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Use of uterine electromyography to diagnose term and preterm labor

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Abstract

Current methodologies to assess the process of labor, 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. Consequently, their predictive values for term or preterm delivery are poor. Uterine contractions are a result of the electrical activity within the myometrium. Measurement of uterine electromyography (EMG) has been shown to detect contractions as accurately as the currently used methods. In addition, changes in cell excitability and coupling required for effective contractions that lead to delivery are reflected in changes of several EMG parameters. Use of uterine EMG can help to identify patients in true labor better than any other method presently employed in the clinic.

Keywords

Uterine electromyography; propagation velocity tocometry; preterm labor; term labor

Introduction

Uterine contractions, at term or preterm, are one of the most common reasons for visits to obstetrical triage (1). Determining which patient with contractions is in true labor and needs to be admitted is, however, difficult. (2). Evidence shows that misjudgments are often made; up to 50% of women admitted with the diagnosis of term or preterm labor are subsequently found not to be in true labor (3,4). On the other hand, 20% of symptomatic patients who are diagnosed as not being in preterm labor will deliver prematurely (5). This has important clinical consequences. Women at term admitted in the latent phase or not yet in labor are more likely to receive medical intervention (electronic monitoring, epidural analgesia, oxytocin and cesarean section) than those admitted in active labor (6-9). These interventions in labor have been associated with increased levels of morbidity and mortality for mothers

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and babies (10-13). In preterm patients, the inability to accurately diagnose preterm labor leads to missed opportunities to improve outcome of premature neonates, and also to unnecessary costs and side-effects of treatments in women who would not deliver preterm regardless of intervention.

There is consequently a great need for a methodology that will accurately identify patients in true labor. Such a method would also be extremely valuable in further research of potential treatments for preterm labor that has been largely hindered by the inability to exclude patients in false labor from analyses.

Currently used methods to diagnose labor

The diagnosis of labor often relies on presence of contractions assessed by tocodynamometry and cervical change assessed by digital cervical examination. Contractions occur commonly in normal pregnancy, and their detection through maternal perception and/or tocodynamometry does not mean the patient is truly in labor (14,15). Indeed, tocodynamometry has very low sensitivity and positive predictive value (PPV) for preterm delivery (14,15). Moreover, digital cervical examination suffers from large variations among examiners, and its prognostic value has also been shown to below (16,17).

There is substantial evidence that measuring the cervical length by transvaginal ultrasound and testing for fetal fibronectin in cervicovaginal fluid can help to identify patients at particularly high risk for preterm delivery (18-20). Cervical length is inversely related to the rate of preterm delivery in both patients presenting with symptoms of preterm labor and in asymptomatic pregnant women (18,19,21,22). Fetal fibronectin is an extracellular matrix glycoprotein, produced by amniocytes and by cytotrophoblast, that normally resides at the decidual–chorionic interface (20). Its presence in the cervicovaginal fluid indicates decidual activation. However, the value of these two tests lies mostly in their high negative predictive values (NPVs), while their PPVs are lower and they do not identify patients who are really going to deliver preterm (23).

None of the currently used clinical methods can, therefore, distinguish between true and false term and preterm labor reliably. We have documented evidence from many studies that recording uterine electrical activity from the abdominal surface can diagnose true labor more accurately than any other method used today.

Role of uterine electromyography (EMG) for diagnosing true labor

The process of parturition, both at term and preterm, involves activation of the myometrium. Several events in the uterine muscle precede labor. Excitability of cells increases due to changes in transduction mechanisms and synthesis of various proteins, including ion channels and receptors for uterotonins (24,25). At the same time, systems that inhibit myometrial activity, such as the nitric oxide system, are downregulated, leading to withdrawal of uterine relaxation (26). Electrical coupling between myometrial cells also increases, and an electrical syncytium allowing the propagation of action potentials from cell to cell is formed (19,20). These changes are required for effective contractions that result in the delivery (expulsion) of the fetus.

Previous studies have established that the electrical activity of the myometrium is responsible for myometrial contractions (27,28) (Figure 1). Extensive studies have been done to monitor uterine contractility using the electrical activity measured from electrodes placed directly on the uterus (29,30). More recent studies published by our group and by others indicate that uterine EMG can be monitored noninvasively from the abdominal surface (26,31-34) (Figure 2).

Measuring uterine EMG activity has similar effectiveness of simple detection of uterine contractions to tocodynamometry, and even compared with an intrauterine pressure catheter (35-38). In addition, EMG can identify the transition from the nonlabor to the labor state of the myometrium. Many studies have shown that different uterine EMG parameters can indicate myometrial properties that distinguish physiological contractions from true term and preterm labor, which is something that the other contraction-monitoring devices cannot do (33,39-41).

Uterine EMG parameters described to date for the diagnosis of true labor

Of all of the possible EMG diagnostic variables, 'timing-related' EMG parameters seem to have the least value in the diagnosis of true labor. We recently analyzed the duration of uterine EMG 'bursts', the interburst interval duration (which is inversely proportional to the frequency of the bursts) and the standard deviation of burst and interburst interval duration in patients admitted with the diagnosis of preterm labor at <34 weeks. None of these parameters differed significantly between the group of patients who delivered within 7 days and those who did not (42). This is not in accordance with some studies, where it was found that the standard deviation of burst duration was smaller and the frequency of bursts higher in labor patients (40,43). We did, however, confirm the findings of Leman et al. and Buhimschi et al., who observed no differences in burst duration between preterm labor patients and women with preterm contractions who did not deliver preterm (33,40). Burst duration and frequency of bursts are the electrical equivalent of the duration and frequency of contractions, and these, not coincidentally, are the only properties of contractions that can be evaluated by tocodynamometry. Thus, their poor predictive values are not surprising, since monitoring uterine activity with tocodynamometry is not helpful in identifying patients in preterm labor (14,38).

Other types of EMG parameters can be categorized as 'amplitude related'. Such parameters may represent the uterine EMG signal power, or alternatively, the EMG signal energy. Buhimschi et al. demonstrated that an increase in power spectrum (PS) peak amplitude precedes delivery (40). Other studies did not confirm these findings (39,43,44). In the previously mentioned study on preterm labor patients, neither PS peak amplitude nor PS median amplitude were significantly higher in patients who delivered within 7 days compared with those who did not. It has been suggested that the major limitation of 'amplitude-related' EMG parameters is the fact that attenuation of myometrial signals occurs more for some patients and less for others, depending on a variance in subcutaneous tissues and a variance in conductivity at the skin–electrode interface. These limitations make the amplitude-related EMG parameters interesting, but perhaps less reliable, in the prediction of true labor.

The third group of EMG parameters can be defined as 'frequency-related' parameters, including PS median and peak frequency. Median frequency, although usually the most important parameter in the analysis of striated muscle EMG (45-47), is rarely reported to be useful in the uterine EMG literature (34). The reason for that is probably the difference in the PS of the signals from the uterine and striated muscle cells. The PS of a striated muscle covers a broad frequency range (20–400 Hz), with a more-or-less bell-shaped distribution of signal energy. Thus, for striated muscle, the median frequency is a most useful parameter in the analysis of these signals. In contrast, uterine EMG signals are filtered in order to exclude most components of motion, respiration and cardiac signals, which yields a narrow 'uterine-specific' band of 0.34–1.00 Hz. In this narrow frequency band produced by the uterus, the location of the power peak differs from one recording to another, and there are often competing 'lesser' power-spectral peaks, not generally of consequence in the broad power spectra of striated muscle. This suggests that the type of narrow-band power distribution found in the uterine-specific range of frequencies may render using the median frequency a less useful parameter for characterizing the uterine electrical signals. Verdenik et al. have, however, reported that as pregnancy approaches term, the median frequency of the uterine electrical activity becomes lower (34). It is not clear why this should be so, since other literature supports shifts to higher frequencies as a transition to labor occurs (29). Furthermore, shifts to lower median frequency in the electrical PS of muscle are generally attributed to muscle fatigue (46). A possible explanation for this is that the median PS frequency for the whole 30 minute EMG recording, and not for each burst separately, was analyzed in that study. It may be that including nonuterine-related electrical information (from the large portions of the recordings ‘in between’ bursts) contributed somehow to this result.

In contrast, PS peak frequency has been one of the most predictive EMG parameters in both human and animal studies (32,39,43). Shifts to higher uterine electrical signal peak frequencies occur during transition from a nonlabor state to both term and preterm labor states, and can be reliably assessed by noninvasive transabdominal uterine EMG measurement (33,39). The PS peak frequency also increases as the measurement-to-delivery interval decreases (39). The best predictive values of PS peak frequency have been identified at different measurement-to-delivery intervals by different authors (33,39). Generally, an increase in PS peak frequency occurs within approximately 24 hours from delivery at term, and before that (within several days from delivery) at preterm gestations (39,42).

We have recently explored a new EMG parameter, the propagation velocity (PV) of uterine EMG signals. It has been shown *in vitro* that the PV of electrical events in the myometrium is increased at delivery when gap junctions are increased (48,49). We demonstrated that PV can be assessed from the noninvasive uterine EMG recording *in vivo* by estimating the time interval between EMG signal arrivals at adjacent electrode pairs (42). We have also shown that PV increases as delivery approaches (Figure 3), and that it may predict term and preterm delivery more reliably than any other EMG parameter investigated so far (Figure 4) (42).

The EMG PV and PS peak frequency both identify true preterm labor more accurately than today’s clinical methods (Figure 4) (42). By combining the PV and PS peak frequency, we constructed a model that predicted spontaneous preterm birth with and area under the receiver-operating-characteristics curve of 0.96 (Table 1). This makes this methodology extremely valuable in everyday clinical practice. When uterine EMG is measured in patients presenting with signs and symptoms of preterm labor and the combination (rescaled sum) of PV and PS peak frequency exceeds the cut-off value of 84.48, this predicts delivery within 7 days with a 100% certainty according to our data (PPV = 100% in 88 patients). Electromyography does, therefore, identify patients who really benefit from early institution of tocolytic therapy, transport to a hospital with facilities for neonatal intensive care and administration of steroids. At the same time, this methodology also identifies patients in false preterm labor who are not going to deliver within the next 7 days. It can, therefore, help to avoid substantial economic costs associated with unnecessary hospitalization, the maternal risks associated with tocolytics and the potential fetal risks associated with steroids. In the case of low PV + PS peak frequency values, it therefore stands to reason that it would be safe not to admit, treat or transfer the patient, regardless of the presence of contractions on tocodynamometry, and regardless of digital cervical examination and transvaginal cervical length results, since all of the changes in the myometrium required for labor are not yet fully established. Other than being extremely important clinically, a methodology to accurately diagnose preterm labor would also be important in the research of new and potentially better treatments for preterm labor (see below).

All of the above-mentioned signal processing techniques are linear techniques. The uterus is, however, a complex non-linear dynamic system, and nonlinear signal processing techniques could potentially be very useful in analyzing such a system. Studies have been done on some nonlinear analysis techniques, such as fractal dimension of the burst of electrical activity and calculation of the sample entropy of the signal, yielding promising results (50,51). Although combination of PV and PS peak frequency differentiates preterm patients in true labor from those in false labor more reliably than any method available today, the addition of nonlinear parameters could make this model even more effective.

Importance of diagnostic tests for monitoring efficacy of treatment for preterm labor

The current standard treatment for preterm labor, i.e. tocolytics, was not shown to have any clear effect on perinatal mortality or on any measure of neonatal morbidity related to prematurity (52). Research of new and potentially more effective treatments for preterm labor is, therefore, extremely important. Development of such treatments, however, depends largely on the tests used to diagnose labor. Current methods do not allow patients in true preterm labor, who would deliver preterm if not treated, to be distinguished from those in 'false' preterm labor, who present with signs and symptoms of labor but would not deliver preterm regardless of treatment. The overall PPV of currently used methods to predict preterm delivery is only about 50%, as mentioned above (3). This inevitably leads to inclusion of patients in 'false' labor into studies of effectiveness of treatments.

A method with higher diagnostic accuracy, such as uterine EMG, would allow the performance of clinical trials on only those patients who are really in true preterm labor. It has been shown that using the EMG of the uterus we are be able to predict preterm delivery very accurately (with a PPV of 100% based on our data; Figure 4, Table 1) (25).

The impact that this technology could have on investigation of new treatments can be illustrated by a hypothetical case of a 10% effective treatment, i.e. a treatment that would prolong pregnancy more effectively than tocolytics in 10% of patients. In order to test for the efficacy of such treatment, one would need to compare a group of patients treated with the drug to a group of patients treated with a placebo. Consider the two studies presented in Figure 5. In the first study, preterm labor would be diagnosed with currently available methods. Fifty of 100 patients diagnosed as being in preterm labor will not deliver preterm regardless of whether they are treated or not. On the other hand, 50 of these 100 patients will deliver preterm if not treated. With equal randomization to treatment groups, 50 patients will receive the 10% effective treatment. Of these, 25 will not be in true preterm labor, and 25 will be in true preterm labor; 2.5 patients in true labor will therefore not deliver preterm due to treatment. Consequently, of the 50 treated patients diagnosed clinically as being in preterm labor, 27.5 (25 who were not at risk in the first place and 2.5 at risk patients who responded to treatment) will not deliver preterm. The response rate will, therefore, be 55% (27.5/50 = 0.55). In the placebo group, 25 patients will not deliver preterm because they were not in true labor in the first place, i.e. 50% response rate (25/50 = 0.50). The difference in treated vs. placebo group is only 0.05. Using a calculation for sample size based on proportions, one would need 3129 total patients recruited to the study to find this small difference with an α of 0.05 and 0.80 power (β).

In the second study, uterine EMG would be used to diagnose preterm labor. As a result, all 100 patients will theoretically be in true labor (PPV = 100%). If patients are randomized equally and there is a 10% response rate, five patients (10%) in the treatment group will respond (not deliver preterm), and zero in the placebo group. Using sample size calculation based on proportions, one would need only 147 patients to find this large difference (again with an α of 0.05 and 0.80 power).

Increased effectiveness of treatment will lower the values in both studies. With a 30% effective treatment, for example, one would need to include 339 patients in the first study, i.e. when currently available methods would be used to diagnose preterm labor, and only 42 patients when using uterine EMG.

This example emphasizes the importance of diagnostic accuracy of uterine EMG or any other method that might be able to predict true preterm labor. It will not only allow physicians to make safer and more cost-effective clinical decisions, but will also eventually lead to development of treatments for preterm labor that will improve neonatal outcome. Even if such treatment existed already, today one would need to include 3129 patients in a study to demonstrate a 10% efficacy, and this would be extremely costly and expose many patients to unneeded treatment. On the other hand, the same rate of efficacy could be demonstrated on only 147 patients using uterine EMG to diagnose preterm labor.

Conclusion

Uterine EMG obtained noninvasively yields valuable information about electrical coupling and excitability of myometrial cells required for labor at term and preterm. Use of uterine EMG can help to identify patients in true labor. This results in better management of term and preterm women presenting with uterine contractions. In addition, this methodology provides a noninvasive and objective means to evaluate various therapeutic interventions for term and especially preterm labor.

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Abbreviations

EMG	electromyography
NPV	negative predictive value
PPV	positive predictive value
PS	power spectrum
PV	propagation velocity

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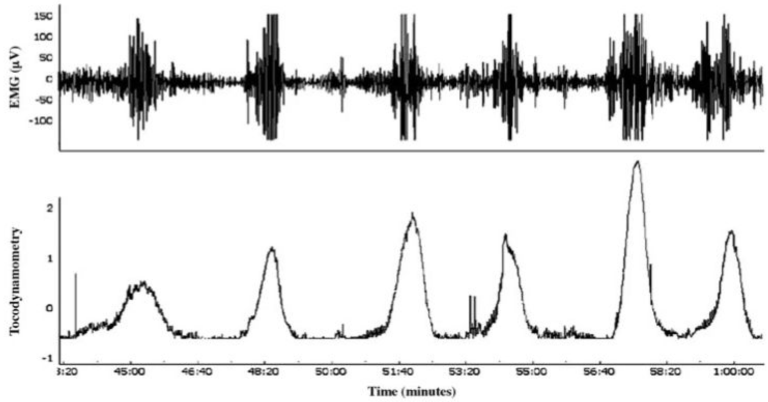

Figure 1.

Electrical activity of the myometrium (EMG activity; top trace) is responsible for uterine contractions. Note the excellent temporal correspondence between EMG and mechanical contractile events (measured by tocodynamometry; bottom trace). The numbers on the y-axis of the tocodynamometry trace are arbitrary units.

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Figure 2.
Electrode placement on the abdominal surface of the patient for performing uterine EMG measurement, to diagnose preterm and term labor.

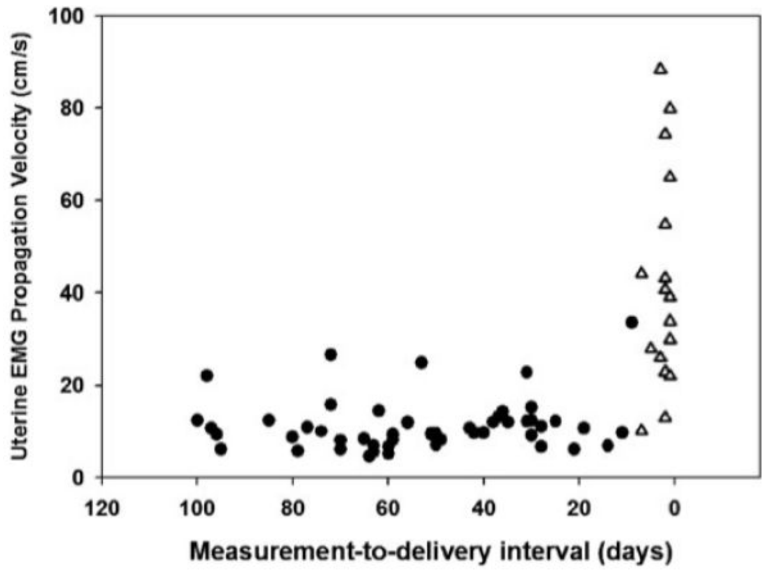

Figure 3.

Uterine EMG propagation velocity increases immediately prior to delivery (data shown for preterm patients). Open triangles, delivery ≤7 days from the measurement; and filled circles, delivery >7 days from the measurement.

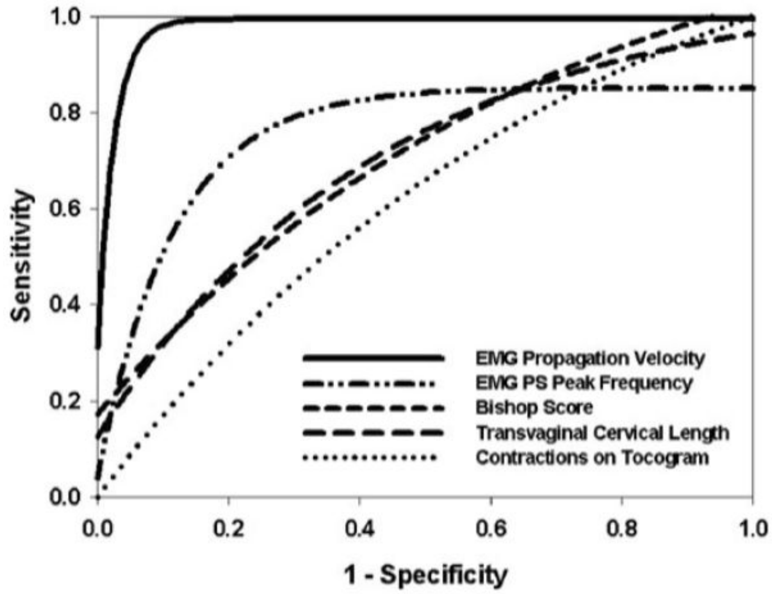

Figure 4.
Comparison of receiver-operating-characteristics curves for EMG parameters [power spectrum (PS) peak frequency and propagation velocity] vs. currently used methods to predict preterm delivery.

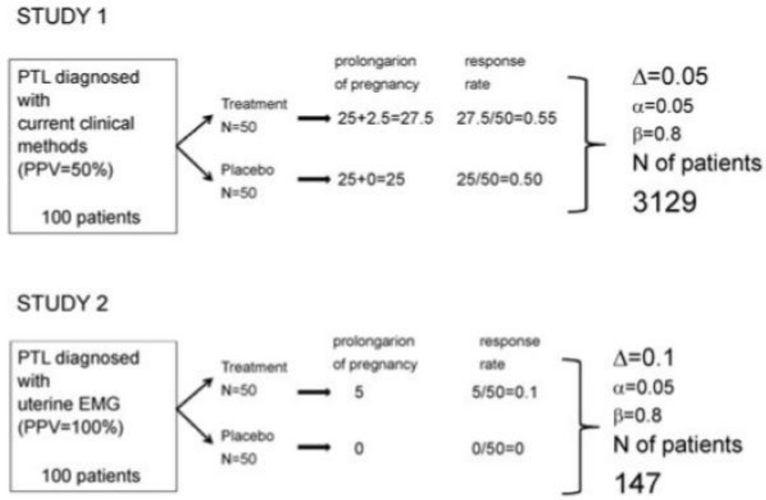

Figure 5.

Illustration of the sample size calculation for two studies examining a hypothetical 10% effective treatment for preterm labor (PTL). In study 1, preterm labor is diagnosed by currently available methods. Consequently, 50% of patients included are not in true preterm labor and will not deliver preterm regardless of treatment. To demonstrate a 10% effect of treatment with an α of 0.05 and 0.80 power, 3129 patients would have to be included in study 1. If preterm labor were to be diagnosed by uterine electromyography (EMG; study 2), all the patients included would be in true preterm labor [positive predictive value (PPV) = 100%]. Only 147 patients would have to be included in this study to demonstrate the same efficacy with the same power.

Table 1

Predictive measures of uterine EMG (rescaled sum of PS peak frequency and propagation velocity) compared with current methods to predict preterm delivery.

Method	AUC	Best cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
EMG (PV + PS peak frequency)	0.96	84.48	70	100	100	90
Bishop score	0.72	10	18	100	100	81
Transvaginal cervical length	0.67	0.7 cm	14	98	50	90
Contractions on tocodynamometry	0.54	Not applicable	35	72	27	79

Abbreviations: AUC, area under the receiver-operating-characteristics curve; EMG, electromyography; NPV, negative predictive value; PPV, positive predictive values; PS, power spectrum; and PV, propagation velocity.