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Biophysical methods of prediction and prevention of preterm labor: uterine electromyography and cervical light-induced fluorescence – new obstetrical diagnostic techniques

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INTRODUCTION

Development of effective means to prevent or reduce the occurrence of preterm delivery depends upon the understanding of the conditions that initiate labor. Successful labor is dependent upon forceful uterine contractions, and softening and dilation of the cervix. It is widely accepted that pharmacological control of uterine contractility, and cervix function would allow better management of patients who are in premature labor, or even in term labor.¹ However, to develop a rational approach to the control of either uterine activity or cervical changes associated with labor, a thorough understanding of the underlying mechanisms which regulate uterine contractility and cervical connective tissue is important. Paramount for the appropriate management of labor is the ability to correctly identify true versus false labor. No clinical methods currently exist to objectively evaluate the state and function of the uterus or cervix during pregnancy.

Preparatory phase to labor

In the past, labor was viewed as the transition from an inactive to an active uterine muscle either by the addition of an uterotonic or withdrawal from tonic progesterone inhibition.² Although those models recognized the importance of progesterone in controlling uterine quiescence, they neither defined precisely the uterine stages of labor nor identified the mechanism of action of the hormones involved. Such models of parturition

did not usually consider the changes in the cervix as an important component of parturition. Experimental and clinical studies with progesterone and its antagonists indicate, however, that parturition is composed of two major steps: a relatively long conditioning (preparatory) phase, followed by a short secondary phase (active labor) (Figure 12.1).^{3,4} The conditioning step leading to the softening of the cervix takes place in a different time frame from the conditioning step of the myometrium, indicating that the myometrium and cervix are regulated in part by independent mechanisms.

Labor

The processes governing changes in the myometrium and cervix ultimately become irreversible, and lead to active labor and delivery. However, there may be a point at which the cervix and uterus are electrochemically and physically prepared for delivery, but during which time there are not effective contractions, nor perceptible dilation. It is during this critical 'interim' phase that there exists the final opportunity to effectively treat the uterus or cervix with tocolytics (in order to prevent preterm labor) by halting, or at least delaying, the process.

After this interim period, which may be exceedingly short, it could be that the uterus is hormonally stimulated to contract (or alternatively freed from inhibition to contract) and the cervix will dilate as a result. Once true active labor has started, delivery might not be delayed for more than a few days in humans because

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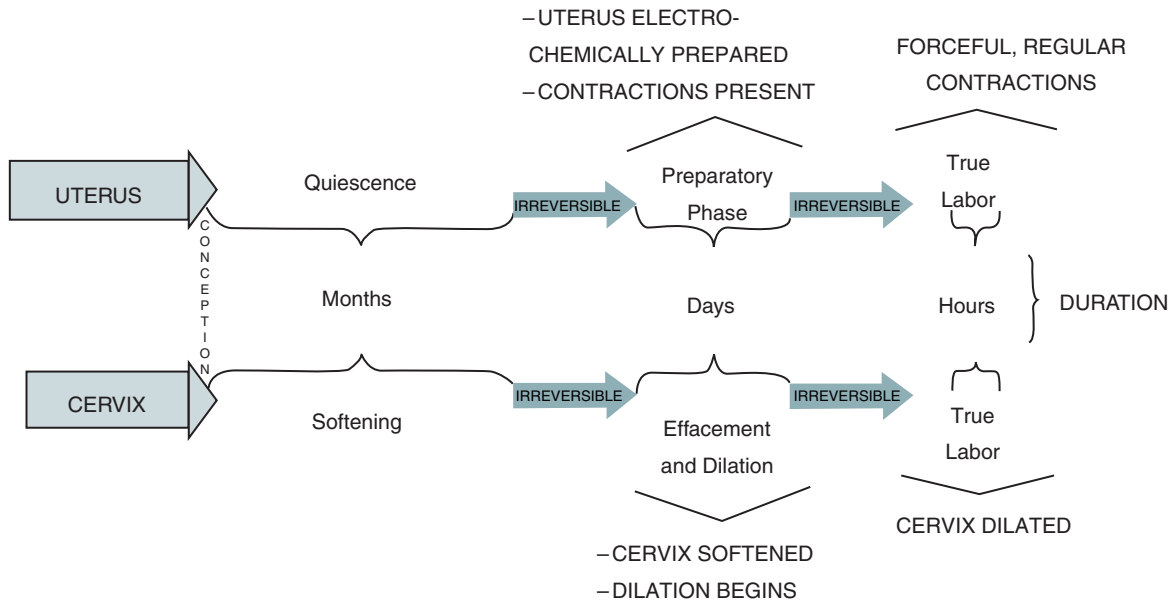


Figure 12.1 A model for the comparison of uterine and cervical evolution through normal parturition (with term delivery). Both organs are regulated by hormonal changes and can be said to exhibit a preparatory phase and a true labor phase. The time period over which the preparatory phase occurs is the primary differing point between the two processes. Note that some phases can be altered with treatments while others presumably cannot. Similarly, some transitions between stages are irreversible.

the changes, which begin in the preparatory phase and culminate with true labor, have by this time become well established and cannot be undone (i.e. irreversible), even with currently available tocolytics. 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, conversion or preparation stages.

Uterus

It has been 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, and so furnishes pathways for the efficient conduction of action potentials. During the greater part of pregnancy, these cell-to-cell channels or contacts are low, causing poor coupling and decreased electrical conductance. This produces quiescence of the muscle for the maintenance of pregnancy. However, at term, cell junctions increase and form an electrical syncytium for producing effective, forceful contractions. The presence of the contacts is controlled by changing estrogen and progesterone levels in the uterus.⁵

As action potentials propagate over the surface of a myometrial cell, the depolarization causes voltage-dependent Ca^{2+} channels (VDCC) to open. Thereafter, Ca^{2+} enters the muscle cell, traveling down its electrochemical gradient to activate the myofilaments, and provokes a contraction. Our research group has demonstrated by reverse transcription polymerase chain reaction (RT-PCR) that the expression of VDCC subunits in the rat myometrium increases during term and preterm labor.⁶ The increased expression, which appears to be controlled by progesterone, likely facilitates uterine contractility during labor by increasing portals for Ca^{2+} entry.

Cervix

The composition of the cervix is in the form of smooth muscle (approximately 10%) and a large component of connective tissue (90%), which consists of collagen, elastin and macromolecular components which make up the extracellular matrix.⁷ A number of biochemical and functional changes occur in cervical connective tissue at the end of pregnancy.⁷⁻⁹ Cervical ripening is a process of softening, effacement, and finally dilatation of the cervix, and is required for appropriate progress

of labor and delivery of the fetus. It is known that the collagen cross-link, pyridinoline, decreases as the cervix softens. Developing a measure of this system would be useful for monitoring the state and function of the cervix generally.

Physiological cervical ripening is an active biochemical process, which involves connective tissue remodeling,⁸ but the mechanism behind this process is not completely understood. Eighty percent of cervical protein is collagen, and 70% of that is in the form of type I collagen and 30% type III collagen.¹⁰ Studies on tissue biopsies have shown that near the end of gestation, and during cervical dilation, the collagen concentration per wet weight is decreasing, the fraction of insoluble collagen shifts towards soluble collagen, and the collagenolytic activity is enhanced in the tissue.¹⁰⁻¹³ Electron microscopic investigations show a dissociation and breakdown of collagen fibers.^{10,14,15} Little is known about the physiological mediators of cervical ripening. Some investigators suggest the mediators of cervical ripening involve an inflammatory process, and have demonstrated leukocyte infiltration, cytokine activation and prostaglandin (PG) release in the collagen tissue.^{10,11,16,17}

Since the exact physiologic mechanism for cervical ripening remains obscure, the action of pharmacologic ripening agents is not entirely clear. PG is widely and successfully used to induce cervical ripening prior to labor induction, but again, the process by which this is accomplished is still unclear. Studies on cervical biopsies from women after PG application demonstrate similar changes in cervical connective tissue as described under physiological ripening, and include an increase in water content, collagenolytic activity, collagen solubility and large proteoglycans.¹⁸⁻²¹

Uterine electromyography (EMG)

Uterine EMG is similar to recording an electrocardiogram (ECG) for heart muscle,^{22,23} and amounts to the acquisition of uterine electrical signals taken noninvasively from the abdominal surface (Figure 12.2). Once adopted by physicians, the EMG methodology could benefit obstetrics in much the same way as the ECG benefits cardiology, when utilized as an everyday tool in the perinatal and labor and delivery clinics. Like the function of the ECG for heart-patient monitoring and classification, the capability of the uterine EMG in utilizing electrical recordings for monitoring contractions in normal pregnancies (Figure 12.2) – as well as for diagnosing or even predicting abnormal conditions such as preterm labor, insufficient labor progress and dystocia, and a host of other problems during parturition – would allow for a timely and effective classification of patients.

EMG is based on the actual function of the uterus, and would enable better treatment and management of those patients than with any currently used tool.

This can be accomplished by analyzing several different types of electrical parameters derived from the recorded raw uterine electrical signals, including the power density spectrum (PDS)²⁴ or wavelet transform,^{25,26} either of which will decompose electrical signals into their individual frequency or ‘scale’ subcomponents. Also, nonlinear signal analysis methods, such as chaoticity or fractal dimension,²⁶ may be implemented. These types of mathematical functions and transforms allow the uterine electrical signal to be quantified. Receiver-operator-characteristics (ROC) curves can then be used to find the best cut-off values and endpoints to use for patient classification or prediction of labor.

Cervical light-induced fluorescence (LIF)

Examination of LIF is a widely utilized research technique in the biosciences, primarily due to the amount of information that it can reveal in terms of molecular and physical states.²⁷ Fluorescence spectra offer important details on the structure and dynamics of macromolecules, and their location at microscopic levels. LIF has been used to examine collagen content in a variety of tissues, including changes in collagen content in cancers.²⁸ This methodology has been used recently to evaluate the cervix (Figure 12.3).

Investigations into the changes in cervical collagen during pregnancy have been noninvasively performed by using the natural fluorescence of collagen. Mature collagen possesses nonreducible hydroxyallysine-based intermolecular cross-links within the primary²⁹ and secondary structures of collagen fibrils³⁰ which fluoresce. The greater the amount of collagen in the tissue, the higher the LIF level measured, and therefore the less ripe is the cervix. Near labor and delivery LIF levels are at a minimum, suggesting the possibility of classification of pregnant patients into those who are or are not in true labor, as well as predicting the time of delivery of the fetus. As with the quantified uterine EMG, ROC analysis provides insight into just exactly what are the best cervical LIF cut-off values and measurement-to-delivery time endpoints for consideration. This cervical-assessment methodology, as in the case of uterine EMG, has been shown to be effective in the classification of patients, and in the prediction of labor and delivery.

BENEFITS OF DIAGNOSIS

Diagnosing labor may be the most important (and perhaps the most difficult) task facing obstetricians today.

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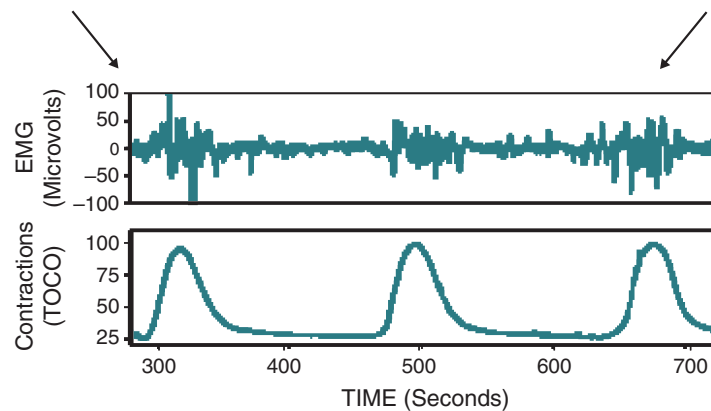


Figure 12.2 The typical uterine electromyography (EMG) setup consists of electrodes placed near the navel close to the midline (which has been determined to yield, generally, the best conduction path from the myometrium to the surface, likely because subcutaneous tissue is thinnest here, especially in late pregnancy). The electrode sites are first prepared by removing excess oils with alcohol, and then by applying a conductive gel. The electrodes are connected to lead wires and cables which pass the uterine EMG signals on to an amplifier/filter. The uterine EMG signals are then displayed on a monitor and stored in a computer for later analysis. Real-time analysis routines are currently being developed to yield a predictive measure while the patient is still being monitored. The tracings at the bottom show the correspondence of uterine EMG burst events to contraction events recorded by tocodynamometer (TOCO) from a laboring patient. The action potentials, as measured by uterine EMG, are actually responsible for the contractions of the uterus, and govern such characteristics as contraction strength, duration, and frequency. The TOCO provides to clinicians only the number of contraction events per unit time and a crude, inaccurate measure of contraction force. Recent studies indicate that the TOCO possesses no objective predictive capability. By contrast, in addition to the number of contraction events per unit time, the uterine EMG signals give critical information about the firing rate and number of action potentials involved during a contraction. As such, the uterine EMG gives a direct measure of the state of myometrial development and preparedness for labor and delivery.

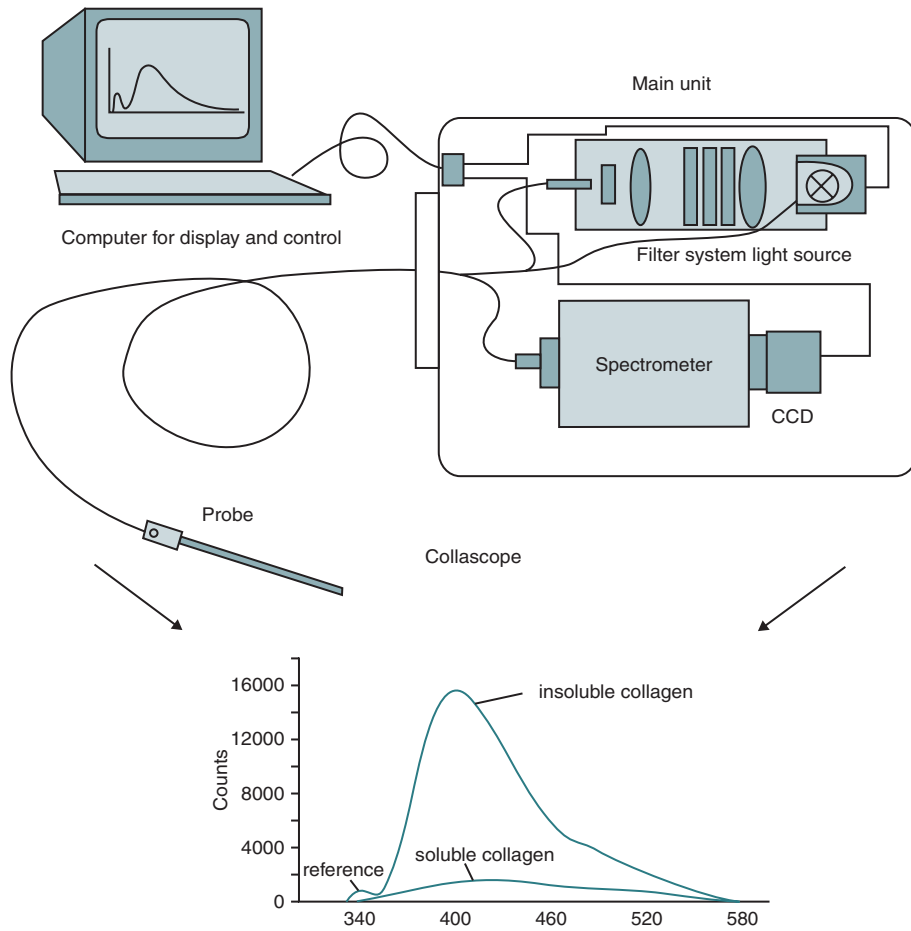


Figure 12.3 Schematic of the collascope, a device built specifically to measure cervical light-induced fluorescence, (LIF). The excitation light source provides light of the proper frequency to elicit fluorescence from cervical collagen pyridinium cross-links, a component which decreases as gestational age increases. The amount of fluorescence produced is proportional to the amount of collagen in the cervix, thereby giving a direct measure of cervical ripeness. The excitation light is applied to the cervix, and fluorescence light is collected from the cervix, via the hand-held probe. The fluorescent light is then separated into frequency components by a spectrometer, and intensity is measured. The results are displayed on a computer screen and stored for later analysis. The trace at the bottom shows the fluorescence spectrum of samples of soluble and insoluble collagen, as measured by the collascope. The LIF ratio value, of the cervix for example, is calculated by taking the peak fluorescent value (which occurs at a wavelength of approximately 390 nm) and dividing by the peak reference value (which occurs at a wavelength of approximately 343 nm). The LIF ratio has been found to be highly predictive of labor in various species, including humans.

Pinpointing exactly when true labor exists – which will lead to delivery – is important for both normal and pathological pregnancies. Predicting labor in normal pregnancies is important for minimizing unnecessary hospitalizations, interventions, and expenses; while accurate prediction and diagnosis of preterm labor will allow practitioners to start treatment earlier in those patients who need it, and avert unnecessary treatment and hospitalization in

patients who are having preterm contractions but who are not in true labor. Unfortunately, currently available methods, including those that are based solely on monitoring contractions or on cervical examination, cannot conclusively detect whether a patient has entered the preparatory, or conditioning, phase of parturition, because changes in these variables may be independent of the preparatory stage, or may not become detectable by

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these methods until a relatively late and inalterable stage has been reached.

WHAT'S OUT THERE NOW – THE CURRENT STATUS OF PARTURITION MONITORING

While several techniques have been adopted to monitor labor, they are either subjective, or do not provide a sufficiently accurate diagnosis or prediction, or both.^{31–41} To date, the most important factor for preventing preterm labor has been constant contact and care from health care practitioners.⁴²

The applied state-of-the-art in labor monitoring is as follows:

- Present uterine monitors are uncomfortable, inaccurate and/or subjective
- Intrauterine pressure catheters (IUPC) are limited by invasiveness, potential for infection, and the need for ruptured membranes
- No currently used method has consistently/reliably predicted preterm labor
- No currently used method has led to effective treatment of preterm labor
- No currently used method makes a direct measurement of both the function and state of either the uterus or the cervix during pregnancy

Multiple preterm labor symptoms are one currently adopted method for monitoring the state of pregnancy in an effort to predict preterm labor (Table 12.1). Such symptoms include cervical dilation and effacement, vaginal bleeding, and ruptured membranes. These signs are determined by a clinician.

Maximal uterine contractions represent the highest observed number of contraction events seen in any 10 min period. This is assessed by a clinician using a tocodynamometer (TOCO). Most physicians agree that these bulky force-transducer devices provide limited information on labor. Contractions measured with the TOCO can be large or small, and can occur with a similar number of contractions per unit time, regardless of whether the patient is in labor or not. The instruments are largely dependent upon the skill of the clinician, but have not changed treatments or improved outcomes following preterm labor.

The Bishop scoring method was introduced as a means of evaluating the cervix in relationship to successful induction. This scoring system attempts to predict the success of induction by assessing five factors: position of the cervix in relation to the vagina, cervical consistency, dilation, effacement, and station of the presenting part. The higher the score, the higher is the rate of success of the induction. A score less than five indicates an unfavorable cervix for induction.

Measuring the length of the cervix via endovaginal ultrasonography has been used to detect premature labor with some degree of success. However, even in combination with other factors, especially with respect to positive predictive capabilities, there is quite a range of possible predictive values (50–71%), and these are obtained only after the onset of preterm labor symptoms, so the application is limited, as is the potential for treatment upon diagnosis using this method. Furthermore, the measurement of the cervical length is made unreliable by varying amounts of urine in the bladder. This throws considerable doubt on the entire procedure.

Table 12.1 Methods to monitor the state of pregnancy used to try to predict preterm birth

Tests	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
Multiple preterm labor symptoms	86.4	50.0	63.5	21.4
Maximal uterine contractions (TOCO)	84.7	6.7	92.3	25.0
Bishop score	32.0	91.4	42.1	87.4
Cervical length (ultrasound)	88.8	40.8	89.5	42.6
Fetal fibronectin (fFN)	18.0	95.3	42.9	85.6
Salivary estriol	71.0	77.0	66.0	84.0
Uterine electromyography (EMG)	75.0	93.3	81.8	90.3
Cervical light-induced fluorescence (LIF)	59.0	100.0	78.9	80.0

For the first six columns, please see refs 31–41; for uterine EMG and cervical LIF, please see refs 51 and 56, respectively.

In the fetal fibronectin (fFN) test for preterm labor, the practitioner places a speculum in the vagina and takes a sample of cervical secretions with a cotton swab. When analyzing the sample, technicians look for fFN, a protein produced by the fetal membranes that serves as the 'glue' that attaches the fetal sac to the uterine lining. This protein is normally found in the vagina during the first half of pregnancy, but if it leaks out of the uterus and shows up there after 22 weeks, that means the 'glue' may be disintegrating ahead of schedule (due to contractions, an injury to the membranes, or normal softening of the membranes).

Estriol level is a very recently proposed test for preterm labor. Estriol starts to appear in the ninth week of pregnancy, and its plasma concentration continues to increase throughout parturition. Estrogens directly affect myometrial contractility, modulate the excitability of myometrial cells, and increase uterine sensitivity to oxytocin. Plasma and salivary estriol levels both peak 3–5 weeks prior to labor in term deliveries as well as in preterm births. Estriol concentration in saliva very closely measures the free estriol concentration in plasma.

Of the currently used methods, IUPC perhaps provides 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 labor. At any rate, no real predictive capability exists for IUPC devices, since they are mostly applied only in the cases where labor has already been diagnosed clinically, which is why they do not appear in the Table 12.1.

Although a few of these methods can identify some of the indirect signs of oncoming labor, none of the current methods offer objective data that accurately predict labor over a broad range of patients. Again, this is probably because none of the currently used methods provide direct information about the function and state of the cervix or uterus. In contrast, the uterine EMG and cervical LIF technologies provide both, and the comparative results are demonstrated in Table 12.1.

UTERINE ELECTROMYOGRAPHY (EMG) AND CERVICAL LIGHT-INDUCED FLUORESCENCE (LIF) STUDIES – AN OVERVIEW

Uterine EMG

There are two commonly used methods to acquire uterine EMG signals abdominally: directly from the uterus via needle electrodes through the abdomen and noninvasively through the use of abdominal-surface electrodes. The earliest uterine EMG studies established that the

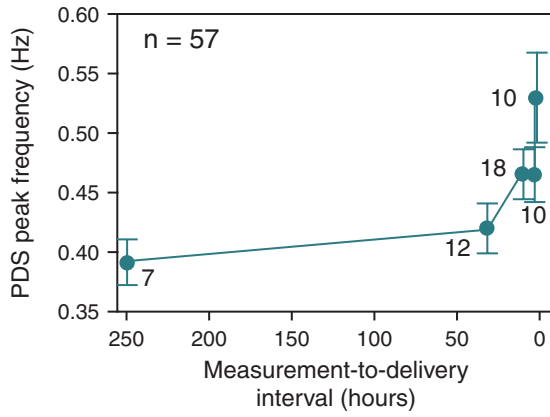
electrical activity of the myometrium is responsible for its contractions.^{43,44} Extensive studies have been done over the past 60 years to monitor uterine contractility using the electrical activity measured from needle electrodes placed on the uterus.^{45–47} This method, of course, has the advantage of providing electrical data directly from the uterus, but has the disadvantage of being invasive and, hence, less desirable. However, more recent studies indicate that uterine EMG activity can be monitored accurately from the abdominal surface.^{48–50}

It has also been established that the uterine electrical signals can be quantified sufficiently with mathematical functions and transforms such as power spectral analysis, so that it is possible to evaluate the state of the uterus for predicting delivery.⁵¹ Experiments have been done to determine whether delivery can be predicted using transabdominal uterine EMG. In one case, a total of 99 patients were grouped as either term delivering (≥ 37 weeks, $n = 57$) or preterm delivering (< 37 weeks, $n = 42$), and uterine EMG was recorded for 30 min in the clinic. Uterine EMG 'bursts' were evaluated to determine the PDS. Measurement-to-delivery time was compared with the average PDS peak frequency. ROC curve analysis was performed for 48, 24, 12, and 8 h from measurement to term delivery, and 6, 4, 2, and 1 day(s) from measurement to preterm delivery.

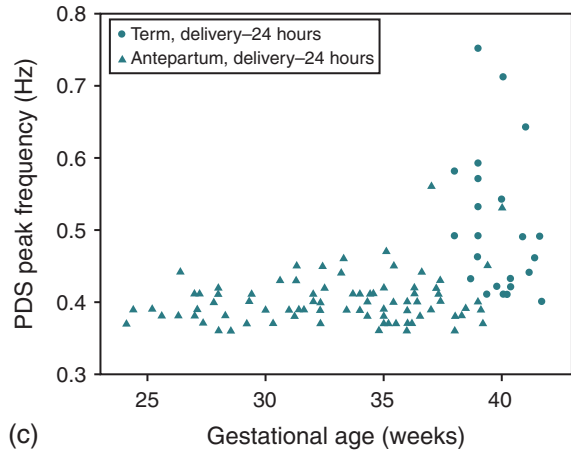
From the analysis, the PDS peak frequency is observed to increase as the measurement-to-delivery interval decreases in both the term (Figure 12.4a) and preterm (Figure 12.4b) groups. ROC curve analysis gives high positive and negative predictive values (PPV and NPV, respectively) for both term and preterm delivery. For term-delivering patients, the maximum overall predictive capability (PPV+NPV) seems to occur at around 24 h from measurement to delivery, with PPV = 85.4% and NPV = 88.9%, and $P < 0.01$. On the other hand, for preterm-delivering patients, the maximum overall predictive capability (PPV+NPV) apparently occurs at around 4 days (96 h) from measurement to delivery, with PPV = 85.7% and NPV = 88.6%, and $P < 0.001$. For term-delivering patients, the average PDS peak frequency is significantly higher for the ≤ 24 h-to-delivery group than for the > 24 h-to-delivery group. For preterm-delivering patients, the average PDS peak frequency is significantly higher in the ≤ 4 days-to-delivery group than in the > 4 days-to-delivery group ($P < 0.05$).

The purpose of another study was to compare uterine EMG of antepartum patients delivering > 24 h from measurement with that of laboring patients delivering < 24 h from measurement.⁵² Fifty patients (group 1, labor, $n = 24$; group 2, antepartum, $n = 26$) were monitored using transabdominal electrodes. Group 2 was recorded at several gestations. Uterine electrical 'bursts' were analyzed by

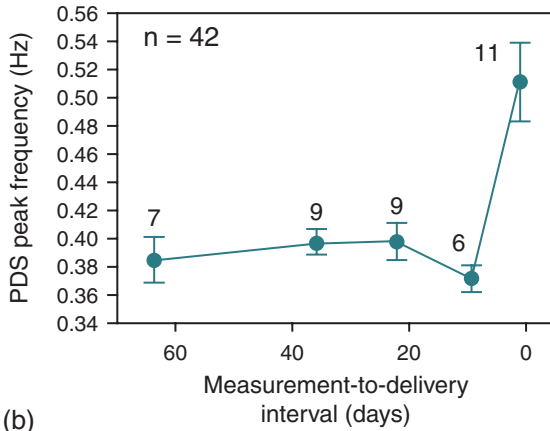
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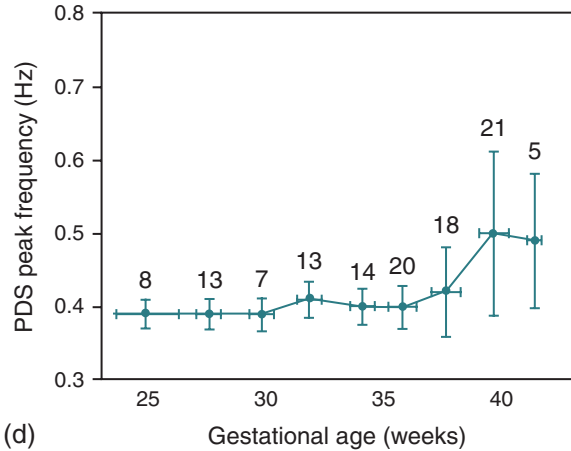
(a)



(c)



(b)



(d)

Figure 12.4 (a) and (b) A rapid increase in uterine electromyography (EMG) action potential frequency was seen in both term- and preterm-delivering patients. For patients delivering spontaneously, this increase occurs about 1 day prior to delivery in term-delivering patients ($n = 57$), and about 4–6 days prior to delivery in preterm-delivering patients ($n = 42$). Such a change in uterine EMG characteristics can be used to predict the time of delivery with a high degree of success. Note that in these two plots, the number of patients at each time-point is indicated. (c) and (d) An increase in uterine EMG occurs at term (for patients delivering spontaneously at term), especially for patients considered to be in labor. This transition from generally low to high uterine EMG action potential frequencies can be used to discern between those patients who are in true labor and those who are not.

power spectrum from 0.34 to 1.00 Hz. The average PDS peak frequency for each patient was plotted against gestational age, and compared between group 1 and group 2. Frequency was partitioned into 6 bins, and associated burst histograms compared.

These experiments reveal a general increase in uterine electrical frequency content as gestational age increased (Figure 12.4c and d), especially at term and near delivery, and that group 1 is significantly higher than group 2 for gestational age (39.87 ± 1.08 versus

32.96 ± 4.26 weeks) and average PDS peak frequency (0.51 ± 0.10 versus 0.40 ± 0.03 Hz). Histograms are also significantly different between the groups, with a tendency to see a greater number of high-frequency events in the labor group. For PDS versus gestation, a correlation coefficient of 0.41, with significance, is seen.

A further investigation was conducted to determine whether the strength of uterine contractions monitored invasively by IUPC could be acquired noninvasively using transabdominal EMG, and to estimate whether

EMG is a better predictor of true labor compared to TOCO.⁵³ Uterine EMG was recorded from the abdominal surface in laboring patients simultaneously monitored with an IUPC ($n = 13$) or TOCO ($n = 24$). Multiple IUPC-measured contraction events per patient, and their corresponding uterine electrical bursts, were randomly selected and analyzed (integral of the pressure curve for intrauterine pressure; integral, frequency, and amplitude of contraction curve for TOCO; and burst energy for EMG). The Mann-Whitney test, Spearman correlation, and ROC analysis were used as appropriate (significance was assumed at a value of $P < 0.05$).

From that study, it is seen that uterine EMG energy correlates strongly with intrauterine pressure ($r = 0.764$; $P < 0.005$). Uterine EMG burst energy levels are significantly higher in patients who deliver within 48 h compared to those who deliver later [median (25%/75%), 96 640 (26 520–322 240) versus 2960 (1560–10 240), $P < 0.001$], whereas none of the TOCO parameters are significantly different. In addition, burst energy levels are highly predictive of delivery within 48 h (area under the ROC curve: $AUC = 0.9531$, $P < 0.0001$) as assessed by ROC analysis.

Cervical LIF

Previous studies demonstrate that the cross-link molecules, hydroxylysyl-pyridinoline and lysyl-pyridinoline, both of which are found in the cervix, have a natural LIF^{29,30} at 390 nm when excited with a 339 nm wavelength light source.⁵⁴ Figure 12.3, in addition to showing a schematic of the collascope instrument, also depicts the spectrum from pure insoluble and soluble collagen type I. Soluble collagen has fewer cross-links and therefore smaller LIF values than insoluble collagen. In rats and guinea pigs, it was previously shown that cervical ripening could be monitored by measuring the changes in the LIF value of cervical collagen.^{54,55}

It has recently been determined that LIF can also be used to observe cervical ripening in pregnant women approaching delivery, and for prediction of the measurement-to-delivery interval.⁵⁶ The purpose of that study was to investigate gestational changes of cervical LIF, and the relationship between LIF and the measurement-to-delivery interval. Fifty patients were included in one of two groups: group 1, 21 healthy pregnant women without signs of labor underwent repeated cervical LIF measurement during the last trimester; group 2, LIF was measured in 29 patients with signs of labor, and the time from measurement to delivery was noted. Cervical LIF was obtained noninvasively with a prototype instrument that was designed specifically for this purpose (collascope). The Spearman correlation, Student *t*-test and ROC analysis were performed ($P < 0.05$).

From this investigation, it is now known that: LIF correlates negatively with gestational age and positively with the measurement-to-delivery interval, is significantly lower in patients who deliver <24 h from measurement compared with those patients who deliver >24 h from measurement (Figure 12.5a); and is predictive of delivery within 24 h (using an LIF cut-off value of 0.57, sensitivity is 59%, specificity is 100%, and PPV and NPV are 100 and 63%, respectively, $P < 0.01$, and AUC is 0.73).

Other work on LIF has sought to define the changes in cervical LIF, after the use of locally applied PG

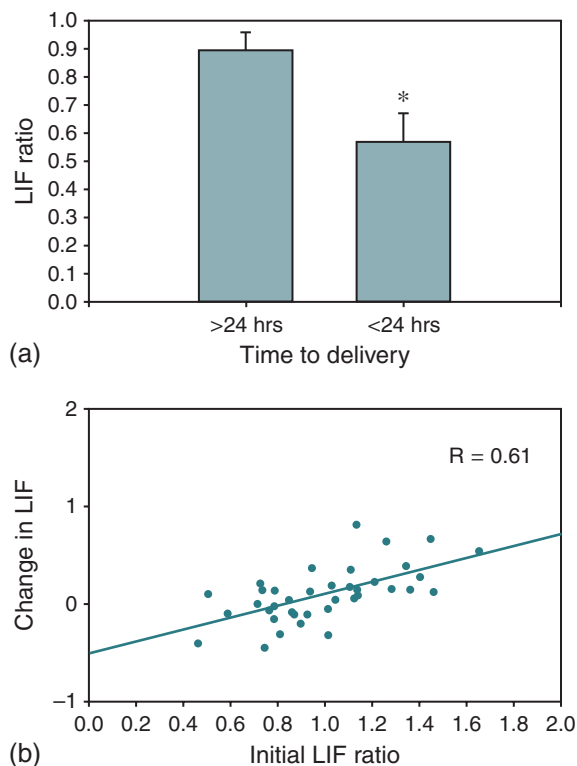


Figure 12.5 (a) The light-induced fluorescence (LIF) ratio is significantly lower ($P < 0.05$) in patients delivering within 24 h of measurement as compared to patients who deliver >24 h from measurement. The lower cervical LIF value indicates the presence of a more ripened cervix. Using receiver-operator-characteristics (ROC) curves with this parameter results in high positive and negative predictive values. (b) A significant correlation ($P < 0.05$) was found between the initial LIF-ratio value and the change in the LIF ratio value after treatment with prostoglandian (PG). This shows that it may be possible to identify which patients are most likely to benefit from such treatments.

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preparations for labor induction at term and the correlation between LIF and the Bishop Score.⁵⁷ The characteristic LIF of cervical collagen was measured from the surface of the cervix, again using a specially designed instrument (collascope) in 41 gravidas undergoing labor induction at term by PG. LIF and the Bishop score were obtained directly before (and then again 4 h after) the administration of PG. The paired Student's t-test, Wilcoxon signed rank test, linear regression, Spearman correlation and Fisher exact tests were used as appropriate.

It has been established from this work that the cervical LIF decreases significantly after PG application [0.982 ± 0.04 (before) to 0.885 ± 0.037 (after), $P = 0.025$]. The decrease in LIF correlates with the initial LIF before PG application ($P = 0.61$; Figure 12.5b). The Bishop score increased in all 41 patients. However, no correlation is seen between LIF versus the Bishop score.

RECENT PILOT EXPERIMENTS

Uterine EMG

Some of our most recent uterine EMG pilot work includes a test of the hypothesis that uterine EMG activity recorded from the abdominal surface of women with preterm contractions is highest in women with failure of tocolysis. Uterine EMG activity was recorded with bipolar electrodes placed on the abdominal surface in 17 pregnant women with preterm contractions. All measurements were done before the initiation of any treatment. Ten women received either $MgSO_4$, indomethacin, or terbutaline for tocolysis. Three out of the 10 delivered within 7 days (group 1), and seven women delivered >7 days after measurement (group 2). Seven additional women were not treated with tocolytics (group 3). Uterine EMG signals were acquired at 100 Hz and band-pass filtered from 0.05 to 4.00 Hz. Electrical bursts were randomly selected and the frequency of the PDS peak in the 0.34–1.00 Hz region was determined using power spectrum analysis. One-way analysis of variance (ANOVA), Bonferroni post-hoc test, and Pearson's correlation were used for statistical analysis (significance $P < 0.05$).

In this study, the gestational age at measurement was not significantly different between the groups. Uterine EMG PDS peak frequency within bursts was significantly higher (Figure 12.6) in group 1 (0.55 ± 0.14 Hz) compared to group 2 (0.40 ± 0.03 Hz), ($P = 0.011$) and group 3 (0.39 ± 0.03 Hz), ($P = 0.006$). Group 2 and 3 were not significantly different. Gestational age at delivery was lower in group 1 (207 days) compared to group 2 (246 days) and group 3 (262 days), but the difference was statistically significant only between group 1 versus group 3 ($P = 0.031$).

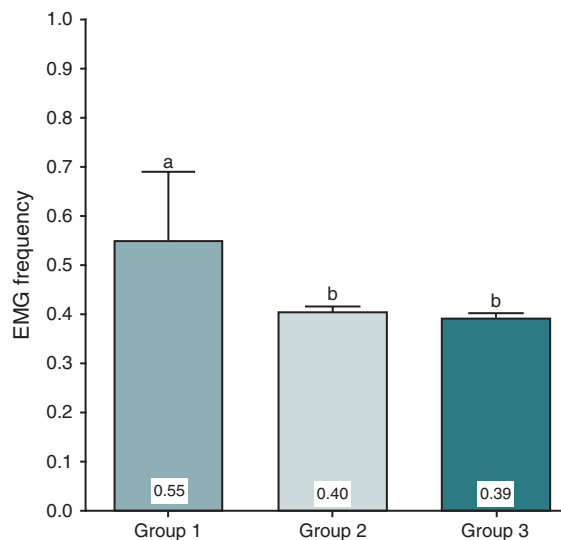


Figure 12.6 For those patients who were treated with tocolytics but who still delivered within 7 days (group 1), the uterine electromyography (EMG) action potential frequency was significantly higher ($P < 0.05$) than in patients who were treated with tocolytics and did not deliver within 7 days (group 2). The latter value was also comparable to that of patients who had low uterine EMG activity and did not require tocolysis (group 3). This indicates that once the uterus is electrochemically prepared for forceful contractions to deliver, current tocolytics may not be effective. The results of this study also indicate the possibility of using uterine EMG to identify those patients who may benefit from tocolysis and those who likely will not.

In another exploratory study, our objective was to determine whether using two EMG parameters together, in a derived multivariate expression, achieves better results than implementing either one alone. Uterine EMG was recorded with abdominal-surface electrodes for 30 min (at 100 Hz in 0.34–1.00 Hz range) from 22 pregnant 'rule-out' patients (gestation 29–41 weeks; contractions but no definitive clinical evidence of true labor). 'Bursts' of uterine activity were analyzed using power spectrum analysis to determine burst total power (P_o) and burst power spectrum peak frequency (F). Measurement-to-delivery time was noted. Patients were divided into two groups: those delivering within 24 h of measurement (G1) and those delivering >24 h from measurement (G2). ROC curves were generated for delivery within 24 h of measurement using P_o and F individually, and also when combined (C) in the multivariate parameter $C = P_o^{0.25} \times F^4$. Positive and negative predictive values (i.e. PPV and NPV), Z, and AUC were all calculated. The Student t-test was used

to compare means of G1 and G2, and True Epistat was used to compare areas under ROC curves ($P, Z < 0.05$ was considered significant).

The mean value for C was significantly higher for G1 than G2 (Figure 12.7). Po, F, and C were predictive of delivery within 24 h (Po: PPV = 0.58, NPV = 0.90, $Z = 2.04$, and AUC = 0.72; F: PPV = 0.83, NPV = 0.81, $Z = 5.33$, and AUC = 0.88; C: PPV = 0.88, NPV = 0.93, $Z = 9.21$, and AUC = 0.95). Statistical comparison of ROC curves showed that C had significantly higher AUC than Po alone, and C gave higher PPV, NPV, and Z values than either Po or F alone.

Cervical LIF

In one of our recent studies, we used the collascope to examine patients with cervical insufficiency (CI). Significantly lower LIF-measured collagen was found in those patients with CI who required a cerclage. LIF in the cervical insufficiency group at 12–25 weeks of gestation was lower than in groups of patients at later times in gestation.

In another investigation, cervical LIF was measured in 10 patients with CI, in 12 pregnant women (second

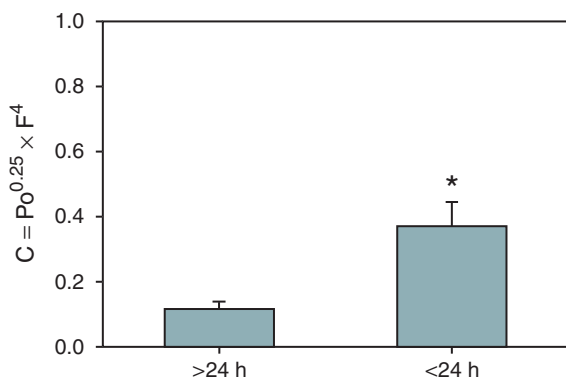


Figure 12.7 Multiple uterine electromyography (EMG) parameters, such as total burst power (Po) and action potential frequency (F), are generally more predictive of labor (in patients delivering spontaneously at term, for example) than are either of the parameters used alone. The values for C in the multivariate expression $C = Po^{0.25} \times F^4$ were significantly higher ($P < 0.05$) for patients delivering within 24 h of measurement as compared to those patients delivering >24 h from measurement. Note that the exponents in the expression were chosen according to the scale of the two independent variables, and in such a way as to insure that changes in one independent variable were equally weighted (with respect to change in C) as were changes in the other independent variable.

trimester, 23–26 weeks) without signs of labor, in 27 pregnant women at term without labor, and in 10 women at term with labor. LIF measurements were taken from the anterior lip of the exocervix using the collascope.

LIF values were 0.26 ± 0.23 in women with CI, 0.51 ± 0.26 in the second trimester, 0.77 ± 0.41 in nonlaboring women at term, and 0.52 ± 0.39 in term labor (Figure 12.8). LIF values were lower in patients with CI compared to all groups, and significantly lower ($P < 0.001$) compared to nonlaboring women at term. Mean gestational age (days) was 111 ± 28 (CI), 176 ± 5 (second trimester), 274 ± 5 (term nonlaboring), and 271 ± 11 (term labor).

Uterine EMG and cervical LIF combined

One of our newest pilot studies characterized differences in uterine EMG and cervical LIF parameters used in conjunction for patients undergoing successful or failed induction. Twelve patients presenting to the labor and delivery area for pitocin induction (for various indications, e.g. postdates, oligo, etc.), had uterine electrical activity and cervical collagen content measured noninvasively using EMG and LIF, respectively, just prior to treatment with pitocin induction agent (standard start dose, 1MU), and then again approximately 4 h later. Patients were divided into two groups: G1, successful induction ($n = 8$); G2, failed induction ($n = 4$). Successful induction was deemed to occur for women who ultimately delivered vaginally within 24 h of induction (although future studies will explore different cut-off points). A multivariate expression, namely EMG/LIF,

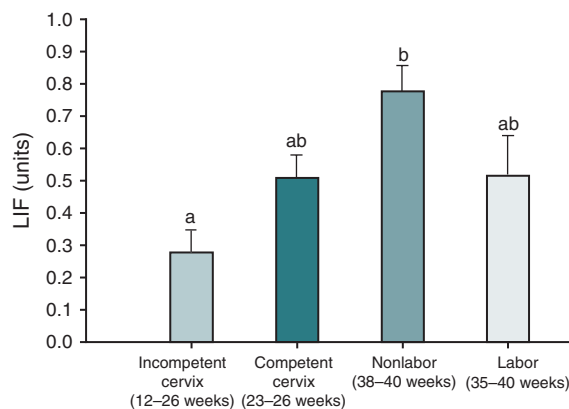


Figure 12.8 Term nonlabor patients have significantly higher ($P < 0.05$) light-induced fluorescence (LIF) ratio, hence more cervical collagen, than those patients with cervical insufficiency. This result admits the possibility of using the collascope for classifying or identifying patients with cervical insufficiency.

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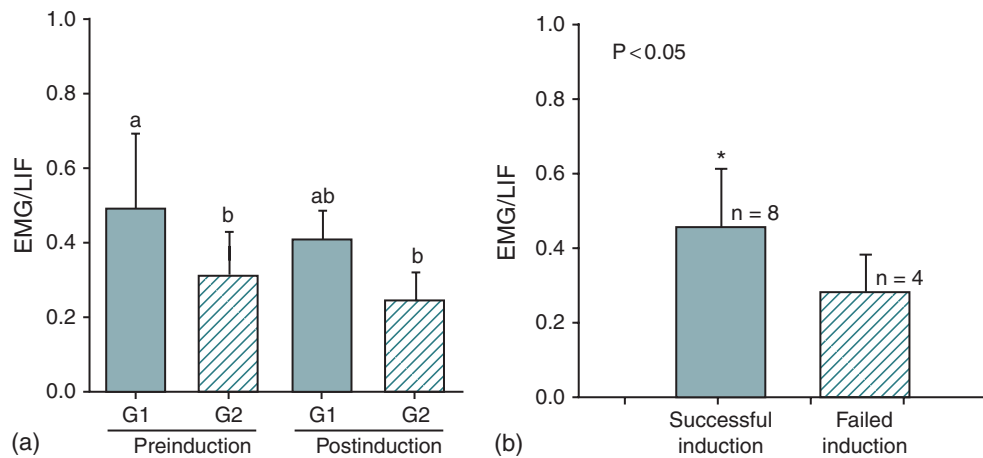


Figure 12.9 (a) Using the electromyography (EMG) and light-induced fluorescence (LIF) ratio, combined in the simple multivariate mathematical expression EMG/LIF, for patients receiving induction agent, showed that the EMG and LIF values, used together in this way, may indicate which patients will benefit from induction and which will not. Both the preinduction and postinduction EMG/LIF values were higher (with the preinduction value having significance, $P < 0.05$) in the group of patients having successful induction (G1) compared to those who had failed induction (G2). (b) Using the composite EMG/LIF value (which is just the average of the pre- and postinduction EMG/LIF values) showed a significantly higher ($P < 0.05$) composite EMG/LIF for G1 compared to G2. The composite score may be useful for determining, after a given period of time, whether such treatment will ultimately succeed, or whether further treatment should be suspended.

was compared for G1 versus G2 between preinduction versus post induction measurements. A composite score, namely the average EMG/LIF activity of each patient, made using the mean of the pre and postinduction values, was also compared between G1 and G2. Initially, one-way ANOVA was used, and post-hoc pair-wise comparisons were then made. The Student t-test was used to compare the composite scores. $P < 0.05$ was considered significant.

For the multivariate expression EMG/LIF, the preinduction measurement for G1 was significantly higher than either the pre- or postinduction measurements for G2 (0.48 ± 0.20 versus 0.31 ± 0.12 and 0.24 ± 0.08 , respectively; Figure 12.9a). The composite score was also significantly higher for G1 compared to G2 (0.45 ± 0.16 versus 0.28 ± 0.10 ; Figure 12.9b).

CONCLUSIONS

An extensive range of studies using the uterine EMG and cervical LIF diagnostic tools has been performed. From these, a number of conclusions can be reached about the function and state of the uterus and cervix during various conditions of parturition. These observations could not

have been made with any of the other currently available patient assessment and monitoring techniques.

Using a spectral parameter, transabdominal uterine EMG predicts delivery within 24 h at term and within 4 days preterm. With the power spectrum analysis, uterine EMG frequency content in antepartum patients is seen to be significantly lower than in laboring patients delivering <24 h from measurement. This indicates that the uterine muscle tissue is capable of generating more rapid polarizations/depolarizations closer to delivery than those produced far from delivery. Such rapid signal fluctuations are indicative of mature uterine development (extensive gap junctions, plethora of ion channels, etc.) necessary for effective contractions to properly expel the fetus. Furthermore, uterine EMG energy values correlate strongly with the strength of uterine contractions and therefore may be a valuable alternative to invasive measurement of intrauterine pressure.

By contrast, TOCO was seen not to have predictive capability, so unlike TOCO, transabdominal uterine EMG could be used routinely to forecast labor and delivery in an objective manner. For example, transabdominal uterine EMG, specifically the signal frequency within the bursts, is significantly higher in women with consecutive failure of tocolysis. These results suggest that EMG

measurements are useful for prediction or monitoring of treatment of preterm contractions. This also indicates that once labor is established, it likely cannot be reversed with present tocolytics.

Uterine EMG parameters can also be combined mathematically for more robust predictive variables. Individually, total burst power and burst spectral frequency content do characterize uterine activity and labor in pregnant humans noninvasively, but together they predict delivery better than each parameter does alone. This predictive nature of combining EMG parameters is born out by the fact that the average value calculated as a result of the mathematical combination of the total power and spectral frequency is higher for patients within 24 h of delivery than those >24 h from delivery. Other multivariate uterine EMG parameters should also be investigated.

Cervical LIF decreases significantly as gestational age increases, and so cervical LIF may be a useful tool to identify patients in whom delivery is imminent. Cervical application of PG decreases the amount of cross-linked collagen as measured by LIF. However, this effect is observed only in patients with a prior high cross-linked collagen level, indicating that once a certain level of cervical ripening is reached, further application of induction agents to the cervix may be futile. Cervical LIF can also be used to identify women with cervical insufficiency so as to aid clinicians in determining the best candidates for cerclage.

Uterine EMG and cervical LIF, in the multivariate expression EMG/LIF, are indicative of successful induction. Specifically, since the pre-pitocin EMG/LIF value was high in those who ultimately had effective treatment, the pretreatment EMG/LIF measurement may determine which patients are most likely to benefit from pitocin induction and which are not. Similarly, in treated patients, the composite score may indicate imminent success or failure of the induction treatment when calculated through 4 h of dosing, and could aid clinicians in deciding on whether or not to continue the treatment.

These methodologies – i.e. uterine EMG and cervical LIF – offer many advantages and benefits not available with present patient monitoring and assessment systems, such as high predictive capability, ease of use and application, and noninvasiveness of measurement. It would likely be of great benefit to obstetrics that these technologies be implemented on a routine basis in the clinic.

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