

Document downloaded from:

<http://hdl.handle.net/10251/108612>

This paper must be cited as:

Garcia-Casado, J.; Ye Lin, Y.; Prats-Boluda, G.; Mas-Cabo, J.; Alberola Rubio, J.; Perales Marín, AJ. (2018). Electrohysterography in the diagnosis of preterm birth: a review. *Physiological Measurement*. 39(2). doi:10.1088/1361-6579/aaad56



The final publication is available at

<http://doi.org/10.1088/1361-6579/aaad56>

Copyright IOP Publishing

Additional Information

Title page

Title of article:

“Electrohysterography in the Diagnosis of Preterm Birth: a Review”

Authors' names:

J. Garcia-Casado¹, Y. Ye-Lin¹, G. Prats-Boluda¹, J. Mas-Cabo¹, J. Alberola-Rubio^{1,2} and A. Perales²

Postal addresses:

1. Centro de Investigación e Innovación en Bioingeniería (CI2B), Universitat Politècnica de València (UPV), Camino de Vera SN, 46022, Valencia, Spain

2. Hospital Universitario y Politécnico La Fe, Avinguda de Fernando Abril Martorell, 106, 46026, Valencia, Spain

e-mail addresses:

jgarcia@ci2b.upv.es, yiyel@ci2b.upv.es, gprats@ci2b.upv.es, jmas@ci2b.upv.es,
palberola.rubio@gmail.com, perales_alf@gva.es,

ORCID ID

0000-0003-1410-2721, 0000-0003-2929-181X, 0000-0002-9362-5055, -, -, -

Abstract

Preterm birth (PTB) is one of the most common and serious complications in pregnancy. About 15 million preterm neonates are born every year, with ratios of 10-15% of total births. In industrialized countries, preterm delivery is responsible for 70% of mortality and 75% of morbidity in the neonatal period. Diagnostic means for its timely risk assessment are lacking and the underlying physiological mechanisms are unclear. Surface recording of the uterine myoelectrical activity (electrohysterogram, EHG) has emerged as a better uterine dynamics monitoring technique than traditional surface pressure recordings and provides information on the condition of uterine muscle in different obstetrical scenarios with emphasis on predicting preterm deliveries.

Objective: A comprehensive review of the literature was performed on studies related to the use of the electrohysterogram in the PTB context. **Approach:** This review presents and discusses the results according to the different types of parameter (temporal and spectral, non-linear and bivariate) used for EHG characterization. **Main results:** Electrohysterogram analysis reveals that the uterine electrophysiological changes that precede spontaneous preterm labor are associated with contractions of more intensity, higher frequency content, faster and more organized propagated activity and stronger coupling of different uterine areas. Temporal, spectral, non-linear and bivariate EHG analyses therefore provide useful and complementary information. Classificatory techniques of different types and varying complexity have been developed to diagnose PTB. The information derived from these different types of EHG parameters, either individually or in combination, is able to provide more accurate predictions of PTB than current clinical methods. However, in order to extend EHG to clinical applications -the recording set-up should be simplified, be less intrusive and more robust – and signal analysis should be automated, without requiring much supervision and yield physiologically interpretable results. **Significance:** This review provides a general background to PTB and describes how EHG can be used to better understand its underlying physiological mechanisms and improve its prediction. The findings will help future research workers to decide the most appropriate EHG features to be used in their analyses and facilitate future clinical EHG applications in order to improve PTB prediction.

Keywords: preterm, diagnosis, electrohysterogram, uterine electromyogram, temporal analysis, spectral analysis, non-linear analysis, bivariate analysis.

1. BACKGROUND

1.1. Relevance of Preterm Birth

1.1.1. *Definition.* Preterm births (PTB) occur between 20 and 22 weeks of gestation (WG) up to 37 (36 +6) WG (ACOG, 2016; Di Renzo *et al.*, 2017).

The classification of prematurity based upon gestational age (GA) and its prevalence is shown in Table 1.

Table 1.- Classification of prematurity based on gestational age and its prevalence in USA in 2013, information extracted from (Frey and Klebanoff, 2016).

Definition	Gestational age (weeks)	Prevalence absolute (relative)
Extremely preterm birth	< 28	0.7 (6.4%)
Very preterm birth	28 to < 32	1.2 (10.5%)
Moderate preterm birth	32 to < 34	1.5 (13%)
Late preterm birth	34 to < 37	8 (70.1%)

1.1.2. *Incidence.* PTB is one of the most serious common and serious complications in pregnancy. About 15 million preterm neonates are born every year, with the highest rates in Africa and North America (Blencowe *et al.*, 2013). More than 450 000 neonates are born prematurely in the United States every year (McCabe *et al.*, 2014). In Europe the PTB rate varies between 5–18%, with only 0.3–0.5% occurring before 28 weeks, obviously with a worse outcome. However, it is not the extremely preterm babies that are the highest burden on society, as they are infrequent, but the children born between 32 and 36 weeks (Di Renzo *et al.*, 2017). Reducing preterm births is a national public health priority all over the world. Despite the development of numerous obstetrical interventions to reduce the burden of prematurity-related morbidity (including tocolysis, antibiotics to prolong latency for preterm rupture of membranes, and home uterine activity monitoring) they have had no apparent effect on reducing the incidence of preterm birth.

1.1.3. *Health Consequences.* Preterm birth is a leading cause of disability-adjusted life year and has both short and long-term consequences. Among the former, in a report from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, the following complications and their prevalence were seen in 8515 very low birth-weight (< 1500 g) infants: respiratory distress 93 %, retinopathy of prematurity 59%, patent ductus arteriosus 46%, bronchopulmonary dysplasia 42%, late-onset sepsis 36%, necrotizing enterocolitis 11%, grade III intraventricular hemorrhage and grade IV IVH – 7 and 9 %, periventricular leukomalacia 3% (Stoll *et al.*, 2010). Although the risk of complications decreases with increasing GA, even moderately preterm infants are at risk for significant mortality and morbidity. As illustrated by a Swedish population-based study of 6674 preterm infants with a GA between 30 and 34 weeks born from 2004 to 2008, the following complications and their frequencies were as follows: hyperbilirubinemia 59%, acute respiratory disease 28%, hypoglycemia 16% and bacterial infection 15% (Altman *et al.*, 2011). In relation to the long term consequences, prematurity is associated with about one third of all infant deaths in the United States and accounts for approximately 45% of children with cerebral palsy, 35% of children with vision impairment and 25% of children with cognitive or hearing impairment (G. Mandy, 2017). Moreover, in preterm survivors there is a high rate of: recurrent hospitalizations (Boyle *et al.*, 2012); long-term neurodevelopment impairment: the risks of medical (cerebral palsy, mental retardation, autism spectrum, major disabilities including blindness, low vision, hearing loss, and epilepsy, etc.), social disabilities (lower educational attainment, income, social security benefits and the establishment of a family) in adulthood increased with decreasing gestational age at birth (Moster, Lie and Markestad, 2008); chronic health problems: developmental programming among low birth weight infants has been associated with problems including obesity, hypertension, insulin resistance, and coronary artery disease.

1.1.4. *Economic Consequences.* Preterm births also entail economic consequences. A review of the literature was carried out in March 2011 in which costs were assessed for different follow-up periods (short, medium or long-term), and for different degrees of prematurity (extreme, early, moderate and late). The results showed that whatever the follow-up period, costs correlated inversely with GA. Despite variations, a global trend of costs was estimated in the short-term period using mean costs from four American studies with similar methodologies. Costs stand at over US\$100,000 for extreme prematurity, between \$40,000 and \$100,000 for early prematurity, between \$10,000 and \$30,000 for moderate prematurity and below \$4500 for late prematurity (Soilly *et al.*, 2014). Based on 2006 estimates of the number of preterm births and the cost of medical care through the first 18 years of life in England and Wales, the total cost to society was estimated to be almost £3 billion (Mangham *et al.*, 2009). The mean incremental cost per child was about £23,000 and cost increased with decreasing GA, with the estimated costs for a very preterm child of £62,000 and £95,000 for an extremely preterm child. The Italian National Health Service estimated at €8,098 the cost for families and social security of infants born under 1500g, or 30 weeks, without prematurity-related morbidities up to the age of 18 months (Cavallo *et al.*, 2015). Although there is evidence that hospital costs represent a considerable portion of the total cost, families also suffer direct economic losses, such as those resulting from paying uncovered drugs, travelling costs, or reduced earnings (working days lost), increased debt, financial worry, unsafe home environment and social isolation.

Not only true PTB involves significant costs, but also false threatened PTB. In fact, fewer than 15% of the women with threatened preterm labor will actually deliver prematurely (Palacio *et al.*, 2007; Lucovnik, Chambliss and Garfield, 2013). In a study by Lucovnik *et al.* (Lucovnik, Chambliss and Garfield, 2013) the mean cost of false threatened PTB was \$20,372 per patient. In most countries, the identification of preterm labor is based only on subjective clinical data, which increases the risk of hospitalization and costs of unnecessary and potentially harmful interventions such as tocolysis and prenatal corticosteroids (Di Renzo *et al.*, 2017). Improving PTB diagnosis will significantly reduce hospital costs. Van Baaren *et al.* (van Baaren *et al.*, 2013) performed a model-based cost-effectiveness analysis to evaluate 7 test-treatment strategies in women with threatened preterm labor from a health-care system perspective. The most cost-effective test strategy was the combination of the cervical length test and fetal fibronectin test. According to this study (van Baaren *et al.*, 2013), implementing this strategy could lead to an annual cost saving of between €2.8 million and €4.4 million in The Netherlands, where about 180,000 babies are delivered annually.

1.2. *Pathophysiology, diagnosis and treatment of Preterm Birth*

1.2.1. *Pathophysiology.* Preterm birth is often regarded as a single outcome in clinical practice but numerous biological mechanisms that vary between individuals are thought to lead to preterm birth. There are multiple well-established risk factors for preterm birth. They include maternal characteristics (maternal age, stress, depression, body mass index, etc.), reproductive history (prior PTB or stillbirth, induced abortion) and current pregnancy characteristics (multiple gestation, vaginal bleeding, short cervical length, etc.). More than twenty of these factors and further information can be found in (Frey and Klebanoff, 2016; Julian N Robinson and Norwitz, 2017). A history of previous spontaneous PTB is the major risk factor for recurrence, and recurrences often occur at the same gestational age. The frequency of recurrent spontaneous PTB was 15 to 30 percent after one spontaneous PTB and increased after two (Julian N Robinson and Norwitz, 2017). The identification of risk factors by clinicians may be useful in guiding the counseling and obstetric management of individual women. However, it is important to stress that risk is not equivalent to causation.

Although the proposed disease mechanisms involved in spontaneous preterm labor are different in nature (infection, vascular disorders, uterine overdistension, decidual senescence, cervical disease, decline in progesterone, breakdown of maternal-fetal tolerance, cervical disease, etc.) increased uterine contractility, cervical dilatation, and rupture of the chorioamniotic membranes are the common pathway (Romero, Dey and Fisher, 2014). In this context, preterm and term labor involve similar clinical events (Romero, Dey and Fisher, 2014). On one hand, the switch of the

myometrium from a quiescent to a contractile state is associated with a shift in signaling from anti-inflammatory to pro-inflammatory pathways, which include chemokines (interleukin-8 (IL-8), cytokines (IL-1 and -6), and contraction-associated proteins (oxytocin receptor, connexin 43, prostaglandin receptors). Progesterone maintains uterine quiescence by repressing the expression of these genes. Increased expression of the microRNA-200 family near term can derepress contractile genes and promote progesterone catabolism (Renthal, Williams and Mendelson, 2013). On the other hand, cervical ripening is mediated by changes in extracellular matrix proteins, as well as alterations in epithelial barrier and immune surveillance properties. Finally, decidual or membrane activation occurs in close proximity to the cervix in preparation for membrane rupture and to facilitate separation of the chorioamniotic membranes and placenta from the uterus (Romero, Dey and Fisher, 2014).

1.2.2. Diagnosis. The diagnosis of preterm labor is generally based on clinical criteria of regular uterine contractions accompanied by a change in cervical dilation, effacement, or both, or initial presentation with regular contractions and cervical dilation of at least 2 cm (ACOG, 2016). E.g., Uterine contractions (≥ 4 every 20 minutes or ≥ 8 in 60 minutes) and Cervical dilation ≥ 3 cm or cervical length (CL) < 20 mm on transvaginal ultrasound or CL 20 to 30 mm and positive fetal fibronectin (fFN) (Lockwood, 2017). Criteria for the diagnosis of preterm labor lack precision because the underlying etiology and sequence of events that precede preterm birth are not completely understood. Symptoms such as painful uterine contractions, pelvic pressure, increased vaginal discharge and low back pain have been associated with preterm birth (Katz, Goodyear and Creasy, 1990; Di Renzo *et al.*, 2017). However, these symptoms can also be common in women with normal pregnancies, making the diagnosis of preterm labor even more challenging. These challenges often result in overdiagnosis in up to 40% of women with preterm labor symptoms (Iams, Johnson and Parker, 1994). Less than 10% of women with the clinical diagnosis of preterm labor actually give birth within 7 days of presentation (Fuchs *et al.*, 2004).

1.2.3. Treatment. Historical nonpharmacological treatments aimed at preventing preterm births in women with preterm labor have included bed rest, abstention from intercourse and orgasm and hydration. Evidence for the effectiveness of these interventions is lacking, and adverse effects have been reported (Sosa *et al.*, 2004). Pharmacologic interventions to prolong pregnancy have included the use of tocolytic drugs to inhibit uterine contractions as well as antibiotics to treat intrauterine bacterial infection. Administration of tocolytic drugs did not result in statistically significant reductions in important clinical outcomes, such as neonatal respiratory distress and survival (Haas *et al.*, 2012). In a practice bulletin, the American College of Obstetricians and Gynecologists (ACOG) opined: "Interventions to reduce the likelihood of delivery should be reserved for women with preterm labor at a gestational age at which a delay in delivery will provide benefit to the newborn". Because tocolytic therapy is generally effective for up to 48 hours, only women with fetuses that would benefit from a 48 hour delay in delivery should receive tocolytic treatment (ACOG, 2016). The upper limit for the use of tocolytic agents to prevent preterm birth is generally 34 WG. On the other hand, the therapeutic agents currently thought to be clearly associated with improved neonatal outcomes include antenatal corticosteroids for maturation of fetal lungs and other developing organ systems and the targeted use of magnesium sulfate for fetal neuroprotection (ACOG, 2016).

A Cervical Pessary (a soft and flexible silicone device) has been proposed as a treatment for preterm birth prevention in cases of single pregnancies with short cervix and twin pregnancies. Since the seminal paper (Goya *et al.*, 2012), in which its use showed a decrease in preterm birth before 34 weeks of gestation (OR 0.19; 95% CI 0.12–0.30) and improvement of neonatal outcome (RR 0.14; 95% CI 0.04–0.39), it has attracted much attention because of its potential advantages over cerclage, non-invasive, cheaper, ease insertion, among others. Nevertheless, the results of pessary studies for prevention of preterm birth in various populations, gave conflicting result and warrants further study prior to routine use (Boelig and Berghella, 2017)

Because therapy and supportive care are continuously upgraded and enhanced, the preterm infants' outcomes are ever-evolving. Efforts to minimize injury, preserve growth, and identify

interventions are being evaluated. Thus, treating and preventing long-term deficits must be developed in the context of a "moving target."

1.3. Current methods of predicting Preterm Birth

One of the biggest challenges in the management of pregnant women with threatened preterm labor is differentiating between the 75% of patients who will not actually deliver early and the remainder who will deliver preterm (Malone, 2016). In a study of 763 women who had unscheduled triage visits for symptoms of preterm labor, only 18% gave birth before 37 WG and only 3% gave birth within 2 weeks of having symptoms (Peaceman *et al.*, 1997). The distinction between true and false preterm labor is often challenging despite the availability of different tools such as digital examination, ultrasound measurement of CL, Bishop score, fFN test, several biomarkers and contraction frequency measurements for PTB prediction. The following is a brief description of the leading methods.

1.3.1. Cervical Length. CL measurements have proved to be useful in predicting preterm labor. A short cervix is significantly associated with an earlier gestational age at delivery and with recurrent preterm birth (Romero *et al.*, 2012). In symptomatic singleton gestations with threatened preterm labor, there is a significant association between knowledge of transvaginal CL and lower incidence of PTB and later gestational age at delivery (Berghella *et al.*, 2017). A sonographic short cervix detected in the second trimester was the best predictor of spontaneous PTB in that study (Berghella *et al.*, 2017). In fact, the Health technology assessment (Honest *et al.*, 2009), systematically reviewed 22 tests of predicting spontaneous PTB and concluded that universal provision of high-quality ultrasound machines in labor wards is more strongly indicated for predicting spontaneous PTB among symptomatic women than direct management (Honest *et al.*, 2009), which suggests that ultrasonographic CL measurement is the gold standard in predicting spontaneous preterm labor.

In low risk singleton pregnancies with a mid-pregnancy CL > 35 mm and without any known risk factors, the risk of spontaneous preterm birth before 37WG is 13% (RR: 2.35; 95% CI: 1.42 - 3.89). This risk is inversely proportional to the size of the cervix, with a shorter cervix predicting a higher risk. Once the cervix reaches ≤ 25 mm the risk of preterm birth will be more than double (RR: 6.19; 95% CI: 3.84 - 9.97) (Iams *et al.*, 1996). Interventions that reduce the risk of spontaneous preterm birth based on transvaginal ultrasound cervical length are available and effective in appropriately selected patients (cerclage, vaginal progesterone), which makes transvaginal ultrasound cervical length an effective screening test. For these reasons, the ACOG and the Society for Maternal-Fetal Medicine (SMFM) recommend screening of all women with singleton gestation and a history of spontaneous preterm birth (grade 1A evidence), while transvaginal ultrasound cervical length screening is reasonable but not mandatory in women without prior preterm birth (McIntosh *et al.*, 2016; Feltovich, 2017). Clinical evidence of cervical length in women with threatened preterm labor reduced the rate of preterm births compared with the absence of this information (22 versus 35 percent; RR 0.64. 95% CI 0.44-0.94; three trials; n = 287 participants), (Berghella *et al.*, 2017). Universal cervical length screening of women with singleton gestations without a prior spontaneous preterm birth was implemented by over two-thirds of institutions with SMFM Fellowship Programs, as of January 2015 (Khalifeh, Quist-Nelson and Berghella, 2017).

1.3.2. Biochemical Markers. Biological fluids (eg, amniotic fluid, urine, cervical mucus, vaginal secretions, serum or plasma, or both, and saliva) have been used to assess the value of biomarkers for predicting PTB. Biomarkers (fFN, Phosphorylated insulin-like growth factor binding protein-1, placental alpha macroglobulin-1, IL6, etc.) have been proposed to improve the prediction accuracy of imminent spontaneous PTB in symptomatic women (Brik *et al.*, 2010, 2011; Lim, Butt and Crane, 2011; Melchor *et al.*, 2017). In a recent study that screened women between 22 and 30 WG with fFN and CL (Esplin *et al.*, 2017), the AUC with fFN level alone was 0.59 (95% CI, 0.56-0.62), for transvaginal cervical length alone was 0.67 (95% CI, 0.64-0.70), and for the combination as continuous variables was 0.67 (95% CI, 0.64-0.70). Hezelgrave *et al.* (Hezelgrave, Shennan and David, 2015) suggested that a combination of a negative biomarker result and a CL

greater than 25 mm suggests such a low chance of delivery within 1 week (less than 5%) that such patients probably do not require admission and treatment. However, the value of these two tests lies mostly in their high negative predictive values, while their positive predictive values are lower and do not identify patients who are really going to deliver preterm. Although the results of observational studies have suggested that knowledge of fFN status or CL may help health care providers to reduce the use of unnecessary resources (Fell et al., 2014; Parisaei et al., 2016), these findings have not been confirmed by randomized trials (Grobman, Welshman and Calhoun, 2004; Ness et al., 2007), or by reviews or metaanalysis (Berghella et al., 2008; Deshpande et al., 2013). Recently, Poletteni et al (Poletteni et al., 2017) systematically reviewed the biomarkers in maternal and fetal compartments to predict PTB and concluded that no single biomarker or combination of such could be identified to reliably predict PTB risk and pregnancy outcome.

1.3.3. Contraction Frequency. The presence of regular uterine contraction is commonly used to diagnose preterm labor. Iams (Iams, 2003) performed a prospective, blinded observational study of uterine contraction frequency to detect and predict preterm labor and birth, respectively. The goal of the study was to assess the sensitivity, specificity, and positive and negative predictive value of various measures of uterine contraction frequency. Data collected from 306 women revealed that this indicator was significantly greater in women who would ultimately deliver before rather than after 35WG. However, both the sensitivity and positive predictive value of any measure of contraction frequency to predict preterm birth were poor (Uterine contraction frequency between 22 to 32 WG, to predict spontaneous birth at < 35 WG sensitivity ranges from 0 to 28.1%, while the positive predictive values were between 0 and 25%). Contraction frequency did not increase significantly within 1 or 2 weeks of an episode of preterm labor. A Cochane systematic review on home uterine monitoring for detecting preterm labor (Urquhart *et al.*, 2017), including 15 studies (6008 enrolled participants), showed that home uterine monitoring may result in fewer admissions to a neonatal intensive care unit but in more unscheduled antenatal visits and tocolytic treatment, with no impact on maternal and perinatal outcomes such as perinatal mortality or incidence of preterm birth. Unfortunately, in both these studies, and in common medical practice, contraction activity is measured by external tocography (TOCO), which has disadvantages and limitations; its efficiency depends on the subjectivity of the clinician, and it may also fail in obese patients (Schlembach *et al.*, 2009). Tight elastic straps are needed to ensure probe pressure and contact, which can cause reflex contractions.

Many other methods have been proposed to predict PTB but their results are either poor or have not been validated (Paternoster *et al.*, 2009; Brik *et al.*, 2010, 2011; Nikolova *et al.*, 2015), so that there is still no currently available reliable PTB prediction technique.

1.4. Electrohysterogram

1.4.1. Why electrohysterography for predicting preterm birth? Current labor assessment methodologies (such as tocodynamometry or intrauterine pressure catheters, fetal fibronectin, cervical length measurement and digital cervical examination) have several major drawbacks: they only measure the onset of labor indirectly and do not detect cellular changes characteristic of true labor, so that their predictive values for term or preterm delivery are poor. Both term and preterm births involve activation of the myometrium. Several events in the uterine muscle precede labor: cell excitability increases due to changes in transduction mechanisms and synthesis of various proteins, including ion channels and receptors for uterotonins (Fuchs *et al.*, 1984; Tezuka *et al.*, 1995). At the same time, the factors that inhibit myometrial activity, such as the nitric oxide system, are downregulated, leading to withdrawal of uterine relaxation (Garfield *et al.*, 1998). Electrical coupling between myometrial cells also increases, and an electrical syncytium allowing the propagation of action potentials from cell to cell is formed (Leitich *et al.*, 1999; Honest *et al.*, 2002). These changes are required for effective contractions that end in the delivery (expulsion) of the fetus.

Since uterine contractions are a result of the electrical activity within the myometrium, the external measurement of uterine electrical activity for monitoring and analyzing uterine contractility can contribute to a better understanding of labor and preterm labor etiology. This

technique records non-invasively the electrical activity associated with the contraction of the myometrial cells of the uterus from the maternal abdominal wall and is called the *uterine electromyogram* (EMG) or *electrohysterogram* (EHG) (see Figure 1). It has been shown to provide better contraction detectability than TOCO (Alberola-Rubio *et al.*, 2013), especially in obese patients (Euliano *et al.*, 2007). In addition, changes in cell excitability and coupling required for effective contractions that lead to delivery are reflected in changes in several EHG parameters (Lucovnik *et al.*, 2011). Several studies have shown that EHG features are ‘dynamic’ and change throughout pregnancy (Devedeux *et al.*, 1993). At early gestational ages uterine electrical activity is scarce and poorly coordinated, however as labor approaches it becomes more and more intense and synchronized (Devedeux *et al.*, 1993; Garfield and Maner, 2007). Many studies have shown that different uterine EMG parameters can indicate myometrial properties that can distinguish between true and ‘false’ labor contractions in term and preterm pregnancies (Fele-Zorz *et al.*, 2008; Schlembach *et al.*, 2009; Sikora *et al.*, 2011). Uterine EMG can help to identify patients in true labor better than any other method presently employed in clinics (Lucovnik *et al.*, 2011). Furthermore, analysis of EHG signals is non-invasive for both fetus and mother, does not require any special facilities or equipment and is relatively low-cost.

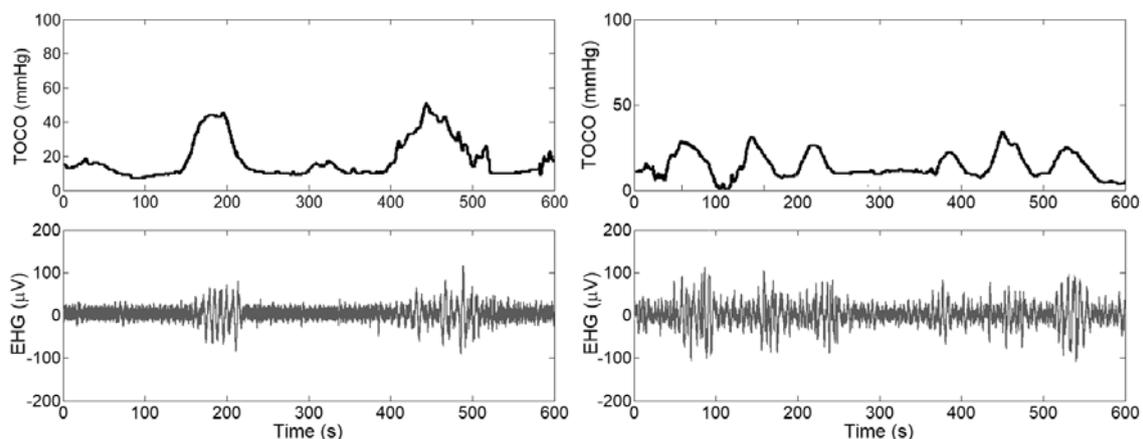


Figure 1. Examples of TOCO and EHG records of women with threat of preterm labor delivering at: >7 days (left) and <7days (right) after the recording. Bursts of higher amplitude and frequency are observed when delivery is approaching.

1.4.2. *Signal components.* Although the exact electrophysiological mechanisms behind EHG generation are still poorly understood, it is well known that they are related to uterine myocyte excitability and to propagation activity in the myometrium. These factors are the basic elements of the EHG signal components, which are the fast wave (FW) and slow wave (SW). It is believed that the SW has no physiological significance, besides the fact that its bandwidth is overlapped with the baseline fluctuation commonly related to skin stretching, abdominal and electrode movements, which make it difficult to interpret. Most studies perform EHG analyses focusing on the FW, which is divided into two components, fast wave low (FWL) and fast wave high (FWH), with peak frequencies between [0.13-0.26] Hz and [0.36-0.88] Hz, respectively (Terrien, Marque and Karlsson, 2007). However, FWH frequency content is believed to extend to higher frequencies, usually up to 3-4 Hz (Fele-Zorz *et al.*, 2008). It is hypothesized that FWL is related to the propagation of the EHG signal and FWH to the excitability of the uterine cells (Devedeux *et al.*, 1993).

Nonetheless, surface EHG amplitude is low (between tenths and hundredths of μV) and its recording is affected by interference, noise and artifacts, including: drift, maternal respiration, maternal ECG, fetal ECG, electromyography noise, power line interference and motion artifacts (Batista *et al.*, 2016). As commented above, baseline drift frequency content can overlap that of the EHG short wave and is usually discarded. The maternal respiratory frequency typically ranges between 12-20 times per minute (0.2-0.33 Hz) and some studies therefore focus on the FWH frequency range (Lucovnik. *et al.*, 2011; Smrdel and Jager, 2015). The frequency content of the maternal and fetal ECG can be as low as 1 Hz (Maner *et al.*, 2003), so that many studies focus on

EHG analysis below 1 Hz (Lucovnik. *et al.*, 2011; Smrdel and Jager, 2015). The electromyographic interference generated by the abdominal muscles has a dominant frequency component at around 30 Hz. This, together with power line interference at 50 or 60 Hz, can be easily cancelled by conventional low-pass filtering. Movement artifacts can completely distort the recorded signal and its whole frequency content. Signal segments with artifacts are usually visually identified and discarded. Efforts are being made to facilitate the automatic identification of movement artifacts (Ye-Lin *et al.*, 2014).

1.4.3. The Term-Preterm EHG Database (TPEHGDB). This is a public database available at Physionet (Goldberger *et al.*, 2000; Fele-Zorz *et al.*, 2008) that has been widely used in term vs preterm EHG studies. A brief description is of interest to the reader for the possible interpretation of the results presented. Records were obtained for this database during regular check-ups either around the 22nd week of gestation or around the 32nd week of gestation. It contains 300 uterine EMG records of 300 pregnancies, of which 262 delivered at term (143 records <26WG, 119 records \geq 26WG) and 38 ended prematurely (19 record <26WG, 19 records \geq 26WG). 4 subgroups are therefore usually considered: preterm recorded early, preterm recorded later, term recorded early and term recorded later. Figure 2 shows the distribution of the database in terms of time to delivery. It should be noted that in most cases recordings were taken \geq 4 weeks before labor, not only for the “early” groups, but also for most of the “late” group for term delivery. All records of pregnancies in which labor was induced or delivery was by Cesarean section were rejected.

Each record was composed of three bipolar channels from 4 electrodes of 30 minutes duration. The first electrode (E1) was placed 3.5 cm to the left and 3.5 cm above the navel; the second electrode (E2) 3.5 cm to the right and 3.5 cm above the navel; the third electrode (E3) 3.5 cm to the right and 3.5 cm below the navel; and the fourth electrode (E4) at 3.5 cm to the left and 3.5 cm below the navel. The differences in the electrical potentials of the electrodes were recorded, producing 3 data channels: S1 = E2 – E1 (first channel); S2 = E2 – E3 (second channel); and S3 = E4 – E3 (third channel). Unfiltered signals and signals filtered in the bandwidths: 0.08Hz to 4Hz, 0.3Hz to 3Hz and 0.3Hz to 4Hz are available.

Clinical information, such as: pregnancy duration; gestation duration at the time of recording; maternal age; number of previous deliveries (parity); previous abortions etc. is also available.

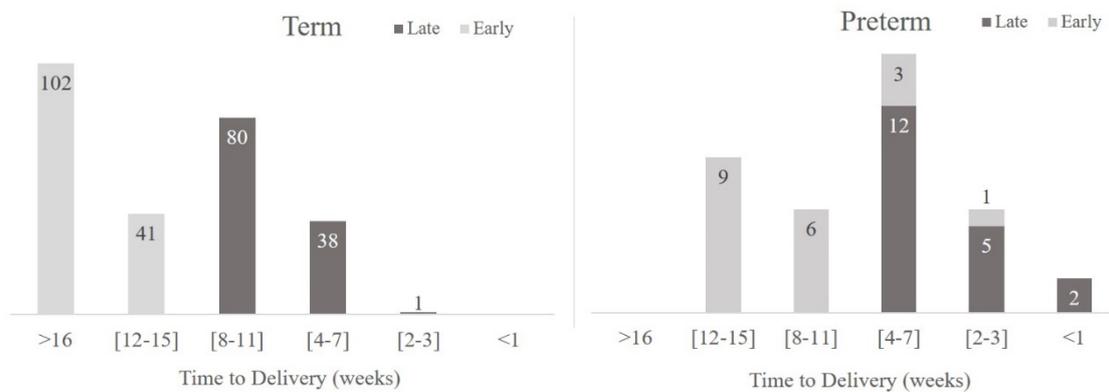


Figure 2. Number of EHG records from the TPEHGDB for different time to delivery intervals.

2. ELECTROHYSTEROGRAPHY FOR DIAGNOSIS OF PRETERM LABOR

As has been mentioned, labor is preceded by two physiological phenomena: increased excitability and increased connectivity among the myometrial cells, changes which are reflected in the EHG. Various ways of characterizing the EHG have been proposed for different aims, mainly predicting preterm and term delivery (Fele-Zorz *et al.*, 2008), but also to study the uterine electrophysiological response to tocolytic agents such as atosiban (Hadar *et al.*, 2013) or nifedipine (Vinken *et al.*, 2010) or to labor induction drugs (Aviram *et al.*, 2014; Benalcazar Parra *et al.*, 2017), to predict the possible need for labor induction in late term pregnancies (Alberola-Rubio *et al.*, 2017), or labor arrest (Euliano *et al.*, 2009; Vasak *et al.*, 2013), among others.

Section 2.1 provides a structured review of the use of EHG for predicting PTB according to the different types of parameter used: temporal and spectral, non-linear and bivariate analysis. This will help future research groups to decide the appropriate EHG features to be used to configure their analyses and thus facilitate future clinical EHG applications. Systematic searches were carried out in PubMed and other NCBI electronic data bases. Since here the focus is on predicting PTB, unless otherwise noted, the selected studies had to include either EHG records from women during spontaneous preterm labor, or from women with a threat of preterm labor, or women who delivered preterm.

2.1. Temporal and Spectral Analysis

It is widely accepted that the changes in uterine muscle that precede labor are reflected in the myoelectrical signal, which can be recorded on the abdominal surface. Traditional signal analysis techniques use temporal and spectral parameters such as duration, amplitude, peak frequency, etc. They are well known by researchers and practitioners and are usually easy to interpret. Numerous works using this type of parameter have been published on predicting PTB under different recording conditions and analysis. Many of them use EHG records from the TPEHGDB (Fele-Zorz *et al.*, 2008), which are taken of physiological conditions during regular check-ups; some indicate that EHG registers were carried out on women under tocolytic treatment after threat of PTB (Lucovnik *et al.*, 2011; Mas-Cabo *et al.*, 2017); others do not indicate whether the women had received tocolytic drugs (Maner and Garfield, 2007; Sikora *et al.*, 2011). Most of the studies focus only on the analysis of the EHG-Burst (Maner and Garfield, 2007; Most *et al.*, 2008; Diab, Marque and Khalil, 2009; Lucovnik *et al.*, 2011; Sikora *et al.*, 2011; Horoba *et al.*, 2016) to separate term and preterm registers, and some others perform a whole EHG record analysis (Fele-Zorz *et al.*, 2008; Smrdel and Jager, 2015). In Table 2 all these features and other relevant information are summarized. Although some works study monopolar signals, most focus on bipolar signals and last between 10 to 60 minutes. In all the included studies spectral and/or temporal parameters are evaluated. The spectral parameters were obtained in bandwidths between 0 to 100 Hz.

2.1.1. *Temporal Parameters.* Amplitude is one of the basic parameters traditionally used to characterize EHG. Contractions of more intensity, and therefore higher EHG amplitude, can be expected as delivery approaches. Nonetheless, the results and potential use of amplitude parameters for preterm labor prediction have been controversial. Fele-Žorž *et al.* analyzed the root-mean-square (RMS) value of the whole EHG recording (approximately 30 minutes) of the 4 different TPEHGDB subgroups, in its three predefined EHG bandwidths (Fele-Zorz *et al.*, 2008). They reported that RMS values did not give clear results on separating preterm and term groups. Horoba *et al.* calculated the RMS values of the EHG-Bursts on the same TPEHGDB and the same bandwidths (0.08 – 4 Hz, 0.3 – 4 Hz, 0.3 – 3Hz) and reported similar findings i.e. there are no great differences between term and preterm deliveries (Horoba *et al.*, 2016). This contrasts with the findings of other authors and could be due to the long interval between the recording day and that of delivery (see Figure 2) of most of the cases in the TPEHGDB. For example, recent EHG recordings on 26 women threatened with preterm labor showed significant differences in the amplitude of whole EHG-recordings from women who delivered preterm and from those that did so at term (Mas-Cabo *et al.*, 2017). However, these differences were only statistically significant in signals recorded by a bipolar concentric electrode and not in bipolar records with conventional disc electrodes. On the other hand, in studies focused on the EHG-Burst in non TPEHGDB databases, Most *et al.* found significant differences in threatened preterm labor women when separating women who delivered in less than 14 days ($499 \pm 96 \mu\text{V}$) vs those who gave birth in more than 14 ($340 \pm 142 \mu\text{V}$) (Most *et al.*, 2008). However the EHG analyses were taken from a broader bandwidth (1 – 1500 Hz) than those commonly used, which discard components at frequencies higher than 4 Hz. Verdenik *et al.* (Verdenik, Pajntar and Leskosek, 2001) performed an EHG-Burst analysis which included 17 preterm women and 30 term women between the 25th and 35th week of gestation and obtained significantly ($p < 0.05$) higher preterm EHG-Burst RMS values ($17.5 \pm 7.78 \mu\text{V}$) among term EHG-Burst RMS ($12.2 \pm 6.25 \mu\text{V}$). Other studies also calculated the EHG-Burst peak-to-peak amplitude (Sikora *et al.*, 2011). They classified the

women into three groups: Group I composed of 27 women in physiological pregnancy, Group II which included 21 women with symptoms of preterm labor and Group III formed by 14 women in their first labor period. They found higher amplitude values for the threatened preterm women ($62.2 \pm 72.3 \mu\text{V}$) than for women in physiological pregnancies ($33.8 \pm 53.6 \mu\text{V}$). However (Horoba *et al.*, 2016) did not find any significant differences between term and preterm amplitude values, but again this study employed TPEHGDB. They also used the area under the EHG-Burst envelope to characterize the EHG signals, but no significant differences were obtained when comparing all term with all preterm registers. The median value of these areas worked for the S2 channel in the 0.08 – 4 Hz bandwidth, to separate early term ($459.5 \mu\text{V}\cdot\text{s}$) and early preterm records ($607 \mu\text{V}\cdot\text{s}$). However, it did not show any other significant differences, and presented inconsistent trends between channels when comparing the same groups. They also studied contraction intensity, which refers to a number of spikes within the EHG-Bursts, to separate preterm and term EHG registers. However, no significant differences were found (Horoba *et al.*, 2016). The autocorrelation zero-crossing, defined as the first zero-crossing starting at the peak in the autocorrelation of the EHG signal, did not give promising results for separating term and preterm records and its effectiveness strongly depended on the selected bandwidth (Fele-Zorz *et al.*, 2008; Horoba *et al.*, 2016).

Other temporal parameters related to EHG features such as duration or standard deviation of the EHG-Burst duration have been analyzed (Maner and Garfield, 2007) and obtained significantly lower EHG-Burst duration standard deviation values for term labor registers than term non-labor records. The same trend was found for preterm labor vs. non-labor records. Nevertheless, no significant differences were obtained between groups in either the mean burst duration or the number of bursts in a given time. The same parameters and mean inter-Burst interval were computed from women who delivered within 7 days and those who gave birth after 7 days, with no significant differences between the groups (Lucovnik. *et al.*, 2011).

2.1.2. Spectral Parameters. Unlike EHG signal amplitude-related parameters, frequency-related parameters are expected to be more comparable from one subject to another and less sensitive to sensor position (Vinken *et al.*, 2009). They are usually calculated from EHG burst windows or from windows that include intercontractile periods. One of the most frequently used spectral parameters is the peak frequency of the power spectrum (PS) of EHG burst, which shifts to higher frequencies when labor is close (Devedeux *et al.*, 1993; Schlembach *et al.*, 2009). It has also been reported that the percentage of time that the uterus shows high frequency activity increases from 10% -20% when far from delivery to about 80% -90% within 24 hours of delivery in term women (Garfield *et al.*, 2005).

For preterm deliveries, Lucovnik et al observed that the PS peak frequencies were significantly higher ($p < 0.05$) in women who delivered within 7 days ($0.56 \pm 0.15 \text{ Hz}$) than in those who gave birth in more than 7 days ($0.44 \pm 0.07 \text{ Hz}$) (Lucovnik. *et al.*, 2011). The PS peak frequency values obtained by Sikora et al (Sikora *et al.*, 2011) were higher for preterm threatened women ($0.32 \pm 0.29 \text{ Hz}$) than for non-threatened ones ($0.25 \pm 0.18 \text{ Hz}$). Again, it should be highlighted that these results were obtained on analog filtered signals between 0.5 Hz and 100 Hz. In another study with a more comprehensive database, the peak frequency, in the range 0.34 – 1 Hz, of the PS of the EHG-Bursts signals was computed (Maner and Garfield, 2007). They included 134 term and 31 preterm EHG records and separated them into four groups: term labor, term non-labor, preterm labor and preterm non-labor. The average peak frequency was significantly higher ($p < 0.05$) for term labor registers ($0.437 \pm 0.045 \text{ Hz}$) than term non-labor ones ($0.392 \pm 0.022 \text{ Hz}$) and also for preterm labor registers ($0.471 \pm 0.046 \text{ Hz}$) against the preterm non-labor records ($0.398 \pm 0.023 \text{ Hz}$). Also, the ratio of the average peak frequency divided by the average standard deviation of burst duration was significantly higher ($p < 0.05$) for term labor records ($0.0505 \pm 0.0275 \text{ Hz/s}$) than term non-labor ones ($0.0226 \pm 0.0108 \text{ Hz/s}$) and also for preterm labor registers ($0.0328 \pm 0.0195 \text{ Hz/s}$) against preterm non-labor ones ($0.0145 \pm 0.00624 \text{ Hz/s}$).

Peak frequency has been computed and analyzed not only for the contractile events but also for whole EHG recordings. Smrdel and Jager (Smrdel and Jager, 2015) studied the spectral content of a 30-minute window of EHG signals from TPEHGDB in the ranges 0.34 – 1 Hz and 0.3 – 4 Hz by using autoregressive methods (AR). They reported that the PS of term delivery records

showed peaks at higher frequencies than the PS of the preterm ones. Fele-Zorz et al also analyzed the whole EHG recording and reported that the peak frequency only worked in the ranges 0.3 - 4 Hz and 0.3 – 3 Hz for separating all registers recorded early vs all registers recorded late (Fele-Zorz *et al.*, 2008). However, in the same study the median frequency of whole EHG records showed significant differences with separate all term vs all preterm delivery records in the ranges 0.3 - 4 Hz and 0.3 – 3 Hz, but not for the 0.08 – 4 Hz range (Fele-Zorz *et al.*, 2008). According to (Smrdel and Jager, 2015), the median frequency worked also in the range 0.3 – 4 Hz for separating term from preterm registers in both early and late records. However, the authors conclude that for the term delivery records the median frequency drops throughout pregnancy and hardly changes for preterm deliveries.

Several studies have also used the median frequency of the PS of EHG-burst but the results were not as good as when computed from whole EHG records. No significant differences were found between women who delivered preterm (0.36 ± 0.06 Hz) and those at term (0.37 ± 0.04 Hz) (Verdenik, Pajntar and Leskosek, 2001). Neither were significant differences found between women delivering preterm in <7days and >7days (Lucovnik. *et al.*, 2011). Nonetheless, the mean value of the median frequency was smaller when delivery was closer (0.64 ± 0.12 Hz vs 0.68 ± 0.05 Hz). On the other hand (Sikora *et al.*, 2011) reported higher PS median frequency values for the preterm threatened women's group (0.35 ± 0.10 Hz) of women in physiological pregnancies (0.30 ± 0.12 Hz), however again no significant differences were observed.

Other spectral parameters, such as the PS mean frequency of the EHG bursts and HF power band/LF power band ratio, have also been studied. However, none provides information that could be used to discriminate between term and preterm registers (Horoba *et al.*, 2016; Mas-Cabo *et al.*, 2017).

Table 2.-Features taken from studies that used temporal and spectral EHG parameters in a PTB context.

<i>Author (Year)</i>	<i>Data Base (n°women)</i>		<i>No. Channels</i>		<i>Registers duration(minutes)</i>	<i>Analysed bandwidth (Hz)</i>	<i>Spectral estimator</i>	<i>Window of analysis</i>	<i>Drugs admin.</i>
	<i>Preterm</i>	<i>Term</i>	<i>Monopolar</i>	<i>Bipolar</i>					
Verdenik (2011)	30	17	0	2	30	0.1 – 4	FFT	EHG-Burst	Yes
Maner (2007)	51	134	0	2	30	0.34 - 1	FFT	EHG-Burst	unknown
Fele-Zorz(2008)	38	262	4	3	30	0.08 – 4 0.3 – 4 0.3 - 3	FFT	Whole EHG record	No
Most(2008)	87	7	9	0	30	1 - 1500	Not indicated	EHG-Burst	No
Sikora (2011)	21 threat of PTB 27 phys. pregnancy 14 labor		0	2	10 - 60	0.5 - 100	Not indicated	EHG-Burst	No
Lucovnik (2011)	88	28	0	2	30	0.34 - 1	FFT	EHG-Burst	Yes
Smrdel (2015)	38	262	4	3	30	0.34 – 1 0.3 - 4	AR	Whole EHG record	No
Horoba (2016)	38	262	4	3	30	0.08 – 4 0.3 – 4 0.3 - 3	FFT	EHG-Burst	No
Mas-Cabo (2017)	50	0	0	1	30 - 60	0.1 – 4	FFT	Whole EHG record	Yes

2.2. Non-linear Analysis

It is well known that the underlying physiological mechanisms of biological systems are non-linear processes that change with time, and hence can be modeled as a non-linear dynamical system. The non-linearity can be attributed to the coupling between the billions of intricately interconnected cells and inherent complex feedback networks. Nagarajan *et al.* used a hierarchy of surrogate algorithms to determine the nature of the process generating the contractions during labor and found that uterine contractions are generated by non-linear processes (Nagarajan *et al.*, 2003). Other authors used the z-score to quantify the difference of the scaling exponents of detrended fluctuation analysis between original data and surrogate data (Moslem *et al.*, 2011). They found not only the nonlinearity of non-invasively recorded uterine EHG, but also that contractions recorded during labor have a much stronger nonlinear character than those recorded during pregnancy. Non-linear signal processing techniques could thus provide additional information on physiological changes during pregnancy and close to labor than linear techniques. Although a considerable number of studies used non-linear EHG parameters to discriminate labor from pregnancy contractions in women who all delivered at term (Maner *et al.*, 2006; Hassan *et al.*, 2011; Alamedine, Khalil and Marque, 2013; Diab *et al.*, 2014), this section focuses on studies directly associated with PTB.

2.2.1. *Entropy Parameters.* The start of labor is likely related to altered levels of myometrial cell connectivity that induce changes in the regularity of the measured EHG signal. For patients with threatened preterm labor symptoms between 24 and 34 WG, a significant increase in approximate entropy computed in the bandwidth 0.24-4 Hz was found in patients who gave premature birth within 7 days, suggesting that the EHG signal becomes more complex as labor approaches (Lemancewicz *et al.*, 2016). However, as the estimator of approximate entropy has been shown to be biased and highly sensitive to the number of signal samples (Ferrario *et al.*, 2006), most authors prefer to use sample entropy, which is more independent of recording length and behaves more consistently, to characterize EHG signals (Fele-Zorz *et al.*, 2008; Radomski *et al.*, 2008; Garcia-Gonzalez *et al.*, 2013; Di Marco *et al.*, 2014; Horoba *et al.*, 2016). Nevertheless, controversial results have been obtained for sample entropy estimated from EHG recordings. Fele-Zorz *et al.* computed sample entropy in different bandwidths (0.08-4, 0.3-3Hz and 0.3-4 Hz) from whole EHG records from the TPEHGDB for discriminating term and preterm delivery (Fele-Zorz *et al.*, 2008). Sample entropy computed in the 0.3-3 Hz bandwidth has been shown to decrease with gestation time, indicating the higher predictability of EHG signals as delivery approaches. Statistically significant differences were obtained for sample entropy between term and preterm delivery records recorded before the 26th GA and between all term and all preterm delivery records (Fele-Zorz *et al.*, 2008). This result was consistent with the findings of other studies, which reported that sample entropy estimated from stationary motion and labor contraction-free intervals in EHG signals using the same database was lower for preterm delivery records than term delivery records (Di Marco *et al.*, 2014). However, when sample entropy was computed for EHG-bursts from the same database, no statistically significant difference was found between preterm and term delivery records (Horoba *et al.*, 2016). Controversially, sample entropy from EHG bursts recorded during preterm labor (20 women) was significantly higher than during term labors (26 women) (Radomski *et al.*, 2008). In another study that analyzed sample entropy values computed from EHG-bursts during the active phase of labor in women at term, a significantly higher value was obtained for patients who had a vaginal delivery than for those who had a caesarean section (Garcia-Gonzalez *et al.*, 2013). From these results it can be inferred that sample entropy of EHG bursts would be better at discriminating between different scenarios during labor than predicting PTB.

The use of entropy parameters has been a matter of discussion; firstly, the nonstationary nature of the EHG signal may affect nonlinearity measures (Hassan *et al.*, 2011) and the wider the window used in the analysis, the harder the assumption of stationarity. Also, entropy parameters can be highly sensitive to sampling frequency, bandwidth of analysis and to length, m , and margin, r , parameters (Fele-Zorz *et al.*, 2008; Diab *et al.*, 2013, 2014). According to Diab *et al.* (Diab *et al.*, 2014), the best area under the curve (AUC) of the receiver operator characteristic

(ROC) of sample entropy for predicting labor was obtained for the 0.1-3 Hz bandwidth. However, Fele-Zorz found that the optimal bandwidth of sample entropy for discriminating between term and preterm delivery records was 0.3-3 Hz (Fele-Zorz *et al.*, 2008). Moreover, EHG signal complexity changes throughout pregnancy and does not necessarily show a monotonous trend, so that GA and time to delivery when recording the records in the database used could also influence the analysis outcome. Indeed, sample entropy values estimated from EHG-bursts were analyzed for different GA intervals from 32 WG to 39 WG and the latent phase of normally progressing labor (Vrhovec and Macek, 2012). They found that this parameter remained constant from 32 to 35 WG, significantly dropped at 36-37 WG, slightly increased at 38 WG and dropped again at 39 WG, while the onset of labor is characterized by relatively high sample entropy values (Vrhovec and Macek, 2012). The presence of large amplitude fluctuations and spikes, typical of EHG signals, may affect the estimated approximate and sample entropy more than signal regularity (Mischi *et al.*, 2017). Mischi *et al.* (Mischi *et al.*, 2017) recently proposed a modification of the original distance metrics aiming at limiting the tolerance dependency on large amplitude fluctuations and spikes. The modified approximate and sample entropy in the 0.3-0.8 Hz bandwidth was performed only in contraction periods from a dataset containing 4 monopolar EHG measurements on patients (34 delivering preterm) with preterm contractions. Thirty-nine out of 120 women were discarded due to technical failures and only 58 women (34 delivering preterm) met the contraction inclusion criteria. While conventional entropy parameters and time reversibility did not show significant differences between term and preterm deliveries, modified entropy parameters showed p-values <0.02 . The results of this work suggest that signs related to the risk of preterm labor are independent of the signal amplitude and are mainly related to the regularity of the normalized EHG time series.

2.2.2. Other non-linear parameters. Correlation dimension and maximal Lyapunov exponent and other parameters computed from whole EHG records in different bandwidths (0.08-4, 0.3-3Hz and 0.3-4 Hz) were proposed to distinguish term and preterm delivery records from the TPEHGDB (Fele-Zorz *et al.*, 2008). No statistically significant differences were obtained for maximal Lyapunov exponent between term and preterm delivery records. Nevertheless, they found that the correlation dimension in the 0.08-4Hz bandwidth presented statically significant differences between term and preterm delivery records recorded before the 26th GA, while no significant differences were found between all term and preterm delivery records (Fele-Zorz *et al.*, 2008).

Other authors analyzed the recurring patterns in stationary motion and labor contraction-free intervals in uterine EMG signals of the TPEHG DB (Di Marco *et al.*, 2014). In comparison to term delivery records, recurrence indices such as percentage recurrence, percentage determinism and entropy and maximum length were higher in preterm delivery records, the individual predictors AUC of preterm birth being around 0.65. The recurrence indices increased with decreasing time to delivery, suggesting regular and recurring patterns with gestation progression (Di Marco *et al.*, 2014).

Lempel-Ziv complexity has also been proposed to characterize EHG signal recorded from 60 patients with threatened preterm labor symptoms between 24 and 34 WG (Lemancewicz *et al.*, 2016). A significant increase of this index was observed for patients who delivered preterm before completing 7 days, suggesting that the EHG signal becomes more complex as labor approaches (Lemancewicz *et al.*, 2016). On the other hand, other studies have found that Lempel-Ziv complexity did not show specific trends in the course of normally progressing labor (Vrhovec and Macek, 2012). Further studies are needed to determine the utility of Lempel-Ziv complexity for predicting preterm labor.

Other parameters have been computed for estimating complexity and order in EHG signals, such as variance entropy, timer reversibility, detrended fluctuation analysis or the Hurst exponent, fractal dimension or fuzzy entropy. However, the capacity of each parameter to differentiate between preterm or term delivery has not been evaluated in most of these parameters, but is used as a predictor input parameter, along with other temporal, spectral and non-linear parameters, which will be dealt with below.

2.3. Propagation and coupling analysis

As previously mentioned, uterine activity is scarce and uncoordinated throughout pregnancy, ensuring fetal nourishment and development (Garfield and Maner, 2007). As labor approaches, uterine contractility increases until strong, propagated and synchronous contractions expel the fetus. Uterine contractility is known to hinge on both the excitability of uterine cells and the propagation of the electrical activity in the uterine muscle (Devedeux *et al.*, 1993). However, most studies on predicting PTB by EHG have traditionally focused on analyzing local uterine excitability, working out univariate parameters from surface EHG recordings. Taking into account the outstanding role of electrical uterine activity propagation on the efficiency of the uterine contractions, bivariate analysis has emerged as a technique that can improve the capacity of EHG to predict the labor horizon (term and preterm). Studies on estimating conduction velocity, propagation patterns, synchronization degree and coupling of EHG recordings at different sites on the abdomen have significantly increased in the last decade.

2.3.1. Conduction Velocity.

The velocity at which an action potential propagates along a fiber or a tissue is referred to as the *conduction* (or *propagation*) *velocity* (CV) (Rabotti and Mischi, 2014). There are numerous studies in the literature on the estimation of CV, both in *in vitro* and *in vivo* experiments, by invasive or non-invasive EHG recordings in pregnant animals. In fact, a review was published regarding the estimation of the CV speed, direction and patterns of the uterine electrical activity (Rabotti and Mischi, 2014). CV has been worked out not only for single spikes within an EHG-burst but also for whole EHG-bursts of uterine electrical activity, due to the fact that these two measures could be biased by different physiological phenomena (Rabotti *et al.*, 2011; de Lau *et al.*, 2013). In the present review, only those studies analyzing the ability of CV values to differentiate human term and preterm deliveries will be mentioned.

Regarding single spike propagation, Lucovnik *et al* evaluated the CV of selected action potentials considering 2 pairs of bipolar recordings from 2 electrodes at a 2.5 cm interelectrode distance (Lucovnik. *et al.*, 2011). EHG signals were recorded in 116 patients (22-term labor, 6-term nonlabor, 20 preterm labor, 68 preterm nonlabor). The CV parameter reached higher values as labor approached in both term and preterm pregnancies. Significant differences were obtained between CV values for preterm patients delivering within 7 days from the recording session *vs* those delivering more than 7 days after ($p < 0.001$), as well as in CV values for term patients delivering within 7 days and more than 7 days. No significant CV differences were found for term and preterm patients who delivered within 7 days from the recording. Notably high CV values (52.56 ± 33.94 cm/s were found in women delivering within 7 days after recording *vs* 11.11 ± 5.13 cm/s for women delivering in more than 7 days after recording) in this study compared to that obtained from noninvasive recordings in pregnant and in-labor women found in previous studies. In de Lau *et al*, CV values of uterine contractions in labor <24 h (7 term women, 2 preterm women) were also higher than for labor >24 h (8 term women, 5 preterm women). However, the CV values were 8.65 ± 1.90 cm s⁻¹ and 5.30 ± 1.47 cm s⁻¹s, respectively, which are significantly lower than those reported by Lucovnik *et al* (Lucovnik. *et al.*, 2011). It should also be noted that a 2x2 (2.5cmx2.5cm) grid of electrodes was used in the former study and a 8x8 (28 mmx 28mm) grid of small electrodes in the latter. Some authors argue that Lucovnik's high values were due to the CV being worked out with only two electrodes, so that only the component of the velocity vector in the direction of the line connection the two electrodes was considered (Rabotti *et al.*, 2011; Rabotti and Mischi, 2014).

CV calculation entails several drawbacks and limitations; in the study by Lucovnik *et al*, it required visual identification of EHG-bursts and their action potentials, which is a major limitation for its use in clinical practice. De Lau *et al* (de Lau *et al.*, 2013) proposed an automatic technique to calculate CV by using the maximum likelihood approach and choosing a weighted cost function with the best estimation accuracy (Rabotti *et al.*, 2010; de Lau *et al.*, 2013). Factors that could limit the clinical application of the proposed automatic technique include the entangled acquisition systems required in extensive multichannel recordings. Although automatic EHG-burst identification in EHG recordings was obtained by working out TOCO-like signals from the

EHG, this automatic identification was supervised by experts to avoid artifacts and interference being present in the recordings. Some authors do not agree with measuring propagation velocity, due to the assumption of the occurrence of linear electrical propagation in the myometrium (Duchene, Marque and Planque, 1990; Devedeux *et al.*, 1993). However, there seems to be some consensus on the use of this hypothesis with small interelectrode distances, although the optimal distances have still not been established (Rabotti and Mischi, 2014).

As regards uterine electrical activity propagation patterns, we did not find any studies on CV and direction of propagation for PTB prediction using EHG surface recordings. When analyzing CV and direction of propagation in term pregnancies, single spikes within an EHG-burst do not usually show a preferential direction in the uterus associated with the imminence of labor, but unpredictable and complex propagation patterns. By contrast, whole EHG-burst propagation patterns are less erratic, with both upward and downward patterns as labor approaches (Lange *et al.*, 2014). These results support the hypothesis that uterine contractions can start in many different areas of the myometrium, but are in disagreement with previous theories supporting preferential downward propagation during labor, with pacemaker regions located on the fundus during active labor (Planes *et al.*, 1984).

2.3.2. Coupling & multivariate analysis. As regards coupling and synchronization parameters, studies on uterine signals mainly focus on the difference between pregnancy and labor contractions or analyze the evolution of the parameters towards delivery by dividing pregnancy contractions into different term groups. Although these studies have rarely been performed on recordings from women who delivered preterm, it is believed that preterm and term labor involves the same mechanisms, the main difference being the GA at which labor occurs. Therefore, although the following studies were on women who delivered at term, they can be considered potentially good indicators for the prediction of preterm delivery.

It should be noted that most of these studies were carried out by a French group at the *Université de Technologie Compiègne* (UTC) using a 4x4 (2.1 cm inter electrode distance) matrix of monopolar electrodes placed on the abdomen. These studies usually involve the computation of connectivity matrixes among EHG channels using different synchronization parameters. In some cases the information is summarized by the mean or median value of elements in the matrix (Hassan *et al.*, 2013). On the other hand, graph theory analysis has also been proposed to delve into the study of the activation regions associated with different situations of uterine activity (labor/nonlabor or evolution of uterine activity during pregnancy), precisely characterize the correlation matrix, and quantify the corresponding connectivity (Nader *et al.*, 2016). This consists of representing a set of nodes (electrodes) interconnected by edges (connectivity values between electrodes). Nader *et al.* evaluate the performance of five methods: Granger causality (GC), nonlinear regression (h^2), general synchronization (H), the imaginary part of the coherence (Icoh) and mean phase coherence (MPC) to estimate the connectivity on a realistic EHG model. The results revealed high performance for H, Icoh and h^2 . Subsequently, Nader carried out synchronization studies on real EHG signals recorded from a 4x4 matrix of electrodes on the abdomen, considering 183 labor (at term) and 247 pregnancy EHG bursts at different WG. The EHG bursts were grouped according to the weeks before labor (WBL) from the recording session: labor, 1WBL, 2 WBL, 3 WBL, 4 WBL and 6 WBL. The imaginary part of the coherence (Icoh) was worked out to obtain connectivity matrices. To transform the connectivity matrix into a graph, the strength of each node *Strength(Icoh)* was calculated. The results revealed that the pregnancy groups do not present clear differences, whereas significant differences were observed between 1WBL and Labor groups. Furthermore, the electrodes placed on the uterine median vertical axis experience greater variations in *Strength(Icoh)* values

As already mentioned, although EHG-burst synchronization parameters seem to give promising results for distinguishing between pregnancy contractions and labor contractions at term, it has rarely been studied in women who delivered preterm. This is probably because it requires a considerable effort to generate a database of these signals due to the prevalence of PTB and that the current setup for a large number of multichannel recordings should be more clinically friendly, especially when recording women with threatened PTB.

2.4. *Classificatory performance of EHG in preterm birth diagnosis*

As a step beyond the analysis of possible trends and significant differences in some EHG parameters, the potential accuracy of the use of EHG has been tested to discriminate preterm vs term labor and preterm labor vs preterm non-labor. Different classificatory strategies have been applied, from the use of simple thresholds to complex machine learning techniques. Here follows a summary of the most relevant results reported. Table 3 shows a summary of the most important features of the cited studies.

2.4.1. Temporal and spectral EHG features. Maner and Garfield implemented an unsupervised artificial neural network (ANN) which classifies every register into one of the four groups defined in their study (preterm labor, preterm non-labor, term labor and term non-labor) (Maner and Garfield, 2007). From all the included EHG records (134 term and 31 preterm) they employed 50% of their data base to train the ANN and set apart the remaining 50% in order to test the classifier. When the peak frequency, the standard deviation of the burst duration and the ratio were used as input features for the ANN, combining the results of training and test classification, 59/75 (79%) of all term labor women, 12/13 (92%) of all preterm labor women, 51/59 (86%) of all term non-labor women, and 27/38 (71%) of all preterm non-labor women were correctly classified.

On the other hand, Marque *et al* (Marque *et al.*, 2007) also employed an ANN to classify the 111 EHG recordings included in their study into preterm (1/3 of the total) or term (2/3 of the total) delivery. They analyzed the EHG signals, acquired in different positions with respect to the placenta (anterior, posterior), in the (0.05 – 16 Hz) bandwidth and performed an EHG-Burst-focused analysis. 257 Bursts were used as learning data and 139 as test data to evaluate the ANN performance. The ANN was fed with the fast wave high and fast wave low components of each EHG-Burst obtained by using the wavelet transform. Two different algorithms were used to train the neural networks: the back propagation momentum (BPM) and the Levenberg-Marquardt algorithm (LM). The results showed that the BPM and the LM provided different results for the three groups considered according to gestational age; the smallest misclassification rate for the BPM (18%) was for the group composed by woman in gestational ages of between (27WG–28WG). However, the LM algorithm achieved a lower misclassification rate (11%) for the (33WG–37WG) group. The BPM provided better sensitivity (Posterior: 0.85; Anterior: 0.90 for BPM against Posterior: 0.82; Anterior: 0.79 for LM) and specificity values (Posterior: 0.93; Anterior: 0.91 for BPM against Posterior: 0.88; Anterior: 0.87 for LM) than the LM, regardless of electrode position with respect to the placenta.

In another study with a smaller database (7 term women and 18 preterm women) (Diab, Marque and Khalil, 2009), wavelet decomposition was also used to decompose each EHG-Burst into 5 levels. The variance of each detail was used as input features for two unsupervised classification algorithms: the unsupervised statistical classification method (USCM) and competitive neural network (CNNM). They distinguished between women registered in the 29 WG who gave birth at different GA (G1: 33 WG, G2: 31 WG, G3: 36 WG). A 9.5% misclassification error was obtained by applying the USCM, and 14.2% by applying CNNM to distinguish between G1 and G2. For discriminating G2 from G3 a classification error of 2.3% was obtained for the USCM and 7.1% by applying the CNNM. This greater classification accuracy was due to all the groups being registered in the same gestational ages and G2 and G3 presenting a bigger difference in the weeks of gestational birth than G1 and G2, so that a greater difference in the frequency content of the two types of EHG-Bursts could be expected.

Sikora *et al.* also performed a classification by using a Lagrangian Support Vector Machine (LSVM). Features of EHG Bursts such as amplitude, mean frequency and peak frequency were used to separate Groups I (physiological pregnancy) and II (women with preterm labor symptoms), obtaining an AUC of 0.690, 0.700 and 0.628, respectively (Sikora *et al.*, 2011).

More recently Fergus *et al* (Fergus *et al.*, 2016) performed a term/preterm classification on the TPEHGDB. They included several temporal and spectral EHG features computed on whole EHG records. The following 12 features were included: integrated EHG, mean absolute value of the EHG, the simple square integral, wavelet length of the signal, Log, RMS, variance, difference

absolute standard deviation of the EHG signal, maximum fractal length, average amplitude change, peak frequency and the median frequency. Some clinical data were available to feed the models. The discriminating capacity of all the features was evaluated by different methods. Seven different ANN were then used to classify these records: back-propagation trained feed-forward neural network classifier, Levenberg–Marquardt trained feed-forward neural network classifier, the perceptron linear classifier, radial basis function neural network classifier, random neural network classifier, the voted perceptron classifier and the discriminative restricted Boltzmann machine classifier. Given that the TPEHGDB is unbalanced (262 term cases against 38 preterm records) they performed the synthetic minority over-sampling technique (SMOTE) in order to obtain 262 term and 262 preterm registers. The best results were obtained for the oversampled data set including the clinical data by the combination of the Levenberg–Marquardt trained Feed-Forward Neural Network, Radial Basis Function Neural Network and the Random Neural Network classifiers, with 91% for sensitivity, 84% for specificity, 94% for the AUC and 12% for the mean error rate.

2.4.2. Non-linear features. The discriminating capacity of different classifiers has been reported with nonlinear input features, in contrast to or together with linear features, estimated from EHG recording so as to differentiate uterine EMG records of term and preterm deliveries using the TPEHGDB, predominantly performing the analysis on the whole EHG record rather than on signal burst segments.

Sample entropy computed from whole EHG recording in the 0.3-4 Hz bandwidth was compared to the PS median frequency (linear feature) estimated by the adaptive autoregressive method for predicting term and preterm delivery records by different classification methods: k-nearest neighbors, linear and quadratic discriminant analysis, support vector machine (SVM) and decision tree (Srnđel and Jager, 2015). Using median frequency and additional clinical information in an oversampled database (SMOTE), quadratic discriminant analysis classifier obtained the best results with a classification accuracy of 86% (SE: 75%; SP:98%) for all records, regardless of the time of recording. For the sample entropy, the best classifier was obtained by the SVM, achieving an accuracy of 87% (SE: 96%; SP:79%) (Srnđel and Jager, 2015). Naeem et al. compared the discriminating ability of a set of linear features and a set of non-linear ones for predicting preterm delivery using three different ANN: Kohonen network, feed-forward back propagation network and trainable cascade-forward back propagation network (Naeem, Seddik and Eldosoky, 2014). The linear features included the mean power frequency, the root mean square (RMS) value of the signal, the frequency peak, median frequency of the signal power spectrum and the autocorrelation zero-crossing while the non-linear features used were: time reversibility, approximate entropy, Lyapunov exponent, correlation dimension, adjusted amplitude Fourier transform, sample entropy, derivative phase space reconstruction and phase space reconstruction based on the singular spectrum approach. ANN using non-linear features achieved better classification results than linear ones, obtaining an accuracy of 92.3%. The trainable cascade-forward back propagation network achieved the best classification accuracy and the Kohonen network obtained the worst classification results, regardless of the linear or nonlinear features (Naeem, Seddik and Eldosoky, 2014).

Other authors combined linear and non-linear features in the inputs of the classifiers: Fergus et al proposed the combination of sample entropy with other temporal and spectral features (root mean square, peak frequency and median frequency) computed from whole EHG recording in the bandwidth 0.34-1Hz for predicting term and preterm delivery records (Fergus *et al.*, 2013). Different classification methods were tested: Linear and quadratic analysis, uncorrelated normal density based classifier, polynomial classifier (PC), logistic classifier, k-nearest neighbors algorithm, decision tree classifier and Parzen classifier. Using the SMOTE technique, the decision tree classifier obtained the best classification performance, achieving an accuracy of 89% (SE: 90.4%; SP: 82.7%). Including clinical information together with the EHG feature obtained a classification accuracy of 95% using the PC, sensitivity and specificity being 96.7% and 90%, respectively.

The empirical mode decomposition technique has also been applied to EHG signals, computing characteristic features from the intrinsic mode function (IMF) resulting from the decomposition

process. Ren et al used the ratios between the Shannon entropy values of both instantaneous amplitude and instantaneous frequency of the first ten IMF components of the whole EHG records (Ren *et al.*, 2015). Six classifiers were tested to discriminate term and preterm delivery records using the SMOTE technique for data balancing: SVM, random forests, multilayer perceptron, AdaBoost, Bayesian network, simple logistic regression. The best classifier AUC was achieved using the AdaBoost classifier, obtaining an AUC of 0.986. On the other hand, Acharya et al first decomposed EHG signal in the 0.3-3 Hz bandwidth into 11 IMFs and then wavelet packet decomposition was implemented up to 6 levels on each IMF (Acharya *et al.*, 2017). Then eight different features were computed for each wavelet coefficient: interquartile range, mean absolute deviation, mean energy, mean Teager-Kaise energy, standard deviation, fractal dimension, fuzzy entropy and sample entropy. Term and preterm delivery records were balanced using the adaptive synthetic sampling approach (ADASYN), an extension of SMOTE. The ten most significant features were selected using the particle swarm optimization technique and the Bhattecharyya method. The SVM classifier with radial basis kernel function was then proposed to differentiate preterm and term delivery records and achieved a classification accuracy of 96.25%, sensitivity and specificity being 95.08% and 97.33%, respectively. These results are remarkable but may be biased due to the unbalanced original database and over-learning could also have affected the results obtained.

All the papers described so far in this section used TPEHGDB records obtained during regular checkups. The previously described work by Mischi et al (Mischi *et al.*, 2017) studied classification ability for the diagnosis of preterm birth from a different database with women admitted to hospital for preterm contractions. The classification ability of 'conventional' and 'modified' versions of approximate and sample entropy and of time reversibility was tested for each feature. The best results were an average AUC of 0.728 and a corresponding average accuracy of 73% obtained for the modified approximate entropy for separating Preterm/Term groups.

2.4.3. Propagation and coupling features. Lucovnik compared the ability of temporal and spectral features worked out from the EHG-burst (Duration, PS peak frequency, median frequency and amplitude) and action potential CV to differentiate preterm labor within 1, 2, 4, 7 and 14 days after recording (Lucovnik. *et al.*, 2011). AUC values were always greater for CV than that of the best temporal and spectral feature (PS peak frequency), ranging from 0.89 to 0.96. These AUC values were similar to those obtained when combining CV and PS peak frequencies, reaching 0.96.

A multivariate multiscale fuzzy entropy algorithm and multivariate multiscale entropy have also been applied to 3-channel EHG signals from the TPEHGDB to assess its capability to predict whether delivery will be at term or preterm (Ahmed *et al.*, 2017). Whole 30-minute EHG recordings were analyzed, which was a great advantage, since EHG-burst segmentation was not required. The ADASYN technique was applied to solve the problem related to the unbalanced database. A total of 23 supervised classifiers were implemented: discriminant analysis, logistic regression, SVM, decision trees, nearest neighbor and ensemble classifiers. Using 9 element feature vectors extracted from multivariate multiscale fuzzy entropy analysis an AUC of 99% and an accuracy of 95% was achieved in differentiating term and preterm delivery records, regardless of the time of recording. These results are good but may be biased due to the unbalanced original database and may also be affected by over-learning.

Finally, the use of other bivariate features to develop classifiers that discriminate term labor from non-labor contractions has also been reported. Hassan et al analyzed and compared the ability of the nonlinear correlation coefficient (h^2) and the traditional spectral features PS peak frequency (PF) and median frequency to differentiate between pregnancy and labor contractions (Hassan *et al.*, 2013). Forty-nine women were enrolled in the study (36 recorded during pregnancy at different gestational ages and 13 in labor -within 24h of recording- giving 174 pregnancy contractions and 115 labor contractions). ROC curves indicated considerably better performance of the nonlinear correlation coefficient ($AUC_{h^2} = 0.85$) than the classical frequency features ($AUC_{PF} = 0.76$ and $AUC_{Med.Freq} = 0.66$) in distinguishing labor contractions from pregnancy contractions. The ability of other features, estimating the degree of synchronization or coupling,

working out the imaginary part of the coherence have also been tested; as is the case of Strength(Icoh), Assortativity, Clustering coefficient or Local Efficiency (Nader *et al.*, 2015). Strength (Icoh) presented greater AUC when separating 247 pregnancy EHG-bursts and 83 of term labor (AUC = 0.801). Radomski tested the performance of multivariate sample entropy, generalized Spearman's correlation coefficient and the combination of both to discriminate between labor and non-labor contractions (Radomski, 2015). Four-channel EHG recording sessions were carried out in three groups of women: 15 women in 2nd period of unifetal labor, 15 pregnant women in their 3rd trimester, and 14 unpregnant women in the follicular phase of a menstrual cycle. All the proposed features were able to differentiate uterine unpregnant activity from labor activity. The combined index yielded the best AUC values in discriminating these groups: unpregnant vs pregnant nonlabor 0.87 ± 0.07 , unpregnant vs labor 0.94 ± 0.05 , pregnant nonlabor vs labor 0.94 ± 0.04 .

Table 3.- Features taken from studies that used EHG parameters in PTB diagnosis.

<i>Author (Year)</i>	<i>Data Base (N° women)</i>		<i>Computed Parameters</i>	<i>Window of analysis</i>	<i>Classifier type</i>	<i>Defined classes</i>	<i>Best performance</i>	<i>Oversampling technique</i>
	Preterm	Term						
Maner (2007)	51	134	Temporal & Spectral	EHG-Burst	ANN	Preterm labor Preterm non-labor Term labor Term non-labor	Acc: 92% (preterm labor)	None
Marque (2007)	37	74	Spectral	EHG-Burst	ANN	Preterm Term	Acc: 82%	None
Diab (2009)	18	7	Temporal & Spectral	EHG-Burst	CNNM	G1: 33 WG G2: 31 WG G3: 36 WG	Acc: 97.7% (G2 vs G3)	None
Sikora (2011)	21 threat of PTB 27 phys. pregnancy 14 labor		Temporal & Spectral	EHG-Burst	LSVM	G1: Physiological pregnancy G2: Preterm labor symptoms	AUC: 0.70	None
Fergus (2016)	38	262	Temporal & Spectral	Whole EHG record	ANN	Preterm labor Term labor	AUC: 0.94 Acc: 88%	SMOTE
Smrdel (2015)	38	262	Non-linear	Whole EHG record	SVM	Preterm labor Term labor	Acc: 87%	SMOTE
Naeem (2014)	38	262	Non-linear	Not indicated	ANN	Preterm labor Term labor	Acc: 92.3%	None
Fergus (2013)	38	262	Temporal & Spectral Non-linear Clinical data	Whole EHG record	PC	Preterm labor Term labor	Acc: 95%	SMOTE

<i>Author (Year)</i>	<i>Data Base (N° women)</i>		<i>Computed Parameters</i>	<i>Window of analysis</i>	<i>Classifier type</i>	<i>Defined classes</i>	<i>Best performance</i>	<i>Oversampling technique</i>
	Preterm	Term						
Ren (2015)	38	262	Temporal & Spectral Non-linear	Whole EHG record	AdaBoost	Preterm labor Term labor	AUC: 0.986	SMOTE
Acharya (2017)	38	262	Temporal & Spectral Non-linear	Whole EHG record	SVM	Preterm labor Term labor	Acc: 96.27%	ADASYN
Mischi (2017)	34	24	Non-linear	EHG-Burst	Statistical Class.	Labor within 1 week Non-labor Preterm labor Term labor	AUC: 0.731 Acc: 73% (Term vs Preterm)	None
Lucovnik (2011)	88	28	Temporal & Spectral CV	EHG-Burst	Statistical Class.	Labor in 1, 2, 4, 7 and 14 days	AUC: 0.96	None
Ahmed (2017)	38	262	Non-linear Multivariate	Whole EHG record	SVM	Preterm labor Term labor	AUC: 0.99 Acc: 95.4%	ADASYN
Hassan (2013)		36 nonlabor 13 labor	Spectral Bivariate	EHG-Burst	Statistical Class.	Term labor Term nonlabor	AUC: 0.85	None
Nader (2015)	247 bursts non-labor 183 bursts labor		Bivariate	EHG-Burst	Statistical Class.	Labor Nonlabor	AUC: 0.801	None
Radomski (2015)	14 Unpregnant	15, 2 nd trim 15, 3 rd trim	Non-linear Bivariate	Whole EHG record	Statistical Class.	Unpregnant Pregnant non-labor Labor	AUC: 0.94	None

3. CONCLUSIONS

3.1. *Background*

The present incidence and consequences of PTB make it not only a major issue in obstetrics, but also a health priority all over the world. Current methods of diagnosis based on CL, Bishop score, frequency of contractions and biomarkers on uterine secretions, as well as its treatment have room for improvement. It is believed that the events associated with the activation of the myometrium that precede labor are reflected in the characteristics of the surface recording of its myoelectrical activity. Surface EHG recording and analysis has emerged as a tool for improving PTB prediction, showing very promising results at the research level. In the present review the many different approaches used are organized according to the type of parameters used i.e. temporal, spectral, non-linear and, most recently, bivariate.

3.2. *Temporal and Spectral Analysis*

It could be expected that, apart for the proximity of labor, the amplitude parameters could be influenced by: the composition or thickness of abdominal layers of the subject being recorded, the size and type of electrodes used, and the interelectrode distance and contact impedance with the skin, among other factors, which limit the robustness of this type of parameter. Nonetheless, several studies reported a significant increase in the EHG amplitude parameters of labor vs non-labor recordings up to two weeks before labor both in term and preterm delivery women. However, if labor occurs more than two weeks after the recording, other factors could mask the changes of signal amplitude at origin and the differences are not significant. On the other hand, the contraction duration parameters did not give good results.

Despite the lack of consensus on the frequency bandwidth to be used for spectral parameters, the peak frequency of EHG burst has shown promising results in discriminating labor vs pregnancy contraction in term and preterm deliveries. It also seems to be a more robust indicator than amplitude parameters, while the median frequency of the EHG burst was a worse indicator. When computed from whole EHG recordings the opposite behavior is obtained; i.e. the peak frequency discrimination ability is poorer and median frequency seems to be a better indicator in these cases.

3.3. *Non-linear Analysis*

It seems that there is no clear trend in the values of non-linear parameters as pregnancy progresses and labor approaches. However, most studies suggest increasingly regular and recurring patterns with gestation progression and higher predictability of the EHG signals as delivery approaches. Parameters such as sample entropy, when computed from whole EHG recording or long segments that include not only EHG bursts but also intercontractile periods, proved to be good predictors of PTB. In contrast, when computed from EHG bursts, traditional entropy parameters seem to be more useful in discriminating between different labor scenarios, e.g. labor recordings at term vs preterm, rather than in predicting PTB. On the other hand, modified entropy from EHG bursts produces good results for discriminating term and preterm delivery although results were poorer in estimating delivery time.

3.4. *Propagation and Coupling Analysis*

In recent years, a significant number of papers have studied the changes in signal propagation, synchronization and coupling between the myoelectrical activity recorded at different sites of the abdomen by means of bivariate parameters. Electrical coupling between myometrial cells intensifies as pregnancy progresses, so that velocity parameters such as CV increase as delivery approaches. In fact, CV individually or together with peak frequency has proven to be a good indicator of labor proximity, discriminating between the contractions of women who gave birth in more or less than 7 days after the recording, both in term and preterm deliveries. In addition, CV was similar for contractions in less than 7 days for both term and preterm delivery, suggesting that, in this respect, the difference only lies in the gestational age at which labor occurs.

On the other hand, synchronization and coupling parameters do not show clear trends in the evolution of synchronization parameters when large term intervals (up to 7WBL) to term labor

are considered. Nonetheless, good discrimination is usually obtained between pregnancy and labor records, with better performance when recorded at least one or two WBL.

3.5. *Classificatory performance of EHG in preterm birth diagnosis*

As regards classifiers that aim to discriminate women who will deliver at term from those who deliver preterm, machine learning techniques with temporal and spectral input features have given very promising results and proved the potential superiority of classification tools from EHG features over the currently used clinical methods such as CL, biomarkers, etc. The use of non-linear features or CV provides even better results and complementary information than those of temporal and spectral analysis i.e. results are improved when EHG features of different kinds are combined.

Although coupling analysis has been little used on patients who delivered preterm, everything indicates that it could be useful for predicting PTB and further research in this area will be carried out in the coming years.

3.6. *General Conclusions*

All in all, it seems that the uterine electrophysiological changes that precede spontaneous labor are associated with contractions of more intensity, higher frequency content, faster propagation and more organized activity and stronger coupling of different uterine areas. Temporal, spectral, non-linear and bivariate analyses of the EHG therefore provide useful and complementary information that should be appropriately combined with clinical information of the subject. In this regard, it should be remembered that despite an enhancement of discriminatory ability when EHG features are combined with clinical information (e.g. WG, Bishop score, CL, age, parity etc.), in term-preterm analysis and in other scenarios such as labor induction, this strategy has not yet been extended. We consider that EHG parameters in the specific context of the subject under study can help to improve the understanding of the underlying mechanisms during pregnancy and labor and enhance PTB prediction. Further studies should explore the best ways of combining all the available information.

One of the main challenges in the field is to obtain surface signals of good quality. Signal amplitude is low, especially earlier in pregnancy, and recordings can be corrupted by motion artifacts during movement and contraction, cardiac and respiratory interference and low frequency drifts. In many studies, a preliminary screening of the records should be carried out, discarding those of poor quality. There is still some way to go along this line, developing tools that can identify and cancel these unwanted components that can lead to an erroneous interpretation of results. In addition, the analysis often requires pre-segmentation of the records to focus on the signal segments during contraction. The robustness of the automated identification of the EHG-burst is another challenge that still needs to be addressed.

Ever more complicated signal processing techniques and classification methods are being applied to EHG in the context of PTB prediction. This firstly allows more information to be extracted from EHG signals and provides better results on the specific conditions of each database. However, it also complicates the physiological interpretation of the parameters and the generalization capacity of the technique. The development of new methods of analysis and signal classification in order to obtain the best discriminating numerical results should not forget that the signal characteristics to be assessed must have a physical interpretation in order not to be rejected by clinical staff. Keeping this in mind, there is still a need to further simplify signal analysis from the final user's standpoint. These should be accurate and require minimal user interaction.

This may be one of the issues that currently affect clinicians' perception of EHG and its analysis, and limit its application in the hospital setting. A 'keep it simple' strategy regarding not only EHG analysis but also its recording could help to build bridges towards its clinical use. In this latter regard, the number of electrodes, size and wiring of signal conditioning and acquisition equipment should be minimized and recording preparation should be simplified and made less time-consuming. New commercial devices have now been released for wireless EHG recording and monitoring. Some are medical products such as the Novii wireless patch system from Monica Healthcare and General Electric or PUREtrace from Nemo Healthcare, and some meant for the

consumer market such as the Bloomlife smart pregnancy wearable from Bloomlife Inc. These allow comfortable and wearable signal acquisition and facilitate clinical and home monitoring. However, they currently lack integrated tools for additional functionalities such as automatic identification of artifacts and contractions, or decision support systems to help to discriminate between labor and non-labor, predicting PTB, induction success, or labor arrest, etc. The integration of advanced signal analysis techniques such as those described in this paper would encourage the clinical use of EHG in obstetrics in general and enhance the prediction and management of PTB in particular.

ACRONYMS:

ACOG	American College of Obstetricians and Gynecologists
ADASYN	adaptive synthetic sampling approach
ANN	artificial neural network
AR	autoregressive methods
AUC	area under curve
BPM	back propagation momentum
CL	cervical length
CNNM	competitive neural network
CV	Conduction velocity
E1	first electrode of TPEHGDB
E2	second electrode of TPEHGDB
E3	third electrode of TPEHGDB
E4	fourth electrode of TPEHGDB
ECG	electrocardiogram
EHG	electrohysterogram
EMG	electromyogram
fFN	fetal fibronectin
FW	fast wave
FWH	fast wave high
FWL	fast wave low
GA	gestational age
GC	Granger causality
H	general synchronization index
h2	Nonlinear correlation coefficient
IMF	intrinsic mode function
IVH	intraventricular hemorrhage
LM	Levenberg-Marquardt algorithm
LSVM	Lagrangian support vector machine
PC	polynomial classifier
PF	peak frequency
PS	power spectrum
PTB	preterm birth
RMS	root-mean-square
ROC	receiver operator characteristic
S1	first channel of TPEHGDB
S2	second channel of TPEHGDB
S3	third channel of TPEHGDB
SMOTE	synthetic minority over-sampling technique
SVM	support vector machine
SW	slow wave
TOCO	tocography
TPEHGDB	term-preterm EHG Database
USCM	unsupervised statistical classification method
WBL	weeks before labor
WG	weeks of gestation

REFERENCES (Harvard alphabetical style)

- Acharya, U. R. *et al.* (2017) 'Automated detection of premature delivery using empirical mode and wavelet packet decomposition techniques with uterine electromyogram signals', *Computers in Biology and Medicine*, 85, pp. 33–42. doi: 10.1016/j.compbiomed.2017.04.013.
- ACOG (2016) 'Practice Bulletin No. 171', *Obstetrics & Gynecology*, 128(4), pp. e155–e164. doi: 10.1097/AOG.0000000000001711.
- Ahmed, M. U. *et al.* (2017) 'A multi variate multiscale fuzzy entropy algorithm with application to uterine EMG complexity analysis', *Entropy*, 19(1), pp. 1–18. doi: 10.3390/e19010002.
- Alamedine, D., Khalil, M. and Marque, C. (2013) 'Comparison of different EHG feature selection methods for the detection of preterm labor', *Comput Math Methods Med*. 2014/01/24, 2013, p. 485684. doi: 10.1155/2013/485684.
- Alberola-Rubio, J. *et al.* (2013) 'Comparison of non-invasive electrohysterographic recording techniques for monitoring uterine dynamics', *Med Eng Phys*. 2013/08/21, 35(12), pp. 1736–1743. doi: 10.1016/j.medengphy.2013.07.008.
- Alberola-Rubio, J. *et al.* (2017) 'Prediction of labor onset type: Spontaneous vs induced; role of electrohysterography?', *Computer Methods and Programs in Biomedicine*. Elsevier, 144, pp. 127–133. doi: 10.1016/j.cmpb.2017.03.018.
- Altman, M. *et al.* (2011) 'Neonatal Morbidity in Moderately Preterm Infants: A Swedish National Population-Based Study', *The Journal of Pediatrics*, 158(2), p. 239–244.e1. doi: 10.1016/j.jpeds.2010.07.047.
- Aviram, A. *et al.* (2014) 'Effect of prostaglandin e2 on myometrial electrical activity in women undergoing induction of labor', *Am J Perinatol*. 2013/08/07, 31(5), pp. 413–418. doi: 10.1055/s-0033-1352486.
- van Baaren, G. J. *et al.* (2013) 'Cost-effectiveness analysis of cervical length measurement and fibronectin testing in women with threatened preterm labor', *Am J Obstet Gynecol*. 2013/06/25, 209(5), p. 436.e1-8. doi: 10.1016/j.ajog.2013.06.029.
- Batista, A. G. *et al.* (2016) 'A multichannel time-frequency and multi-wavelet toolbox for uterine electromyography processing and visualisation', *Computers in Biology and Medicine*. Elsevier. doi: 10.1016/j.compbiomed.2016.07.003.
- Benalcazar Parra, C. *et al.* (2017) 'Characterization of Uterine Response to Misoprostol based on Electrohysterogram', *Proceedings of the 10th International Joint Conference on Biomedical Engineering Systems and Technologies*, (Biostec), pp. 64–69. doi: 10.5220/0006146700640069.
- Berghella, V. *et al.* (2008) 'Fetal fibronectin testing for reducing the risk of preterm birth.', *The Cochrane database of systematic reviews*. Edited by V. Berghella. Chichester, UK: John Wiley & Sons, Ltd, (4), p. CD006843. doi: 10.1002/14651858.CD006843.pub2.
- Berghella, V. *et al.* (2017) 'Cervical length screening for prevention of preterm birth in singleton pregnancy with threatened preterm labor: systematic review and meta-analysis of randomized controlled trials using individual patient-level data', *Ultrasound in Obstetrics & Gynecology*, 49(3), pp. 322–329. doi: 10.1002/uog.17388.
- Blencowe, H. *et al.* (2013) 'Born Too Soon: The global epidemiology of 15 million preterm births', *Reproductive Health*, 10(Suppl 1), p. S2. doi: 10.1186/1742-4755-10-S1-S2.
- Boelig, R. C. and Berghella, V. (2017) 'Current options for mechanical prevention of preterm birth', *Seminars in Perinatology*, 41(8), pp. 452–460. doi: 10.1053/j.semperi.2017.08.003.
- Boyle, E. M. *et al.* (2012) 'Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population based cohort study', *BMJ*, 344. Available at: <http://www.bmj.com/content/344/bmj.e896> (Accessed: 24 August 2017).
- Brik, M. *et al.* (2010) 'Phosphorylated insulin-like growth factor binding protein-1 and cervical measurement in women with threatening preterm birth', *Acta Obstet Gynecol Scand*. 2009/12/08, 89(2), pp. 268–274. doi: 10.3109/00016340903443668.
- Brik, M. *et al.* (2011) 'Cervical interleukin-6 as a predictive test for preterm delivery in symptomatic women: preliminary results.', *European journal of obstetrics, gynecology, and reproductive biology*, 155(1), pp. 14–8. doi: 10.1016/j.ejogrb.2010.11.001.

- Cavallo, M. C. *et al.* (2015) 'Cost of care and social consequences of very low birth weight infants without premature- related morbidities in Italy.', *Italian journal of pediatrics*, 41(1), p. 59. doi: 10.1186/s13052-015-0165-z.
- Deshpande, S. N. *et al.* (2013) 'Rapid fetal fibronectin testing to predict preterm birth in women with symptoms of premature labour: a systematic review and cost analysis.', *Health technology assessment (Winchester, England)*, 17(40), pp. 1–138. doi: 10.3310/hta17400.
- Devedeux, D. *et al.* (1993) 'Uterine electromyography: a critical review', *Am J Obstet Gynecol.* 1993/12/01, 169(6), pp. 1636–1653. Available at: <http://www.sciencedirect.com/science/article/pii/000293789390456S>.
- Diab, A. *et al.* (2013) 'Effect of decimation on the classification rate of non-linear analysis methods applied to uterine EMG signals', *IRBM*, 34(4–5), pp. 326–329. doi: 10.1016/j.irbm.2013.07.010.
- Diab, A. *et al.* (2014) 'Performance analysis of four nonlinearity analysis methods using a model with variable complexity and application to uterine EMG signals', *Medical Engineering & Physics*, 36(6), pp. 761–767. doi: 10.1016/j.medengphy.2014.01.009.
- Diab, M. O., Marque, C. and Khalil, M. (2009) 'An unsupervised classification method of uterine electromyography signals: Classification for detection of preterm deliveries', *Journal of Obstetrics and Gynaecology Research*, 35(1), pp. 9–19. doi: 10.1111/j.1447-0756.2008.00981.x.
- Duchene, J., Marque, C. and Planque, S. (1990) 'Uterine EMG Signal : Propagation Analysis', in [1990] *Proceedings of the Twelfth Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. IEEE, pp. 831–832. doi: 10.1109/IEMBS.1990.691421.
- Esplin, M. S. *et al.* (2017) 'Predictive Accuracy of Serial Transvaginal Cervical Lengths and Quantitative Vaginal Fetal Fibronectin Levels for Spontaneous Preterm Birth Among Nulliparous Women.', *JAMA*, 317(10), pp. 1047–1056. doi: 10.1001/jama.2017.1373.
- Euliano, T. Y. *et al.* (2007) 'Monitoring contractions in obese parturients: electrohysterography compared with traditional monitoring', *Obstet Gynecol.* 2007/05/02, 109(5), pp. 1136–1140. doi: 10.1097/01.aog.0000258799.24496.93.
- Euliano, T. Y. *et al.* (2009) 'Spatiotemporal electrohysterography patterns in normal and arrested labor', *Am J Obstet Gynecol.* 2009/01/06, 200(1), p. 54 e1-7. doi: 10.1016/j.ajog.2008.09.008.
- Fele-Zorz, G. *et al.* (2008) '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.* 2008/04/26, 46(9), pp. 911–922. doi: 10.1007/s11517-008-0350-y.
- Fell, D. B. *et al.* (2014) 'Evaluation of the impact of fetal fibronectin test implementation on hospital admissions for preterm labour in Ontario: a multiple baseline time-series design.', *BJOG : an international journal of obstetrics and gynaecology*, 121(4), pp. 438–46. doi: 10.1111/1471-0528.12511.
- Feltovich, H. (2017) 'Cervical Evaluation: From Ancient Medicine to Precision Medicine.', *Obstetrics and gynecology*, 130(1), pp. 51–63. doi: 10.1097/AOG.0000000000002106.
- Fergus, P. *et al.* (2013) 'Prediction of preterm deliveries from EHG signals using machine learning', *PLoS One*. 2013/11/10, 8(10), p. e77154. doi: 10.1371/journal.pone.0077154.
- Fergus, P. *et al.* (2016) 'Advanced artificial neural network classification for detecting preterm births using EHG records', *Neurocomputing*, 188, pp. 42–49. doi: 10.1016/j.neucom.2015.01.107.
- Ferrario, M. *et al.* (2006) 'Comparison of Entropy-Based Regularity Estimators: Application to the Fetal Heart Rate Signal for the Identification of Fetal Distress', *IEEE Transactions on Biomedical Engineering*, 53(1), pp. 119–125. doi: 10.1109/TBME.2005.859809.
- Frey, H. A. and Klebanoff, M. A. (2016) 'The epidemiology, etiology, and costs of preterm birth', *Seminars in Fetal and Neonatal Medicine*, 21(2), pp. 68–73. doi: 10.1016/j.siny.2015.12.011.
- Fuchs, A. R. *et al.* (1984) 'Oxytocin receptors in the human uterus during pregnancy and parturition.', *American journal of obstetrics and gynecology*, 150(6), pp. 734–41. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6093538> (Accessed: 22 August 2017).
- Fuchs, I. B. *et al.* (2004) 'Sonographic cervical length in singleton pregnancies with intact membranes presenting with threatened preterm labor', *Ultrasound in Obstetrics and Gynecology*, 24(5), pp. 554–557. doi: 10.1002/uog.1714.

- G. Mandy, M. (2017) 'Short-term complications of the preterm infant', *UpToDate*.
- Garcia-Gonzalez, M. T. *et al.* (2013) 'Characterization of EHG contractions at term labor by nonlinear analysis', *Conf Proc IEEE Eng Med Biol Soc.* 2013/10/11, 2013, pp. 7432–7435. doi: 10.1109/embc.2013.6611276.
- Garfield, R. E. *et al.* (1998) 'Control and assessment of the uterus and cervix during pregnancy and labour', *Human Reproduction Update*, 4(5), pp. 673–695. Available at: <http://humupd.oxfordjournals.org/content/4/5/673.full.pdf>.
- Garfield, R. E. *et al.* (2005) 'Comparing uterine electromyography activity of antepartum patients versus term labor patients', *American Journal of Obstetrics and Gynecology*, 193(1), pp. 23–29. doi: 10.1016/j.ajog.2005.01.050.
- Garfield, R. E. and Maner, W. L. (2007) 'Physiology and electrical activity of uterine contractions', *Semin Cell Dev Biol.* 2007/07/31, 18(3), pp. 289–295. doi: 10.1016/j.semcdb.2007.05.004.
- Goldberger, A. L. *et al.* (2000) 'PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals.', *Circulation*, 101(23), pp. E215–20. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10851218> (Accessed: 25 August 2017).
- Goya, M. *et al.* (2012) 'Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial', *The Lancet*, 379(9828), pp. 1800–1806. doi: 10.1016/S0140-6736(12)60030-0.
- Grobman, W. A., Welshman, E. E. and Calhoun, E. A. (2004) 'Does fetal fibronectin use in the diagnosis of preterm labor affect physician behavior and health care costs? A randomized trial.', *American journal of obstetrics and gynecology*, 191(1), pp. 235–40. doi: 10.1016/j.ajog.2003.11.034.
- Haas, D. M. *et al.* (2012) 'Tocolytic therapy for preterm delivery: systematic review and network meta-analysis.', *BMJ (Clinical research ed.)*, 345(oct09_2), p. e6226. doi: 10.1136/bmj.e6226.
- Hadar, E. *et al.* (2013) 'Effect of an oxytocin receptor antagonist (atosiban) on uterine electrical activity', *Am J Obstet Gynecol.* 2013/06/04, 209(4), p. 384 e1–7. doi: 10.1016/j.ajog.2013.05.053.
- Hassan, M. *et al.* (2011) 'Comparison between approximate entropy, correntropy and time reversibility: application to uterine electromyogram signals', *Med Eng Phys.* 2011/04/19, 33(8), pp. 980–986. doi: 10.1016/j.medengphy.2011.03.010.
- Hassan, M. *et al.* (2013) 'Better pregnancy monitoring using nonlinear correlation analysis of external uterine electromyography', *IEEE Trans Biomed Eng.* 2012/11/30, 60(4), pp. 1160–1166. doi: 10.1109/tbme.2012.2229279.
- Hezelgrave, N. L., Shennan, A. H. and David, A. L. (2015) 'Tests to predict imminent delivery in threatened preterm labour', *BMJ*, 350(may21 10), pp. h2183–h2183. doi: 10.1136/bmj.h2183.
- Honest, H. *et al.* (2002) 'Accuracy of cervicovaginal fetal fibronectin test in predicting risk of spontaneous preterm birth: systematic review.', *BMJ (Clinical research ed.)*, 325(7359), p. 301. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12169504> (Accessed: 22 August 2017).
- Honest, H. *et al.* (2009) 'Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling.', *Health technology assessment (Winchester, England)*, 13(43), pp. 1–627. doi: 10.3310/hta13430.
- Horoba, K. *et al.* (2016) 'Early predicting a risk of preterm labour by analysis of antepartum electrohysterographic signals', *Biocybernetics and Biomedical Engineering*. Nałęcz Institute of Biocybernetics and Biomedical Engineering of the Polish Academy of Sciences, 36(4), pp. 574–583. doi: 10.1016/j.bbe.2016.06.004.
- Iams, J. D. *et al.* (1996) 'The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network.', *The New England journal of medicine*, 334(9), pp. 567–72. doi: 10.1056/NEJM199602293340904.
- Iams, J. D. (2003) 'What have we learned about uterine contractions and preterm birth? The HUAM Prediction Study.', *Seminars in perinatology*, 27(3), pp. 204–11. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12889587> (Accessed: 22 August 2017).
- Iams, J. D., Johnson, F. F. and Parker, M. (1994) 'A prospective evaluation of the signs and

symptoms of preterm labor.', *Obstetrics and gynecology*, 84(2), pp. 227–30. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8041535> (Accessed: 22 August 2017).

Julian N Robinson and Norwitz, E. R. (2017) 'Preterm birth: Risk factors and interventions for risk reduction', *UpToDate*.

Katz, M., Goodyear, K. and Creasy, R. K. (1990) 'Early signs and symptoms of preterm labor.', *American journal of obstetrics and gynecology*, 162(5), pp. 1150–3. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2140235> (Accessed: 22 August 2017).

Khalifeh, A., Quist-Nelson, J. and Berghella, V. (2017) 'Universal cervical length screening for preterm birth prevention in the United States', *The Journal of Maternal-Fetal & Neonatal Medicine*, 30(12), pp. 1500–1503. doi: 10.1080/14767058.2016.1220521.

Lange, L. *et al.* (2014) 'Velocity and directionality of the electrohysterographic signal propagation', *PLoS One*. 2014/01/28, 9(1), p. e86775. doi: 10.1371/journal.pone.0086775.

de Lau, H. *et al.* (2013) 'Automated conduction velocity analysis in the electrohysterogram for prediction of imminent delivery: a preliminary study', *Comput Math Methods Med*. 2014/02/04, 2013, p. 627976. doi: 10.1155/2013/627976.

Leitch, H. *et al.* (1999) 'Cervical length and dilatation of the internal cervical os detected by vaginal ultrasonography as markers for preterm delivery: A systematic review.', *American journal of obstetrics and gynecology*, 181(6), pp. 1465–72. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10601930> (Accessed: 22 August 2017).

Lemancewicz, A. *et al.* (2016) 'Early diagnosis of threatened premature labor by electrohysterographic recordings – The use of digital signal processing', *Biocybernetics and Biomedical Engineering*, 36(1), pp. 302–307. doi: 10.1016/j.bbe.2015.11.005.

Lim, K., Butt, K. and Crane, J. M. (2011) 'SOGC Clinical Practice Guideline. Ultrasonographic cervical length assessment in predicting preterm birth in singleton pregnancies.', *Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC*, 33(5), pp. 486–99. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21639971> (Accessed: 22 August 2017).

Lockwood, C. (2017) 'Diagnosis of preterm labor and overview of preterm birth', *UpToDate*.

Lucovnik, M. *et al.* (2011) 'Noninvasive uterine electromyography for prediction of preterm delivery', in *American Journal of Obstetrics and Gynecology*, p. 228.e1-228.e10. doi: 10.1016/j.ajog.2010.09.024.

Lucovnik, M. *et al.* (2011) 'Use of uterine electromyography to diagnose term and preterm labor', *Acta Obstet Gynecol Scand*. 2011/01/19, 90(2), pp. 150–157. doi: 10.1111/j.1600-0412.2010.01031.x.

Lucovnik, M., Chambliss, L. R. and Garfield, R. E. (2013) 'Costs of unnecessary admissions and treatments for "threatened preterm labor"', *American Journal of Obstetrics and Gynecology*, 209(3), p. 217.e1-217.e3. doi: 10.1016/j.ajog.2013.06.046.

Malone, F. D. (2016) 'What is New in the Management of Acute Preterm Labor?: Best Articles From the Past Year.', *Obstetrics and gynecology*, 127(2), pp. 398–9. doi: 10.1097/AOG.0000000000001284.

Maner, W. L. *et al.* (2003) 'Predicting term and preterm delivery with transabdominal uterine electromyography', *Obstet Gynecol*. 2003/06/12, 101(6), pp. 1254–1260.

Maner, W. L. *et al.* (2006) 'Characterization of abdominally acquired uterine electrical signals in humans, using a non-linear analytic method', *Med Biol Eng Comput*. 2006/08/26, 44(1–2), pp. 117–123. doi: 10.1007/s11517-005-0011-3.

Maner, W. L. and Garfield, R. E. (2007) 'Identification of human term and preterm labor using artificial neural networks on uterine electromyography data', *Ann Biomed Eng*. 2007/01/18, 35(3), pp. 465–473. doi: 10.1007/s10439-006-9248-8.

Mangham, L. J. *et al.* (2009) 'The Cost of Preterm Birth Throughout Childhood in England and Wales', *PEDIATRICS*, 123(2), pp. e312–e327. doi: 10.1542/peds.2008-1827.

Di Marco, L. Y. *et al.* (2014) 'Recurring patterns in stationary intervals of abdominal uterine electromyograms during gestation', *Medical & Biological Engineering & Computing*, 52(8), pp.

707–716. doi: 10.1007/s11517-014-1174-6.

Marque, C. K. *et al.* (2007) 'Preterm labour detection by use of a biophysical marker: the uterine electrical activity', *BMC Pregnancy Childbirth*. 2007/06/19, 7 Suppl 1, p. S5. doi: 10.1186/1471-2393-7-s1-s5.

Mas-Cabo, J. *et al.* (2017) 'Electrohysterogram Signals from Patients with Threatened Preterm Labor: Concentric Ring Electrode Vs Disk Electrode Recordings', *Proceedings of the 10th International Joint Conference on Biomedical Engineering Systems and Technologies*, (Biostec), pp. 78–83. doi: 10.5220/0006155000780083.

McCabe, E. R. B. *et al.* (2014) 'Fighting for the next generation: US Prematurity in 2030.', *Pediatrics*, 134(6), pp. 1193–9. doi: 10.1542/peds.2014-2541.

McIntosh, J. *et al.* (2016) 'The role of routine cervical length screening in selected high- and low-risk women for preterm birth prevention.', *American journal of obstetrics and gynecology*, 215(3), pp. B2-7. doi: 10.1016/j.ajog.2016.04.027.

Melchor, J. C. *et al.* (2017) 'Retrospective cohort study of PAMG-1 and fetal fibronectin test performance in assessing spontaneous preterm birth risk in symptomatic women attending an emergency obstetrical unit.', *Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. doi: 10.1002/uog.18892.

Mischi, M. *et al.* (2017) 'Dedicated entropy measures for early assessment of pregnancy progression from single-channel electrohysterography.', *IEEE transactions on bio-medical engineering*, pp. 1–1. doi: 10.1109/TBME.2017.2723933.

Moslem, B. *et al.* (2011) 'Detrended Fluctuation Analysis of uterine electromyography', in *2011 1st Middle East Conference on Biomedical Engineering*. IEEE, pp. 450–453. doi: 10.1109/MECBME.2011.5752161.

Most, O. *et al.* (2008) 'Can myometrial electrical activity identify patients in preterm labor?', *Am J Obstet Gynecol*. 2008/10/22, 199(4), p. 378 e1-6. doi: 10.1016/j.ajog.2008.08.003.

Moster, D., Lie, R. T. and Markestad, T. (2008) 'Long-Term Medical and Social Consequences of Preterm Birth', *New England Journal of Medicine*, 359(3), pp. 262–273. doi: 10.1056/NEJMoa0706475.

Nader, N. *et al.* (2015) 'Classification of pregnancy and labor contractions using a graph theory based analysis', in *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. IEEE, pp. 2876–2879. doi: 10.1109/EMBC.2015.7318992.

Nader, N. *et al.* (2016) 'A node-wise analysis of the uterine muscle networks for pregnancy monitoring', in *2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. IEEE, pp. 712–715. doi: 10.1109/EMBC.2016.7590801.

Naeem, S. M., Seddik, A. F. and Eldosoky, M. A. (2014) 'New technique based on uterine electromyography nonlinearity for preterm delivery detection', *Journal of Engineering and Technology Research*. Academic Journals, 6(7), p. 107–114, November 2014. doi: 10.5897/jetr2013.0332.

Nagarajan, R. *et al.* (2003) 'Analysis of uterine contractions: a dynamical approach', *J Matern Fetal Neonatal Med*. 2003/10/18, 14(1), pp. 8–21. doi: 10.1080/jmf.14.1.8.21.

Ness, A. *et al.* (2007) 'Does knowledge of cervical length and fetal fibronectin affect management of women with threatened preterm labor? A randomized trial.', *American journal of obstetrics and gynecology*, 197(4), p. 426.e1-7. doi: 10.1016/j.ajog.2007.07.017.

Nikolova, T. *et al.* (2015) 'Comparison of a novel test for placental alpha microglobulin-1 with fetal fibronectin and cervical length measurement for the prediction of imminent spontaneous preterm delivery in patients with threatened preterm labor.', *Journal of perinatal medicine*, 43(4), pp. 395–402. doi: 10.1515/jpm-2014-0300.

Palacio, M. *et al.* (2007) 'The use of a variable cut-off value of cervical length in women admitted for preterm labor before and after 32 weeks', *Ultrasound in Obstetrics and Gynecology*, 29(4), pp. 421–426. doi: 10.1002/uog.3950.

Parisaei, M. *et al.* (2016) 'Implementation of foetal fibronectin testing: Admissions, maternal interventions and costs at 1 year.', *Journal of obstetrics and gynaecology: the journal of the*

Institute of Obstetrics and Gynaecology, 36(7), pp. 888–892. doi: 10.3109/01443615.2016.1168374.

Patnoster, D. *et al.* (2009) 'Phosphorylated insulin-like growth factor binding protein-1 in cervical secretions and sonographic cervical length in the prediction of spontaneous preterm delivery.', *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*, 34(4), pp. 437–40. doi: 10.1002/uog.6428.

Peaceman, A. M. *et al.* (1997) 'Fetal fibronectin as a predictor of preterm birth in patients with symptoms: a multicenter trial.', *American journal of obstetrics and gynecology*, 177(1), pp. 13–8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9240576> (Accessed: 24 August 2017).

Planes, J. G. *et al.* (1984) 'External recording and processing of fast electrical activity of the uterus in human parturition.', *Medical & biological engineering & computing*, 22(6), pp. 585–91. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6503388> (Accessed: 28 August 2017).

Polettini, J. *et al.* (2017) 'Biomarkers of spontaneous preterm birth: a systematic review of studies using multiplex analysis.', *Journal of perinatal medicine*, 45(1), pp. 71–84. doi: 10.1515/jpm-2016-0097.

Rabotti, C. *et al.* (2010) 'Noninvasive estimation of the electrohysterographic action-potential conduction velocity', *IEEE Trans Biomed Eng.* 2010/05/13, 57(9), pp. 2178–2187. doi: 10.1109/tbme.2010.2049111.

Rabotti, C. *et al.* (2011) 'Electrohysterographic propagation velocity for preterm delivery prediction', *Am J Obstet Gynecol.* 2011/09/02, 205(6), p. e9–10; author reply e10. doi: 10.1016/j.ajog.2011.06.071.

Rabotti, C. and Mischi, M. (2014) 'Propagation of electrical activity in uterine muscle during pregnancy: a review', *Acta Physiol (Oxf)*. 2014/11/14. doi: 10.1111/apha.12424.

Radomski, D. *et al.* (2008) 'Assessment of Uterine Contractile Activity during a Pregnancy Based on a Nonlinear Analysis of the Uterine Electromyographic Signal', in *Information Technologies in Biomedicine*. Berlin, Heidelberg: Springer Berlin Heidelberg, pp. 325–331. doi: 10.1007/978-3-540-68168-7_37.

Radomski, D. S. (2015) 'A nonlinear parameterization of multivariate electrohysterographical signals', *Computers in Biology and Medicine*, 67, pp. 13–20. doi: 10.1016/j.compbiomed.2015.10.005.

Ren, P. *et al.* (2015) 'Improved Prediction of Preterm Delivery Using Empirical Mode Decomposition Analysis of Uterine Electromyography Signals', *PLOS ONE*. Edited by M. A. Lebedev, 10(7), p. e0132116. doi: 10.1371/journal.pone.0132116.

Renthal, N. E., Williams, K. C. and Mendelson, C. R. (2013) 'MicroRNAs—mediators of myometrial contractility during pregnancy and labour', *Nature Reviews Endocrinology*, 9(7), pp. 391–401. doi: 10.1038/nrendo.2013.96.

Di Renzo, G. C. *et al.* (2017) 'Preterm Labor and Birth Management: Recommendations from the European Association of Perinatal Medicine', *The Journal of Maternal-Fetal & Neonatal Medicine*, 30(17), pp. 2011–2030. doi: 10.1080/14767058.2017.1323860.

Romero, J. *et al.* (2012) 'The prediction of recurrent preterm birth in patients on 17-alpha-hydroxyprogesterone caproate using serial fetal fibronectin and cervical length.', *American journal of obstetrics and gynecology*, 207(1), p. 51.e1-5. doi: 10.1016/j.ajog.2012.04.024.

Romero, R., Dey, S. K. and Fisher, S. J. (2014) 'Preterm labor: one syndrome, many causes', *Science*. 2014/08/16, 345(6198), pp. 760–765. doi: 10.1126/science.1251816.

Schlembach, D. *et al.* (2009) 'Monitoring the progress of pregnancy and labor using electromyography', *Eur J Obstet Gynecol Reprod Biol.* 2009/03/13, 144 Suppl, pp. S33-9. doi: 10.1016/j.ejogrb.2009.02.016.

Sikora, J. *et al.* (2011) 'Recognition of premature threatening labour symptoms from bioelectrical uterine activity signals', *Archives of Perinatal Medicine*, 17(2), pp. 97–103.

Smrdel, A. and Jager, F. (2015) 'Separating sets of term and pre-term uterine EMG records', *Physiological Measurement*. IOP Publishing, 36(2), pp. 341–355. doi: 10.1088/0967-3334/36/2/341.

- Soilly, A. L. *et al.* (2014) 'Economic analysis of the costs associated with prematurity from a literature review', *Public Health*, 128(1), pp. 43–62. doi: 10.1016/j.puhe.2013.09.014.
- Sosa, C. *et al.* (2004) 'Bed rest in singleton pregnancies for preventing preterm birth', in Sosa, C. (ed.) *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd, p. CD003581. doi: 10.1002/14651858.CD003581.pub2.
- Stoll, B. J. *et al.* (2010) 'Neonatal Outcomes of Extremely Preterm Infants From the NICHD Neonatal Research Network', *PEDIATRICS*, 126(3), pp. 443–456. doi: 10.1542/peds.2009-2959.
- Terrien, J., Marque, C. and Karlsson, B. (2007) 'Spectral characterization of human EHG frequency components based on the extraction and reconstruction of the ridges in the scalogram', *Conf Proc IEEE Eng Med Biol Soc.* 2007/11/16, 2007, pp. 1872–1875. doi: 10.1109/iembs.2007.4352680.
- Tezuka, N. *et al.* (1995) 'Changes in transcripts encoding calcium channel subunits of rat myometrium during pregnancy.', *The American journal of physiology*, 269(4 Pt 1), pp. C1008-17. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7485440> (Accessed: 22 August 2017).
- Urquhart, C. *et al.* (2017) 'Home uterine monitoring for detecting preterm labour', in Urquhart, C. (ed.) *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd, p. CD006172. doi: 10.1002/14651858.CD006172.pub4.
- Vasak, B. *et al.* (2013) 'Uterine electromyography for identification of first-stage labor arrest in term nulliparous women with spontaneous onset of labor', *Am J Obstet Gynecol.* 2013/06/04, 209(3), p. 232 e1-8. doi: 10.1016/j.ajog.2013.05.056.
- Verdenik, I., Pajntar, M. and Leskosek, B. (2001) 'Uterine electrical activity as predictor of preterm birth in women with preterm contractions', *Eur J Obstet Gynecol Reprod Biol.* 2001/04/13, 95(2), pp. 149–153. Available at: http://ac.els-cdn.com/S0301211500004188/1-s2.0-S0301211500004188-main.pdf?_tid=9aaa9fee-b37a-11e3-8205-00000aab0f6b&acdnat=1395682671_5557293f3dac7e45bf9b7840755308ba.
- Vinken, M. P. *et al.* (2009) 'Accuracy of frequency-related parameters of the electrohysterogram for predicting preterm delivery: a review of the literature', *Obstet Gynecol Surv.* 2009/07/25, 64(8), pp. 529–541. doi: 10.1097/OGX.0b013e3181a8c6b1.
- Vinken, M. P. *et al.* (2010) 'Nifedipine-induced changes in the electrohysterogram of preterm contractions: feasibility in clinical practice', *Obstet Gynecol Int.* 2010/07/09, 2010, p. 325635. doi: 10.1155/2010/325635.
- Vrhovec, J. and Macek, A. (2012) 'An Uterine Electromyographic Activity as a Measure of Labor Progression', in *Applications of EMG in Clinical and Sports Medicine*. InTech. doi: 10.5772/25526.
- Ye-Lin, Y. *et al.* (2014) 'Automatic identification of motion artifacts in EHG recording for robust analysis of uterine contractions', *Comput Math Methods Med.* 2014/02/14, 2014, p. 470786. doi: 10.1155/2014/470786.