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REVIEW

Alvarez waves in pregnancy: a comprehensive review

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Abstract
Alvarez waves are local rhythmic contractions of the myometrium with high frequency and low intensity. They can be detected using internal or external tocography and electrohysterography. Some researchers correlate these small contractions with the initiation of labor, since they have been described as a pattern representing the uterine response to prostaglandin production. Other authors either do not validate a causality relation between Alvarez waves and labor or suggest that they have low predictive value for preterm labor. Alvarez waves' research has become a multidisciplinary subject with inputs ranging from medical science, biomedical engineering, and related areas. A comprehensive review is herein conducted to summarize the state of the art regarding Alvarez waves and their role in the initiation of labor, namely in preterm birth. The results show that a large number of studies have analyzed and characterized Alvarez waves without necessarily digging into their relationship with labor. Publications were categorized in three groups: (A) reports about morphology and characterization of Alvarez waves; (B) publications reporting a positive causality relation between Alvarez waves and labor; and (C) publications reporting an absence of causality regarding the previous hypothesis. Studies in group B outnumbered those in group C. A critical analysis is presented.

Keywords Alvarez waves · Electrohysterography · Uterine electromyography · Preterm and term labor · Uterine biophysics

Introduction

Uterine contractions may be recorded as early as 9 weeks of gestation (Alvarez and Caldeyro-Barcia 1950). In the first trimester, the uterus undergoes irregular and uncoordinated contraction patterns (Cunningham et al. 2016), which, typically, result in ineffective uterine contractions (Trojner Bregar et al. 2016). This unproductive pattern may be justified by low level cell-to-cell communications (Sims et al. 1982; Miller et al. 1989). The coordination and transmission of the contractile waves are optimized by the formation of communication bridges between the cells of the uterine smooth muscle, known as gap junctions, and the increase of oxytocin receptors (Cunningham et al. 2016). The gap junctions' channel formation improves the efficiency of the uterine contractions, which will become progressively stronger with the approaching of the gestational term, and are a contributive factor to the cervical ripening (Garfield et al. 1998). These gap junctions facilitate and increase the propagation of the electrical activity through the whole uterine muscle (Mansour et al. 1991) and allow for a synchronous and effective uterine contractility (Miyoshi et al. 1998). Prostaglandins play an important role in the initiation of labor (Ivani et al. 2001). Uterine contractility at term increases as a result of activation and stimulation of the myometrium. This stimulation is one of the factors responsible for the change from uterine quiescence to a contractile state enabled by differential expression of prostaglandin receptors within the myometrium and fetal membranes (Ivani et al. 2001; Khan et al. 2008). During pregnancy, the levels of primary prostaglandins (prostaglandin E_2 and prostaglandin F_2) in amniotic fluid and peripheral plasma

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are relatively low (Ivani et al. 2001). Weeks before term, the concentration of prostaglandins increases. With the onset of labor, a further increase is registered (Keirse and Turnbull 1973; Keirse et al. 1974).

Early contractions are normally painless and become more synchronized as term approaches (Garfield et al. 2005). Contractions have been reported to increase in intensity and duration in, approximately, 4-week observation windows (Dickinson et al. 1997).

Uterine contractions can be detected by cardiotocography (TOCO), internal uterine pressure catheter (IUPC), and the electrohysterogram (EHG) (Maul et al. 2004; Garfield and Maner 2007; Rabotti 2010; Haran et al. 2012; Rooijakkers et al. 2013; Alberola-Rubio et al. 2013). The main contraction types are classified as follows:

- The Braxton-Hicks contractions were firstly described in 1871 (Longo and Hicks 1975). Braxton-Hicks, also known as false labor contractions are usually non-rhythmic and appear randomly (Devedeux et al. 1993; Cunningham et al. 2016).
- Alvarez and Caldeyro Barcia (Alvarez and Caldeyro-Barcia 1950) identified a new type of uterine contractions, later named as Alvarez waves, also referred to as uterine irritability (Smyth 1958), low amplitude high frequency (LAHF) waves (Csapo and Sauvage 1968; Newman et al. 1987; Roberts et al. 1995; Alamedine 2015), and small waves (Kawarabayashi et al. 1988). These Alvarez waves are local rhythmic contractions (Alvarez and Caldeyro-Barcia 1950; Roberts et al. 1995) of higher frequency, low amplitude (Esgalhado et al. 2020b), and short duration (Marque et al. 1986). Murray described LAHF activity as small contractions that may be uterine response to uterine prostaglandin production (Murray 2007a; Murray 2007b). In this paper, the use of these four terms to label this contraction type will be made interchangeably, according to the term selected by each researcher group that is being referred.
- Some other types of contraction-related waves include the *Longue Durée Basse Fréquence* (LDBF) waves which have been reported as long duration events (several minutes) and frequency ranging from 0 to 1 Hz (Marquel et al. 1995). LDBF waves are rare and are associated with uterine hypertonia (Chendeb et al. 2010; Chandraharan 2017). They may be of value for preterm birth diagnosis (Khalil and Duchene 2000).
- Khalil et al. (Khalil and Duchene 2000) described low amplitude contractions as Leman waves. These contractions are usually lost in the detection process due to poor signal-to-noise ratio (Chendeb 2006).

Table 1 describes the reported onset and offset of the main contraction types relatively to the gestational age, according to the referred authors (Alvarez and Caldeyro-Barcia 1950; Marquel et al. 1995; Khalil and Duchene 2000; Raines and Cooper 2020). Both Alvarez and Braxton Hicks occur during most of the pregnancy.

Despite the existence of different contraction types, the aim of this report is to review the literature contributions concerning Alvarez waves only.

The paper outlines as follows: In the "Alvarez wave description" section, a description of the Alvarez waves is presented. A review of the relation between these waves and labor is performed in the "Alvarez waves and connection to labor" section. Finally, some conclusions are presented.

Alvarez wave description

Alvarez waves were named after Hermógenes Alvarez, who first registered them in the early fifties (Alvarez and Caldeyro-Barcia 1950). In this pioneer study, Alvarez and Caldeyro Barcia placed intramuscular pressure electromanometers into the myometrium wall, as a sensor of uterine pressure, after the 3rd month of pregnancy. Following this invasive procedure, a rhythmic type of contraction was reported and believed to represent unsynchronized local uterine activity that usually is not perceived by women (Alvarez and Caldeyro-Barcia 1950) but could be recorded via external tocodynamometry (Newman 2005). Alvarez and Caldeyro Barcia verified that these contraction patterns occur randomly in different parts of the uterus, being consequently local contractions. In a subsequent work, Alvarez et al. identified local contractions in labor that were named as 2nd degree incoordination activity or uterine fibrillation, which were deemed inefficient to make labor progression (Alvarez and Caldeyro-Barcia 1954).

Cobo reported that Alvarez waves were replaced by contractions of amplitude range similar to Braxton-Hicks and higher occurrence rate, in eight pregnant women who developed pre-eclampsia (Cobo 1963). Alvarez waves were described as having a high occurrence rate (10 to 20 every 10 min) and low intensity (2 to 4 mmHg).

Warkentin studied the uterine activity recorded by external tocography in late pregnancy and verified that the Alvarez wave amplitude range as being 4 to 11 cm of water (Warketin 1976a).

Newman et al. examined 142 pregnant women, between 23 and 36 weeks' gestation, who underwent daily ambulatory tocodynamometry to determine the significance of the LAHF contractility pattern (Newman et al. 1987). In this study, it was concluded that LAHF were significantly more prevalent in multifetal gestations. This pattern was considered as having a low predictive value for preterm labor. Moreover, it was verified that parameters such as parity and gestational age had no effect on the occurrence of LAHF.

Table 1 Contraction monitoring techniques

Study	Contraction type	Onset	Offset
(Alvarez and Caldeyro-Barcia 1950)	Alvarez waves	9th week of gestation	End of pregnancy
(Raines and Cooper 2020)	Braxton-Hicks*	6-week gestation	End of pregnancy
(Marquel et al. 1995)	*Longue Durée Basse Fréquence*	23th week of pregnancy	-
(Khalil and Duchene 2000)	Leeman waves	Rare events	

*Not usually felt until the second or third trimester of the pregnancy

Kawarabayashi et al. studied 6363 TOCO from 578 patients, ranging between 20 and 42 weeks of gestation (Kawarabayashi et al. 1988). Components labeled as small waves were described as a regular and rhythmic pattern, lasting 10 min or more. These researchers reported these components' presence during pregnancy between 20th and 42nd weeks with a decreasing rate stage by stage, without relevant differences between 31st to 36th weeks and 37th to 42nd weeks. The appearance rate was higher in mid pregnancy (28% at 21 weeks' gestation) and was null after 41 weeks of pregnancy.

Scheerer et al. studied 8 sets of 20 TOCO strips with durations between 60 and 120 min (Scheerer et al. 1990). They described the LAHF waves as a pattern with an amplitude lower than 5 mmHg, duration less than 30 s, and an occurrence rate of 1–3 min. All records were evaluated by 8 physicians and nurses. They concluded that observer variabilities in the LAHF duration estimation would reduce the clinical significance of the LAHF pattern.

Newman et al. analyzed 110 uterine activity strips with excessive contractions, which resulted in unscheduled visits (Newman et al. 1991). They described the LAHF contractility as a pattern with an amplitude lower than 5 mmHg, with occurrence rate varying between 1 and 3 min.

Marque et al. used the EHG to characterize one Alvarez wave instance in the time and frequency domains (Marquel et al. 1995). These waves were characterized as low amplitude contractions, with short duration (30 s to 1 min), high occurrence rate (1 every 1 or 2 min), and a spectral frequency peak superior to 0.2 Hz. This work introduced the EHG capability for the representation of Alvarez waves.

Alvarez waves have been reported having frequency band between 0 and 1 Hz (Batista et al. 2016). Esgalhado et al. (Esgalhado et al. 2020b) have defined two different subtypes of Alvarez waves: Alvarez Low (AlvL) and Alvarez High (AlvH). This was done through the application of an unsupervised clustering method, where Braxton-Hicks contractions were also characterized (Esgalhado et al. 2020b). AlvL and AlvH were found to have frequency energy peaks between 0.2 and 0.3 Hz and 0.3 and 0.4 Hz, respectively.

Batista et al. developed a method to visualize contraction sequencing, Braxton-Hicks, AlvH, and AlvL, in different regions of the myometrium, using EHG multichannel recordings (Batista et al. 2021). In this study, it was introduced a visual tool for evaluation of Alvarez wave presence both in the spatial and time domains.

More recently, the interest in Alvarez Waves increased as a result of the EHG application, given its superior sensitivity and predictive value, compared to the TOCO and identical to the IUPC (Hadar et al. 2015)(Euliano et al. 2013). Using the IUPC as the gold standard, another study (Euliano et al. 2013) confirmed the superiority of the EHG over the TOCO, for labor monitoring. Table 2 describes the contraction detection techniques presented in this work.

Table 3 summarizes the Alvarez waves' research report evolution, according to author and date. It is patent that the application of the EHG to the Alvarez wave detection and analysis had its debut in 1995 with the works of Marque et al. (Marquel et al. 1995). Also stands out by observing the column description relative to Frequency Band that only the studies based on the EHG reported values for this parameter.

Figure 1 represents the result of an unsupervised clustering operation over a data set of 3061 contractions that where automatically detected and delineated using an envelope energy method (Esgalhado et al. 2020a). A subsequent clustering allowed the identification of three contraction types, from where the AlvL and AlvH stood out as two identities with different spectral signatures (Esgalhado et al. 2020b).

Figure 2 shows an example of AlvL (left column) and AlvH (right column) waveforms (top row) and Welch spectra (bottom row). The plots are the result of the application of the methods presented in (Esgalhado et al. 2020b).

Alvarez waves and connection to labor

Predicting preterm: a general approach

Preterm birth, defined as a delivery that occurs before 37 weeks of gestation, is still one of the leading causes of

Table 2 Contraction monitoring techniques

Sensor	Sensor type	Number of sensors	Application	Invasive
TOCO	Pressure	1 in clinical settings	After 24 weeks of gestation (Smyth 1957)	No
EHG	Electric potential	Between 2 and 64	After 19 weeks of gestation (Gondry et al. 1993)	No
IUPC	Pressure	1 in clinical settings	After membrane rupture (Hadar et al. 2015)	Yes
Intramuscular manometer	Pressure	Between 1 and 4	After 9 weeks of gestation (Alvarez and Caldeyro-Barcia 1950)	Yes

neonatal morbidity and mortality worldwide (Chawanpaiboon et al. 2019). Despite its prevalence (estimated in 7% globally) and severity, the mechanisms for this condition are not completely understood (Son and Miller 2017). Predicting the occurrence of spontaneous preterm birth is a challenge in the current obstetrics practice. Its importance is paramount — both due to the possibility of implementing strategies that decrease the risk for its occurrence (such as the supplementation with vaginal progesterone in high-risk patients), but also because this prediction allows clinicians to timely ensure fetal lung maturation and neuroprotection when indicated, both decidedly associated with improved neonatal outcomes in premature infants; and plan in-utero transferal to a tertiary center with equipped neonatology (Kennedy and O'dwyer 2019).

There are some recognized risk factors for premature birth, the main being previous history of preterm birth (Koullali et al. 2016). Other factors, such as ethnicity, low socio-economic status, maternal weight, smoking, and periodontal status, seem to play a minor role (Koullali et al. 2016). Despite these associations, the prediction of preterm birth based on personal history alone is not reliable, since the majority of spontaneous preterm deliveries occur in women with no identifiable risk factor for this condition (Son and Miller 2017).

One of the most accurate predictors for spontaneous preterm birth is a short cervical length (measured through transvaginal ultrasound) between 16 and 24 weeks of gestation. Shorter cervical lengths are associated with a higher risk of premature birth. Different cut-offs for cervical length have been suggested by several groups, most ranging from 15 to 30 mm (Son and Miller 2017; Glover and Manuck 2018; Ville and Rozenberg 2018; Suff et al. 2019).

Fetal fibronectin, a glycoprotein found in the amniotic membranes, can be detected in cervical and vaginal secretions in all pregnancies. Fibronectin levels ≥50 ng/mL at > 22 weeks of gestation have been suggested by some authors to be associated with higher risk for spontaneous preterm birth, although there are conflicting results from other groups. Consequently, its utility in clinical practice is mainly to improve screening accuracy in association with cervical length (Koullali et al. 2016; Son and Miller 2017; Glover and Manuck 2018; Ville and Rozenberg 2018; Suff et al. 2019).

Placental alfa microglobulin-a (partosure®) is also increased in the vaginal secretions of women with higher risk for preterm birth. Similarly to fetal fibronectin, its main utility is to improve screening accuracy in association with cervical length, particularly in the intermediate-risk group: cervical length 15–30 mm (Koullali et al. 2016; Kennedy and O'dwyer 2019).

Other markers, such as amniotic and cervical-vaginal fluid interleukin 6 and C-Reactive Protein, have been suggested by some authors to be increased in cases of spontaneous preterm birth, although they are still investigational markers, not currently used in clinical practice (Glover and Manuck 2018; Suff et al. 2019). Serum proteomics (Glover and Manuck 2018; Suff et al. 2019), genomics (Glover and Manuck 2018; Suff et al. 2019), and circulating-RNA (Stower 2018) are also promising fields of research for novel biomarkers.

In the particular case of multiple pregnancies, the risk for preterm birth is exponentially increased. In asymptomatic women, the best clinical predictors for preterm delivery in this population are cervical length (<20–25 mm at 20–24 weeks of gestation) and the cervical fibronectin test, the latter with a good negative predictive value. For symptomatic women, no reliable marker has yet been identified (Fuchs and Senat 2016).

Predicting preterm using electrohysterography

Typically preterm prediction is based on subjective and inaccurate methods. The EHG has been considered as a new promising tool for detecting preterm delivery (de Lau et al. 2014). A comprehensive review of electrohysterography in the diagnosis of preterm birth was presented (Garcia-Casado et al. 2018). Two challenges are identified in this work: the dependency on the quality of the obtained surface signals and the robustness of the automated EHG burst identification.

Prats-Boluda et al. used random forest (RF), extreme learning machine (ELM), and K-nearest neighbors (KNN) for imminent labor prediction. Women under tocolytic therapy were

Table 3 Alvarez description summary

Study reference	Sensor	Alvarez occurrence	Frequency band	Signal amplitude	Signal duration	Highlights
(Alvarez and Caldeyro-Barcia 1950)	Intramuscular manometer	10 to 30 contractions per 10 min	N.A.	0.3–11 cm of water	-	- Alvarez wave presence from 9th week up to the end of pregnancy. -Not perceived by women.
(Cobo 1963)	Intramuscular manometer	10 to 20 contractions in 10 min	N.A.	2 to 4 mmHg	-	-Alvarez waves replaced by contractions of amplitude range similar to Braxton-Hicks and higher occurrence rate, in eight pregnant women who developed pre--eclampsia.
(Warketin 1976a)	TOCO	60 to 80% of total contractions	N.A.	4 to 11 cm of water	-	- Alvarez waves present in the last 6 weeks of normal term gestation. - Observed a decrease in this pattern as labor approached.
(Newman et al. 1987)	TOCO	- Less than 60% TOCO presence between 23 and 36 weeks' gestation. - 1- to 2-min intervals	N.A.	Inferior to 5 mmHg	-	- Pregnancies with preterm births were preceded by a greater than average weekly proportion of LAHF. - Not very predictive for preterm delivery.
(Kawarabayashi et al. 1988)	TOCO	Occurrence rate up to 28% in each gestational week recordings	N.A.	-	30 s or less	- Small wave pattern is regular and rhythmic, lasting 10 min or more. - Present between 20th and 42nd weeks. Decreasing rate stage by stage with no differences between 31st to 36th and 37th to 42nd weeks.
(Newman et al. 1991)	TOCO	Occurring every 1–2 min	N.A.	Inferior to 5 mmHg	-	- No differences were identified in uterine activity between women with true and threatened preterm labor.
(Scheerer et al. 1990)	TOCO	Interval of 1 to 3 min	N.A.	Inferior to 5 mmHg	Inferior to 30 s	- Difficult to determine clinical significance of LAHF pattern due to the significant inter and intra-observer variabilities in the estimation of the LAHF.
(Martin et al. 1991)	TOCO	-	N.A.	-	Inferior to 30 s	-LAHF prevalent in all groups. - Diminished or disappeared in those who did not develop preterm labor.
(Marquel et al. 1995)	EHG	One every 1 or 2 min	Spectral peak at 0.2 Hz	-	Between 30 s and 1 min	- Alvarez waves are localized and non-propagative events. - Study conducted between 23rd and 34th weeks.
(Murray 2007a; Murray 2007b)	TOCO	Once every 2 to 4 h	N.A.	-	Inferior to 30 s	- LAHF are occasionally felt by the woman.
(Chendeb et al. 2010)	EHG	Between 30 and 60 per hour	Between 0.2 and 1 Hz		-	- Alvarez waves appear during the first 30 weeks of human pregnancy.
(Esgalhado et al. 2020b)	EHG	-	AlvH: 0.3–0.4 Hz AlvL: 0.2–0.3 Hz	AlvH: 27.2 ±18.6 µV (RMS) AlvL: 22.3 ±16.6 µV (RMS)	AlvH: 20–117 s AlvL: 20–110 s	- Found two different Alvarez wave subtypes (AlvL and AlvH).

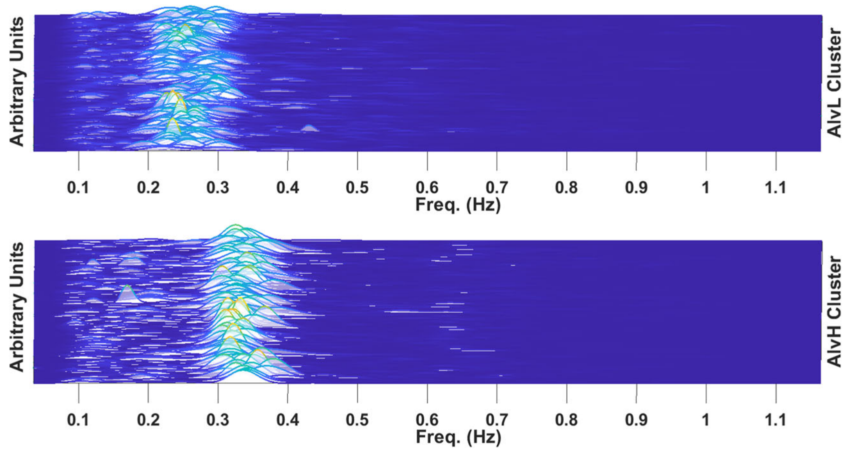

Fig. 1 Welch spectra representation of Alvarez contractions. Top plot: 360 Alvarez Low contractions; Bottom plot: 137 Alvarez High contractions. Adapted from Esgalhado et al. (2020b)

targeted. RF and ELM provided the highest F1-score values with the latter outperforming the former (Prats-Boluda et al. 2021).

An unsupervised machine learning approach has been presented by Fergus et al. for the classification of term and preterm recordings (Fergus et al. 2013). An improvement of the existing studies was reported with 96% specificity and 95% area under the curve value. An 8% global error was obtained using the polynomial classifier. In another study (Lucovnik et al. 2016), it has been determined that the accuracy of the EHG and its predictive value for preterm delivery are not affected by obesity.

Entropy measures were tested for their contribution to recognize the onset of labor and the risk of preterm delivery (Mischi et al. 2018). *SampEn* and *ApEn* produced the best results, being reported an outperformance relatively to the reference methods.

Vandwiele et al. reported the methodological inconsistencies deriving from the application of oversampling before data partitioning for training and testing sets in the context of the preterm prediction with the EHG (Vandewiele et al. 2021).

De Lau et al. studied the correlation between the mechanical activity of the uterus during labor and the derived EHG. A maternal respiration component was identified and characterized in terms of average frequency, amplitude, and peak speed. The procedure can lead to increase the robustness of the EHG-dependent methods, regarding this movement artifact (de Lau et al. 2013). The conduction velocity analysis of the EHG has been used as a tool for the diagnosis of the imminent preterm delivery (de Lau et al. 2014). In this study, an automatic selection of contractions based on an estimation of the IUP and the corresponding delay were used.

Alvarez waves as a labor inductors

Alvarez waves are local events in the myometrium that were recognized by some authors as having the ability to trigger the development of more synchronous contractions with superior intensity that subsequently lead to term or preterm labor (Murphy 1943; Bell 1983; Kawarabayashi et al. 1988; Martin et al. 1991; Roberts et al. 1995). Table 4 summarizes

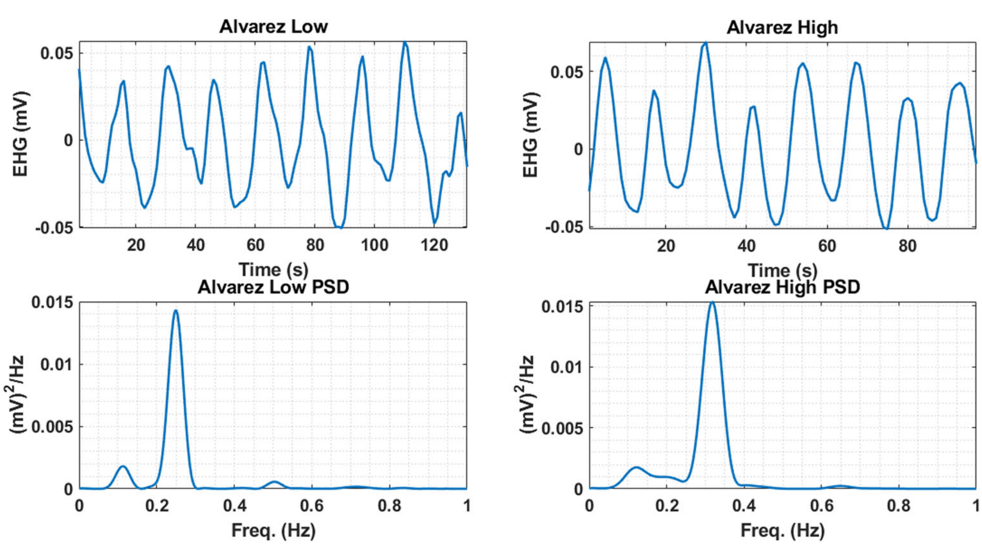

Fig. 2 AlvL (left column) and AlvH (right column) waveforms (top row) and Welch spectra (bottom row). The dominant frequency peak distinguishes both Alvarez types. The plots were obtained using the methodology presented in Esgalhado et al. (2020b)

Table 4 Alvarez wave labor inductor hypothesis

Study reference	Labor evaluation	Sensor	Study sample	Highlights
(Smyth 1958)	Labor	TOCO	-	- When uterine irritability considerably increases, labor is imminent.
(Nakae 1978)	Preterm	TOCO	78	- Small waves increased in women with preterm labor, who were receiving tocolytic treatment.
(Creasy et al. 1984)	Preterm	-	-	- There is a relationship between preterm labor and LAHF activity in cases where these contraction patterns appear in 30% or more of the recording strip.
(Kawarabayashi et al. 1988)	Preterm	TOCO	578	- Small waves were frequently registered during preterm periods, mainly in early preterm pregnancy phases. - Increase in small waves' activity in 42.3% of patients with premature labor.
(Newman et al. 1989)	Preterm	-	54 singleton pregnancies 30 twin pregnancies 34 triplet pregnancies	- Significantly greater proportion of LAHF contractility in triplet gestations.
(Mueller-Heubach and Guzick 1989)	Preterm	-	5457	- Identified seventeen risk factors for preterm labor. - 35% of patients who presented uterine irritability before 37 weeks' gestation had a preterm labor.
(Martin et al. 1991)	Preterm	TOCO	98	- Patients with premature membranes rupture and placenta *previa* had LAHF contractions, and the majority occurred in those who subsequently developed preterm labor.
(Miller et al. 1991)	Labor	TOCO	40	- LAHF onset after two different types of intravaginal prostaglandin E_2 administration for pre-induction cervical ripening. In both cases, it was observed an increase in LAHF contractions, with different onset times.
(Roberts et al. 1995)	Preterm	TOCO	2637	- Compared with the group of patients with other risk factors, pregnant women with uterine irritability, delivered more frequently before 30 weeks. - Pregnant women with uterine irritability were more likely to deliver early compared to the other high-risk groups. - Maternal age and parity for women with uterine irritability were not significantly different from those patients with other risk factors.
(Hanke 2001)	Preterm	-	2080	- Uterine irritability was more frequent in the group with preterm births.
(Blickstein and Keith 2006)	Preterm	TOCO	-	- Recurrent preterm labor in patients with singleton or multiple pregnancies for patients receiving β-mimetic therapy. - A subsequent return of excessive levels of LAHF contractions.
(Murray 2007a; Murray 2007b)	Preterm	TOCO	-	- LAHF is associated with abruption, preterm labor, infection, or ketonuria due to dehydration.

the authors in favor of a preterm delivery predisposition when Alvarez waves are registered.

Considered as the leading cause of perinatal morbidity and mortality, preterm birth presents a public health concern (Trotter 1980). Premature infants remain vulnerable, since they have a higher risk for short- and long-term complications, including respiratory distress syndrome (Randis 2008), chronic lung disease, cardiovascular disorders, and retinopathy (Boardman 2008; Randis 2008). They are also at risk for neurodevelopmental disabilities such as cerebral palsy, developmental delay, and mental retardation (Soleimani et al. 2014).

The underlying causes of a preterm delivery are not always fully understood. However, there are well recognized factors that predispose to preterm labor, such as prior preterm delivery, maternal infections, multifetal gestation, uterine, and cervical abnormalities (Creasy et al. 1980; Mueller-Heubach and Guzick 1989; Roberts et al. 1995). Mueller-Heubach et al. identified seventeen risk factors for preterm labor, and remarked that 35% of patients who presented uterine irritability before 37 weeks' gestation had preterm labor (Mueller-Heubach and Guzick 1989).

Smyth studied uterine irritability and suggested high irritability values as the initiator of labor (Smyth 1958). It was stated that the biological uterine irritability can be assessed by measuring the minimal dose of oxytocin required to produce a perceptible change in myometrial activity.

Nakae classified each contraction pattern recorded by the TOCO and verified that small waves increased in preterm labor cases, under tocolytic treatment (Nakae 1978).

Creasy et al. observed that, if LAHF activity is present in 30% or more of the recording strip, this fact would predispose for a preterm delivery outcome (Creasy et al. 1984).

Kawarabayashi et al. observed an increase in small waves' activity in 42.3% of patients with premature labor (Kawarabayashi et al. 1988) and remarked this contraction pattern representing some degree of contractility and as being ominous for the outcome of the pregnancy in general. It was stated that small waves were frequently observed during preterm gestational ages, particularly in early preterm periods of pregnancy. Furthermore, the occurrence of these waves was not related with a poor prognosis in preterm labor, if large phasic contractions were eliminated by tocolysis with β_2-stimulant treatment.

Newman et al. studied the influence of the fetal number in uterine activity and suggested that in triplet gestations, the LAHF pattern played a role in the "silent" cervical changes (Newman et al. 1989).

Martin et al. studied 98 pregnant women with different risks for preterm delivery, such as early premature rupture of membranes (35 cases), placenta *previa* (21 cases), blunt abdominal trauma (22 cases), and post-surgery (20 cases) (Martin et al. 1991). These researchers observed an increased incidence of LAHF in patients with premature rupture of membranes (31 of 35) and placenta *previa* (18 of 21). The majority of LAHF contractions were observed when the uterus was likely more irritable, such as in cases of post-surgery.

Roberts et al. compared 17186 patients with well-defined high-risk factors for preterm delivery with 2637 women experiencing uterine irritability to determine whether this condition could represent a high-risk factor for preterm labor (Roberts et al. 1995). In this study, the authors ranked uterine irritability as the fifth most common reason for the indication of additional monitoring for preterm risk, after prior preterm delivery, multifetal gestation, and uterine and cervical abnormalities. Their study points out that 13% of patients having uterine irritability are reported as developing preterm labor, thus indicating that patients with uterine irritability should be considered a concern for the healthcare provider. Also, it is mentioned that women with uterine irritability develop more resistance to conventional tocolytic therapy. The authors of this work also commented on the deficit of some documental data in the existing reports, thus prompting for more research investments in this area.

Hanke et al. studied a population of 2080 women and concluded that uterine irritability was more frequent in the group with preterm births (Hanke 2001).

Miller et al. monitored 40 pregnant women at term, between 38 and 43 weeks who required induction of labor with an unfavorable cervix (Miller et al. 1991). TOCO was used to monitor ambulatory uterine activity. The authors evaluated the LAHF onset after two different types of intravaginal prostaglandin E_2 administration methods (gel and pessary) for cervical ripening pre-induction. For the 20 patients treated with the gel, LAHF contractions were detected in the first hour, attaining a peak within 4 h. The remaining 20 patients treated with the pessary registered an onset of increased LAHF between the 5th and the 8th hour. For both cases, it was reported a connection between LAHF and the initiation of sustained high-amplitude contractions, in 50% of the gel and 80% of the pessary cases.

Lam et al. investigated recurrent preterm labor in singleton and multiple pregnancies for patients receiving β-mimetic therapy (Blickstein and Keith 2006). In these conditions, preterm labor is reported to be characterized by excessive levels of LAHF.

Murray et al. reported LAHF activity as being associated with maternal dehydration and being probably an uterine response to the antidiuretic hormone which has a weak effect similar to oxytocin (Murray 2007a). LAHF were, in this study, described as occurring up to 72 h before the beginning of preterm labor, being these contractions related to placental abruption or infection, such as a urinary tract infection, which induces the cytokine-prostaglandin cascade that stimulates uterine contractions.

Murray et al. stated that LAHF are often observed when coupling between the myometrium cells increases (Murray and Huelsmann 2009).

Hypothesis of Alvarez waves weak or non-correlation with labor

Considering preterm labor as a multifactor process, some authors present a different vision of the relationship between Alvarez waves and delivery. Table 5 summarizes the authors in favor of a weak or non-correlation between preterm delivery and Alvarez waves.

Table 5 Weak links between Alvarez waves and labor

Study reference	Sensor	Study sample	Highlights
(Warketin 1976b)	TOCO	- 214 tocolysis cases - 473 non tocolysis cases	- Alvarez wave activity decreases towards labor for tocolysis and non-tocolysis cases.
(Newman et al. 1987)	TOCO	142	- Despite LAHF being significantly more frequent in patients who developed preterm labor, LAHF pattern is not sufficiently predictive of preterm labor.
(Newman et al. 1991)	-	110	- Neither maternal symptoms nor uterine contractions' characteristics, including LAHF, besides the contraction frequency, could differentiate true from threatened preterm labor.

Warkentin studied the uterine activity recorded by external tocography in late pregnancy and verified that Alvarez waves decrease towards delivery, while contractions and phases of inactivity increase (Warketin 1976a). To clarify the mechanism underlying the tocolysis, and using weeks before delivery (WBD) as a time reference, Warkentin reported an increase in the Braxton-Hicks percentage towards labor, both for tocolysis and non-tocolysis cases (Warketin 1976b). The number of studied cases was 214 for tocolysis and 473 for non-tocolysis. For 1 WDB, the ratio between Braxton-Hicks and Alvarez waves was slightly lower for tocolysis cases, thus implying a reduced impact of the latter in labor. Both clinical scenarios showed a decrease in the Alvarez percentage towards labor. For the tocolysis and non-tocolysis cases, that percentage ranged from 88.1±11.0 to 56.9±22.5, and 75.9 ±24.2 to 63.1±23.4, respectively. Concerning the Alvarez wave part of this study, their occurrence rate is reported to decrease in both clinical scenarios, along the WBD reference. Moreover, for the tocolytic case, this occurrence rate increases in all WBD, except for the last (WBD = 1).

The Newman et al.'s study included 142 women using home-based external TOCO recordings (Newman et al. 1987). Monitoring took place between 23 and 36 gestational weeks. Ninety-two women were previously diagnosed with high risk of preterm labor, whereas the remaining were considered at low preterm risk. Most women (136 of 142) had at least one episode of LAHF. All the 50 women from the low-risk group delivered at term and 50% of women included in the high-risk group had a preterm infant. The LAHF activity was more often prevalent among women who developed preterm labor compared to women who delivered at term, although this pattern occurred in less than 60% of the time in all cases. The tocolytic therapy administration resulted in a 50% reduction of the time where LAHF pattern is present, even though, the therapy did not eliminate it. Despite these results, the authors considered that LAHF waves provided limited information as well as low predictive value for preterm labor.

Newman et al. reviewed 110 home uterine monitoring strips to identify if uterine activity characteristics, such as LAHF activity, contraction amplitude and duration, mean duration between contractions, and contraction rhythmicity, allowed for differentiation between true and threatened preterm labor (Newman et al. 1991). It was concluded that maternal symptoms and uterine contractions' characteristics, such as the LAHF, could not differentiate true from threatened preterm labor, except for contraction occurrence rate.

Conclusions

Pregnancy monitoring for term and preterm delivery evaluation is an important subject in prenatal assessment. Namely, preterm risk evaluation has been and still is an issue that would benefit from further research and innovative methodologies. Since their debut in the prenatal research field, in early fifties, some researchers have considered Alvarez waves as having the potential to contribute as a marker to term or preterm labor. However, despite some favorable scientific reports in this matter, an established and consensual methodology that could be translated to clinical use is still not present. Considering that preterm labor remains one the most relevant obstetric conditions, the search for a reliable marker for this event is still an ongoing initiative. This paper presented a comprehensive outlook of the state of the art in this matter, regarding Alvarez waves, dividing the report pool in three main categories:

A. Morphology and characterization of Alvarez waves (twelve reports in Table 3);

B. Positive outcome relatively to the causality relation between Alvarez waves and labor (twelve reports in Table 4);
C. Negative outcome or uncertain about the causality relation between Alvarez waves and labor (three reports in Table 5).

The following considerations are relevant:

- The reports of category A span from 1950 to 2020, thus suggesting that intrinsic characterization of Alvarez waves is still an ongoing project;
- Reports using the EHG belong to category A only. There seems to still exist some work to do regarding using the EHG signal to explore the Alvarez wave potential;
- Twelve to three ratio seems to endorse category B relatively to C;
- None of the referred authors provided a biological description behind the Alvarez wave interaction with labor or significant insights about their genesis mechanisms.

Category B and C discrepancy may rely in the fact that all studies are based on detected Alvarez waves in the TOCO and identified as such. All these studies critically depend on the accuracy of this operation. Being that Alvarez waves are characterized by low amplitude events, possibly approaching levels similar to uterine baseline activity, it might be expected that a number of these events may be undetectable in the TOCO. This would also lead to an overrepresentation of Braxton-Hicks over Alvarez waves, since the former have higher amplitude relatively to the latter.

Alvarez wave recognition accuracy may also be responsible for the detected differences between reports in category A, relatively to these contractions' characterization, such as duration, amplitude, and occurrence rate.

In this review article, the superior sensitivity of the EHG over the TOCO has been referred; thus, it is expected that Alvarez wave recognition using the EHG will provide better outcome regarding detection accuracy and delineation. This would be a crucial step forward in the assessment of the Alvarez waves' role in the pregnancy development.

Independently of the used sensor, Alvarez waves are non-stationary stochastic signals to which an array of signal processing methods can be applied. Some of these methods require the time and frequency resolution that only the EHG can provide.

The understanding and characterization of uterine contractile activity, as part of prenatal healthcare, should include a broader vision where Alvarez waves are sequenced with other uterine contractile events, namely the Braxton-Hicks.

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