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Use of uterine EMG and cervical LIF in monitoring pregnant patients

Robert E. Garfield, William L. Maner, Holger Maul, George R. Saade

Objectives Review the uterine electromyography (EMG) and cervical light-induced fluorescence (LIF) devices and their role in the evaluation of uterine and cervical function in comparison with present methods.

Design Review of recent studies.

Setting University of Texas Medical Branch Labour and Delivery Clinics.

Population Various groups of pregnant women.

Methods We have developed and recently improved non-invasive methods to evaluate quantitatively uterine electrical signals from the abdominal surface and cervical collagen.

Main outcome measures Uterine EMG utilised power density spectrum (PDS) peak frequency and total power (P_0) and cervical LIF utilising LIF ratio.

Results Human studies indicate that uterine and cervical performance can be successfully monitored during pregnancy using EMG and LIF, respectively, and the assessment of uterine and cervical function can both be used to influence patient management in a variety of conditions associated with labour, more than can currently available methods.

Conclusions The potential benefits of the proposed instrumentation include the following: a reduction in the rate of preterm birth, improved maternal and perinatal outcome, better monitoring of treatment, decreased caesarean section rate and better research methods for understanding uterine and cervical function.

INTRODUCTION

Preterm birth and its attendant complications are among the most important health problems in the world today, contributing to handicap and about 85% of all perinatal deaths.[1] Preterm neonates with birthweights less than 2500 g represent about 10% of the total number of babies born each year.

The complications of preterm birth include significant neurological, mental, behavioural and pulmonary problems in later life. Among the preterm survivors, the rate of neurological impairment varies from 10% to 20% and growth restriction occurs in approximately 20% of the surviving infants. The development of effective methods to prevent or reduce the incidence of preterm birth depends upon the understanding of the mechanisms that initiate labour.

The pharmacological control of uterine contractility would allow better management of women who are in spontaneous preterm labour. To develop a rational approach to the control of uterine activity, a thorough understanding of the mechanism by which labour is initiated is important. Of particular importance for appropriate management of spontaneous preterm labour is the ability to identify true rather than false labour. There are no clinical methods currently in use to evaluate objectively the function of the uterus or cervix during pregnancy.

During the past six years, our group has developed and improved two methods to evaluate effectively and objectively uterine contractility and cervical function during pregnancy. Both methods are noninvasive, easy to learn, rapidly performed and allow for the quantitative estimation of uterine contractile activity and cervical ripening. These systems permit the attending physician to differentiate between the labour *versus* the non-labour state of both the uterus and cervix. They may contribute to a better understanding of term and preterm labour and to monitoring treatments.

For many years, labour was viewed as the transition from an inactive to an active muscle either by the addition of a uterotonin or withdrawal of tonic progesterone inhibition.[2] Although past models recognised the importance of progesterone in controlling uterine quiescence, they neither defined precisely the uterine stages of labour nor identified the mechanism of action of the hormones involved. In addition, the models of parturition did not consider the changes in the cervix as an important component of parturition. The results of experimental and clinical studies with

Division of Reproductive Sciences, Department of OB-GYN, University of Texas Medical Branch, Galveston, Texas, USA

Correspondence: Professor R. E. Garfield, Division of Reproductive Sciences, Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston Texas 77555-1062, USA.

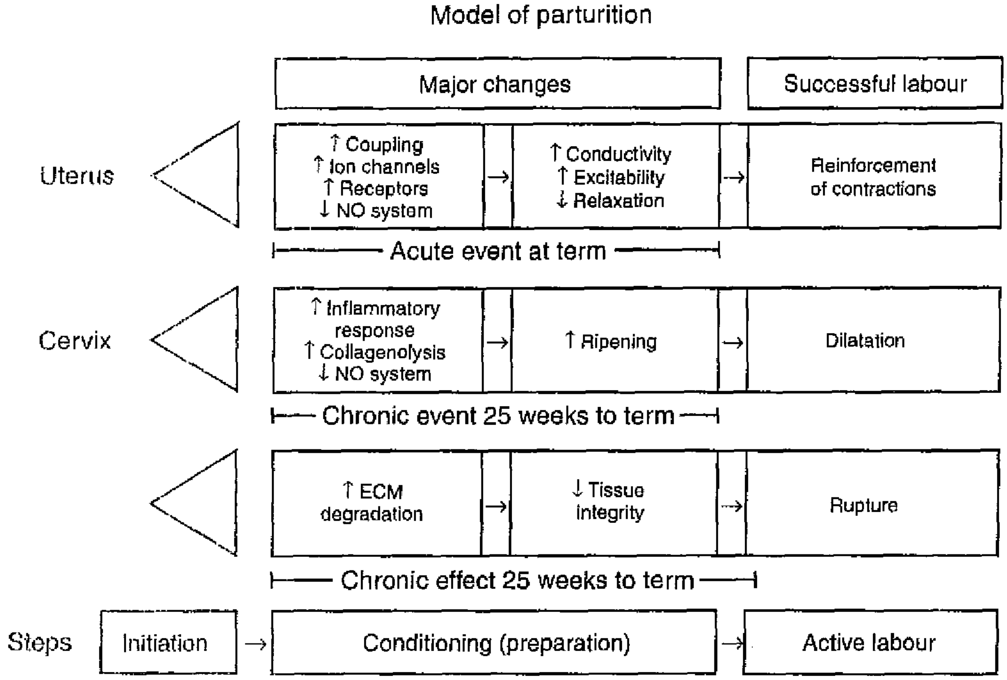

Fig. 1. Model of uterine and cervical development during parturition. The uterus and cervix go through changes as they prepare for labour and ultimately for delivery. These changes may be driven, at least partially, by independently timed mechanisms.[27]

progesterone and its antagonists indicate that parturition is composed of two major steps: a relatively long conditioning (preparatory) phase, followed by a short secondary phase (active labour)[3,4] (Fig. 1). The conditioning step leading to the softening of the cervix takes place in a different time frame from the conditioning step of the uterus and myometrium, indicating that the myometrium and cervix are regulated in part by independent mechanisms.

We and others have shown that myometrial cells are coupled together electrically by gap junctions composed of connexin proteins.[5] The grouping of connexins provides channels of low electrical resistance between cells that facilitate pathways for the efficient conduction of action potentials. Throughout most of pregnancy, and in all species studied, these cell-to-cell channels or contacts are few, indicating poor coupling and decreased electrical conductance.

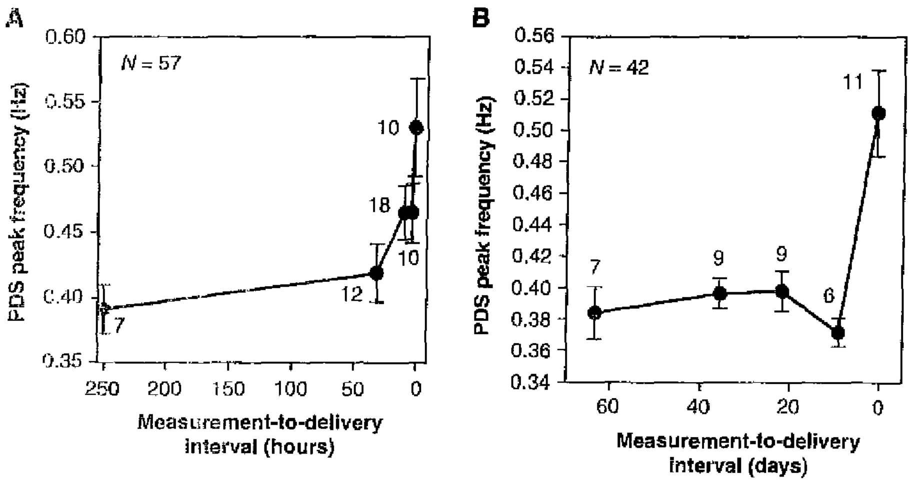

Fig. 2. (A) Power spectrum peak frequency within uterine electrical bursts remains relatively low for term-delivering patients far removed from delivery and increases most dramatically within about 24 hours of delivery. All patients included delivered spontaneously. (B) Power spectrum peak frequency within uterine electrical bursts remains relatively low for preterm-delivering patients far removed from delivery and increases most dramatically within about four days of delivery. All patients included delivered spontaneously.[16]

Table 1a. The PPV increases dramatically as the measurement-to-delivery interval (Golden Standard) increases from 8 to 48 hours, whereas the NPV decreases only slightly at 24 hours, but drops significantly at 48 hours prior to delivery.

MTD interval (hours)	PPV	NPV	Sensitivity	Specificity	Cutoff	z	AUC	*P*
8	0.545	1.000	1.000	0.394	0.395	3.05	0.706	<0.005
12	0.750	1.000	1.000	0.542	0.395	3.31	0.745	<0.001
24	0.854	0.889	0.976	0.533	0.373	3.03	0.760	<0.010
48	0.938	0.556	0.918	0.625	0.373	3.00	0.783	<0.005

MTD = mean time to delivery.

This condition favours quiescence of the myometrium and the maintenance of pregnancy. At term, however, the cell junctions increase and form an electrical syncytium required for effective contractions. The presence of the contacts seems to be controlled by changing oestrogen and progesterone levels in the uterus.[5] As action potentials propagate over the surface of a myometrial cell, the depolarisation causes voltage-dependent Ca^{2+} channels (VDCC) to open. When this occurs, Ca^{2+} enters the muscle cell down its chemical gradient to activate the myofilaments and provoke a contraction. We have recently demonstrated by reverse transcriptase polymerase chain reaction that the expression of VDCC subunits in the rat myometrium increases during term and preterm labour.[6] The increased expression, which appears to be controlled by progesterone withdrawal, may facilitate uterine contractility during labour by increasing portals for Ca^{2+} entry.

The cervix is composed of smooth muscle (*ca.* 10%) and a large component of connective tissue (90%) consisting of collagen, elastin and macromolecular components, which make up the extracellular matrix.[7] Many biochemical and functional changes occur in cervical connective tissue towards term.[7–9] This process of cervical ripening results in softening, effacement and finally dilation of the cervix. Ripening is required for the normal progression of labour and delivery of the fetus. The exact mechanisms controlling the cervical ripening process are largely unknown.

At some point, the processes governing changes in the myometrium and cervix become irreversible and ultimately lead to active labour and delivery. Once active labour has started, delivery might not be delayed for more than few days in humans because the changes, which occur in this preparatory phase, have by this time become well established and cannot be reversed, especially not with currently available tocolytics. Active labour, leading eventually to the delivery of the fetus and placenta, starts with the onset of coordinated uterine contractions. In our opinion, the key to understanding parturition and to developing suitable treatment methods is to understand the processes by which the myometrium and the cervix undergo these conditioning or conversion stages. Unfortunately, using currently available methods, including those that are based solely on monitoring contractions and manual cervical examination, cannot conclusively detect whether a patient has entered the conditioning step because changes in these variables may be independent of this preparatory stage, or may not become detectable by these methods until a relatively late and irreversible stage.

The diagnosis of labour is the most difficult and important task facing medical practitioners in maternity care today. Knowing that true labour that will lead to delivery has begun, as well as predicting when it will start, is important for both normal and complicated pregnancies. Prediction of labour in normal pregnancies is important for minimising unnecessary hospitalisations, interventions and expenses. On the other hand, accurate prediction and diagnosis of spontaneous preterm labour will also allow clinicians to start treatment early in women with true labour and avert unnecessary treatment and hospitalisation in women who are simply having preterm contractions, but who are not in true labour. Even cervical change may not be an accurate indicator of true labour, as a large percentage of women with established cervical change do not deliver preterm when not treated with tocolytics.[10]

While several techniques (described later) have been adopted to monitor labour, they are subjective and/or do not provide accurate diagnosis or prediction. To date, the most important key to preventing preterm labour has been constant contact and care from health care practitioners.[11]

Table 1b. The PPV peaks at four days prior to delivery, while the NPV increases only slightly as the measurement-to-delivery time increases from one to six days. The z value, AUC value and the best cutoff of the PDS peak frequency parameter are generally higher for preterm patients than for term patients.

MTD interval (days)	PPV	NPV	Sensitivity	Specificity	Cutoff	z	AUC	*P*
1	0.750	0.868	0.375	0.971	0.480	4.74	0.851	<0.001
2	0.714	0.486	0.556	0.939	0.463	5.86	0.884	<0.001
4	0.857	0.886	0.600	0.969	0.463	7.01	0.906	<0.001
6	0.818	0.903	0.750	0.933	0.446	6.79	0.890	<0.001

MTD = mean time to delivery.

The current state of labour monitoring can be summarised as follows:

1. methods are subjective and/or inaccurate;
2. intrauterine pressure catheters are limited by invasiveness and need for ruptured membranes;
3. uterine monitors are uncomfortable, inaccurate and/or subjective;
4. no currently used method has been successful at predicting preterm labour;
5. no currently used method has lead to effective treatment of preterm labour; and
6. no currently used method makes a direct measurement of both the function and state of the uterus or the cervix during pregnancy.

While a few methods can identify some of the signs of impending labour, none of the current methods offer objective data which accurately predict labour. The techniques range in complexity from simple patient self-awareness to complex electronic pressure sensors.

The identification of electrical activity in excitable tissue has been known for about 150 years. Recording of electrical depolarisations and repolarisations of contracting striated muscle has been around for over 100 years. More recently, smooth muscle has been monitored, leading to the investigation of uterine electrical activity.

Today, the electrocardiogram (ECG) is the most common, most versatile and generally the most efficient means of monitoring normal heart function[12] and in diagnosing a host of cardiac abnormalities including ischaemic heart disease, ventricular and supraventricular rhythms and other disease-related abnormalities. The diagnostic process involves careful evaluation of the recorded heart muscle signals, which involve the characteristic deflections (PQRST) in the voltage measured. These electrical signals give a direct quantitative measure of the ion changes in the heart tissue itself, and the analysis of the electrical recordings can determine if the heart is in a normal or abnormal state. Patients are then classified and managed accordingly.

The impact of the ECG on cardiac research and on medicine has been immense. So far, no diagnostic method has proven itself to be a better tool,[13] and this was all accomplished by analysis of the externally and non-invasively acquired electrical signals of the heart muscle during heart-muscle contractions.

In the same way, the uterine electromyography (EMG)—which, similarly, amounts to the acquisition of uterine electrical signals taken non-invasively from the abdominal surface—could benefit obstetrics when adopted by physicians, and when utilised as an everyday tool in the antenatal and labour wards and clinics. Similar to the function of the ECG for cardiac monitoring, uterine EMG can be used to monitor uterine electrical recordings in normal pregnancies, or to diagnose or even predict abnormal conditions such as preterm labour, insufficient labour progress and dystocia. The EMG would permit effective classification of women, based on uterine function, and would enable much better treatment and management of those women than any currently available tool. Uterine EMG signals are completely different in magnitude and configuration from heart ECG signals, and special methods have to be adopted to analyse them.

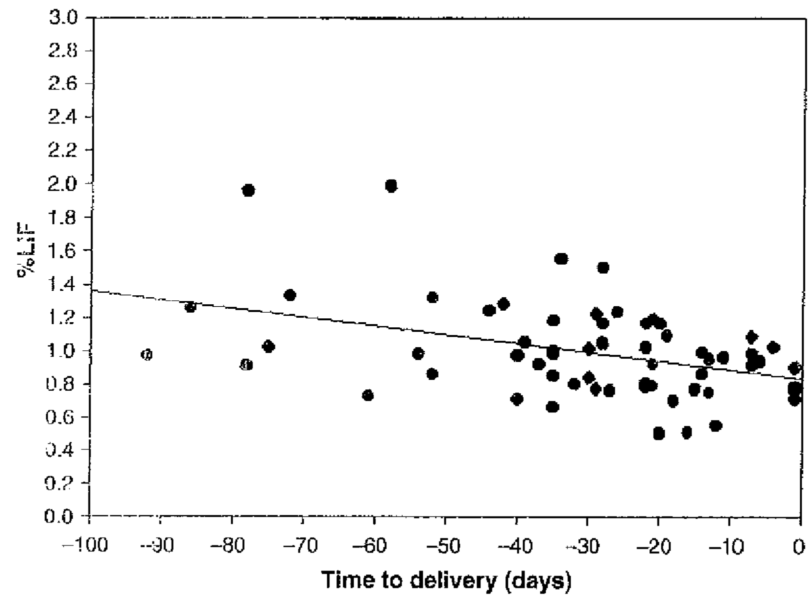

Fig. 3. In 13 patients measured variously at gestations from 24 to 40 weeks who had already delivered, a significant ($P < 0.05$) correlation ($R = 0.37$) was seen between the measurement to delivery interval and the LIF ratio.[17]

Fluorescence spectroscopy is a widely used research tool in biosciences, which reveals important information with respect to molecular and physical states.[14] Fluorescence spectra provide important details on the structure and dynamics of macromolecules and their location at microscopic levels. Fluorescence spectroscopy has been used to examine the collagen content of a variety of tissues including some cancers.[15] We have used this methodology to evaluate the cervix.

METHODS AND RESULTS

We performed human studies (Institutional Review Board approval was obtained, and studies were conducted in accordance with proper ethical standards), wherein a technique known as power spectrum analysis was performed on uterine electrical data from term and preterm women who presented with signs and symptoms of labour, but in whom differentiation between false and true labour could not be made clinically.[16] The average power density spectrum (PDS) peak frequency was determined for each woman and plotted against the woman's measurement-to-delivery interval (Figs 2A and B). Receiver operator characteristic (ROC) curves were generated for endpoints of 8, 12, 24 and 48 hours. Tables 1a and 1b show the results of the ROC analysis, including the corresponding positive and negative predictive values (PPV and NPV), respectively.

We concluded that labour and subsequent delivery can be predicted successfully using non-invasive uterine EMG.

One study involving cervical collagen was conducted to investigate gestational changes in cervical light-induced fluorescence (LIF), an index for cross-linked collagen, to estimate whether LIF correlates with the time-to-delivery interval and is predictive of delivery within 24 hours.[17] Twenty-one healthy gravidae without signs of labour had LIF measured approximately weekly during the last trimester. Overall, 13 of the women had already delivered by the time analysis was complete, and they were included in a correlation analysis for time to delivery. Additionally, 31 women, with inconclusive signs of labour, were assessed in the third trimester. Cervical LIF was obtained non-invasively using an instrument specifically designed for this purpose (Collascope). In the longitudinal group, LIF measurements negatively correlated with gestational age ($R = -0.340$; $P < 0.05$) and with time to delivery ($R = 0.370$; $P < 0.05$; $n = 13$; Fig. 3). In the women with inconclusive signs of labour, those who delivered within 24 hours of measurement had significantly lower LIF than those who delivered more than 24 hours from measurement (mean [SD]: 0.571 [0.413] *vs* 0.894 [0.228]; $P < 0.05$; Fig. 4). ROC analysis showed that LIF was predictive of delivery within 24 hours (area under ROC curve: 0.73; $P < 0.01$; sensitivity = 59%, specificity = 100%, PPV = 78.9% and NPV = 80.0%, at an LIF cutoff of 0.57).

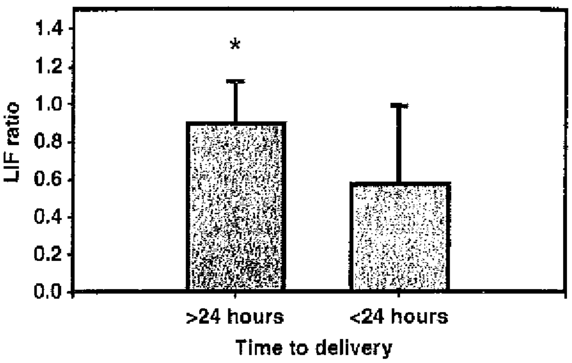

Fig. 4. In the 29 rule-out patients, a significant difference ($P < 0.05$) was seen between those delivering within 24 hours ($n = 19$) of cervical LIF measurement and those delivering more than 24 hours ($n = 12$) from cervical LIF measurement (mean [SD]: 0.571 [0.413] *vs* 0.894 [0.228]).[17]

We concluded from these studies that cervical LIF values decrease significantly as gestational age increases and are predictive of delivery within 24 hours.

DISCUSSION

From our studies as well as those of others, it is clear that in forecasting labour and delivery, the effectiveness of the technologies generally accepted into clinical practice are limited, especially in relation to sensitivity and PPVs, as compared with EMG and LIF.[18]

Of the currently used methods, intrauterine pressure catheters perhaps provide the best information concerning the state of the pregnancy, but the invasive nature of this procedure can increase the risk of infection or cause more serious complications. Such infections could be a risk factor for preterm labour.[19] No real predictive capability exists for intrauterine pressure catheter devices because they are mainly used in cases where labour has already been diagnosed clinically, which is why they do not appear in the table discussed earlier.

External tocodynamometer monitoring devices are used in over 90% of all hospital births. Physicians have been quick to adopt these devices because they supply uterine contraction data with little risk. Most agree that these devices provide limited information on labour and that they are dependent on the skills of the examiner. These instruments have not changed treatments or improved outcomes following preterm labour. Generally, these instruments cannot be used to predict true preterm labour.

Tocodynamometer devices are also inaccurate. Many different variables affect the pressure measurement, such as instrument placement, amount of fat and uterine wall pressure. In addition, tocodynamometry of uterine contractions is equivalent to measuring cardiac contractions and heart function with a contraction transducer placed on the chest. The amount of information about normal and abnormal muscle contraction can never be achieved with these devices.

Home uterine activity monitoring (HUAM), based on external tocodynamometer recordings, has been used in an effort to predict spontaneous preterm labour and decrease the frequency of preterm birth.[20] However, HUAM has been shown to be no better in lowering the frequency of preterm birth than weekly contact with a nurse.[21] The lack of significant clinical usefulness of HUAM is related to the inability to differentiate between false and true contractions.

Measuring the length of the cervix via endovaginal ultrasonography has been used to detect spontaneous preterm labour[22,23] with some degree of success. Even in combination with other factors, with respect to positive predictive capabilities, there is a range of possible predictive values, from 50% to 71%. These are obtained only after the onset of symptoms of spontaneous preterm labour, so the method is limited in its potential for diagnosis and treatment.

Cervicovaginal fetal fibronectin (FFN) has recently been suggested as a screening method for women at risk of spontaneous preterm labour. Several studies[24,25] have shown that FFN might be of benefit predict spontaneous preterm labour, but other studies indicate that FFN has limited value.[26] The value of the FFN assay lies in its high NPV (i.e. it has the ability to identify patients that are not at risk of spontaneous preterm labour and preterm birth).

CONCLUSION

We believe that physicians can now begin to use the uterine EMG and cervical LIF instruments to their advantage and to the benefit of pregnant women in their own clinics. With refinements, these tools could be used routinely with little or no training of the clinician. Considering the need for, and benefits of, this technology, better patient management and classification might lead to a reduction in perinatal mortality and morbidity.

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