Use of Non-invasive Uterine Electromyography in the Diagnosis of Preterm Labour

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Abstract

Predictive values of methods currently used in the clinics to diagnose preterm labour are low. This leads to missed opportunities to improve neonatal outcomes and, on the other hand, to unnecessary hospitalizations and treatments. In addition, research of new and potentially more effective preterm labour treatments is hindered by the inability to include only patients in true preterm labour into studies. Uterine electromyography (EMG) detects changes in cell excitability and coupling required for labour and has higher predictive values for preterm delivery than currently available methods. This methodology could also provide a better means to evaluate various therapeutic interventions for preterm labour. Our manuscript presents a review of uterine EMG studies examining the potential clinical value that this technology possesses over what is available to physicians currently. We also evaluated the impact that uterine EMG could have on investigation of preterm labour treatments by calculating sample sizes for studies using EMG vs. current methods to enrol women. Besides helping clinicians to make safer and more cost-effective decisions when managing patients with preterm contractions, implementation of uterine EMG for diagnosis of preterm labour would also greatly reduce sample sizes required for studies of treatments.

Key words: Cervical length, preterm delivery, preterm labour, preterm birth, tocodynamometry, uterine electromyography.

Introduction

None of the currently used methods reliably distinguish between true and false preterm labour (Iams, 2003). Up to 50% of women admitted with the diagnosis of preterm labour are subsequently found not to be in true labor (McPheeters et al., 2005). On the other hand, 20% of symptomatic patients that are diagnosed as not being in preterm labour will deliver prematurely (McPheeters et al., 2005). This leads to missed opportunities to improve outcome of premature neonates, and also to unnecessary costs and side effects of treatments. In addition, women in false preterm labour who would not deliver preterm regardless of treatment are constantly included into analyses of treatment's efficacy. Very large studies are therefore needed for these analyses to be adequately powered, which significantly hinders the research of potentially better preterm labour treatments.

Several changes occur in the myometrium prior to preterm labour. Excitability of cells increases, systems that inhibit myometrial activity decrease and, at the same time, systems that stimulate myometrial activity increase (Tezuka et al., 1995; Yuan & Lopez Bernal, 2007; Fuchs et al., 1984). Electrical coupling between myometrial cells also increases and an electrical syncytium required for effective contractions is formed (Balducci et al., 1993; Garfield et al., 1988). Non-invasive measurement of uterine electromyography (EMG) yields information about these changes by measuring the electrical properties of the myometrium (Leman et al., 1999; Maner et al., 2003; Buhimschi et al., 1997; Marque et al., 2007; Rabotti et al., 2010; Lucovnik et al., 2011).

The aim of this manuscript is to review current knowledge on potential clinical value of uterine EMG in the diagnosis of preterm labour. We also evaluated the impact this technology could have on investigation of new preterm labour treatments.

Currently used methods to diagnose preterm

The diagnosis of preterm labour still often relies on presence of contractions. However, contractions occur commonly in normal pregnancy. In fact, they are one of the most common reasons for visits to obstetrical triage (Bennett et al., 1998). The currently available methodology to evaluate contractions – **tocodynamometry (TOCO)** – does not allow clinicians to determine which patient is in true preterm labour and needs to be admitted, treated and possibly transferred to a hospital with a neonatal intensive care unit. Unfortunately, TOCO became a standard of care without ever undergoing vigorous clinical trials, in an age 40 years ago when such trials were in their infancy. TOCO measures the change in shape of the abdominal wall as a function of uterine contractions and, as a result, is a qualitative rather than quantitative method (Freeman, 2002). It has been shown in several studies that monitoring uterine activity with TOCO has a low sensitivity and positive predictive value for preterm delivery (Iams, 2003; Peaceman et al., 1997; Iams et al., 2002).

Cervical dilation, effacement, consistency, position, and station of the presenting part, determined by **manual examination**, are components of the Bishop scoring system. The score was not primarily developed for this purpose, but is often used clinically as a predictor of preterm delivery. However, the assessment of the cervix by digital exam is subjective, and its prognostic values have also been shown to be low (Gomez et al., 1994; Jackson et al., 1992).

There is now substantial evidence that measuring **cervical length** by transvaginal ultrasound and testing for **fetal fibronectin** in cervicovaginal fluid can help to avoid unnecessary treatment due to high negative predictive values of these tests (Iams et al., 1996; Leitich et al., 1999; Fuchs et al., 2004; Tsoi et al., 2005). Although a short cervical length indicates a higher risk for preterm delivery, it does not identify patients in true preterm labour reliably. Many women with short cervices, even those presenting with symptoms of preterm labour, do not deliver prematurely (Iams, 2003; Fuchs et al., 2004; Tsoi et al., 2005). Fetal fibronectin is an extracellular matrix glycoprotein produced by amniocytes and cytotrophoblast that normally resides at the decidual-chorionic interface (Honest et al., 2002). Its presence in the cervicovaginal fluid indicates decidual activation. Similar to cervical length, however, the positive predictive value of fetal fibronectin is low and many patients with a positive test do not deliver preterm (Iams, 2003).

There is consequently a great need for a method with a high positive predictive value for preterm delivery that would accurately identify patients in true preterm labour.

Accuracy of uterine electromyography in prediction of preterm delivery

Myometrial activation, required for effective contractions and true labour, is characterized by molecular changes leading to changes in the EMG activity of the myometrium (Buhimschi et al., 1997; Leman et al., 1999; Maner et al., 2003; Marque et al., 2007; Rabotti et al., 2010; Lucovnik et al., 2011). Extensive studies have been done in the last 60 years to monitor uterine EMG from electrodes placed on the uterus (Figueroa et al., 1990; Devedeux et al., 1993; Wolfs & van Leeuwen, 1997). More recent studies indicate that uterine EMG can be monitored non-invasively from the abdominal surface (Fig. 1) (Buhimschi & Garfield 1996; Buhimschi et al., 1998; Garfield et al., 1998).

Studies demonstrated similar effectiveness of transabdominal uterine EMG as compared to TOCO and intrauterine pressure catheter measurements in detecting contractions (Maul et al., 2004). 'Bursts' of electrical (EMG) signals are responsible for uterine contractions (Fig. 2).
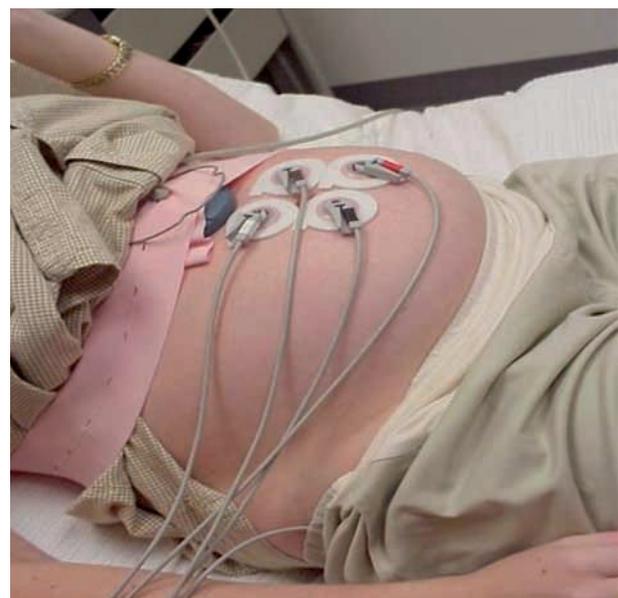
Fig. 1. — Electrode placement on the abdominal surface for non-invasive uterine electromyography (EMG) recording.
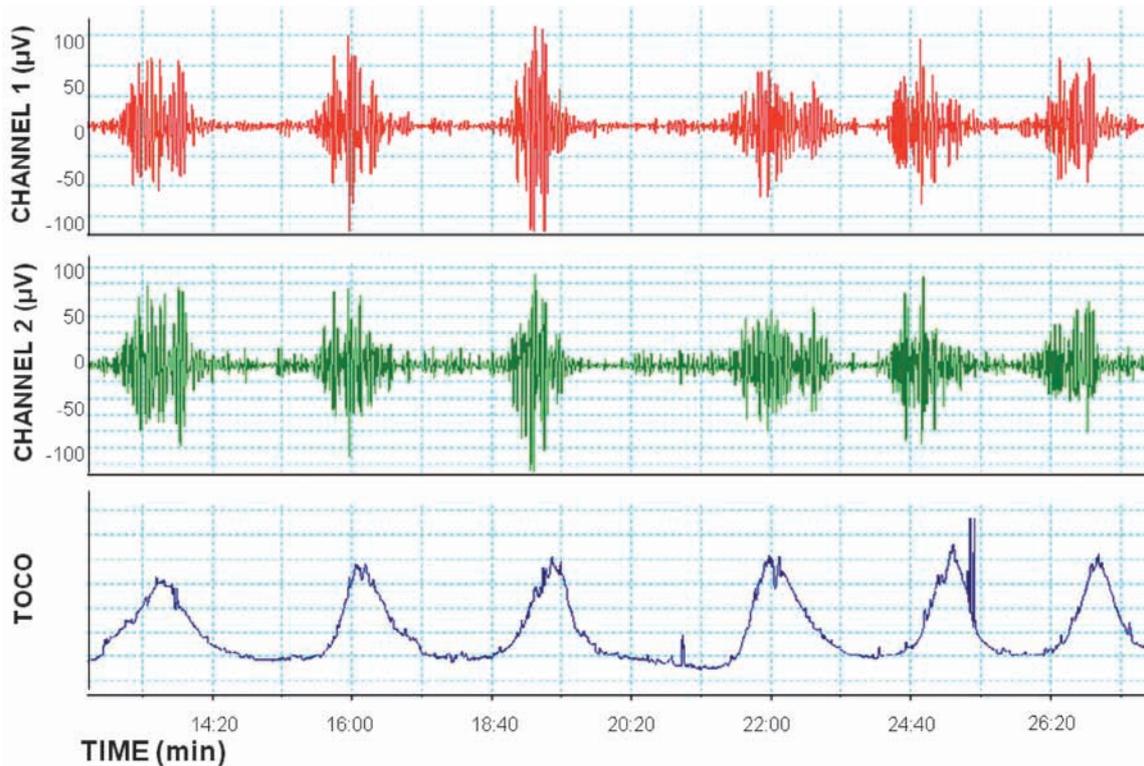
Fig. 2. — Electromyographic (EMG) activity is responsible for uterine contractions. Top traces show a sample EMG recording from two electrode pairs (channels 1&2). Note the excellent temporal correspondence between EMG and mechanical contractile events (measured by TOCO).

In addition, it has been shown that EMG yields valuable information about the changes in the electrical properties of the myometrium. These changes are the direct consequence of increased electrical excitation and coupling between myometrial cells that are required for preterm labour. Several EMG parameters can indicate the onset of labour. EMG bursts have been reported to be more frequent and their duration more constant in true labour (Buhimschi et al., 1997; Maner & Garfield, 2007). An increase in peak amplitude and frequency of EMG signals, assessed by power-spectrum (PS) analysis, has also been observed prior to preterm labour (Buhimschi et al., 1997; Maner et al., 2003). A more recent study showed that propagation velocity (PV) of uterine EMG signals, estimated from the time interval between signal arrivals at adjacent electrode pairs, increases as preterm delivery approaches (Fig. 3) (Lucovnik et al., 2011).

The combination (rescaled sum) of EMG PV and PS peak frequency yielded higher predictive values for preterm delivery than any EMG parameter alone. Receiver-operating-characteristics curve analysis for PV + PS peak frequency had an area under the curve of 0.96 for prediction of preterm delivery within 7 days (Lucovnik et al., 2011). Therefore, uterine EMG has been shown to be much more accurate in diagnosing preterm labour than all the methods currently used clinically (Fig. 4).

Currently used methods versus electromyography to calculate the number of women needed in studies of preterm labour treatments

Although perinatal mortality rate due to prematurity has decreased dramatically over the past four decades in high-income countries, this reduction resulted from improvements in neonatal care for premature babies, and has occurred in spite of our inability to prevent preterm delivery once preterm labour is established (Gyetvai et al., 1999; Hack & Fanaroff 1999; Giles & Bisits 2007). Development of effective preterm labour treatments that would prolong pregnancy sufficiently to allow further intra-uterine growth and improve neonatal outcomes depends largely on the tests used to diagnose preterm labour.

Uterine EMG can identify true preterm labour more accurately than the currently used methods (see above). Consequently, this methodology could be extremely important for research of new preterm labour treatments, because it allows the inclusion of only
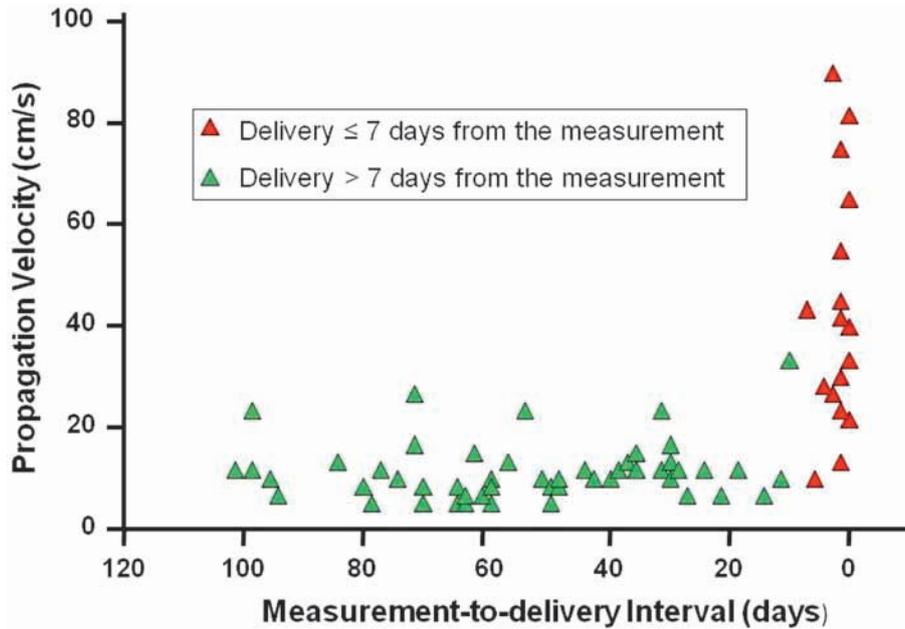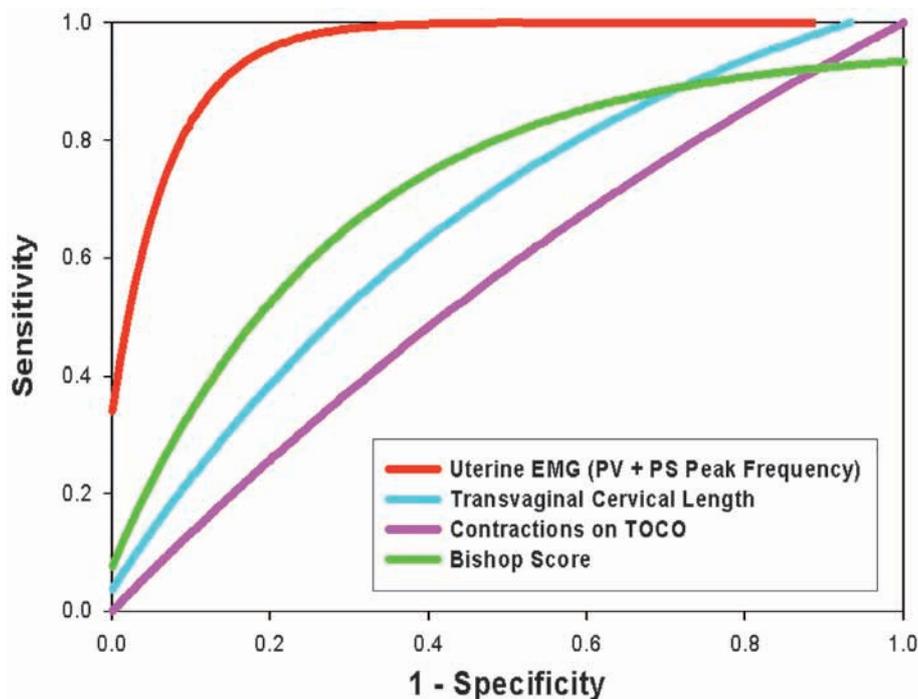
Fig. 3. — Uterine electromyography propagation velocity increases as the measurement-to-delivery interval decreases. (Adapted from Lucovnik et al., 2011).

women in true preterm labour into studies. To evaluate the potential impact of uterine EMG on investigation of new preterm labour treatments, we calculated sample sizes required for studies using EMG vs. various current methods to enrol women.

The following diagnostic methods have been considered: uterine EMG, digital cervical examination, cervical length measurement, TOCO, fetal fibro-

nectin test, and a combination of currently used methods in the clinics. We utilized the cut-offs for which positive predictive values (PPVs) have previously been reported in the literature: uterine EMG (rescaled sum of propagation velocity and PS peak frequency > 84.48) (PPV = 100%), Bishop score ≥ 4 for digital cervical examination (PPV = 42%), ≥ 4 contractions per hour on TOCO (PPV = 25%),

Fig. 4. — Comparison of receiver-operating-characteristics (ROC) curves for uterine electromyography (EMG) parameters (rescaled sum of propagation velocity [PV] and power spectrum [PS] peak frequency) and currently used clinical methods to predict preterm delivery within 7 days. (Adapted from Lucovnik et al., 2011).
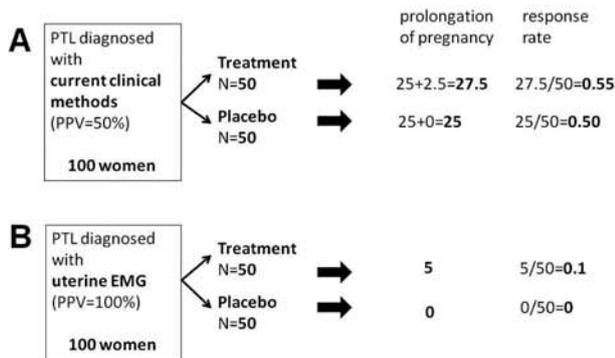
Fig. 5. — Method used to determine response rates used for sample size calculation. Figure illustrates two randomized studies of 10% effective treatment for preterm labour (PTL). Study A utilizes currently available methods to diagnose PTL and include women in the study; study B utilizes uterine electromyography (EMG). *PPV positive predictive value*.

concentration of fetal fibronectin ≥ 50 ng/mL (PPV = 43%), and cervical length of both < 30 mm and < 15 mm (PPV = 23% and PPV = 57%, respectively) (Gomez et al., 1994; Iams, 2003; Lucovnik M et al., 2011). As 50% of patients diagnosed with preterm labour do not deliver prematurely, we alleged the PPV of the combination of all methods used to diagnose preterm labour in the clinics today to be 50% (McPheeters et al., 2005). We then used these predictive values to determine the proportions of women who will not deliver preterm (response rates) in the groups treated with hypothetical treatments of various efficacies (10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100% effective) vs. placebo.

We used sample size calculation based on proportions to determine how many case (treated) and control (placebo) women would be needed to reject the null hypothesis that the preterm delivery rates for cases and controls are equal with probability (power) 0.8 (80%) ($\beta = 0.8$). Type I error probability was 0.05 (5%) ($\alpha = 0.05$). Uncorrected chi-squared statistic was used to evaluate the null hypothesis. The software used for statistical analysis was PS: Power and Sample Size Calculation version 3.0 (Vanderbilt Medical Center, Nashville, TN, USA).

The following example illustrates the method of sample size calculation. Using the currently available combination of diagnostic tests, 50 of 100 women included in the study because diagnosed as being in preterm labour will not deliver preterm regardless of whether they will be treated or not (McPheeters et al., 2005). On the other hand, 50 of these 100 women will deliver preterm if not treated. If treated with a 10% effective treatment, 55 of them will not deliver preterm, while 45 will. In order to test for the efficacy of such treatment one would need to compare a group of women treated with the

drug to a group of women treated with a placebo. With equal randomization to treatment groups, 50 women will receive the 10% effective treatment. 25 of these will not be in true preterm labour, and 25 will be in true preterm labour. Theoretically, 2.5 women in true labour will not deliver preterm due to treatment. Consequently, of the 50 treated women diagnosed clinically as being in preterm labour, 27.5 (25 who were not at risk in the first place and 2.5 at risk women who responded to treatment) women will not deliver preterm. The response rate will, therefore, be 55% (27.5 / 50 = 0.55). In the placebo group, 25 women will not deliver preterm because they were not in true labour in the first place, thus 50% response rate (25/50 = 0.50). Utilizing a calculator for sample size based on proportions, one can now determine how many women would have to be recruited to the study to find this small difference with an α of 0.05 and 0.8 power (β). When using the uterine EMG all 100 women will theoretically be in true labour (PPV = 100% based on our previously published data) (Lucovnik M et al., 2011). If women are randomized equally, 5 women (10%) in the treatment group will not deliver preterm (10% response rate; 5/50 = 0.1), and 0 in the placebo group (0% response rate; 0/50 = 0). Again, utilizing sample size calculator based on proportions, one can determine how many women would need to be included in the study to find this significantly larger difference (with an α of 0.05 and 0.8 power) (Fig. 5).

Table I shows that significantly smaller numbers of women would be needed to demonstrate the efficacy of treatment (or to reliably refute its effectiveness) using uterine EMG as compared to other diagnostic methods.

In the case of a hypothetically 10% effective treatment, for example, one would need to include 10134 women in the study, if the inclusion criteria would be a cervical length < 30 mm. 9096 women would need to be recruited with ≥ 4 contractions on TOCO per hour as the inclusion criteria. 5686 women would be the needed sample size with the increased concentration (≥ 50 ng/mL) of fetal fibronectin in the cervicovaginal secretions. With a Bishop score ≥ 4 one would need to include 4266 women, and with a cervical length < 15 mm, 2398 women. 3130 women would need to be included in the study using the combination of these methods. If uterine EMG would be utilized, on the other hand, the same effectiveness could be demonstrated in a study including only 148 women.

With more effective treatments the number of women needed for studies are lower. However, these numbers are always significantly lower for studies utilizing uterine EMG, regardless of how effective the treatment would be (Table I).

Table I. — Sample sizes needed to demonstrate effectiveness of treatment (with $\alpha = 0.05$ and $\beta = 0.8$) using different methods to include women into studies.

Method used to include women	Number of women needed to demonstrate effectiveness of treatment									
	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Uterine EMG	148	68	42	28	22	16	12	8	6	4
Combination of Currently Used Methods	3130	774	340	186	116	76	54	38	28	22
Digital Cervical Examination (Bishop Score ≥ 4)	4266	1044	452	246	152	100	70	50	36	28
Transvaginal Cervical Length										
< 15 mm	2398	602	342	148	92	58	44	32	24	18
< 30 mm	10134	2434	1034	552	336	236	152	108	78	58
Contractions on TOCO ≥ 4/h	9096	2188	932	500	304	200	138	98	72	52
Fetal Fibronectin ≥ 50 ng/mL	5686	1380	592	320	196	130	90	64	46	34

Legend: EMG electromyography; TOCO tocodynamometry.

Conclusions

Non-invasive measurement of uterine EMG can identify true preterm labour more accurately than the currently used methods. It can identify patients who will 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, uterine EMG also identifies patients who, although presenting with signs and symptoms of preterm labour, are not going to deliver preterm. This can help to avoid substantial economic costs associated with unnecessary hospitalization and transport, the maternal risks associated with tocolytics, and the potential fetal risks associated with steroids.

In addition, use of uterine EMG to diagnose preterm labour and include women in studies of preterm labour treatments would significantly reduce the sample sizes required for such studies to have an adequate statistical power. This is true, regardless of how effective the treatment is. As a result, uterine EMG can lead to significant savings of time, effort, and money, when researching new methods or drugs to prevent preterm delivery.

Disclosure

Drs Lucovnik and Novak-Antolic have no financial interest in the technology described in the manuscript and therefore have no conflict of interest.

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