UNIVERSITAT POLITÈCNICA DE VALÈNCIA

Centro de Investigación e Innovación en Bioingeniería

PhD in Technologies for Health and Well-Being

Biomarker identification based on human electrohysterography for the early detection of risk in different obstetric scenarios: preterm birth, induction of labour and postpartum.

María del Alba Díaz Martínez

Yiyao Ye Lin
Gema Prats Boluda

March 2024

No hay nadie menos afortunado
que el hombre a quien la adversidad olvida,
pues no tiene oportunidad de ponerse a prueba.

Séneca

Acknowledgements

Me gustaría expresar mi más sincero agradecimiento a todas las personas que contribuyeron de alguna manera al desarrollo de esta tesis con las siguientes líneas.

En primer lugar, a todas las voluntarias que aceptaron participar en cada uno de los diferentes estudios, ya que nada de esto hubiera sido posible sin ellas.

A mis directoras de tesis, por su orientación y dedicación a lo largo de este proyecto, que han sido fundamentales para impulsar el desarrollo de mi conocimiento y alcanzar nuevos niveles de excelencia en cada paso.

Quisiera también agradecer profundamente a mis compañeros y amigos en el departamento de Obstetricia y Ginecología del Hospital La Fe, pues su experiencia y perspectiva compartida durante las largas horas de discusión sobre fisiología, protocolo obstétrico y práctica clínica habitual han enriquecido enormemente mi trabajo. Así como a los que trabajan en el Centro de Investigación e Innovación en Bioingeniería de la Universidad Politécnica, pues su conocimiento y experiencia han sido una fuente invaluable de aprendizaje y crecimiento. En particular a Pepe, por brindarme la oportunidad y fomentar mi desarrollo constantemente, y a Ángel y Roge, por enseñarme tantísimo sobre tantas cosas en lo que dura una taza de café. Ha sido la combinación de todos ellos lo que ha constituido los cimientos de mi formación como ingeniera biomédica en el campo del procesamiento de señal obstétrica.

Sin olvidar, por supuesto, a mi familia y amigos, cuyo ánimo, comprensión y apoyo constantes han sido indispensables ahora y siempre. Especialmente a Àngel, quien viviendo conmigo cada día del proceso, hoy desempeña un papel esencial en que esté escribiendo estas palabras.

Abstract

During pregnancy, women undergo physiological, metabolic, and morphological changes that could lead to significant maternal-foetal risks. Firstly, preterm birth is the leading cause of infant mortality, with a prevalence 10% in single (SG) and 50% in multiple gestations (MG). The characterisation of uterine activity, as well as the comparison between SG and MG, may thus help to better understand and manage this pathology. Secondly, induction of labour (IOL) is associated with an increased risk of maternal mortality and morbidity when the latent phase of labour is excessively prolonged, especially in nulliparous women. However, the literature is sparse and the uterine electrophysiological response to the IOL drug has not been clearly observed. In this sense, the study of biomarkers based on electrohysterography (EHG) could help to early detect the risk of IOL failure and guide clinical decisions accordingly. Thirdly, postpartum haemorrhage (PPH) constitutes one of the main causes of maternal mortality in the world. Its prevalence is 2-6%, causing the death of 75,000 women each year. The main cause is uterine atony, so EHG becomes the ideal tool to assess the state of the uterus and indicate the PPH risk based on the absence or not of activity. Therefore, the aim of the present doctoral thesis is the identification of EHG-biomarkers for the early detection of high-risk obstetrical situations. For this purpose, the EHG signal and obstetric databases were generated for each scenario at University and Polytechnic Hospital La Fe. The greater impulsivity and predictability in MG compared to SG during the third trimester, in addition to the significant correlation between EHG-biomarkers and foetal weight, suggested an electromechanical coupling between overdistension and surface-recorded myoelectric activity. As for IOL, the successful group showed a significant increase in the number of contractions and cellular excitability, along with reduced complexity, from 2-3 hours after the IOL drug administration. No significant changes from baseline activity were observed in the failed group. Parity-based comparison reported a higher progression ratio of signal amplitude for the parous group. Myoelectric activity in vaginal postpartum was found to be more frequent and intense, in addition to exhibit a greater cellular excitability than in caesarean deliveries. Discriminatory capacity of EHG-biomarkers for early risk detection in various obstetric contexts has advanced current electrophysiological knowledge of the uterus *in vivo*. The translation of the EHG to clinical practice will entail the signal processing automation, culminating in the creation of generalised and robust predictive models that support clinical decision-making, improve birth planning and management, prevent maternal and foetal complications and optimise the allocation of hospital resources.

Resumen

Durante la gestación, la mujer experimenta cambios fisiológicos, metabólicos y morfológicos que podrían conllevar importantes riesgos materno-fetales. En primer lugar, el parto prematuro es la principal causa de mortalidad infantil, con una prevalencia del 10% en gestaciones únicas (SG) y del 50% en gestaciones múltiples (MG). Por tanto, la caracterización de la actividad uterina, así como la comparación entre SG y MG, puede ayudar a comprender y manejar mejor esta patología. En segundo lugar, la inducción del parto (IOL) se asocia a un mayor riesgo de mortalidad y morbilidad materna cuando la fase latente del parto se prolonga excesivamente, especialmente en mujeres nulíparas. Sin embargo, la literatura es escasa y no se ha observado claramente la respuesta electrofisiológica uterina al fármaco de IOL. En este sentido, el estudio de biomarcadores basados en la electrohisterografía (EHG) podría ayudar a detectar precozmente el riesgo de fracaso de la IOL y orientar las decisiones clínicas en consecuencia. En tercer lugar, la hemorragia posparto (PPH) constituye una de las principales causas de mortalidad materna en el mundo. Su prevalencia es del 2-6%, y causa la muerte de 75.000 mujeres cada año. La principal causa es la atonía uterina, por lo que la EHG se convierte en la herramienta ideal para valorar el estado del útero e indicar el riesgo de PPH en función de la ausencia o no de actividad. Por ello, el objetivo de la presente tesis doctoral es la identificación de EHG-biomarcadores para la detección precoz de situaciones obstétricas de alto riesgo. Para ello, se generaron las bases de datos de señal EHG y de datos obstétricos para cada escenario en el Hospital Universitario y Politécnico La Fe. La mayor impulsividad y predictibilidad en MG respecto a SG durante el tercer trimestre, así como la correlación significativa entre los EHG-biomarcadores y el peso fetal, sugirió un acoplamiento electromecánico entre la sobredistensión y la actividad mioeléctrica registrada en superficie. En cuanto a la IOL, el grupo de éxito mostró un aumento significativo del número de contracciones y de la excitabilidad celular, junto con una menor complejidad, a partir de 2-3 horas tras la administración del fármaco de IOL. No se observaron cambios significativos con respecto a la actividad basal en el grupo de fracaso. La comparación basada en la paridad reportó una mayor ratio de progresión de la amplitud de la señal en el grupo de parosas. La actividad mioeléctrica en el postparto vaginal resultó ser más frecuente e intensa, además de exhibir una mayor excitabilidad celular que en los partos por cesárea. La capacidad discriminatoria de los biomarcadores de EHG para la detección precoz del riesgo en diversos contextos obstétricos ha hecho avanzar el conocimiento electrofisiológico actual del útero *in vivo*. La traslación del EHG a la práctica clínica requerirá la automatización del procesamiento de señales, para culminar en la creación de modelos predictivos generalizados y robustos que apoyen la toma de decisiones clínicas, mejoren la

planificación y gestión del parto, prevengan complicaciones maternas y fetales y optimicen la asignación de recursos hospitalarios.

Resum

Durant la gestació, la dona experimenta canvis fisiològics, metabòlics i morfològics que podrien comportar importants riscos matern-fetals. En primer lloc, el part prematur és la principal causa de mortalitat infantil, amb una prevalença del 10% en gestacions úniques (SG) i del 50% en gestacions múltiples (MG). Per tant, la caracterització de l'activitat uterina, així com la comparació entre SG i MG, ajuda a millorar la comprensió i gestió d'esta patologia. En segon lloc, la inducció del part (IOL) s'associa a un major risc de mortalitat i morbiditat materna quan la fase latent del part es prolonga excessivament, especialment en dones nul·lípares. No obstant això, la literatura és escassa i no s'ha observat clarament la resposta electrofisiològica uterina al fàrmac d'IOL. En este sentit, l'estudi de biomarcadors basats en la electrohisterografia (EHG) pot ajudar a detectar precoçment el risc de fracàs de la IOL i orientar les decisions clíniques en conseqüència. En tercer lloc, l'hemorràgia postpart (PPH) constituïx una de les principals causes de mortalitat materna en el món. La seua prevalença és del 2-6%, i causa la mort de 75.000 dones cada any. La principal causa és l'atonia uterina, per la qual cosa l'EHG es convertix en la ferramenta ideal per a valorar l'estat de l'úter i indicar el risc de PPH en funció de l'absència o no d'activitat. Per tant, l'objectiu de la present tesi doctoral és la identificació de biomarcadors d'EHG per a la detecció precoç de situacions d'alt risc obstètric. En este propòsit, s'han generat les bases de dades de senyals d'EHG i informació obstètrica de cada escenari en estudi a l'Hospital Universitari i Politècnic La Fe. La major impulsivitat i predictibilitat en MG respecte a SG durant el tercer trimestre, així com la correlació significativa entre els biomarcadors d'EHG i el pes fetal, va suggerir un acoblament electromecànic entre la sobredistensió i l'activitat mioelèctrica registrada en superfície. Pel que fa a l'IOL, el grup exitós va mostrar un augment significatiu del nombre de contraccions i de l'excitabilitat cel·lular, així com una menor complexitat, a partir de 2-3 hores tras l'administració del fàrmac de IOL. No es van observar canvis significatius respecte a l'activitat basal en el grup de fracàs. La comparació basada en la paritat va reportar una major ràtio de progressió de l'amplitud del senyal en el grup de paroses. L'activitat mioelèctrica en el postpart vaginal va ser més freqüent i intensa, a més d'exhibir una major excitabilitat cel·lular en els parts per cesària. La capacitat discriminatòria dels biomarcadors d'EHG per a la detecció precoç del risc en diversos contextos obstètrics ha fet avançar el coneixement electrofisiològic actual de l'úter *in vivo*. La translació de l'EHG a la pràctica clínica requerirá l'automatització del processament de senyals, per a culminar en la creació de models predictius generalitzats i robustos que donen suport a la presa de decisions clíniques, milloren la planificació i gestió del part, previnguen complicacions matern-fetals i optimitzen l'assignació de recursos hospitalaris.

List of Tables

List of Figures

Nomenclature

ACOG American College of Obstetricians and Gynecologists

APL Active Period of Labour

A_{pp} Peak-to-peak Amplitude

ART Assisted Reproductive Techniques

BLZ Binary Lempel-Ziv

BMI Body Mass Index

BS Bishop Score

BubbEn Bubble Entropy

CF Maternal Cardiac frequency

CFW Calculated Foetal Weight

CL Cervical Length

CSR Elective Caesarean Delivery

DAP Maternal Diastolic Arterial Pressure

DF Dominant Frequency

EBA EHG-Burst Analysis

EHG Electrohysterography

fFN Fetal Fibronectin

FuzzyEn Fuzzy Entropy

FW Fast Wave

FWH Fast Wave High

FWL Fast Wave Low

GAD Gestational Age at Delivery

GF Failed Induction of Labour Group

GS Successful Induction of Labour Group

GS_N Nulliparous with Successful Induction of Labour

GS_P Parous with Successful Induction of Labour

Hb Maternal Hemoglobin

HFD Higuchi's Fractal Dimension

H/L Ratio High/Low Ratio

Il-1β Interleukin-1β

IL-6 Interleukin-6

IOL Induction of Labour

IUPC Intrauterine Pressure Catheter

KFD Katz's Fractal Dimension

KHE Kurtosis of the Hilbert Envelope

MDF Median frequency

MG Multiple Gestation

MIOL Mechanical Induction of Labour

MNF Mean frequency

NCT Number of contractions

NE Normalized Energy per sub-band

NICE National Institute for Health and Care Excellence

NO Nitric Oxide

PAMG-1 Placental alpha-microglobulin-1

PIOL Pharmacological Induction of Labour

PPH Postpartum Hemorrhage

PROM Premature Rupture of Membranes

PTB Preterm Birth

PSD Power Spectral Density

RMS Root Mean Square

SampEn Sample Entropy

SAP Maternal Systolic Arterial Pressure

SG Single Gestation

SMFM Society for Maternal-Fetal Medicine

SNR Signal Noise Ratio

SO2 Maternal Saturation of Oxygen

SpEn Spectral Entropy

SW Slow Wave

TOCO External Cardiotocography

TPL Thread of Preterm Labour

UAI Uterine Activity Index

VGN Vaginal Delivery

WBW Whole Bandwidth

WEWA Whole-EHG Window Analysis

WHO World Health Organization

WoG Weeks of Gestation

Contents

Chapter 1

Introduction

Throughout life, the uterus has a fundamental role from the menstrual cycle through pregnancy, childbirth, and the puerperium. A better understanding of its anatomy and physiology lays the foundation for knowledge and research related to this crucial organ of the female reproductive system, answering questions that arise when entering gynaecology and obstetrics. In routine clinical practice, this knowledge supports informed decision-making by guiding the diagnosis of uterine disorders and the development of effective treatments.

1.1 Biology of the uterus

As the central organ in gestation, the uterus fulfils the reproductive purpose. It receives and ensures the development of the fertilised oocyte during pregnancy and, once the gestation period is complete, facilitates its expulsion. Thereafter, the uterus resumes its menstrual function, demonstrating remarkable adaptability by transforming its structure and morphology during these crucial stages of the reproductive cycle [1].

1.1.1 Anatomy and function of the uterus

The non-pregnant uterus is a pear-shaped organ located in the pelvic cavity, between the bladder in front and the rectum behind, as can be seen in Figure 1.1. It consists of two main but unequal parts: the cervix or uterine cervix is the smaller lower portion that projects into the vagina, while the body or corpus is the larger upper portion. The isthmus is the junction between the two and is of particular obstetric relevance because it forms the lower uterine segment during pregnancy

providing support and a protective barrier against infection. At each superolateral margin of the body are the uterine cornets, out of which the fallopian tubes and ovaries emerge. Finally, the fundus is defined as the convex upper uterine segment between the tubal insertion points [1].

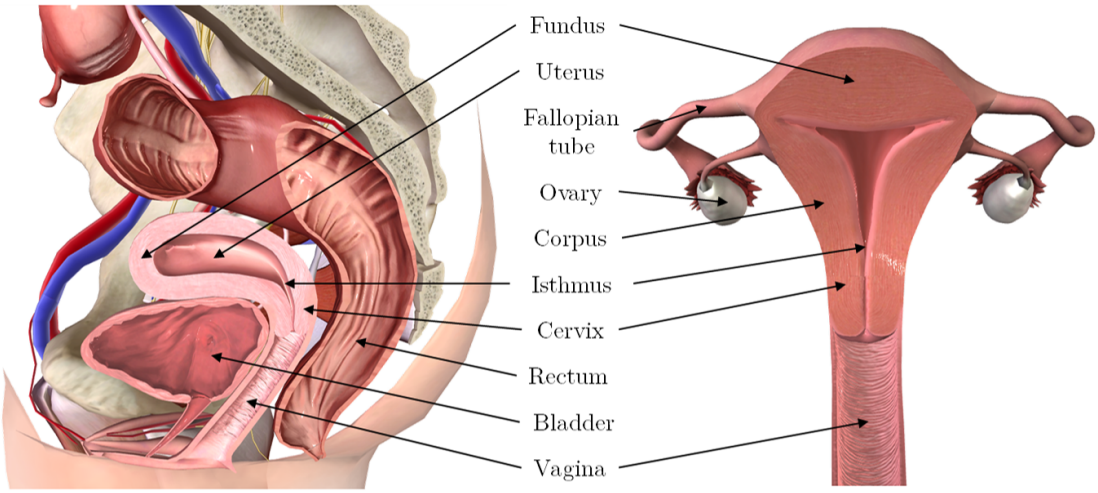

Figure 1.1: Cross-sectional view of the anatomical uterine structure. Partially modified from [2].

On the one hand, the cervix has a cylindrical shape, measures approximately 20-30 millimetres length and has two apertures at the ends: the internal one, which opens into the endometrial cavity, and the external one, which forms the exposed part of the vagina. It comprises the exocervix, lined with stratified squamous epithelium; the endocervix, which forms the canal connecting the external cervical os to the uterus, lined with columnar epithelium; the external cervical cavity, which varies with childbirth; the endocervical canal secretes mucus, forming a plug that prevents the ascent of germs; the internal cervical cavity, which acts as a sphincter during pregnancy; and the squamocolumnar intersection, which is usually found at the external cervical os and is subject to variation depending on factors such as age and sex; the internal cervical cavity, which acts as a sphincter during pregnancy; and the squamocolumnar intersection, which is usually found at the external cervical os and is subject to variation depending on factors such as age, menstrual cycle, pregnancy or contraceptive use [3]. Composed mainly of fibrous connective tissue of extracellular matrices such as collagen, elastin and proteoglycan, the cervix also has a cellular portion consisting of smooth muscle cells, fibroblasts, epithelium, and blood vessels to a lesser extent. This structure aims to protect the uterine cavity by acting as a barrier against pathogens, to control the passage of sperm during fertilisation, to maintain pregnancy by supporting the uterus, and finally to facilitate delivery by allowing passage to the foetus as it thins and

shortens during the maturation process [1, 4]. It is also through this channel that the menstrual products are expelled.

On the other one, the corpus is flattened and triangular in shape. It is the most active segment of the uterus and is composed by three distinct layers of tissue [1, 4]:

- The uterine cavity is lined with **endometrium**, composed of an overlying epithelium, invaginating glands and a supporting vascular stroma. It is further divided into a functional layer that is shed with each menstruation and a basal layer that regenerates the functional layer after each shedding. The endometrium thus varies greatly in response to hormonal fluctuations throughout the menstrual cycle. It also plays a crucial role in the implantation of a fertilised egg and, if pregnancy occurs, in the nourishment of the developing embryo. During the gestation, it widens and vascularises to provide a suitable environment for foetal development.

- A major component of the uterus consists of the **myometrium**, which contains bundles of smooth muscle held together by connective organised in three layers. The outer layer is made up of longitudinal fibres arranged in flattened fascicles covering the superficial part, and transverse fibres on the inner part forming a continuous and regular plane. The middle layer originates in the fallopian tubes and its spiral fibres, which enclose and circumscribe the venous sinuses, form the thickest of the three. The inner layer has longitudinal fibres grouped in longitudinal fascicles that constitute the uterine fundus and horizontal fibres that are situated internally as concentric rings in contact with the endometrium. Its main function is to contract during childbirth to facilitate delivery, but it also plays a major role during the evacuation of menstruation or in assisting the movement of sperm through the uterus during fertilisation. During pregnancy, the myometrium undergoes a high rate of cellular hypertrophy and hyperplasia, resulting in a considerable increase in size and thickness. The non-pregnant uterus weighs between 60 grams and has a capacity of 20 ml, during gestation it becomes 20 times heavier and its capacity increases by a factor of 250. This increase in the size and number of smooth muscle cells is essential for the uterus to exert powerful and effective contractions during labour. Gradual growth to provide a developmental environment for the foetus in the abdominal cavity causes displacement of adjacent organs and a change in the shape of the original pear to a more oval shape, as can be seen in Figure 1.2. From the 12th week of pregnancy, the uterus begins to protrude from the pubic bone, around the 20th week it usually reaches the navel, between the 28th and 32nd week it is normally located at the level of the sternum and continues to

grow until in the last weeks of pregnancy it may press against the upper ribs. In addition, as the myometrial fibres are intertwined around the myometrial vessels, haemostasis is allowed during the third stage of labour.

- The **perimetrium** is the outermost layer of the uterine wall. It consists of connective tissue and serous membrane. Covering the outer surface, it provides structural support to the uterus and helps it to anchor in the pelvic cavity.

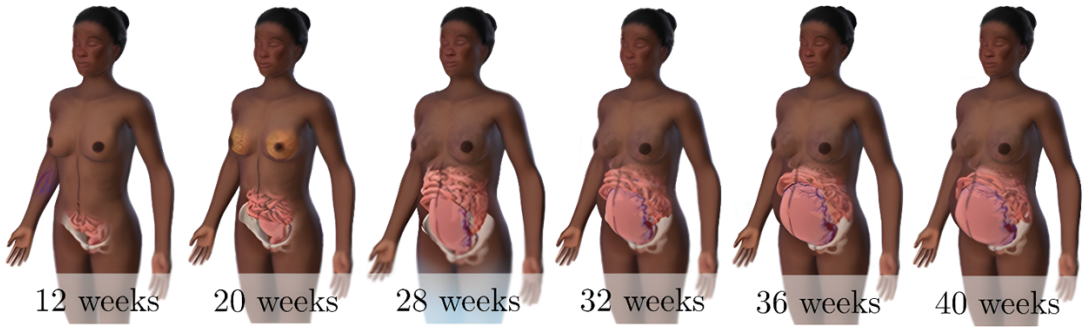

Figure 1.2: Pregnant body evolution during pregnancy. Partially modified from [2].

1.1.2 Origin of the contractions

A better understanding of the mechanism that trigger and regulate uterine contraction is essential to ensure maternal-fetal safety during both pregnancy and childbirth [5, 6]. Excitable cell behaviour is based on the passage of charged ions through transmembrane proteins located in the cell membrane which act as channels, either active or passive. The exchange of sodium, calcium, potassium, and chloride ions between the intra- and extracellular media defines the resting potential, ranging in utero between -70 and -55 mV, and defined as the difference of potentials inside and outside the lipid membrane [6, 7]. At the cellular level, it is the rapid and significant influx of calcium into de intracellular medium that triggers the contraction in the uterus [7]. The concentration of this ion in the extracellular medium is two orders of magnitude higher than in the intracellular medium. As a result, myosin binds to actin, allowing the thin actin filaments to move over the thick myosin filaments, thereby pulling the dense bodies and causing the intermediate filaments to constrict the myometrial cells by up to 80% of their original length [5], as can be seen in Figure 1.3. Actin-myosin dynamic is modulated by the Ca2+ CaM complex, which enhances the activity between these

two filaments. Upon binding to the complex, the enzyme MLCK[1] is activated, resulting in phosphorylation of the myosin light chains. During this process, ATP[2] is converted to ADP[3] by hydrolysis, inducing a structural alteration in myosin. The globular portions of myosin displace the actin filaments causing a reduction in muscle length leading to force and movement [5, 7].

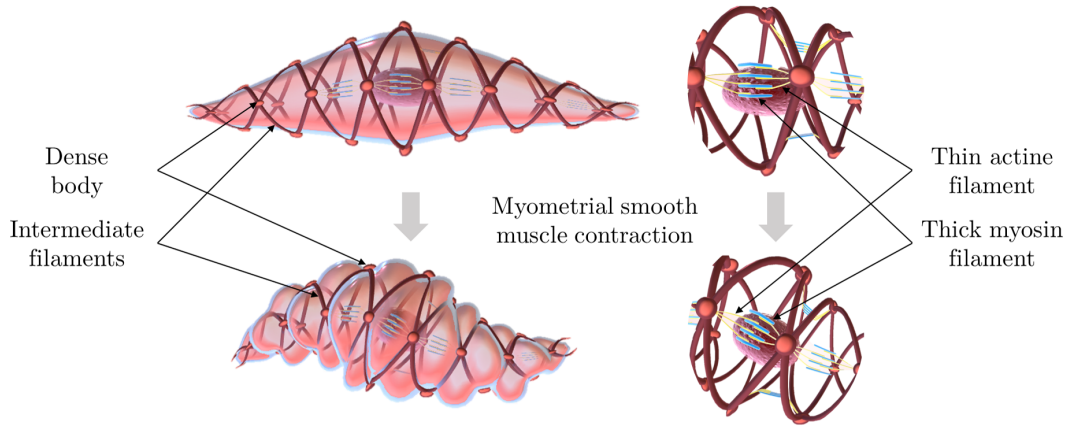

Figure 1.3: Myometrial contraction scheme. Partially modified from [2].

The uterus becomes progressively more excitable towards the end of pregnancy, until it finally develops rhythmic contractions that increase intrauterine pressure and thus provide the force necessary for labour to progress and expel both foetus and placenta [1, 5]. In order to generate sufficient pressure, the contraction must be synchronised at the organ level, as tissue laxity would dampen uncoordinated efforts. The cause of the contractile stimulus initiation in the uterus is currently unidentified. There is no evidence that this organ has specialized pacemaker cells as in the heart, in fact, each depolarisation front may be located in a different area at each contraction. Current literature suggests that any cell can acquire this role and then propagate the stimulus to neighbouring cells in the presence of oxytocic agents and overdistension, with the roles being interchanged at each contraction [8]. For intense contractions such as those of labour, a high concentration of prostaglandins released by the placenta, an increased oestrogen to progesterone ratio, and stretching or irritation of the cervix must be added to the previous [5].

As for the coordination, gap junctions are found connecting the interior of the myometrial cells, providing intercellular channels with low resistance ion passage to the electrical impulse. Although the density and number of these connections is

[1]Myosin Light Chain Kinase
[2]Adenosine triphosphate
[3]Adenosine diphosphate

scarce during the early stages of gestation, favouring uterine quiescence, there is a considerable increase in these connections peaking at the time of delivery, as well as in actin and myosin filaments [7, 9]. At birth, gap junctions present a density about 1000 per cell in human tissue [10]. These changes prepare the myometrium to easily transmit contractile stimuli to neighbouring cells, thus turning the uterus into a functional syncytium at delivery. After childbirth, myometrial excitability and contractility decrease because of gap junction endocytosis [7, 9].

1.1.3 Uterine contractility during pregnancy and labour

In early gestation, the pregnant uterus has low and uncoordinated electrical activity, often resulting in ineffective contractions. However, as the time of delivery approaches, the uterus becomes progressively more excitable and its activity more intense and synchronised until it finally develops rhythmic contractions strong enough to expel the baby. The hormonal and mechanical changes that this organ undergoes are believed to be responsible for inducing the intense contractions responsible for labour [1].

As for the hormonal factors, the first one is the increased ratio of oestrogen to progesterone, both of which are secreted by the ovary at first and in later pregnancy by the placenta. While progesterone contributes to uterine quiescence by increasing the intracellular calcium and decreasing the excitability, oestrogen has the opposite effect by promoting the creation of junctions between adjacent cells and activating calcium binding-dependent channels [1]. Both steroid hormones are produced at progressively higher levels, until the seventh month when progesterone secretion becomes constant. Second, oxytocin will contribute to the drive on the myometrium to increase contractility making the contractions more intense and frequent [6]. During the last months, the uterine muscle increases its receptors and the rate of secretion of this hormone increases considerably towards labour. Thirdly, both the cortisol secreted in the adrenal glands and the high concentration of prostaglandins produced by the foetal membranes could also increase the intensity of contractions [1].

As for mechanical factors, the simple stretching of the uterine musculature can enhance its contractility, even if it is intermittent due to foetal movements. This is reflected, for example, in the fact that Multiple Gestation (MG) give birth prematurely 6 times more often than Single Gestation (SG) [11]. Stretching or irritation of the cervical nerves has been suggested that can initiates reflexes in the body of the uterus, but the effect could also simply be due to myogenic transmission of signals from the cervix to the body of the uterus [1].

On the other hand, the mechanism underlying the slow and weak rhythmicity of the uterus that transforms into strong labour contractions is still unknown. However, the positive feedback theory of the labour hypothesises that the stretching of the cervix as a result of the passage of the foetal head is great enough to cause a strong reflex increase in contractility of the uterine corpus. This would push the baby towards the outer end of the vagina, feeding the process until the baby is expelled. In addition, the stretching of the cervix also involves an increased secretion of oxytocin, known as the Ferguson reflex [12], which makes contractions more regular and stronger. One may wonder about the many cases of false labour, where contractions get stronger and stronger and then disappear. However, for positive feedback to continue, each new positive feedback cycle must be stronger than the previous one. If at any time after the onset of labour some contractions fail to re-excite the uterus sufficiently, the positive feedback could go into a retrograde decline, and the labour contractions would fade [1].

The main physiological contraction types are classified as follows:

- **Alvarez contractions** occur in the latency phase of labour [13]. They are identified as short, regular and rhythmic [13, 14], with a low intensity around 2-4 mmHg [15]. Due to their low amplitude, they are usually not perceptible to the mother [15]. Appear with a frequency of 1 contraction per minute and with a very local influence[13, 15].

- **Braxton-Hicks contractions**, also known as false labour contractions [9, 16], present a higher amplitude and influence zone, along with lower frequency of occurrence and duration, than Alvarez contractions [1, 15]. Usually, they appear from 20 weeks onwards in a random, non-rhythmic manner [1, 9]. These contractions are thought to help tone the uterus and prepare it for real labour. They feel like a temporary tightening of the abdomen, do not normally cause cervical dilatation and are painless [1].

- **Long duration low frequency waves** can occur throughout gestation characterised, as the name suggests, by a long duration and a low frequency of occurrence [17]. Their occurrence is understood as a sign of uterine hypertonia, which may be detrimental to foetal wellbeing [1, 18].

- **Labour contractions** are characterised by being regular in frequency and duration, gradually increasing in intensity as expulsion approaches [4, 19]. During the latency phase, the frequency of contractions is 3 every 10 minutes with an intensity of 28 mmHg and duration of 30-45 seconds, the uterine tone is 8 mmHg [19, 20]. The frequency and intensity of contractions gradually increases throughout the active phase of labour to 4 contractions every 10

minutes with an intensity of 41 mmHg and duration off 45-60 seconds, the average tone is 10 mmHg [4, 20]. In the expulsive period of labour, the frequency is 5 contractions every 10 minutes with an intensity of 47 mmHg and duration of 45-60 seconds, the tone is 12 mmHg [4, 20].

- In the postpartum, the uterus continues contracting to expelling birth debris, assist in stopping the bleeding and returning the uterus to a size close to pre-pregnancy [1]. **Postpartum contractions** can be quite intense and frequent with intervals of a few minutes between them and durations similar to those of the expulsive phase of labour [16]. Generally, they are more noticeable during the first 24 hours after delivery and usually continue for a few days after delivery, although their intensity and frequency typically decreases as the uterus contracts and recovers. This type of contraction can become painful, especially during the feeding of the baby [1].

In addition, the generation of contractions in the uterus and the cervical effacement are closely related, although the sequence of these occurrence of processes is controversial. On the one hand, effacement may precede the generation of contractions in order to facilitate the path of contractions during dilatation. On the other hand, contractions could be in crescendo before the cervix is completely effaced, as in the case of false labour contractions. The fact is that the sequence of events changes even between pregnancies of the same patient, so prenatal care professionals have to monitor both factors at each check-up visit [8].

1.2 Risk situations during pregnancy, labour and postpartum

During gestation and postpartum, a myriad of difficulties can arise that disrupt the natural course of labour. Complications may manifest themselves in the form of problems that compromise maternal-fetal well-being and require specialised clinical care and subsequent follow-up. Preterm birth, cervical ripening in prolonged pregnancy and postpartum haemorrhage are the three main scenarios addressed in this dissertation.

1.2.1 Preterm birth. Prevalence in multiple gestation.

Preterm birth (PTB) is 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 [21]. Later preterm (34-37 WoG) and moderate preterm (32-34 WoG) account for the bulk of the PTB with 85%. Among the remainder, 10% are very preterm (28-32 WoG) and 5% extremely preterm (<28 WoG) [22].

Given its impact on neonatal mortality, long-term health issues, and healthcare economics, PTB represents a significant public health challenge. It constitutes one of the leading causes of perinatal mortality and caused 2.3 million deaths in children under 5 years of age worldwide in 2019 [23, 24]. Survivors face an elevated risk of issues related to visual, neurodevelopmental, and cognitive functions, as well as conditions like cerebral palsy. Furthermore, they often experience extended hospital stays due to respiratory, metabolic, or infectious complications [23, 25]. Therefore, the economic implications of PTB go beyond the immediate costs of neonatal intensive care units. Besides the significant psychological and economic strain imposed on affected families, PTB entails the long-term increase in the use of specialised medical, social and educational services, and the potential loss of economic productivity. The average initial annual cost of a PTB is 8,565€, 5.4 times more than a full-term birth. This cost can soar to 74,009€ in the case of very or extremely PTBs [22, 25].

Risk factors for PTB can be categorized primarily into maternal characteristics, ultrasound indicators, and biochemical markers. Maternal factors include MG, extreme maternal age, extreme Body Mass Index (BMI), maternal comorbidities (diabetes, hypertension, anaemia or autoimmune diseases to name a few), polyhydramnios, urinary tract or foetal membrane infections, periodontitis, vitamin D deficiency, smoking, illicit drug or alcohol use during pregnancy, race, maternal malnutrition or malnutrition, chronic or acute stress, history of previous preterm labour or miscarriage, *in vitro* fertilisation treatments and premature detachment of membranes, among others. Ultrasound techniques for gestational monitoring mainly detect shortening and effacement of the Cervical Length (CL) risk factors, together with inadequate foetal growth. Important biochemical markers include elevated levels of C-reactive protein, the presence of fetal fibronectin in cervical secretion and a low level of progesterone [26, 27].

Prenatal care from the very beginning of pregnancy allows for the identification of risk factors and the appropriate monitoring and management of pre-existing medical conditions. In women with a history of cervical incompetence or insufficiency, cervical cerclage is often performed to keep the cervix closed. A healthy lifestyle and stress management are also highly recommended [28–30]. In case of threatened PTB, the patient is hospitalised and tocolytics are administered to stop uterine contractions and thus the progress of labour. This allows the clinician to mature the fetal lungs with corticosteroids and the brain with magnesium sulphate to reduce the risk of complications in the event of early delivery. Should the delivery be unavoidable, the newborn is admitted to the neonatal intensive care

unit where respiratory support, specialised feeding and intensive medical care are provided [22].

Despite major advances in modern medicine, PTB rate continues to rise, as is the case in the United States, going from 9.63% in 2015 [31] to 10.48% in 2021 [32]. This growing rate may be related to the ever-increasing maternal age at gestation because of the socio-economic changes our society has undergone [31, 32]. Since the turn of the century, births among women aged 35-39 have increased by 30.5 per cent and by 48 per cent among women over 40 [33]. However, fertility and fecundability continue declining progressively from the age of 32 and 37, respectively, as a consequence of the reduction in the quality and number of oocytes [34]. For this reason, the demand for assisted reproductive technologies is steadily increasing [35, 36] and so is the occurrence of multiple pregnancies [34, 35]. Currently, the worldwide incidence of MG post-treatment is around 20%, ranging from <10% in several Nordic countries [36] to 30% in the USA [37], significantly higher than the 1-2% in natural conceptions [36]. In the case of MG, the prevalence of PTB was 59.94% compared to 8.42% in singletons in 2020 [37]. Consequently, they are at especially great risk of neonatal death, perinatal complications and somatic pathologies, physical and neuropsychological developmental disorders, formation of congenital malformations and disability [38].

1.2.2 Prolonged pregnancy and induction of labour

Timely onset of labour and delivery is key to reduce fetal and infant death and long-term morbidity [39]. In contrast to PTB, in which the onset of labour is caused by the sudden release of various stimulatory effects [40], term labour in humans is caused by the release of uterine inactivity [41]. Generally, human gestation lasts 40 weeks from the first day of the last menstrual period, during which time uterine quiescence and cervical competence allow for the proper development and nourishment of the foetus [39].

The American College of Obstetricians and Gynecologists (ACOG) has classified term deliveries according to gestational age at labour as: early term (37 0/7 to 38 6/7), full term (39 0/7 to 40 6/7), late term (41 0/7 to 41 6/7) and post-term (42 0/7 and beyond) [42]. A Cochrane review analysing 34 randomised clinical trials and 21,000 women, treated expectantly or who had their labour terminated, reported lower perinatal deaths, caesarean section rates, neonatal intensive care unit admissions and higher 5-minute Apgar scores in induced deliveries [43]. In addition, a prospective Swedish study involving more than 2 million singleton low-risk pregnancies at 37-42 WoG, the risk of death or neurological complications was found to be highest among early term pregnancies. In contrast, the risk of adverse

fetal, infant and neurodevelopmental outcomes was found to be lowest at 39-41 WoG [44]. Risk factors described for post-term pregnancy are previous post-term pregnancy, nulliparity, obesity and advanced maternal age [45].

In this case where the risk of continuing the pregnancy outweighs the benefits to the foetus, the mother or both, termination of pregnancy should be considered [46, 47]. For this need, the only available alternatives are the Induction of Labour (IOL) and caesarean section. The former is preferred to the latter if there are no contraindications to vaginal delivery as it is less invasive, allows for a quicker recovery and has fewer risks of complications [47, 48]. Leading organisations established the recommendation for late term IOL in low-risk pregnancies such as the World Health Organization (WHO) in 2018 [46] and the National Institute for Health and Care Excellence (NICE) guidelines endorsed it in primiparas in 2021 [49]. In turn, the ACOG discourage delaying labour until full term in 2021 if there is a medical or obstetric indication for earlier delivery and proposed a long list of recommendations on the timing of delivery for several specific conditions [50]. Moreover, 41-week induction has shown an 80% probability of being cost-effective, especially in nulliparas, with a willingness to pay of 22,000€ for the prevention of adverse perinatal outcome and 50,000€ for the prevention of severe composite adverse perinatal outcome [51].

Induction of labour

IOL involves the obstetric techniques and methods, whether pharmacological or mechanical, designed to artificially stimulate the uterus before the spontaneous onset of labour, thereby promoting the onset of contractions that trigger labour and the fetoplacental unit expulsion [46, 48]. It is considered a topic of great obstetric interest as not only is it the most frequent procedure in routine clinical practice, but the number of pregnant women undergoing the procedure is on the rise. In England it increased from 22% in 211 to 33% in 2022 [52], in Australia from 26% in 1998 to 34% in 2021 [53], in Sweden from 19% to 25% between 2018 and 2020 [54], in the United States from 9.5% in 1990 to 29.4% in 2019 [37], and in Spain from 18.6% in 2010 to 34.2% in 2018 [55].

Common indications for IOL are rupture of membranes without labour, gestational hypertension, oligohydramnios, foetal distress, post-term pregnancy and various maternal conditions such as chronic hypertension and diabetes. Of note, IOL is not exclusive to prolonged labour, but is also employed in cases in which expectant management is no longer an option, such as premature rupture of mem-

branes, pre-eclampsia, eclampsia, HELLP syndrome[4], gestational hypertension, chronic hypertension, foetal demise, maternal diabetes, foetal growth restriction, chorioamnionitis, placental abruption, oligohydramnios, hepatic cholestasis, Rh isoimmunisation with foetal anaemia or twin gestation [48]. Induction or augmentation of labour is contraindicated in most of the diseases that impede spontaneous labour. The few maternal contraindications are related to the type of anterior uterine incision, contracted or distorted pelvic anatomy, abnormally implanted placentas and rare conditions such as active vaginal herpes infection or cervical cancer [48, 56]. Fetal factors include umbilical cord prolapse, severe hydrocephalus, malpresentation or fetal distress. Breech presentation, foetal macrosomia, previous cesarean and twin gestation are considered relative contraindications and must be assessed on an individual basis considering the maternal characteristics, together with the experience and guidelines established in each hospital [1, 48].

In the broadest sense, if IOL does not result in vaginal delivery, regardless of the time from the start of the process, it is considered to have failed [57]. In 2012, ACOG defined failed IOL as failure to achieve regular contractions and cervical changes under oxytocin effect after 12-18 hours following amniotomy, or 24 hours with intact membranes. Cervical ripening duration is not included in the computation or definition of failed IOL [58]. Experiencing a prolonged latent phase has been associated with an increased risk of maternal and perinatal complications, including elevated rates of obstetric intervention, cesarean section, chorioamnionitis, admission to the neonatal intensive care unit, and significant blood loss. However, no clear turning point has been defined at which the risk rises considerably, making the interpretation and subsequent translation into clinical recommendations extremely challenging [57]. After IOL with oxytocin combined with amniotomy in a group of 509 women, 39% delivered vaginally after 6 hours, 28% after 9 hours and 13% after 12 hours. The conclusion was that oxytocin should be administered for at least 12 hours after rupture of membranes before sentencing the IOL as failed, defined as failure to progress to the active phase (dilatation>4cm and 90% effacement) [59]. In 2014, the results of a joint workshop between ACOG and Society for Maternal-Fetal Medicine (SMFM) on safe prevention of first caesarean section were published. Recommendations here include, maternal and foetal status permitting, minimising caesarean sections due to failed IOL of labour by allowing longer latent phases (up to 24 hours from the start of IOL), administration of oxytocin for at least 12-18 hours after bag rupture and consideration of active labour from 6 cm dilation onwards [60].

Determining the status of the cervix prior to IOL is essential for predicting its outcome in daily clinical practice. Of note, the indication for IOL usually occurs

[4]The acronym HELLP is derived from its main clinical features: haemolysis (H), elevated liver enzymes (EL) and low platelet levels (LP).

with an unfavourable cervix, so the procedure is divided into a first phase of cervical ripening or pre-induction, and a second of uterine contractions augmentation in case the labour process has not been triggered spontaneously after the first one [48]. The former is a complex process involving remodelling of connective tissue by reducing collagen and proteoglycan concentrations while increasing water content, resulting in physical softening and distensibility of the cervix that eventually leads to cervical effacement and partial cervical dilatation [16]. The most used cervical assessment system is the modified Bishop Score (BS), which considers cervical conditions by scoring dilatation, effacement, consistency, and position of the cervix, adding the height of the foetal presentation [61]. The result is a score in the range 0-13, as can be seen in Table 1.1.

Table 1.1: Bishop score punctuation [61].

Cervical factor	**Score**			
	0	*1*	*2*	*3*
Dilatation (cm)	Closed	1 or 2	3 or 4	>4
Consistency	Firm	Medium	Soft	none
Effacement (%)	<40%	40-60%	60-80%	>80%
Position	Posterior	Central	Anterior	none
Fetal station	-3	-2	-1 or 0	+1, +2

Although a high score (BS≥8) is useful as a measure of cervical maturity and performs well in predicting the likelihood of vaginal delivery, a low score (BS≤6) does not yield as accurate for predicting the likelihood of IOL failure, prolonged labour, or caesarean section [48, 49]. In addition, the cervical consistency component is assessed subjectively, conferring minimal reproducibility to the measure [48, 62]. Transvaginal ultrasound measurement of CL is the only biophysical marker that has been considered as an alternative to BS, although it has been found to have low sensitivity and specificity for predicting successful IOL [63]. Other obstetric variables such as CL or foetal weight have also been attempted to predict IOL outcome. The reported values of area under the receiver operating curve are respectively 0.5-0.7 [64–66] and 0.6 [64] versus 0.4-0.7 for BS [65, 66], implying the poor predictive ability of these variables and the need to establish new reliable biomarkers for the prediction of IOL outcome.

Methods for induction of labour

According to the approach and methods used to stimulate labour, IOL techniques can be broadly divided into pharmacological (PIOL) and mechanical

(MIOL). On the one hand, the first methods developed to ripen the cervix and induce labour were MIOL, which include:

- The procedure of **membrane sweeping**, also known as Hamilton manoeuvre, consists of separating the lower part of the foetal membranes from the lower uterine segment by rotating the finger through 360^o, leading to the release of prostaglandins with subsequent cervical ripening and initiation of labour. Its practice is not routinely performed in all pregnancies, as there is no evidence that it improves maternal or neonatal outcome, although it does shorten the time to spontaneous onset of labour without increasing the risk of infection, so it could be offered to women over 39 WoG seeking to accelerate the onset of labour. This procedure is endorsed by WHO [46], ACOG [50] and NICE [49].

- **Amniotomy** is the intentional perforation or rupture of the amniotic sac by an obstetrician [67]. This is a commonly used, inexpensive and low-resource method may be performed to influence the speed of labour, allow more direct monitoring of foetal status or qualitative assessment of amniotic fluid, among others [1]. Using this technique does not seem to shorten the duration of the first and second stages of labour under standard progression of labour [68]. Although if the cervix is partially dilated and effaced, it has proven to be an effective method for IOL. The major drawback is the unpredictable and occasionally long interval until the onset of labour in which the foetus is compromised [1, 69].

- **Hygroscopic dilators** are designed to absorb moisture and gradually expand within the cervical canal. By disrupting the interface between the amnion and the decidua, it causes the secretion of prostaglandins by local action contributing to the active modification of the cervix in addition to the passive mechanical dilatation caused by the presence of the dilator in the cervical canal [48, 70]. Their safety in improving cervical dilatation contrasts with their inability to improve the overall success of IOL. No significant reduction in caesarean delivery rates or in the achievement of vaginal deliveries in the first 24 hours after application has been found [67, 70]. Therefore, they are predominantly used in first-trimester abortion induction [1].

- **Transcervical catheters** stand out for their low cost, reversibility, and lack of serious side effects [71, 72]. Placement up to the internal cervical os, filling to the maximum allowable volume by infusion of sterile saline and clamping the device to the patient's thigh to create tension is a common technique in clinical practice for cervical ripening, as seen in Figure 1.4.

Prior to placement, sterilisation of the cervical canal and verification of foetal presentation and exclusion of placenta praevia, usually by abdominal ultrasound, are required. The balloon catheter remains in the extra-amniotic space until spontaneous expulsion or until 12-24 hours after insertion [1, 48]. Often it requires the subsequent augmentation of contractions with oxytocin, which is frequently associated with a higher rate of dysfunctional deliveries and cesarean sections [71, 72]. The oxytocin regimen can be started just after catheter removal [67] or even simultaneously, this practice increased the rate of deliveries in the first 24 hours in a randomized trial [73]. Although the double-balloon or Cook's catheter has been designed and marketed specifically for cervical ripening, the single-balloon or Foley catheter has been widely used in clinical practice for this purpose. In terms of efficacy, safety and patient satisfaction both are similar, although Foley is more cost-effective [74].

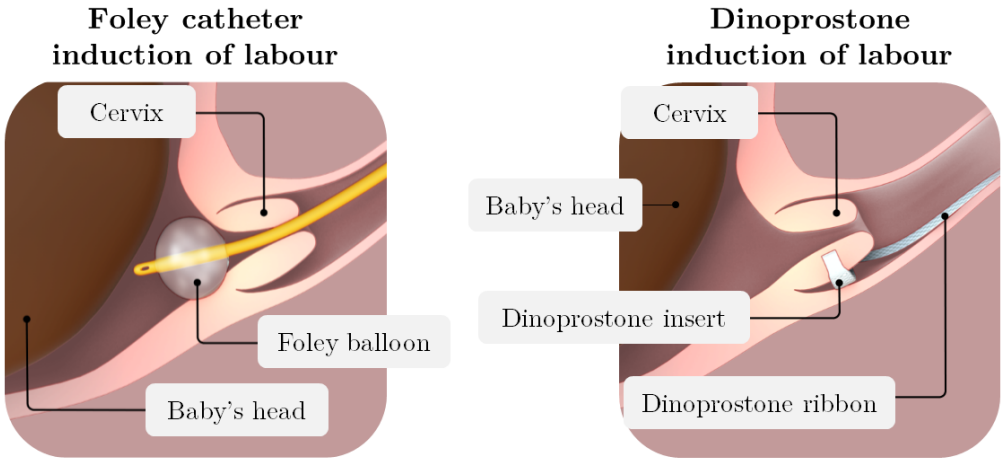

Figure 1.4: Dinoprostone slow-release ribbon and foley catheter placement scheme for pharmacological and mechanical induction of labour [75].

On the other hand, MIOL methods have been partly substituted by PIOL methods, which include:

- **Misoprostol** or synthetic prostaglandin E1 was originally developed as a preventive treatment for peptic ulcer. Its use as a cervical ripening agent was approved in 2008 by the Spanish Medicines Agency in low doses and in 2009 it was endorsed by ACOG [76]. At the electrophysiological level, prostaglandin E1 acts on cervical cells by increasing the concentration of intracellular cyclic

adenosine monophosphate (cAMP), causing inhibition of smooth muscle contraction and relaxation of collagen fibres in the cervix. As a result, electrical resistance in the tissue is reduced and conduction of electrical impulses is facilitated, allowing the cervix to dilate and efface more efficiently. Misoprostol is administered in tablets, is economical and easy to store due to its stability at room temperature. Routes of administration of misoprostol have been described as vaginal, oral, sublingual, and rectal. Absorption of the drug is rapid and serum levels vary according to the route chosen, although due to its pharmacokinetics the likelihood of achieving regular and prolonged uterine activity is greater via the vaginal route compared to the oral route [77]. The optimal dose and time interval of misoprostol administered is controversial. While the 50μg dose achieves higher delivery rates within 24 hours of the first dose with less need for subsequent oxytocin, the 25μg dose shows a safer profile with a lower probability of tachysystole, hyperstimulation, caesarean section due to risk of fetal distress, neonatal internal care unit admission and meconium amniotic fluid aspiration [1, 48].

- **Dinoprostone** is a synthetic analogue of prostaglandin E2 and a recognised agent for cervical ripening approved by the Spanish Medicine Agency in 1999. In contrast to E1, E2 binds to EP2 and EP4 receptors on cervical cells, raising intracellular calcium levels and triggering focused cell contraction, inhibition of collagen synthesis and increased vascularisation. Dinoprostone is more expensive than misoprostol and its instability at room temperature requires refrigerated preservation. It is commercially available as a 0.2mg/ml gel (Prepidil ®), 10μg slow-release vaginal insert (Propess ®) and suppository, being the latter used not for cervical ripening but for termination of pregnancy between 12-20 weeks or evacuation of the uterus after fetal death up to 28 weeks [1]. Comparing the rates of uterine tachysystole (>5 contractions in 10 minutes) and fetal heart rate alterations between E1 and E2, literature reviews seem to converge that both drugs have a similar safety profile [48, 78]. However, the long tail of the vaginal insert allows for easy removal of the wafer in cases of risk of loss of fetal well-being, such as uterine tachysystole or fetal heart rate abnormalities. For this reason, as well as the fact that it provides a constant dose of 0.3mg/h, it represents the preferred method in our setting. It is used as a single dose placed transversally in the posterior vaginal fornix, as can be seen in Figure 1.4. The insertion is removed after 12 hours or before labour, and at least 30 minutes before administration of oxytocin to avoid complications related to excess uterine contractility [1, 48].

- Cervical ripening and increased contractions are in many cases merely a continuum when spontaneous labour is not achieved after the first stage.

Oxytocin was approved in 1976 by the Spanish Medicines Agency and has been used ever since for the augmentation of labour. This peptide hormone binds to its specific receptors located on the membrane of uterine muscle cells, activates L-type voltage-dependent calcium channels causing a substantial increase in intracellular calcium and triggering its oxytocic effect manifested as more intense and frequent contractions [1]. Uterine sensitivity to oxytocin increases progressively throughout pregnancy, as more and more myometrial oxytocin receptor binding sites are present [79]. Its action is dose-dependent, so that at low doses there is complete relaxation after the contractile period, while at high doses there is an increase in basal tone [80]. Parenteral administration is recommended as it allows for better and more controlled dosage and by infusion pump or slow drip to avoid adverse cardiovascular effects. It has a short plasma half-life of 3-6 minutes, and its concentration stabilises after 40 minutes [81]. The administration protocol usually starts with a low dose and is gradually adjusted according to uterine response under close clinical supervision, as it can cause tachysystole, uterine rupture and amniotic fluid embolism, to name but a few [82]. A 2016 meta-analysis found that intravenous oxytocin administration in combination with amniotomy and vaginal misoprostol were the two approaches most likely to achieve vaginal delivery within the first 24 hours [83].

As a research alternative for pharmacological IOL, Nitric Oxide (NO) has also been reported in the literature. It is a free radical gas with a half-life shorter than four seconds, is thought to be an essential mediator in the process of cervical ripening because its main physiological effect on uterine muscle is to relax it. NO donors such as isosorbide mononitrate and glyceryl trinitrate have been studied for cervical ripening but have been found to be less clinically effective than prostaglandins in this process. A large meta-analysis found that the use of NO donors did not reduce the rate of caesarean delivery compared to other treatments, but were significantly associated with more headaches, nausea, and vomiting [1, 84]. The combined use of mechanical and pharmacological techniques has also been explored, but neither has been translated to the clinical praxis either due to inconsistent results. Some authors support the idea that it improves the efficacy of cervical ripening [85, 86], while others suggest that the mechanical and pharmacological agents act independently rather than synergistically [87, 88].

In conclusion, prostaglandin E2 and Foley catheter represent the most used techniques for cervical ripening in clinical practice. A similar rate of vaginal delivery in the first 24 hours, delivery ending by caesarean and women with an unfavourable cervix 12-24 hours after ripening onset has been found for both methods. In contrast, Foley catheter was found to require oxytocin augmentation

more frequently. However, there was a substantial reduction in tachysystole and hyperstimulation with changes in fetal heart rate [67, 74]. Other studies, however, found the Foley catheter to be the least effective induction technique, although they agreed that it carried less risk [89]. Despite the increased rate of IOL and the importance of understanding the myoelectric response to this process, whether pharmacological or mechanical in nature, to shed light on the underlying mechanism and provide a sound basis for clinical decision making, it is relevant to note that so far there are no studies comparing this response using objective methods. For more details and results, please refer to Chapter 4.

1.2.3 Postpartum haemorrage: vaginal and cesarean delivery

In the field of postpartum care, the ACOG has introduced the notion of the fourth trimester, emphasising the importance of the 12 weeks after delivery [90]. This concept underscores the need for a holistic assessment that encompasses physical, social, and psychological aspects of maternal well-being. A major cause of maternal morbidity and mortality during the postpartum is the global obstetric emergency of Postpartum Hemorrhage (PPH), which complicates 1-10% deliveries [91, 92]. Its highest prevalence occurs in Africa (5.1%-25.7%), followed by North America (4.3%-13%) and Asia (1.9%-8%) [93]. Although most maternal deaths occur in low- and middle-income countries, possibly because of disparities in medical care, high-income countries are experiencing an increase in incident PPH associated with increasing maternal age at delivery, caesarean delivery, multiple pregnancy and IOL [92–97]. Cases of PPH in Canada increased from 5.1% in 2003 to 6.2% in 2010 [96] and in the United States from 2.9% in 2010 to 3.2% in 2014 [97].

Classically, PPH has been defined as a quantified blood loss of more than 500 ml in vaginal deliveries and more than 1,000 ml in caesarean sections [98]. It usually lasts for 24 h, which is called immediate PPH, though some cases can occur up to six weeks after delivery, which is known as delayed PPH [99]. However, the definition was not focused on clinical signs and symptoms of PPH, hindering its early detection in many cases [98]. The ACOG redefined PPH in 2017 as a blood loss equal to or greater than 1,000 ml or a blood loss accompanied by signs or symptoms of hypovolaemia occurring within 24 hours of delivery, regardless of the route of delivery [100]. Alternatively, the Royal College of Obstetricians and Gynaecologists describes PPH as mild (between 500 and 1,000 ml) and severe (more than 1,000 ml) [101]. However, estimation of blood volume lost remains unreliable in many cases, so special attention should be paid to the general clinical

condition of the patient [102]. Visual estimation is citeerred to as part of the assessment of blood loss, although its high potential to underestimate bleeding has led to the proposal of additional tools for more objective estimation, such as gravimetric measurement, direct blood collection techniques and assessment of clinical parameters. Yet, it is believed that the estimated blood loss is usually only about half of the actual one [1]. Recently, some guidelines have incorporated the shock index and obstetric early warning systems into their recommendations for assessing haemorrhage [101, 103].

Although there are several identifiable risk factors for PPH, most cases occur unexpectedly [100]. The commonest aetiology is uterine atony accounting for 70% of the cases, it citeers to the incapacity of the uterus to effectively contracts before delivery. It may be anticipated after prolonged labour particularly with the use of oxytocin, in pregnancies complicated by chorioamnionitis, high parity, general anaesthesia and other factors leading to uterine overdistension such as multiple fetal gestation, polyhydramnios and fetal macrosomia [100, 104]. Genital tract trauma constitutes 15-20% of cases, being mainly attributed to perineal or cervical lacerations, perineal haematomas, episiotomies, or uterine rupture, and generally occur in uncontrolled or operative vaginal deliveries [100, 104, 105]. Other factors such as retention of conception products can increase the risk of PPH by 3.5 times, with risk factors including placenta succenturiasis and previous instrumental procedures [100, 106]. Finally, clotting disorders both hereditary (von Willebrand's disease, haemophilia, and idiopathic thrombocytopenic purpura) or acquired (anticoagulant therapy and disseminated intravascular coagulopathy following abruptio placentae, pre-eclampsia with severe features, intrauterine fetal death, sepsis, or amniotic fluid embolism), uterine inversion and abnormal placental implantation should be considered [98, 100, 104, 107].

Uterine atony refers to the inadequate contraction of the uterine corpus myometrial cells in response to endogenous oxytocin [108]. During the third stage of labour, expulsion of the placenta causes disruption of the spiral arteries [108]. These arteries shed their smooth muscle cell covering throughout pregnancy, making them dependent on other muscle contractions for maternal blood flow to the foetus [109]. Under normal conditions, the uterus would contract effectively and continuously, compressing the vessel endings and thus stopping the bleeding. This contraction also helps the uterus to regain a non-pregnant size. A further complication may be the failure to expel any remaining pregnancy products that may remain in the uterine cavity [108]. After vaginal delivery, parturients with previous history of PPH, nulliparous, induced labour, prolonged labour, or previous episiotomy require special attention. Even if delivery has occurred physiologically, the risk of PPH may be increased after episiotomy [106]. Lately, the association between PPH and caesarean delivery has been increasing, as has the risk of hys-

terectomy in pregnancies with placenta praevia [102, 110, 111]. In this setting, PPH definition may be controversial. The average blood loss in a lower segment elective caesarean delivery is 487 ml and in an emergency caesarean after a period of labour 1000 ml. Uterine atony seems to predominate as a side effect after caesarean section [108, 112]. Myometrial exhaustion (increased or prolonged labour), overdistension (multiple pregnancy, polyhydramnios), functional or anatomical distortion (placenta praevia, fibroids or rare abnormalities of the uterus such as arteriovenous malformations), as well as infection may be reasons for inadequate contraction and inability to limit blood loss in this case. In addition, risk factors for PPH following caesarean section are amnionitis, general anaesthesia, pre-eclampsia, fetal macrosomia, multiple pregnancy, leiomyomas, hemopathies, placenta praevia, intrapartum or antepartum haemorrhage, preterm delivery and prolonged labour [113–115].

Active management of the third stage of labour involves prophylactic administration of a uterotonic agent prior to delivery of the placenta, as well as delayed clamping and controlled traction of the umbilical cord [116]. In terms of PPH prevention, treatment focuses on restoring uterine contraction and maintaining maternal haemodynamic stability through transfusion protocols, surgical interventions in some cases, and with the cornerstone in most cases being the administration of the uterotonic [117, 118]. In 2018, the WHO recommended the use of 10 IU of oxytocin or 400μg of misoprostol in all deliveries for PPH prevention, while the use of 100μg of carbetocin due to its high cost and ergonometrine (200μg alone or 5 IU with oxytocin) due to its incompatibility with hypertensive disorders were defined as context-specific recommendations. The use of injectable prostaglandins was discouraged [119]. Pickering's work suggests that if the cost of carbetocin were lower it could be crowned as the predominant option due to its high effectiveness and low incidence of adverse events. The incremental cost-effectiveness ratio for prevention of PPH with carbetocin compared with prevention with oxytocin was £928 per case of PPH $\geq$500 mL avoided, £22,900 per case of PPH $\geq$1000 mL avoided, and £894,514 per major outcome averted [120].

In the absence of a timely recognition and appropriate treatment, women can suffer shock, organ dysfunction and even death. It is estimated that around 75,000 women die each year from PPH, almost a quarter of maternal deaths worldwide [121]. Survivors may suffer significant morbidities such as organ failure, severe anaemia, fatigue, transfusion complications, acute respiratory thrombosis, sepsis and potentially require intensive care or surgery [122, 123]. In addition, it can lead to longer hospital stays and increased healthcare costs. The average cost of a red blood cell transfusion is estimated to be about 1,957€ per patient with acute anaemia without severe symptoms [124], and costs for PPH surgery range from 275€ for manual exploration of the uterine cavity to 875€ for hysterectomy [125].

1.3 Clinical techniques to monitor pregnancy progress and predict delivery imminence

As part of prenatal care, maternal-foetal well-being is closely tracked through the evolution of uterine activity and foetal heart rate pattern mainly, in addition to the surveillance of maternal biophysical parameters, such as arterial blood pressure and blood glucose levels, and the follow-up of foetal development. Monitoring allows the early identification of possible complications and enables the physicians to respond promptly if necessary.

1.3.1 Biochemical markers of inflammation

Several biochemical markers of inflammation have been studied for their predictive capacity in relation to imminent delivery. Changes in these biomarkers could provide crucial information about gestational progress and help health professionals make informed decisions about antenatal care. Below is a description of the principal ones and how they may evolve during gestation and postpartum, along with their efficacy in predicting PTB outcome [126]:

- **Fetal Fibronectin (fFN)** is a protein which helps maintain the amniotic sac attached to the lining of the uterus during pregnancy. If this bond is broken, fFN can leak into the vagina. The fFN test is indicated between 22 and 34 weeks of pregnancy, as after 35 weeks the natural course of pregnancy makes vaginal discharge normal. Due to its low positive predictive value, the scientific community has insufficient evidence to state whether this test should be used in the management of women with symptomatic PTB [127, 128].

- **Placental alpha-microglobulin-1 (PAMG-1)** is a protein produced by the placenta, present in the amniotic fluid during pregnancy and a specific marker of Premature Rupture of Membranes (PROM). Its detection in the cervix, usually between 24 and 35 weeks of gestation, has been widely used in the prediction of PTB outcome because of its association with PROM. It is noteworthy that the PAMG-1 and fFN tests have similar accuracy in detecting PTB in less than 7 days [129].

- **Interleukin-1β (Il-1β)** is a proinflammatory cytokine that influences the coordination of proinflammatory and prolabour gene regulation in intrauterine tissues. Il-1β is also a potent stimulator of prostaglandin synthesis and

contributes to progesterone withdrawal. Besides Il-1β related pathways are increased during the third trimester in women who give birth prematurely [27]. Screening threshold for Il-1β are still under study and although preliminary results are promising, further research is required to assess whether this biomarker could improve the prediction of PTB, either independently or collectively [130, 131]

- **Interleukin-6 (IL-6)** is a pro-inflammatory cytokine involved in implantation, pregnancy and delivery. It has the ability to stimulate the amnion and decidual cells, leading to an increase in prostaglandins and thus potentially to trigger premature contractions. Intensively investigated as a screening biomarker for PTB, measured in vaginal discharge, it has outperformed PAMG-1 in predicting PTB in both univariate and multivariate studies. However, diagnosis of intra-amniotic inflammation based on IL-6 in amniotic fluid may under-represent the true extent of intrauterine inflammation [27, 132].

In summary, no biochemical screening method currently exists in clinical practice to accurately identify women at real risk of PTB to provide a patient-oriented strategy to continue the pregnancy as long as possible, thus minimising negative consequences and filtering out women with false Thread of Preterm Labour (TPL) to avoid unnecessary interventions and reduce hospital costs [26].

1.3.2 Cervical assessment

In low-risk pregnancies, the cervix remains long and closed throughout gestation to provide the growing foetus with support and protection from ascending pathogens. In mid-gestation, it is a useful method for predicting the likelihood of subsequent preterm delivery in asymptomatic women [1, 133]. Essential employed methods to assess the cervix are:

- **Digital examination** provides the most integral assessment of the cervix, evaluating its dilatation, length, consistency and position, in addition to the foetal station [133, 134]. The scoring of these five categories led to the definition of the BS, which is currently the most widely used cervical assessment system in routine clinical practice [134, 135]. An elevated BS correlates with a high likelihood of successful IOL. However, digital palpation is subjective and depends largely on the experience of the examiner [133].

- **Ultrasound** involves the use of conductive gel and an ultrasound transducer, that can be placed over the perineum (the region between the vagina and the

anus), over the abdomen or inside the vagina of the patient. Transabdominal scanning allows assessment of the pelvic region and cervix even in early pregnancy when the cervix is furthest from the vagina. Transvaginal scanning offers a more accurate image due to its proximity to the structures, although its applicability may be limited in early pregnancy when the cervix is further away from the external vaginal orifice [133]. Although all three techniques provide high-resolution images, transperineal [133] and transvaginal ultrasound [136] location of the probe may be uncomfortable for the patient. In addition, transvaginal has the potential to transmit vaginal infections, including human papillomavirus [137]. In a comparative study, transabdominal ultrasound reported a lower proportion of cases where it was able to measure CL (46%), compared to transperineal (98%) and transvaginal (100%) [136]. Furthermore, the measurement accuracy may be diminished by obesity [133] or the anatomy of the patient [133, 138, 139]. Bladder volume at the time of measurement may also distort the result [133].

Besides assessing CL, these methods can also identify further significant findings, such as cervical canalisation, cervical mucus accumulation and placental-related problems. Findings such as these may have important clinical implications in the monitoring of pregnancy and the detection of PTB risks.

1.3.3 Uterine dynamics

Standard techniques in clinical practice are based on the measurement of the pressure increase provoked in each contraction, directly (internal) or indirectly (external). Clinical parameterization takes into account the basal tone, the lowest pressure recorded between contractions, and the acme, the highest peak of the pressure curve. The intensity, duration and frequency of contractions are also measured since an irregular pattern or excessive intensity could lead to maternal-foetal complications.

External cardiotocography

External Cardiotocography (TOCO) is currently the most widely used technique for monitoring the frequency and duration of contractile, together with the foetal heart rate. It is a harmless, non-invasive, and easy to use technique that can be used at different stages of gestation and labour, since it can be used with a closed cervix and intact membranes.

Recording involves the placement of a pressure transducer on the maternal abdomen, which measures the increase in surface tension occurring during each

uterine contraction, as can be seen in Figure 1.5. Under contraction, the uterus stiffens and presses against the sensor. This pressure causes a mechanical deformation in the sensor, leading to an expansion or contraction of the strain gauge material and thus to a change in electrical resistance. The resistive value measurement provides the graphical log, in which the contractions are represented as curves from which the intensity, duration and frequency of contractions over time can be obtained. A doppler ultrasound sensor is also placed on the mother's womb to monitor the foetal heart rate and thus foetal well-being. High frequency sound waves are emitted and their change in frequency is measured after bouncing off the foetal heart. The cardiotocograph displays the evolution of the foetal heart rate alongside the evolution of the contractions [140].

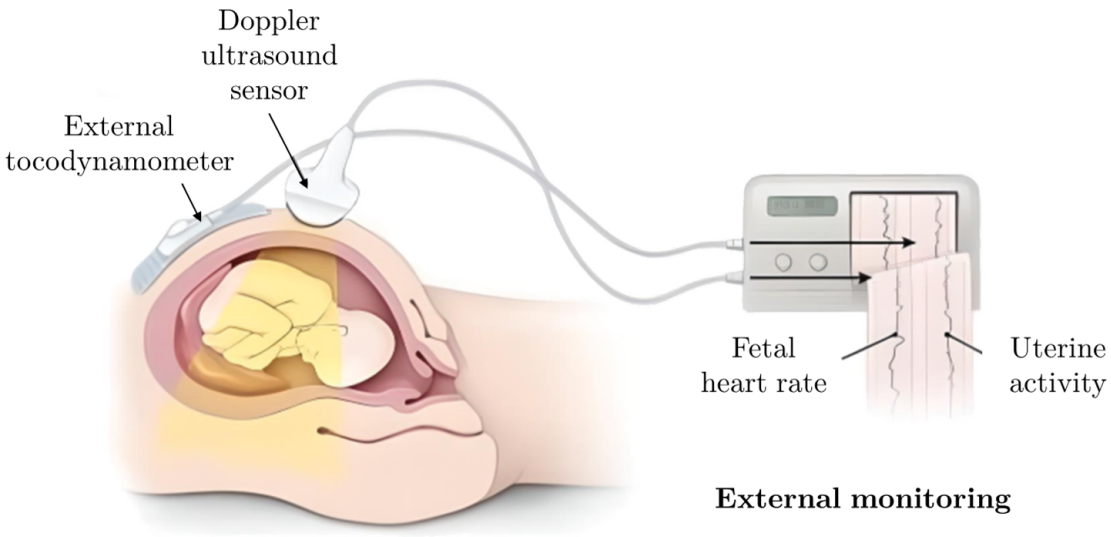

Figure 1.5: External monitoring of uterine activity and foetal heart rate. Partially modified from [141].

For proper functioning, the sensors require constant recalibration and repositioning by expert personnel. In addition, obesity, local muscle tension, maternal abdominal contractions, the area where the sensor is placed, the maternal and fetal position or the tension of the strap holding the sensor can greatly affect the measurement. On the downside, the information provided is qualitative and does not provide accurate information on internal pressure, nor does it allow for the measurement of tone [140, 142].

Intrauterine pressure

The Intrauterine Pressure Catheter (IUPC) is considered the gold standard for monitoring uterine contractions and assessing their frequency, duration, and intensity. In contrast to TOCO, the IUPC involves the insertion of a catheter directly into the uterine cavity through the cervix, allowing accurate measurement of the mechanical effect of contractions, as can be seen in Figure 1.6. The invasiveness of this technique provides a very accurate measurement of intrauterine pressure during contractions, making it particularly valuable in late labour. However, its use requires rupture of membranes and some cervical dilatation, which limits its applicability during early gestation or when membranes remain intact [143, 144].

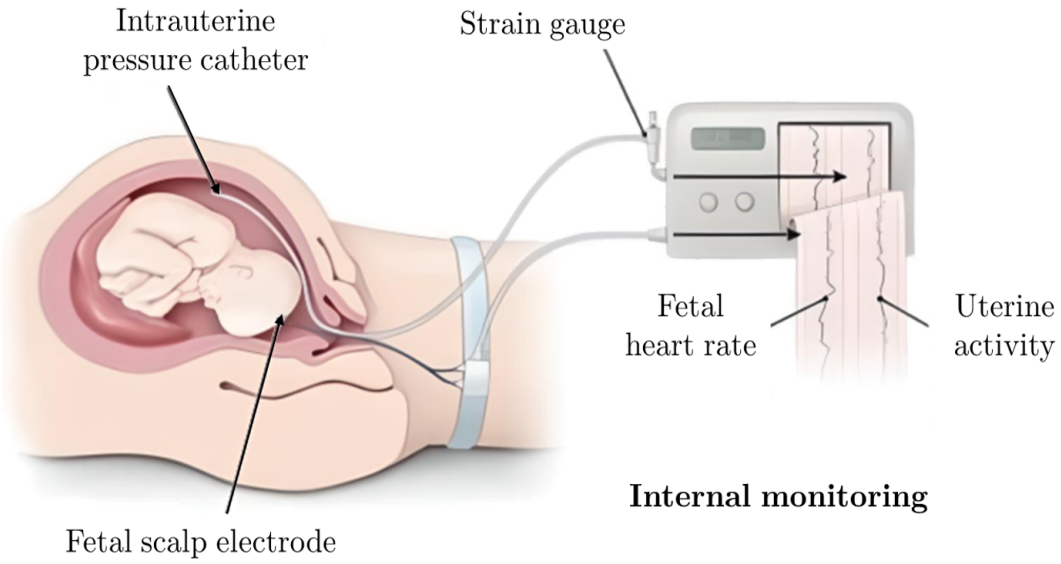

Figure 1.6: Internal monitoring of uterine activity and foetal heart rate. Partially modified from [141].

Located at the termination of the IUPC is a small pressure-sensitive membrane. When uterine contraction exerts pressure on the sensor, it deforms and its electrical resistance changes in response to the magnitude of the pressure. Changes in electrical resistance are transduced into electrical signals that represent real-time intrauterine pressure. The continuous intrauterine pressure measurement provided by the IUPC offers advantages such as the possibility to measure basal tone, amplitude, duration, frequency of onset and relaxation time between contractions quantitatively and accurately. This measurement is not affected by maternal position or obesity. A second sensor used in internal cardiotocography to monitor

the fetal heart rate is the fetal scalp electrode. It is placed directly on the fetal scalp through the cervix during labour to detect and provide an accurate measurement of the fetal heartbeat [143].

However, its routine use has been discouraged due to complications associated with its invasive nature, limiting its use to obese patients. Specifically, the likelihood of intra-amniotic infections is extremely elevated. Other associated complications, although less frequent, could be uterine perforation or foetal haemorrhage [143, 145].

1.4 Electrohysterography

As mentioned in the previous sections, monitoring contractions is of vital importance during gestation and delivery. Nonetheless, the techniques frequently employed in standard clinical practice either lack of precision and require constant repositioning by the healthcare providers as TOCO or involve substantial risks as IUPC.

In this context, the Electrohysterography (EHG) or uterine electromyogram has emerged as an alternative non-invasive and sensitive monitoring technique. It is the result of surface sensing by electrode placement of the depolarisation and repolarisation of the billions of underlying myometrial cells [7, 9]. This electrical activity has been shown to correlate with the mechanical activity into which the contractions are translated and thus with the IUPC, even better than the TOCO, as shown in Figure 1.7 [146]. Due to its high sensitivity and specificity, EHG has been postulated as a powerful tool for the characterisation of dynamics during gestation, labour and postpartum. Moreover, the EHG has the advantage of not requiring repositioning or recalibration, is much less affected by obesity and is able to sense contractions from 19 weeks gestation as opposed to 24 weeks when the TOCO begins to detect them [7, 15].

The configuration of the recording protocol in EHG studies varies widely in the literature. Although three or four electrodes with 3 to 4 cm between them and a cross or cross-shaped distribution are usually used [40], up to 16 electrodes can be placed with their centres 1.7 cm apart and arranged in an array. The bulk of the electrodes are placed over the uterine region, except for the reference and mass electrodes, which are generally placed over the iliac crests. The duration of the recordings ranges from 30 minutes in the traditional PTB scenario, up to 4 continued hours [19] or 12 discontinuous hours for the IOL progress characterization [147]. Of note, implementation of the studies in clinical practice should not impede or hinder the use of routine measurement equipment,

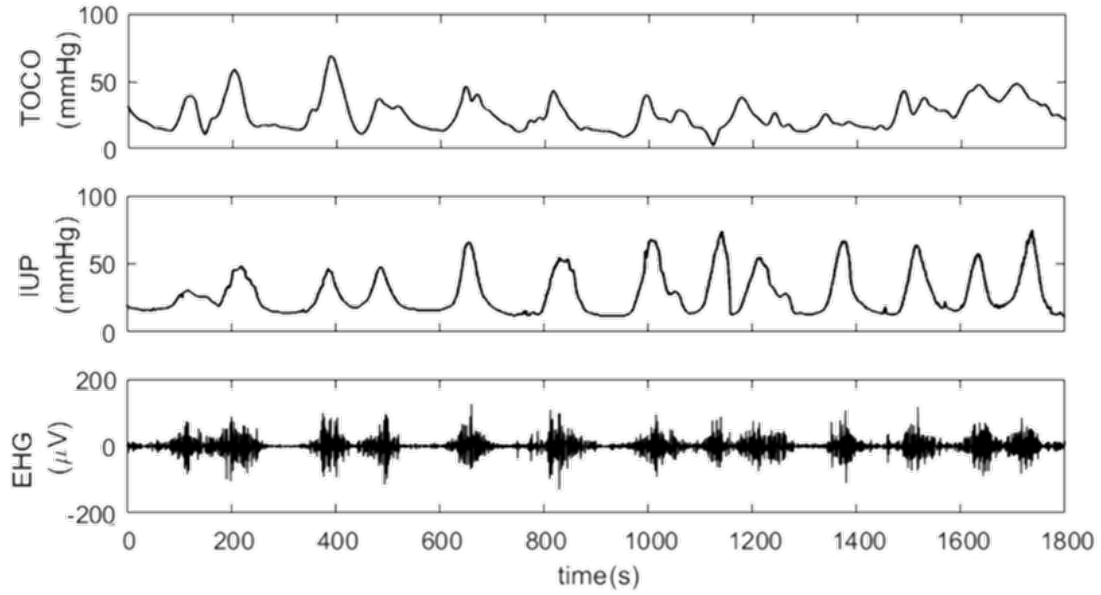

Figure 1.7: Simultaneous recordings of TOCO, IUPC and bipolar EHG [146].

nor should it inconvenience patients. Consequently, the EHG recording protocol simplification should be fundamental in the translation to the clinic, especially important in the case of IOL where the patient begins to experience painful labour contractions and must be under observation for many hours.

1.4.1 Electrohysterographic signal components

While the electrophysiological mechanisms underlying the generation of EHG are not completely understood yet, they are known to be linked to the excitability of uterine myocytes and the myometrial propagation capacity of the wavefront. Two distinct components can be found in the EHG, the action potential bursts or EHG-Bursts associated with contractions and the intermediate basal electrical activity, as can be seen in Figure 1.8. The bursts in turn are composed of the Slow Wave (SW) and the Fast Wave (FW). The former is supposed to generate the electrical conditions needed for cells to contract, while the latter is associated with the contractile activity itself [148, 149]. Most EHG-based studies focus on the FW component, which is further divided into Fast Wave Low (FWL) with peak frequencies between 0.13-0.26 Hz and Fast Wave High (FWH) with peak frequencies between (0.34-0.88) Hz [9, 148, 150]. Yet, the frequency content of the FWH is believed to extend up to 3-4 Hz [150]. FWL has been extensively related

in the literature to EHG signal propagation and FWH to uterine cell excitability [40].

The amplitude of the EHG-bursts is quite low and ranges between tens and hundreds of microvolts. Major sources of interference are maternal electrocardiographic signal 1.38-1.5 Hz, maternal respiration 0.2-0.34 Hz, fetal electrocardiographic signal 2-3 Hz, motion artifacts, or others such as electromyographic noise 30 Hz or electromagnetic noise 50 or 60 Hz though they remain outside the bandwidth of interest. As motion artifacts can both temporally and spectrally distort the signal, artifact segments are usually visually identified by experts and discarded, albeit the scientific community is devoting great efforts to their automatic identification. Although the EHG signal is typically analysed and parameterized in the Whole Bandwidth (WBW) defined between 0.1-4 Hz, the literature widely embraces the usage of the FWH bandwidth in order to mitigate the previously described interferences [40, 151].

1.4.2 Electrohysterographic signal analysis

The EHG signal is parameterized for a thorough understanding of uterine activity and its influence on obstetric outcomes. The main approaches are the EHG-Burst Analysis (EBA) and the Whole-EHG Window Analysis (WEWA).

On the one hand, the use of EBA requires the identification of the start and end of each non-artifacted EHG-burst in the recording, usually manually and by experts. Then, the parameterization is applied to each individual contraction allowing the extraction of detailed information about the contractions, such as their count and duration quantification. However, in addition to the associated complication and difficulty in including subtle or low-intensity contractions in the analysis, this type of segmentation represents an important milestone for EHG to make the leap to the real-time monitoring devices needed in routine clinical practice.

On the other hand, the WEWA approach vastly simplifies the segmentation process by requiring only the identification of motion artifacts and breathing interference to be discarded. The remaining signal is then windowed, and parameters are calculated on each of these, as can be seen in Figure 1.8. This broader analysis allows a continuous evolution of the entire EHG over time, as well as including basal activity in the assessment.In the literature, the range of mobile window duration is variable, ranging from 1 minute to the complete signal [150, 152, 153], as well as its offset varying from 1 sample to the full window size [150, 152]. On the downside, it may provide less detailed information compared to EBA.

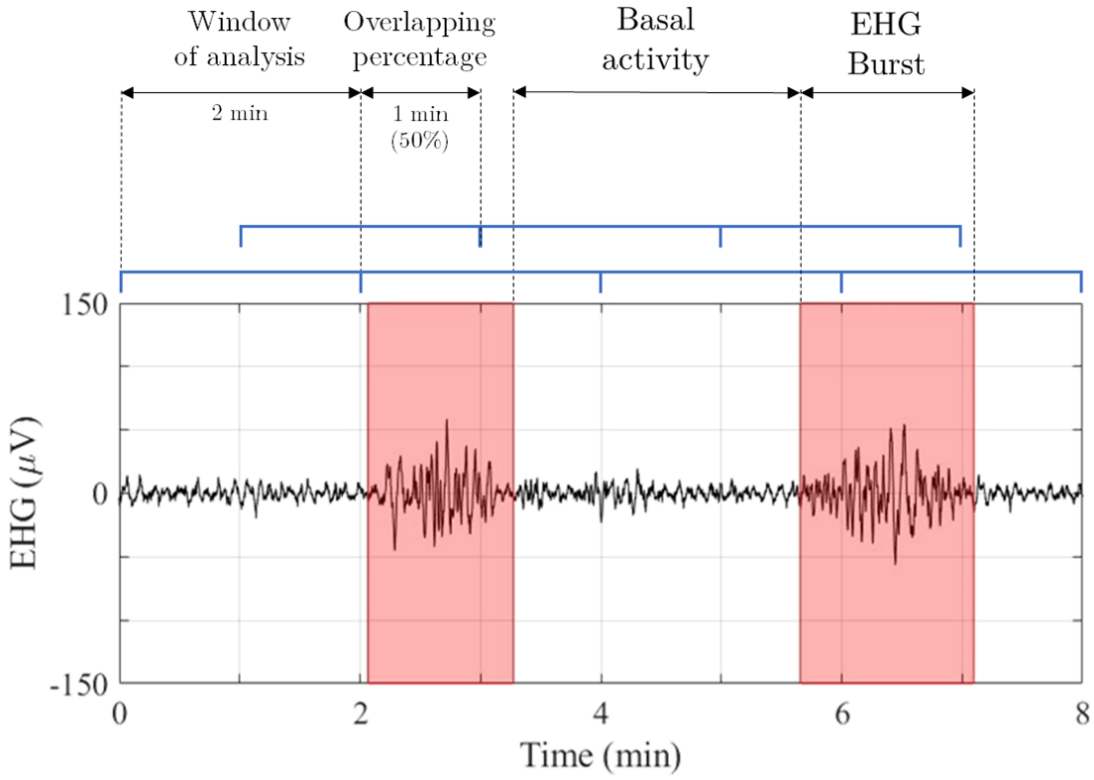

Figure 1.8: Identification of the EHG-bursts (in red) and basal activity along with the representation of the WEWA methodology. Own elaboration figure.

Once the physiological sections are segmented, a set of temporal, spectral or non-linear parameters can be employed to characterise them. As a result, the evolution of uterine contractile activity throughout pregnancy or even the response to uterotonic or tocolytic agents can be revealed. The detailed calculated parameters formulation in the thesis for the characterisation of the EHG signals in the different obstetric scenarios analysed can be found in the Appendix A.

1.4.3 Uterine electrophysiological changes

As pregnancy progresses, the uterus undergoes substantial changes to accommodate and allow the proper development of the gestational products, as well as to provide the necessary conditions for the expulsion of the foetus at the time of delivery. After delivery, the dynamics are reversed until myometrial activity returns to the level of the non-pregnant uterus. The analysis and monitoring of these EHG-biomarkers not only provide an in-depth understanding of the underlying

electrophysiology but could have important implications for obstetric monitoring and maternal-fetal health assessment [40, 154].

Electrophysiological changes during gestation

Amplitude-related EHG-parameters from human recordings have been shown to exhibit an upward tendency due to the increased number of cells involved in a contraction as labour approaches [7, 155], as exemplified in 1.9. Robust analysis of EHG-biomarkers indicated that the 90th percentile of the Root Mean Square (RMS) best discriminates between preterm and term labour [154]. Similarly, the shift of spectral content toward higher frequencies as gestation progresses has been identified [156, 157]. Although the commonly used to detect proximity to labour parameter of Dominant Frequency (DF) can show an increasing trend as gestation progresses, it has not been shown to be sufficiently sensitive to discern between preterm and term deliveries during gestation [150, 154]. However, significant differences have been found in the comparison between the Active Period of Labour (APL) and delivery, especially at the 90th percentile [154, 158]. Non-linear parameters reported lower values the more imminent the delivery [150, 152, 154], with better results discerning preterm births in the 10th percentile FWH analysis [154]. Sample Entropy (SampEn) is the most widely used measure for quantifying signal complexity. Therefore, it is to be expected to see its values drop progressively as the time of delivery approaches [159] and to be lower for preterm deliveries [150].

Nevertheless, these findings have been obtained exclusively from SGs and have not been contrasted with the electrophysiological evolution of the high-risk group of MGs. Appearing to be impervious to PTB preventive treatments designed for singletons [160], literature suggest that MGs may have alternative pathways to promote uterine activity and thus PTB [161]. *In vitro* myometrial strip studies have associated uterine overdistension with a significant increase in inflammatory cytokines and prostaglandins in primate models, linking mechanical stress-induced inflammation and PTB [162, 163]. However, there was no evidence to support the link between uterine contractility and uterine distension in the human *in vivo* system until now, see Chapter 3.A remarkable evolution can be seen in the rat electromyographic recordings in Figure 1.10, between day 18 (A) and 21 (B) of pregnancy. Small, disordered amplitude variations in EHG and IUPC amplitude in the former, become a more coordinated activity in the latter. The trend continues upwards until the time of delivery (C), where the amplitude and frequency of the bursts are considerably greater than during gestation. Note that in C, the pressure exerted by the uterus is maximal. Although the uterus can trigger the mechanisms necessary for the expulsion of the foetus in the preterm delivery

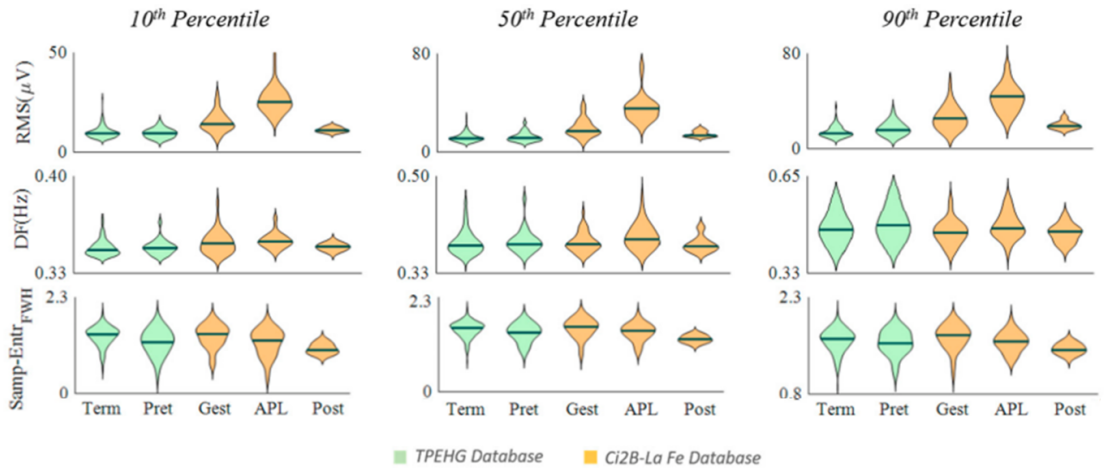

Figure 1.9: Robust characterisation of uterine myoelectric activity in different obstetric scenarios (term, preterm, gestation, active period of labour (APL) and postpartum) for the public database TPEHG (green) and Ci2B-La Fe (orange). RMS, DF and SampEn (Samp-Entr) were assesed. Partially modified from [154]

scenario (D) and shows a similar pattern to that at term (C), its preparation is not complete, and its performance is not equally efficient. The linear graph (E) shows a progressively increasing evolution of the amount of electrical activity as a function of the gestational weeks.

Electrophysiological changes during induction of labour

As discussed in Section 1.2.2, labour is induced when its delay endangers maternal-foetal welfare. The increase in prostaglandins, usually locally, involved in the process of cervical ripening has a significant impact on the contractile capacity of myometrial cells. As can be seen in Figure 1.11, mild contractions every 7 minutes with interspersed small deflections are shown in the tocodynamometry trace before the process onset. After two hours with dinoprostone as the method of IOL, the pattern changes to periods of long-lasting, irregular, disturbing contractions with short resting periods. These spike traces of variable amplitude can be interpreted as stimulation of the onset of contractions by the drug without global synchronisation, although depending on how it evolves it could derive in uterine tachysystole. Similar results are shown in the tocographic recording of uterine response to the well-known induction drug of oxytocin. As before, subtle scarce contractions appear before the drug and the pattern becomes irregular early in the process. As the process continues and the dose is increased, the dynamics become regular with 4 contractions every 10 minutes and adequate

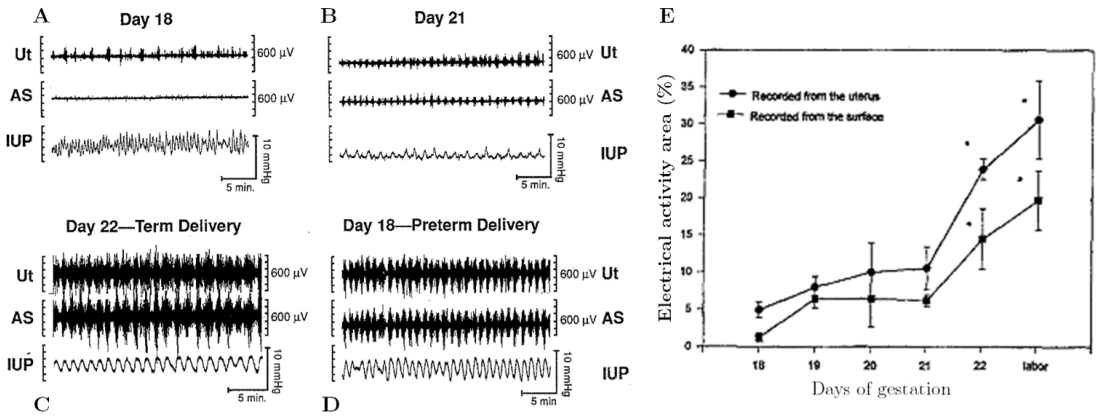

Figure 1.10: Electromyographic recordings of uterus (Ut, upper channel), abdominal surface (AS, middle channel) and intrauterine pressure (IUP, lower channel) of pregnant rats and electrical activity representation (percentage area of burst activity) on different days of gestation and during delivery. Partially modified from [164].

rest between contractions. Transition results from the increase in intrauterine pressure in the ascending phase of contraction as a consequence of the enhanced excitability and contractility effect of the drug on myocytes. Higher pressures facilitate mechanotransduction signalling and synchronisation, initiating a positive feedback loop that will lead to delivery [165].

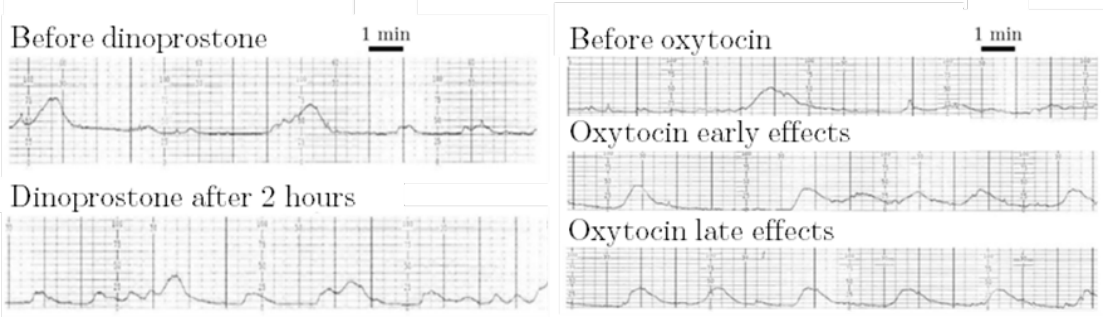

Figure 1.11: Tocodynamometric recording of the electrophysiological response of uterine activity to induction with dinoprostone (left) and oxytocin (right) at various time points [165].

Detailed studies of the evolution of the uterine activity response to IOL drugs to date also observed this evolution in the electrohysterographic recordings during the first 4 hours of IOL towards an increasing number of contractions, while shortening their duration and increasing their amplitude [19, 147, 166], which the authors described as increased organisation of the contraction within the tissue [19, 166].

Contraction strength, or signal intensity, is directly proportional to the fraction of participating uterine myocytes [167] and was characterised in this work from Peak-to-peak Amplitude (A_{pp}) in microvolts, as depicted in figure 1.12.

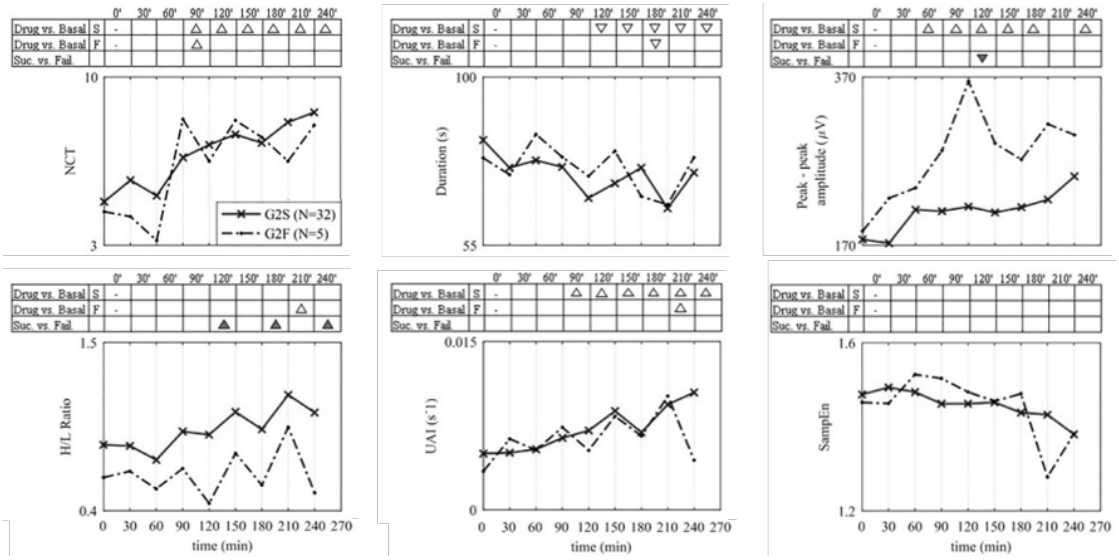

Figure 1.12: Evolution of temporal, spectral and non-linear parametrization for Dinoprostone induction of labour (IOL) [19]. Success of IOL was defined as achieve active period of labour (APL). G2S: Group of successful IOL. G2F: Group of failed IOL. NCT: Number of contractions. UAI: Uterine Activity Index. SampEn: Sample Entropy.

The trend in the evolution of cellular excitability reflected in spectral parameters is also upward, with more marked trends for patients with successful IOLs. However, the pharmacokinetics of dinoprostone are slower compared to other drugs such as misoprostol. The Uterine Activity Index (UAI) was therefore proposed by Toth to intensify that tendency as an alloy between recruitment capacity and muscle cell excitability. In the comparison between IOLs that reached the active period of labour and those that did not, he found significant differences from minute 30 for those induced with oxytocin and from minute 210 with dinoprostone [168]. The comparison between UAI and High/Low Ratio (H/L Ratio) in Benalcazar's study reveals significant discrepancies between these parameters, with significant differences from baseline starting from the 90th minute in a sustained manner for UAI [19].

Eventually, it was only the work of Benalcazar that assessed the complexity of the EHG-bursts and thus the progression towards a functional syncytium capable of expelling the foetus and placenta [19], despite being widespread in the characterisation and prediction of the outcome of PTB [40]. The benchmark

for this purpose is SampEn, which was found to be significantly lower only for misoprostol maturations reaching active delivery after 150 minutes from induction onset [19].

These findings suggest the need for longer recordings and more restrictive definitions of IOL success that limit the effect of confounding factors [19, 168]. Firstly, defining successful IOL as reaching the APL within 24 hours of the onset of cervical ripening may suppress the effect of the clinical protocol's administration of oxytocin to promote uterine dynamics. One recent study with 115 SG and mainly nulliparous gestations undergoing ripening with dinoprostone between 40 and 41 weeks of gestation reported an accuracy of 85%, considering both obstetric variables and EHG-biomarkers [169]. For the sake of minimising this drawback and improving the predictive capability of future forecasting systems, only the outcome in the first 24 hours should be considered. Progression rates and EHG-biomarkers in the characterisation of the uterine response to the IOL drug are discussed in Chapter 4. Secondly, the effect of parity on IOL success may not been extensively studied in the literature. However, a study of 1172 nulliparous and 918 parous patients found that multiparous patients reached the APL earlier and deliver significantly faster than nulliparous after dinoprostone insertion, in addition to requiring oxytocin less frequently and having a lower rate of cesarean section [170]. Survival curves in Figure 1.13 show that this effect occurs regardless of whether cervical ripening was carried out with misoprostol, dinoprostone or Foley catheter, suggesting that parity holds particular significance as an indicator of the success of IOL [171, 172].

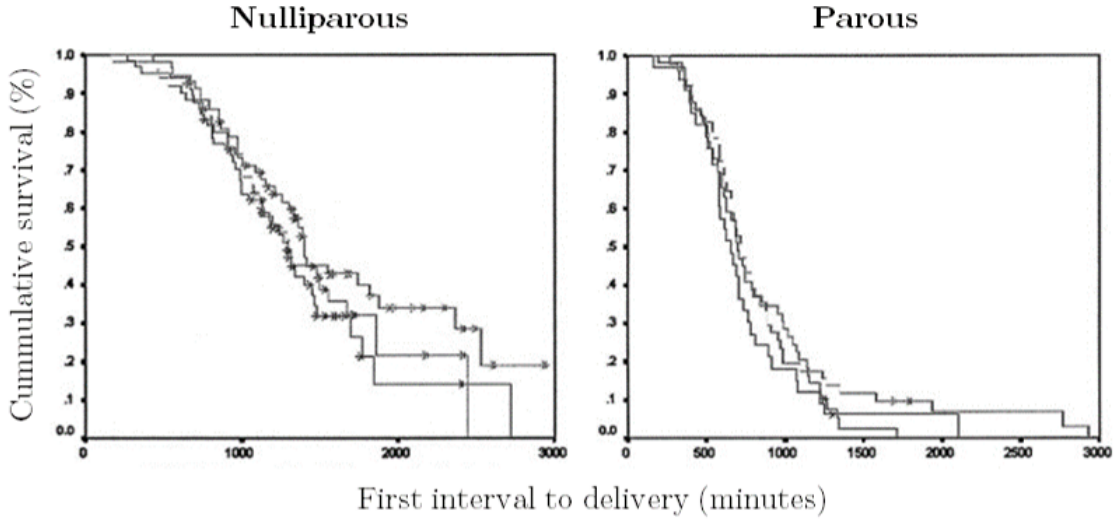

Figure 1.13: Kaplan-Meier plots of nulliparous and parous patients [172].

Even a high-resolution multichannel recording system based on simultaneous recording of EHG and magnetic resonance imaging revealed that the contractions of nulliparous women tended to affect a larger portion of the uterus than those of multiparous women, although the sample size was very low and may not cover the entire biological variability of this populations [173]. For a characterisation of the evolution of the dynamics and comparison in terms of parity during the first 5 hours of IOL with dinoprostone, consult Chapter 4.

Electrophysiological changes in the postpartum

The puerperium currently defines the postpartum period during which pregnancy-induced anatomical and physiological changes in the mother return to the pre-pregnancy state and is estimated to last 4-6 weeks [1]. PPH control is the result of contraction and retraction of the intertwined myometrial fibres surrounding the maternal spiral arteries in the placental bed. Myometrial contraction compresses the arteries and veins, thus obliterating their lumens and activating both the co-agulation and fibrinolysis cascade [1, 174].

The biomechanical processes responsible for the expulsion of the placenta and its membranes begin with the detachment of the membranes during the first stage of labour and slowly extend upwards from the internal os [175]. As the baby's trunk detaches, the uterine muscle fibres undergo a very powerful contraction, greatly reducing the size and volume of the uterus. These events are probably facilitated by the spiral arrangement of the uterine muscle fibres, so that the reduction in uterine volume leads to a reduction in the surface area of the placental site. As the placenta is a relatively rigid and inelastic structure, the surface area of its attachment site decreases when it is strongly compressed [174]. Ultrasonographic investigations identified a phase of contraction prior to detachment, with the time of thickening varying between patients and determining the total duration of the third stage of labour [176]. Another important mechanical effect is that of early umbilical cord clamping, which, although it accelerates placental abruption, increases initial haemorrhage [174].

As any muscular activity, uterine contractility relies on hormonal stimuli, being mainly oxytocin and prostaglandins involved in the postpartum period [174]. In general terms, oxytocin causes an increase in uterine contractions by acting on its specific receptors. However, a clear relationship has not been demonstrated either because receptor density cannot be taken into account, because plasma levels do not reflect oxytocin concentrations in the myometrium, or because of the effect of oxytocinase which denatures oxytocin before it reaches its site of action [177]. Moreover, therapeutic oxytocic agents used to augment labour are

sometimes associated with uterine atony in the third stage [178]. On the other hand, the prostaglandins PGE2 and PGF2α have been shown to be potent inducers of myometrial contractility, playing a crucial role in postpartum haemostasis [174]. Plasma levels of prostaglandin metabolites were measured during and up to 48 hours postpartum, peaking at 10 minutes after placental separation [179]. The subsequent rapid decline in these levels suggested that prostaglandins arise from cell necrosis or disorganisation, either at the placental site or in the fetal membranes [174, 179].

The commonest cause of PPH is uterine atony, which occurs when the relaxed myometrium fails to contract the blood vessels that pass through its fibres. Given that up to one-fifth of maternal cardiac output enters the uteroplacental circulation, PPH may be responsible for early exsanguination [174]. Factors such as retained placenta or placental fragments, uterine distension prior to delivery or dysfunctional postpartum contraction may complicate postpartum haemostasis [174, 180]. Lower segment implantation is associated with increased risk of PPH, especially in placenta praevia and placenta accreta, where the lower segment musculature is considered less suitable for postpartum contraction [180].

The aforementioned physiological alterations directly influence uterine contractility, as shown in Figure 1.9. With respect to the active period of labour, cellular amplitude and excitability seem to be considerably reduced, while the coordination of contraction tends to increase [154]. Indeed, just because oxytocin concentrations (in both cord arterial blood and amniotic fluid) in labouring women regardless of outcome have been found to be significantly higher than in elective caesarean sections, the latter are expected to have weaker and more infrequent activity [181]. Furthermore, the progressive coupling and synchronisation of contractions that have been occurring throughout labour are expected to be absent when the extraction of the foetus has occurred artificially and suddenly. Therefore, to focus exclusively on the analysis of the frequency and strength of contractions, to which standard clinical techniques are limited, may wrongly assume that the important information about dynamics resides in the tissue and not in the whole organisation of the organ. Also, as postpartum dynamics progressively weaken and abdominal surface tension and amniotic fluid are lost, monitoring with these tools is greatly complicated. In any case, many questions remain about how best to incorporate contraction monitoring into practice to optimise care in an era of obstetrics where the high rate of caesarean section is a major concern [182]. The application of EHG in the characterisation of the uterine signal in the postpartum period differentiating vaginal and caesarean deliveries can be found in Chapter 5.

Chapter 2

Justification and objectives

Monitoring uterine activity during gestation and postpartum provides essential information on both maternal-fetal wellbeing and the progression of pregnancy and labour. Its characteristics undergo significant changes throughout gestation due to the changes in excitability and propagability that the uterus endures in preparation for delivery, culminating in the intense and coordinated contractions necessary for labour. The early onset of this process can lead to premature termination of pregnancy, resulting in a high rate of infant mortality and morbidity. Similarly, monitoring myoelectrical activity is also crucial when labour is induced, either due to post-term gestation or other causes that imply that prolonging pregnancy poses a greater risk than triggering it. In this case, knowing when and how contractile patterns begin to appear is key to quantify them and be able to predict the time to delivery for better obstetric management of the pregnant woman. Finally, uterine atony in the postpartum period can lead to massive haemorrhage and even death of the patient, so detecting uterine contractions in this context is essential in order to minimise the risks.

Conventional obstetric monitoring focuses on fetal heart rate and uterine activity using highly invasive methods, such as the IUPC, or subjective and less sensitive methods that require great attention from healthcare staff, such as the TOCO. EHG has emerged as a non-invasive technique that outperforms others by providing more accurate and detailed information about uterine contractions by considering the bioelectrical modifications that occur at the cellular level. However, its usefulness in different clinical scenarios still needs to be verified before this technique can be transferred to hospital use.

2.1 Main objective

The main objective of the present doctoral thesis is to evaluate the capability of EHG-based tools to assist clinicians in making optimal decisions regarding the management and planning of pregnancy and childbirth in common and specific clinical scenarios of maternal-foetal risk such as PTB, IOL and PPH. Electrohysterographic recording, together with the usual obstetric indicators in clinical practice, can provide new relevant information for the early detection of PTB, assessing successful IOL and the risk of PPH that will facilitate an optimal and earlier selection of possible treatments and management of hospital resources to improve the health of both the mother and the foetus and reduce costs.

2.2 Specific objectives

The general objective was broken down into the following specific objectives:

- Objective 1. To analyse the similarities and differences in uterine myoelectric activity in routine controls throughout the third trimester of women with SG and MG.
- Objective 2. To identify biomarkers in electrohysterographic recordings that allow early discrimination between successful and unsuccessful pharmacological IOL.
- Objective 3. To determine differences in postpartum uterine myoelectric activity in vaginal deliveries and elective caesarean sections for the early detection of PPH.

Chapter 3

Overdistention accelerates electrophysiological changes in uterine muscle towards labour in multiple gestations

Complete reference

Diaz-Martinez, A., Prats-Boluda, G., Monfort-Ortiz, R., Garcia-Casado, J., Roca-Prats, A., Tormo-Crespo, E., Nieto-del-Amor, F., Diago-Almela, V., & Ye-Lin, Y. (2024). Overdistention Accelerates Electrophysiological Changes in Uterine Muscle Towards Labour in Multiple Gestations. Innovation and Research in BioMedical engineering, 45(3), 100837.

Abstract

Preterm birth (PTB) 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 true PTB from cases of false threats. Electrohysterography (EHG) has emerged as an alternative technique for predicting PTB in single gestation (SG) women. Despite the high prevalence of PTB in multiple gestation (MG), which can reach up to 60%, there is still no evidence in the literature on their uterine myoelectric activities in the *in vivo* system. In this context, we therefore aimed to characterise and compare for the first time non-invasively the myoelectric activity in the uterine *in vivo* system for both SG and MG women of similar gestational age during regular check-ups by means of a set of temporal, spectral and non-linear EHG-parameters. We also attempted to assess the influence of uterine overdistension on uterine myoelectric activity using foetal weight as an indirect distension measure. In comparison to SG, the MG EHG exhibited significantly higher impulsiveness and higher predictability, as reflected in the kurtosis of the Hilbert envelope and entropy measures, suggesting accelerated uterine electrophysiological changes towards labour. Several EHG parameters were also found to significantly correlate with foetal weight, including amplitude, signal impulsiveness and entropy measures, suggesting an electromechanical coupling between

uterine overdistension and contractile activity in the *in vivo* system. These results highlight the importance of including uterine overdistension as a risk factor for early detection and designing personalised therapeutic interventions to prevent PTB, especially in MG.

Keywords
Overdistention Effect; Multiple Gestation; EHG-Biomarkers; Electrohysterography; Preterm Birth; Single Gestation.

3.1 Introduction

3.1.1 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 [23]. Survival is associated with an increased risk of visual, neurodevelopmental and cognitive impairment, cerebral palsy, or prolonged hospital admissions for respiratory, metabolic, or infectious morbidities [23, 25]. 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 [25]. 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 [25].

Despite the significant progress of modern medicine in pregnancy care, PTBs are still on the rise [31, 32]. In the United States, they rose from 9.63% in 2015 [31] to 10.48% in 2021 [32]. This upward trend has been broadly associated with an increase in maternal age. In Europe and the United States, childbearing age increased by 14% between 1980 and 2021 due to socio-cultural changes [31, 32]. 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 [33]. 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 [34]. Due to this, assisted reproductive technologies (ART) are becoming increasingly popular [36].

The extensive use of ART has raised the rate of multiple gestation (MG) [34]. In fact, the occurrence of MG after ART hovers around 20% worldwide, ranging from <10% in several Nordic countries [36] to 30% in the USA [37], well above the 1-2% in natural conceptions [36]. 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 [36, 162]. The incidence of PTB is notably up to six times higher in MGs [36], 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%) [37]. 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 [38].

Treatments for the prevention of PTB in SG, such as tocolytic therapy, progesterone, and cervical cerclage, appear to be ineffective in MGs [160], which may suggest that MGs have distinct pathways that promote uterine contractility and thus trigger PTB

[161]. 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 [163]. However, there is no evidence to support a link between uterine contractility and uterine distension in the *in vivo* human system.

3.1.2 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 [160], although these methods have been found to be subjective or inaccurate in predicting PTB [160, 161]. Firstly, tocodynamometry requires constant transducer repositioning and is strongly influenced by the tightness of the binding, maternal-foetal movement, and maternal obesity [161]. Secondly, although CL measurement is the most cost-effective method used in hospital practice [160], the results can be considerably biased by the examiner's experience [163]. 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 [160, 163]. 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 minimizing the negative consequences and ruling out women with false PTB threats to avoid unnecessary interventions and reduce hospital costs [160].

Electrohysterography (EHG) has emerged as an alternative technique for preventing PTB due to its high sensitivity [26]. In fact, it has been shown to outperform traditional tocodynamometry in monitoring uterine dynamics [161] as well as being barely influenced by obese patients [26]. The EHG technique involves recording the intermittent action potential bursts associated with uterine contractions and basal activity when the uterus is at rest [26, 142]. 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, while the latter is associated with cell excitability and mainly distributes its energy between 0.34 and 4 Hz [26].

In early gestation, electrical physiological activity is low and uncoordinated. 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 [26]. Simultaneously, there is an increase in cellular excitability due to changes in the transduction mechanisms and in the synthesis of various proteins [162]. These changes are responsible for generating a more intense and synchronized signal as gestation progresses [142], ultimately leading to high-intensity contractions capable of

expelling the foetus at delivery [26, 142, 163]. 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 [26, 142]. The EHG signal has also been shown to become more predictable as pregnancy progresses, with lower signal complexity [142]. However, previous studies in the literature have focused on analyzing EHG in SG, with MG being an exclusion criterion [142, 144, 161]. To our knowledge, there are at present no descriptive studies in the literature on the characterization of EHG in the MG *in vivo* system. The aim of this study was therefore to characterize and compare the uterine myoelectrical activity of SG and MG women attending regular check-ups. We also sought to determine the relationship between uterine overdistension and EHG characteristics of the *in vivo* system.

3.2 Materials and methods

3.2.1 Study Design

A prospective observational cohort study was conducted 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 [127]. 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 the 32nd WoG) [183]. 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 [34].

Factors for exclusion from the study due to their bias included 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.

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.

3.2.2 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. The calculated foetal weight (CFW) at recording was estimated by the foetal percentile of birth weight using the reverse of the traditional Hadlock formulation [184].

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 ($\alpha = 0.05$).

3.2.3 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 Figure 3.1. 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, where the signal is expected to present the highest signal-noise ratio [144]. 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 [7].

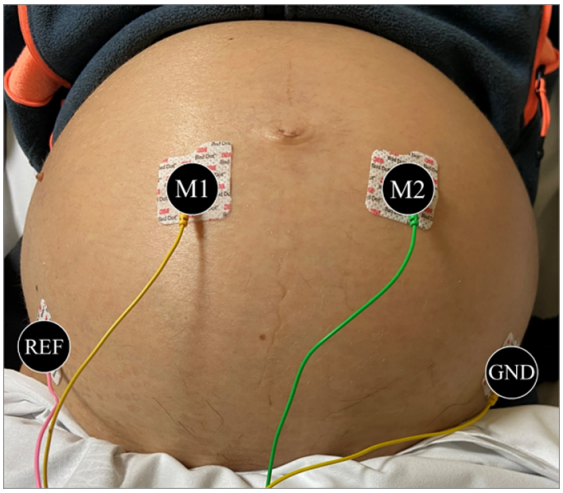

Figure 3.1: Electrode positions for uterine myoelectrical recording. M1: monopolar electrode 1. M2: monopolar electrode 2. REF: Reference electrode. GND: Ground electrode.

3.2.4 EHG Signal Analysis

Since the spectral EHG content is mainly distributed between 0.1-4 Hz [26], the monopolar EHG signals were bandpass filtered in this bandwidth (5^{th} order Butterworth bandpass filter of zero phase) and then downsampled at 20 Hz to maintain the trade-off between temporal resolution and computational cost [142]. 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 [161].

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 [142, 151]. However, previous studies have revealed the feasibility of whole window analysis to characterize EHG signals [40, 142]. 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. The signal analysis was conducted on 120-second moving windows with a 50% overlap, the window length being a compromise between computational cost and preserving the representative segment of the recordings [142].

A set of 8 temporal, spectral, and non-linear parameters were calculated for each EHG analysis window. The root mean square (RMS) [151] and Hilbert envelope kurtosis (KHE) [185] worked out in the whole bandwidth (WBW) characterized the intensity and impulsiveness of uterine myoelectrical activity, respectively [142]. For the spectral parametrization, the median frequency (MDF) [151] was calculated in 0.2-1 Hz to minimize the influence of cardiac interference (>1 Hz) and baseline fluctuation [142]. 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 [26, 142]. 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 [162]. 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) [150, 154] and bubble entropy (BubbEn) [186] in both FWH and WBW to quantify signal predictability [40, 150, 154]. The MG group, which is assumed to have an accelerated biophysical process, can be expected to show lower values for the non-linear parameters.

Due to the low occurrence of uterine contraction events in EHG recordings, we calculated the 10th, 50th, and 90th percentiles of all the analysed windows to obtain representative values for the records [154]. 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 [187]. The Wilcoxon rank sum test (α=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.

3.3 Results

Of the total number of 78 recordings, 51 were SG and the remaining 27 MG. Table 3.1 summarizes 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.

Table 3.1: 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	$< 0.001^*$

Figure 3.2 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.

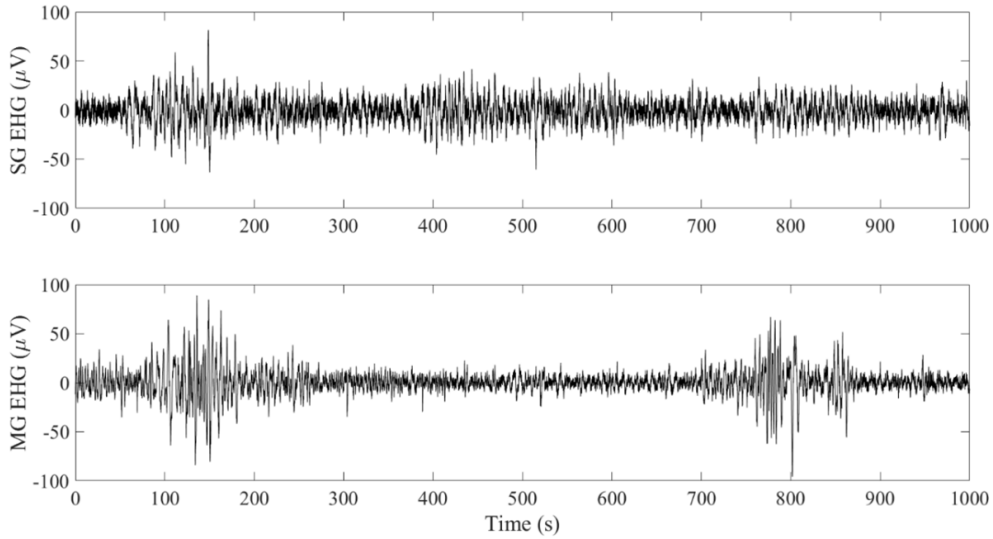

Figure 3.2: Electrohysterographic (EHG) recordings from Single (SG) and Multiple Gestations (MG) performed during the 31st gestational week.

Figure 3.3 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 3.2.

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 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 10^{th} 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 10^{th} and 50^{th} 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 90^{th}

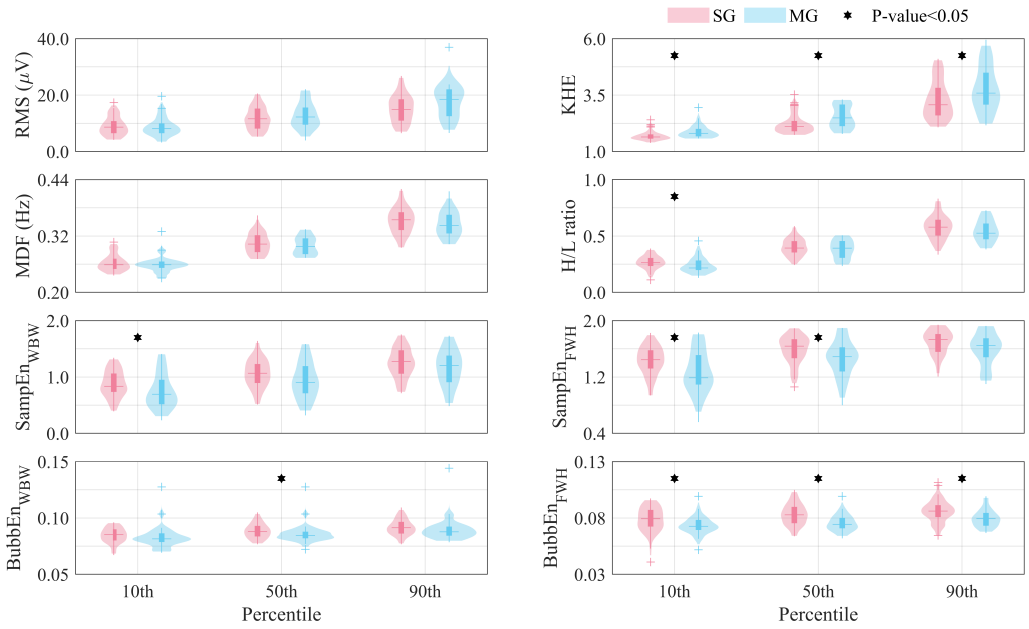

*Figure 3.3: Distribution of 10th, 50th, and 90th percentiles of temporal, spectral, and non-linear parameters for Single (SG) and Multiple Gestations (MG). Statistical differences (p-value< 0.05) between groups are indicated by *. RMS: Root Mean Square. KHE: Kurtosis Hilbert Envelope. MDF: Median Frequency. SampEn: Sample Entropy. BubbEn: Bubble Entropy. WBW: Whole Bandwidth. FWH: Fast Wave High.*

percentile. BubbEn at FWH provided the highest statistical power (94.2% and 87.2% for the 50^{th} and 90^{th} percentiles, respectively). The CL statistical power (79.3%) was lower than that of BubbEn in the FWH.

Table 3.3 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 90^{th} 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 90^{th} percentile of SampEn and 10^{th} percentile of BubbEn computed in WBW.

3.4 Discussion

3.4.1 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

Table 3.2: 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*	*50th*
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	-

uterine contractility of this group [162]. Only a few studies have compared human uterine contractility between SG and MG using biopsies obtained from women undergoing an elective caesarean section [162, 163]. 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 textitin vitro study [162]. The main difference in Turton's comparison is the more frequent and shorter contractions in the case of MG [162]. 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 [40, 154, 162].

Neither did we find any significant differences in the spectral parameters between SG and MG, suggesting that these groups have similar cell excitability [6, 154]. 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 [162, 163], so that the shift of spectral content to higher frequencies may not yet have occurred [188]. Spectral parameters are apparently not sensitive enough to assess the possible change in the degree of excitability so far from delivery, which in fact have been shown to increase sharply a few days before birth [156, 188].

Table 3.3: 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	**10th Percentile**		**50th Percentile**		**90th 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*	-	-

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 [151, 154, 189]. Consequently, the greater degree of orderliness in uterine activity observed in MGs could be an early biomarker of proximity of delivery. Our result also suggest 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 [190]. 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 [154, 190]. 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 [190].

In the percentile analysis, we found that the 10th percentile of KHE and 50th and 90th 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) [191].

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.

3.4.2 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 [6]. 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 [6, 192, 193]. In our work, the CL inversely correlated with CFW, this latter being an indirect estimator of uterine overdistension [162, 163]. Our results suggest that even in asymptomatic MG, cervical incompetence may be due to the rapid uterine changes caused by overdistension [193].

Although the physiopathology remains unclear, there is increasing evidence that the elevated risk of PTB in MG women is related to excessive uterine distension [162, 163]. The gradual increase in volume during pregnancy leads to significant muscle proliferation and remodelling, which is magnified in MGs [163]. This phenomenon could be responsible for prematurely unbalancing the quiescence mechanisms during gestation [163], although the results are controversial in this regard [161]. Chronic mechanical stretching of smooth muscle is supposed to alter not only the mechanical but also electrical function [161, 163, 194]. In fact, Wu et al found that both chronic and acute stretching increased cellular excitability and could initiate delivery [195]. Turton et al also found that uterine contractility were 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) [162]. Stretching has also been shown to stimulate oxytocin receptor expression, which promotes uterine contractility [161, 162], and leads to increased collagen expression and improved focal adhesion between myocytes and the extracellular matrix [161, 196]. 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 Gsα, prostaglandin E2 receptors and connexin-43 gap junctions' density in myometrium [161], 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 [197].

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 [194, 198]. For example, the enhanced expression of stretch-activated potassium-specific channels (TREK-1) [194, 198], leading to reduced myometrium contractile activity [194], especially in MG [198]. 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 [199]. However, these compensatory mechanisms appear to have a certain threshold of myometrial overdistension, beyond which they cease to be effective and labour is triggered [163].

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 [162, 163]. 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 [200] or some concomitant diseases as polyhydramnios [163]. Secondly, uterine contractility is governed by the complex regulation of multiple ion channels, which may result in a highly variable response in different subjects [161]. Finally, the recording of surface uterine myoelectric activity may depend on multiple factors, such as body mass index, skin-electrode preparation or placental position [142, 201].

3.4.3 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 [202, 203] 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.

3.5 Conclusions

We found that the EHG signal from MGs exhibited higher impulsiveness and predictability than SGs at the beginning of the third trimester of gestation, as reflected in KHE, SampEn and BubbEn, respectively. We also confirmed the relationship between uterine overdistension and surface recorded myoelectric activity, revealing the pathway of electromechanical coupling in uterine smooth muscle.

This work provides new and relevant information on uterine electrophysiology in the MG *in vivo* system, which is an important gap in the current state of the art. Our results also indicated the EHG-biomarkers that could be used to early detect the risk of PTB, which would allow clinicians to design earlier personalized therapeutic interventions to better prevent PTB.

Funding This work was supported by the Spanish Ministry of Economy and Competitiveness, the European Regional Development Fund (PID2021-124038OB-I00).

Conflict of interest The authors declare no conflict of interest.

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.

Author contributions 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.

Chapter 4

Uterine Myoelectrical Activity as Biomarker of Successful Induction with Dinoprostone: Influence of Parity

Complete reference

Diaz-Martinez, A., Monfort-Ortiz, R., Ye-Lin, Y., Garcia-Casado, J., Nieto-Tous, M., Nieto-Del-Amor, F., Diago-Almela, V., & Prats-Boluda, G. (2023). Uterine myoelectrical activity as biomarker of successful induction with Dinoprostone: Influence of parity. Biocybernetics and Biomedical Engineering, 43(1), 142-156.

Abstract

The prolonged latent phase of Induction of Labour (IOL) is associated with increased risks of maternal mortality and morbidity. Electrohysterography (EHG) has outperformed traditional clinical measures monitoring labour progress. Although parity is agreed to be of particular relevance to the success of IOL, no previous EHG-related studies have been found in the literature. We thus aimed to identify EHG-biomarkers to predict IOL success (active phase of labour in $\leq$24h) and determine the influence of the myoelectrical response on the parity of this group. Statistically significant and sustained differences between the successful and failed groups were found from 150 minutes in amplitude and non-linear parameters, especially in Spectral Entropy and in their progression rates. In the nulliparous-parous comparison, parous women showed statistically significantly higher amplitude progression rate. These biomarkers would therefore be useful for early detection of the risk of induction failure and would help to develop more robust and generalizable IOL success-prediction systems.

Keywords

Electrohysterography; Labour Induction; Dinoprostone; Parity; Prolonged Labour; EHG-Biomarker.

4.1 Introduction

4.1.1 General overview of induction of labour

Induction of labour (IOL), defined as the process of artificially stimulating the uterus to start labour [46], is indicated when the outcome for the fetus, the mother, or both is expected to be better than waiting for the spontaneous start of labour and to prevent situations of risk such as prolonged labour, postpartum haemorrhage, foetal distress or traumatic birth [46, 47]. Due to recent changes in the obstetric population's characteristics (higher maternal age, increased maternal weight and weight gain, larger newborn weights), there is a growing trend for intervention in current clinical management of labour, including IOL [204, 205] whose prevalence is around 25% worldwide [46] and 33% in Europe [206].

Pharmacological agents such as prostaglandins are commonly used to ripen the cervix and stimulate uterine contractions to promote vaginal delivery before the spontaneous onset of labour [47]. The IOL process may take between 24 and 48 hours, but its success is not guaranteed [19, 207]. In fact, up to 33% of induced patients do not respond to induction with prostaglandins or oxytocin [208]. Indeed, pharmacological induction is associated with longer hospital stays and more frequent complications than spontaneous onset of labour [209]. These include hypertonic and hyperdynamic uterine activity, foetal heart rate abnormalities, uterine rupture, meconium aspiration, water intoxication and cord prolapse post amniorrexis [210]. IOL also increases the risk of caesarean delivery by 20%, with prolonged labour being one of its main causes (11.65%) [209] and also of instrumental deliveries for both medical and elective inductions [211]. In addition, there is consistent evidence that the increased duration of the latent phase of labour results in increased maternal morbidity [209, 212]. In comparison to the Active Phase of Labour (APL) in more than 24h, women who achieved APL$\leq$24h were found to have a 3.19 times lower risk of caesarean delivery, 3.23 times of chorioamnionitis, 2.98 times of endometriosis, 1.5 times of postpartum haemorrhage and, 1.59 and 1.68 times of Apgar less than 7 after one and five minutes [212]. Early identification of induction failure and intervention could reduce the maternal-foetal mortality and morbidity associated with prolonged labour due to the increased risk of postpartum haemorrhage and sepsis, foetal distress and asphyxia [209]. It is estimated that the cost of a caesarean after failed induction can reach $7,595 (1.3 times a standard caesarean section) in the USA [213]. In addition to the significant impact on maternal and neonatal health, IOL overloads delivery rooms and affects health care costs, with an annual cost of more than $2 billion in the USA [214]. The development of a robust and reliable system to aid IOL decision making would therefore be a key factor in enabling clinicians to better plan and manage deliveries, prevent maternal and foetal complications and optimise hospital resources.

4.1.2 Risk factors for failed induction of labour

Previous studies have identified numerous risk factors for failure of induction, such as prolonged labour, advanced maternal age, early gestational age, maternal obesity, comorbidities, oligohydramnios, foetal macrosomia, nulliparity, and unfavourable cervix [135, 207]. The influence of parity on IOL is widely described in the literature [47, 65, 170, 171, 207, 215, 216]. Nulliparous women not only have a higher IOL rate than parous women (42.9% versus 31.8%) [47], but also have a 2.9 times higher risk of suffering from induction failure [171]. Almost half of IOLs in nulliparous women end up in instrumental delivery [211] and 37% in caesarean section, being much lower in parous women (10%) [217]. Friedman [215, 216] first described differences in the progress of labour, finding slower progress in the first and second stages of labour (latent and active phase) for nulliparous than parous women [216]. Despite the fact that current obstetric management can substantially reduce the duration of the active phase of labour, labour progress in nulliparous women has been found to be slower than in parous [170]. In fact, the first Consensus Document on Obstetric Care suggests up to two hours of pushing in the case of parous women and three for nulliparous women before diagnosing labour arrest in the second stage [60]. Batinelli et al found that labour in parous women differed from nulliparous in term of the timing of the birth, perineal lacerations and the maternal and foetal outcome [207], suggesting that parity is of special relevance as a predictor of IOL success [135, 207].

Another IOL risk factor is unfavourable cervix assessed by the Bishop score (BS) [134, 135], which is a common method of predicting labour induction success in obstetrics. The BS summarizes various characteristics of cervical status in the form of a score based on: dilatation, effacement, station, consistency and position. Each element is scored from 0 to 3 points, the sum of which is the total BS [134]. However, this measure has been proven to be subjective and has low reproducibility [134, 218]. Bastani et al. [66] found that the accuracy of the BS to predict induction success was low (area under the curve = 0.39), as was the area under the curve to predict induction success for other obstetric characteristics: 0.69 for cervical length [65, 66], 0.72 for cervical dilatation [65] and 0.60 for foetal weight [64], so that no reliable models are currently available to predict the outcome of labour induction in clinical practice.

4.1.3 The role of electrohysterography in obstetrics

Uterine contractile activity tends to push the foetus downwards and is a key mechanism in labour together with the aforementioned cervical effacement. The electrophysiological state of the uterus may thus provide relevant information to determine the labour outcome. Electrohysterography (EHG) consists of the abdominal surface of recording of the uterine myoelectric activity generated by billions of myometrial cells. EHG recordings are made up of two different components: the Slow Wave and the Fast Wave. The former is supposed to generate the electrical conditions needed for cells to contract and

the latter is associated with the contractile activity itself [151, 154]. The Fast Wave is usually subdivided into two components: the Fast Wave Low, which has been associated with signal propagation; and the Fast Wave High, which is related to cellular excitability [154, 219]. Terrien [220] has suggested the peak frequency of the Fast Wave Low ranges from 0.13 to 0.26 Hz and that of the Fast Wave High from 0.34 to 4 Hz. However, there is some controversy in the literature on the bandwidths of these components. The 0.1 to 0.2 frequency range is strongly influenced by the baseline oscillation and as cardiac activity mostly affects frequencies above 1 Hz, many studies consider 0.2-1 Hz to characterise the spectrum of EHG-Bursts [19, 151, 154, 202]. EHG has been shown to outperform traditional clinical tocography in detecting uterine contractions or EHG-Bursts during pregnancy and delivery [151, 202] and is especially useful for obese patients [205].

Some studies have revealed that the EHG amplitude rises as labour approaches due to increased recruitment of the cells involved in contraction [19, 151, 152, 221]. At the same time, the spectral content of the EHG signal shifts towards higher frequencies due to increased cell excitability [40, 148, 151, 188, 222]. The EHG signal also becomes more regular and organised, as suggested by the non-linear parameters [19, 40, 151, 154, 223, 224] so that temporal, spectral and non-linear parameters have been widely used to characterise them. Previous studies demonstrated the ability of EHG parameters to distinguish the usual 'ineffective' contractions during pregnancy from those associated with imminent labour ('effective' contractions), with promising results for predicting labour [169, 209], preterm labour [222, 225, 226] and imminent labour in women with threatened preterm labour [225, 227], achieving an accuracy of up to 99.7% when predicting preterm labour [228]. As labor approaches activity becomes synchronous in order to ultimately expel the foetus, many researchers are focusing on the degree of coupling and synchronization of uterine contractions [219, 229, 230]. Since these studies require many electrodes on the abdomen, they mainly focus on scenarios less stressful to the mother, such as predicting preterm labor, and have achieved accuracies of up to 91% [229]. Table 4.1 summarises some recently published studies in labour prediction with EHG: preterm vs. term prediction; labor vs non-labour or imminent labour in women with threatened preterm labor. We have included the database used for the studies; the type of EHG segmentation used: Whole EHG Window Analysis (WEWA) or EHG-Burst Analysis (EBA); parameters calculated and prediction accuracy.

In contrast, few studies have been found that examine the uterine myoelectric response to labour induction drugs [19, 147, 168] despite their significant relevance as outlined above. Aviram et al. [147] studied the evolution of uterine activity during the first 12 hours after Dinoprostone (E2 prostaglandins) administration. No significant changes in mean uterine muscle electrical activity were identified 0-2 hours after the drug administration but a substantial increase was found after 2-8h. In a similar study comparing electrohysterographic activity between successful and failed inductions [168], significant changes in the uterine activity index were found 210 minutes after Dinoprostone administration. In a former work we found no significant sustained changes in uterine myoelectric activity with respect to baseline activity (before drug administration) during the first 4 hours of induction with Dinoprostone [19] or any

significant differences in the drug response of uterine myoelectric activity between induction success and failure in this period, having defined induction success as the achievement of APL at any time [19]. This could indicate an important bias in that study, since oxytocin is usually administered in clinical practice to promote uterine contractility if a woman does not achieve APL in less than 24h. We hypothesised that those women who achieved APL$\leq$24h may exhibit a faster uterine myoelectric response to the drug than those who did not. On the other hand, as far as we are aware no study has been published focusing on the analysis of the parity effect on uterine myoelectrical activity during IOL.

The aim of this study was therefore to characterise and compare the uterine myoelectric response between induction success and failure in pregnant women given Dinoprostone drug during the first hours of IOL, induction success being defined as those women who achieved APL$\leq$24h. In addition, we also aimed to assess the effect of parity on uterine myoelectric response to labour induction drugs, with the general purpose of identifying biomarkers for early detection of the risk of induction failure. For this, we determined the changes in uterine contractility by analysing a set of temporal, spectral and non-linear EHG characteristics during the first 5 hours of IOL. Significant sustained differences with respect to baseline activity from 2-3 hours after labour induction onset were found for successful inductions in EHG-biomarkers related to the number of uterine cells recruited, excitability and predictability of uterine contractions, with no significant changes for failed inductions. Successful inductions also exhibited a significantly higher progression rate (steeper slope) of these biomarkers during IOL than failed cases. As for the influence of parity, parous women with successful IOL resulted in a significantly higher progression rate of EHG signal amplitude.

Table 4.1: Selected recently published articles labour prediction with EHG. Sc: Scenario. CrD: contractions detection. BPL: biomarkers of preterm labour. PrPL: prediction of preterm labour. ImPL: imminent labour in women with threatened preterm labor. BL: biomarkers of labour. PDB: Private Database. BW: bandwidth. WEWA: Whole EHG Window Analysis. EBA: EHG-Burst Analysis. Acc: Accuracy. NA: Not available.

Sc	**Author (year)**	**Database**	**Length (min)**	**BW (Hz)**	**Analysis window**	**Acc (%)**	**Significant parameters**
PrPL	Fergus (2013) [153]	300 recordings (TPEHG)	30	0.34-1	WEWA	90.8	Root Mean Square, Median and Peak Frequency, Sample Entropy
PrPL	Idowu (2014) [231]	300 recordings (TPEHG)	30	0.34-1	WEWA	92.4	Root Mean Square, Median and Peak Frequency, Sample Entropy
BPL	Horoba (2016) [222]	300 recordings (TPEHG)	30	0.08-4, 0.3-4, 0.3-3	WEWA	NA	Area, Auto-Correlation, Power, Max. Frequency, Median and Mean Frequency, Sample Entropy, Corr. Dim.
BPL	Lemancewicz (2016) [223]	60 recordings (PDB)	30-45	0.24-4	EBA	NA	Approximate Entropy, Binary Lempel-Ziv
BPL, PrPL	Sadi-Ahmed (2017) [232]	30 recordings (TPEHG)	30	0.08-4	WEWA	95.7	Huang-Hilbert Transform, Intrinsic Mode Functions
CrD	Muszynski (2018) [203]	51 recordings (ICLEHG)	30-60	0.1-0.34	EBA	96.0	H2 Coefficient

Sc	Author (year)	Database	Length (min)	BW (Hz)	Analysis window	Acc (%)	Significant parameters
BPL, PrPL	Mischi (2018) [225]	58 recordings (PDB)	30	0.3-0.8	EBA	73.0	Sample and Approximate Entropy
PrPL	Asmi (2018) [224]	300 recordings (TPEHG)	30	0.34-3	WEWA	95.8	Higuchi Fractal Dimension, Detrended Fluctuation Analysis
BPL, PrPL	Jager (2018) [233]	326 recordings (TPEHGT, TPEHG)	30	0.08-1, 1-2.2, 2.2-3.5, 3.5-5	WEWA	100.0	Sample Entropy, Median frequency, Peak Amplitude
CrD	Hao (2019) [221]	34 recordings (PDB)	30	0-3	EBA	81.0	Power, Sample Entropy
BL	Chen (2019) [226]	122 recordings (ICLEHG)	8-86	0.1-3	EBA	90.0	Sample Entropy, Wavelet Coefficients
PrPL	You (2019) [234]	254 recordings (TPEHG)	30	0.08-4, 0.3-4, 0.3-3	WEWA	94.7	Root Mean Square, Mean Normalized Frequency, Peak and Median Frequency, Approximated Entropy, Sample Entropy
BPL, ImPL	Mas-Cabo (2019) [152]	88 recordings (PDB)	30-60	0.1-4	WEWA and EBA	NA	Peak-to-Peak Amplitude, Mean and Dominant Frequency, Sample and Spectral Entropy, Time Reversibility, Binary and Multistate Lempel-Ziv

Sc	**Author (year)**	**Database**	**Length (min)**	**BW (Hz)**	**Analysis window**	**Acc (%)**	**Significant parameters**
CrD, BL	Allahem (2020) [235]	369 recordings (TPEHG, TPEHGT and ICLEHG)	30	NA	EBA	99.5	Amplitude, Number Of Contractions
BPL, PrPL	Peng (2020) [236]	300 recordings (TPEHG)	20	0.08-4	WEWA	93.0	Sample Entropy, Median and Mean Frequency, Wavelet Coefficients, Auto-Regression.
PrPL	Prats-Boluda (2021) [227]	140 recordings (PDB)	30	0.1-4	WEWA	93.4	23 temporal, spectral and non-linear EHG parameters and 6 Obstetrical variables
BPL, PrPL	Saleem (2020) [229]	26 recordings (PDB)	30	0-5	EBA	91.0	Granger Causality
PrPL	Xu (2020) [237]	300 recordings (TPEHG)	30	NA	NA	75.0	Root mean Square, Peak and Median Frequencies, Sample Entropy
PrPL	Nieto-del-Amor (2021) [190]	326 recordings (TPEHG and TPEHGT)	30	0.1-4, 0.2-0.34, 0.34-4, 0.34-1	WEWA	91.6	18 temporal, spectral and non-linear EHG parameters and 5 Obstetrical variables
PrPL	Lou (2022) [238]	300 recordings (TPEHG)	30-60	0.08-4, 0.3-3, 0.3-4	EBA	75.0	Approximate and Sample Entropy

Sc	Author (year)	Database	Length (min)	BW (Hz)	Analysis window	Acc (%)	Significant parameters
PrPL	Allahem (2022) [239]	469 EHG (ICLEHG, TPEHG, TPEHGT and OB-1) + 552 cardiotocography (CTU-CHB) recordings	30	NA	WEWA	95.7	Amplitude, Median and Mean Frequency, Gestational Age, Maternal Age, Parity
BPL, ImPL	Zhang (2022) [219]	219 recordings (PDB)	30	0.34-1	WEWA	NA	Multivariate Sample and Direct Transfer Entropy, Mutual Information, Correlation Coefficient, Coherence, Direct Partial Granger Causality
BPL, PrPL	Mohammadi (2022) [228]	300 records (TPEHG)	30	0.08-4	WEWA	99.7	Empirical Mode Decomposition: Root Mean Square, Sample Entropy, Teager-Kaiser Energy

4.2 Materials and methods

4.2.1 Study design

A prospective observational cohort study was conducted on pregnant women admitted for cervical ripening by Dinoprostone (10mg, Propess, Ferring SAU) inserted into the posterior vaginal fornix with removal after at least 12 hours in the University and Polytechnic Hospital La Fe (Valencia, Spain). Foetal macrosomia, multiple pregnancies, advanced maternal age (>45 years), severe preeclampsia, placenta praevia, premature rupture of membranes, vaginal bleeding during pregnancy, suspected foetal compromise (growth restriction, oligohydramnios, known foetal anomalies, etc.) and active cardiac, renal, pulmonary or hepatic disease; were factors for exclusion from this study due to their bias. This work adhered to the guidelines of the Declaration of Helsinki and was approved by the hospital's Institutional Review Board (Register Number 2018/0530). Patients were informed of the nature of the study and gave their written informed consent. Women who achieved APL before 24 hours were included in the successful induction group (GS) and the remainder in the failed induction group (GF). The possible difference between nulliparous and parous women was analysed in the successful induction group. Since the failed induction group did not show notable uterine myoelectric activity response to the drug during the early hours of induction, as reported in the literature [19], this comparison was not included. EHG recordings began 30 minutes before drug administration and lasted until approximately 300 minutes afterwards.

The clinical data collected during the study included: maternal age, Body Mass Index (BMI), number of previous gestations, parity, gestational age at delivery, initial BS, increment of BS during IOL (12h after insertion), achievement of APL, time to achieve APL, time to delivery, vaginal delivery ending, requirement for oxytocin, arterial newborn pH, venous newborn pH and foetal newborn weight. The chi-square test was used to detect statistically significant differences in nominal variables between the groups. Ordinal variables were compared using the Wilcoxon rank-sum test. Continuous variables were compared with the Student's t-test or Wilcoxon rank-sum test, according to whether or not they were considered normal by the Shapiro-Wilk test.

4.2.2 Recording protocol and EHG acquisition

For the EHG recording sessions, the abdominal surface was prepared by gentle exfoliation with 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 4.1. Two electrodes (M1 and M2) were symmetrically positioned with respect to the median axis at a distance of 6 cm from each other. Taking into account the gestational age of the women who underwent IOL, we decided to place the electrodes

midway between the pubic symphysis and the uterine fundus, near to the navel, where signals were expected to present the highest SNR [240, 241]. The other two electrodes were placed on each hip to provide reference and ground biopotentials. Both monopolar signals were conditioned by a custom-made wireless recording module, providing a 2059 V/V gain in the 0.1-150 Hz bandwidth and digitalised by a 24 bit analogue-to-digital converter at 500 Hz [242].

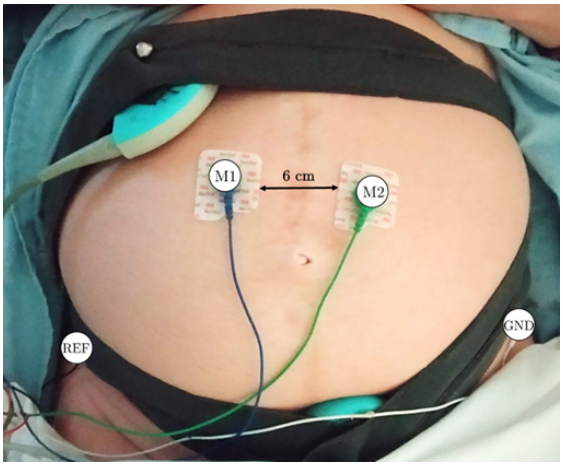

Figure 4.1: Electrodes positioning for uterine myoelectrical recording. M1: monopolar electrode 1. M2: monopolar electrode 2. REF: Reference electrode. GND: Ground electrode.

The digitalised monopolar EHG signals were filtered between 0.1-4 Hz (5th order Butterworth bandpass filter of zero phase), as the spectral content of the EHG is mainly distributed in that range, and then downsampled at 20 Hz to maintain the trade-off between temporal resolution and computational cost [152, 154, 243]. A bipolar signal was then calculated as their difference (M2-M1) to reduce common-mode interferences and increase signal quality [142, 151]. Uterine contractions were then identified by two experts [243], in which each EHG-burst was related to substantial changes in amplitude and frequency with respect to the baseline tone with durations longer than 40 seconds and without respiratory interference or motion artefacts [151, 152, 202].

4.2.3 EHG parametrisation

A set of temporal, spectral, and non-linear parameters were computed to characterise uterine contractions.

Temporal parameters

Since obstetricians are familiar with monitoring and managing IOL, we included the following temporal parameters: Number of Contractions (NCT) and Root Mean Square (RMS), calculated in 0.1-4 Hz, as a measure of amplitude related to uterine contraction intensity [151, 152, 202, 221, 244].

$$\mathrm{RMS}(x[n]) = \sqrt{\frac{1}{N}\sum_{k=1}^{N} x[k]^2} \tag{4.1}$$

Where $x[n]$ represents an EHG contraction time series and N represents its sample size. As labour progresses, the contractions are more frequent and of higher intensity, which is equivalent to a higher signal amplitude [19, 151]. Both NCT and RMS are expected to show an upward trend throughout IOL.

Spectral parameters

As the spectral content is expected to shift towards higher frequencies due to increased cell excitability as delivery approaches, we computed the Mean Frequency (MNF) [19, 222], defined as the centroid frequency of the power spectrum and is obtained as follows:

$$\mathrm{MNF}(x[n]) = \frac{\sum_{k=f_L}^{f_H} \mathrm{PSD}[k] \cdot f[k]}{\sum_{k=f_L}^{f_H} \mathrm{PSD}[k]} \tag{4.2}$$

Where PSD represents the power spectral density of EHG-bursts and f the frequency distribution. The f_H and the f_L are, respectively, the upper and lower cut-off frequencies of the target bandwidth. In this work, we computed the MNF in 0.2-1 Hz to minimise the negative influence of the remainder baseline fluctuation in 0.1-0.2 Hz and the cardiac interference above 1 Hz [151, 233].

We also worked out the Uterine Activity Index (UAI) [19], which provides combined information from the temporal and spectral domains. UAI was defined as the product of the peak-to-peak amplitude of the signal (A_{pp}) and the H/L Ratio divided by duration of contractions.

$$\text{H/L Ratio} = \frac{\sum_{f_{L1}=0.34}^{f_H=1} \mathrm{PSD}[k]}{\sum_{f_L=0.2}^{f_H=0.34} \mathrm{PSD}[k]} \tag{4.3}$$

$$\mathrm{UAI}(x[n]) = \frac{A_{PP}(x[n]) \cdot \text{H/L Ratio}(x[n])}{\mathrm{Duration}(x[n])} \tag{4.4}$$

Where PSD represents the power spectral distribution, H/L Ratio is the normalized energy of high frequency components (0.34-1 Hz) to low frequency ones (0.2-0.34 Hz).

Non-linear parameters

As labour approaches, myoelectric activity also tends to become more organised and predictable, giving rise to a downward trend in the non-linear parameters [19, 190]. In this work, we also computed a set of non-linear parameters computed in the Fast Wave High bandwidth to provide robust EHG characterisation since it has been shown to better detect preterm labour and/or imminent labour [151, 154]: Sample Entropy [151, 154], Spectral Entropy [19, 151, 243], Binary Lempel-Ziv [154, 223, 245] and Higuchi Fractal Dimension [224, 246].

Firstly, Sample Entropy (SampEn) is a statistically measure for determining the regularity of a time series based on the existence of patterns without any previous knowledge about the source generating the dataset [150, 247]. It represents the probability that similar patterns (delay vectors) in a time series will remain similar once the pattern lengths are increased (extended delay vectors), thereby providing a natural measure of the time series regularity [247, 248]. Formally, given a time series $x[n]$ of length N, a pattern vector $a_j = \{x_j, x_{j+1}, \ldots, x_{j+m-1}\}$ of length m is defined. $U^m(r)$ expresses the probability that the time series matches the pattern within a threshold r determined by the Chebyshev distance function $d[|x_m(j) - x_m(i)|](i \neq j)$.

$$U^m(r) = \frac{1}{N-m-1} \cdot \frac{1}{N-m} \sum_{i=1}^{N-m} \sum_{\substack{j=1 \\ j \neq i}}^{N-m} [\text{num. of times } d[|x_m[j] - x_m[i]|] < r] \quad (4.5)$$

SampEn is then defined as the negative natural logarithm of the probability that two similar sequences remain similar at the next point within a tolerance, where self-comparisons are not included when calculating probability. For this work we used $m = 2$ and $r = 0.15$, as described in [19]. This parameter has been widely used both in the discrimination of preterm delivery [154, 244] and also in characterising the evolution of the delivery process [19, 243].

$$\text{SampEn}(m, r, N) = \begin{cases} -\ln\left(U^{m+1}(r)/U^m(r)\right), & \text{if } U^{m+1} \neq 0 \wedge U^m \neq 0 \\ -\ln\left(N - m + 1/N - m\right), & \text{otherwise} \end{cases} \quad (4.6)$$

Therefore, the lower value of sample entropy the more self-similarity in the time series, which is equivalent to a higher organization degree or signal regularity. The higher value of sample entropy the lower signal regularity and higher randomness of time series [247, 248].

Secondly, Spectral Entropy (SpEn) is a measure of the uncertainty associated with the occurrence of a particular event at a given frequency [249]. It is computed by applying

the Shannon Entropy formula to the normalised PSD of a time series $x[n]$, such that the normalised energy of each of the frequency points is considered as a probability [250].

$$PSD_n(x[n]) = \frac{\text{PSD}(x[n])}{\sum_{k=0}^{\frac{f_m}{2}} \text{PSD}[k]} \tag{4.7}$$

$$\text{SpEn}(x[n]) = -\frac{\sum_{k=0}^{\frac{f_m}{2}} PSD_n[k] \cdot \log_2(PSD_n[k])}{\log_2(M)} \tag{4.8}$$

Where $\text{PSD}_n[k]$ is the probability distribution of power spectral density of the target signal, M is the number of frequency points for which the power spectrum of the signal has been estimated and f_m is the sampling frequency. Physically, SpEn provides information about disorder in the frequency spectrum, so that the sharper the frequency distribution, the lower the value of the parameter. Widely used to assess the progress of labour induction [19, 169, 243], but also in prediction of preterm labour [152]. SpEn is expected to decrease as the time of delivery approaches, suggesting a higher degree of organisation in the EHG signal spectrum.

Thirdly, the Binary Lempel-Ziv (BLZ) is a measure of the variation regularity in the time series [251, 252]. The time series of the signal $x[n]$ is firstly transformed into a finite binary sequence $S(i)$ from left-to-right comparison with a threshold T_d [251]. This can be expressed mathematically as:

$$S(i) = \begin{cases} 0, & \text{si } x(i) < T_d, \\ 1, & \text{en caso contrario} \end{cases} \tag{4.9}$$

For this we set up $T_d = 0$. The resulting binary sequence is scanned sequentially looking for distinct structures or patterns, building up a dictionary that summarises the sequences seen so far [251]. Let $S = \{S(i), \forall i = 1, \ldots, n\}$ denote a symbolic sequence; $S(i, j)$ denotes a sub-sequence of S that starts at position i and ends at position j; $V(S)$ denotes the set of all sub-sequences $\{S(i, j), i = 1, 2, \ldots, n; j \geq i\}$. Starting with $i = 1$ and $j = 1$, a substring $S(i, j)$ is compared with $V(S)$. If $S(i, j)$ is present in $V(S)$, then increase j by 1 and repeat the process. Otherwise, the complexity counter $c(n)$ is increased by one unit, since a new sub-sequence of consecutive characters is encountered, and updates $i = j + 1$, while the process continues until it scans the whole symbolic sequence. Physically, as labour induction progresses, uterine contractions becomes more regular, which should be reflected by lower BLZ complexity, characterized by a small number of patterns [19].

Finally, in signal analysis the fractal dimension is an index of complexity and fragmentation, comparing how the details of a signal's pattern change when measured on different scales [224, 246]. It has been shown to provide relevant information in predicting preterm labour [224] and to differentiate between successful and failed labour induction

[243]. In this work, we found the Higuchi fractal dimension (HFD) to be one of the most accurate and consistent fractal dimension estimation algorithms for non-periodic and irregular physiological time series signals [224, 246]. Given a time series $x(n)$, consisting of N points and a parameter $k_{max} \geq 2$, for each $k \in 1, \ldots, k_{max}$, $m \in 1, \ldots, k$, the length $L_m(k)$ is defined as:

$$L_m(k) = \frac{N-1}{\frac{N-m}{k} \cdot k^2} \sum_{i=1}^{N-m/k} |x[m+i \cdot k] - x[m+(i-1) \cdot k]| \tag{4.10}$$

Then the average length $L_m(k)$ was calculated and yielded the mean curve length $L(k)$ for each k.

$$L(k) = \frac{\sum_{m=1}^{k} L_m(k)}{k} \tag{4.11}$$

HFD was thus estimated as the slope of the best linear least squares fit of the plot of $ln(L(k))$ versus $ln(1/k)$ [246].

Due to the intrinsic variability of uterine contractility, we analysed the response of uterine myoelectrical activity to the induction drug in time intervals of 30 minutes (analysis window). We had 11 windows per record: 1 in basal condition (before drug administration) and 10 to assess the response during the first five hours of IOL. The median value of the EHG-bursts present in a 30-minute window was worked out for each plot, to obtain a single representative value per analysis window of each recording session. The mean of the parameters in the 30-minute windows was then calculated for each group, as shown in Figure 4.2. To characterise the progression rate of uterine myoelectric activity throughout IOL, the slope of the median values of the 30-minute windows (a total of 11 samples) was also calculated for individual parameters and patients ($\Delta p_i / \Delta t$).

4.2.4 Statistical analysis

We then analysed the possible differences in uterine myoelectrical response between successful and failed (GS vs. GF) inductions and identified any differences in uterine myoelectric activity between nulliparous and parous women in the induction success group during IOL (GS_N vs. GS_P). To do that we first determined whether there were significant changes with respect to baseline activity for individual EHG parameters and groups (GS, GF, GS_N and GS_P) in each analysis window in the first 5 hours of IOL using the Wilcoxon signed-rank test (α=0.05). We also determined any significant differences by means of the Wilcoxon rank sum test (α=0.05) for each EHG parameter and analysis window between the groups (GS vs. GF and GS_N vs. GS_P). Significant differences were considered to be sustained when they appeared in 4 or more consecutive 30-minute analysis windows. Finally, we worked out the Wilcoxon rank sum test (α=0.05) to analyse differences in the progression rates in the above-mentioned groups.

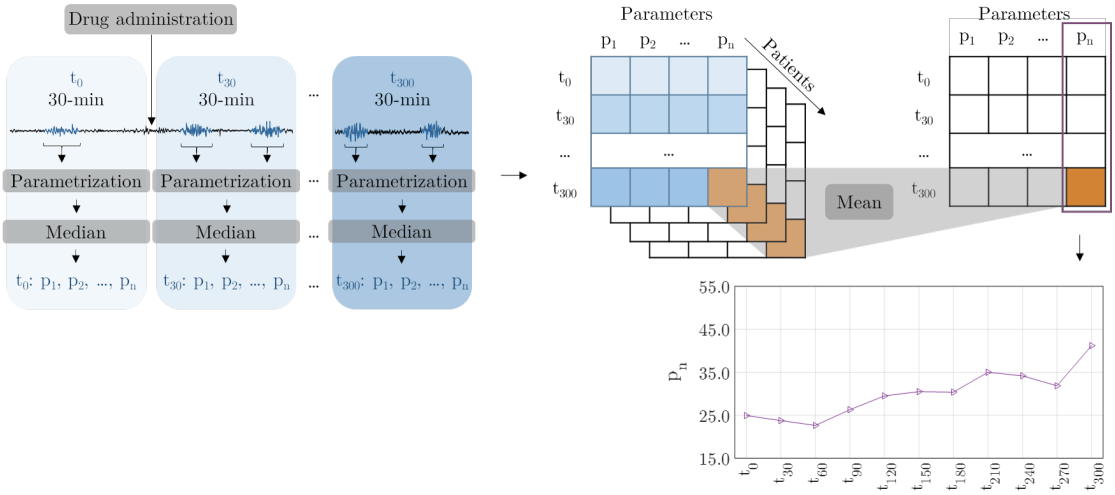

Figure 4.2: Flowchart of the parameter computation process.

4.3 Results

4.3.1 Obstetric data and outcomes of labour induction

The 35 women who achieved APL before 24 hours were included in the successful induction group (GS) and the remaining 22 in the failed induction group (GF), either because they did not reach APL or because they did so, far from the start of induction (>24h). The possible difference between the 16 nulliparous (GS_N) and 19 parous (GS_P) women in the successful induction group was also analysed. In the GF, 16 were nulliparous and 6 were parous. Obstetric, delivery and newborn characteristics are summarised in Table 4.2 for both scenarios. Due to the group segregation bias, as expected, GS presented a significantly higher rate of achieving APL, shorter time to APL and delivery, reduced oxytocin augmentation and higher rate of vaginal delivery than GF. GS presented significantly lower BMI and higher progression in BS (ΔBS) than GF. No significant differences were found between the GS_N and GS_P groups except for the number of gestations and parity, which was associated with the segregation criterion.

*Table 4.2: 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. NW: Newborn Weight. p-value: Wilcoxon Rank-sum test p-value (in bold: statistically significant difference, p<0.05). *: The statistical test was applied only to those achieving APL.*

Variable		**GS**	**GF**	**P-value**	**GS$_N$**	**GS$_P$**	**P-value**
Maternal age (years)	$\mu \pm \sigma$	33.9±5.9	34.5±5.2	0.805	32.4±5.4	35.3±6.0	0.119
BMI (kg/m^2)	$\mu \pm \sigma$	25.6±6.6	27.7±8.1	**0.037**	25.6±8.5	25.6±3.1	0.884
Gestations	$\mu \pm \sigma$	2.1±1.2	1.8±1.5	0.065	1.3±0.5	2.8±1.1	**<0.001**
Parity	$\mu \pm \sigma$	0.7±0.7	0.7±0.7	0.073	0.0±0.0	1.3±0.5	**<0.001**
GAD (weeks)	$\mu \pm \sigma$	40.6±0.6	40.5±0.7	0.801	40.6±0.6	40.5±0.5	0.224
Initial BS	$\mu \pm \sigma$	3.5±1.7	2.9±1.3	0.329	3.6±1.8	3.3±1.5	0.795
ΔBS	$\mu \pm \sigma$	3.9±2.6	2.0±1.5	**0.021**	3.1±2.1	4.6±2.9	0.237
Achieve APL	N	35/35	15/22	**0.002**	16/16	19/19	-
*Time to APL (h)**	$\mu \pm \sigma$	11.7±5.8	28.0±3.2	**<0.001**	12.8±6.3	10.7±5.4 0.417	
Vaginal ending	N	33/35	12/22	**0.001**	14/16	19/19	0.397
*Time to Del. (h)**	$\mu \pm \sigma$	14.7±7.7	32.1±10.0	**<0.001**	17.4±8.7	12.4±6.0	0.085
Oxytocin	N	0/35	16/22	**<0.001**	0/16	0/19	-
Arterial pH	$\mu \pm \sigma$	6.8±1.7	6.6±2.1	0.653	6.8±1.8	6.9±1.7	1.000
Venial pH	$\mu \pm \sigma$	7.1±1.2	7.3±0.1	0.420	7.3±0.1	6.9±1.7	0.344
NW (kg)	$\mu \pm \sigma$	3.5±0.4	3.4±0.3	0.166	3.5±0.4	3.5±0.4	0.882

4.3.2 Comparative of the success and failure of the labour induction

The evolution of uterine myoelectric activity parameters in response to the Dinoprostone labour induction drug are represented in Figure 4.3 for the GS (blue) and GF (orange) groups. A steady increase in NCT was observed in the GS group throughout the recording session. Statistically significant sustained differences with respect to the baseline were found in GS from 60 minutes to the end. GF showed no specific trend with abrupt changes. Differences between the GS and GF groups for NCT were only found at 270 minutes from induction onset. As for the NCT progression rate, it did not show any significant difference between GS and GF (see violin plot Figure 4.3). The RMS parameter showed a clear upward trend in GS after 60 minutes, suggesting increased intensity of uterine contractions, while this phenomenon was not observed in GF. Significant differences from the baseline were only found at 300 minutes in GS, but not in the GF group. GS showed a significantly higher amplitude than GF at 150, 180 and 270 minutes, with no sustained differences. Of note, GS presented a significantly higher RMS progression rate than GF in the first 5 hours of induction, with a significant statistical difference, as shown by their violin plots.

In the spectral parameters, MNF presented a progressive upward trend for GS with significant sustained differences with respect to basal activity from 150 minutes until the end of the recording. Despite showing a similar trend to that of GS, the GF group did not show any statistical difference from the baseline, which may be due to the wide variability of this parameter in the GF group. Differences were only found between GF and GS at baseline. On the other hand, UAI resulted in a remarkable upward trend with significant sustained differences from baseline in GS from 120 minutes, which were not observed in GF. We also found significant differences between GS and GF for UAI at 150, 180 and 270 min. Even though the MNF also showed slightly higher slope values for GS, the between-group slope difference (GF vs GS) was only found for UAI as depicted in the corresponding violin plot.

Finally, as expected, non-linear parameters showed a decreasing trend in the GS group as IOL progressed. In comparison to baseline activity, the GS group obtained significant differences at some time intervals from the third hour after induction onset, without being sustained over time, for SampEn, BLZ and HFD. However, SpEn resulted in statistically significant sustained differences from 210 to the end of the recording. Again, no significant difference was found with respect to basal activity in the GF group. Significant differences between GS and GF were obtained at 150-210 and 300 for SampEn, BLZ and HFD. SpEn showed significant sustained differences between the GS and GF groups from 90 to 300 min. It is noteworthy that all non-linear parameters revealed a significantly more negative progression rate for GS than GF, with slopes statistically different.

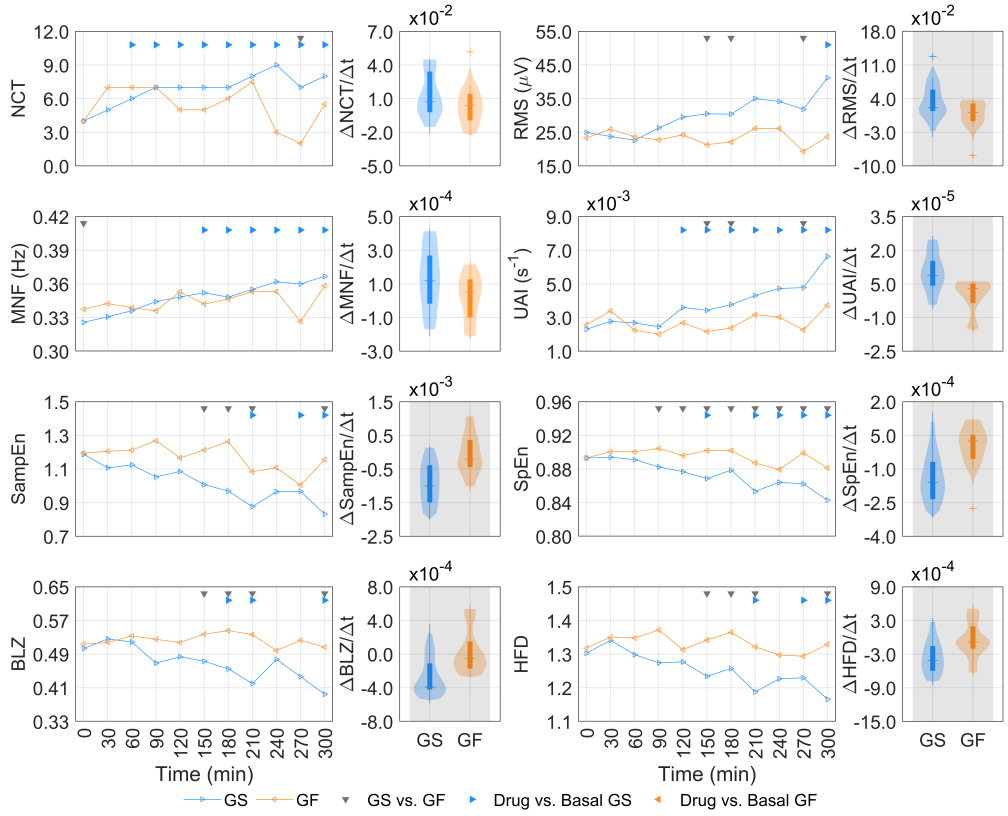

Figure 4.3: Temporal evolution of temporal, spectral and non-linear parameters and violin plots of their slopes for success (GS) and failure (GF) groups. Statistical differences between groups are indicated by grey downward-pointing triangles and with respect to basal activity by blue rightward (GS) and orange leftward (GF) triangles. In the violin plots statistical differences between GS and GF slopes are indicated by grey shading.

4.3.3 Comparative of nuliparous and parous uterine myoelectrical activity in labour induction success

Figure 4.4 shows the median values of the EHG parameters throughout the recording session calculated for both GS_N and GS_P, together with the violin plots of their slope distributions. GS_N showed a more pronounced increasing NCT trend throughout the recording session than GS_P, obtaining a significant difference with respect to baseline activity at some time intervals, which was not reached in GS_P group. Statistically significant differences between GS_N and GS_P were only found at 60, 270 and 300 minute time intervals. As for RMS, parous women showed higher amplitude than nulliparous ones, with no significant differences between them, although GS_P had a significantly higher progression rate than GS_N.

Again, GS_N exhibited a more marked upward trend for MNF and UAI than GS_P, with significant sustained differences with respect to baseline activity from 210 and 240 m, respectively, for GS_N, but not for the GS_P group. We found no significant difference for either MNF or UAI or in their slopes between nulliparous and parous women.

Both GS_N and GS_P presented a similar downward tendency for non-linear parameters as labour induction progressed, GS_P achieved significant differences to baseline at some time intervals from the third hour in the four non-linear parameters, although this was not sustained over time. In contrast, GS_N reached significant SpEn differences to basal in most windows after 150 minutes, but this was not sustained over time. Differences were achieved for BLZ and HFD at 300 minutes. GS_P seemed to present a more negative progression rate for non-linear parameters than GS_N throughout the recording session, but without significant differences.

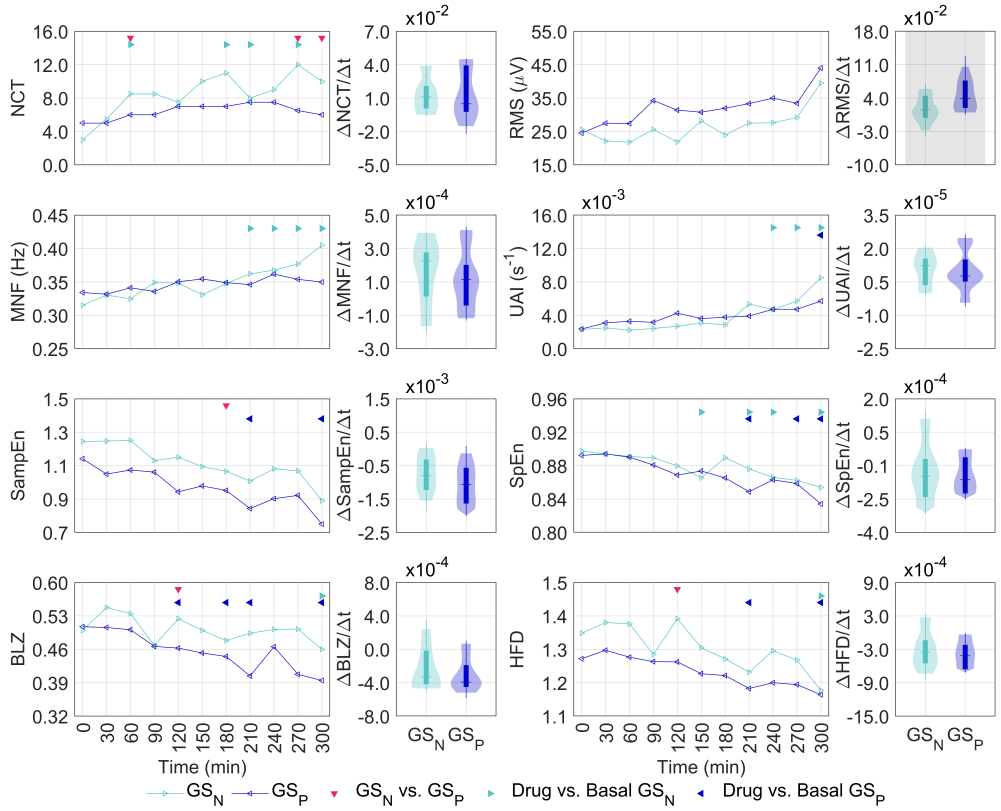

Figure 4.4: Temporal evolution of temporal, spectral and non-linear parameters and violin plots of their slopes for the Nulliparous (GS_N) and Parous Group of Success (GS_P). Statistical differences between groups are indicated by inverted pink triangles and with respect to basal activity by blue rightward (GS_N) and black leftward (GS_P) triangles. In the violin plots, statistical differences between GS_N and GS_P slopes are indicated by grey shading.

4.4 Discussion

4.4.1 Labour induction success vs. failure

In this work we analysed and compared the difference in myoelectric uterine response to the Dinoprostone induction drug between women who achieved APL in less than 24h from IOL onset (GS) and the remainder (GF). Firstly, as labour induction progressed, the uterine myoelectric activity of the GS showed an increasing trend in temporal and spectral parameters, suggesting a higher number of cells involved in contraction and also greater cell excitability [19]. This result is consistent with the fact that the increased concentration of prostaglandins E2 may induce increased myometrial contractility, this phenomenon being the indirect response of cervical ripening rather than a direct effect on the myometrium [208]. We also found that the set non-linear parameters worked out showed a downward trend for the GS group, suggesting an increased degree of organisation and predictability of the EHG signal. These findings agree with our previous studies [19, 243].

We also found significant sustained changes from baseline in NCT after 60 minutes for spectral parameters from between 120-150 minutes and after 210 minutes for SpEn in the GS group. Our results are consistent with other findings in the literature that stated that changes from EHG basal activity were achieved between 2-8 hours after administration of Dinoprostone [147] and were especially marked around the fifth hour [207, 253]. Our results also agree with the pharmacokinetics of Dinoprostone: in [254] it was reported that the peak plasma level and the median time to obtain sustained uterine activity was at 60-120 and 127 minutes respectively after administration of vaginal Dinoprostone insert [254].

We did not obtain any significant change in uterine myoelectric activity in the GF group in comparison to baseline activity. During the first hours of IOL onset, these patients' lack of response to the drug could be related to their expression of prostaglandin receptors EP1, EP3 and EP4 in the cervix tissue, which has been shown to play an important role in delivery [208]. Konopka et al. showed that upregulated EP1 mRNA expression was associated with induction failure [255]. The increased expression of contractile EP3 and reduced expression of relaxatory EP4 in the GF group has also been reported [256]. The faster response of uterine myoelectric activity in GS is consistent with the shorter time to achieve APL, shorter time to delivery and lower percentage of women requiring oxytocin augmentation from obstetric data, which is in agreement with other findings in the literature [64, 212]. It should be noted that there is some controversy over the influence of the BMI on labour induction outcomes. Batinelli [207] and Pitarello [65] found it irrelevant, while Prado et al. suggested that a lower BMI indicated a higher probability of vaginal delivery [64]. In the present work, we found that the GF group had a significantly higher BMI than GS. Since our database was relatively small, future studies will be needed to corroborate this result.

We also found significant differences between induction success and failure, especially for non-linear parameters, which we had not found in a previous study in which we only analysed the first four hours after induction onset [19]. This discrepancy could be mainly due to the definition of the induction success group, which is somewhat controversial [135]. It has been defined as achieving vaginal delivery within 24h [170, 212] or 48h [257] after the start of labour induction [170] to any time after the start of labour induction [207]. In the present work, we opted for time-to-APL$\leq$24h to avoid the bias due to oxytocin administration further promoting uterine contractility in women who do not achieve APL in 24 hours. Achieving APL after 24h may be related to the increased cell excitability associated with using of exogenous oxytocin, which is not attributable to the response to Dinoprostone.

Finally, the GS group presented a significantly higher slope than GF in almost all the EHG parameters, suggesting that the progression rate of uterine contractility contains relevant information to determine labour induction success. As the progression rate involves analysing repeated measures from different time intervals, this is undoubtedly a more reliable measure than a single measure from a specific time interval, due to intrinsic uterine contractility variability. To our knowledge, this is the first time this type of EHG-biomarker has been reported and it could be helpful in designing robust and generalizable labour induction success prediction systems.

4.4.2 Influence of parity on uterine myoelectric response during IOL

The parity effect on the IOL outcome has been extensively studied in the literature [60, 65, 171, 207]. In general, nulliparous women seem to be less responsive than parous to Dinoprostone: a greater need for oxytocin and longer time to achieve both APL and vaginal delivery [170]. In fact, according to Batinelli et al [207], the trend changes in the Kaplan-Meier curves from the fifth hour onwards are mainly caused by the parous population, as nulliparous show this change from the eighth hour onwards [253]. Moreover, Juhasova [258] found faster cervical dilatation rates in parous than nulliparous, which could be associated with the fact that dilatation in nulliparous is preceded by a thinning of the cervix, whereas in parous both occur simultaneously [171]. In addition, nulliparous are associated with a higher risk of IOL failure [171, 207], which the literature suggests could be influenced by cervical stiffness [171]. Our results on obstetric data and outcomes of labour induction are in agreement with this, although no significant differences were found. In fact, only 50% of the nulliparous women included in the present study achieved APL$\leq$24h compared to 83% of the parous women.

In this work we specifically focused on the analysis of the effect of parity on the response of uterine myoelectric activity to the induction drug reaching APL$\leq$24h, which has been little studied to date. We found a significantly higher number of contractions in nulliparous than in parous women after 4 hours, which is consistent with other

authors who reported that NCT was significantly lower in women with a previous delivery [259]. By contrast, we also found that parous women presented a greater uterine contraction amplitude than nulliparous women, with no significant differences at a specific time interval. This finding is consistent with the literature, given that a previous pregnancy may induce a greater number of gap-junctions in the myometrium [260]. Likewise, we found a significantly higher rate of amplitude progression in parous women, which may suggest that parous women have a greater response to prostaglandin E2. Our results partially support Ryan's findings, which reported that nulliparous have a lower uterine contractility response to oxytocin than parous women in an in vitro setting [261], as both prostaglandin E2 and oxytocin are induction drugs that promote uterine contractility. Our results of greater contraction amplitude in parous women, although with no significant differences between both groups, are consistent with [259]. In that work, it was found that women with more than one previous delivery showed a higher mean contractile force than nulliparous ones, which has been proven to be related to contraction amplitude [146]. Physiologically, vaginal parity has been linked to reduced collagen alignment and poorer biomechanical properties without affecting the overall histomorphology of the tissue [262], which may be related to the faster cervical dilatation rates in parous women [204]. Therefore, the combined interaction between uterine contractility and cervical dilatation may explain why the uterus of parous women appears to require significantly less effort to complete vaginal delivery than that of nulliparous women.

On the other hand, Prevost found that higher parity was related to lower endogen oxytocin generation and consequently to lower cell excitability [263]. This agrees with our MNF results, which are associated with cell excitability [219]. We found that the GS_P group (with no grand parous women) exhibited slightly lower values and progression rates than the GS_N group, with no significant difference. The non-linear parameters of the EHG showed no statistically significant differences between nulliparous and parous except for some isolated time interval and none between them. Despite of that the physiological interpretation of non-linear parameters is still unclear, we speculate that the slightly lower signal complexity in parous women may be linked with the increased coupling or synchronization degree between cells. As labor approaches, the increase of both number and density of gap junctions [7, 10] gives rise to an enhanced signal propagability and higher synchronization degree at myometrium level. Indeed, using magnetomyometriogram it has been shown that parous women exhibited higher synchronization degree than nulliparous women from 36 weeks of gestation onwards [264]. Since EHG is the result of weighted sum of uterine myoelectric activity around the electrodes, an enhanced propagability is reflected as an increased signal amplitude of parous women (figure 4.4) [40]. Our hypothesis is that the more synchronized and propagated the action potentials (high connectivity between myometrium cells) the more reduced pattern number in EHG signals, which is equivalent to a more organized signal [265].

To sum up, the main differences between nulliparous and parous women consist of structural changes in the cervix, which have been associated with a higher rate

of cervical dilatation in parous women. At the myometrium level, we found a lower number of contractions but faster evolution (greater progression rate) of the amplitude of the signal in parous women, but no significant differences in cell excitability or signal predictability and complexity. It is therefore important to take these factors into account when designing an induction success prediction system.

4.4.3 Limitations of the study

Despite obtaining consistent results, the present study has some limitations. Firstly, the size of the database could lead to some bias in the analysis due to intrinsic biological variability. Future work will aim to increase the sample size to corroborate the present results and to design robust and generalizable induction success prediction systems based on EHG and obstetric data.

Secondly, two approaches are commonly used in EHG signal analysis, [151]: whole EHG window analysis [154, 219, 228] and EHG-burst analysis [229, 235, 238]. The former facilitates segmenting the process, since it only requires the removal of motion artefacts from the EHG records and does not involve discrimination between uterine contraction and baseline activity [243]. Our previous study found that EHG-burst analysis to be more suitable for characterising the uterine myoelectric response to the induction drug than whole EHG-window analysis [243], while in this work the manual segmentation of contractions performed by experts in a double-blind process to reduce bias is inherently subjective and cumbersome for large datasets. Multiple systems for the automatic detection of contractions in EHG recordings during routine pregnancy monitoring [202, 203] and/or threatened preterm labour [202, 235] can be found in recent studies. The performance of this system in the labour induction has yet to be tested, as there may be a higher rate of movement artefacts due to maternal and foetal stress associated with imminent labour [266, 267]. Also, the EHG-bursts associated with contraction can exhibit subtle changes in the latent phase of labour, making it really challenging to detect uterine contractions in this scenario.

Thirdly, we here characterised the EHG signal by assessing the degree of cell recruitment and excitability as well as uterine contraction complexity and regularity. Other indicators have been proposed based on the synchronization degree of multichannel EHG recordings to determine the uterine the degree of coupling of the uterine cell which is directly related to the formation of the gap junction union, e.g.: iCOH [40, 188], non-linear H2 [188, 203], NPCMI [188, 268], partial Granger causality [219, 229] and partial transfer entropy [219]. Despite of the physiological interpretation of the synchronization measures, which could provide complementary information to temporal, spectral and non-linear measures, in this work we preferred to use a simplified protocol considering the highly stressful situation of labour induced for women and clinicians in clinical practice [267]. Also, a simplified protocol that does not radically alter routine clinical praxis will facilitate transferring the EHG technique to clinics. However, future work on additional simultaneous EHG recording electrodes will address the problem of obtaining additional

information on the degree of synchronisation to predict successful labour induction. Despite these limitations, our findings pave the way to investigating any differences in uterine myoelectric response to other drugs, which will help to optimise drug doses and administration routes.

4.5 Conclusions

In this work, we analysed the different uterine myoelectric responses to Dinoprostone between labour induction success (APL≤24h) and failure groups (the remainder). We found significant sustained differences in EHG-biomarkers with respect to baseline activity from 2-3 hours after the start of labour induction in the successful induction group: increased number of contractions and Mean Frequency (associated with cell excitability) and reduction of SampEn and SpEn (associated with reduced complexity). In contrast, no significant changes from baseline activity were found for failed induction group. Women with successful inductions also showed a statistically higher rate of progression (steeper slope) of amplitude of the EHG-bursts and the spectral UAI parameter, and statistically lower slopes for the whole set of non-linear parameters.

We also determined the influence of parity on uterine myoelectric response to a labour induction drug in those women who achieved APL≤24h. Nulliparous women showed a higher number of contractions and larger changes in the mean frequency progression rate than parous women, with no significant differences between them. No differences were found in the non-linear parameters between nulliparous and parous women. The most relevant finding at the myometrium level consisted of a significantly higher progression rate of the EHG signal amplitude in parous women.

The present study not only expanded current information on electrophysiological knowledge of the in-vivo response of uterine myoelectric activity to the induction drug without the confounding factor of exogenous oxytocin, but also identified new EHG-biomarkers that could allow the early detection of the risk of induction failure. We therefore propose that they should be used to develop robust and generalizable induction success prediction systems to help clinicians to optimise induction decision-making, to better plan and manage deliveries, to prevent maternal and foetal complications and their associated mortality and morbidity and optimise hospital resources.

Funding 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).

Conflict of interest The authors declare no conflict of interest and that the funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Ethics approval This work adhered to the guidelines of the Declaration of Helsinki and was approved by the hospital's Institutional Review Board (Register Number 2018/0530). Patients were informed of the nature of the study and gave their written informed consent.

Author contributions **Alba Diaz-Martinez**: Conceptualization, Software, Formal analysis, Investigation, Data Curation, Writing - original draft, Visualization. **Rogelio Monfort-Ortiz**: Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing - review & edit, Supervision. **Yiyao Ye-Lin**: Conceptualization, Methodology, Validation, Resources, Writing - original draft, Supervision, Project administration, Funding acquisition. **Javier Garcia-Casado**: Conceptualization, Methodology, Validation, Resources, Writing - review & edit, Funding acquisition. **Mar Nieto-Tous**: Conceptualization, Investigation, Data Curation. **Félix Nieto-Del-Amor**: Software, Formal analysis, Writing - review & edit, Visualization. **Vicente Diago-Almela**: Methodology, Validation, Resources, Writing - review & edit, Supervision, Funding Acquisition. **Gema Prats-Boluda**: Conceptualization, Methodology, Validation, Resources, Writing original draft - review & edit, Supervision, Funding Acquisition.

Chapter 5

A Comparative Study of Vaginal Labour and Caesarean Section Postpartum Uterine Myoelectrical Activity

Complete reference

Diaz-Martinez, A., Mas-Cabo, J., Prats-Boluda, G., Garcia-Casado, J., Cardona-Urrego, K., Monfort-Ortiz, R., Lopez-Corral, A. Arriba-Garcia, M., Perales, A. & Ye-Lin, Y. (2020). A Comparative Study of Vaginal Labor and Caesarean Section Postpartum Uterine Myoelectrical Activity. Sensors 2020, Vol. 20, Page 3023, 20(11), 3023.

Abstract

Postpartum hemorrhage (PPH) is one of the major causes of maternal mortality and morbidity worldwide, with uterine atony being the most common origin. Currently there are no obstetrical techniques available for monitoring postpartum uterine dynamics, as tocodynamometry is not able to detect weak uterine contractions. In this study, we explored the feasibility of monitoring postpartum uterine activity by non-invasive electrohysterography (EHG), which has been proven to outperform tocodynamometry in detecting uterine contractions during pregnancy. A comparison was made of the temporal, spectral, and non-linear parameters of postpartum EHG characteristics of vaginal deliveries and elective cesareans. In the vaginal delivery group, EHG obtained a significantly higher amplitude and lower kurtosis of the Hilbert envelope, and spectral content was shifted toward higher frequencies than in the cesarean group. In the non-linear parameters, higher values were found for the fractal dimension and lower values for Lempel-Ziv, sample entropy and spectral entropy in vaginal deliveries suggesting that the postpartum EHG signal is extremely non-linear but more regular and predictable than in a cesarean. The results obtained indicate that postpartum EHG recording could be a helpful tool for earlier detection of uterine atony and contribute to better management of prophylactic uterotonic treatment for PPH prevention.

Keywords
Electrohysterogram; Uterine Myoelectrical Activity; Postpartum Hemorrhage; Signal Characterization; Uterotonic Therapy.

5.1 Introduction

Postpartum hemorrhage (PPH) is defined as more than 500 mL and 1000 mL of bleeding following vaginal or cesarean delivery, respectively, and is one of the major causes of maternal mortality and morbidity worldwide [115]. The global prevalence of PPH is about 6% of all deliveries [95] although this varies considerably according to the source, and is higher after cesarean (6%) than vaginal deliveries (2-4%) [269]. Without effective recognition and management, women rapidly experience shock, organ dysfunction, and even death [121]. It is estimated that around 75,000 women die of PPH each year, one every 7 min [121], or almost a quarter of maternal deaths worldwide [121]. More than half of these deaths occur within 24 h of delivery, mostly from excessive bleeding [270]. The developing countries continue to experience higher numbers of maternal deaths: in 2015, the maternal mortality ratio in these was 239 per 100,000 live births compared to 12 in the developed countries [204]. Nevertheless, recent studies have shown an increasing trend in PPH in developed countries [94].

Women who survive PPH may present significant morbidities including: hypotension, organ failure, severe anemia, fatigue, transfusion complications, thrombosis, acute respiratory distress syndrome, sepsis, and may need intensive care or further surgical interventions [122, 123]. It may also involve a prolonged hospital stay and higher costs for the health system. In 2013, the total cost amounted to more than $6 million for 28,000 cases of PPH in Egypt [271]. Prick estimates that the average cost of a red blood cell transfusion is about €1957 per acute anemic patient without severe anemic symptoms [124], and Castiel reports that the costs of PPH surgery range from €275 for manual exploration of the uterine cavity to €875 for hysterectomy [125].

Numerous PPH risk factors have been reported, including fetal macrosomia (over 4000 g), pregnancy-induced hypertension, pregnancy generated by assisted reproduction, severe vaginal or perineal laceration, weight gain over 15 kg during pregnancy, history of PPH, multiple pregnancies, primigravida, grand multiparity, advanced age, preterm births, genital tract injuries, non-use of oxytocin for PPH prophylaxis, labor induction, cesarean delivery and intra-uterine fetal deaths [272]. However, as most women who experience PPH have no risk factors, clinicians should be prepared to treat it at every delivery [119]. Currently, no early detection techniques are available for the preventive management of prophylactic uterotonic treatment. In addition, post-delivery blood loss is seldom measured in clinical practice because it is not clear whether it improves care and outcomes [269]. Furthermore, the blood loss requiring an intervention depends on a number of factors, including whether the patient is anemic [269].

Common causes of PPH include: uterine atony and trauma such as genital tract injuries, retained placental tissue and failure of the blood coagulation system, uterine atony being responsible for most cases (75-90%) [273], which is related to the inability of the uterus to contract after the expulsion of the fetus. PPH can be fatal in a hypotonic uterus without contractions and retractions of the myometrium to compress the torn

blood vessels in placental separation and obliterate the lumen, as long as the maternal blood coagulation mechanism is normal [16]. However, if the myometrium near to a naked implantation site contracts and retracts vigorously, severe bleeding from the placental implantation site is unlikely, even if maternal coagulation is severely affected [16], so that monitoring uterine contractile activity after delivery could greatly help early PPH detection.

The gold standard for monitoring uterine contractions is intrauterine pressure, which measures the overall pressure by inserting a catheter. This is an invasive technique that requires membrane rupture and also increases the likelihood of intrapartum infection, as well as uterine perforation or placental abruption [145]. In clinical practice, the commonly used technique for monitoring uterine dynamics during pregnancy and labor is external tocodynamometry (TOCO), which consists of recording abdominal wall distension caused by uterine contractions [274]. This indirect measurement technique tends to be inaccurate, depend greatly on proper positioning and is adversely influenced by maternal obesity [142], while the lack of sensitivity for detecting weak or localized contractions makes it unsuitable for monitoring postpartum uterine dynamics. So at the present, there is no tool that can accurately assess postpartum uterine dynamics.

Electrohysterography (EHG) has emerged as an alternative for non-invasive monitoring of uterine dynamics. This technique involves recording on the abdominal surface the uterine myoelectrical activity associated with the contraction of myometrial cells. Previous studies have shown that EHG outperforms TOCO in detecting uterine contractions during pregnancy and labor [142, 144, 274] and is especially useful in obese patients [185, 275]. Other studies have found that intrauterine pressure can be precisely estimated from EHG recordings [146, 276, 277]. It has also been proven that EHG contains relevant information on the electrophysiological uterine conditions and can be used for identifying effective contractions that trigger labor, besides non-effective physiological contractions during pregnancy [278].

It is well known that as labor approaches, EHG signal amplitude increases due to the major recruitment of cell numbers involved in contractions, while the signal spectral content shifts to a higher frequency because of increased cell excitability [278]. Other studies have proposed non-linear parameters for characterizing EHG signals, such as sample entropy, Lempel-Ziv, and time reversibility [150, 152, 223, 279, 280] and found that as labor progresses, the EHG signal is more organized, signal predictability increases and signal complexity decreases, although some of these results have been controversial.

Prediction systems for distinguishing between term and preterm labor [153, 268, 281, 282] and labor induction success [169] by means of EHG have also been reported. It has recently been used to record uterine activity in non-pregnant women, which is much weaker than during pregnancy and labor [283]. However, so far, its ability to record postpartum uterine activity has not been assessed.

Taking into account the higher blood loss in women with elective cesarean delivery over vaginal deliveries and the fact that postpartum uterine activity is a natural

fundamental mechanism that prevents PPH, our hypothesis was that there are differences in the postpartum uterine dynamics after vaginal and elective cesarean deliveries. The aim of this work was, therefore, to determine the feasibility of the non-invasive detection of postpartum uterine myoelectrical activity and to detect any differences between the postpartum EHG signals after vaginal deliveries (VGN) and elective cesarean sections (CSR).

5.2 Materials and Methods

5.2.1 Signal Acquisition

A total of 33 EHG recordings were conducted on women with single low-risk term pregnancies ($\geq$37 weeks) admitted in the Polytechnic and University Hospital La Fe (Valencia, Spain) and delivered either vaginally (13 women, VGN) or by elective cesarean section (20 women, CSR). Fetal macrosomia, polyhydramnios, multiple pregnancies, and large advanced maternal age (>45 years) were factors for exclusion from the study because of the bias they could introduce in the results. The EHG recording lasted approximately 60 min and was performed during the first three hours after delivery. This study adhered to the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of the hospital (register number 2018/0519). Patients were informed about the nature of the study and gave their written informed consent. Prophylactic uterotonic treatment was given to each patient according to hospital protocol so as to promote uterine contractions to prevent PPH: 20 international units of oxytocin for VGN, 100 μg carbetocin (Duratobal) for CSR.

The clinical data collected during the study were: maternal age, body mass index (BMI), parity, previous cesarean, fetal weight, hemoglobin (Hb), hematocrit, Cardiac Frequency (CF), Systolic Arterial Pressure (SAP), Diastolic Arterial Pressure (DAP), and Saturation of Oxygen (SO2). Vital signs were measured at the time of admission and 24 h after delivery to determine any postpartum hemodynamic changes. The Wilcoxon rank-sum test was used to detect statistically significant differences in obstetric data between the VGN and CSR groups (α= 0.05).

The EHG recordings were taken after the patient had left the operating theater in the case of CSR, or delivery ward in the case of VGN. Before each recording session, 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 single-use Ag/AgCl electrodes (Red Dot 2660-5, 3M, St. Paul, MN, USA) were then placed as shown in Figure 5.1. Two electrodes (M1 and M2) were symmetrically positioned with respect to the median axis over the uterine fundus at a distance of 3 cm from each other to obtain two monopolar EHG recordings. Two electrodes were placed on each hip to provide reference and ground biopotentials. This

configuration was chosen to simplify the acquisition protocol and allow recordings from the reduced-size uterus after delivery. Both monopolar signals were conditioned by a custom-made wireless recording module, providing a 2059 V/V gain in the 0.1-150 Hz bandwidth and digitized by a 24 bit analog-to-digital converter at 500 Hz [242].

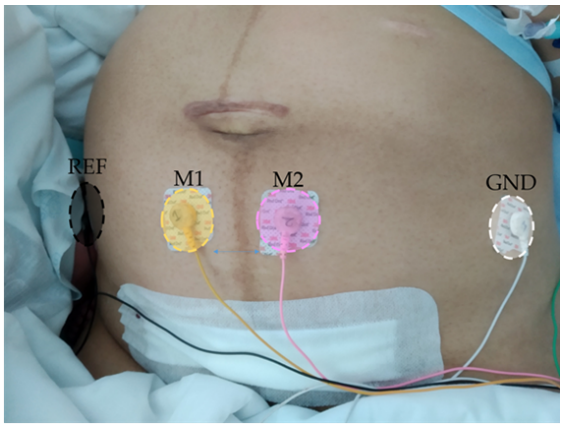

Figure 5.1: Electrodes positioning for postpartum uterine myoelectrical recording.

5.2.2 Data Analysis

Since the EHG spectral content is mainly distributed between 0.1-4 Hz [284], digitized monopolar EHG signals were filtered in that range (zero-phase 5th order Butterworth band-pass filter) then downsampled at 20 Hz to maintain the trade-off between temporal resolution and computational cost. Once the monopolar signals were conditioned, a bipolar signal was calculated as their difference (M2-M1) to reduce common-mode interferences and increase signal quality [142]. Motion-artifacts segments were visually identified by three different experts and discarded from the study. In case of disagreement, the decision was taken through a blind majority vote based on their reports.

EHG parameters were worked out in moving windows of 120 s with a 50% overlap which was shown to be able to analyze representative sections of the EHG signal at a reasonable computational cost, better than 60, 300, and 600 s [152]. The median value of all the analysis windows was computed to obtain a single representative value of each EHG parameter per recording session.

A set of temporal, spectral, and non-linear parameters were selected to characterize postpartum EHG signal: peak-to-peak amplitude [284], kurtosis of the Hilbert envelope (KHE) [285], median and dominant frequency [150, 152], normalized energy (NE) [286], sample entropy [159], spectral entropy [287], Lempel-Ziv binary complexity [252], and Katz fractal dimension (KFD) [288]. All of these were computed in the 0.1-4 Hz bandwidth, except for the spectral parameters, which were computed in 0.2-1 Hz to minimize the influence of cardiac interference and baseline fluctuation [278].

Peak-to-peak amplitude is directly related to uterine contraction intensity and is frequently used for EHG characterization [284]. Since the presence of scar tissue in elective cesarean sections could interrupt the propagation of action potentials or locally change the propagation direction [289], we also computed kurtosis of the Hilbert signal envelope, which is a measure of signal impulsiveness, as it has been shown to increase the strength of abrupt changes [285]. Higher KHE values are thus expected for impulse-like signals.

Spectral parameters were used to assess cell excitability [148]. An increase in cell excitability turns into a shift to higher frequencies in the EHG signal, as happens in advanced pregnancy and labor [19, 152]. Median and dominant frequency were computed because they are commonly used to characterize EHG signals [150, 152]. The median frequency of the spectrum was computed as the frequency at which the total of the upper and lower parts of the frequency-power spectrum are the same [150]. Dominant frequency was obtained as the frequency with maximum power spectral density [152]. NE was also computed to determine the variations in the energy in a high-frequency subband of the EHG spectrum (0.34-0.6Hz), which is associated with the fast wave high component of the EHG, normalized with respect to the total energy in the 0.2-1Hz band [286].

$$\mathrm{NE}(x[n]) = \frac{\sum_{k=f_L}^{f_H} \mathrm{PSD}[k]}{\sum_{k=0.2\mathrm{Hz}}^{1\mathrm{Hz}} \mathrm{PSD}[k]} \tag{5.1}$$

Where $\mathrm{PSD}[f_i]$ is the power spectral density using a periodogram with a Hamming window length of 120 s. Greater values of the defined spectral parameters are associated with greater uterine cell excitability.

Non-linear parameters have also been proposed to characterize the electrophysiological state of the uterus through the EHG signal recordings [40]. Both sample and spectral entropy measure the regularity of a finite time series in the time and spectral domains respectively and estimate the extent to which the data does not arise from a random process. A higher value of these parameters is associated with a more chaotic series [150, 159]. Lempel-Ziv [252, 287] assesses signal complexity by counting the number of different patterns in a time series, while the Katz fractal dimension [288] is a measure of self-similarity signal complexity [290].

The Wilcoxon rank-sum test was performed to assess statistical differences ($\alpha = 0.05$) in each EHG feature values for the VGN and CSR groups. The statistical effect size was also computed as the difference between means divided by the standard deviation of the "control group", in this case VGN [187, 291]. According to Cohen's guide, an effect size < 0.2 is considered a small difference effect; 0.3-0.5 is considered a moderate effect difference and > 0.5 reveals a large or "important" difference effect [292].

5.3 Results

Obstetric data and vital sign variation for both VGN and CSR are shown in Table 5.1. No statistical differences were found between the groups, except for the number of previous cesareans, which is an elective cesarean decision factor.

Figure 5.2 shows examples of postpartum EHG bipolar signals of two women who delivered vaginally (upper trace) and by cesarean section (lower trace). As can be appreciated, only subtle changes in amplitude and/or the frequency with respect to basal activities were registered, due to the weak postpartum uterine contractions, which made it difficult to visually identify postpartum EHG-bursts in the recording. Apparently, women who deliver vaginally present more and higher amplitude uterine contractions than cesarean deliveries. Impulsive-like signals were occasionally present in women who delivered by cesarean section.

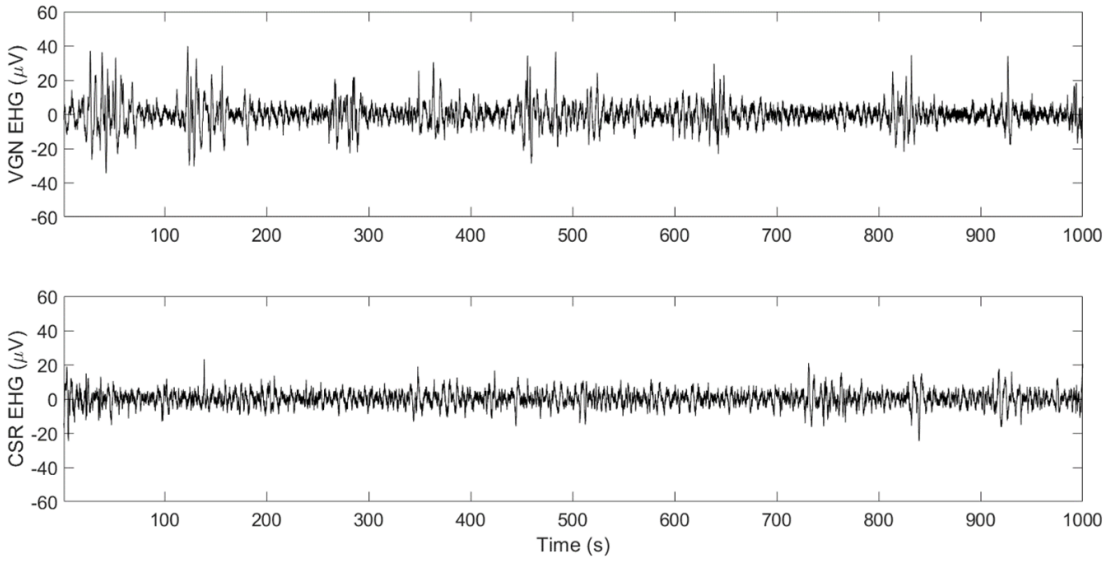

Figure 5.2: Example of postpartum electrohysterography (EHG) bipolar recordings from women who delivered vaginally (VGN, upper trace) and by cesarean section (CSR, lower trace).

Figure 5.3 shows the box and whisker plots of different EHG parameters for both VGN and CSR groups, including the corresponding uncorrected p-value of the statistical test, while Table 5.2 shows the mean and standard deviation of EHG parameters for both groups. Firstly, vaginal deliveries presented a significantly higher amplitude than elective cesarean sections (VGN 66.44±26.62 μV vs. CSR 45.60±20.78 μV, p-value=0.027, and effect size of 0.78). For the kurtosis of the Hilbert envelope (KHE), VGN obtained a significantly lower value than the CSR group (VGN 2.30±0.36 vs. CSR 2.71±0.39, p-

Table 5.1: Mean and standard deviation values of the obstetric data and vital sign variation before and 24 h after delivery in the study population. Values in bold indicate significant differences between groups (α<0.05). CSR: elective caesarean delivery. VGN: vaginal delivery. BMI: Body Mass Index. CF: Cardiac Frequency. SAP: Systolic Arterial Pressure. DAP: Diastolic Arterial Pressure.

Variable	**CSR** $\mu \pm \sigma$	**VGN** $\mu \pm \sigma$
Maternal age (years)	32.80±5.70	33.92±7.95
BMI (kg/m^2)	28.40±4.90	27.52±4.10
Parity	0.05±0.22	0.23±0.44
Previous caesarean	**0.45±0.51**	**0.00±0.00**
Fetal weight (g)	3279±386	3326±365
Δ*Hb (g/dL)*	−1.14±0.94	−1.43±1.25
Δ*Hematocrit (%)*	−3.94±2.77	−3.39±4.22
Δ*CF (bpm)*	3.85±13.68	−0.54±8.36
Δ*SAP (mmHg)*	−18.15±20.12	−4.31±15.33
Δ*DAP (mmHg)*	−5.30±11.36	−2.23±17.54
Δ*SO2 (%)*	0.00±2.12	0.70±1.57

value=0.003, and high effect size of 1.18), suggesting a higher impulsive-like character in this group.

For non-linear parameters, the binary Lempel-Ziv computed from the VGN group was 0.37±0.08, which was slightly smaller than that obtained for CSR (0.39±0.05), although this difference was not significant (p-value=0.155 and effect size of 0.31). Similarly, VGN sample entropy was lower than that of CSR (VGN 0.88±0.23 vs. CSR 0.92±0.18), with no significant differences (p-value=0.451 and effect size of 0.19). However, spectral entropy was significantly lower for the VGN group (VGN 0.88±0.02 vs. CSR 0.89±0.02, p-value=0.019 and effect size of 0.69). We also found that the VGN Katz fractal dimension was significantly higher than that of the CSR (VGN 1.08±0.03 vs. CSR 1.05±0.03, p-value=0.004 and effect size of 1). It can be verified that those parameters that present statistically significant differences have an effect size value greater than 0.5, at which the difference between vaginal and cesarean section groups is considered both significant and important.

5.4 Discussion

PPH still causes a significant number of deaths among pregnant women. Although the main risk factors are known, there is currently no consensus on its prevention. Since the most common cause of PPH is associated with uterine atony, in this work we proposed

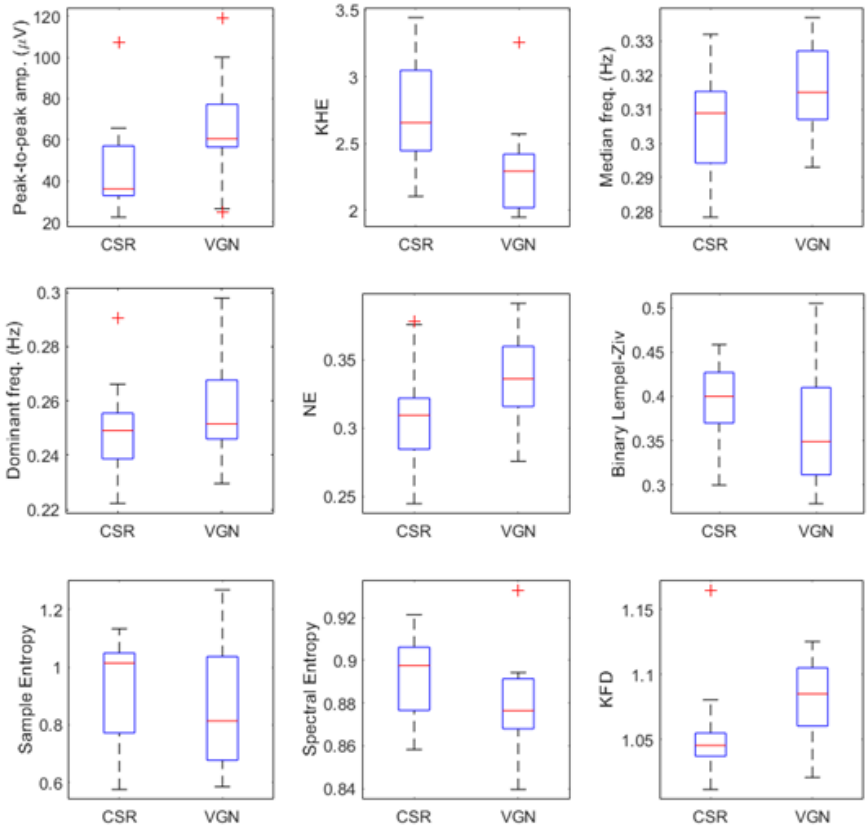

Figure 5.3: Distribution of postpartum EHG parameters for cesarean (CSR) and vaginal (VGN) deliveries.

to use the EHG technique for monitoring postpartum uterine activity for early detection of uterine atony for PPH prevention. For the first time, we reported the feasibility of recording postpartum uterine myoelectrical activity on the abdominal surface. Although we were able to corroborate the presence of uterine contractile activity in the postpartum EHG recordings (see Figure 5.2), the changes in both amplitude and frequency with respect to basal activity were very subtle, so that it was difficult to accurately identify the onset and offset of uterine contractions in the EHG signal. We also checked the feasibility of identifying uterine contractions in the Teager energy operator in a moving window (not shown), which has been proposed to successfully estimate intrauterine pressure from EHG recordings in the active phase of labor [146, 277], although no substantial improvement was found. It was therefore not possible to characterize the EHG-bursts as traditionally performed in EHG analysis during pregnancy and labor [152, 284].

A whole window analysis was performed to characterize postpartum EHG signals during the study, which was previously used to predict preterm labor in women during regular check-ups [150, 153] and for differentiating women with threatened preterm

Table 5.2: Mean and standard deviation values of the obstetric data and vital sign variation before and 24 h after delivery in the study population. Values in bold indicate significant differences between groups (α<0.05). CSR: elective caesarean delivery. VGN: vaginal delivery. BMI: Body Mass Index. CF: Cardiac Frequency. SAP: Systolic Arterial Pressure. DAP: Diastolic Arterial Pressure.

Variable	**CSR** $\mu \pm \sigma$	**VGN** $\mu \pm \sigma$	**P-value**	**Effect size**
A_{pp} (μV)	**45.60±20.78**	**66.44±26.62**	**0.027**	0.78**
KHE	**2.71±0.39**	**2.30±0.36**	**0.003**	1.18**
MDF (Hz)	0.31±0.02	0.32±0.01	0.086	0.76**
DF (Hz)	0.25±0.02	0.26±0.02	0.258	0.42*
NE	**0.31±0.04**	**0.34±0.03**	**0.040**	0.80**
BLZ	0.39±0.05	0.37±0.08	0.155	0.31*
Samp-Ent	0.92±0.18	0.88±0.23	0.451	0.19
Sp-Ent	**0.89±0.02**	**0.88±0.02**	**0.019**	0.69**
KFD	**1.05±0.03**	**1.08±0.03**	**0.004**	1.00**

labor who delivered in less and more than seven days and outperformed EHG-burst analysis [152]. In this regard, the whole window analysis, which includes both EHG-bursts associated with uterine contractions and basal activity during uterine quiescence, has the inherent advantage of being easier to integrate in subsequent embedded systems to automatically extract useful information from the EHG signal. Such systems would also need to detect and suppress motion-artifacted segments, which was performed manually in the present study. Future work will focus on developing new automatic algorithms or adapting approaches previously applied to EHG in the active phase of labor [266] to this specific obstetric scenario.

As this is a pioneering study, both the number and the specific characteristics that best describe postpartum uterine activity and possible differences between vaginal and cesarean deliveries are initially unknown. Statistical tests of the EHG parameters were considered as 'independent', with no p-value corrections, so that the number of characteristics used would not affect the significance level of the comparison. As an alternative, we also computed Cohen's effect size [291]. Results show remarkable differences in postpartum uterine myoelectrical activity between women who deliver vaginally and by elective caesarean. Although drugs were administered to promote contractile activity in all cases, the use of different drugs according to the delivery outcome (VGN: oxytocin, CSR: carbetocin) can partially affect the results. Carbetocin was preferred for caesareans for practical reasons, since this drug only requires a single dose. It is not extensively used since it is more expensive than oxytocin. The specific effects of each drug on different types of births may be studied in future work. Despite this, the results for both groups are in line with what could be expected. A caesarean can be considered a non-physiological interruption of pregnancy before spontaneous vaginal

labor occurs, so that postpartum CSR uterine activity could be expected to be more similar to activity during pregnancy and VGN more like labor.

Taking the electrophysiological changes during pregnancy towards vaginal labor into account [278], we hypothesized that postpartum VGN uterine contractions are more frequent and intense than in CSR and that postpartum uterine cells are more excitable in VGN. All this agrees with the results obtained, which show higher amplitude and greater spectral content at higher frequencies for VGN than CSR. The higher values of median or dominant frequency could support this shift and the associated higher cell excitability. This is in line with the higher proportion of signal power in the [0.34-0.6] Hz bandwidth-indicated by NE, since it was reported that the appearance of the contractions is associated with an increase in the fast wave high band [293]. We also found the Hilbert transform envelope kurtosis of the VGN signal was significantly lower than in CSR, suggesting that postpartum uterine myoelectrical activity after caesarean deliveries presents a greater degree of impulsiveness, which may be related to the interruption or abrupt changes in the direction of action potential propagation due to incised tissue. These results disagree with De Lau et al., who found that previous cesarean patients with an intact uterine scar showed similar inter-channel correlation or propagation direction of EHG during labor to the control group without scars [289]. The discrepancy could be because we carried out the EHG recording immediately after delivery on unscarred tissue.

We also found that VGN postpartum myoelectrical activity is more regular and organized than CSR, which is revealed in lower values of binary Lempel-Ziv, sample entropy and spectral entropy, although only the latter was significantly different. The fractal dimension of postpartum EHG for VGN was significantly higher than for CSR, suggesting a higher non-linear degree of the signal. These results on VGN vs CSR comparison again agree with the trends and differences reported when comparing EHG records during labor (or close to it) with pregnancy recordings further from labor. In this respect, previous studies found significantly lower sample entropy in women who underwent regular medical check-ups and gave birth prematurely than in term patients [150]. Mas Cabo found reduced signal complexity and higher signal regularity and predictability in women with threatened preterm labor who delivered in less than seven days than those who delivered in more than seven days [152], while Maner found that the EHG signal fractal dimension during the active phase of labor with frequent uterine contractions is significantly higher than for antepartum patients with sporadic physiological pregnancy contractions [294].

To summarize, the results obtained suggest that VGN postpartum uterine contractions are more frequent, intense and the uterine cells are more excitable than in CSR, i.e., higher oxytocin levels, which promote uterine contractility, may be present in VGN women regardless of the drug used to prevent PPH. Our finding is consistent with other studies that found fetal oxytocin levels in the umbilical artery were significantly higher after vaginal deliveries than CSR, due to a stress-related stimulation of oxytocin producing cells particularly during vaginal delivery [295]. Yusoff found that oxytocin concentration

in both spontaneous labor and vaginal delivery and non-elective CSR after labor was significantly higher in both umbilical arterial plasma and amniotic fluid than for CSR [181]. They also found that oxytocin is present in fetal urine, suggesting that during spontaneous labor oxytocin is produced by the fetus and flows towards the maternal circulation [181].

This work has proven the feasibility of recording and characterizing postpartum uterine activity and paves the way to providing clinicians with relevant information and feedback to assist in choosing the most efficient and cost-effective strategy for prophylactic uterotonic management: oxytocin receptor agonists (oxytocin and carbetocin), prostaglandin analogues (misoprostol, sulprostone, carboprest), ergot alkaloids (ergometrine/methylergometrine) or a combination of these [119]. Pickering found that carbetocin was the most effective strategy and oxytocin the least costly strategy when including adverse events in the analysis. The incremental cost-effectiveness ratio for PPH prevention in a comparison of carbetocin andoxytocin was £928 per case of PPH≥500 mL avoided; £22.900 per case of PPH≥1000 mL avoided; and £894.514 per major outcome averted [120]. Morfaw found that 600 μg misoprostol as an add-on to oxytocin to prevent postpartum haemorrhage significantly reduced the odds of PPH (from 4.4% to 1.5%) [296]. Using a more comprehensive database, we can further analyze and compare postpartum uterine activity between carbetocin and oxytocin for both vaginal and cesarean deliveries.

5.5 Conclusions

This work has shown the feasibility of non-invasive monitoring of postpartum uterine myoelectrical activity and comparing the postpartum EHG characteristics of vaginal and cesarean deliveries. Uterine myoelectrical activity in women who delivered vaginally is more frequent, intense and the uterine cells seem to be more excitable than those involved in cesarean deliveries in our database, which is reflected in higher signal EHG amplitude and a spectral content shift to higher frequencies. For non-linear EHG parameters, women who delivered vaginally seem to show lower values than the cesarean group in Lempel-Ziv, sample entropy, and spectral entropy, hinting increased signal regularity and predictability. These results suggest that postpartum EHG recording could be a helpful tool for early detection of uterine atony, which would be helpful in predicting PPH risk and thus help clinicians to prevent it by better management of prophylactic uterotonic treatment.

Funding This work was supported by the Spanish Ministry of Economy and Competitiveness, the European Regional Development Fund (MCIU/AEI/FEDER, UE RTI2018-094449-A-I00-AR) and the Generalitat Valenciana (GV/2018/104 and AICO/2019/220).

Conflict of interest The authors declare no conflict of interest and that the funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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 2018/0519). Patients were informed about the nature of the study and gave their written informed consent.

Author contributions Conceptualization, G.P.B., J.G.C., Y.Y.L. and A.P.; methodology, G.P.B., J.G.C. and Y.Y.L.; software, J.M.C. and A.D.M.; validation, G.P.B., Y.Y.L. and A.D.M.; formal analysis, A.D.M. and K.C.U.; investigation, R.M.O., A.L.C. and M.D.G.; resources, G.P.B., Y.Y.L. and J.G.C.; data curation, R.M.O., A.D.M. and K.C.U.; writing—original draft preparation A.D.M. and Y.Y.L.; writing—review and editing, G.P.B. and J.G.C.; visualization, A.D.M.; supervision, A.P. and J.G.C.; project administration, Y.Y.L.; funding acquisition, Y.Y.L. and G.P.B. All authors have read and agreed to the published version of this paper.

Chapter 6

General discussion

Quantitative assessment of uterine activity is potentially helpful throughout pregnancy, labour and postpartum to early recognise complications and appropriate intervention when acute risks are detected. Unfortunately, current evaluation methods employed in clinical practice for monitoring uterine activity are either inaccurate or invasive, see 1.3. The ever-increasing researched non-invasive EHG technique has shown great potential for routine monitoring myoelectrical activity evolution during gestation, delivery and postpartum, as well as in high-risk obstetric scenarios.

The present thesis therefore contributes to increase the knowledge of the electrophysiological changes experienced during pregnancy, along with the differences with respect to the overdistended uterine state experienced by the MGs or the uterine myoelectric activity response to IOL drug without the exogenous exytocin effect. Furthermore, the characterisation of myoelectrical activity in the puerperium has gone beyond the state of the art by assessing the excitability and the degree of cellular arrangement, thus opening up a pioneering line of study in this field.

6.1 Recommendations for the electrohysterographic recording acquisition

Given the low amplitude of surface EHG signals (tens of microvolts), particularly during the antepartum and postpartum periods, recordings are susceptible to be severely affected by multiple interference and artifacts. These may include drift, maternal breathing, maternal and foetal electrocardiogram, electromyographic noise, power line interference, and motion artifacts [40, 297]. Skin preparation, electrodes positioning, interference reduction and signal processing are essential in this regard. For each recording performed during the development of the present thesis, the skin preparation was carried out by gentle exfoliation and subsequent cleaning of the surface with

alcohol. As for the electrodes, flexible single-use electrodes with a long-lasting conductive adhesive were employed, thereby reducing the skin-electrode interface impedance [4]. Being adhesive allows the patient a greater degree of mobility and longer recordings, thus representing a key step from research setting to clinical use.

Furthermore, anatomical landmarks have been used for electrode positioning, as is done in the acquisition of precordial cardiac leads [298], in order to reduce the bias that may be introduced by the gradual deformation of the abdominal surface in response to the large increase in volume of the uterus during gestation, inter-patient biological variability and organ localisation due to increased uterine size [1]. In case of the regular check-ups and IOL databases generated as part of the Ci2B-La Fe research collaboration, the electrodes were placed symmetrically with respect to the abdominal midline at the midpoint between the pubic symphysis and the fundus, which has been shown to provide a better signal-to-noise ratio due to its higher uterine muscle fiber density [142]. Due to the uterine post-delivery retraction and the spatial limitation of the scar in case of caesarean section, the electrodes in the PPH were placed symmetrically with respect to the mid-axis on the uterine fundus, in an attempt to resemble previous protocols while capturing as much signal as possible. The reference and mass electrodes were always placed on the iliac crests. Remarkably, our electrode arrangement is equivalent to the E3 electrode pair in the public TPEHG database, which has been employed to discriminate between preterm and term deliveries [150, 226] and to study changes in SW directionality and changes with imminent delivery [149].

In literature, numerous studies also fucused their effort to enhacence EHG signal quality [266, 299–302]. Since the interference frequency content such as baseline drift and maternal respiratory rate are below FWH bandwidth and others such as maternal electrocardiogram can be as low as 1 Hz [303], many studies focus on EHG analysis between 0.3-1 Hz [299, 300]. Advanced filtering methods such as Empirical Modal Decomposition, Independent Component Analysis or the Wavelet Transform will be required to extract possible overlapping interferences when the research is focused on the study of the WBW of the EHG [40], with hybrid methods having shown very promising prospective [40, 301]. On the other hand, maternal-foetal motion artefacts have the potential to completely distort the recorded signal and all its frequency content, requiring their identification for subsequent discard. Although efforts are being made to facilitate their automatic identification [266, 302], the procedure is currently carried out in a delayed and manual manner by experts in EHG signal processing, which represents a major drawback when it comes to approach it to routine clinical practice.

Previous studies have proven that adherence to these criteria enables the identification of the risk of PTB [154, 230] with an area under curve of 87.1±4.3% [304], the discrimination of imminent labour in TPL [152, 265] with an F1-score up to 90.2±4.4% [227], the differentiation of successful from unsuccessful IOLs [19, 166, 169, 275] with an accuracy of 93.5±1.5%, or even generating a IUPC-like signal with a maximum pressure error of 16.02 mmHg [146].

6.2 Assessment of EHG-biomarkers in high-risk obstetrical scenarios

Detailed interpretation of each EHG-biomarker can be consulted in detail below in this subsection. For a schematic overview of the results, please refer to Appendix B.

6.2.1 Temporal EHG-biomarkers

As time of delivery approaches, the capacity of the uterus to recruit myometrial cells is increasing and thus contractions are expected to increase in intensity accordingly [7, 9]. Therefore, amplitude characterisation has become a staple in the monitoring of uterine activity during routine clinical practice, as discussed in 1.3, and consequently an established EHG-parameter as well [40]. However, the results and potential use of amplitude EHG-biomarkers have been controversial in the literature, as they are highly dependent on inter-electrode distance, position relative to the uterus, skin preparation, thickness of the underlying fat layer, or gestational age at the time of recording, among others [40, 305].

Both Fele and Horoba did not report conclusive results for the study of RMS as an EHG-biomarker in the public database TPEHGDB for different bandwidths, as the differences between term and preterm deliveries were not significant [150, 222]. In contrast, Most found differences in RMS when separating TPL who delivered in less than 14 days from those who delivered later in an own database, although the bandwidth used in this study was much wider than usual (1-1500Hz) [306]. However, Mas-Cabo also found no significant difference in A_{pp} between those who gave birth before or after 14 days from the time of registration of PTB threat cases [152]. A subsequent robust characterisation of uterine myoelectric activity in different obstetric settings, where four groups were assessed throughout gestation and a fifth during postpartum, found no differences between the term and preterm groups [154], but a clear RMS upward trend was seen as gestation progressed, reaching a maximum in the APL and decreasing again in the postpartum group. In addition, Benalcazar identified an increasing trend of A_{pp} with sustained differences in the IOL process with respect to baseline activity for different induction drugs [19].

Consistent with the above, no differences in amplitude parameters were found in Chapter 3 when comparing MG and SG, possibly because neither group has developed the necessary physiological mechanisms to produce large amplitude contractions due to the remoteness of delivery. In fact, RMS values are considerably lower than those reported in Chapter 4, in which parturition is expected to be forthcoming. In the cross-sectional IOL study, amplitud-related parameter did not show no sustained difference respect to baseline activity. Conversely, the longitudinal measure of the progression ratio reported significant differences in both the assessment of APL$\leq$24h and the study of

the influence of parity. Of note, the longitudinal approach eliminates potential biases introduced by variation in interelectrode distance, difference in abdominal adipose layer thickness between patients and skin preparation. As for postpartum, those delivered via VGN showed a greater amplitude than CSRs in Chapter 5, suggesting that labour may have helped the functional syncytium to work more efficiently during the delivery process, thus favouring a higher contraction intensity.

The KHE represents an innovative biomarker in the field of EHG signal characterisation. It has demonstrated exceptional performance in obstetric risk scenarios where uterine activity was largely disordered and the characteristic contractions of the APL (well differentiated from basal activity, short and of large amplitude) are virtually absent, as in the case of Chapters 3 entailing regular check-ups during third trimester and Chapter 5 with postpartum recordings. In contrast, it appears to be unable to distinguish subtle changes in signal impulsivity in scenarios where labour is imminent, as in Chapter 4.

6.2.2 Spectral EHG-biomarkers

Cell excitability is enhanced with increasing gestational age, resulting in a shift of the spectral content towards higher frequencies [9, 278]. Spectral parameters have been shown to be more reliable than amplitude-related parameters, as they exhibit less biological variability and are also expected to be less sensitive to electrode position [40, 156].

MDF and MNF of the power spectrum have been widely reported in the literature, although without conclusive results in terms of discrimination between threats and real cases of PTB. Although Mas-Cabo [307] and Fele [150] found the MDF capable of significantly differentiating term pregnancies and PTBs, neither Verdenik [308] nor Lucovnik [300] reported disparities for the same comparisons. In contrast, differences have been reported between TPL groups that gave birth in less than 15 days and those that did not in MNF, MDF and H/L Ratio [265, 307]. In addition, literature points out during IOL process differences from baseline begining 60-90 minutes after drug administration in the case of misoprostol and are practically non-existent in the case of dinoprostone due to the rapid pharmacokinetics of the former [19, 166]. Moreover, PIOL showed significantly higher values than MIOL in MNF from 150 minutes onwards [75].

Spectral parameters have been shown to increase sharply a few days before birth [156, 188, 303], so they may not be sensitive enough to assess the change in the degree of excitability in early gestation. Accordingly, significant differences were not found between SG and MG in Chapter 3. As outlined in Chapter 4, significant sustained differences from baseline activity in spectal parameters from minute 150 onwards. The definition of GS as APL$\leq$24h has allowed us to eliminate the bias of oxytocin administration and identify significant differences in the evolution of uterine cellular excitability in response to dinoprostone as an IOL drug for the first time. Finally, uterine activity of the VGN

postpartum in Chapter 5 shows a higher power spectral content in the range 0.34-0.6 than for the CSR group possibly due to the coordinated effort it has made during the last hours prior to recording.

Another less common parameter is the NE of the 0.34-0.6 Hz bandwidth, where the power of near-delivery contractions is mainly concentrated, normalised by the 0.1-1 Hz bandwidth [266]. Mas-Cabo found this EHG-biomarker capable of discerning between PTBs occurring before or after 14 days from the time of recording [307]. It has also been identified as one of the parameters that provide the most relevant information on cell excitability [309]. Its performance is remarkable as significant differences were found in each of the three obstetric scenarios as different as those presented in the previous Chapters 3, 4 and 5.

Therefore, EHG-biomarkers related to power spectral density do not seem to be sensitive enough to assess the possible change in the degree of excitability up to the time of impending delivery.

6.2.3 Non-linear EHG-biomarkers

Preparing the uterus for delivery also leads to improved cellular connectivity and propagation of contractile wavefronts, which is reflected in the EHG signal as a decrease in its complexity [7, 10]. The use of entropy-based parameters has been subject to debate mainly because the non-stationary nature of the EHG-signal can affect this metrics [279], especially with overly large analysis window sizes [40], besides being highly sensitive to large amplitude fluctuations [225], sampling frequency, bandwidth of analysis, and length and hyperparameters [150, 310, 311].

One of the most commonly used non-linear metrics is SampEn. Mas-Cabo identified no trend for SampEn associated with imminent delivery when computed between 0.34-4Hz in women with TPL (25-36 WoG) [152]. In contrast, Vrhovec found a significant reduction in SampEn (0.3-3Hz) as labour approached in the last trimester of pregnancy (32-39 WoG), with particular emphasis on the transition from APL to delivery [280]. No differences were also reported for SampEn computed in the WBW in Chapter 3, except for the 10th percentile suggesting an enhanced organisation in the basal activity at this point of the gestation. Moreover, the FWH computation seems to hold a higher degree of information and magnifies the differences between MGs and SGs, as does the work of Mas-Cabo in the comparison of gestation versus APL [154]. As for the IOL process with dinoprostone, neither Benalcazar-Parra's work [19] nor that of Chapter 4 have reported sustained significant changes from baseline activity, even though the longitudinal rate of progression seems to be a promising metric. On the other hand, Mas-Cabo's work showed that VGN has significantly lower values than APL for both WBW and FWH and for all percentiles [154], although no changes in the temporal organization of the signal between the different types of postpartum were found in Chapter 5. The SampEn parameter has exhibited commendable performance in all three scenarios under study.

BLZ is also a frequently used measure to characterise complexity and regularity of signals in the time domain, with higher values relating to more complex and near-random patterns [251, 287]. Lemancewicz found a significant increase in BLZ (0.24-4 Hz) in patients with threatened PTB who gave birth in less than 7 days (24-34 WoG) [223]. Both Mas-Cabo [152] and Lemancewicz [223] reported the reliability of BLZ in determining impending labour. Other studies reported that BLZ does not follow a monotonous trend in normal gestational progression [154, 280]. Similarly, Benalcazar-Parra found no differences with respect to baseline activity or between IOL success and failure groups for any of the cervical ripening drugs studied [19]. Furthermore, although it is assumed that BLZ may have redundant information when compared to other time-domain regularity metrics such as SampEn or FuzzyEn [309]. In fact, it has shown equal or worse performance than these two in scenarios far from delivery such as those in Chapters 3 and 5, or closer such as the one in Chapter 4.

Applying SpEn calculation in FWH for the first time on EHG records with threatened PTB, Mas-Cabo identified a promising decreasing trend of the EHG-biomarker as the time of delivery approached [152]. Later on, the author reaffirmed this result by identifying the persistent SpEn trend in FWH throughout gestation and APL, decreasing again in the postpartum period [154]. In Chapter 4, SpEn vastly outperform the rest of non-linear EHG-biomarkers, with significant differences found in the progression ratio, between GS and GF from the 90-minute time frame onwards, and with respect to basal activity in GS from 150-minute time frame onwards. These results are consistent with the significantly higher values in MIOL from minute 90 onwards in the comparison of IOL methods [75]. Moreover, differences between VGN and CSR postpartum in SpEn in Chapter 5 were also found to be significant, while BLZ and SampEn failed in discriminating between these groups. Since SpEn assesses the signal regularity in the spectral domain, its supremacy over other non-linear parameters based on the time domain suggests a higher content of relevant information in the spectral content ordering.

In terms of simplicity, accuracy and cost-effectiveness to discriminate between signals of different complexity, the application of HFD stands out for research and medical diagnosis from other widely used linear and spectral analysis EHG-parameters [246]. In addition, its combined use with other linear and non-linear measures showed complementarity or even better results [246]. In fact, it has been reported that HFD provides the most accurate estimates for the whole range of theoretical fractal dimension values than KFD [312, 313], although its robustness may be lower against noise than the latter [312]. However, contemporary research incorporates fractal dimension calculation in the field of electrohysterography mostly as input parameters of prediction systems [224, 309], rather than studying their individual capacity to discriminate between different degrees of signal complexity in high-risk obstetric scenarios [40]. Pioneering work by Maner described a significant increase the fractal dimension of contractile uterine activity in patients who delivered in less than 24 hours versus those who delivered in more time [294]. Consistently, HFD calculated in FWH has achieved a remarkable performance on discrimination between GS and GF, finding significant differences from 150 minutes after dinoprostone administration. In case of Chapter 3, HFD has reported lower complexity

for MGs compared to SGs, while KFD has not been able to identify the changes (unpublished results). Since scale invariance appears to be the underlying mechanism for the physiological function of the contraction in preparation for labour [294], EHG-biomarkers based on fractal dimension estimation may therefore be an excellent tool to quantify its complexity.

6.2.4 Approaches for electrohysterographic analysis: WEWA and EBA

A dual approach has been adopted for the characterization of EHG signals in the present thesis. As raised in Subsection 1.4.2, the contraction amplitude variation from basal activity is subtle in antepartum and postpartum stages, thus hindering the accurate identification of the onset and termination of uterine contraction events. Therefore, a growing trend is towards the implementation of WEWA due to its ability to simplify the segmentation process and include subtle contractions [152], bringing closer the possibility of implementing real-time EHG processing systems, a fundamental requirement for its application in clinical practice. Moreover, there are obstetric scenarios in which identification of the onset and termination of the contractile events is not feasible, as the amplitude increase corresponding to the contraction with respect to the basal activity is quite subtle, and WEWA analysis represents the only option for characterisation of uterine activity, as is the case of Chapter 3 and 5. Of note, the generalised use of WEWA may not be the optimal choice since its performance is highly dependent on the obstetric context under analysis. Although WEWA has demonstrated its superiority in predicting the outcome of TPL [152], during the IOL process it has been found that this technique provides less information than EBA [243].

In the PTB context, both techniques have been widely used. However, Mas-Cabo demonstrated superior discriminatory ability between threatened PTB patients who delivered before or after 7 days for the non-linear parameters obtained by WEWA [152]. Further work has also found differences for MDF (0.1-1 Hz) and SampEn computed in WBW when the analysis was given by WEWA, but not in the case of EBA [307]. In contrast, EBA has been described as providing more information than WEWA during the IOL process, regardless of parity [243]. Possibly as a consequence of the fact that the contractions closer to the delivery (greater amplitude, intensity and differentiation with respect to the basal activity) are organised within the functional syncytium, thus including these segments between contractions does not provide additional discriminatory information.

6.3 Overdistension effect on uterine activity in multiple gestation

Uterine overdistension has been documented as one of the mechanical factors that could trigger spontaneous PTB [40, 314]. Several studies have provided evidence to support it both in the case of MG [162, 163] and in the presence of polyhydramnios [163], situations in which the the amniotic sac content is significantly increased. Therefore, it seems to be a maximum at which the uterus can be distended without altering its function. Direct measurements on biopsied human myometrial strips by Turton showed an augmented frequency of contraction occurrence and an enhanced response to oxytocin as muscle overdistension increased. In this work, biopsies were performed during caesarean section delivery. Consequently, neonatal birth weight was used as estimation of uterine stretch, yielding significant correlations with contractile activity [162]. Further research by Waldorf in pigtail macaques correlated increased uterine wall tension with the appearance of what they call 'inflammatory pulse', all associated with PTB, as described in Chapter 1.3.1. Human donor strips showed a similar response to mechanical stretch (Il-1β, IL-6 and IL-8[1] mRNA[2]), presence of polyhydramnios (IL-6 and TNF-α[3] mRNA) and MG (IL-6, IL-8, CCL2[4]) as in primates [163]. In addition, they conducted a genetic study revealing genes involved in tissue remodelling and muscle growth differentially expressed in non-human primate tissue following artificial uterine overdistension applied with a catheter. Biopsies of human uterine strips from women with polyhydramnios and twins confirmed that these genes were similarly expressed, suggesting that the effect of mechanical overdistension can affect the muscle function of the human uterus even at the deepest level [163].

As evidenced, only biopsied myometrial response to overdistension has been documented in the current literature and its behaviour may differ from that which might occur when the whole organ operates as a functional syncytium [165]. Despite the potential advantage of EHG for the study of uterine muscle in its natural environment and function, no previous work characterising the *in vivo* uterine activity of MG has been found, , although this group is of particular obstetric relevance due to its elevated PTB rate [37]. In this respect, Chapter 3 provides novel insights into how uterine overdistension in MGs may affect uterine electrophysiological activity. Based on the example of Turton [162], foetal weight at the time of uterine activity assessment was considered as the overdistension estimation. Since EHG recordings were performed during regular gestational check-ups, the approximation was given by a regression based on the well-known Hadlock's formula and the newborn percentile [315]. Electromechanical coupling in uterine smooth muscle captured by surface EHG has significantly correlated foetal

[1] Interleukin-8
[2] Messenger ribonucleic acid
[3] Tumour necrosis factor alpha
[4] C-C motif chemokine ligand 2

weight and signal amplitude and non-linearity characteristics, with in some cases even lower correlation with CL. In addition, EHG-biomarkers have detected higher impulsivity and predictability of early third trimester MG with respect to SG. Similar EHG signal characteristics have been clinically linked to higher gestational age and, ultimately, to readiness for the onset of labour [40, 154, 162]. Therefore, all indications point to a potential use of this new knowledge in the early detection of the risk of PTB in MG.

This pilot research paves the way for the comparative study of overdistension estimates, combining the information obtained from EHG-biomarkers with the traditional blood-based ones or genes expression, evaluating this scenario in the presence of pathology or response to different drugs, and seeking other spontaneous PTB triggers that may act together with or independently of overdistension.

6.4 Electrophysiological uterine activity in response to the induction drug

Few works on the characterisation of uterine myoelectric response to IOL drugs [19, 75, 147, 166, 168, 316] and the prediction of their outcome based on EHG recordings [169] have been published to date. Furthermore, only theCi2B-La Fe research group has gone beyond the characterisation of signal intensity evolution and encompassed spectral and non-linearity characteristics [19, 166, 316]. Although their study of the electrophysiological response to misoprostol reported significant changes between the IOL success and failure groups in temporal and spectral parameters, these were minimal in case of dinoprostone [19]. Findings in the dinoprostone IOL group achieving APL revealed clear trends with sustained differences from baseline activity 60-120 minutes after the drug administration but only in NCT, duration of the contractions, A_{pp} and UAI [19, 48, 166]. This result was found to be consistent with Yount's pharmacokinetic study, which observed that plasma levels peaked between 60-120 minutes after dinoprostone administration, with a median time to sustained uterine activity of 127 minutes after administration [254]. However, comparing the success and failure groups induced with dinoprostone, Benalcazar found no significant differences [19, 48, 166], unlike Aviram who found significant evolution 2-8 hours after the administration [147], thus prompting the prolongation of the EHG recording for future assessment of this scenario. Of note, dinoprostone is currently the preferred pharmacological choice in clinical practice for IOL because of its ease of withdrawal and ability to provide a consistent dose, while misoprostol is falling out of use in our setting, see Chapter 1.2.

The standard clinical practice administer oxytocin to women who have failed to reach APL after 24h of cervical ripening to promote uterine contractility, potentially introducing a major bias into Benalcazar-Parra's research as success was considered to be achieving APL at any time after drug administration. In Chapter 4, APL>24h has been considered as IOL failure, not only to eliminate the confounding effect of exogenous

oxytocin, but also because it allows early identification and clinical intervention to reduce the risk of caesarean section, chorioamnionitis, endometriosis, postpartum haemorrhage or sepsis, foetal distress and asphyxia, to name but a few [209, 212]. New success IOL criteria (APL≤24h) and the extension of the registers up to 5 hours enabled the identification of numerous and sustained significant differences from baseline and the differentiation between GS and GF in the electrophisiological response to dinoprostone during the first hours of the IOL process, specially in case of non-linear EHG-biomarkers.

In addition, literature has traditionally reported longer durations in the first [216] and second stages of labour [216, 317] for nulliparous women, possibly as a result of their higher rate of dysfunctional uterine contractility [318, 319]. However, human myometrial biopsied strip studies have found no intrinsic differences in the functional parameters of contractions in relation to parity, except for a slightly higher frequency of onset and intensity of contraction in parous women [259]. Consistently, findings in Chapter 4 infer that parity has no relevant influence on the uterine myoelectric response to dinoprostone as IOL drug when considering APL≤24h, apart from the signal amplitude progression ratio which was found to be higher in parous women. Notably, the database does not include any large parous, which may bias the generalisability of the results.

Electrophysiological knowledge of the *in vivo* response of uterine myoelectric activity to the IOL drug without the confounding factor of exogenous oxytocin, as well as new EHG-biomarkers, could allow early detection of the risk of induction failure.

6.5 Postpartum uterine monitoring challenges and the promise of electrohysterography

Uterine contractions play a crucial role in expelling the placenta and minimizing blood loss after childbirth [16, 273]. PPH is responsible for almost 25% of the maternal deaths worldwide and a major cause of morbidity [122, 123]. Its early diagnosis and treatment are essential for maternal well-being, although its diagnosis still represents a major challenge. Since uterine atony is the main cause of PPH [273], extensive efforts have been directed toward monitoring postpartum contractions and understanding its underlying physiology through traditional IUPC [320] and TOCO [321], or even electromyographic monitors [322, 323]. The repetitive palpation of the uterine fundus is the commonest method to identify uterine atony, but its efficacy relies on the consistent presence and proficiency of caregivers. In turn, IUPC can objectively measure both frequency and intensity of contractions, but it is an invasive method with widely reported complications such as uterine perforation [145, 324] or infection [145]. In addition, postpartum measurements with IUPC are often inadequate or incomplete [320], as the catheter is often dislodged during labour and placenta delivery [320, 325]. Although considered the standard method for uterine monitoring during labour, the TOCO is generally removed immediately after delivery as the external tension of the abdominal wall decreases after delivery, thus

complicating the measurement. However, in the Japanese population the TOCO has been shown to be able to capture uterine activity up to two hours postpartum [321]. Of note, the lower mean BMI in this cohort may pose a problem for its widespread use [321, 323], due to the low technique sensitivity in presence of thick abdominal dipose tissue layer [305]. Furthermore, authors report that some of the contractile waves were not identifiable and suggest future examinations with a more accurate uterine monitoring method [321].

A major advantage of EHG over traditional methods of uterine activity monitoring is that it is less skewed by overweight nor does it require constant recalibration and repositioning [40, 151, 326]. The sensitivity of EHG has been shown to be superior compared to TOCO in women with a BMI>30 kg/m2 during the first and second stages of labour [142, 144]. Therefore, it is expected that this trend will also continue in the postpartum period and provide added value for postpartum monitoring of uterine contractions. Furthermore, it has been reported that estimation of intrauterine pressure from EHG recordings is feasible [146, 276, 277] and that EHG contains more relevant information about uterine electrophysiological conditions, being able to discern between physiological and labouring contractions [278]. Based on previous research that emphasized the need for an effective method of postpartum uterine monitoring to enhance our understanding of postpartum uterine contractions and related blood loss [321, 322], EHG provides a promising solution to objectively quantify the presence or absence of uterine activity through its simple protocol and low-cost set-up.

In Chapter 5, the feasibility of monitoring and electrophisiological characterised the fourth stage of labour or postpartum uterine activity by EHG has been established, regardless of whether the delivery was by vaginal delivery or caesarean section. EHG signals after delivery need to be interpreted differently compared to the intrapartum period, as the characteristics of uterine activity change after delivery and expulsion of the placenta [323]. Rosen's work identified a shorter duration of contractions in the third stage of labour compared to the second, but no difference in intensity [322]. Subsequent work confirmed that there is significant variation between the different phases before and after delivery, as well as poorer readability of the tracings after delivery [323]. Comparison of uterine activity after vaginal versus caesarean delivery, discussed in Chapter 5, lies in its possible relationship to uterine atony and the resulting potential PPH. Given the greater blood loss in women with elective caesarean delivery compared to vaginal deliveries [327] and the fact that postpartum uterine activity is a key natural mechanism preventing PPH [273, 328, 329], the work was focused in finding the possible differences in recorded uterine dynamics. In fact, it has been found that the contraction occurrence is highest during the pushing phase and decreases progressively up to one hour after delivery, being lower in case of PPH [323]. Significant EHG-biomarkers pointed to a stronger, less impulsive and more organised activity in the case of recodings in postpartum after vaginal delivery, possibly due to the need to coordinate uterine myoelectric activity for effective expulsion during labour. This knowledge significantly enhances comprehension pertaining to postpartum uterine dynamics, thereby fostering advancements in patient

care within the critical context of PPH, even though considerable research remains to be done in this field.

6.6 Current limitations and prospects for future research

In spite of the outstanding quality and innovative results, the research presented above is not without limitations that should be taken into account. First, inter-patient biological variability introduces a potential bias, thus expanding the sample size of the cohorts in future studies could help mitigate this effect leading to more robust and generalisable results. In case of Chapter 3, broadening the range of gestational ages under study would confirm or refute the hypothesis supported by our work about distension and its role in accelerating the processes underlying uterine contractile activity. Regarding Chapter 4, expanding the database seems crucial to enhance the reliability and generalisability of the EHG-biomarkers results and lead to the development of future robust IOL success prediction systems based on EHG-biomarkers and obstetric data, especially due to the lack of inclusion of large parous. As for Chapter 5, the inclusion of high-risk PPH pregnancies would improve understanding of the occurrence of uterine atony after delivery and allow the correlation of EHG-biomarkers with PPH indicators such as haematocrit loss after delivery to be studied.

Second, the lack of an standardised EHG recording protocol is another considerable source of uncertainty, which makes it difficult to compare results across current investigations and to build knowledge of clinical relevance [40, 330]. The proposal to use anatomical landmarks for electrode placement may help to compensate for variations in size and volume of the uterus during gestation, as discussed in section 6.1. As a result, a single generalised protocol covering all stages of pregnancy would be established, which would greatly simplify the electrode placement process and ensure greater consistency and accuracy in the acquisition of electrohysterographic data throughout gestation. Simplicity of our protocol, with a single bipolar mirrored recording with respect to the midline, has reported sufficient and high quality information to discern cases of obstetric risk during regular check-ups such as MG, GS from GF in the case of IOL and VGN from CSR in the postpartum. However, the optimal number of electrodes without disturbing the patient remains to be determined, as the simplicity of single bipolar recording does not allow for the calculation of more complex metrics focused on the estimation of conduction velocity, propagation patterns, synchronisation levels and coupling of EHG recordings at various abdominal locations [40]. A question then arises as to whether they are useful for real clinical practice and diagnosis or whether their purpose is to understand the physiological processes underlying uterine contraction and preparation for childbirth.

Third, considerable potential remains to improve the methodology by automating the detection of both contractions and physiological sections, as the current manual

process is cumbersome and expert time-consuming [40, 151]. A double-blind expert segmentation process was employed in the studies in thesis, which could potentially introduce an expert subjectivity bias and thus reduce the reproducibility of the results. Although a growing number of studies in the literature have attempted to identify the EHG segments of interest automatically [202, 203, 266, 302] reaching sensitivities as high as 96% for contraction detection [202] and 90.7% for physiological sections [266], further research is needed to ensure an acceptable performance for clinical practitioners when running these algorithms in real-time systems [40, 151]. This research is mainly focused on settings close to the APL, where contractions are highly differentiated from the basal activity [266, 302]. Next step entails the translation of this knowledge to obstetric settings where myoelectrical activity is more disorganised, such as antepartum or postpartum. Ultimately, further efforts will be necessary to ensure the applicability of automatic segmentation tools irrespective of the gestational stage at the recording time. Once achieved this goal, biases associated with manual identification will have been completely eliminated, ensuring the effectiveness and replicability of the procedure and bridging the technology gap for its widespread use.

Fourth, a vast literature exists on several maternal-foetal factors that are postulated to modulate uterine contractility. Prominent examples are the previously discussed overdistention [162, 163] and parity [216, 317]. Furthermore, the impact of the previous caesarean section scar on postpartum dynamics would be relevant to explore, as this factor could significantly influence the efficacy of uterine contractions and thus contribute to the risk of PPH in Chapter 5. Likewise, uterine contractility appears to decrease with maternal age [331, 332] and elevated BMI due to changes in the structure and function of uterine muscle tissue [333–335], refer to Appendix C for additional information. Since many of these studies have assessed the potential impact of factors on uterine activity employing only TOCO, EHG presents itself as an alternative capable of furnishing more precise and comprehensive outcomes.

Fifth, a significant gap is currently evident in exploring the relationship between standard clinical practice techniques and EHG. This gap is manifested in the limited research devoted to the comprehensive study of biochemical markers such as IL-6 or PAMG-1 and their relationship with EHG-biomarkers, as well as in the case of the acclaimed CL. In Chapter 3, the statistical power of CL (79.3%) has been surpassed by KHE (85.2% 10th percentile) and BubbEn computed at FWH (94.2% 50th percentile and 87.2% 90th percentile) in discriminating uterine activity of SG and MG during the third trimester of gestation, although they assess different approaches to uterine preparation for delivery. Reinforcing therefore that the comparison and integration of biomarkers of different nature could provide innovative and relevant information on the physiological processes underlying uterine activity and events associated with childbirth. Regarding the IOL process, future research should focus on the study of differences in uterine myoelectric response with other drugs, doses, routes of administration or induction methods commonly employed in routine clinical practice, such as MIOL, which is indicated because of its lower risk of hyperstimulation and uterine rupture in cases of previous caesarean section or MG.

Chapter 7

Conclusions

This chapter delves into the conclusions drawn and assesses whether they offer a novel contribution, aligned with the specific objectives outlined in Chapter 2.

Objective 1. To analyse the similarities and differences in uterine myoelectric activity in routine controls throughout the third trimester of women with SG and MG.

The characterisation of electrohysterographic patterns in women with SG and MG during regular third trimester check-ups in Chapter 3 constitutes the first electrophisiological exploration of uterine myoelectric activity in women with MG *in vivo*. In particular, a strong correlation between uterine overdistension and myoelectric activity has been identified in the *in vivo* system. In comparison to SG, MG showed greater impulsivity and predictability in myoelectric patterns. Recognition of excessive overdistension as a risk factor for PTB could lead to increased accuracy in discriminating between real and false TPL at an early stage.

Objective 2. To identify biomarkers in electrohysterographic recordings that allow early discrimination between successful and unsuccessful pharmacological IOL.

Uterine myoelectric response to dinoprostone as IOL drug within the first 5h after the administration has been characterised. acsGS (APL$\leq$24h) has reported sustained significant differences with respect to basal activity for NCT, MNF and SpEn, while GF (APL>24h) has not shown significant evolution. NE and SpEn appear to be promising EHG-biomarkers for predicting IOL outcome. As for parity influence a significantly higher rate of progression of IOL amplitude has been found for parous women. The extended recording time and the new criteria for the definition of GS or GF, which excludes the bias arising from the protocolised administration of oxytocin, have allowed the identification of robust and reliable EHG-biomarkers.

Objective 3. To determine differences in postpartum uterine myoelectric activity in vaginal deliveries and elective caesarean sections for the early detection of PPH.

As the first comprehensive analysis of EHG-biomarkers in the postpartum period, Chapter 5 highlights the ability of EHG to detect the subtle postpartum uterine activity characteristics through a non-invasive manner. Results have shown that vaginal deliveries exhibit more intense contractions, greater cellular excitability, impulsivity and organisation. These findings suggest a promising role for EHG in detecting uterine atony for the prevention of PPH, offering a valuable tool for monitoring uterine activity and anticipating possible complications in the immediate postpartum period.

Therefore, the present thesis has significantly contributed to the identification of EHG-biomarkers, which not only broaden the understanding of the electrophysiological knowledge underlying myoelectrical activity, but also establish the foundation to assist healthcare professionals in decision-making across multiple obstetric high-risk scenarios.

Chapter 8

Related publications

This section include those publications related to the content of the thesis addressing specific aspects, complementary data or related research that enhance the understanding of the research field. Use this section as an additional resource for those interested in further research and contributions.

8.1 Comparative Study of Uterine Myoelectrical Response to Labour Induction Drugs in Nulliparous and Parous Women with Different EHG Analysis Techniques

Complete reference

Díaz-Martínez, A., Monfort-Ortiz, R., Ye-Lin, Y., Garcia-Casado, J., Nieto-del-Amor, F., Diago-Almela, V.J., Rey-Ferreira, I., Nieto-Tous, M., Prats-Boluda, G. Comparative Study of Uterine Myoelectrical Response to Labour Induction Drugs in Nulliparous and Parous Women with Different EHG Analysis Techniques. IEEE 2021 - 9th Edition, International Conference on e-Health and Bioengineering. Lassi, Rumania, November 2021.

Abstract

Induction of labour (IOL) is one of the most widespread practices to promote the onset of labour when maternal-fetal well-being is compromised. Currently, the monitoring of this procedure in clinical practice is performed with subjective and poorly reproducible techniques such as tocography and cervical assessment, without taking into account other obstetric variables of special relevance as parity. Electrohysterography (EHG) has emerged as a promising alternative due to its usefulness and non-invasiveness. Traditionally, EHG has been characterized by analyzing the EHG-bursts (EBA) associated with uterine contractions and computing temporal, spectral and nonlinear parameters. Recent studies characterize the EHG by considering both EHG-burst and basal activity (WEWA). The first objective of this study was to discern which analysis technique presented the best performance for EHG characterization during IOL. Subsequently, differences in uterine myoelectric response to IOL drugs in nulliparous and parous women were analyzed and compared. EHG recordings were performed during the first 4 hours of IOL in 15 nulliparous and 10 parous women. EBA results showed a greater number of parameters with significant differences with their corresponding baseline ones than WEWA, as well as a greater slope in both parity groups. Parous women presented greater amplitude and more pronounced downward trends for nonlinear parameters than nulliparous, especially for Sample and Spectral Entropy, which is associated with a greater predisposition to achieve Active Period of Labour that is corroborated by obstetric variables. Moreover, future efforts seem necessary to study in depth the differences between parity groups in order to correctly characterize and interpret their evolution.

Keywords

Induction of labour; EHG-Burst analysis; Whole-EHG Window analysis; Nulliparous; Parous.

Introduction

Induction of labour (IOL) is certainly one of the most frequently performed obstetric procedures in the world. It is carried out in an ever-increasing number of cases due to the obstetric populations changes, such as increased maternal age or weight, and their management, as with the inclusion of analgesia [204]. A recent study suggests that IOL occurs in 42.9% of nulliparous women and 31.8% of parous women. In addition, the highest prevalence occurs at 41 weeks of pregnancy (63.4% in nulliparous and 50.1% in parous) [47].

It is generally accepted that IOL is indicated when outcome for the fetus, the mother or both are expected to be better than waiting for the spontaneous start of labour; but also to prevent certain outcomes such as cesarean section, prolonged labour, postpartum haemorrhage or traumatic birth [47]. During this procedure, vaginal delivery is intended to occur by stimulating uterine contractions before the spontaneous onset of labour. To facilitate this, pharmacological agents such as Dinoprostone, which softens and thins the cervix, are often used. The problem is that the procedure can take 24-48 hours and its success is not guaranteed, so the delivery may end with a cesarean section [166, 207]. A reliable technique to predict its success would be essential to minimize long waits, maternal-fetal exhaustion and suffering, as well as medical costs.

In clinical practice, the standard methods used to predict the success of IOL is the Bishop Score Index and monitor uterine dynamics by tocography. However, these measures are subjective and, especially Bishop Score has low reproducibility [142]. Furthermore, nowadays, there seems to be a general agreement among experts that parity is an important factor to be considered [135]. Vaharatian et al. found nulliparous women to be: more likely to have a slower times in both first (dilatation) and second stage of labour (birth), to deliver at a higher gestational age and to require more probably oxytocin [336].

Efforts have been made to address the IOL success predictive problem from other perspectives, such as the use of electrohysterographic techniques in conjunction with machine learning models [293]. Electrohysterography (EHG) is a non-invasive technique and has been shown to offer certain advantages to monitor uterine dynamics over traditional tocodynamometry, such as no need for repositioning and being less affected by obesity [142]. EHG records contain basal tone, associated with the resting state of the uterus, and EHG-bursts. The latter are composed by two components: a Slow Wave [0.014-0.033 Hz] and a Fast Wave, comprising the latter: the Fast Wave Low, associated with EHG propagation [0.13-0.26 Hz]; and the Fast Wave High (FWH), related to uterine cell excitability [0.36-1Hz] [19]. The EHG analysis is usually focused on the FWH to minimize respiratory and cardiac interferences [19]. Although only EHG-Burst Analysis (EBA) has been evaluated in the setting of IOL, other methods are beginning to prevail, such as Whole-EHG Window Analysis (WEWA) due to its simplification of the segmentation process and its ability to include subtle contractions [152]. In the setting

of threatened preterm labour WEWA has demonstrated superiority in predicting the outcome [152].

Therefore, the first objective of the present work was to discern which analysis technique, EBA or WEWA, allows a better characterization of the uterine myoelectric response during the first hours of IOL with Dinoprostone from EHG recordings. As a second objective, these EHG recordings were characterized and analyzed according to parity in search of possible differences.

Database and methods

EHG Database

This study included 25 EHG records performed at the Hospital Universitari i Politècnic La Fe (Valencia, Spain) in singleton pregnancies (>40 weeks) that achieved active period of labour in less than 24 hours and whose indication for IOL was prolongation of pregnancy. There were 15 nulliparous women and 10 that had had at least one previous delivery. Risk of loss of maternal-fetal well-being cases were excluded. EHG Recordings comprised 30 minutes of basal activity (before the drug administration) followed by 4 hours after Dinoprostone administration. This study adhered to the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of the hospital (register number 2018/0530). Patients were informed about the nature of the study and gave their written informed consent. The recordings were conducted and the signals were conditioned as described in [19, 337], resulting in a bipolar signal filtered in the range 0.1-4 Hz with a sampling frequency of 20 Hz.

Table 8.1 shows the obstetric data collected for both groups: maternal age, body mass index, parity, pre-IOL and post-IOL Bishop Score, time to achieve active period of labour (APL) since drug administration and time to birth since APL.

Table 8.1: Obstetric data and outcomes of labour induction of women enrolled in the study, mean ± standard deviation or number of cases. BS: Bishop score. (*): significant p-value, lower than 0.05.

Variable		**Nulliparous** *n=15*	**Parous** *n=10*	**P-Value**
Maternal age (years)	$\mu \pm \sigma$	33.4±5.0	35.5±3.3	0.240
BMI (kg/m2)	$\mu \pm \sigma$	25.9±8.8	25.0±4.0	0.509
Parity	$\mu \pm \sigma$	0.0±0.0	1.3±0.5	<0.001*
Pre-IOL BS	$\mu \pm \sigma$	3.8±1.8	3.8±1.8	0.968
Post-IOL BS	$\mu \pm \sigma$	6.4±2.9	9.4±2.3	0.036*
Time admin-APL (h)	$\mu \pm \sigma$	14.7±6.7	9.8±6.4	0.065
Time APL-birth (h)	$\mu \pm \sigma$	5.9±5.1	1.0±0.9	0.003*

Signal characterization

An expert segmentation of the records was performed for WEWA and EBA. In the case of the former, segments with a significant abrupt increase in amplitude compared to baseline or contractile activity, not associated with a physiological event, as well as respiratory interference associated with the appearance of periodic components (0.2-0.4Hz) were discarded [190]. In the case of the latter, each EHG-burst was related to substantial amplitude and frequency changes concerning the basal tone with durations superior than 40 seconds, and without respiratory interference or motion artifacts [152].

As for EBA, a set of temporal, spectral and non-linear parameter was calculated for each uterine contraction. Specifically it included: Root Mean Square (RMS) [152], Mean Frequency (MNF) [152], Binary Lempel-Ziv Complexity (BLZ) [19], Sample Entropy [19], Fuzzy Entropy [230], Spectral Entropy [230] and Higuchi Fractal Dimension (HFD) [230]. All parameters were calculated in the FWH, except for MNF which was calculated at 0.2-1 Hz to minimize the influence of cardiac interference and baseline fluctuation as in previous EHG works [278]. According to the literature, as the time of delivery approaches, myoelectric activity tends to become more organized while undergoing a shift of spectral content toward higher frequencies [19], resulting in contractions of greater amplitude but shorter duration [19]. Therefore, RMS and MNF are expected to show an upward trend throughout IOL process; while the non-linear parameters are expected to do the opposite [4, 19]. For WEWA, the same parameters were calculated in 120 seconds moving windows with 50% overlap, a combination that had previously been shown to be able to analyze representative sections of the EHG signal with reasonable computational cost [152]. For both EBA and WEWA, the median value for each 30-minute time interval was calculated to obtain a single representative value of each EHG parameter per time interval in each recording session.

Statistical analysis

Wilcoxon rank sum test (α=0.05) was performed to determine whether there were significant changes in EHG parameters in the first 4 hours of IOL or not. For this purpose, parameters associated with the EBA and the WEWA obtained every 30 minutes after drug administration were compared with baseline ones. A comparison at each temporal 30-minute frame between EBA and EBA parameters was also worked out. The same procedure was performed to assess possible differences between nulliparous and parous groups. Differences between obstetric variables for both groups were tested using the same test (Table 8.1).

Results

Regarding obstetric data, for the parous group, significantly higher values were obtained for Post-IOL Bishop Score and lower for time to delivery, which is in agreement with the literature [336]. Although the initial status was comparable, as they had a similar Pre-IOL Bishop Score (3.75±1.83 vs. 3.83±1.80), it appears that the muscle fibers of

parous may respond to the drug differently, as they end up reaching APL significantly faster (9.83±6.43 vs. 14.71±6.72).

As for EHG, initially, a comparison between EBA and WEWA was carried out. Figure 8.1 shows the trends of the parameters for both EBA and WEWA corresponding to the nulliparous group, as well as the statistical analysis results. Regarding RMS, EBA shows a greater slope than WEWA and reaches higher values, as expected, because WEWA includes basal activity. RMS changes with respect to baseline are not statistically significant and the differences found between groups are not maintained [19]. With respect to MNF, both methods show a monotonic upward trend during the IOL process. Statistically significant differences were found in MNF between baseline and signals at 180 and 240 in both EBA and WEWA, in contrast to other similar studies where women were not segregated by parity and none was found [19]. For both WEWA and EBA, nonlinear parameters tend to decrease as IOL progresses (see Figure 8.1), suggesting that electrical activity becomes more regular and less complex as delivery approaches, in accordance with the literature [4]. However, in general, for WEWA the values are higher and the slopes are less negative than in EBA, especially in Spectral Entropy. Sample and Fuzzy Entropy showed statistically significant differences against baseline at 180 and 240 time intervals. Spectral Entropy presented statistically significant differences between methods at almost all time intervals except at 180, perhaps a larger sample would attenuate biological variability effect reducing the dispersion. The higher slopes found in EBA together with the higher number of statistically significant differences seem to indicate a higher information content on the electrophysiological evolution of the uterus.

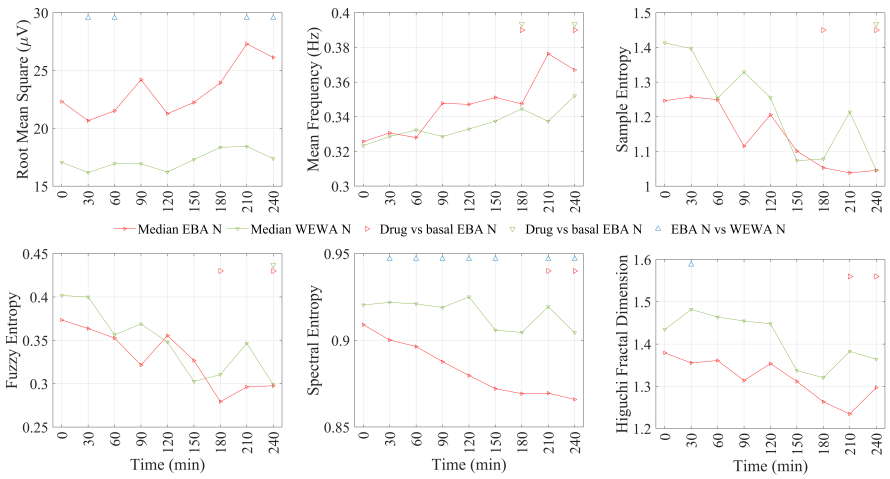

Figure 8.1: Temporal median values parameters evolution for the nulliparous group in 30-minute segments representation for both EBA and WEWA. Basal activity is plotted at time zero. Statistical differences ($\alpha<0.05$) between methods are indicated by blue triangles. Similarly, statistical differences ($\alpha<0.05$) with respect to basal activity correspond to red (EBA) and green (WEWA) triangles.

Secondly, a comparison of the response of uterine activity to Dinoprostone between nulliparous and parous pregnant women during IOL was performed for the first time in this obstetric context. Results of EBA and WEWA for both parity groups are quite similar, so only the comparison using EBA has been presented in Figure 8.2. The parous group exhibits greater RMS values throughout the record with differences from baseline at 150 and 210. The MNF is slightly higher at the beginning for the parous group, but without differences between groups. Benalcazar et al. [19] did not find them either. By contrast, the lower values of the nonlinearity parameters as well as their higher slope, especially in the Sample Entropy, seem to indicate a higher degree of signal ordering and a greater predisposition to achieve APL in parous women. This effect may be due to increased cell connectivity generated in the previous birth or to the massive exposure to endogenous prostaglandins that the previous birth entailed. However, no significant differences were obtained between the evolutions of the characteristics of uterine myoelectric activity between groups in any of the analysis sections. Increasing the database would allow to more robustly confirm the existence of differences in the uterine myoelectric response to Dinoprostone labour induction drug, between nulliparous and parous groups, promoting the development of group-specific IOL success prediction systems.

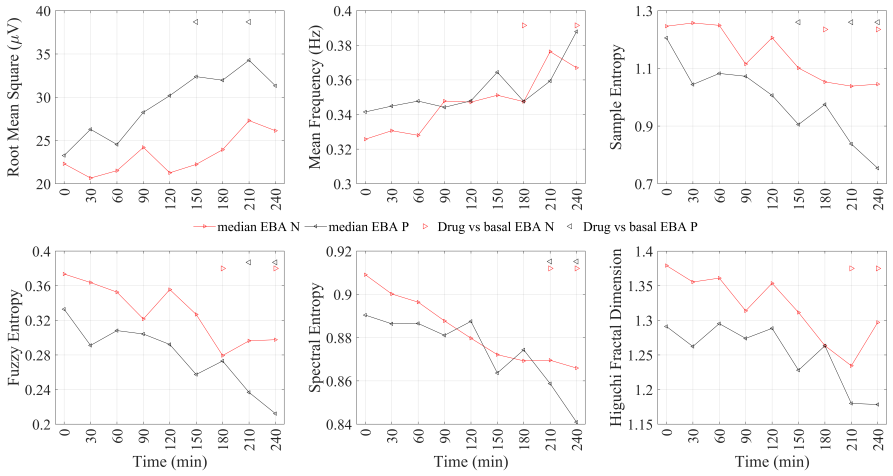

Figure 8.2: Temporal median values parameters evolution for EBA in 30-minute segments representation for both nulliparous (N) and parous (P) groups. Basal activity is plotted at time zero. Statistical differences (α<0.05) with respect to basal activity correspond to red (N) and black (P) triangles.

Conclusions

The EBA seems to provide more information on the evolution of the IOL process in both nulliparous and parous women than WEWA EHG analysis. In addition,

segregation by parity has allowed us to find differences in uterine myoelectric response to Dinoprostone induction drug: higher amplitude and steeper descending slopes for nonlinear parameters, especially for Sample and Spectral Entropy from minute 180 onwards were found, indicating a greater predisposition to achieve APL by parous women, which are corroborated by obstetric variables. Therefore, the differences found are considered relevant to be taken into account in future work related to both characterization and prediction of IOL success.

Acknowledgements The collaboration of the HUP La Fe has been fundamental for the development of this work. In addition, the Ministry of Economy and Competitiveness, the European Regional Development Fund (MCIU/AEI/FEDER, EU RTI2018-094449-A-I00-AR) and the Generalitat Valenciana (AICO/2019/220) have supported it.

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

Complete reference
Diaz-Martinez, A., Ye-Lin, Y., Monfort-Ortiz, R., Garcia-Casado, J., Rey-Ferreira, I.,Nieto-Del-Amor, F., Diago-Almela, V., Luis Martinez-De-Juan, J., & Prats-Boluda, G. (2023). Comparison of the Electrophysiological Myoelectrical Activity Evolution in Induction of Labor with Pharmacological and Mechanical Methods. BIOSIGNALS 2023 - 16th International Conference on Bio-Inspired Systems and Signal Processing, 66-73.

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 labour 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.

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

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 [338]. Indications for IOL include elective induction at 40 weeks, prolonged pregnancy, pregnancy-induced hypertension or diabetes, oligohydramnios, intrauterine growth restriction and Rh isoimmunisation [338, 339].

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 [340], while the worldwide prevalence is estimated by the WHO at 25% [46]. 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 [32, 57]. 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 [57]. 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 [213]. 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 [214]. 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) [339]. 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 [71, 338]. 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. 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 [72, 214]. 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 [341].

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 [144, 214]. Despite being widely employed, BS has been shown to be subjective and has poor reproducibility, making it a poor predictor of IOL outcome [135]. 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 [151, 154, 202], especially in the growing population of obese patients [154, 205]. 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 [9]. 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 [190]- and by the fast wave (FW), which can be further divided into two components [9, 148]: 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 [19, 154]. Although the frequency content of FWH is thought to extend up to 3-4 Hz [150], a high proportion of studies focus down to 1Hz perhaps as a consequence of maternal cardiac interference (1.38-1.5 Hz) [151].

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.

Materials and methods

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 labour 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.

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 8.3. 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.

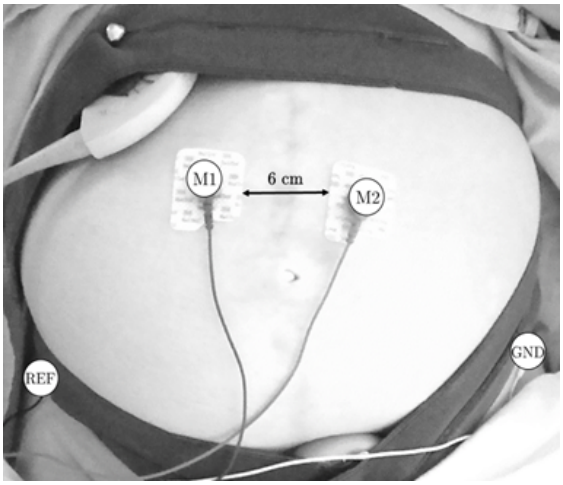

Figure 8.3: Electrodes positioning for uterine myoelectrical recording. M1: monopolar electrode 1. M2: monopolar electrode 2. REF: Reference electrode. GND: Ground electrode.

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 [242]. 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 [203, 342], 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 labour [19].

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 [154, 243]. A bipolar signal was then computed as its difference (M2-M1) to reduce common-mode interference and increase signal quality [151, 154]. 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 [151, 154, 243].

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 [154, 243]. As labour progresses, contractions are more frequent and of greater intensity, which is equivalent to a higher signal amplitude [151, 243]. 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 [154, 222] to minimise the influence of cardiac interference and baseline fluctuation [151]. Successful IOL is associated with an increase in MNF [243]. Finally, Spectral Entropy (SpEn) [151, 243] and Higuchi Fractal Dimension (HFD) [243, 246] were computed as non-linearity parameters. It was done in the FWH bandwidth to provide a robust characterisation of the EHG [151, 154]. 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 [19, 243].

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) [19, 243]. 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.

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 8.2. 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 8.2: 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-value**
Maternal age (years)	$\mu \pm \sigma$	32.2±5.5	34.0±5.6	0.241
BMI (kg/m2)	$\mu \pm \sigma$	24.6±4.2	26.05±7.5	0.124
Gestations	$\mu \pm \sigma$	2.1±0.7	2.0±1.4	0.212
Parity	$\mu \pm \sigma$	0.1±0.4	0.6±0.7	**0.009**
GAD (weeks)	$\mu \pm \sigma$	39.4±1.5	40.7±0.5	**<0.005**
Initial BS	$\mu \pm \sigma$	3.1±1.2	2.6±2.6	0.427
ΔBS	$\mu \pm \sigma$	2.1±1.8	3.3±4.6	0.967
Time to APL (h)	$\mu \pm \sigma$	25.9±6.9	16.4±9.1	**<0.005**
Time to Del. (h)	$\mu \pm \sigma$	29.2±6.0	20.8±12.1	**<0.005**
Vaginal ending	N	19/21	46/52	0.806

The uterine myoelectric activity parameters in response to the IOL is represented in Figure 8.4 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.

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.

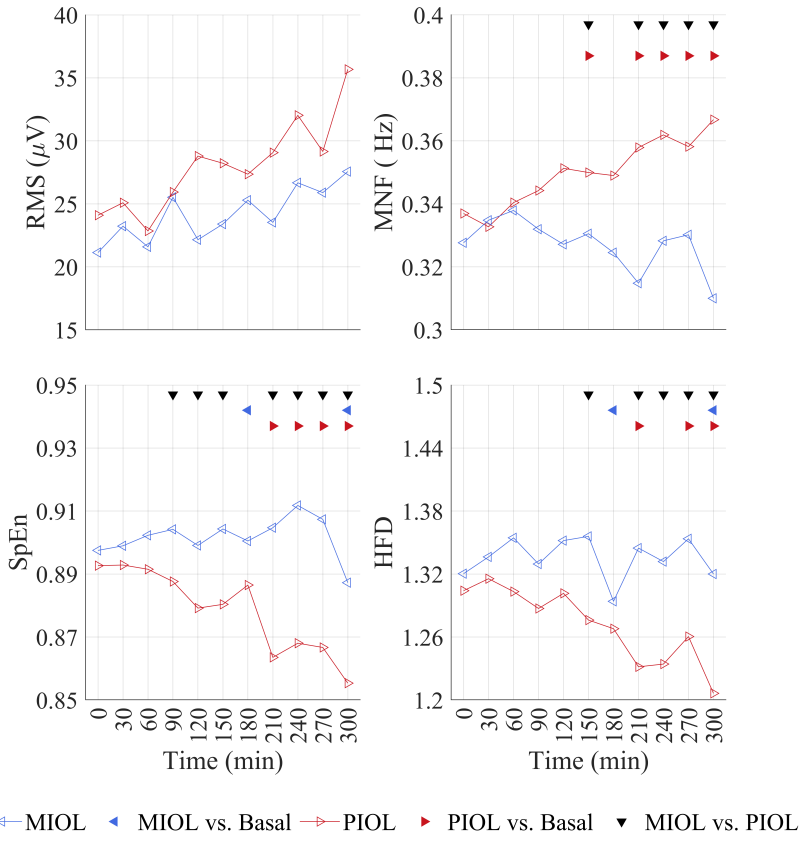

Figure 8.4: Temporal evolution of temporal, spectral and non-linear parameters for mechanical (MIOL) and Pharmacological Induction of Labour (PIOL) groups. Statistical differences between groups are indicated by black downward-pointing triangles and with respect to basal activity by blue leftward (MIOL) and red rightward (PIOL) triangles.

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 [343]. 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 [243]. 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 [344].

Finally, the time from the induction onset to the active period of labour was significantly shorter for PIOL. Our results are consistent with Wang's meta-analysis [345] 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 [346], we found no significant changes between induction methods.

Of note, while the uterine electrophysiological response to PIOL has been researched previously [19, 243], 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 [338, 345], 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 [347]. In addition, Pennell [346] 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.

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).

Awards This work has been awarded the Best Student Paper Award Certificate in the 16th International Conference on Bio-inspired Systems and Signal Processing (BIOSIGNALS/BIOSTEC).

Chapter 9

Bibliographic references

[1] F. G. Cunningham, K. J. Leveno, J. S. Dashe, B. L. Hoffman, C. Y. Spong, and B. M. Casey, *Williams obstetrics*, 26th Editi, F. G. Cunningham, Ed. Mc Graw Hill, 2022, ISBN: 978-1-26-046274-6.

[2] M. Triola and J. Qualter, *BioDigital*, 2012. [Online]. Available: https://www.biodigital.com/ (visited on 01/15/2024).

[3] Anatomy Team UK, *Cervix: Anatomy, Parts, Diagram, Images, Function, Structure*, 2018. [Online]. Available: https://anatomy.co.uk/cervix/{\#}:{~}:text=Thecervixisdividedintotwosections{\%}3AThe,CervixâĂŞItslocationinthehumanbody. (visited on 10/05/2023).

[4] J. Alberola-Rubio, "Estudio electrofisiológico del útero humano durante el embarazo a partir de registros no invasivos de electrohisterograma", PhD thesis, 2016.

[5] J. E. Hall and M. E. Hall, *Guyton and Hall. Textbook of Medical Physiology*, 14th Editi. Elyse O'Grady, 2021, ISBN: 978-0-323-59712-8.

[6] S. Arrowsmith, A. Kendrick, J.-A. Hanley, K. Noble, and S. Wray, "Myometrial physiology - time to translate?", *Exp. Physiol.*, vol. 99, no. 3, pp. 495–502, 2014, ISSN: 09580670. DOI: 10.1113/expphysiol.2013.076216.

[7] R. E. Garfield and W. L. Maner, "Physiology and electrical activity of uterine contractions", *Semin. Cell Dev. Biol.*, vol. 18, no. 3, pp. 289–295, 2007, ISSN: 1084-9521. DOI: 10.1016/j.semcdb.2007.05.004.

[8] R. C. Young, "The uterine pacemaker of labor", *Best Pract. Res. Clin. Obstet. Gynaecol.*, vol. 52, pp. 68–87, 2018, ISSN: 15216934. DOI: 10.1016/j.bpobgyn.2018.04.002.

[9] D. Devedeux, C. Marque, S. Mansour, G. Germain, and J. Duchêne, "Uterine electromyography: A critical review", *Am. J. Obstet. Gynecol.*, vol. 169, no. 6, pp. 1636–1653, 1993, ISSN: 00029378. DOI: 10.1016/0002-9378(93)90456-S.

[10] R. E. Garfield, M. G. Blennerhassett, and S. M. Miller, "Control of myometrial contractility: role and regulation of gap junctions.", *Oxf. Rev. Reprod. Biol.*, vol. 10, pp. 436–90, 1988, ISSN: 0260-0854. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/3072507.

[11] M. Giuffrè, E. Piro, and G. Corsello, "Prematurity and twinning", *J. Matern. Neonatal Med.*, vol. 25, no. sup3, pp. 6–10, 2012, ISSN: 1476-7058. DOI: 10.3109/14767058.2012.712350.

[12] J. Ferguson, " A Study of the Motility of the Intact Uterus at Term. Surgery Gynecology, and Obstetrics", *Surg. Gynecol. Obstet.*, vol. 73, pp. 359–366, 1941.

[13] H ALVAREZ and R CALDEYRO, "Contractility of the human uterus recorded by new methods.", *Surg. Gynecol. Obstet.*, vol. 91, no. 1, pp. 1–13, 1950, ISSN: 0039-6087. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/15442821.

[14] W. F. Roberts, K. G. Perry, R. W. Naef, J. F. Washburne, and J. C. Morrison, "The irritable uterus: A risk factor for preterm birth?", *Am. J. Obstet. Gynecol.*, vol. 172, no. 1, pp. 138–142, 1995, ISSN: 00029378. DOI: 10.1016/0002-9378(95)90102-7.

[15] S. Russo, A. Batista, F. Esgalhado, C. R. Palma Dos Reis, F. Serrano, V. Vassilenko, and M. Ortigueira, "Alvarez waves in pregnancy: a comprehensive review", *Biophys. Rev.*, vol. 13, pp. 563–574, 2021. DOI: 10.1007/s12551-021-00818-5/Published.

[16] F. G. Cunningham, K. J. Leveno, S. J. Bloom, C. Y. Spong, J. S. Dashe, B. L. Hoffman, B. M. Casey, and J. S. Sheffield, *Williams Obstetrics*, 24th Editi. New York, NY, USA: McGraw-Hill, 2015, ISBN: 978-0-07-179894-5.

[17] C. Marque, J. Gondry, J. Rossi, N. Baaklini, and J. Duchêne, "Surveillance des grossesses à risque par électromyographie utérine", *RBM-Revue Eur. Technol. Biomed.*, vol. 17, no. 1, pp. 25–31, 1995, ISSN: 02220776. DOI: 10.1016/S0222-0776(00)88906-3.

[18] M. Chendeb, M. Khalil, D. Hewson, and J. Duchên, "Classification of non stationary signals using multiscale decomposition", *J. Biomed. Sci. Eng.*, vol. 03, no. 02, pp. 193–199, 2010, ISSN: 1937-6871. DOI: 10.4236/jbise.2010.32025.

[19] C. Benalcazar-Parra, Y. Ye-Lin, J. Garcia-Casado, R. Monfort-Orti, J. Alberola-Rubio, A. Perales, and G. Prats-Boluda, "Electrohysterographic characterization of the uterine myoelectrical response to labor induction drugs", *Med. Eng. Phys.*, vol. 56, pp. 27–35, 2018. DOI: 10.1016/j.medengphy.2018.04.002.

[20] R. Caldeyro-Barcia and J. Poseiro, "Physiology of uterine contraction", *Clin. Obstet. Gynecol.*, vol. 3, no. 2, pp. 386–410, 1960. [Online]. Available: https://journals.lww.com/clinicalobgyn/citation/1960/06000/physiology{_}of{_}the{_}uterine{_}contraction.11.aspx.

[21] World Health Organization, "ICD-11 for Mortality and Morbidity Statistics", Tech. Rep., 2022, pp. 1187–1194. [Online]. Available: https://icd.who.int/browse11/l-m/en{\#}/http{\%}3A{\%}2F{\%}2Fid.who.int{\%}2Ficd{\%}2Fentity{\%}2F1992303076.

[22] E. B. da Fonseca, R. Damião, and D. A. Moreira, "Preterm birth prevention", *Best Pract. Res. Clin. Obstet. Gynaecol.*, vol. 69, pp. 40–49, 2020, ISSN: 1521-6934. DOI: 10.1016/J.BPOBGYN.2020.09.003.

[23] S. Chawanpaiboon, J. P. Vogel, A. B. Moller, P. Lumbiganon, M. Petzold, D. Hogan, S. Landoulsi, N. Jampathong, K. Kongwattanakul, M. Laopaiboon, C. Lewis, S. Rattanakanokchai, D. N. Teng, J. Thinkhamrop, K. Watananirun, J. Zhang, W. Zhou, and A. M. Gülmezoglu, "Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis", *Lancet Glob. Heal.*, vol. 7, no. 1, e37–e46, 2019, ISSN: 2214109X. DOI: 10.1016/S2214-109X(18)30451-0.

[24] J. Perin, A. Mulick, D. Yeung, F. Villavicencio, G. Lopez, K. L. Strong, D. Prieto-Merino, S. Cousens, R. E. Black, and L. Liu, "Global, regional, and national causes of under-5 mortality in 2000–19: an updated systematic analysis with implications for the Sustainable Development Goals", *Lancet Child Adolesc. Heal.*, vol. 6, no. 2, pp. 106–115, 2022, ISSN: 23524642. DOI: 10.1016/S2352-4642(21)00311-4.

[25] J. Jacob, M. Lehne, A. Mischker, N. Klinger, C. Zickermann, and J. Walker, "Cost effects of preterm birth: a comparison of health care costs associated with early preterm, late preterm, and full-term birth in the first 3 years after birth", *Eur. J. Heal. Econ.*, vol. 18, pp. 1041–1046, 2017. DOI: 10.1007/s10198-016-0850-x.

[26] Z. A. Oskovi Kaplan and A. S. Ozgu-Erdinc, "Prediction of Preterm Birth: Maternal Characteristics, Ultrasound Markers, and Biomarkers: An Updated Overview", *J. Pregnancy*, vol. 2018, pp. 1–9, 2018, ISSN: 20902735. DOI: 10.1155/2018/8367571.

[27] A. L. Areia and A. Mota-Pinto, "Inflammation and Preterm Birth: A Systematic Review", *Reprod. Med. 2022, Vol. 3, Pages 101-111*, vol. 3, no. 2, pp. 101–111, 2022, ISSN: 2673-3897. DOI: 10.3390/REPRODMED3020009.

[28] N. K. Lowe, "A Review of Factors Associated With Dystocia and Cesarean Section in Nulliparous Women", *J. Midwifery Women's Heal.*, vol. 52, no. 3, pp. 216–228, 2007, ISSN: 15269523. DOI: 10.1016/j.jmwh.2007.03.003.

[29] E. Amabebe and D. O. Anumba, "Psychosocial stress, cortisol levels, and maintenance of vaginal health", *Front. Endocrinol. (Lausanne).*, vol. 9, no. SEP, p. 403 253, 2018, ISSN: 16642392. DOI: 10.3389/FENDO.2018.00568/BIBTEX.

[30] R. C. Johnson and P. Slade, "Obstetric complications and anxiety during pregnancy: is there a relationship?", *J. Psychosom. Obstet. Gynecol.*, vol. 24, no. 1, pp. 1–14, 2003, ISSN: 0167-482X. DOI: 10.3109/01674820309042796.

[31] B. E. Hamilton, J. A. Martin, M. J. K. Osterman, A. K. Driscoll, and L. M. Rossen, "Births: Provisional Data for 2016", *Vital Stat. Rapid Release*, vol. 2, pp. 1–21, 2017. [Online]. Available: https://www.cdc.gov/nchs/data/vsrr/report002.pdf.

[32] B. E. Hamilton, J. A. Martin, and M. J. K. Osterman, "Births: Provisional Data for 2021", *Vital Stat. Rapid Release*, vol. 20, pp. 1–11, 2022. [Online]. Available: https://www.cdc.gov/nchs/products/index.htm..

[33] D. o. E. United Nations and S. A. P. Division, "World Population Prospects 2022, Online Edition", Tech. Rep., 2022. [Online]. Available: https://population.un.org/wpp/Download/Standard/MostUsed/.

[34] E. Attali and Y. Yogev, "The impact of advanced maternal age on pregnancy outcome", *Best Pract. Res. Clin. Obstet. Gynaecol.*, vol. 70, pp. 2–9, 2021, ISSN: 1521-6934. DOI: 10.1016/J.BPOBGYN.2020.06.006.

[35] M. V. Sauer, "Reproduction at an advanced maternal age and maternal health", *Fertil. Steril.*, vol. 103, no. 5, pp. 1136–1143, 2015, ISSN: 15565653. DOI: 10.1016/j.fertnstert.2015.03.004.

[36] G. M. Chambers and W. Ledger, "Economic implications of multiple pregnancy following assisted reproductive technologies", *Semin. fetal neonatal Med.*, vol. 19, no. 4, pp. 254–261, 2014, ISSN: 1878-0946. DOI: 10.1016/J.SINY.2014.04.004.

[37] M. J. K. Osterman, B. E. Hamilton, J. A. Martin, A. K. Driscoll, and C. P. Valenzuela, "Births: Final Data for 2020", *Natl. Vital Stat. Reports*, vol. 70, no. 17, pp. 1–50, 2022. [Online]. Available: https://www.cdc.gov/nchs/products/index.htm..

[38] S. F. Bakhodirova, G. A. Ikhtiyarova, and S. S. Davlatov, "Features of perinatal outcomes in women after supporting reproductive technologies", *Eur. J. Mol. Clin. Med.*, vol. 7, no. 2, pp. 6350–6356, 2020, ISSN: 2515-8260.

[39] P Pallavee, A. Vishalakshi, and ·. A. Vishalakshi, *Prolonged Pregnancy*. Singapore: Springer, Singapore, 2023, pp. 373–385, ISBN: 10.1007/9789811. DOI: 10.1007/978-981-19-6145-8_27.

[40] J. García-Casado, Y. Ye-Lin, G. Prats-Boluda, J. Mas-Cabo, J. Alberola-Rubio, and A. Perales, "Electrohysterography in the diagnosis of preterm birth: a review", *Physiol. Meas.*, vol. 39, no. 2, pp. 1–23, 2018. DOI: 10.1088/1361-6579/aaad56.

[41] A López Bernal, J Rivera, G. N. Europe-Finner, S Phaneuf, and G Asbóth, "Parturition: activation of stimulatory pathways or loss of uterine quiescence?", *Adv. Exp. Med. Biol.*, vol. 395, pp. 435–51, 1995, ISSN: 0065-2598. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/8713997.

[42] American College of Obstetricians and Gynecologists, "Definition of Term Pregnancy", *Am. Coll. Obstet. Gynecol. Com. Obstet. Pract. Soc. Matern. Med.*, vol. 579, pp. 1–2, 2017. [Online]. Available: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2013/11/definition-of-term-pregnancy.

[43] P. Middleton, E. Shepherd, J. Morris, C. A. Crowther, and J. C. Gomersall, "Induction of labour at or beyond 37 weeks' gestation", *Cochrane database Syst. Rev.*, vol. 7, no. 7, 2020, ISSN: 1469-493X. DOI: 10.1002/14651858.CD004945.PUB5.

[44] N. Razaz, G. M. Muraca, K. Fink, A. Boutin, S. John, S. Lisonkova, O. Stephansson, S. Cnattingius, and K. S. Joseph, "Time of delivery among low-risk women at 37-42 weeks of gestation and risks of stillbirth and infant mortality, and long-term neurological morbidity", *Paediatr. Perinat. Epidemiol.*, vol. 36, no. 4, pp. 577–587, 2022, ISSN: 1365-3016. DOI: 10.1111/PPE.12868.

[45] A. W. Olesen, O. Basso, and J. Olsen, "Risk of recurrence of prolonged pregnancy", *BMJ*, vol. 326, no. 7387, p. 476, 2003, ISSN: 1756-1833. DOI: 10.1136/BMJ.326.7387.476.

[46] World Health Organization, "WHO recommendations: Induction of labour at or beyond term", Geneva, Tech. Rep., 2018, pp. 1–43. [Online]. Available: https://apps.who.int/iris/bitstream/handle/10665/277233/9789241550413-eng.pdf.

[47] P. Middleton, E. Shepherd, and C. A. Crowther, "Induction of labour for improving birth outcomes for women at or beyond term", *Cochrane Database Syst. Rev.*, vol. 5, no. 5, pp. 1–114, 2018, ISSN: 1469493X. DOI: 10.1002/14651858.CD004945.pub4.

[48] R. Monfort-Ortiz, "Maduración pre-inducción de parto. Comparación entre dinoprostona y misoprostol con objetivación de dinámica uterina mediante electrohisterografía: un enfoque pragmático", PhD thesis, Facultad de medicina i odontologia, Valencia, 2019, pp. 1–216.

[49] National Institute for Health and Care Excellence, "Inducing labour NICE guideline", NICE, Tech. Rep., 2021, pp. 1–41. [Online]. Available: www.nice.org.uk/guidance/ng207.

[50] C. Gyamfi-Bannerman, A. B. Gantt, and R. S. Miller, "Medically Indicated Late-Preterm and Early-Term Deliveries", *Obstet. Gynecol.*, vol. 138, no. 1, e35–e39, 2021, ISSN: 0029-7844. DOI: 10.1097/AOG.0000000000004447.

[51] A. Bruinsma, J. K. Keulen, R. van Eekelen, M. van Wely, J. C. Kortekaas, J. van Dillen, J. A. van de Post, B. W. Mol, and E. de Miranda, "Cost-effectiveness analysis of induction of labour at 41 weeks and expectant management until 42 weeks in low risk women (INDEX trial)", *Eur. J. Obstet. Gynecol. Reprod. Biol. X*, vol. 17, pp. 1–10, 2023, ISSN: 25901613. DOI: 10.1016/j.eurox.2023.100178.

[52] NHS Digital, *NHS Maternity Statistics, England - 2021-22*, 2022. [Online]. Available: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2021-22{\#} (visited on 09/25/2023).

[53] Australian Institute of Health and Welfare, "Australia's mothers and babies", Australian Institute of Health and Welfare, Tech. Rep., 2023. [Online]. Available: https://www.aihw.gov.au/getmedia/bf03fda0-6d37-46f3-8ba6-9c3ebadc26f8/Australia-s-mothers-and-babies.pdf?inline=true.

[54] National board of Health and Welfare, "Statistics on Pregnancies, Deliveries and Newborn Infants 2020", National board of Health and Welfare, Tech. Rep., 2021, pp. 1–4. [Online]. Available: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2021-12-7653.pdf.

[55] Ministerio de Sanidad, "Atención perinatal en España. Análisis de los recursos físicos, humanos, actividad y calidad de los servicios hospitalarios, 2010-2018", Misiterio de sanidad, Tech. Rep., 2021. [Online]. Available:

https://www.sanidad.gob.es/estadEstudios/estadisticas/docs/Informe{_}Atencion{_}Perinatal{_}2010-2018.pdf.

[56] "ACOG Practice Bulletin No. 106: Intrapartum Fetal Heart Rate Monitoring: Nomenclature, Interpretation, and General Management Principles", *Obstet. Gynecol.*, vol. 114, no. 1, pp. 192–202, 2009, ISSN: 0029-7844. DOI: 10.1097/AOG.0b013e3181aef106.

[57] N. K. Ayala and D. J. Rouse, "Failed induction of labor", *Am. J. Obstet. Gynecol.*, pp. 1–6, 2022, ISSN: 0002-9378. DOI: 10.1016/J.AJOG.2021.06.103.

[58] C. Y. Spong, V. Berghella, K. D. Wenstrom, B. M. Mercer, and G. R. Saade, "Preventing the first cesarean delivery: summary of a joint Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, and American College of Obstetricians and Gynecologists Workshop", *Obstet. Gynecol.*, vol. 120, no. 5, pp. 1181–1193, 2012, ISSN: 1873-233X. DOI: 10.1097/AOG.0B013E3182704880.

[59] D. J. Rouse, J. Owen, and J. C. Hauth, "Criteria for failed labor induction: prospective evaluation of a standardized protocol", *Obstet. Gynecol.*, vol. 96, no. 5, pp. 671–677, 2000, ISSN: 0029-7844. DOI: 10.1016/S0029-7844(00)01010-3.

[60] A. B. Caughey, A. G. Cahill, J. M. Guise, and D. J. Rouse, "Safe prevention of the primary cesarean delivery", *Am. J. Obstet. Gynecol.*, vol. 210, no. 3, pp. 179–193, 2014, ISSN: 0002-9378. DOI: 10.1016/J.AJOG.2014.01.026.

[61] E. H. BISHOP, "PELVIC SCORING FOR ELECTIVE INDUCTION.", *Obstet. Gynecol.*, vol. 24, no. 2, pp. 266–8, 1964, ISSN: 0029-7844. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/14199536.

[62] E. F. Faltin-Traub, M. Boulvain, D. L. Faltin, P. Extermann, and O. Irion, "Reliability of the Bishop score before labour induction at term", *Eur. J. Obstet. Gynecol. Reprod. Biol.*, vol. 112, no. 2, pp. 178–181, 2004, ISSN: 0301-2115. DOI: 10.1016/S0301-2115(03)00336-1.

[63] C. J. Verhoeven, B. C. Opmeer, S. G. Oei, V. Latour, J. A. Van Der Post, and B. W. Mol, "Transvaginal sonographic assessment of cervical length and wedging for predicting outcome of labor induction at term: A systematic review and meta-analysis", *Ultrasound Obstet. Gynecol.*, vol. 42, no. 5, pp. 500–508, 2013, ISSN: 09607692. DOI: 10.1002/uog.12467.

[64] C. A. d. C. Prado, E. Araujo Júnior, G. Duarte, S. M. Quintana, G. Tonni, R. d. C. Cavalli, and A. C. Marcolin, "Predicting success of labor induction in singleton term pregnancies by combining maternal and ultrasound variables.", *J. Matern. Fetal. Neonatal Med.*, vol. 29, no. 21, pp. 3511–3518, 2016, ISSN: 1476-4954. DOI: 10.3109/14767058.2015.1135124.

[65] P. d. R. P. Pitarello, C. Tadashi Yoshizaki, R. Ruano, and M. Zugaib, "Prediction of successful labor induction using transvaginal sonographic cervical measurements", *J. Clin. Ultrasound*, vol. 41, no. 2, pp. 76–83, 2012, ISSN: 00912751. DOI: 10.1002/jcu.21929.

[66] P. Bastani, K. Hamdi, F. Abasalizadeh, P. Pourmousa, and F. Ghatrehsamani, "Transvaginal ultrasonography compared with Bishop score for predicting cesarean section after induction of labor", *Int. J. Womens. Health*, vol. 3, no. 1, pp. 277–280, 2011, ISSN: 11791411. DOI: 10.2147/IJWH.S20387.

[67] M. D. de Vaan, M. L. ten Eikelder, M. Jozwiak, K. R. Palmer, M. Davies-Tuck, K. W. Bloemenkamp, B. W. J. Mol, and M. Boulvain, "Mechanical methods for induction of labour", *Cochrane Database Syst. Rev.*, no. 10, pp. 1–375, 2019, ISSN: 1469493X. DOI: 10.1002/14651858.CD001233.pub3.

[68] R. M. Smyth, C. Markham, and T. Dowswell, "Amniotomy for shortening spontaneous labour", *Cochrane Database Syst. Rev.*, no. 6, pp. 1–68, 2013. DOI: 10.1002/14651858.cd006167.pub4.

[69] L. Bricker and M. Luckas, "Amniotomy alone for induction of labour", *Cochrane Database Syst. Rev.*, no. 4, pp. 1–63, 2000, ISSN: 14651858. DOI: 10.1002/14651858.CD002862.

[70] G. J. Gilson, D. J. Russell, L. A. Izquierdo, C. R. Qualls, and L. B. Curet, "A prospective randomized evaluation of a hygroscopic cervical dilator, Dilapan, in the preinduction ripening of patients undergoing induction of labor", *Am. J. Obstet. Gynecol.*, vol. 175, no. 1, pp. 145–149, 1996, ISSN: 00029378. DOI: 10.1016/S0002-9378(96)70264-8.

[71] S. Geethanjali and S. Palli, "Comparative study of induction of labour with Dinoprostone gel versus mechanical dilatation in unfavorable cervix (low Bishop Score)", *J. Cardiovasc. Dis. Res.*, vol. 13, no. 5, pp. 1946–1954, 2022, ISSN: 0975-3583,0976-2833. [Online]. Available: https://jcdronline.org/admin/Uploads/Files/62f0c7eb0188c4.90521932.pdf.

[72] R. Salim, N. Zafran, Z. Nachum, G. Garmi, N. Kraiem, and E. Shalev, "Single-balloon compared with double-balloon catheters for induction of labor: A randomized controlled trial", *Obstet. Gynecol.*, vol. 118, no. 1, pp. 79–86, 2011, ISSN: 00297844. DOI: 10.1097/AOG.0b013e318220e4b7.

[73] C. N. Schoen, G. Grant, V. Berghella, M. K. Hoffman, and A. Sciscione, "Intracervical Foley Catheter with and Without Oxytocin for Labor Induction: A Randomized Controlled Trial", *Obstet. Gynecol.*, vol. 129, no. 6, pp. 1046–1053, 2017, ISSN: 1873233X. DOI: 10.1097/AOG.0000000000002032.

[74] Y. R. Liu, C. X. Pu, X. Y. Wang, and X. Y. Wang, "Double-balloon catheter versus dinoprostone insert for labour induction: a meta-analysis", *Arch. Gynecol. Obstet.*, vol. 299, no. 1, pp. 7–12, 2019, ISSN: 14320711. DOI: 10.1007/s00404-018-4929-8.

[75] A. Diaz-Martinez, Y. Ye-Lin, R. Monfort-Ortiz, J. Garcia-Casado, I. Rey-Ferreira, F. Nieto-Del-Amor, V. Diago-Almela, J. Luis Martinez-De-Juan, and G. Prats-Boluda, "Comparison of the Electrophysiological Myoelectrical Activity Evolution in Induction of Labor with Pharmacological and Mechanical Methods", *BIOSIGNALS 2023 - 16th Int. Conf. Bio-inspired Syst. Signal Process.*, pp. 66–73, 2023. [Online]. Available: https://orcid.org/0000-0003-1410-2721.

[76] ACOG Committee on Practice Bulletins, "ACOG Practice Bulletin No. 107: Induction of labor.", *Obstet. Gynecol.*, vol. 114, no. 2 Pt 1, pp. 386–397, 2009, ISSN: 0029-7844. DOI: 10.1097/AOG.0b013e3181b48ef5.

[77] K. R. Meckstroth, A. K. Whitaker, S. Bertisch, A. B. Goldberg, and P. D. Darney, "Misoprostol Administered by Epithelial Routes", *Obstet. Gynecol.*, vol. 108, no. 3, Part 1, pp. 582–590, 2006, ISSN: 0029-7844. DOI: 10.1097/01.AOG.0000230398.32794.9d.

[78] C. Taliento, M. Manservigi, M. Tormen, R. Cappadona, I. Piccolotti, S. Salvioli, G. Scutiero, and P. Greco, "Safety of misoprostol vs dinoprostone for induction of labor: A systematic review and meta-analysis", *Eur. J. Obstet. Gynecol. Reprod. Biol.*, vol. 289, pp. 108–128, 2023, ISSN: 18727654. DOI: 10.1016/j.ejogrb.2023.08.382.

[79] A.-R. Fuchs, F. Fuchs, P. Husslein, and M. S. Soloff, "Oxytocin receptors in the human uterus during pregnancy and parturition", *Am. J. Obstet. Gynecol.*, vol. 150, no. 6, pp. 734–741, 1984, ISSN: 00029378. DOI: 10.1016/0002-9378(84)90677-X.

[80] S. Arrowsmith and S. Wray, *Oxytocin: Its mechanism of action and receptor signalling in the myometrium*, 2014. DOI: 10.1111/jne.12154.

[81] G Rydén and I Sjöholm, "The metabolism of oxytocin in pregnant and non-pregnant women.", *Acta Obstet. Gynecol. Scand. Suppl.*, vol. 9, Suppl 9:37, 1971, ISSN: 0300-8835. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/5287107.

[82] E. J. Hayes and L. Weinstein, "Improving patient safety and uniformity of care by a standardized regimen for the use of oxytocin", *Am. J. Obstet. Gynecol.*, vol. 198, no. 6, 622.e1–622.e7, 2008, ISSN: 00029378. DOI: 10.1016/j.ajog.2008.01.039.

[83] Z. Alfirevic, E. Keeney, T. Dowswell, N. J. Welton, N. Medley, S. Dias, L. V. Jones, G. Gyte, and D. M. Caldwell, "Which method is best for the induction of labour? A systematic review, network meta-analysis and cost-effectiveness analysis", *Health Technol. Assess. (Rockv).*, vol. 20, no. 65, pp. 1–583, 2016, ISSN: 20464924. DOI: 10.3310/hta20650.

[84] A. Ghosh, K. R. Lattey, and A. J. Kelly, "Nitric oxide donors for cervical ripening and induction of labour", *Cochrane Database Syst. Rev.*, no. 12, pp. 1–225, 2016, ISSN: 1469493X. DOI: 10.1002/14651858.CD006901.pub3.

[85] R. Polónia-Valente, S. Costa, C. Coimbra, J. Xavier, R. Figueiredo, T. Ferraz, A. P. Machado, and M. Moucho, "Labor induction with a combined method (pharmacologic and mechanical): A randomized controlled trial.", *J. Gynecol. Obstet. Hum. Reprod.*, vol. 52, no. 9, p. 102 649, 2023, ISSN: 2468-7847. DOI: 10.1016/j.jogoh.2023.102649.

[86] H. B. Gomez, M. K. Hoffman, R. Caplan, K. Ruhstaller, M. H. H. Young, and A. C. Sciscione, "Buccal vs vaginal misoprostol combined with Foley catheter for cervical ripening at term (the BEGIN trial): a randomized controlled trial.", *Am. J. Obstet. Gynecol.*, vol. 224, no. 5, 524.e1–524.e8, 2021, ISSN: 1097-6868. DOI: 10.1016/j.ajog.2021.02.016.

[87] O. A. Rust, M Greybush, R. O. Atlas, K. J. Jones, and J Balducci, "Preinduction cervical ripening. A randomized trial of intravaginal misoprostol alone vs. a combination of transcervical Foley balloon and intravaginal misoprostol.", *J. Reprod. Med.*, vol. 46, no. 10, pp. 899–904, 2001, ISSN: 0024-7758. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/11725734.

[88] M Greybush, C Singleton, R. O. Atlas, J Balducci, and O. A. Rust, "Preinduction cervical ripening techniques compared.", *J. Reprod. Med.*, vol. 46, no. 1, pp. 11–7, 2001, ISSN: 0024-7758. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/11209625.

[89] B. Sangram Singh, K. Joshi, and S. Pajai, "Intra-cervical Foley Balloon Catheter Versus Prostaglandins for the Induction of Labour: A Literature Review", *Cureus*, vol. 15, no. 1, pp. 1–6, 2023. DOI: 10.7759/cureus.33855.

[90] A. Stube, T. Auguste, and M. Gulati, "ACOG Committee Opinion No. 736: Optimizing Postpartum Care", *Obstet. Gynecol.*, vol. 131, no. 5, e140–e150, 2018, ISSN: 0029-7844. DOI: 10.1097/AOG.0000000000002633.

[91] A. Borovac-Pinheiro, R. C. Pacagnella, J. G. Cecatti, S. Miller, A. M. El Ayadi, J. P. Souza, J. Durocher, P. D. Blumenthal, and B. Winikoff, "Postpartum hemorrhage: new insights for definition and diagnosis", *Am. J. Obstet. Gynecol.*, vol. 219, no. 2, pp. 162–168, 2018, ISSN: 10976868. DOI: 10.1016/j.ajog.2018.04.013.

[92] W. R. Sheldon, J. Blum, J. P. Vogel, J. P. Souza, A. M. Gülmezoglu, B. Winikoff, and WHO Multicountry Survey on Maternal, "Postpartum haemorrhage management, risks, and maternal outcomes: findings from the World Health Organization Multicountry Survey on Maternal and Newborn Health", *BJOG*, vol. 121 Suppl, pp. 5–13, 2014, ISSN: 1471-0528. DOI: 10.1111/1471-0528.12636.

[93] C. Calvert, S. L. Thomas, C. Ronsmans, K. S. Wagner, A. J. Adler, and V. Filippi, "Identifying regional variation in the prevalence of postpartum haemorrhage: a systematic review and meta-analysis", *PLoS One*, vol. 7, no. 7, e41114, 2012, ISSN: 1932-6203. DOI: 10.1371/JOURNAL.PONE.0041114.

[94] M. Knight, W. M. Callaghan, C. Berg, S. Alexander, M.-H. Bouvier-Colle, J. B. Ford, K. Joseph, G. Lewis, R. M. Liston, C. L. Roberts, J. Oats, and J. Walker, "Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group", *BMC Pregnancy Childbirth*, vol. 9, no. 1, p. 55, 2009, ISSN: 1471-2393. DOI: 10.1186/1471-2393-9-55.

[95] G. Carroli, C. Cuesta, E. Abalos, and A. M. Gulmezoglu, *Epidemiology of postpartum haemorrhage: a systematic review*, 2008. DOI: 10.1016/j.bpobgyn.2008.08.004.

[96] A. Mehrabadi, S. Liu, S. Bartholomew, J. A. Hutcheon, M. S. Kramer, R. M. Liston, and K. S. Joseph, "Temporal Trends in Postpartum Hemorrhage and Severe Postpartum Hemorrhage in Canada From 2003 to 2010", *J. Obstet. Gynaecol. Canada*, vol. 36, no. 1, pp. 21–33, 2014, ISSN: 1701-2163. DOI: 10.1016/S1701-2163(15)30680-0.

[97] S. C. Reale, S. R. Easter, X. Xu, B. T. Bateman, and M. K. Farber, "Trends in Postpartum Hemorrhage in the United States From 2010 to 2014", *Anesth. Analg.*, vol. 130, no. 5, E119–E122, 2020, ISSN: 1526-7598. DOI: 10.1213/ANE.0000000000004424.

[98] M. F. Escobar, A. H. Nassar, G. Theron, E. R. Barnea, W. Nicholson, D. Ramasauskaite, I. Lloyd, E. Chandraharan, S. Miller, T. Burke, G. Ossanan, J. Andres Carvajal, I. Ramos, M. A. Hincapie, S. Loaiza, D. Nasner, A. H. Nassar, G. H. Visser, E. R. Barnea, M. F. Escobar, Y. H. Kim, W. K. Nicholson, R. Pacagnella, D. Ramasauskaite, G. Theron, and A. Wright,

"FIGO recommendations on the management of postpartum hemorrhage 2022", *Int. J. Gynecol. Obstet.*, vol. 157, no. Suppl.1, pp. 3–50, 2022, ISSN: 18793479. DOI: 10.1002/ijgo.14116.

[99] D. Chelmow, "Postpartum haemorrhage: prevention.", *BMJ Clin. Evid.*, vol. 2011, pp. 1–111, 2011, ISSN: 1752-8526. [Online]. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3275142.

[100] L. E. Shields, D. Goffman, and A. B. Caughey, "Practice Bulletin No. 183: Postpartum Hemorrhage", *Obstet. Gynecol.*, vol. 130, no. 4, e168–e186, 2017, ISSN: 1873-233X. DOI: 10.1097/AOG.0000000000002351.

[101] J. M. Anderson and D. Etches, *Prevention and management of postpartum hemorrhage*, 2007. DOI: 10.1111/1471-0528.14178.

[102] J. D. Dahlke, H. Mendez-Figueroa, L. Maggio, A. K. Hauspurg, J. D. Sperling, S. P. Chauhan, and D. J. Rouse, "Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines", *Am. J. Obstet. Gynecol.*, vol. 213, no. 1, 76.e1–76.e10, 2015, ISSN: 10976868. DOI: 10.1016/j.ajog.2015.02.023.

[103] S. Fawcus, "Alerts for managing postpartum haemorrhage", *South African Med. J.*, vol. 108, no. 12, pp. 1013–1017, 2018, ISSN: 20785135. DOI: 10.7196/SAMJ.2018.V108I12.13420.

[104] Y. Oyelese and C. V. Ananth, "Postpartum hemorrhage: epidemiology, risk factors, and causes", *Clin. Obstet. Gynecol.*, vol. 53, no. 1, pp. 147–156, 2010, ISSN: 1532-5520. DOI: 10.1097/GRF.0B013E3181CC406D.

[105] L. Sentilhes, B. Merlot, H. Madar, F. Sztark, S. Brun, and C. Deneux-Tharaux, "Postpartum haemorrhage: prevention and treatment", *Expert Rev. Hematol.*, vol. 9, no. 11, pp. 1043–1061, 2016, ISSN: 1747-4094. DOI: 10.1080/17474086.2016.1245135.

[106] E. Sheiner, L. Sarid, A. Levy, D. S. Seidman, and M. Hallak, "Obstetric risk factors and outcome of pregnancies complicated with early postpartum hemorrhage: A population-based study", *J. Matern. Neonatal Med.*, vol. 18, no. 3, pp. 149–154, 2005, ISSN: 14767058. DOI: 10.1080/14767050500170088.

[107] A. Evensen, J. M. Anderson, and P. Fontaine, "Postpartum Hemorrhage: Prevention and Treatment.", *Am. Fam. Physician*, vol. 95, no. 7, pp. 442–449, 2017, ISSN: 1532-0650. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/28409600.

[108] A. Koutras, Z. Fasoulakis, A. Syllaios, N. Garmpis, M. Diakosavvas, A. Pagkalos, T. Ntounis, and E. N. Kontomanolis, "Physiology and Pathology of Contractility of the Myometrium", *In Vivo (Brooklyn).*, vol. 35, no. 3, pp. 1401–1408, 2021, ISSN: 0258-851X. DOI: 10.21873/INVIVO.12392.

[109] E. T. Abrams and J. N. Rutherford, "Framing postpartum hemorrhage as a consequence of human placental biology: an evolutionary and comparative perspective", *Am. Anthropol.*, vol. 113, no. 3, pp. 417–430, 2011, ISSN: 0002-7294. DOI: 10.1111/J.1548-1433.2011.01351.X.

[110] N. Higgins, S. K. Patel, and P. Toledo, "Postpartum hemorrhage revisited: new challenges and solutions", *Curr. Opin. Anaesthesiol.*, vol. 32, no. 3, pp. 278–284, 2019, ISSN: 1473-6500. DOI: 10.1097/ACO.0000000000000717.

[111] D. Gilmandyar and L. L. Thornburg, "Surgical management of postpartum hemorrhage", *Semin. Perinatol.*, vol. 43, no. 1, pp. 27–34, 2019, ISSN: 1558-075X. DOI: 10.1053/J.SEMPERI.2018.11.006.

[112] J. Moodley, R. C. Pattinson, S. Fawcus, M. G. Schoon, N. Moran, and P. M. Shweni, "The Confidential Enquiry into Maternal Deaths in South Africa: a case study", *BJOG*, vol. 121, pp. 53–60, 2014, ISSN: 14710528. DOI: 10.1111/1471-0528.12869.

[113] S. Ononge, F. Mirembe, J. Wandabwa, and O. M. Campbell, "Incidence and risk factors for postpartum hemorrhage in Uganda", *Reprod. Health*, vol. 13, no. 1, pp. 1–7, 2016, ISSN: 17424755. DOI: 10.1186/S12978-016-0154-8/TABLES/2.

[114] T. Kawakita, N. Mokhtari, J. C. Huang, and H. J. Landy, "Evaluation of Risk-Assessment Tools for Severe Postpartum Hemorrhage in Women Undergoing Cesarean Delivery", *Obstet. Gynecol.*, vol. 134, no. 6, pp. 1308–1316, 2019, ISSN: 1873233X. DOI: 10.1097/AOG.0000000000003574.

[115] S. Ngwenya, "Postpartum hemorrhage: Incidence, risk factors, and outcomes in a low-resource setting", *Int. J. Womens. Health*, vol. 8, pp. 647–650, 2016, ISSN: 11791411. DOI: 10.2147/IJWH.S119232.

[116] C. M. Begley, G. M. Gyte, D. Devane, W. McGuire, A. Weeks, and L. M. Biesty, "Active versus expectant management for women in the third stage of labour", *Cochrane Database Syst. Rev.*, vol. 2019, no. 2, pp. 1–150, 2019, ISSN: 14651858. DOI: 10.1002/14651858.CD007412.PUB5.

[117] A. Metin Gülmezoglu, P. Lumbiganon, S. Landoulsi, M. Widmer, H. Abdel-Aleem, M. Festin, G. Carroli, Z. Qureshi, J. P. Souza, E. Bergel, G. Piaggio, S. S. Goudar, J. Yeh, D. Armbruster, M. Singata, C. Pelaez-Crisologo, F. Althabe, P. Sekweyama, J. Hofmeyr, M. E. Stanton, R. Derman, and D. Elbourne, "Active management of the third stage of labour with and

without controlled cord traction: A randomised, controlled, non-inferiority trial", *Lancet*, vol. 379, no. 9827, pp. 1721–1727, 2012, ISSN: 1474547X. DOI: 10.1016/S01406736(12)60206-2.

[118] G. J. Hofmeyr, N. T. Mshweshwe, and A. M. Gülmezoglu, "Controlled cord traction for the third stage of labour", *Cochrane Database Syst. Rev.*, vol. 2017, no. 3, pp. 1–34, 2015, ISSN: 1469493X. DOI: 10.1002/14651858.CD008020.PUB2/PDF/CDSR/CD008020/CD008020.PDF.

[119] J. P. Vogel, M. Williams, I. Gallos, F. Althabe, and O. T. Oladapo, "WHO recommendations on uterotonics for postpartum haemorrhage prevention: what works, and which one? Handling editor Seye Abimbola", *BMJ Glob Heal.*, vol. 4, p. 1466, 2019. DOI: 10.1136/bmjgh-2019-001466.

[120] K. Pickering, I. D. Gallos, H. Williams, M. J. Price, ·. A. Merriel, D. Lissauer, ·. A. Tobias, ·. G. Justus Hofmeyr, ·. A. Coomarasamy, · Tracy, E Roberts, and T. E. Roberts, "Uterotonic Drugs for the Prevention of Postpartum Haemorrhage: A Cost-Effectiveness Analysis", *PharmacoEconomics-Open*, vol. 3, pp. 163–176, 2019. DOI: 10.1007/s41669-018-0108-x.

[121] World Health Organization, *WHO recommendations Uterotonics for the prevention of postpartum haemorrhage*, W. H. Organization, Ed. Geneva: World Health Organization, 2018, ISBN: 9789241550420. [Online]. Available: http://apps.who.int/bookorders..

[122] W. M. Callaghan, E. V. Kuklina, and C. J. Berg, "Trends in postpartum hemorrhage: United States, 1994–2006", *Am. J. Obstet. Gynecol.*, vol. 202, no. 4, 353.e1–353.e6, 2010, ISSN: 00029378. DOI: 10.1016/j.ajog.2010.01.011.

[123] A. L. Marshall, U. Durani, A. Bartley, C. E. Hagen, A. Ashrani, C. Rose, R. S. Go, and R. K. Pruthi, "The impact of postpartum hemorrhage on hospital length of stay and inpatient mortality: a National Inpatient Sample-based analysis.", eng PT - Journal Article SB - AIM SB - IM, *Am. J. Obstet. Gynecol.*, vol. 217, no. 3, 344.e1–344.e6, 2017, ISSN: 1097-6868. DOI: 10.1016/j.ajog.2017.05.004.

[124] B. W. Prick, J. J. Duvekot, P. E. van der Moer, N. van Gemund, P. C. van der Salm, A. J. Jansen, D. J. van Rhenen, B. W. Mol, and C. A. Uyl-de Groot, "Cost-effectiveness of red blood cell transfusion vs. non-intervention in women with acute anaemia after postpartum haemorrhage", *Vox Sang.*, vol. 107, no. 4, pp. 381–388, 2014, ISSN: 14230410. DOI: 10.1111/vox.12181.

[125] D. Castiel, P. H. Bréchat, B. Benoît, B. Nguon, E. Gayat, P. Soyer, R. Rymer, and E. Barranger, "Coût total des actes chirurgicaux dans la prise en charge des hémorragies de la délivrance", *Gynecol. Obstet. Fertil.*, vol. 36, no. 5, pp. 507–515, 2008, ISSN: 17696682. DOI: 10.1016/j.gyobfe.2008.03.009.

[126] E. E. Hadley, L. S. Richardson, M. R. Torloni, and R. Menon, "Gestational Tissue Inflammatory Biomarkers at Term Labor: A Systematic Review of Literature", *Am. J. Reprod. Immunol.*, vol. 79, no. 2, pp. 1–66, 2018, ISSN: 16000897. DOI: 10.1111/AJI.12776.

[127] G. Faron, L. Balepa, J. Parra, J. F. Fils, and L. Gucciardo, "The fetal fibronectin test: 25 years after its development, what is the evidence regarding its clinical utility? A systematic review and meta-analysis", *J. Matern. Neonatal Med.*, vol. 33, no. 3, pp. 493–523, 2018, ISSN: 14764954. DOI: 10.1080/14767058.2018.1491031.

[128] V. Berghella and G. Saccone, "Fetal fibronectin testing for reducing the risk of preterm birth", *Cochrane Database Syst. Rev.*, vol. 2019, no. 7, pp. 1–23, 2019, ISSN: 14651858. DOI: 10.1002/14651858.CD006843.PUB3.

[129] Y. Çekmez, G. Kiran, E. T. Haberal, and M. Dizdar, "Use of cervicovaginal PAMG-1 protein as a predictor of delivery within seven days in pregnancies at risk of premature birth", *BMC Pregnancy Childbirth*, vol. 17, no. 1, pp. 1–5, 2017, ISSN: 14712393. DOI: 10.1186/S12884-017-1427-0/TABLES/3.

[130] R. Manning, C. P. James, M. C. Smith, B. A. Innes, E. Stamp, D. Peebles, M. Bajaj-Elliott, N. Klein, J. N. Bulmer, S. C. Robson, and G. E. Lash, "Predictive value of cervical cytokine, antimicrobial and microflora levels for pre-term birth in high-risk women", *Sci. Reports 2019 91*, vol. 9, no. 1, pp. 1–11, 2019, ISSN: 2045-2322. DOI: 10.1038/s41598-019-47756-7.

[131] J. Li, J. Ge, N. Ran, C. Zheng, Y. Fang, D. Fang, Q. Yang, and Y. Ma, "Finding the priority and cluster of inflammatory biomarkers for infectious preterm birth: a systematic review", *J. Inflamm. (United Kingdom)*, vol. 20, no. 1, pp. 1–11, 2023, ISSN: 14769255. DOI: 10.1186/S12950-023-00351-0/FIGURES/6.

[132] A. Roca-Prats, A. Diaz-Martinez, M. Albaladejo-Belmonte, J. Alberola-Rubio, R. Monfort-Ortiz, M. L. Martínez-Triguero, B. Marcos-Puig, and A. Perales-Marín, "Outperformance of interleukin-6 over placental alpha microglobulin-1 in predicting preterm delivery in symptomatic women", *Am. J. Obstet. Gynecol. MFM*, vol. 5, no. 10, p. 101 125, 2023, ISSN: 2589-9333. DOI: 10.1016/J.AJOGMF.2023.101125.

[133] K. O. Kagan and J. Sonek, "How to measure cervical length", *Ultrasound Obstet. Gynecol.*, vol. 45, no. 3, pp. 358–362, 2015, ISSN: 1469-0705. DOI: 10.1002/UOG.14742.

[134] K. C. Wormer, A. Bauer, and A. E. Williford, *Bishop Score*, 2021. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK470368/ (visited on 09/15/2022).

[135] A. M. Marconi, "Recent advances in the induction of labor", *F1000Research*, vol. 8, no. F1000 Faculty Rev-1829, pp. 1–11, 2019, ISSN: 1759796X. DOI: 10.12688/f1000research.17587.1.

[136] K. Raungrongmorakot, N. Tanmoun, P. Ruangvutilert, D. Boriboonhirunsarn, P. Tontisirin, and W. Butsansee, "Correlation of uterine cervical length measurement from transabdominal, transperineal and transvaginal ultrasonography.", *J. Med. Assoc. Thai.*, vol. 87, no. 3, pp. 326–32, 2004, ISSN: 0125-2208. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/15117051.

[137] R. F. Hamm, C. A. Combs, and C. M. Davidson, "Society for Maternal-Fetal Medicine Special Statement: Reducing the risk of transmitting infection by transvaginal ultrasound examination", *Am. J. Obstet. Gynecol.*, vol. 223, no. 3, B2–B6, 2020, ISSN: 10976868. DOI: 10.1016/j.ajog.2020.05.043.

[138] D. Paladini, "Sonography in obese and overweight pregnant women: clinical, medicolegal and technical issues", *Ultrasound Obstet. Gynecol.*, vol. 33, no. 6, pp. 720–9, 2009, ISSN: 1469-0705. DOI: 10.1002/uog.6393.

[139] C. Simioni and E. Araujo Júnior, "The role of mid-trimester ultrasound scan: scope and limitations", *Rev. Assoc. Med. Bras.*, vol. 69, no. 8, e20230567, 2023, ISSN: 18069282. DOI: 10.1590/1806-9282.20230567.

[140] R. M. Grivell, Z. Alfirevic, G. M. Gyte, and D. Devane, "Antenatal cardiotocography for fetal assessment", *Cochrane Database Syst. Rev.*, vol. 2015, no. 9, pp. 1–39, 2015, ISSN: 1469493X. DOI: 10.1002/14651858.CD007863.PUB4.

[141] Anna University Lecture Notes, *Factors That Contribute to Normal Labor - The Three Ps*. [Online]. Available: https://www.brainkart.com/article/Factors-That-Contribute-to-Normal-Labor---The-Three-Ps{_}25661/ (visited on 01/15/2024).

[142] J. Alberola-Rubio, G. Prats-Boluda, Y. Ye-Lin, J. Valero, A. Perales, and J. Garcia-Casado, "Comparison of non-invasive electrohysterographic recording techniques for monitoring uterine dynamics", *Med. Eng. Phys.*, vol. 35, no. 12, pp. 1736–1743, 2013, ISSN: 13504533. DOI: 10.1016/j.medengphy.2013.07.008.

[143] L. M. Harper, A. L. Shanks, M. G. Tuuli, K. A. Roehl, and A. G. Cahill, "The risks and benefits of internal monitors in laboring patients", *Am. J. Obstet. Gynecol.*, vol. 209, no. 1, 38.e1–38.e6, 2013, ISSN: 1097-6868. DOI: 10.1016/J.AJOG.2013.04.001.

[144] T. Y. Euliano, M. T. Nguyen, S. Darmanjian, S. P. McGorray, N. Euliano, A. Onkala, and A. R. Gregg, "Monitoring uterine activity during labor: a comparison of 3 methods", eng PT - Comparative Study PT - Journal Article PT - Research Support, N.I.H., Extramural SB - AIM SB - IM, *Am. J. Obstet. Gynecol.*, vol. 208, no. 1, 66.e1–6, 2013, ISSN: 1097-6868. DOI: 10.1016/j.ajog.2012.10.873.

[145] F. A. Wilmink, F. F. Wilms, R. Heydanus, B. W. Mol, and D. N. Papatsonis, "Fetal complications after placement of an intrauterine pressure catheter: A report of two cases and review of the literature", *J. Matern. Neonatal Med.*, vol. 21, no. 12, pp. 880–883, 2008, ISSN: 14767058. DOI: 10.1080/14767050802220508.

[146] C. Benalcazar-Parra, J. Garcia-Casado, Y. Ye-Lin, J. Alberola-Rubio, Á. Lopez, A. Perales-Marin, and G. Prats-Boluda, "New electrohysterogram-based estimators of intrauterine pressure signal, tonus and contraction peak for non-invasive labor monitoring", *Physiol. Meas.*, vol. 40, no. 8, pp. 1–24, 2019, ISSN: 13616579. DOI: 10.1088/1361-6579/ab37db.

[147] A. Aviram, N. Melamed, E. Hadar, O. Raban, L. Hiersch, and Y. Yogev, "Effect of prostaglandin E2 on myometrial electrical activity in women undergoing induction of labor", *Am. J. Perinatol.*, vol. 31, no. 5, pp. 413–418, 2014, ISSN: 10988785. DOI: 10.1055/S-0033-1352486.

[148] J. Terrien, C. Marque, and B. Karlsson, "Spectral characterization of human EHG frequency components based on the extraction and reconstruction of the ridges in the scalogram", in *29th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*, vol. 54, IEEE, 2007, pp. 1872–1875, ISBN: 978-1-4244-0787-3. DOI: 10.1109/IEMBS.2007.4352680.

[149] M. Albaladejo-Belmonte, G. Prats-Boluda, Y. Ye-Lin, R. E. Garfield, and J. Garcia-Casado, "Uterine slow wave: directionality and changes with imminent delivery", *Physiol. Meas.*, vol. 43, no. 8, p. 085 005, 2022, ISSN: 0967-3334. DOI: 10.1088/1361-6579/AC84C0.

[150] G. Fele-Žorž, G. Kavšek, Ž. Novak-Antolič, and F. Jager, "A comparison of various linear and non-linear signal processing techniques to separate uterine EMG records of term and pre-term delivery groups", *Med. Biol. Eng. Comput.*, vol. 46, no. 9, pp. 911–922, 2008, ISSN: 01400118. DOI: 10.1007/s11517-008-0350-y.

[151] J. Xu, Z. Chen, H. Lou, G. Shen, and A. Pumir, "Review on EHG signal analysis and its application in preterm diagnosis", *Biomed. Signal Process. Control*, vol. 71, p. 103 231, 2022, ISSN: 17468094. DOI: 10.1016/j.bspc.2021.103231.

[152] J. Mas-Cabo, G. Prats-Boluda, A. Perales, J. Garcia-Casado, J. Alberola-Rubio, and Y. Ye-Lin, "Uterine electromyography for discrimination of labor imminence in women with threatened preterm labor under tocolytic treatment", *Med. Biol. Eng. Comput.*, vol. 57, no. 2, pp. 401–411, 2019, ISSN: 0140-0118. DOI: 10.1007/s11517-018-1888-y.

[153] P. Fergus, P. Cheung, A. Hussain, D. Al-Jumeily, C. Dobbins, and S. Iram, "Prediction of Preterm Deliveries from EHG Signals Using Machine Learning", *PLoS One*, vol. 8, no. 10, Z. Wei, Ed., pp. 1–16, 2013, ISSN: 1932-6203. DOI: 10.1371/journal.pone.0077154.

[154] J. Mas-Cabo, Y. Ye-Lin, J. Garcia-Casado, A. Díaz-Martinez, A. Perales-Marin, R. Monfort-Ortiz, A. Roca-Prats, Á. López-Corral, and G. Prats-Boluda, "Robust Characterization of the Uterine Myoelectrical Activity in Different Obstetric Scenarios", *Entropy*, vol. 22, no. 7, p. 743, 2020, ISSN: 1099-4300. DOI: 10.3390/e22070743.

[155] A. J. Krapohl, G. G. Myers, and R Caldeyro-Barcia, "Uterine contractions in spontaneous labor. A quantitative study", *Am. J. Obstet. Gynecol.*, vol. 106, no. 3, pp. 378–87, 1970, ISSN: 0002-9378. DOI: 10.1016/0002-9378(70)90363-7.

[156] M. P. G. C. Vinken, C. Rabotti, M. Mischi, and S. G. Oei, "Accuracy of Frequency-Related Parameters of the Electrohysterogram for Predicting Preterm Delivery", *Obstet. Gynecol. Surv.*, vol. 64, no. 8, pp. 529–541, 2009, ISSN: 0029-7828. DOI: 10.1097/OGX.0b013e3181a8c6b1.

[157] W. L. Maner and R. E. Garfield, "Identification of Human Term and Preterm Labor using Artificial Neural Networks on Uterine Electromyography Data", *Ann. Biomed. Eng.*, vol. 35, no. 3, pp. 465–473, 2007, ISSN: 0090-6964. DOI: 10.1007/s10439-006-9248-8.

[158] R. E. Garfield, W. L. Maner, L. B. MacKay, D. Schlembach, and G. R. Saade, "Comparing uterine electromyography activity of antepartum patients versus term labor patients", *Am. J. Obstet. Gynecol.*, vol. 193, no. 1, pp. 23–29, 2005, ISSN: 00029378. DOI: 10.1016/j.ajog.2005.01.050.

[159] J. Vrhovec, A. Macek Lebar, and D. Rudel, "Evaluating uterine electrohysterogram with entropy", *IFMBE Proc.*, vol. 16, no. 1, pp. 144–147, 2007, ISSN: 16800737. DOI: 10.1007/978-3-540-73044-6_36.

[160] S. Stock and J. Norman, "Preterm and term labour in multiple pregnancies", *Semin. Fetal Neonatal Med.*, vol. 15, no. 6, pp. 336–341, 2010, ISSN: 1878-0946. DOI: 10.1016/J.SINY.2010.06.006.

[161] F. Lyall, S. J. Lye, T.-G. Teoh, F. Cousins, G. Milligan, and S. C. Robson, "Expression of Gsα, Connexin-43, Connexin-26, and EP1, 3, and 4 Receptors in Myometrium of Prelabor Singleton Versus Multiple Gestations and the Effects of Mechanical Stretch and Steroids on Gsα", *J. Soc. Gynecol. Investig.*, vol. 9, no. 5, pp. 299–307, 2002, ISSN: 1071-5576. DOI: 10.1177/107155760200900508.

[162] P. Turton, S. Arrowsmith, J. Prescott, C. Ballard, L. Bricker, J. Neilson, and S. Wray, "A Comparison of the Contractile Properties of Myometrium from Singleton and Twin Pregnancies", *PLoS One*, vol. 8, no. 5, W. Yan, Ed., e63800, 2013, ISSN: 1932-6203. DOI: 10.1371/journal.pone.0063800.

[163] K. M. Waldorf, N. Singh, A. R. Mohan, R. C. Young, L. Ngo, A. Das, J. Tsai, A. Bansal, L. Paolella, B. R. Herbert, S. R. Sooranna, G. M. Gough, C. Astley, K. Vogel, A. E. Baldessari, T. K. Bammler, J. MacDonald, M. G. Gravett, L. Rajagopal, and M. R. Johnson, "Uterine overdistention induces preterm labor mediated by inflammation: observations in pregnant women and nonhuman primates", *Am. J. Obstet. Gynecol.*, vol. 213, no. 6, 830.e1, 2015, ISSN: 10976868. DOI: 10.1016/J.AJOG.2015.08.028.

[164] C. Buhimschi and R. E. Garfield, "Uterine contractility as assessed by abdominal surface recording of electromyographic activity in rats during pregnancy", *Am. J. Obstet. Gynecol.*, vol. 174, no. 2, pp. 744–753, 1996, ISSN: 0002-9378. DOI: 10.1016/S0002-9378(96)70459-3.

[165] R. C. Young, P. S. Marinescu, and N. S. Seligman, "Monitoring uterine contractions during labor: current challenges and future directions", *Am. J. Obstet. Gynecol.*, vol. 228, no. 5, S1192–S1208, 2023, ISSN: 10976868. DOI: 10.1016/j.ajog.2022.10.039.

[166] C. Benalcazar-Parra, R. Monfort-Orti, Y. Ye-Lin, G. Prats-Boluda, J. Alberola-Rubio, A. Perales, J. Garcia-Casado, and J. Garcia, "Comparison of labour induction with misoprostol and dinoprostone and characterization of uterine response based on electrohysterogram", *J. Matern. Neonatal Med.*, vol. 32, no. 10, pp. 1586–1594, 2017, ISSN: 1476-4954. DOI: 10.1080/14767058.2017.1410791.

[167] A. Csapo, "The diagnostic significance of the intrauterine pressure", *Obstet. Gynecol. Surv.*, vol. 25, no. 5, pp. 403–435, 1970, ISSN: 0029-7828. DOI: 10.1097/00006254-197005000-00001.

[168] T. Toth, "Transcutaneous electromyography of uterus in prediction of labor outcome induced by oxytocine and prostaglandine shapes", *Gynaecol. Perinatol.*, vol. 14, no. 2, pp. 75–85, 2005. [Online]. Available: https://www.researchgate.net/publication/289002028{_}Transcutaneous{_}electromyography{_}of{_}uterus{_}in{_}prediction{_}of{_}labor{_}outcome{_}induced{_}by{_}oxytocine{_}and{_}prostaglandine{_}shapes.

[169] C. Benalcazar-Parra, Y. Ye-Lin, J. Garcia-Casado, R. Monfort-Ortiz, J. Alberola-Rubio, A. Perales, and G. Prats-Boluda, "Prediction of Labor Induction Success from the Uterine Electrohysterogram", *Hindawi. J. Sensors.*, vol. 2019, pp. 1–12, 2019. DOI: 10.1155/2019/6916251. [Online]. Available: https://doi.org/10.1155/2019/6916251.

[170] O. Kandemir, H. Dede, S. Yalvac, O. Aldemir, B. Yirci, N. Yerebasmaz, and S. Esin, "The Effect of Parity on Labor Induction with Prostaglandin E2 Analogue (Dinoprostone): An Evaluation of 2090 Cases", *J. Pregnancy Child Heal.*, vol. 2, no. 2, pp. 1–5, 2015, ISSN: 2376-127X. DOI: 10.4172/2376-127X.1000149.

[171] D. Delvin Anggriani, L. Herawati, and Ernawati, "Parity as failure determinants of labor induction in Bangka Belitung", *Mater. Obstet. Gynecol.*, vol. 24, no. 3, pp. 79–83, 2016. DOI: 10.20473/mog.V24I32016.79-83.

[172] P. Barrilleaux, J. A. Bofill, D. A. Terrone, E. F. Magann, W. L. May, and J. C. Morrison, "Cervical ripening and induction of labor with misoprostol, dinoprostone gel, and a foley catheter: A randomized trial of 3 techniques", *Am. J. Obstet. Gynecol.*, vol. 186, no. 6, pp. 1124–1129, 2002, ISSN: 00029378. DOI: 10.1067/mob.2002.123821.

[173] A. G. Cahill, Z. Wen, H. Wang, P. Zhao, Z. Sun, A. L. Schwartz, and Y. Wang, "Analysis of Electrophysiological Activation of the Uterus During Human Labor Contractions", *JAMA Netw. Open*, vol. 5, no. 6, e2214707–e2214707, 2022, ISSN: 25743805. DOI: 10.1001/JAMANETWORKOPEN.2022.14707.

[174] R. U. Khan and H. El-Refaey, "Pathophysiology of postpartum hemorrhage and third stage of labor", in *A Compr. Textb. Postpartum Hemorrhage*, A Arulkumaran, M Karoshi, L. Keith, A. Lalonde, and C B-Lynch, Eds., 2nd Editio, London: Sapiens Publishing, 2012, pp. 94–100. [Online]. Available: https://www.glowm.com/resource-type/resource/textbook/title/a-comprehensive-textbook-of-postpartum-hemorrhage-2{\%}3Csup{\%}3End{\%}3C-sup{\%}3E-edition/resource-doc/1275.

[175] A. N. de Groot, "The role of oral (methyl)ergometrine in the prevention of postpartum haemorrhage", *Eur. J. Obstet. Gynecol. Reprod. Biol.*, vol. 69, no. 1, pp. 31–36, 1996, ISSN: 03012115. DOI: 10.1016/0301-2115(95)02531-6.

[176] A. Herman, Z. Weinraub, I. Bukovsky, S. Arieli, P. Zabow, E. Caspi, and R. Ron-El, "Dynamic ultrasonographic imaging of the third stage of labor: New perspectives into third-stage mechanisms", *Am. J. Obstet. Gynecol.*, vol. 168, no. 5, pp. 1496–1499, 1993, ISSN: 00029378. DOI: 10.1016/S0002-9378(11)90788-1.

[177] J. J. Hirst, R. Chibbar, and B. F. Mitchell, "Role of oxytocin in the regulation of uterine activity during pregnancy and in the initiation of labor", *Semin. Reprod. Endocrinol.*, vol. 11, no. 3, pp. 219–233, 1993, ISSN: 07348630. DOI: 10.1055/S-2007-1018836/BIB.

[178] S. Phaneuf, G. Asbóth, M. P. Carrasco, B. R. Liñares, T. Kimura, A. Harris, and A. L. Bernal, "Desensitization of oxytocin receptors in human myometrium", *Hum. Reprod. Update*, vol. 4, no. 5, pp. 625–633, 1998, ISSN: 1355-4786. DOI: 10.1093/HUMUPD/4.5.625.

[179] W. A. Noort, B. van Bulck, A. Vereecken, F. A. de Zwart, and M. J. Keirse, "Changes in plasma of PGF2α and PGI2 metabolites at and after delivery at term", *Prostaglandins*, vol. 37, no. 1, pp. 3–12, 1989, ISSN: 0090-6980. DOI: 10.1016/0090-6980(89)90027-0.

[180] J Konje and R Whalley, "Bleeding in late pregnancy", in *High-risk Pregnancy Manag. Options*, D James, P Steer, C Weiner, and B Gonik, Eds., London: Saunders, 1994, pp. 119–136.

[181] M. Y. Dawood, C. F. Wang, R Gupta, and F Fuchs, "Fetal contribution to oxytocin in human labor.", *Obstet. Gynecol.*, vol. 52, no. 2, pp. 205–9, 1978, ISSN: 0029-7844. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/683660.

[182] S. E. Gee and H. A. Frey, "Contractions: Traditional concepts and their role in modern obstetrics", *Semin. Perinatol.*, vol. 44, no. 2, p. 151 218, 2020, ISSN: 01460005. DOI: 10.1016/j.semperi.2019.151218.

[183] L. Reicher, Y. Fouks, and Y. Yogev, "Cervical Assessment for Predicting Preterm Birth—Cervical Length and Beyond", *J. Clin. Med. 2021, Vol. 10, Page 627*, vol. 10, no. 4, p. 627, 2021, ISSN: 2077-0383. DOI: 10.3390/JCM10040627.

[184] M. S. Esplin, M. A. Elovitz, J. D. Iams, C. B. Parker, R. J. Wapner, W. A. Grobman, H. N. Simhan, D. A. Wing, D. M. Haas, R. M. Silver, M. K. Hoffman, A. M. Peaceman, S. N. Caritis, S. Parry, P. Wadhwa, T. Foroud, B. M. Mercer, S. M. Hunter, G. R. Saade, and U. M. Reddy, "Predictive Accuracy of Serial Transvaginal Cervical Lengths and Quantitative Vaginal Fetal Fibronectin Levels for Spontaneous Preterm Birth Among Nulliparous Women", *J. Am. Med. Assoc.*, vol. 317, no. 10, pp. 1047–1056, 2017, ISSN: 0098-7484. DOI: 10.1001/jama.2017.1373.

[185] T. Y. Euliano, M. T. Nguyen, D. Marossero, and R. K. Edwards, "Monitoring contractions in obese parturients: electrohysterography compared with traditional monitoring.", eng PT - Comparative Study PT - Journal Article PT - Research Support, U.S. Gov't, Non-P.H.S SB - AIM SB - IM, *Obstet. Gynecol.*, vol. 109, no. 5, pp. 1136–40, 2007, ISSN: 0029-7844. DOI: 10.1097/01.AOG.0000258799.24496.93.

[186] F. Nieto-Del-amor, R. Beskhani, Y. Ye-Lin, J. Garcia-Casado, A. Diaz-Martinez, R. Monfort-Ortiz, V. J. Diago-Almela, D. Hao, and G. Prats-Boluda, "Assessment of Dispersion and Bubble Entropy Measures for Enhancing Preterm Birth Prediction Based on Electrohysterographic Signals", *Sensors 2021, Vol. 21, Page 6071*, vol. 21, no. 18, p. 6071, 2021, ISSN: 1424-8220. DOI: 10.3390/S21186071.

[187] P. D. Ellis, *The essential guide to effect sizes: Statistical power, meta-analysis, and the interpretation of research results*. Cambridge University Press, 2010, ISBN: 9780521194235. DOI: 10.1017/CBO9780511761676.

[188] J. Mas-Cabo, Y Ye-Lin, J Garcia-Casado, J Alberola-Rubio, A Perales, and G Prats-Boluda, "Uterine contractile efficiency indexes for labor prediction: A bivariate approach from multichannel electrohysterographic records", *Biomed. Signal Process. Control*, vol. 46, pp. 238–248, 2018. DOI: 10.1016/j.bspc.2018.07.018.

[189] A. Diaz-Martinez, R. Monfort-Ortiz, Y. Ye-Lin, J. Garcia-Casado, M. Nieto-Tous, F. Nieto-Del-Amor, V. Diago-Almela, and G. Prats-Boluda, "Uterine myoelectrical activity as biomarker of successful induction with Dinoprostone: Influence of parity", *Biocybern. Biomed. Eng.*, vol. 43, no. 1, pp. 142–156, 2023, ISSN: 02085216. DOI: 10.1016/j.bbe.2022.12.004.

[190] F. Nieto-Del-Amor, Y. Ye-Lin, J. Garcia-Casado, A. Diaz-Martinez, M. G. Martínez, R. Monfort-Ortiz, and G. Prats-Boluda, "Dispersion entropy: A measure of electrohysterographic complexity for preterm labor discrimination", *Proc. 14th Int. Jt. Conf. Biomed. Eng. Syst. Technol. (BIOSTEC 2021)*, vol. 4, pp. 260–267, 2021. DOI: 10.5220/0010316602600267.

[191] H. C. Parkington, M. A. Tonta, S. P. Brennecke, and H. A. Coleman, "Contractile activity, membrane potential, and cytoplasmic calcium in human uterine smooth muscle in the third trimester of pregnancy and during labor", *Am. J. Obstet. Gynecol.*, vol. 181, no. 6, pp. 1445–1451, 1999, ISSN: 00029378. DOI: 10.1016/S0002-9378(99)70390-X.

[192] S. Wray, "Insights into the uterus", *Exp. Physiol.*, vol. 92, no. 4, pp. 621–631, 2007, ISSN: 09580670. DOI: 10.1113/expphysiol.2007.038125.

[193] A. Shulman, E. Jauniaux, A. Holmes, S. Maschiach, and R. Maymon, "Vaginal sonography of the cervix for the prediction of "time to delivery"in ART twins gestations", *Twin Res.*, vol. 5, no. 4, pp. 255–259, 2012, ISSN: 1369-0523. DOI: 10.1375/13690520260186416.

[194] K. Monaghan, S. A. Baker, L. Dwyer, W. C. Hatton, K. Sik Park, K. M. Sanders, and S. D. Koh, "The stretch-dependent potassium channel TREK-1 and its function in murine myometrium", *J. Physiol.*, vol. 589, no. 5, pp. 1221–1233, 2011, ISSN: 00223751. DOI: 10.1113/jphysiol.2010.203869.

[195] Y. Y. Wu, C. A. Singer, and I. L. Buxton, "Variants of Stretch-Activated Two-Pore Potassium Channel TREK-1 Associated with Preterm Labor in Humans", *Biol. Reprod.*, vol. 87, no. 4, pp. 96–97, 2012, ISSN: 00063363. DOI: 10.1095/BIOLREPROD.112.099499.

[196] O. Shynlova, J. A. Mitchell, A. Tsampalieros, B. L. Langille, and S. J. Lye, "Progesterone and gravidity differentially regulate expression of extracellular matrix components in the pregnant rat myometrium", *Biol. Reprod.*, vol. 70, no. 4, pp. 986–992, 2004, ISSN: 0006-3363. DOI: 10.1095/BIOLREPROD.103.023648.

[197] R. E. Sheldon, C. Mashayamombe, S. Q. Shi, R. E. Garfield, A. Shmygol, A. M. Blanks, and H. A. Van Den Berg, "Alterations in gap junction connexin43/connexin45 ratio mediate a transition from quiescence to excitation in a mathematical model of the myometrium", *J. R. Soc. Interface*, vol. 11, no. 101, 2014, ISSN: 17425662. DOI: 10.1098/RSIF.2014.0726.

[198] Z. Yin, W. He, Y. Li, D. Li, H. Li, Y. Yang, Z. Wei, B. Shen, X. Wang, Y. Cao, and R. A. Khalil, "Adaptive reduction of human myometrium contractile activity in response to prolonged uterine stretch during term and twin pregnancy. Role of TREK-1 channel", *Biochem. Pharmacol.*, vol. 152, pp. 252–263, 2018, ISSN: 0006-2952. DOI: 10.1016/J.BCP.2018.03.021.

[199] Y. Dang, W. Li, V. Tran, and R. A. Khalil, "EMMPRIN-Mediated Induction of Uterine and Vascular Matrix Metalloproteinases during Pregnancy and in Response to Estrogen and Progesterone", *Biochem. Pharmacol.*, vol. 86, no. 6, pp. 734–747, 2013, ISSN: 18732968. DOI: 10.1016/J.BCP.2013.06.030.

[200] J. Bacelis, J. Juodakis, K. M. Adams Waldorf, V. Sengpiel, L. J. Muglia, G. Zhang, and B. Jacobsson, "Uterine distention as a factor in birth timing: retrospective nationwide cohort study in Sweden", *BMJ Open*, vol. 8, no. 10, p. 22 929, 2018, ISSN: 20446055. DOI: 10.1136/BMJOPEN-2018-022929.

[201] M. Almeida, H. Mouriño, A. G. Batista, S. Russo, F. Esgalhado, C. R. dos Reis, F. Serrano, and M. Ortigueira, "Electrohysterography extracted features dependency on anthropometric and pregnancy factors", *Biomed. Signal Process. Control*, vol. 75, p. 103 556, 2022, ISSN: 1746-8094. DOI: 10.1016/J.BSPC.2022.103556.

[202] X. Song, X. Qiao, D. Hao, L. Yang, X. Zhou, Y. Xu, and D. Zheng, "Automatic recognition of uterine contractions with electrohysterogram signals based on the zero-crossing rate", *Sci. Rep.*, vol. 11, no. 1, pp. 1–10, 2021, ISSN: 2045-2322. DOI: 10.1038/s41598-021-81492-1.

[203] C Muszynski, T Happillon, K Azudin, J.-B. Tylcz, D Istrate, and C Marque, "Automated electrohysterographic detection of uterine contractions for monitoring of pregnancy: feasibility and prospects", *BMC Pregnancy Childbirth*, vol. 18, no. 1, p. 136, 2018, ISSN: 1471-2393. DOI: 10.1186/s12884-018-1778-1.

[204] E. Ashwal, M. Y. Livne, J. I. Benichou, R. Unger, L. Hiersch, A. Aviram, A. Mani, and Y. Yogev, "Contemporary patterns of labor in nulliparous and multiparous women", *Am. J. Obstet. Gynecol.*, vol. 222, no. 3, 267.E1–267.E9, 2020, ISSN: 10976868. DOI: 10.1016/j.ajog.2019.09.035.

[205] L. Q. Krogh, S. Boie, T. B. Henriksen, J. Thornton, J. Fuglsang, and J. Glavind, "Induction of labour at 39 weeks versus expectant management in low-risk obese women: study protocol for a randomised controlled study", *BMJ Open*, vol. 12, no. 4, e057688, 2022, ISSN: 20446055. DOI: 10.1136/BMJOPEN-2021-057688.

[206] C. Cans, A. Colver, I. Krägeloh-Mann, M.-J. Platt, J. de la Cruz, R. Curran, M. Loane, R. Greenlees, and H. Dol, "European perinatal health report. Health and care of pregnant women and babies in Europe in 2010", European Perinatal Health Report, Tech. Rep., 2013, pp. 1–252. [Online]. Available: www.europeristat.com.

[207] L. Batinelli, A. Serafini, N. Nante, F. Petraglia, F. M. Severi, and G. Messina, "Induction of labour: clinical predictive factors for success and failure", *J. Obstet. Gynaecol. (Lahore).*, vol. 38, no. 3, pp. 352–358, 2018, ISSN: 13646893. DOI: 10.1080/01443615.2017.1361388.

[208] R. Bakker, S. Pierce, and D. Myers, "The role of prostaglandins E1 and E2, dinoprostone, and misoprostol in cervical ripening and the induction of labor: a mechanistic approach", *Arch Gynecol Obs.*, vol. 296, no. 2, pp. 167–179, 2017. DOI: 10.1007/s00404-017-4418-5.

[209] S. N. Vasist, P. Bhat, S. Ulman, and H. Hebbar, "Identification of contractions from Electrohysterography for prediction of prolonged labor", *J. Electr. Bioimpedance*, vol. 13, no. 1, pp. 4–9, 2022. DOI: 10.2478/JOEB-2022-0002.

[210] P. Wagura, A. Wasunna, A. Laving, D. Wamalwa, and P. Ng'ang'a, "Prevalence and factors associated with preterm birth at kenyatta national hospital", *BMC Pregnancy Childbirth*, vol. 18, no. 1, p. 107, 2018, ISSN: 1471-2393. DOI: 10.1186/s12884-018-1740-2.

[211] C. J. Verhoeven, A. Oudenaarden, M. A. Hermus, M. M. Porath, S. G. Oei, and B. W. Mol, "Validation of models that predict Cesarean section after induction of labor", *Ultrasound Obstet. Gynecol.*, vol. 34, no. 3, pp. 316–321, 2009, ISSN: 09607692. DOI: 10.1002/uog.7315.

[212] J. E. Triebwasser, J. Vanartsdalen, E. K. Kobernik, K. Seiler, and E. S. Langen, "Assessing Maternal and Fetal Risks Associated with Prolonged Induction of Labor", *Am. J. Perinatol.*, vol. 36, no. 5, pp. 455–459, 2019, ISSN: 10988785. DOI: 10.1055/S-0038-1675642/ID/JR180255-14.

[213] G. Nicholson and P. Cyr, "Cost Of Failed Labor Induction: A Us Hospital Perspective", *Value Heal.*, vol. 16, no. 3, A75, 2013, ISSN: 1098-3015. DOI: 10.1016/J.JVAL.2013.03.339.

[214] A. J. Kaimal, S. E. Little, A. O. Odibo, D. M. Stamilio, W. A. Grobman, E. F. Long, D. K. Owens, and A. B. Caughey, "Cost-effectiveness of elective induction of labor at 41 weeks in nulliparous women", *Am. J. Obstet. Gynecol.*, vol. 204, no. 2, 137.e1–137.e9, 2011, ISSN: 00029378. DOI: 10.1016/j.ajog.2010.08.012.

[215] E. A. Friedman, "Primigravid Labor", *Obstet. Gynecol.*, vol. 6, no. 6, pp. 567–589, 1955, ISSN: 0029-7844. DOI: 10.1097/00006250-195512000-00001.

[216] E. Friedman, "Labor in multiparas: a graphicostatistical analysis", *Obstet. Gynecol.*, vol. 8, no. 6, pp. 691–703, 1956. [Online]. Available: https://journals.lww.com/greenjournal/Citation/1956/12000/A{_}graphicostatistical{_}analysis.7.aspx.

[217] P. C. Tan, A. Othman, S. T. Win, J. G. S. Hong, N. Elias, and S. Z. Omar, "Induction of labour from 39 weeks in low-risk multiparas with ripe cervixes: A randomised controlled trial", *Aust. New Zeal. J. Obstet. Gynaecol.*, vol. 61, no. 6, pp. 882–890, 2021, ISSN: 1479-828X. DOI: 10.1111/AJO.13377.

[218] D. G. Kolkman, C. J. Verhoeven, S. J. Brinkhorst, J. A. Van Der Post, E. Pajkrt, B. C. Opmeer, and B. J. Mol, "The bishop score as a predictor of labor induction success: A systematic review", *Am. J. Perinatol.*, vol. 30, no. 8, pp. 625–630, 2013, ISSN: 07351631. DOI: 10.1055/S-0032-1331024/ID/JR12M0145-39.

[219] Y. Zhang, D. Hao, L. Yang, X. Zhou, Y. Ye-Lin, and Y. Yang, "Assessment of Features between Multichannel Electrohysterogram for Differentiation of Labors", *Sensors 2022, Vol. 22, Page 3352*, vol. 22, no. 9, p. 3352, 2022, ISSN: 1424-8220. DOI: 10.3390/S22093352.

[220] J. Terrien, C. Marque, J. Gondry, T. Steingrimsdottir, and B. Karlsson, "Uterine electromyogram database and processing function interface: An open standard analysis platform for electrohysterogram signals", *Comput. Biol. Med.*, vol. 40, no. 2, pp. 223–230, 2010, ISSN: 0010-4825. DOI: 10.1016/J.COMPBIOMED.2009.11.019.

[221] D. Hao, Q. Qiu, X. Zhou, Y. An, J. Peng, L. Yang, and D. Zheng, "Application of decision tree in determining the importance of surface electrohysterography signal characteristics for recognizing uterine contractions", *Biocybern. Biomed. Eng.*, vol. 39, no. 3, pp. 806–813, 2019, ISSN: 0208-5216. DOI: 10.1016/J.BBE.2019.06.008.

[222] K. Horoba, J. Jezewski, A. Matonia, J. Wrobel, R. Czabanski, and M. Jezewski, "Early predicting a risk of preterm labour by analysis of antepartum electrohysterograhic signals", *Biocybern. Biomed. Eng.*, vol. 36, no. 4, pp. 574–583, 2016, ISSN: 02085216. DOI: 10.1016/J.BBE.2016.06.004.

[223] A. Lemancewicz, M. Borowska, P. Kuć, E. Jasińska, P. Laudański, T. Laudański, and E. Oczeretko, "Early diagnosis of threatened premature labor by electrohysterographic recordings - The use of digital signal processing", *Biocybern. Biomed. Eng.*, vol. 36, no. 1, pp. 302–307, 2016, ISSN: 02085216. DOI: 10.1016/J.BBE.2015.11.005.

[224] P. S. Asmi, K. Subramaniam, and N. V. Iqbal, "Classification of fractal features of uterine EMG signal for the prediction of preterm birth", *Biomed. Pharmacol. J.*, vol. 11, no. 1, pp. 369–374, 2018, ISSN: 24562610. DOI: 10.13005/BPJ/1381.

[225] M. Mischi, C. Chen, T. Ignatenko, H. De Lau, B. Ding, S. G. Guid Oei, and C. Rabotti, "Dedicated Entropy Measures for Early Assessment of Pregnancy Progression From Single-Channel Electrohysterography", *IEEE Trans. Biomed. Eng.*, vol. 65, no. 4, pp. 875–884, 2018, ISSN: 1558-2531. DOI: 10.1109/TBME.2017.2723933.

[226] L. Chen, Y. Hao, and X. Hu, "Detection of preterm birth in electrohysterogram signals based on wavelet transform and stacked sparse autoencoder", *PLoS One*, vol. 14, no. 4, e0214712, 2019, ISSN: 1932-6203. DOI: 10.1371/JOURNAL.PONE.0214712.

[227] G. Prats-Boluda, J. Pastor-Tronch, J. Garcia-Casado, R. Monfort-Ortíz, A. Perales Marín, V. Diago, A. Roca Prats, and Y. Ye-Lin, "Optimization of Imminent Labor Prediction Systems in Women with Threatened Preterm Labor Based on Electrohysterography", *Sensors*, vol. 21, no. 7, p. 2496, 2021, ISSN: 1424-8220. DOI: 10.3390/S21072496.

[228] S. Mohammadi Far, M. Beiramvand, M. Shahbakhti, and P. Augustyniak, "Prediction of Preterm Delivery from Unbalanced EHG Database", *Sensors*, vol. 22, no. 4, p. 1507, 2022, ISSN: 14248220. DOI: 10.3390/S22041507.

[229] S. Saleem, A. Saeed, S. Usman, J. Ferzund, J. Arshad, J. Mirza, and T. Manzoor, "Granger causal analysis of electrohysterographic and tocographic recordings for classification of term vs. preterm births", *Biocybern. Biomed. Eng.*, vol. 40, no. 1, pp. 454–467, 2020, ISSN: 02085216. DOI: 10.1016/J.BBE.2020.01.007.

[230] J. Mas-Cabo, G Prats-Boluda, J Garcia-Casado, J Alberola-Rubio, A Perales, and Y Ye-Lin, "Design and Assessment of a Robust and Generalizable ANN-Based Classifier for the Prediction of Premature Birth by means of Multichannel Electrohysterographic Records", *J. Sensors*, vol. 7, pp. 1–13, 2019. DOI: 10.1155/2019/5373810.

[231] I. O. Idowu, P. Fergus, A. Hussain, C. Dobbins, and H. Al-Askar, "Advance artificial neural network classification techniques using EHG for detecting preterm births", *Proc. - 2014 8th Int. Conf. Complex, Intell. Softw. Intensive Syst. CISIS 2014*, pp. 95–100, 2014. DOI: 10.1109/CISIS.2014.14.

[232] N. Sadi-Ahmed, B. Kacha, H. Taleb, and M. Kedir-Talha, "Relevant Features Selection for Automatic Prediction of Preterm Deliveries from Pregnancy ElectroHysterograhic (EHG) records", *J. Med. Syst.*, vol. 41, no. 12, p. 204, 2017, ISSN: 1573-689X. DOI: 10.1007/S10916-017-0847-8.

[233] F. Jager, S. Libenšek, and K. Geršak, "Characterization and automatic classification of preterm and term uterine records", *PLoS One*, vol. 13, no. 8, e0202125, 2018, ISSN: 19326203. DOI: 10.1371/JOURNAL.PONE.0202125.

[234] J. You, Y. Kim, W. Seok, S. Lee, D. Sim, K. S. Park, and C. Park, "Multivariate Time–Frequency Analysis of Electrohysterogram for Classification of Term and Preterm Labor", *J. Electr. Eng. Technol.*, vol. 14, no. 2, pp. 897–916, 2019, ISSN: 1975-0102. DOI: 10.1007/s42835-019-00118-9.

[235] H. Allahem and S. Sampalli, "Automated uterine contractions pattern detection framework to monitor pregnant women with a high risk of premature labour", *Informatics Med. Unlocked*, vol. 20, p. 100 404, 2020, ISSN: 2352-9148. DOI: 10.1016/J.IMU.2020.100404.

[236] J. Peng, D. Hao, L. Yang, M. Du, X. Song, H. Jiang, Y. Zhang, and D. Zheng, "Evaluation of electrohysterogram measured from different gestational weeks for recognizing preterm delivery: a preliminary study using random Forest", *Biocybern. Biomed. Eng.*, vol. 40, no. 1, pp. 352–362, 2020, ISSN: 0208-5216. DOI: 10.1016/J.BBE.2019.12.003.

[237] J. Xu, Z. Chen, Y. Lu, X. Yang, and A. Pumir, "Improved Preterm Prediction Based on Optimized Synthetic Sampling of EHG Signal", 2020. DOI: https://doi.org/10.48550/arXiv.2007.01447.

[238] H. Lou, H. Liu, Z. Chen, Z. Zhen, B. Dong, and J. Xu, "Bio-process inspired characterization of pregnancy evolution using entropy and its application in preterm birth detection", *Biomed. Signal Process. Control*, vol. 75, p. 103 587, 2022, ISSN: 1746-8094. DOI: 10.1016/J.BSPC.2022.103587.

[239] H. Allahem and S. Sampalli, "Automated labour detection framework to monitor pregnant women with a high risk of premature labour using machine learning and deep learning", *Informatics Med. Unlocked*, vol. 28, p. 100 771, 2022, ISSN: 23529148. DOI: 10.1016/j.imu.2021.100771.

[240] Y. Xu, D. Hao, M. J. Taggart, and D. Zheng, "Regional identification of information flow termination of electrohysterographic signals: Towards understanding human uterine electrical propagation", *Comput. Methods Programs Biomed.*, vol. 223, p. 106 967, 2022, ISSN: 0169-2607. DOI: 10.1016/J.CMPB.2022.106967.

[241] C. Rabotti, M. Mischi, J. O. Van Laar, G. S. Oei, and J. W. Bergmans, "Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals", *Physiol. Meas.*, vol. 29, no. 7, pp. 829–841, 2008, ISSN: 0967-3334. DOI: 10.1088/0967-3334/29/7/011.

[242] Y. Ye-Lin, J. Bueno-Barrachina, G. Prats-boluda, R. Rodriguez de Sanabria, and J. Garcia-Casado, "Wireless sensor node for non-invasive high precision electrocardiographic signal acquisition based on a multi-ring electrode", *Measurement*, vol. 97, pp. 195–202, 2017, ISSN: 0263-2241. DOI: 10.1016/J.MEASUREMENT.2016.11.009.

[243] A. Diaz-Martinez, R. Monfort-Ortiz, Y. Ye-Lin, J. Garcia-Casado, F. Nieto-Del-Amor, V. J. Diago-Almela, I. Rey-Ferreira, M. Nieto-Tous, and G. Prats-Boluda, "Comparative Study of Uterine Myoelectrical Response to Labour Induction Drugs in Nulliparous and Parous Women with Different EHG Analysis Techniques", *2021 Int. Conf. e-Health Bioeng.*, pp. 1–4, 2021, ISSN: 2575-5145. DOI: 10.1109/EHB52898.2021.9657548.

[244] J. Xu, M. Wang, J. Zhang, Z. Chen, W. Huang, G. Shen, and M. Zhang, "Network Theory Based EHG Signal Analysis and its Application in Preterm Prediction", *IEEE J. Biomed. Heal. Informatics*, vol. 26, no. 7, pp. 2876–2887, 2022, ISSN: 21682208. DOI: 10.1109/JBHI.2022.3140427.

[245] M. Talebinejad, A. D. C. Chan, and A. Miri, "A Lempel-Ziv complexity measure for muscle fatigue estimation", *J. Electromyogr. Kinesiol.*, vol. 21, no. 2, pp. 236–41, 2011, ISSN: 1873-5711. DOI: 10.1016/j.jelekin.2010.12.003.

[246] S. Kesić and S. Z. Spasić, "Application of Higuchi's fractal dimension from basic to clinical neurophysiology: A review", *Comput. Methods Programs Biomed.*, vol. 133, pp. 55–70, 2016, ISSN: 0169-2607. DOI: 10.1016/J.CMPB.2016.05.014.

[247] J. S. Richman and J. R. Moorman, "Physiological time-series analysis using approximate and sample entropy", *Am. J. Physiol. - Hear. Circ. Physiol.*, vol. 278, no. 6 47-6, pp. 2039–2049, 2000, ISSN: 03636135. DOI: 10.1152/ajpheart.2000.278.6.H2039.

[248] A. Delgado-Bonal and A. Marshak, "Approximate Entropy and Sample Entropy: A Comprehensive Tutorial", *Entropy*, vol. 21, no. 6, p. 541, 2019. DOI: 10.3390/e21060541.

[249] D. Devi, S. Sophia, and S. R. Boselin Prabhu, "Deep learning-based cognitive state prediction analysis using brain wave signal", *Cogn. Comput. Human-Robot Interact. Princ. Pract.*, pp. 69–84, 2021. DOI: 10.1016/B978-0-323-85769-7.00017-3.

[250] C. E. Shannon, "A Mathematical Theory of Communication", *Bell Syst. Tech. J.*, vol. 27, no. 3, pp. 379–423, 1948, ISSN: 15387305. DOI: 10.1002/J.1538-7305.1948.TB01338.X.

[251] A. Lempel and J. Ziv, "On the Complexity of Finite Sequences", *IEEE Trans. Inf. Theory*, vol. 22, no. 1, pp. 75–81, 1976, ISSN: 15579654. DOI: 10.1109/TIT.1976.1055501.

[252] M. Aboy, R. Hornero, D. Abásolo, and D. Álvarez, "Interpretation of the Lempel-Ziv complexity measure in the context of biomedical signal analysis", *IEEE Trans. Biomed. Eng.*, vol. 53, no. 11, pp. 2282–2288, 2006, ISSN: 00189294. DOI: 10.1109/TBME.2006.883696.

[253] S. W. Rhomadona, M. N. Widyawati, and S. Suryono, "Monitoring of Uterus Electrical Activities using Electromyography in Stage I Induction Labor", *J. Phys. Conf. Ser.*, vol. 1179, pp. 1–6, 2018. DOI: 10.1088/1742-6596/1179/1/012133.

[254] S. M. Yount and N. Lassiter, "The Pharmacology of Prostaglandins for Induction of Labor", *J. Midwifery Womens. Health*, vol. 58, no. 2, pp. 133–144, 2013, ISSN: 1542-2011. DOI: 10.1111/JMWH.12022.

[255] C. K. Konopka, W. G. Glanzner, M. L. Rigo, M. T. Rovani, F. V. Comim, P. B. Gonçalves, E. N. Morais, A. Q. Antoniazzi, C. F. Mello, and I. B. Cruz, "Responsivity to PGE2 labor induction involves concomitant differential prostaglandin E receptor gene expression in cervix and myometrium", *Genet. Mol. Res. GMR*, vol. 14, no. 3, pp. 10 877–10 887, 2015, ISSN: 1676-5680. DOI: 10.4238/2015.SEPTEMBER.9.25.

[256] N. Roos, C. S. Blesson, O. Stephansson, B. Masironi, Y. Vladic Stjernholm, G. Ekman-Ordeberg, and L. Sahlin, "The expression of prostaglandin receptors EP3 and EP4 in human cervix in post-term pregnancy differs between failed and successful labor induction", *Acta Obstet. Gynecol. Scand.*, vol. 93, no. 2, pp. 159–167, 2014, ISSN: 1600-0412. DOI: 10.1111/AOGS.12300.

[257] U. Indraccolo, G. Scutiero, and P. Greco, "Sonographic Cervical Shortening after Labor Induction is a Predictor of Vaginal Delivery", *Rev. Bras. Ginecol. e Obstet.*, vol. 38, no. 12, pp. 585–588, 2016. DOI: 10.1055/s-0036-1597629.

[258] J. Juhasova, M. Kreft, R. Zimmermann, and N. Kimmich, "Impact factors on cervical dilation rates in the first stage of labor", *J. Perinat. Med.*, vol. 46, no. 1, pp. 59–66, 2018. DOI: 10.1515/jpm-2016-0284.

[259] G. A. Ryan, S. M. Nicholson, D. J. Crankshaw, and J. J. Morrison, "Maternal parity and functional contractility of human myometrium in vitro in the third trimester of pregnancy", *J. Perinatol.*, vol. 39, no. 3, pp. 439–444, 2019, ISSN: 1476-5543. DOI: 10.1038/s41372-019-0312-2.

[260] S. Gerli, A. Favilli, C. Giordano, V. Bini, and G. C. Di Renzo, "Single indications of induction of labor with prostaglandins and risk of cesarean delivery: A retrospective cohort study", *J. Obstet. Gynaecol. Res.*, vol. 39, no. 5, pp. 926–931, 2013, ISSN: 1447-0756. DOI: 10.1111/JOG.12000.

[261] G. A. Ryan, D. J. Crankshaw, and J. J. Morrison, "Effects of maternal parity on response of human myometrium to oxytocin and ergometrine in vitro", *Eur. J. Obstet. Gynecol. Reprod. Biol.*, vol. 242, pp. 99–102, 2019, ISSN: 18727654. DOI: 10.1016/j.ejogrb.2019.09.006.

[262] A. Feola, S. Abramowitch, K. Jones, S. Stein, and P. Moalli, "Parity negatively impacts vaginal mechanical properties and collagen structure in rhesus macaques", *Am. J. Obstet. Gynecol.*, vol. 203, no. 6, 595.e1–8, 2010, ISSN: 0002-9378. DOI: 10.1016/J.AJOG.2010.06.035.

[263] M. Prevost, P. Zelkowitz, T. Tulandi, B. Hayton, N. Feeley, C. S. Carter, L. Joseph, H. Pournajafi-Nazarloo, E. Y. Ping, H. Abenhaim, and I. Gold, "Oxytocin in pregnancy and the postpartum: Relations to labor and its management", *Front. Public Heal.*, vol. 2, pp. 1–9, 2014, ISSN: 22962565. DOI: 10.3389/FPUBH.2014.00001/BIBTEX.

[264] R. B. Govindan, E. Siegel, S. Mckelvey, P. Murphy, C. L. Lowery, and H. Eswaran, "Tracking the Changes in Synchrony of the Electrophysiological Activity as the Uterus Approaches Labor Using Magnetomyographic Technique", *Reprod. Sci.*, vol. 22, no. 5, pp. 595–601, 2015, ISSN: 1933-7191. DOI: 10.1177/1933719114556484.

[265] J. Mas-Cabo, G. Prats-Boluda, Y. Ye-Lin, J. Alberola-Rubio, A. Perales, and J. Garcia-Casado, "Characterization of the effects of Atosiban on uterine electromyograms recorded in women with threatened preterm labor", *Biomed. Signal Process. Control*, vol. 52, pp. 198–205, 2019, ISSN: 17468094. DOI: 10.1016/j.bspc.2019.04.001.

[266] Y. Ye-Lin, J. Garcia-Casado, G. Prats-Boluda, J. Alberola-Rubio, and A. Perales, "Automatic identification of motion artifacts in EHG recording for robust analysis of uterine contractions", *Comput. Math. Methods Med.*, vol. 2014, pp. 1–11, 2014, ISSN: 17486718. DOI: 10.1155/2014/470786.

[267] J. Kagwisage, B. S Balandya, A. B Pembe, and P. GM Mujinja, "Health Related Quality of Life Post Labour Induction with Misoprostol Versus Dinoprostone At Muhimbili National Hospital in Dar Es Salaam, Tanzania: A cross Sectional Study", *East African Heal. Res. J.*, vol. 4, no. 1, pp. 58–64, 2020, ISSN: 2520-5285. DOI: 10.24248/EAHRJ.V4I1.622.

[268] J. Mas-Cabo, G. Prats-Boluda, J. García-Casado, A. Perales Marin, J. Alberola-Rubio, A. López Corral, and Y. Ye-Lin, "Caracterización de la actividad eléctrica uterina durante la gestación, el parto y el postparto", in *Actas del XXXVII Congr. Anu. la Soc. Española Ing. Biomédica,*, Santander: ISBN 978-84-09-16707-4, 2019, pp. 379–382. DOI: ISBN978-84-09-16707-4.

[269] Zahid, *Postpartum haemorrhage | National Health Portal Of India*, 2017. [Online]. Available: https://www.nhp.gov.in/disease/gynaecology-and-obstetrics/postpartum-haemorrhage (visited on 03/16/2020).

[270] J. P. Souza, A. M. Gülmezoglu, G. Carroli, P. Lumbiganon, and Z. Qureshi, "The world health organization multicountry survey on maternal and newborn health: study protocol", *BMC Health Serv. Res.*, vol. 11, pp. 1–10, 2011, ISSN: 14726963. DOI: 10.1186/1472-6963-11-286.

[271] M. Vlassoff, H. A. Abdalla, V. Gor, A. H. A., and V. Gor, "The Cost to the Health System of Postpartum Hemorrhage in Egypt", Guttmacher Institute, New York, Tech. Rep., 2016, pp. 3–15. [Online]. Available: https://www.guttmacher.org/report/cost-of-postpartum-hemorrhage-in-egypt.

[272] T. Fukami, H. Koga, M. Goto, M. Ando, S. Matsuoka, A. Tohyama, H. Yamamoto, S. Nakamura, T. Koyanagi, Y. To, H. Kondo, F. Eguchi, and H. Tsujioka, "Incidence and risk factors for postpartum hemorrhage among transvaginal deliveries at a tertiary perinatal medical facility in Japan", *PLoS One*, vol. 14, no. 1, pp. 1–8, 2019, ISSN: 19326203. DOI: 10.1371/journal.pone.0208873.

[273] J. E. Lutomski, B. M. Byrne, D. Devane, and R. A. Greene, "Increasing trends in atonic postpartum haemorrhage in Ireland: An 11-year population-based cohort study", *BJOG An Int. J. Obstet. Gynaecol.*, 2012, ISSN: 14700328. DOI: 10.1111/j.1471-0528.2011.03198.x.

[274] E. Hadar, T. Biron-Shental, O. Gavish, O. Raban, and Y. Yogev, "A comparison between electrical uterine monitor, tocodynamometer and intra uterine pressure catheter for uterine activity in labor", *J. Matern. Neonatal Med.*, vol. 28, no. 12, pp. 1367–1374, 2015, ISSN: 14764954. DOI: 10.3109/14767058.2014.954539.

[275] C. Benalcazar Parra, A. Tendero, Y. Ye-Lin, J. Alberola-Rubio, A. Perales Marin, J. Garcia-Casado, and G. Prats-Boluda, "Feasibility of labor induction success prediction based on uterine myoelectric activity spectral analysis", *Proc. 11th Int. Jt. Conf. Biomed. Eng. Syst. Technol.*, vol. 4, pp. 70–77, 2018. DOI: 10.5220/0006649400700077.

[276] T. Euliano, M. Skowronski, D. Marossero, J. Shuster, and R. Edwards, "Prediction of intrauterine pressure waveform from transabdominal electrohysterography", *J. Matern. Neonatal Med.*, vol. 19, no. 12, pp. 803–808, 2006, ISSN: 14764954. DOI: 10.1080/14767050601023657.

[277] M. J. Rooijakkers, C. Rabotti, S. G. Oei, R. M. Aarts, and M. Mischi, "Low-complexity intrauterine pressure estimation using the Teager energy operator on electrohysterographic recordings", *Physiol. Meas.*, vol. 35, no. 7, pp. 1215–1228, 2014, ISSN: 13616579. DOI: 10.1088/0967-3334/35/7/1215.

[278] D. Schlembach, W. L. Maner, R. E. Garfield, and H. Maul, "Monitoring the progress of pregnancy and labor using electromyography", *Eur. J. Obstet. Gynecol. Reprod. Biol.*, vol. 144, S33–S39, 2009, ISSN: 18727654. DOI: 10.1016/j.ejogrb.2009.02.016.

[279] M. Hassan, J. Terrien, C. Marque, and B. Karlsson, "Comparison between approximate entropy, correntropy and time reversibility: Application to uterine electromyogram signals", *Med. Eng. Phys.*, vol. 33, no. 8, pp. 980–986, 2011, ISSN: 13504533. DOI: 10.1016/j.medengphy.2011.03.010.

[280] J. Vrhovec and A. Macek, "An Uterine Electromyographic Activity as a Measure of Labor Progression", in *Appl. EMG Clin. Sport. Med.* InTech, 2012. DOI: 10.5772/25526.

[281] U. R. Acharya, V. K. Sudarshan, S. Q. Rong, Z. Tan, C. M. Lim, J. E. Koh, S. Nayak, and S. V. Bhandary, "Automated detection of premature delivery using empirical mode and wavelet packet decomposition techniques with uterine electromyogram signals.", eng PT - Journal Article, *Comput. Biol. Med.*, vol. 85, no. 1879-0534 (Electronic), pp. 33–42, 2017, ISSN: 1879-0534. DOI: 10.1016/j.compbiomed.2017.04.013. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/28433870.

[282] P. Ren, S. Yao, J. Li, P. A. Valdes-Sosa, and K. M. Kendrick, "Improved prediction of preterm delivery using empirical mode decomposition analysis of uterine electromyography signals", *PLoS One*, vol. 10, no. 7, 2015, ISSN: 19326203. DOI: 10.1371/journal.pone.0132116.

[283] F. Sammali, N. P. M. Kuijsters, B. C. Schoot, M. Mischi, and C. Rabotti, "Feasibility of Transabdominal Electrohysterography for Analysis of Uterine Activity in Nonpregnant Women", *Reprod. Sci.*, vol. 25, no. 7, pp. 1124–1133, 2018, ISSN: 1933-7205. DOI: 10.1177/1933719118768700.

[284] H. Maul, W. L. Maner, G. Olson, G. R. Saade, and R. E. Garfield, "Non-invasive transabdominal uterine electromyography correlates with the strength of intrauterine pressure and is predictive of labor and delivery", *J. Matern. Neonatal Med.*, vol. 15, no. 5, pp. 297–301, 2004, ISSN: 14767058. DOI: 10.1080/14767050410001695301.

[285] S. Shukla, S. K. Singh, and D. Mitra, "An efficient heart sound segmentation approach using kurtosis and zero frequency filter features", *Biomed. Signal Process. Control*, vol. 57, p. 101 762, 2020, ISSN: 17468094. DOI: 10.1016/j.bspc.2019.101762.

[286] Y. Ye-Lin, J. Alberola-Rubio, G. Prats-boluda, A. Perales, D. Desantes, and J. Garcia-Casado, "Feasibility and Analysis of Bipolar Concentric Recording of Electrohysterogram with Flexible Active Electrode", *Ann. Biomed. Eng.*, vol. 43, no. 4, pp. 968–976, 2015, ISSN: 0090-6964. DOI: 10.1007/s10439-014-1130-5.

[287] X. S. Zhang, R. J. Roy, and E. W. Jensen, "EEG complexity as a measure of depth of anesthesia for patients", *IEEE Trans. Biomed. Eng.*, vol. 48, no. 12, pp. 1424–1433, 2001, ISSN: 00189294. DOI: 10.1109/10.966601.

[288] M. J. Katz, "Fractals and the analysis of waveforms", *Comput. Biol. Med.*, vol. 18, no. 3, pp. 145–156, 1988, ISSN: 00104825. DOI: 10.1016/0010-4825(88)90041-8.

[289] H. de Lau, K. T. Yang, C. Rabotti, M. Vlemminx, G. Bajlekov, M. Mischi, and S. G. Oei, "Toward a new modality for detecting a uterine rupture: electrohysterogram propagation analysis during trial of labor after cesarean", *J. Matern. Neonatal Med.*, vol. 30, no. 5, 2017, ISSN: 14764954. DOI: 10.1080/14767058.2016.1178227.

[290] B. S. Raghavendra and D. Narayana Dutt, "Computing Fractal Dimension of Signals using Multiresolution Box-counting Method", *Int. J. Inf. Math. Sci.*, vol. 6, pp. 55–65, 2010.

[291] G. S. Fisch, I. L. Cohen, E. C. Jenkins, and W. T. Brown, "Screening developmentally disabled male populations for fragile X: The effect of sample size", *Am. J. Med. Genet.*, vol. 30, no. 1-2, pp. 655–663, 1988, ISSN: 01487299. DOI: 10.1002/ajmg.1320300166.

[292] J. Cohen, *Statistical Power Analysis for the Behavioral Sciences*, 2nd. New York: Lawrence Erlbaum Associates, 1988, ISBN: 0-8058-0283-5.

[293] J. Alberola-Rubio, J. Garcia-Casado, G. Prats-Boluda, Y. Ye-Lin, D. Desantes, J. Valero, and A. Perales, "Prediction of labor onset type: Spontaneous vs induced; role of electrohysterography?", *Comput. Methods Programs Biomed.*, vol. 144, pp. 127–133, 2017. DOI: 10.1016/j.cmpb.2017.03.018.

[294] W. L. Maner, L. B. MacKay, G. R. Saade, and R. E. Garfield, "Characterization of abdominally acquired uterine electrical signals in humans, using a non-linear analytic method.", *Med. Biol. Eng. Comput.*, vol. 44, no. 1-2, pp. 117–23, 2006, ISSN: 0140-0118. DOI: 10.1007/s11517-005-0011-3.

[295] G. Marchini, H. Lagercrantz, J. Winberg, and K. Uvnäs-Moberg, "Fetal and maternal plasma levels of gastrin, somatostatin and oxytocin after vaginal delivery and elective cesarean section", *Early Hum. Dev.*, vol. 18, no. 1, pp. 73–79, 1988, ISSN: 03783782. DOI: 10.1016/0378-3782(88)90044-8.

[296] F. Morfaw, M. Fundoh, C. Pisoh, B. Ayaba, L. Mbuagbaw, L. N. Anderson, and L. Thabane, "Misoprostol as an adjunct to oxytocin can reduce postpartum-haemorrhage: a propensity score–matched retrospective chart review in Bamenda-Cameroon, 2015–2016", *BMC Pregnancy Childbirth*, vol. 19, no. 1, p. 257, 2019, ISSN: 1471-2393. DOI: 10.1186/s12884-019-2407-3.

[297] A. G. Batista, S. Najdi, D. M. Godinho, C. Martins, F. C. Serrano, M. D. Ortigueira, and R. T. Rato, "A multichannel time–frequency and multiwavelet toolbox for uterine electromyography processing and visualisation", *Comput. Biol. Med.*, vol. 76, pp. 178–191, 2016, ISSN: 0010-4825. DOI: 10.1016/J.COMPBIOMED.2016.07.003.

[298] J. C. Edwards and J. B. Vander Veer, "A study of the chest leads of the electrocardiogram with an evaluation of the positions of the precordial electrode", *Am. Heart J.*, vol. 16, no. 4, pp. 431–448, 1938, ISSN: 00028703. DOI: 10.1016/S0002-8703(38)90780-X.

[299] A. Smrdel and F. Jager, "Separating sets of term and pre-term uterine EMG records", *Physiol. Meas.*, vol. 36, no. 2, p. 341, 2015, ISSN: 0967-3334. DOI: 10.1088/0967-3334/36/2/341.

[300] M. Lucovnik, W. L. Maner, L. R. Chambliss, R. Blumrick, J. Balducci, Z. Novak-Antolic, and R. E. Garfield, "Noninvasive uterine electromyography for prediction of preterm delivery", *Am. J. Obstet. Gynecol.*, vol. 204, no. 3, 228.e1–228.e10, 2011, ISSN: 00029378. DOI: 10.1016/j.ajog.2010.09.024.

[301] R. Martinek, M. Ladrova, M. Sidikova, R. Jaros, K. Behbehani, R. Kahankova, and A. Kawala-Sterniuk, *Advanced bioelectrical signal processing methods: Past, present, and future approach—part iii: Other biosignals*, 2021. DOI: 10.3390/s21186064.

[302] J.-B. Tylcz, C. Muszynski, J. Dauchet, D. Istrate, and C. Marque, "An Automatic Method for the Segmentation and Classification of Imminent Labor Contraction From Electrohysterograms", *IEEE Trans. Biomed. Eng.*, vol. 67, no. 4, pp. 1133–1141, 2020, ISSN: 0018-9294. DOI: 10.1109/TBME.2019.2930618.

[303] W. L. Maner, R. E. Garfield, H. Maul, G. Olson, and G. Saade, "Predicting term and preterm delivery with transabdominal uterine electromyography", *Obstet. Gynecol.*, vol. 101, no. 6, pp. 1254–1260, 2003, ISSN: 0029-7844. DOI: 10.1016/S0029-7844(03)00341-7.

[304] J. Mas-Cabo, G. Prats-Boluda, J. Garcia-Casado, J. Alberola-Rubio, R. Monfort-Ortiz, C. Martinez-Saez, A. Perales, and Y. Ye-Lin, "Electrohysterogram for ANN-Based Prediction of Imminent Labor in Women with Threatened Preterm Labor Undergoing Tocolytic Therapy", *Sensors*, vol. 20, no. 9, p. 2681, 2020, ISSN: 1424-8220. DOI: 10.3390/s20092681.

[305] C. Nordander, J. Willner, G. Å Hansson, B. Larsson, J. Unge, L. Granquist, and S. Skerfving, "Influence of the subcutaneous fat layer, as measured by ultrasound, skinfold calipers and BMI, on the EMG amplitude", *Eur. J. Appl. Physiol.*, vol. 89, no. 6, pp. 514–519, 2003, ISSN: 14396319. DOI: 10.1007/S00421-003-0819-1/METRICS.

[306] O. Most, O. Langer, R. Kerner, G. B. David, and I. Calderon, "Can myometrial electrical activity identify patients in preterm labor?", *Am. J. Obstet. Gynecol.*, vol. 199, no. 4, 378.e1–6, 2008, ISSN: 1097-6868. DOI: 10.1016/j.ajog.2008.08.003.

[307] J. Mas-Cabo, "Análisis de la señal electrohisterográfica durante la gestación para la predicción del parto prematuro", Tech. Rep., 2015.

[308] I. Verdenik, M. Pajntar, and B. Leskošek, "Uterine electrical activity as predictor of preterm birth in women with preterm contractions", *Eur. J. Obstet. Gynecol. Reprod. Biol.*, vol. 95, no. 2, pp. 149–153, 2001, ISSN: 03012115. DOI: 10.1016/S0301-2115(00)00418-8.

[309] F. Nieto-Del-amor, G. Prats-Boluda, J. L. Martinez-De-juan, A. Diaz-Martinez, R. Monfort-Ortiz, V. J. Diago-Almela, and Y. Ye-Lin, "Optimized Feature Subset Selection Using Genetic Algorithm for Preterm Labor Prediction Based on Electrohysterography", *Sensors 2021, Vol. 21, Page 3350*, vol. 21, no. 10, p. 3350, 2021, ISSN: 1424-8220. DOI: 10.3390/S21103350.

[310] A. Diab, M. Hassan, B. Karlsson, and C. Marque, "Effect of decimation on the classification rate of non-linear analysis methods applied to uterine EMG signals", *IRBM*, vol. 34, no. 4-5, pp. 326–329, 2013, ISSN: 19590318. DOI: 10.1016/j.irbm.2013.07.010.

[311] A. Diab, M. Hassan, C. Marque, and B. Karlsson, "Performance analysis of four nonlinearity analysis methods using a model with variable complexity and application to uterine EMG signals", *Med. Eng. Phys.*, vol. 36, no. 6, pp. 761–767, 2014, ISSN: 13504533. DOI: 10.1016/j.medengphy.2014.01.009.

[312] R. Esteller, G. Vachtsevanos, J. Echauz, and B. Litt, "A Comparison of waveform fractal dimension algorithms", *IEEE Trans. Circuits Syst. I Fundam. Theory Appl.*, vol. 48, no. 2, pp. 177–183, 2001, ISSN: 10577122. DOI: 10.1109/81.904882.

[313] G. E. Polychronaki, P. Y. Ktonas, S Gatzonis, A Siatouni, P. A. Asvestas, H Tsekou, D Sakas, and K. S. Nikita, "Comparison of fractal dimension estimation algorithms for epileptic seizure onset detection", *J. Neural Eng.*, vol. 7, no. 4, p. 046 007, 2010, ISSN: 1741-2560. DOI: 10.1088/1741-2560/7/4/046007.

[314] R. Romero, S. K. Dey, and S. J. Fisher, "Preterm labor: one syndrome, many causes", *Science*, vol. 345, no. 6198, pp. 760–765, 2014, ISSN: 1095-9203. DOI: 10.1126/SCIENCE.1251816.

[315] F. P. Hadlock, R. B. Harrist, and J. Martinez-Poyer, "In utero analysis of fetal growth: A sonographic weight standard", *Radiology*, vol. 181, no. 1, pp. 129–133, 1991, ISSN: 00338419. DOI: 10.1148/RADIOLOGY.181.1.1887021.

[316] C. Benalcazar Parra, R Montfort-Orti, Y. Ye-Lin, J. Alberola-Rubio, A. Perales Marin, J. Mas-Cabo, J. Garcia-Casado, and G. Prats-Boluda, "Characterization of Uterine Response to Misoprostol based on Electrohysterogram", *Proc. 10th Int. Jt. Conf. Biomed. Eng. Syst. Technol. (BIOSTEC 2017)*, pp. 64–69, 2017. DOI: 10.5220/0006146700640069.

[317] National Institute for Health and Care Excellence, "Intrapartum care for healthy women and babies (Clinical guideline 190)", Tech. Rep., 2014, pp. 1–6. [Online]. Available: https://www.nice.org.uk/guidance/cg190.

[318] T. Lavender, Z. Alfirevic, and S. Walkinshaw, "Effect of different partogram action lines on birth outcomes: A randomized controlled trial", *Obstet. Gynecol.*, vol. 108, no. 2, pp. 295–302, 2006, ISSN: 00297844. DOI: 10.1097/01.AOG.0000226862.78768.5c.

[319] S. Kenyon, J. Sanders, L. Middleton, and T. Johnston, "What is the best treatment to reduce the need for caesarean section in nulliparous women at term with delayed first stage of labour?", *BMJ*, vol. 357, pp. 1–6, 2017, ISSN: 17561833. DOI: 10.1136/bmj.j2469.

[320] M. N. Schorn, "Uterine Activity During the Third Stage of Labor", *J. Midwifery Womens. Health*, vol. 57, no. 2, pp. 151–155, 2012, ISSN: 1526-9523. DOI: 10.1111/j.1542-2011.2011.00130.x.

[321] Y. Masuzawa and K. Yaeko, "Uterine activity during the two hours after placental delivery among low-risk pregnancies: an observational study", *J. Matern. Neonatal Med.*, vol. 30, no. 20, pp. 2446–2451, 2017, ISSN: 1476-7058. DOI: 10.1080/14767058.2016.1253057.

[322] H. Rosen, L. Salzer, L. Hiersch, A. Aviram, A. Ben-Haroush, and Y. Yogev, "Uterine electric activity during the third stage of labor; a look into the physiology of a deserted stage", *J. Matern. neonatal Med.*, vol. 27, no. 9, pp. 921–925, 2014, ISSN: 1476-7058. DOI: 10.3109/14767058.2013.846315.

[323] K. M. Thijssen, M. J. van den Broek, F. A. Koenraads, J. I. Cantineau-Goedegebuure, D. N. Papatsonis, B. G. van Willigen, J. P. Dieleman, M. B. van der Hout-van der Jagt, M. E. Westerhuis, and S. G. Oei, "Detection of postpartum uterine activity with electrohysterography", *Eur. J. Obstet. Gynecol. Reprod. Biol.*, vol. 291, pp. 23–28, 2023, ISSN: 03012115. DOI: 10.1016/j.ejogrb.2023.10.005.

[324] K. M. Rood, "Complications Associated with Insertion of Intrauterine Pressure Catheters: An Unusual Case of Uterine Hypertonicity and Uterine Perforation Resulting in Fetal Distress after Insertion of an Intrauterine Pressure Catheter", *Case Rep. Obstet. Gynecol.*, vol. 2012, pp. 1–3, 2012, ISSN: 2090-6684. DOI: 10.1155/2012/517461.

[325] B. A. Akin, H. G. Justus, N. V. Cheryl, B. A. Akin, H. G. Justus, and N. V. Cheryl, "Measuring postpartum uterine contractions during the third stage of labour: a pilot study, using a novel minimally invasive technique", *Open J. Obstet. Gynecol.*, vol. 1, no. 3, pp. 128–130, 2011, ISSN: 2160-8792. DOI: 10.4236/OJOG.2011.13023.

[326] M. W. Vlemminx, K. M. Thijssen, G. I. Bajlekov, J. P. Dieleman, M. B. Van Der Hout-Van Der Jagt, and S. G. Oei, "Could electrohysterography be the solution for external uterine monitoring in obese women?", *J. Perinatol. 2018 385*, vol. 38, no. 5, pp. 580–586, 2018, ISSN: 1476-5543. DOI: 10.1038/s41372-018-0065-3.

[327] S. F. Bell, A. Watkins, M. John, E. MacGillivray, T. L. Kitchen, D. James, C. Scarr, C. M. Bailey, K. P. Kelly, K. James, J. L. Stevens, T. Edey, R. E. Collis, and P. W. Collins, "Incidence of postpartum haemorrhage defined by quantitative blood loss measurement: A national cohort", *BMC Pregnancy Childbirth*, vol. 20, no. 1, pp. 1–9, 2020, ISSN: 14712393. DOI: 10.1186/s12884-020-02971-3.

[328] American College of Obstetricians and Gynecologists, "ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 76, October 2006: postpartum hemorrhage.", *Obstet. Gynecol.*, vol. 108, no. 4, pp. 1039–1047, 2006, ISSN: 0029-7844. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/17012482.

[329] B. T. Bateman, M. F. Berman, L. E. Riley, and L. R. Leffert, "The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries", *Anesth. Analg.*, vol. 110, no. 5, pp. 1368–1373, 2010, ISSN: 00032999. DOI: 10.1213/ANE.0B013E3181D74898.

[330] Félix Nieto del Amor, "Design and Assessment of a Computer-Assisted Artificial Intelligence System for Predicting Preterm Labor in Women Attending Regular Check-Ups. Emphasis in Imbalance Data Learning Technique", PhD thesis, Universitat Politècnica de València, Valencia, 2023, pp. 1–172.

[331] S. Arrowsmith, H. Robinson, K. Noble, and S. Wray, "What do we know about what happens to myometrial function as women age?", *J. Muscle Res. Cell Motil.*, vol. 33, no. 3-4, pp. 209–217, 2012, ISSN: 01424319. DOI: 10.1007/s10974-012-9300-2.

[332] G. Gimpl, K. Burger, E. Politowska, J. Ciarkowski, and F. Fahrenholz, "Oxytocin receptors and cholesterol: Interaction and regulation", *Exp. Physiol.*, vol. 85, no. SPEC. ISS. 2000, ISSN: 09580670. DOI: 10.1111/j.1469-445X.2000.tb00006.x.

[333] H. W. Quartero and C. H. Fry, "Placental corticotrophin releasing factor may modulate human parturition", *Placenta*, vol. 10, no. 5, pp. 439–443, 1989, ISSN: 01434004. DOI: 10.1016/0143-4004(89)90054-4.

[334] C. Prendergast, "Maternal phenotype: how do age, obesity and diabetes affect myometrial function?", *Curr. Opin. Physiol.*, vol. 13, pp. 108–116, 2020, ISSN: 24688673. DOI: 10.1016/j.cophys.2019.10.016.

[335] C. Benedetto, F. Petraglia, L. Marozio, L. Chiarolini, P. Florio, A. R. Genazzani, and M. Massobrio, "Corticotropin-releasing hormone increases prostaglandin F2α activity on human myometrium in vitro", *Am. J. Obstet.*

Gynecol., vol. 171, no. 1, pp. 126–131, 1994, ISSN: 00029378. DOI: 10.1016/0002-9378(94)90457-X.

[336] A. Vahratian, M. K. Hoffman, J. F. Troendle, and J. Zhang, "The Impact of Parity on Course of Labor in a Contemporary Population", *Birth*, vol. 33, no. 1, pp. 12–17, 2006, ISSN: 0730-7659. DOI: 10.1111/j.0730-7659.2006.00069.x.

[337] A. Diaz-Martinez, J. Mas-Cabo, G. Prats-Boluda, J. Garcia-Casado, K. Cardona-Urrego, R. Monfort-Ortiz, A. Lopez-Corral, M. D. Arriba-Garcia, A. Perales, and Y. Ye-Lin, "A Comparative Study of Vaginal Labor and Caesarean Section Postpartum Uterine Myoelectrical Activity", *Sensors 2020, Vol. 20, Page 3023*, vol. 20, no. 11, p. 3023, 2020. DOI: 10.3390/S20113023.

[338] N. Reshme, R. Samal, P. Padmaja, S. Shalini, and K. Radhika, "Induction of Labour –Foleys Catheter Vs Dinoprostone Gel: A Randomized Controlled Trial", in *Curr. Pract. Med. Sci.* 1st ed., vol. 3, Book Publisher International (a part of SCIENCEDOMAIN International), 2022, ch. 4, pp. 58–67, ISBN: 978-93-5547-540-4. DOI: 10.9734/bpi/cpms/v3/16488D.

[339] X. Liu, Y. Wang, F. Zhang, X. Zhong, R. Ou, X. Luo, and H. Qi, "Double- versus single-balloon catheters for labour induction and cervical ripening: A meta-analysis", *BMC Pregnancy Childbirth*, vol. 19, no. 1, pp. 1–13, 2019, ISSN: 14712393. DOI: 10.1186/s12884-019-2491-4.

[340] J. A. Martin, B. E. Hamilton, M. J. K. Osterman, and A. K. Driscoll, "Births: Final Data for 2019", Centers for Disease Control and Prevention, Hyattsville, MD, Tech. Rep. 2, 2021, pp. 1–51. DOI: 10.15620/cdc:100472.

[341] M. Jozwiak, K. W. Bloemenkamp, A. J. Kelly, B. W. Mol, O Irion, and M Boulavain, "Mechanical methods for induction of labour", *Cochrane database Syst. Rev.*, vol. 42, no. 3, pp. 674–680, 2012, ISSN: 1469-493X. DOI: 10.1002/14651858.CD001233.PUB2.

[342] Y. Xu, D. Hao, and D. Zheng, "Analysis of Electrohysterographic Signal Propagation Direction during Uterine Contraction: the Application of Directed Information", *2020 42nd Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*, pp. 21–25, 2020, ISSN: 1557170X. DOI: 10.1109/EMBC44109.2020.9175423.

[343] H. Kruit, H. Wilkman, A. Tekay, and L. Rahkonen, "Induction of labor by Foley catheter compared with spontaneous onset of labor after previous cesarean section: a cohort study", *J. Perinatol. 2017 377*, vol. 37, no. 7, pp. 787–792, 2017, ISSN: 1476-5543. DOI: 10.1038/jp.2017.50.

[344] C. Villalain, I. Herraiz, M. S. Quezada, P. Gómez Arriaga, E. Simón, E. Gómez-Montes, and A. Galindo, "Labor Induction in Late-Onset Fetal Growth Restriction: Foley Balloon versus Vaginal Dinoprostone", *Fetal Diagn. Ther.*, vol. 46, no. 1, pp. 67–74, 2019, ISSN: 1015-3837. DOI: 10.1159/000491784.

[345] H. Wang, S. Hong, Y. Liu, Y. Duan, and H. Yin, "Controlled-release dinoprostone insert versus Foley catheter for labor induction: a meta-analysis", *Matern. neonaral Med.*, vol. 29, no. 14, pp. 2382–2388, 2015, ISSN: 14764954. DOI: 10.3109/14767058.2015.1086331.

[346] C. E. Pennell, J. J. Henderson, M. J. O'Neill, S. McCleery, D. A. Doherty, and J. E. Dickinson, "Induction of labour in nulliparous women with an unfavourable cervix: A randomised controlled trial comparing double and single balloon catheters and PGE2 gel", *BJOG An Int. J. Obstet. Gynaecol.*, vol. 116, no. 11, pp. 1443–1452, 2009, ISSN: 14700328. DOI: 10.1111/j.1471-0528.2009.02279.x.

[347] W. F. Rayburn, "Preinduction cervical ripening: Basis and methods of current practice", *Obstet. Gynecol. Surv.*, vol. 57, no. 10, pp. 683–692, 2002, ISSN: 00297828. DOI: 10.1097/00006254-200210000-00022.

[348] T. Yukio Fukuda, J. Oliveira Echeimberg, J. E. Pompeu, P. Roberto, G. Lucareli, S. Garbelotti, R. O. Gimenes, and A. Apolinário, "Root Mean Square Value of the Electromyographic Signal in the Isometric Torque of the Quadriceps, Hamstrings and Brachial Biceps Muscles in Female Subjects", Tech. Rep. 1, 2010, pp. 32–39. [Online]. Available: https://go.gale.com/ps/i.do?id=GALE{\%}7CA227012906{\&}sid=googleScholar{\&}v=2.1{\&}it=r{\&}linkaccess=abs{\&}issn=1537064X{\&}p=AONE{\&}sw=w{\&}userGroupName=anon{~}ee4f8ee8{\&}aty=open-web-entry.

[349] P. Borghesani, P. Pennacchi, and S. Chatterton, "The relationship between kurtosis- and envelope-based indexes for the diagnostic of rolling element bearings", *Mech. Syst. Signal Process.*, vol. 43, no. 1-2, pp. 25–43, 2014, ISSN: 08883270. DOI: 10.1016/j.ymssp.2013.10.007.

[350] K. S. R. Murty and B Yegnanarayana, "Epoch Extraction From Speech Signals", *IEEE Trans. Audio. Speech. Lang. Processing*, vol. 16, no. 8, pp. 1602–1613, 2008, ISSN: 1558-7916. DOI: 10.1109/TASL.2008.2004526.

[351] T. J. Ulrich, *Envelope calculation from the Hilbert transform*, 2006. [Online]. Available: https://www.researchgate.net/publication/257547765{_}Envelope{_}Calculation{_}from{_}the{_}Hilbert{_}Transform (visited on 01/22/2024).

[352] A. Phinyomark, S. Thongpanja, H. Hu, P. Phukpattaranont, and C. Limsakul, "The Usefulness of Mean and Median Frequencies in Electromyography Analysis", *Comput. Intell. Electromyogr. Anal. - A Perspect. Curr. Appl. Futur. Challenges*, 2012. DOI: 10.5772/50639.

[353] F. B. Stolen, C. J. De Luca, and C. J. De Luca, "Frequency Parameters of the Myoelectric Signal as a Measure of Muscle Conduction Velocity", *IEEE Trans. Biomed. Eng.*, vol. BME-28, no. 7, pp. 515–523, 1981, ISSN: 15582531. DOI: 10.1109/TBME.1981.324738.

[354] L. Y. Di Marco, C. Di Maria, W. C. Tong, M. J. Taggart, S. C. Robson, and P. Langley, "Recurring patterns in stationary intervals of abdominal uterine electromyograms during gestation", *Med. Biol. Eng. Comput.*, vol. 52, no. 8, pp. 707–716, 2014, ISSN: 17410444. DOI: 10.1007/S11517-014-1174-6/TABLES/5.

[355] P. Li, C. Karmakar, J. Yearwood, S. Venkatesh, M. Palaniswami, and C. Liu, "Detection of epileptic seizure based on entropy analysis of short-term EEG", *PLoS One*, vol. 13, no. 3, M. Bazhenov, Ed., e0193691, 2018, ISSN: 1932-6203. DOI: 10.1371/journal.pone.0193691.

[356] F. Nieto-del Amor, "Estudio comparativo de las diferentes medidas de entropía para la predicción del parto prematuro", Universitat Politécnica de Valencia, Tech. Rep., 2019.

[357] G. Manis, M. Aktaruzzaman, and R. Sassi, "Bubble Entropy: An Entropy Almost Free of Parameters", *IEEE Trans. Biomed. Eng.*, vol. 64, no. 11, pp. 2711–2718, 2017, ISSN: 0018-9294. DOI: 10.1109/TBME.2017.2664105.

[358] T. Higuchi, "Approach to an irregular time series on the basis of the fractal theory", *Phys. D Nonlinear Phenom.*, vol. 31, no. 2, pp. 277–283, 1988, ISSN: 01672789. DOI: 10.1016/0167-2789(88)90081-4.

[359] V. Sharma, G. Colleran, B. Dineen, M. B. Hession, G. Avalos, and J. J. Morrison, "Factors influencing delivery mode for nulliparous women with a singleton pregnancy and cephalic presentation during a 17-year period", *Eur. J. Obstet. Gynecol. Reprod. Biol.*, vol. 147, no. 2, pp. 173–177, 2009, ISSN: 03012115. DOI: 10.1016/j.ejogrb.2009.08.015.

[360] S. Wray, "Insights from physiology into myometrial function and dysfunction", *Exp. Physiol.*, vol. 100, no. 12, pp. 1468–1476, 2015, ISSN: 1469445X. DOI: 10.1113/EP085131.

[361] W. R. Cohen and E. A. Friedman, "The assessment of labor: a brief history.", *J. Perinat. Med.*, vol. 46, no. 1, pp. 1–8, 2018, ISSN: 1619-3997. DOI: 10.1515/jpm-2017-0018.

[362] C. S. Buhimschi, I. A. Buhimschi, C. Yu, H. Wang, D. J. Sharer, M. P. Diamond, A. P. Petkova, R. E. Garfield, G. R. Saade, and C. P. Weiner, "The effect of dystocia and previous cesarean uterine scar on the tensile properties of the lower uterine segment", *Am. J. Obstet. Gynecol.*, vol. 194, no. 3, pp. 873–883, 2006, ISSN: 00029378. DOI: 10.1016/j.ajog.2005.09.004.

[363] R. Floyd and S. Wray, "Calcium transporters and signalling in smooth muscles", *Cell Calcium*, vol. 42, no. 4-5, pp. 467–476, 2007, ISSN: 01434160. DOI: 10.1016/j.ceca.2007.05.011.

[364] M. J. Taggart, C. B. Menice, K. G. Morgan, and S. Wray, "Effect of metabolic inhibition on intracellular Ca2+ phosphorylation of myosin regulatory light chain and force in rat smooth muscle", *J. Physiol.*, vol. 499, no. 2, pp. 485–496, 1997, ISSN: 00223751. DOI: 10.1113/jphysiol.1997.sp021943.

[365] Jie Zhang, A. Kendrick, S. Quenby, and S. Wray, "Contractility and calcium signaling of human myometrium are profoundly affected by cholesterol manipulation: implications for labor?", *Reprod. Sci.*, vol. 14, no. 5, pp. 456–66, 2007, ISSN: 1933-7205. DOI: 10.1177/1933719107306229.

[366] R. D. Smith, E. B. Babiychuk, K. Noble, A. Draeger, and S. Wray, "Increased cholesterol decreases uterine activity: Functional effects of cholesterol alteration in pregnant rat myometrium", *Am. J. Physiol. - Cell Physiol.*, vol. 288, no. 5 57-5, pp. 982–988, 2005, ISSN: 03636143. DOI: 10.1152/ajpcell.00120.2004.

[367] N. S. Carlson, T. L. Hernandez, and K. J. Hurt, "Parturition dysfunction in obesity: Time to target the pathobiology", *Reprod. Biol. Endocrinol.*, vol. 13, no. 1, pp. 1–14, 2015, ISSN: 14777827. DOI: 10.1186/s12958-015-0129-6.

[368] S. Lisonkova, G. M. Muraca, J. Potts, J. Liauw, W.-S. Chan, A. Skoll, and K. I. Lim, "Association Between Prepregnancy Body Mass Index and Severe Maternal Morbidity.", *JAMA*, vol. 318, no. 18, pp. 1777–1786, 2017, ISSN: 1538-3598. DOI: 10.1001/jama.2017.16191.

[369] S. Santos, E. Voerman, P. Amiano, H. Barros, L. J. Beilin, A. Bergström, M.-A. Charles, L. Chatzi, C. Chevrier, G. P. Chrousos, E. Corpeleijn, O. Costa, N. Costet, S. Crozier, G. Devereux, M. Doyon, M. Eggesbø, M. P. Fantini, S. Farchi, F. Forastiere, V. Georgiu, K. M. Godfrey, D. Gori, V. Grote, W. Hanke, I. Hertz-Picciotto, B. Heude, M.-F. Hivert, D. Hryhorczuk, R.-C. Huang, H. Inskip, A. M. Karvonen, L. C. Kenny, B. Koletzko, L. K. Küpers, H. Lagström, I. Lehmann, P. Magnus, R.

Majewska, J. Mäkelä, Y. Manios, F. M. McAuliffe, S. W. McDonald, J. Mehegan, E. Melén, M. Mommers, C. S. Morgen, G. Moschonis, D. Murray, C. Ní Chaoimh, E. A. Nohr, A.-M. Nybo Andersen, E. Oken, A. J. J. M. Oostvogels, A. Pac, E. Papadopoulou, J. Pekkanen, C. Pizzi, K. Polanska, D. Porta, L. Richiardi, S. L. Rifas-Shiman, N. Roeleveld, L. Ronfani, A. C. Santos, M. Standl, H. Stigum, C. Stoltenberg, E. Thiering, C. Thijs, M. Torrent, S. C. Tough, T. Trnovec, S. Turner, M. M. H. J. van Gelder, L. van Rossem, A. von Berg, M. Vrijheid, T. G. M. Vrijkotte, J. West, A. H. Wijga, J. Wright, O. Zvinchuk, T. I. A. Sørensen, D. A. Lawlor, R. Gaillard, and V. W. V. Jaddoe, "Impact of maternal body mass index and gestational weight gain on pregnancy complications: An individual participant data meta-analysis of European, North American and Australian cohorts", *HHS Public Access*, vol. 126, no. 8, pp. 984–995, 2019, ISSN: 00067431. DOI: 10.2307/40084596.

[370] A. S. Poobalan, L. S. Aucott, T. Gurung, W. C. S. Smith, and S. Bhattacharya, "Obesity as an independent risk factor for elective and emergency caesarean delivery in nulliparous women–systematic review and meta-analysis of cohort studies.", *Obes. Rev.*, vol. 10, no. 1, pp. 28–35, 2009, ISSN: 1467-789X. DOI: 10.1111/j.1467-789X.2008.00537.x.

[371] J. Zhang, L. Bricker, S. Wray, and S. Quenby, "Poor uterine contractility in obese women.", *BJOG*, vol. 114, no. 3, pp. 343–8, 2007, ISSN: 1470-0328. DOI: 10.1111/j.1471-0528.2006.01233.x.

[372] M. I. Cedergren, "Non-elective caesarean delivery due to ineffective uterine contractility or due to obstructed labour in relation to maternal body mass index", *Eur. J. Obstet. Gynecol. Reprod. Biol.*, vol. 145, no. 2, pp. 163–166, 2009, ISSN: 03012115. DOI: 10.1016/j.ejogrb.2009.05.022.

[373] J. Y. Kim, W. H. Wu, J. H. Jun, J. Sohn, and Y. S. Seo, "Effects of corticotropin-releasing hormone on the expression of adenosine triphosphate-sensitive potassium channels (Kir6.1/SUR2B) in human term pregnant myometrium", *Obstet. Gynecol. Sci.*, vol. 61, no. 1, pp. 14–22, 2018, ISSN: 22878580. DOI: 10.5468/ogs.2018.61.1.14.

Appendix A

Parameters for electrohysterographic signal characterization

Once the physiological sections of interest have been segmented, signal characterisation is performed using a set of parameters that may be of a temporal, spectral or nonlinear nature. In this way, the natural evolution of uterine contractile activity throughout pregnancy or even the response to uterotonic or tocolytic agents can be revealed.

A.1 Temporal parametrization

Given the familiarity of obstetricians with the monitoring and management of myoelectric activity based on counting, duration and intensity of contractions, its inclusion is becoming increasingly common to facilitate the adoption of the technique in clinical praxis and the application of prior knowledge. The **Duration of Contractions** is given by the difference in seconds between the start and end of the contraction, thus this metric and the **Number of Contractions (NCT)** can only be reported by using EBA. Standard deviation of EHG-burst duration was found significantly lower for term labour records than for term nonlabour ones, the same trend but without differences was found in the comparison of preterm versus non preterm [157]. In terms of amplitude, as gestation progresses, the rate of cell recruitment and hence contractile intensity is expected to increase [284]. Typically, it is characterised by the **Peak-to-Peak to Amplitude ($\mathbf{A}_{pp}$)** [40, 284] or **Root Mean Square (RMS)** [40, 284, 348] computed in the WBW as described in Equations A.1 and A.2 respectively, where x represents a physiological EHG time series and N represents its sample size.

$$A_{PP}(x[n]) = \max(x[n]) - \min(x[n]) \tag{A.1}$$

$$\mathrm{RMS}(x[n]) = \sqrt{\frac{1}{N}\sum_{k=1}^{N} x[k]^2} \tag{A.2}$$

The kurtosis of a signal is defined as the ratio of the fourth central moment to the squared second central moment of the signal [349], and is considered a measure of the impulsivity of the signal since it describes the distribution of the input signal [285]. Since the contractions are presented as transient pulses that occur cyclically in the EHG signal, the kurtosis calculation may present peaks in these areas of instantaneous energy fluctuations. The impulsivity of the signal at these locations can be improved by taking the signal **Kurtosis of the Hilbert Envelope (KHE)** [285, 350], providing localised peaks at the locations of contractile events. Given a modulated time series $x[n] = \sin(\omega t)\sin(\Omega t)$, with $\omega > \Omega$, the Hilbert envelope can be constructed from the absolute value of the analytic function $\widetilde{x}_h[n] = x[n] + jx_h[n]$ [350, 351], where $jx_h[n]$ is the Hilbert transformation of the signal $x[n]$. Standing $E(\cdot)$ for the expectation operation, the kurtosis of the zero-mean signal envelope is given by A.3. To capture the transient impulse around the location of the uterine contraction, the short-term kurtosis of the signal is normally calculated by taking a rectangular window [285].

$$\mathrm{KHE}(x[n]) = \frac{E(|\widetilde{x}_h[n]|)^4}{[E(|\widetilde{x}_h[n]|)^2]^2} \tag{A.3}$$

A.2 Spectral parametrization

Unlike amplitude-related parameters, spectral features are expected to be less sensitive to sensor placement and more comparable between subjects [156]. Increased myometrial excitability along the physiological continuum of pregnancy is reflected in a shift of spectral content towards higher frequencies at the end of the gestation [9]. Prior studies have shown spectral content to shift towards higher frequencies 24 hours before delivery in term patients and 4 days before in preterm patients [303], with the evolution being non-linear when longer time horizons are considered [152, 303].

The characterisation of the distribution of the spectral content is broadly given from the **Mean Frequency (MNF)** and **Median Frequency (MDF)**. The former is defined as the centroid frequency of the power spectrum, and the latter as the frequency that divides the total energy of the spectrum into equal parts [150, 352], determined respectively as in Equations A.4 and A.5 where PSD corresponds to the power spectral density distribution, f to each of the frequencies in the range in which it has been computed and f_m to the sample frequency. Relevant information about the recruitment dynamics of muscle fibers can be extracted from these parameters [9, 150], although median calculations are more robust to the presence of random noise than the mean [353].

$$\text{MNF}(x[n]) = \frac{\sum_{k=f_L}^{f_H} \text{PSD}[k] \cdot f[k]}{\sum_{k=f_L}^{f_H} \text{PSD}[k]} \tag{A.4}$$

$$\sum_{k=0}^{MDF} \text{PSD}[k] = \sum_{k=MDF}^{N} \text{PSD}[k] = \frac{1}{2} \sum_{k=0}^{f_m/2} \text{PSD}[k] \tag{A.5}$$

Other estimations can be given from the **Dominant Frequency (DF)**, the **Normalized Energy per sub-band (NE)**, or the **High/Low Ratio (H/L Ratio)**. Firstly, DF refers to the frequency at which PSD peaks and can be calculated at WBW and FWH. The shift of the peak frequency from lower to higher frequencies as labour approaches can be intuitively explained by a more frequent cell-to-cell propagation of action potentials at the myometrial level [150, 154, 156]. Secondly, the NE computes the energy ratio between a given frequency range and the total (0.2-1Hz), as shown in Equation A.6, where f_L and f_H represents the lower and higher frequencies of the bandwidth of interest. Traditionally, NE_1 (f_{L1}=0.2Hz, f_{H1}=0.34Hz), NE_2 (f_{L2}=0.34Hz, f_{H2}=0.6Hz), and NE_3 (f_{L3}=0.6Hz, f_{H3}=1Hz) have been defined [286]. Thirdly, the H/L Ratio is nothing more than the dimensionless ratio between the high frequency energy (0.34-1Hz) and the low frequency energy (0.2-0.34Hz) computed as in Equation A.7.

$$\text{NE}(x[n]) = \frac{\sum_{k=f_L}^{f_H} \text{PSD}[k]}{\sum_{k=0.2\text{Hz}}^{1\text{Hz}} \text{PSD}[k]} \tag{A.6}$$

$$\text{H/L Ratio}(x[n]) = \frac{NE_2(x[n]) + NE_3(x[n])}{NE_1(x[n])} \tag{A.7}$$

The **Uterine Activity Index (UAI)** is a relatively recent parameter that has gained some presence in the signal characterization field as it is able to enhance the pattern of myoelectrical activity as the time of delivery approaches based on the upward trends of A_{pp} and H/L Ratio together with the downward trend of contraction duration [19], as stated in Equation A.8.

$$\text{UAI}(x[n]) = \frac{A_{PP}(x[n]) \cdot \text{H/L Ratio}(x[n])}{\text{Duration}(x[n])} \tag{A.8}$$

A.3 Non-linear parametrization

Perhaps the most widely used measure of non-linearity is the **Sample Entropy (SampEn)** due to its independence to recording length [149, 225, 354]. Formally, given a time series $x[n]$ of length N, a pattern vector $a_j = x_j, x_{j+1}, ..., x_{j+m-1}$ of length m is defined. $U^m(r)$ in Equation A.9 expresses the probability that the time series

matches the pattern within a threshold r determined by the Chebyshev distance function $d[|x_m(j) - x_m(i)|]$ $(i \neq j)$.

$$U^m(r) = \frac{1}{N-m-1} \cdot \frac{1}{N-m} \sum_{i=1}^{N-m} \sum_{\substack{j=1 \\ j \neq i}}^{N-m} [\text{num. of times } d[|x_m[j] - x_m[i]|] < r] \quad \text{(A.9)}$$

Then, SampEn is defined in Equation A.10 as the negative natural logarithm of the conditional probability that two sequences within a given numerical series of length N that are similar in m samples $(m < N)$ remain similar in $m+1$ samples, according to a tolerance and ignoring self-matches [150, 247]. Therefore, this metric represents the probability that similar patterns (lag vectors) in a time series remain similar once pattern lengths (extended lag vectors) are increased, thus providing a natural measure of time series regularity [247, 248], whereby higher values are associated with a higher rate of information production [248] and therefore longer time to delivery [19, 154].

$$\text{SampEn}(m, r, N) = \begin{cases} -\ln\left(U^{m+1}(r)/U^m(r)\right), & \text{if } U^{m+1} \neq 0 \wedge U^m \neq 0 \\ -\ln\left(N-m+1/N-m\right), & \text{otherwise} \end{cases} \quad \text{(A.10)}$$

Another widely spread approach is the measurement of the time series regularity variance from the **Binary Lempel-Ziv (BLZ)** [19, 154]. Initially, the time series of the signal $x[n]$ is converted into a finite binary sequence by left-to-right comparison with a threshold T_d [251, 252].The resulting binary sequence $S(i)$ is sequentially scanned for distinctive structures or patterns, building a dictionary that summarises all the sequences found so far [251]. Let $S = S(i), \forall i = 1, ..., n$ represent a symbolic sequence; $S(i, j)$ be a subsequence of S starting at position i and ending at j; and $V(S)$ denotes the set of all subsequences $S(i, j), i = 1, 2, \ldots, n; j \geq i$. Starting with $i = 1$ and $j = 1$, a substring $S(i, j)$ is compared with $V(S)$. If $S(i, j)$ can be found in $V(S)$, then j increases by 1 and then the process repeats. Otherwise, the complexity counter $c(n)$ is incremented one unit, as a new consecutive characters subsequence is encountered, and updates $i = j + 1$, while the process continues until the entire symbolic sequence is scanned. Physically, as labour progresses, uterine contractions becomes more regular, which should be reflected by lower BLZ complexity by a small number of patterns [19, 154].

Due to the non-linear nature of biological systems, the use of different entropy measures to characterise EHG signals has been proposed [154, 186]. By definition, **Fuzzy Entropy (FuzzyEn)** does not count on the absolute probability of similar vectors according to the hard thresholding criterion as applied in SampEn or BLZ. Instead, it estimates the probability that two vectors are similar based on the fuzzy membership criterion [355]. Considering a time series of N points $u(i), 1 \leq i \leq N$, first step is to state space reconstruction. This is done by forming $(N - m\tau)$ vectors $X(i)$

by $X(i) = u(i), u(i+\tau), ..., u(i+(m-1)\tau), 1 \leq i \leq N - m\tau$, where m indicates the embedding dimension and τ the time delay. In the next step, the similar vectors are ranked. For this purpose, the distance between $X(i)$ and $X(j)$ $(1 \leq i, j \leq N - m\tau, i \neq j)$ is defined by $d_{i,j} = max(|u(i+k) - u(j+k)|, 0 \leq k \leq m-1)$ and then calculate the average probability that the vectors $X(j), j = 1, 2, ..., N - m\tau, i \neq j$ are similar to $X(i)$ in terms of degree of membership degree following with A.11, being r the threshold parameter.

$$A_i^m(r) = \frac{1}{N - m\tau} \sum_{j=1, j\neq i}^{N-m\tau} e^{-ln(2)(\frac{d_{i,j}}{r})^2} \tag{A.11}$$

Finally, the FuzzyEn value of the time series $u(i)$ is then calculated as in A.12 [355]. A downward evolution of BLZ values during labour induction has been described in the literature [243], as well as a good separability at fast wave high discerning real cases of PTB among threats [356].

$$\text{FuzzyEn}(m, \tau, r) = -ln \frac{\sum_{i=1}^{N-m\tau} A_i^{m+1}(r)}{\sum_{i=1}^{N-m\tau} A_i^m(r)} \tag{A.12}$$

A critical aspect of any definition of entropy revolves around the selection of the fitting parameters used to obtain a practical estimate. **Bubble Entropy (BubbEn)** arises with the aim of reducing the importance of this selection, since small variations in these parameters can drastically change the results. Not only does this method investigate the rank of the elements within the vectors, but it also evaluates the reallocation performed to order these elements [357]. With the BubbEn, the necessity to define r is eliminated as well as the importance of the second parameter m is minimised, suggesting in fact a parameter-free definition of entropy [186, 357].

BubbEn is based on the application of a metric on the effort required during the permutation procedure. Depending on the n_i swaps required, each vector X_i of m elements is ordered in ascending order. Vectors requiring the same sorting effort are then grouped by generating the histogram of n_i values and normalised by dividing by $N - m + 1$ to obtain the probabilities p_i, describing how likely a given number of swaps n_i is. It is then computed for each p_i the *Rényi* entropy according with A.13. By this procedure the number of possible unique states is reduced and a coarser-grained distribution based on inherent correlations is created.

$$H_{swaps}^m(X) = -log \sum_{i=1}^{n} p - i^2 \tag{A.13}$$

For each of the vectors with $m+1$ elements, this process is repeated. Finally, BubbEn is calculated according to the equation A.14 [357]. BubbEn has been found to outperform

SampEn or FuzzyEn in discriminating patients with preterm and term deliveries by some authors [186].

$$BubbEn(x[n]) = \frac{H_{swaps}^{m+1} - H_{swaps}^{m}}{log(m+1/m-1)} \tag{A.14}$$

Spectral Entropy (SpEn) is a measure of the uncertainty associated with the occurrence of a particular event at a given frequency [249, 250]. It is computed as shown in A.16 by applying the Shannon entropy formula to the normalised PSD of a time series $x[n]$ A.15, so that the normalised energy of each of the frequency points is considered as a probability [250]. M is the number of frequency points for which the power spectrum of the signal has been estimated and f_m is the sampling frequency. As delivery approaches, ordering in the frequency spectrum sharpens the frequency distribution and decreases the parameter value [169].

$$PSD_{norm}(x[n]) = \frac{\mathrm{PSD}(x[n])}{\sum_{k=0}^{\frac{fm}{2}} \mathrm{PSD}[k]} \tag{A.15}$$

$$\mathrm{SpEn}(x[n]) = -\frac{\sum_{k=0}^{\frac{fm}{2}} PSD_{norm}[k] \cdot \log_2(PSD_{norm}\ [k])}{\log_2(M)} \tag{A.16}$$

Fractal dimension analysis, as an index of complexity and fragmentation of the EHG signal, has been shown to provide relevant information in the prediction of PTB [224] and discern successful IOL [189, 243]. It is based on comparing changes in the details of the pattern of a signal when measured at different scales [224, 246], thus quantifying the increasing organisation of myometrial activity until it peaks just before the process of labour reflected by a decreasing value [189, 243].

One of the most accurate and consistent fractal dimension estimation algorithms for non-periodic and irregular physiological time series signals is the **Higuchi's Fractal Dimension (HFD)** [224, 246, 358]. Given a time series $x(n)$, consisting of N points and a parameter $k_{max} \geq 2$, for each $k \in 1, \ldots, k_{max}$, $m \in 1, \ldots, k$, the length $L_m(k)$ is defined in Equation A.17 [358].

$$L_m(k) = \frac{N-1}{\frac{N-m}{k} \cdot k^2} \sum_{i=1}^{N-m/k} |x[m+i \cdot k] - x[m+(i-1) \cdot k]| \tag{A.17}$$

The average length $L_m(k)$ is then calculated and the average length of the curve $L(k)$ for each k is obtained as in Equation A.18.

$$L(k) = \frac{\sum_{m=1}^{k} L_m(k)}{k} \tag{A.18}$$

Last, the HFD is calculated as the slope of the best linear least squares fit of the plot of $ln(L(k))$ versus $ln(1/k)$ [246, 358].

However, the selection of fractal dimension estimation measures in electrophysiological signals is paramount. Thus, an alternative to HFD may be the **Katz's Fractal Dimension (KFD)**, which has been shown to be a more consistent and less noise-sensitive method in certain encephalographic scenarios [312]. In the classical definition of the fractal dimension calculation $FD = log_{10}(L)/log_{10}(d)$, where L stands for the total length of the curve (or sum of distances between successive points) and d represents the diameter estimation based on the distance between the first point in the sequence and the point in the sequence providing the furthest distance, the result depends on the units of measurement used. The KFD approach solves this problem by normalising the time series from the average distance between successive points a as $FD = log_{10}(L/a)/log_{10}(d/a)$. Therefore, by defining n as the number of steps in the curve ($n = L/a$), the KFD can be writen as in A.19 [288].

$$KFD = \frac{log_{10}(n)}{log_{10}(d/L) + log_{10}(n)} \tag{A.19}$$

Appendix B

EHG-biomarkers significance in different high-risk obstetric settings

The parametrization findings for the obstetrical scenarios explored in the present thesis are presented in tabular form in Table B.1, accompanied by additional unpublished results. A color-coded system has been utilized to emphasize the statistical significance of these results: cells are shaded red and labeled "N" if no significant differences were detected between the compared groups, and green with a "Y" if significant distinctions were identified. For the labour induction scenario, significance was considered when for three or more consecutive 30-minute time intervals after the administration of the induction drug the parameter showed statistical significance with respect to baseline activity. Instances in which three or more 30-minute time intervals exhibited a significant difference from baseline, but only two were consecutive, were considered scattered and were shaded in yellow with an "S". In addition, Δ stands for the parameter progression ratio.

The EHG signal analysis in the regular check-ups and PPH scenarios was conducted using WEWA based on the impracticality of precisely identifying the onset and cessation of contractions, as well as having previously demonstrated its superiority to EBA in similar contexts scenarios [152]. On the other hand, the IOL setting was assessed by EBA, as previous studies suggest that the technique is able to extract more information from the signal and therefore offer a higher discriminatory capacity regarding the outcome of the induction [243]. Of note, these techniques have shown a similar trend for each family of parameters, suggesting a comparable performance, see Subsection 1.4.2 and Appendix A.

Table B.1: EHG parametrization results during the third trimester of gestation, the induction of labor, and the postpartum.

Parameters		**Regular check-up**			**APL≤24h**				**PPH**
		10th perc	*50th perc*	*90th perc*	*GS*	*GF*	*GS vs GF*	Δ	
Temporal	NCT	-	-	-	Y	N	N	N	-
	A_{pp}	N	N	N	N	N	S	Y	Y
	RMS	N	N	N	N	N	S	Y	-
	KHE	Y	Y	Y	N	N	N	N	Y
Spectral	MNF	N	N	N	Y	N	N	N	-
	MDF	N	N	N	Y	N	N	Y	N
	DF	N	N	N	Y	N	N	N	N
	NE	Y	N	N	Y	N	N	N	Y
	H/L Ratio	Y	N	N	Y	N	N	N	-
Non-linear WBW	SampEn	Y	N	N	N	N	S	N	N
	BubbEn	N	Y	N	S	N	S	N	-
	SpEn	N	N	N	N	N	N	N	Y
	BLZ	N	N	N	N	N	N	N	N
	FuzzyEn	Y	Y	N	N	N	N	N	-
	HFD	Y	N	N	Y	N	S	N	-
	KFD	N	N	N	N	N	S	N	Y
Non-linear FWH	SampEn	Y	Y	N	S	N	Y	Y	-
	BubbEn	Y	Y	Y	N	N	N	N	-
	SpEn	N	N	N	Y	N	Y	Y	-
	BLZ	N	N	N	S	N	Y	Y	-
	FuzzyEn	Y	Y	N	S	N	Y	Y	-
	HFD	Y	N	N	S	N	Y	Y	-
	KFD	N	N	N	S	N	S	Y	-

Appendix C

Obstetric factors affecting myometrial contractility

The identification of reliable predictors that can influence the obstetric decision-making is a crucial area of research that can transform women's childbirth experience in a near future. Although significant advances in understanding the physiology and clinical pathophysiology of myometrial contractile function have been described [6, 7, 9], the identification of EHG-biomarkers has been in many cases truncated or slowed due to heterogeneity of criteria in defining groups under study and neglect of confounding variables. For this reason, the potential effect of a growing number of maternal, foetal, ultrasound and biochemical factors on uterine contractility is currently of increasing interest to explore [28]. The approach to the development and generalisation of EHG-biomarkers aims to bridge the existing gaps in the knowledge of the electrophysiological processes underlying contraction and the prediction of obstetrically significant outputs, providing valuable information to advance maternal-foetal health care.

C.1 Interplay of previous pregnancies with uterine contractility

By exploring the impact of previous pregnancies on current uterine contractility, a key dimension to our understanding of the underlying physiological processes is added. In the delivery context, parous women have reported shorter durations in the first [216] and second stages of labour [216, 317]. Possibly related to the fact that dysfunctional uterine contractility has been observed in up to 30% of nulliparous women [318, 319], frequently leading to failure of labour progression and increased medical interventions and caesarean deliveries [319, 359]. However, in vitro studies have revealed that there are no intrinsic differences in the functional parameters of human uterine contractions in relation to

parity, except for the frequency of occurrence and a trend of increasing contractile force with parity, albeit not significant [259]. Consideration must be given to the possibility of bias in the study, as the biopsied myometrial strip may not behave identically to when it is part of a complete organ [165]. Despite the major advances achieved in the understanding of the mechanisms underlying labour [360], the maternal-foetal physiological connections between the efficiency of uterine contraction, cervical dilatation and the descent of the foetal head remain incompletely understood [259, 361]. It has been postulated that the faster rate of cervical dilatation in nulliparous compared to multiparous women may be related to the fact that dilatation in nulliparous is preceded by cervical thinning, whereas in multiparous both occur simultaneously [171]. Furthermore, nulliparous are associated with a higher risk of IOL failure [171, 207], which according to the literature could be influenced by cervical stiffness [171]. In fact, only 50% of nulliparas included in the Chapter 4 study achieved an APL$\leq$24h, compared with 83% of nulliparas. Likewise, scarring from a previous caesarean section may also weaken the uterine wall and reduce its ability to contract [362].

C.2 Influence of maternal age and weight on uterine contractility

A myriad of maternal-foetal factors, encompassing demographic parameters to the gravid woman's health status, have been discerned as conceivable modulators influencing uterine contraction dynamics throughout gestation. Firstly, maternal ageing has been associated in the non-pregnant uterus with significant decreases in contractility for both spontaneous and depolarisation-induced contractions [259, 331], being muscle atrophy and down-regulation of calcium channels the proposed main culprits [363, 364]. However, contractile capacity in the pregnant uterus greatly differs from woman to woman [331] and only the response to oxytocin is affected by tissue ageing [331, 332], possibly in relation to changes in membrane lipids [365, 366], such as the increase in cholesterol with age. The marked differences between the age-related decline in strength beyond the age of 30 years in the non-pregnant uterus, and the absence of differences in the pregnant state during this period, demonstrates that the uterus retains its responsiveness to gestational hormones and that the growth of the pregnant uterus, and the increased myofibrillar protein content may abolish any previous age-related strength deficit [331].

Obesity increases the risk of maternal and perinatal complications [367, 368] such as gestational diabetes, pre-eclampsia, preterm delivery, congenital anomalies and foetal macrosomia [334, 369]. In terms of uterine contractility, obese women are reported to be at increased risk of experiencing prolonged and difficult childbirth. Dysfunctional labour and ineffective uterine contractility are leading causes of unplanned caesarean sections in obese women [370–372]. In addition, obese women who give birth vaginally have been found to experience greater blood loss compared to women of normal weight [371], suggesting impaired uterine contractility. At the molecular level, some mechanisms

by which obesity may affect labour have been researched. Dyslipidaemia, inflammation, and pro-inflammatory cytokines, as well as alterations in adipokine levels, may influence uterine contractility [334]. Studies on isolated human myometrium have demonstrated that Corticotropin-Releasing Hormone can potentiate the contractile activity of oxytocin [333, 334] and prostaglandin-F2α [334, 335]. In addition, decreased levels of corticotropin-releasing hormone associated with obesity may affect the expression of K_{ATP} channels [1] and therefore the uterine contractility [334, 373].

[1]Ionic channels present in the cell membrane that regulate the flow of potassium ions (K+) across the cell membrane in response to changes in adenosine triphosphate (ATP) levels.