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

M. LUCOVNIK, Z. NOVAK-ANTOLIC, R.E. GARFIELD

St. Joseph’s Hospital and Medical Center, Downtown Campus at TGen
445 N 5th Street, Phoenix, AZ 85004, USA.
Correspondence at: Robert.Garfield@DignityHealth.org

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 labour

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 cervixes, 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 intraperine 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.
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 intrauterine 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
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 fibronectin 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%),
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%) (β = 0.8). Type I error probability was 0.05 (5%) (α = 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.

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).
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.

References

Balducci J, Risek B, Gilula NB et al. Gap junction formation in human myometrium: a key to preterm labor. Am J Obstet Gynecol. 1993;168:1609-15.

Bennett TA, Kotelchuck M, Cox CE et al. Pregnancy-associated hospitalizations in the United States in 1991 and 1992: a comprehensive view of maternal morbidity. Am J Obstet Gynecol. 1998;178:346-54.

Buhimschi C, Boyle MB, Garfield RE. Electrical activity of the human uterus during pregnancy as recorded from the abdominal surface. Obstet Gynecol. 1997;90:102-11.

Buhimschi C, Boyle MB, Saade GR et al. Uterine activity during pregnancy and labor assessed by simultaneous recordings from the myometrium and abdominal surface in the rat. Am J Obstet Gynecol. 1998;178:811-22.

Buhimschi C, Garfield RE. Uterine contractility as assessed by abdominal surface recording of electromyographic activity in rats during pregnancy. Am J Obstet Gynecol. 1996;174:744-53.

Devedeux D, Marque C, Mansour S et al. Uterine electromyography: A critical review. Am J Obstet Gynecol. 1993;169(6):1636-53.

Figueroa JP, Honnebier MB, Jenkins S et al. Alteration of 24-hour rhythms in myometrial activity in the chronically catetherized pregnant rhesus monkey after a 6-hour shift in the light-dark cycle. Am J Obstet Gynecol. 1990;163(2):648-54.

Fuchs AK, Hruska M, Hesslein P et al. Oxytocin receptors in the human uterus during pregnancy and parturition. Am J Obstet Gynecol. 2004;190:734-9.

Fuchs F, Tsai J, Hruška M, Miller SM. Control of myometrial contractility: role and regulation of gap junctions. Oxf Reprod Biol. 1988;10:436-90.

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 | 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 | 2398 | 602 | 342 | 148 | 92  | 58  | 44  | 32  | 24  | 18   |
| < 15 mm                     | 10134 | 2434 | 1034 | 552 | 336 | 236 | 152 | 108 | 78  | 58   |
| < 30 mm                     | 9096 | 2188 | 932 | 500 | 304 | 200 | 138 | 98  | 72  | 52   |
| Contractions on TOCO ≥ 4/h   | 5686 | 1380 | 592 | 320 | 196 | 130 | 90  | 64  | 46  | 34   |
| Fetal Fibronectin ≥ 50 ng/mL |     |     |     |     |     |     |     |     |     |      |

Legend: EMG electromyography; TOCO tocodynamometry.
Garfield RE, Saade G, Buhimschi C et al. Control and assessment of the uterus and cervix during pregnancy and labour. Hum Reprod Update. 1998;4:673-95.
Giles W, Bisits A. Preterm labour. The present and future of tocolysis. Best Pract Res Clin Obstet Gynaecol. 2007;21:857-68.
Gomez R, Galasso M, Romero R et al. Ultrasonographic examination of the uterine cervix is better than cervical digital examination as a predictor of the likelihood of premature delivery in patients with preterm labor and intact membranes. Am J Obstet Gynecol. 1994;171:956-64.
Gyetvai K, Hannah ME, Hodnett ED et al. Tocolytics for preterm labor: a systematic review. Obstet Gynecol. 1999;94:869-77.
Hack M, Fanaroff AA. Outcomes of children of extremely low birthweights and gestational age in the 1990’s. Early Hum Dev. 1999;53:193-218.
Honest H, Bachmann LM, Gupta JK et al. Accuracy of cervicovaginal fetal fibronectin test in predicting risk of spontaneous preterm birth: systematic review. BMJ. 2002; 325:301.
Iams JD. Prediction and Early Detection of Preterm Labor. Obstet Gynecol. 2003;101:402-12.
Iams JD, Newman RB, Thom EA et al. Frequency of uterine contractions and the risk of spontaneous preterm delivery. N Engl J Med. 2002;346:250-5.
Iams JD, Goldenberg RL, Meis PJ et al. The length of the cervix and the risk of spontaneous premature delivery. N Engl J Med. 1996;334:567-72.
Jackson GM, Ludmir J, Bader TJ. The accuracy of digital examination and ultrasound in the evaluation of cervical length. Obstet Gynecol. 1992;79:214-8.
Leitch H, Egarter C, Kaider A et al. Cervicovaginal fetal fibronectin as a marker for preterm delivery: A meta-analysis. Am J Obstet Gynecol. 1999;180:1169-76.
Leman H, Marque C, Gondry J. Use of electrohysterogram signal for characterization of contractions during pregnancy. IEEE Trans Biomed Eng. 1999;46:1222-9.
Lucovnik M, Maner WL, Chambliss LR et al. Noninvasive uterine electromyography for prediction of preterm delivery. Am J Obstet Gynecol. 2011;204:228.e1-10.
Maner WL, Garfield RE, Maul H et al. Predicting term and preterm delivery with transabdominal uterine electromyography. Obstet Gynecol. 2003;101:1254-60.
Maner WL, Garfield RE. Identification of human term and preterm labor using artificial neural networks on uterine electromyography data. Ann Biomed Eng. 2007;35:465-73.
Marque C, Terrien J, Rihanu S et al. Preterm labour detection by use of a biophysical marker: the uterine electrical activity. BMC Pregnancy Childbirth. 2007;7(Suppl 1):S5.
Maul H, Maner WL, Olson G et al. Non-invasive transabdominal uterine electromyography correlates with the strength of intrauterine pressure and is predictive of labor and delivery. J Matern Fetal Neonatal Med. 2004;15(5):297-301.
McPheeters ML, Miller WC, Hartmann KE et al. The epidemiology of threatened preterm labor: a prospective cohort study. Am J Obstet Gynecol. 2005;192:1325-30.
Peaceman AM, Andrews WW, Thom JM et al. Fetal fibronectin as a predictor of preterm birth in patients with symptoms: A multicenter trial. Am J Obstet Gynecol. 1997;177:13-8.
Rabotti C, Misch M, Oei SG et al. Noninvasive estimation of the electrohysterographic action-potential conduction velocity. IEEE Trans Biomed Eng. 2010;57:2178-87.
Tezuka N, Ali M, Chwalisz K et al. Changes in transcripts encoding calcium channel subunits of rat myometrium during pregnancy. Am J Physiol. 1995;269:1008–17.
Tsoi E, Fuchs IB, Rane S et al. Sonographic measurement of cervical length in threatened preterm labor in singleton pregnancies with intact membranes. Ultrasound Obstet Gynecol. 2005;25:353-6.
Wolfs GM, van Leeuwen M. Electromyographic observations on the human uterus during labour. Acta Obstet Gynecol Scand. 1979;90:1-61.
Yuan W, Lopez Bernal A. Cyclic AMP signalling pathways in the regulation of uterine relaxation. BMC Pregnancy Childbirth. 2007;7(Suppl 1):S10.