10th	50th	90th
RMS	3.4	14.4	49.3
KHE	85.2	75.2	60.3
MDF	8.2	16.6	16.7
H/L Ratio	37.4	16.1	25.5
$SampEn_{WBW}$	49.5	41.4	21.8
$BubbEn_{WBW}$	6.0	15.1	6.4
$SampEn_{FWH}$	69.2	62.0	52.5
$BubbEn_{FWH}$	58.8	94.2	87.2
CL	-	79.3	-

higher values for all percentiles in MG, with a relatively high maximum statistical power (>60%) for the 10th percentile.

In the characterisation of spectral content, MG showed a slightly lower MDF and H/L ratio than SG, regardless of the percentile. A significant difference between groups was only obtained for the H/L ratio and 10th percentile, although its statistical power was relatively low (37.4%).

MG exhibited lower values for both for non-linear parameters SampEn and BubbEn than SG for all percentiles and bandwidths. In the WBW, a significant difference between the groups was found for SampEn and BubbEn when computed in the 10th and 50th percentile, respectively, despite the statistical power being less than 50%. However, the non-linear parameters calculated in the FWH bandwidth better discriminated both groups, with significant differences obtained in all cases except for SampEn in the 90th percentile. BubbEn at FWH provided the highest statistical power (94.2% and 87.2% for the 50th and 90th percentiles, respectively). The CL statistical power (79.3%) was lower than that of BubbEn in the FWH.

Table 3 shows the Spearman's correlation coefficient between each EHG parameter and CFW as well as their p-values. In general, the relationships were relatively weak with correlations below 0.25. RMS exhibited a significant positive correlation with the CFW for the 90th percentile. KHE showed a positive significant correlation with the CFW, regardless of the percentile considered. Higher CFW was significantly related with lower values of CL and entropy measures, except for the 90th percentile of SampEn and 10th percentile of BubbEn computed in WBW.

4. Discussion

4.1. Changes in multiple gestation

Despite the fact that premature contractile activation is the basis of PTB with remarkable prevalence among MGs, there is hardly any information available on the uterine contractility of this group [9]. Only a few studies have compared human uterine contractility

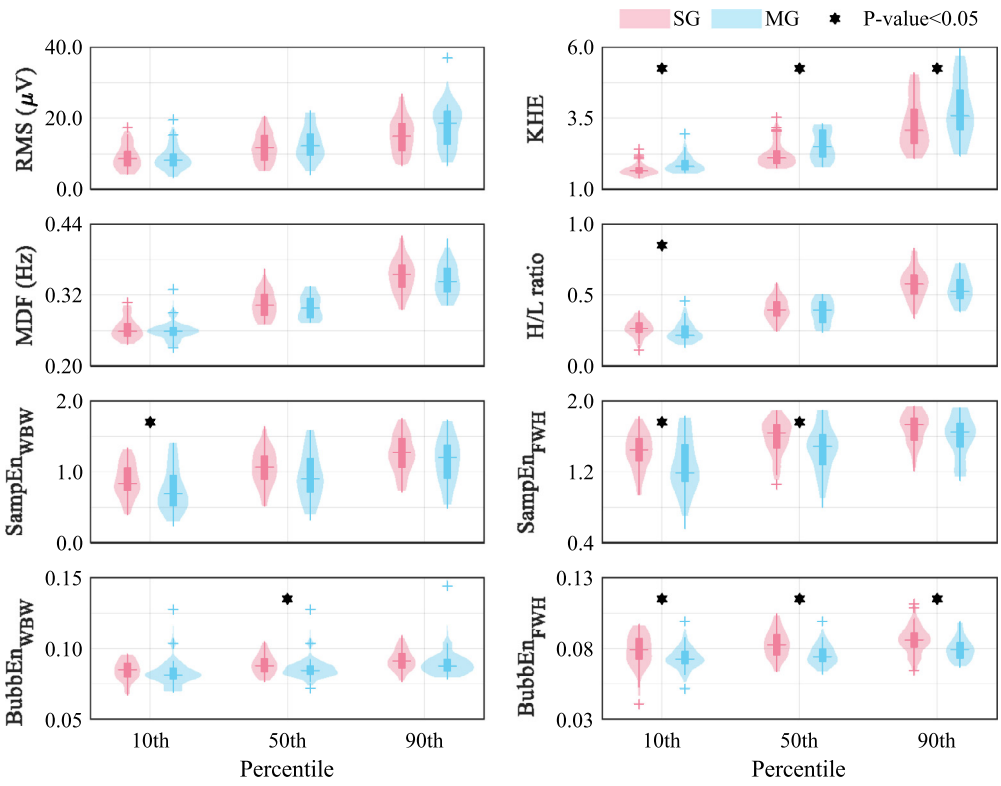

Fig. 3. Distribution of 10th, 50th and 90th percentiles of temporal, spectral and non-linear parameters for Single (SG) and Multiple Gestations (MG). Statistical differences (p-value < 0.05) between groups are indicated by *. RMS: Root Mean Square. KHE: Kurtosis Hilbert Envelope. MDF: Median Frequency. SampEn: Sample Entropy. BubbEn: Bubble Entropy. WBW: Whole Bandwidth. FWH: Fast Wave High.

Table 3
Spearman correlation coefficient (r) and its p-value of the electrohysterography characteristics with the calculated foetal weight. P-values are marked with (*) if significant ($\alpha < 0.05$). RMS: Root Mean Square. KHE: Kurtosis of the Hilbert Envelope. MDF: Medium Frequency. SampEn: Sample Entropy. BubbEn: Bubble Entropy. WBW: Whole Bandwidth. FWH: Fast Wave High. CL: Cervical Length.

Variable	10^{th} Percentile		50^{th} Percentile		90^{th} Percentile	
	r	P-value	*r*	P-value	*r*	P-value
RMS	0.084	0.467	0.173	0.131	0.311	0.006*
KHE	0.372	0.001*	0.378	0.001*	0.279	0.013*
MDF	−0.002	0.983	0.003	0.980	−0.027	0.816
H/L Ratio	−0.221	0.052	−0.073	0.524	−0.074	0.517
$SampEn_{WBW}$	−0.340	0.002*	−0.302	0.007*	−0.219	0.054
$BubbEn_{WBW}$	−0.199	0.080	−0.275	0.015*	−0.261	0.021*
$SampEn_{FWH}$	−0.303	0.007*	−0.317	0.005*	−0.279	0.013*
$BubbEn_{FWH}$	−0.276	0.014*	−0.370	0.001*	−0.313	0.005*
CL			−0.321	0.004*		

between SG and MG using biopsies obtained from women undergoing an elective caesarean section [9,16]. To our knowledge, this is the first time that uterine electrophysiological activity has been characterized *in vivo* from MG women attending regular check-ups.

The absence of significant differences in the signal RMS between SG and MG in our results is in agreement with those found by Turton, in which similar maximum contraction intensity was found for both groups in an *in vitro* study [9]. The main difference in Turton's comparison is the more frequent and shorter contractions in the case of MG [9]. We found a significantly higher KHE for MG, which could be related to the onset of uterine contraction and to a marked increase in amplitude with respect to the baseline, resulting in a sharper and more concentrated distribution of the envelope amplitude. This higher EHG signal impulsiveness has been clinically related to older gestational age and ultimately to readiness for the onset of labour [9,20,22].

EHG spectral parameters progressively change throughout pregnancy [20,24,26], although their most noticeable changes occur few days before delivery [22,35]. In term gestation, the frequency power has been shown to increase gradually from 24 to 39 Weeks of Gestation (WoG) in women delivering at term [42]. In case of preterm labour, the median frequency has been found to be significantly higher than women with term labour [34]. EHG spectral parameters were considered as one of most reliable features to determine delivery proximity due to its sensitivity to labour imminence (<7 days), which is of vital importance to predict imminent and/or preterm labour by new incoming data [24,35,43]. In this work, we didn't find any significant differences in the spectral parameters between SG and MG, suggesting that these groups have similar cell excitability [22,44]. This finding in the MDF and H/L ratio parameters could be associated with the fact that the EHG recordings were performed considerably further from the time of delivery than in other studies in the literature [9,16], so that the shift of spectral content to higher frequencies may not yet have occurred [45].

Our results on the non-linear parameters indicate a better organised uterine myoelectric activity in MG than SG, regardless of bandwidth and percentile, leading to a lower value for both SampEn and BubbEn. It has been shown that uterine myoelectric activity in SG becomes more organised and predictable as labour approaches [20,22]. Consequently, the greater degree of orderliness in uterine activity observed in MGs could be an early biomarker of proximity of delivery. Our result also suggests that non-linear parameters are more sensitive to subtle changes in EHG than temporal and spectral parameters and could be a useful EHG-biomarker for preventing PTB [39]. The non-linear parameters calculated in the FWH bandwidth notably outperformed those of the WBW in discriminating between SG and MG, which is in agreement with our previous studies [22,39]. Furthermore, BubbEn has been shown to discriminate better and with a higher statistical power between

SG and MG than SampEn, which is also consistent with previous work [39]. Physiologically, FWL associated with uterine propagability depends mainly on cell-cell coupling, which is linked to the existence and amount of gap junction [25]. It is well known that gap junction channels increase sharply a few days before delivery and reach their maximum during parturition [25,46]. Therefore, when EHG recording is performed far from birth, cell-cell coupling is relatively low [25,46,47]. In other words, the FWL component far from parturition may correspond to more localized events, because the action potential may not propagate throughout the uterus. Consequently, these FWL components exhibit low predictability. By contrast, signal predictability of FWH components seems to better discriminate between single and multiple gestation women. This finding may be related to the fact that uterine overdistension in multiple gestation women as discussed latter may promote uterine contractility, increasing its occurrence frequency as shown in home monitoring [48,49] and also the signal predictability in the FWH bandwidth.

In the percentile analysis we found that the 10^{th} percentile of KHE and 50^{th} and 90^{th} of BubbEn provided a higher discriminative power between SG and MG. Since the recordings were performed quite far from delivery with few uterine contractile events, our results thus suggest that the difference between SG and MG groups mainly lies in the resting potential at basal activity. Our results agree with other authors who found an increase in the resting membrane potential at delivery (-70 mV during pregnancy vs. -55 mV at delivery) [50].

To sum up, MG showed significantly higher KHE together with lower SampEn and BubbEn than SG. The differences identified in the EHG characteristics are assumed to be attributable to either the SG or MG type of pregnancy, as no significant differences were found in maternal age, maternal body mass index, parity and gestational age at the time of registration. Our results also support that both BubbEn and KHE outperform CL in differentiating SG and MG, the latter being one of the most widely used delivery proximity biomarkers in clinical settings to prevent PTB. Although further work is needed to corroborate our findings, they do suggest that KHE and BubbEn show promising potential as tools for predicting PTB.

4.2. Role of uterine distension

The excitation-contraction coupling in the myometrium is a key aspect of better understanding uterine electrophysiology and designing more effective strategies to prevent PTB, in addition to other obstetric complications [44]. The higher rate of PTB in MG may suggest early inhibition of the mechanisms responsible for uterine quiescence, triggering uterine contractility, which in turn causes the effacement of the cervix and increases the risk of PTB [44,51]. In our work, the CL inversely correlated with CFW, this latter being an indirect estimator of uterine overdistension [9,16]. Our results suggest that even in asymptomatic MG, cervical incompetence may be due to the rapid uterine changes caused by overdistension [51].

Although the physiopathology remains unclear, there is increasing evidence that the elevated risk of PTB in MG women is related to excessive uterine distension [9,16]. The gradual increase in volume during pregnancy leads to significant muscle proliferation and remodelling, which is magnified in MGs [16]. This phenomenon could be responsible for prematurely unbalancing the quiescence mechanisms during gestation [16], although the results are controversial in this regard [12]. Chronic mechanical stretching of smooth muscle is supposed to alter not only the mechanical but also electrical function [12,16,52]. Tissue stretching may play a role synchronizing distant parts of the uterine muscle [53,54]. The main stretch-activated channels are Ca2+ and Na+ current channels, which cause membrane depolarisation, thus inducing the opening of voltage-dependent calcium channels [55,56]. That is, uterine overdistension in women with multiple gestation may increase uterine contractility. In fact, Wu et al. found that both chronic and acute stretching increased cellular excitability and could initiate delivery [57]. Turton et al. also found that uterine contractility was positively correlated with increased levels of stretching and found that the response to oxytocin was greater for MG myometrial strips (contraction amplitude >2.5 times spontaneous ones in MG vs. 1.3 times in SG) [9]. Stretching has also been shown to stimulate oxytocin receptor expression, which promotes uterine contractility [9,12], and leads to increased collagen expression and improved focal adhesion between myocytes and the extracellular matrix [12]. Myocyte-to-myocyte adhesion is essential for the uterus to function as an electromechanical syncytium.

In contrast, Lyall found that non-labouring SG and MG showed similar G$s\alpha$, prostaglandin E2 receptors and connexin-43 gap junctions' density in myometrium [12], suggesting similar propagation of action potentials, irrespective of gestational type. However, other types of gap junction-forming connexins were not studied and this could be a potential bias, given that altering the gap junction ratio between connexin-43 and connexin-45 may suppose the transition between quiescence to excitation in the myometrium [58].

Our results suggest a slight increase in uterine contractility (e.g. RMS) in MG without significant differences with respect to SG. This could be related to the fact that additional mechanisms triggered by prolonged overdistension have been identified to counteract its effects and promote uterine quiescence [52,59]. For example, the enhanced expression of stretch-activated potassium-specific channels (TREK-1) [52,59], leading to reduced myometrium contractile activity [52], especially in MG [59]. Prolonged stretching of the rat uterus was also associated with greater expression of matrix metalloproteinases 2 and 9, which inhibit myometrial contraction and promote uterine relaxation [60]. However, these compensatory mechanisms appear to have a certain threshold of myometrial overdistension, beyond which they cease to be effective and labour is triggered [16].

We also obtained a significant correlation between uterine myoelectric activity and CFW at the time of recording, which is an indirect estimator of uterine overdistension [9,16]. Certain reasons can be cited for not obtaining higher correlations. Firstly, uterine distension depends not only on foetal weight but also on other factors such as maternal height [61] or some concomitant diseases as polyhydramnios [16]. Secondly, uterine contractility is governed by the complex regulation of multiple ion channels, which may result in a highly variable response in different subjects [12]. Finally, the recording of surface uterine myoelectric activity may depend on multiple factors, such as body mass index, skin-electrode preparation or placental position [18].

4.3. Limitations and future lines of research

In spite of its promising results, the present study is not exempt from limitations. Firstly, the sample size is relatively small, which may introduce a bias due to biological variability. Future studies with a larger database would thus be necessary to corroborate our results. Secondly, we compared the SG and MG electrohysterographic characteristics only between 28 and 32 WoG. Future efforts should thus be directed at characterising uterine myoelectric activity throughout the entire third trimester of pregnancy in both SG and MG. This would provide new and valuable information to better understand the underlying mechanism triggering PTB and thus to design a patient-oriented strategy for better prevention. Thirdly, the physiological EHG segments were identified visually by experts, which is a considerably time-consuming process. However, the development of automatic systems for the detection of uterine

contraction and physiological sections is on the rise [20] and will greatly enhance the transferability of the EHG technique to clinical practice. Future work should therefore be directed towards the automatic extraction of EHG-biomarkers from recordings without the need for expert intervention.

Despite the aforementioned reservations, we believe that this work not only contributes significantly to uterine electrophysiology but could also be used for better prevention of PTB in clinical practice.

5. Conclusions

We found that MGs' EHG signal exhibited higher impulsiveness and predictability than SGs' in early third gestational trimester, as reflected in KHE, SampEn and BubbEn, respectively. By contrast, no noticeable difference in cell excitability was found between SG and MG women when the records are carryout out far from delivery, which confirm its sensitivity to labour imminence. Also, the relationship between uterine overdistension and surface recorded myoelectric activity was confirmed, revealing the electromechanical coupling pathway in uterine smooth muscle. We thus highly recommended to consider the uterine overdistension, especially in MG women, to determine preterm labour risk for a better prevention in clinical practice.

New relevant information on uterine electrophysiology in the *in vivo* MG system is provided in this work, addressing an important gap in the current state-of-the-art. The results also suggested EHG-biomarkers contextualized in its obstetric scenario (SG vs. MG, and other obstetric data) would provide valuable information for early detection of PTB risk, which would allow clinicians to design earlier personalised therapeutic interventions to better prevent PTB.

Ethics approval

This study adhered to the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of the hospital (register number 2022-205-1). Patients were informed about the nature of the study and gave their written informed consent.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Informed consent and patient details

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article and that this report does not contain any personal information that could lead to their identification.

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CRediT authorship contribution statement

Conceptualization, A.D.-M., G.P.-B., R.M.-O., J.G.-C., V.D.-A., Y.Y.-L.; Methodology, A.D.-M., G.P.-B., Y.Y.-L.; Software, A.D.-M., F.N.-A.; Validation, A.D.-M., R.M.-O., F.N.-A.; Formal analysis, A.D.-M.; Investigation, A.D.-M., R.M.-O., A.R.-P., E.T.-C.; Resources, G.P.-B., R.M.-O., A.R.-P., J.G.-C., V.D.-A., Y.Y.-L.; Data curation, A.D.-M., R.M.-O., A.R.-P., E.T.-C.; First writing, A.D.-M., Y.Y.-L.; Review writing, G.P.-B., R.M.-O., J.G.-C., Y.Y.-L.; Visualization, A.D.-M.; Supervision, A.D.-M., G.P.-B., R.M.-O., J.G.-C., V.D.-A., Y.Y.-L.; Project administration, G.P.-B., R.M.-O., Y.Y.-L.; Funding acquisition, G.P.-B., R.M.-O., J.G.-C., V.D.-A., Y.Y.-L.

Declaration of competing interest

The authors declare that they have no known competing financial or personal relationships that could be viewed as influencing the work reported in this paper.

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