Uterine EMG and Cervical LIF - Promising Technologies in Obstetrics

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Abstract: No current objective measures exist to determine uterine or cervical function during pregnancy, or to accurately predict term or preterm labor and delivery. Uterine electromyography (EMG) and cervical light-induced fluorescence (LIF) studies were performed in term and pre-term animals and humans to evaluate the state and function of the uterus and cervix, and to determine the predictive capability of measurements made using these new technologies. Both uterine EMG and cervical LIF produced high positive and negative predictive values, compared to other currently-used methods. Uterine EMG and cervical LIF show great promise as diagnostic tests during pregnancy and for patient monitoring in obstetrics.

Keywords: Uterus, EMG, cervix, LIF, labor, parturition.

INTRODUCTION

Perhaps the most important health problem in obstetrics today is pre-term birth and its associated complications. Preterm birth is the primary reason for infant morbidity and mortality, accounting for around 35% of all health care spending on infants [1]. Preterm birth affects more than 12% of births in the USA [2] and of these, 40-50% have been related to preterm labor [2-4]. Pre-term neonates, with birthweights less than 2500 g, represent about 10% of the total number of babies born each year. The complications of pre-term birth include significant neurological, mental, behavioral and pulmonary problems in later life. Among the pre-term 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 pre-term birth depends upon the understanding of the mechanisms that initiate labor. The greatest burden of preterm birth is in developing countries, where much of the fatality and morbidity is secondary to infectious diseases [5]. Increased preterm labor risks in undeveloped countries include: malaria and hyperpyrexia, HIV suppression of the immune system leading to additional infection with tuberculosis, syphilis and intestinal parasites, and bacterial vaginosis.

PHYSIOLOGY

Labor has been viewed as the transition from an inactive muscle either by the addition of a uterotonin or withdrawal of tonic progesterone inhibition [6]. Although past 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. 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 progesterone and its antagonists indicate that parturition (and uterine contractility) is composed of several major steps, with a relatively short conditioning phase followed by active labor [7, 8]. The conditioning step leading to the softening of the cervix takes place in a different and longer time frame from the conditioning step of the myometrium, indicating that the myometrium and cervix are regulated by independent mechanisms.

Our studies, as well as those of others, have demonstrated that myometrial cells are coupled together electrically by gap junctions composed of connexin proteins [9]. 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. This condition favors quiescence of the myometrium and the maintenance of pregnancy. At term, however, the cell junctions increase and form an electrical synctium required for effective contractions. The presence of the contacts seems to be controlled by changing estrogen and progesterone levels in the uterus. As action potentials propagate over the surface of a myometrial cell, the depolarization causes voltage-dependent Ca$^{2+}$ channels (VDCC) to open. When this occurs, Ca$^{2+}$ enters the muscle cell down its electro-chemical gradient to activate the myofilaments and provoke a contraction. We have also demonstrated by reverse transcriptase polymerase chain reaction that the expression of VDCC subunits in the rat myometrium increases during term and pre-term labor [10]. The increased expression, which appears to be controlled by progesterone withdrawal, may facilitate uterine contractility during labor by increasing portals for Ca$^{2+}$ entry.

The composition of the cervix is smooth muscle (10%) and a large component of connective tissue (90%) consisting of collagen, elastin and macromolecular components, which make up the extracellular matrix [11]. Many biochemical and
functional changes occur in cervical connective tissue towards term [11-13]. This process of cervical ripening results in softening, effacement and finally dilation of the cervix. Ripening is required for the normal progression of labor and delivery of the fetus. The exact mechanisms controlling the cervical ripening process are largely unknown.

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. We believe 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 pre-term labor) by reversing the process. After the interim phase, 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 the changes, which begin in the preparatory phase, and culminate at the end of the interim phase, have by this time become well established and cannot be undone, even with currently available tocolytics (Fig. 1).

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, 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 conditioning step, because changes in these variables may be independent of the preparatory stage, or may not become detectable by these methods until a relatively late and irreversible stage has been reached.

**MONITORING DURING PREGNANCY (AND DIAGNOSIS OF LABOR)**

Diagnosis of labor is one of the most difficult and important tasks facing medical practitioners in maternity care today. Knowing that true labor (which will lead to delivery) has begun, as well as predicting when it will start, is important for both normal and aberrant pregnancies. Prediction of labor in normal pregnancies is important for minimizing unnecessary hospitalizations, interventions and expenses. On the other hand, accurate prediction and diagnosis of spontaneous pre-term labor will also allow clinicians to start treatment early in women with true labor and avert unnecessary treatment and hospitalization in women who are simply having pre-term contractions, but who are not in true labor. Even noticeable dynamic cervical change may not be an accurate indicator of true labor, as a large percentage of women with established cervical change do not deliver pre-term when not treated with tocolytics [14].

To date, the most important key to preventing pre-term labor has been constant contact and care from health care practitioners [15].

The state of labor monitoring, with currently-used clinical methods, can be summarized as follows:

1. current methods are subjective and/or inaccurate;
2. intrauterine pressure catheters are limited by invasiveness and need for ruptured membranes;
3. uterine contraction monitors (e.g. tocodynamometer - TOCO) are uncomfortable, inaccurate and/or subjective;
4. no method has been successful at predicting pre-term labor;

![Fig. 1. Model of parturition depicting the chronic changes of the cervix and the acute changes in the myometrium. Some changes are reversible while others are not. Still others may be slowed or prevented by using treatments.](image-url)
5. no method has lead to effective treatment of pre-term labor; and
6. no method makes an objective measurement of both function and state of the uterus or the cervix during pregnancy.

Few current assessment methods can identify signs of impending labor, and none of them offer objective data that accurately predict labor. Uterine electromyography (EMG) and cervical light-induced fluorescence (LIF) are two emerging alternative technologies that may prove to be valuable contributions to the solution of this problem (Figs. 2A and 2B).

In the same way that modern electrocardiography (ECG) has clearly benefited heart patients [16-21], uterine EMG which, similarly, amounts to the acquisition of electrical signals taken non-invasively from surface electrodes, would likely benefit obstetric patients when adopted by physicians, and when utilized as an everyday tool in the antenatal and labor wards and clinics. Like the function of the ECG for cardiac monitoring, uterine EMG can be used to monitor uterine electrical recordings in normal pregnancies in order to diagnose or even predict abnormal conditions such as pre-term labor, insufficient labor progress, or dystocia [22]. This has been done by analyzing several different types of electrical parameters derived from the raw recorded uterine

Fig. (2A). The typical uterine 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.
Fig. (2B). Schematic of the Collascope, a device built specifically to measure cervical light-induced fluorescence, or 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 approximately 390nm wavelength), and dividing by the peak reference value (which occurs at approximately 343nm wavelength). The LIF-ratio has been found to be highly predictive of labor in various species, including humans.

electrical signals, including the power density spectrum (PDS), which decomposes electrical signals into their individual frequency components. On the other hand, fluorescence spectroscopy, a widely used research tool in biosciences, can reveal important information with respect to molecular and physical states. 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. We have used this LIF methodology to successfully evaluate the cervix in a number of studies. This was accomplished by calculating the amount of fluorescent light emitted from the cervix at the specific fluorescence frequency of collagen.

Once calculated, uterine EMG and cervical LIF values can be compared to gestational age, delivery outcome, or measurement-to-delivery intervals using receiver operator characteristic (ROC) curves. This gives a measure of predictability by determining the number of true and false positive and negative cases, which in turn is used to find positive and negative predictive values (PPV and NPV, respectively). The uterine EMG and cervical LIF monitoring methods, therefore, could permit effective classification of women, could enable much better treatment and management of those women than the currently available tools, and could also allow for labor prediction. Such forecasting of labor in normal (term-delivery) pregnancies is important for minimizing unnecessary hospitalizations, interventions and expense, while prediction and diagnosis of spontaneous preterm labor will allow clinicians to start any necessary treatment early in women with true labor, and avert unnecessary treatment and hospitalization in women who are not in true labor. These two translational devices, used alone or in conjunction, would therefore aid in patient monitoring. In the studies described below, we outline human and animal experiments designed to test the use of uterine EMG and cervical LIF.
UTERINE EMG STUDIES IN HUMANS

Prediction of Labor

We performed a human study wherein standard medical electrodes were used to non-invasively acquire uterine EMG data from the abdominal surface. A technique known as power spectrum analysis was then performed on the uterine electrical data from term and pre-term women who presented with signs and symptoms of labor, but in whom differentiation between false and true labor could not be made clinically [25]. The average PDS peak frequency was determined for each woman and plotted against the woman's measurement-to-delivery interval (Figs. 3A and 3B).

![Graph A](image)

**Fig. (3). A:** An acute increase occurs in the PDS peak frequency just prior to delivery (within approximately 24 hours from delivery) in patients delivering spontaneously at term (≥37 weeks gestation). Note that for clarity, individual data points are indicated for 40+ hours. **B:** A similar increase occurs in the PDS peak frequency prior to delivery (within approximately 4 days of delivery) in patients delivering spontaneously prior to term (<37 weeks gestation). Note that for clarity, individual data points are indicated for 10+ days.

Comparison of PDS peak frequency showed a significantly higher value for term patients within 24 hours of labor and for pre-term patients within 4 days of labor, as compared to non-labor controls (Figs. 4A and 4B). Our results are supported by recent work from other groups [26-29] that show either quantification of basal uterine activity or changes in one or more uterine EMG parameters during labor, although it must be emphasized that sampling rates, electric/magnetic filtering characteristics, and analysis techniques in these other studies varied.

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 PPV and NPV, respectively. From the tables, one sees that the PPV and NPV are high at the time-from-measurement-to-delivery endpoints investigated.

We concluded that labor (and subsequent delivery) could be predicted successfully using non-invasive uterine EMG by observing the change to higher frequencies in the electrical signals. We believe that these higher frequencies are attributable to a lowering of myometrial cellular threshold potentials, an increasing of myometrial cellular resting potentials, increases in size and number of ion channels, and/or increases in gap junctions, any one or all of these occurring as the uterus becomes electrochemically prepared for labor.

Longitudinal Changes

Patient uterine-burst EMG amplitude was shown to remain low and steady as gestation increases in longitudinally-measured patients (i.e. multiple measurements made serially on the same patient as gestation increased), and becoming maximal during labor. However, amplitude alone was not successful in determining the onset of labor. We performed experiments to evaluate other EMG variables, such as PDS peak frequency and uterine burst electrical energy for differentiating patient categories, forecasting parturition, and for monitoring patient progress longitudinally more effectively than traditional methods such as tocodynamometry. The PDS peak frequency was seen to be significantly lower for longitudinal patients early in gestation, and sharply increased for those who delivered at term (Fig. 5).

We concluded that there is an increase in electrical frequency (thought to be due to an increase in excitability and conduction), which occurs in the myometrium during its preparation for labor.

Induction Effect

In one study, we compared the effects on the uterine EMG for the induction agents misoprostol and prepidil. Non-invasive surface electrodes were used to acquire the uterine EMG signals trans-abdominally, as with all of our human studies. The patients were grouped according to the induction agent used. Uterine EMG activity from each patient was recorded for 30 minutes just prior to treatment with the induction agent, and was recorded for another 30 minutes, 4 hours after treatment with the induction agent.

Either misoprostol (50 µg, 6 patients) or prepidil (200 µg, 5 patients) was applied for cervical ripening. The mean electrical activity of each of the 30-minute periods was calculated and the increase or decrease in the mean activity was found for each patient. The average increase in EMG activity was calculated for each group. Misoprostil caused an
Fig. (4A,B). For patients delivering spontaneously at term, a significantly higher PDS peak frequency was seen for patients delivering within 24 hours of EMG measurement as compared to those delivering more than 24 hours from EMG measurement (Fig. A). For patients delivering spontaneously preterm, a significantly higher PDS peak frequency was seen for patients delivering within 4 days of EMG measurement as compared to those delivering more than 4 days from EMG measurement (Fig. B).

Table 1A. Predictive Capability of Uterine EMG (Term Patients)

<table>
<thead>
<tr>
<th>Time to delivery</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Days</td>
<td>93.8</td>
<td>55.6</td>
<td>.918</td>
<td>.625</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>1 Day</td>
<td>85.4</td>
<td>88.9</td>
<td>.976</td>
<td>.533</td>
<td>&lt;.010</td>
</tr>
<tr>
<td>12 Hours</td>
<td>75.0</td>
<td>100.0</td>
<td>1.000</td>
<td>.542</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>8 Hours</td>
<td>54.5</td>
<td>100.0</td>
<td>1.000</td>
<td>.394</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>

Table 1B. Predictive Capability of Uterine EMG (Pre-Term Patients)

<table>
<thead>
<tr>
<th>Time to delivery</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Days</td>
<td>81.8</td>
<td>90.3</td>
<td>.750</td>
<td>.933</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4 Days</td>
<td>85.7</td>
<td>88.6</td>
<td>.600</td>
<td>.969</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2 Days</td>
<td>71.4</td>
<td>88.6</td>
<td>.556</td>
<td>.939</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 Day</td>
<td>75.0</td>
<td>86.8</td>
<td>.375</td>
<td>.971</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

increase in uterine EMG activity for a greater percentage of patients compared to prepidil (Fig. 6A), and the average increase was only significant when using misoprostol (Fig. 6B).

From this, we concluded that it is possible to use trans-abdominal EMG for quantitatively measuring uterine activity during treatments.

UTERINE EMG STUDIES IN ANIMALS

The aim of this particular work was to analyze records of uterine electrical activity made from the abdominal surface of pregnant and laboring rats to examine whether similar quantitative information can be extracted as from direct recording from the uterine muscle [30]. Electrical activity during pregnancy (non-labor, days 18 to 22), term labor (day 22), and pre-term labor (onapristone injected on day 18, delivery on day 19) was measured with use of electrodes attached to the uterine wall and to the abdominal surface. The fast Fourier transform and wavelet transforms were obtained for representative electromyographic bursts. Power spectra were generated. Intrauterine pressure was also measured. As a result of this investigation, several parameters were identified for use in following the progressive increase in uterine activity that occurs in preparation for and during labor. Analyses of amplitude, frequency, and percent time active were found to be effective methods for objec-
Fig. (5). Antepartum patients who ultimately delivered spontaneously at term (measured at several time-points) tended to maintain relatively low PDS peak frequency values, while labor patients delivering spontaneously at term had relatively high PDS peak frequency values.

Fig. (6A,B). A higher percentage of patients showed an increase in uterine EMG activity after treatment with Misoprostol than after treatment with Prepidil (Fig. A). The average increase in EMG activity was significantly higher (paired t-test) after Misoprostol treatment, but not after Prepidil treatment. When considering all treatments, there was a significant increase in uterine EMG activity after treatment as compared to before treatment (Fig. B).

...tively determining the efficiency of uterine contractions. Most of the changes in these parameters appeared in the last 24 hours before delivery (Figs. 7 and 8).

...Other similar unpublished studies also showed dramatic increases in uterine EMG frequency and magnitude near and during labor and delivery at term (Fig. 9a) and preterm (Fig. 9b). Other groups have performed animal uterine EMG studies, and their work also shows that uterine EMG parameters can quantify uterine contractile activity, and/or can characterize changes therein [31-33].

We concluded that recording of uterine electromyographic activity from the abdominal surface would be useful in following the progression of pregnancy and in predicting and diagnosing labor by observing various parameters, including a change to higher frequencies in the electrical signals. As with the human data, we believe that these higher frequencies are attributable to a lowering of myometrial cellular threshold potentials, an increasing of myometrial cellular resting potentials, increases in size and number of ion channels, and/or increases in gap junctions, any one or all of these occurring as the uterus becomes electrochemically prepared for labor.

CERVICAL LIF STUDIES IN HUMANS
Prediction of Labor

Thirty-one (31) women, with inconclusive signs of labor, were assessed in the third trimester. Cervical LIF was obtained non-invasively using an instrument specifically designed for this purpose (Collascope) [34]. LIF was measured from the 12:00 position of the cervix three successive times and the results were averaged. In women with clinically inconclusive signs of labor, 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. 10).
Fig. (7). Electromyographic recordings from uterus (Ut, upper trace), abdominal surface (AS, middle trace), and intraperitoneal pressure (IUP, bottom trace) from pregnant rats on day 19 of gestation, day 21 of gestation, labor at term (Day 22, TL), and preterm labor (Day 19, PL), after onapristone administration. A, On day 19 of gestation, uterine electromyographic activity is irregular and of low amplitude with no discernible signal at the abdominal surface. There is low-amplitude change in intraperitoneal pressure that is not clearly related to electrical activity. B, Record from rat on day 21, showing appearance of small bursts. C, Typical record from rat on day 22 of gestation during active delivery. Uterine electromyographic activity was characterized by regular, high-amplitude, long-duration bursts of action potentials. D, Preterm labor was induced on day 19 of gestation with onapristone. Note that the intensity of uterine activity produced is similar to that occurring during spontaneous term labor, C.

Fig. (8). Representative uterine and surface bursts of LMG activity along with their power density spectra (power density in microvolts/sec and frequency in hertz). A and D, On day 19 of gestation, power density spectra analysis showed low values with relatively flat power density
spectra on both uterine (Ut) and abdominal surface (As) sites. B and E, Term labor (TL) was characterized by significant increases in uterine and surface electrical power. Uterine and surface EMG activity had similar power spectra, although surface power was lower. C and F, Preterm labor (PL) was also characterized by increases in electrical power of both uterine and surface activity. Peak electrical power and frequency domain of EMG activity were similar for both uterus and surface.

Fig. (9A,B). Dramatic and significant increases in the uterine EMG energy and intrauterine pressure are seen in term-delivering rats just prior to the onset of labor (on approximately day 22 of gestation). The two parameters were shown to correlate. Dramatic and significant increases in the uterine EMG energy and intrauterine pressure are seen in preterm-delivering rats (treated with an induction agent) just prior to the onset of labor (on approximately day 18 of gestation). The two parameters were shown to correlate.

Fig. (10). A significantly lower average cervical LIF ratio was observed in those patients delivering within 24 hours of LIF measurement as compared to those delivering more than 24 hours from measurement.

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).

We concluded from this study that cervical collagen decreases significantly as gestational age increases and are predictive of delivery within 24 hours.

Longitudinal Changes

Another experiment involving cervical collagen was conducted to estimate whether LIF correlates with the time-to-delivery interval [34]. Twenty-one healthy gravidae without signs of labor had LIF measured approximately weekly during the last trimester. Each cervical collagen fluorescence measurement was accomplished in 10 seconds. For each patient and time point, the mean of three measurements from different spots around the 12 o'clock position of the exocervix was found. In all, 98 LIF measurements (median, 4 measurements; range, 2–11 measurements per patient) were taken. 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. 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. 11).

We concluded that cervical collagen decrease, as measured non-invasively by LIF, occurs gradually over time, reaching a critical value just before labor and delivery.

Induction Effect

We compared cervical collagen changes after prostaglandin treatment in 41 patients [35]. Several cervical LIF measurements were taken prior to treatment with induction agent for each patient and averaged. Several measurements were then taken and averaged from the same patients 4 hours after treatment with the induction agent. This study showed significant decreases (P<0.05) in LIF values of the cervix four hours after treatment (0.885±0.037) in patients with high values before treatment (0.982±0.040), but no change in patients with low values before treatment (Figs. 12A and 12B).

Paired Student's t-test, Wilcoxon Signed Rank test, Linear Regression, Spearman correlation and Fisher Exact
A significant negative correlation was found between the LIF ratio and the gestational age.

For those patients needing cervical induction treatment (i.e. cervical collagen content too high), a significant decrease was seen in the cervical collagen, as measured by LIF, when comparing average LIF values before and after treatment with prostaglandins (Fig. A). For those patients with ripened cervices (i.e. collagen content reduced), no change was seen in the cervical collagen, as measured by LIF, when comparing average LIF values before and after treatment with prostaglandins (Fig. B).

The changes in cervical resistance mirrored those in cervical collagen content and the nadir in both occurred about two days prior to the onset of labor.

Our conclusion was that cervical preparation for delivery does not occur acutely at the time of labor and that cervical collagen content determines cervical resistance.

In another experiment, LIF was used to investigate in-vivo changes of cervical collagen in guinea pigs during...
gestation and following sodium nitroprusside treatment [37]. LIF of cervical collagen was measured from the surface of the exocervix in anesthetized non-pregnant and timed-pregnant guinea pigs at different times of gestation. Measurements were also performed in guinea pigs at mid-gestation before, and 8 hours after, intra-cervical treatment with sodium nitroprusside. Collagen fluorescence decreased significantly as pregnancy progressed, reached lowest values at delivery, and increased gradually postpartum. Treatment with sodium nitroprusside, but not with the vehicle, caused a significant decrease in LIF.

We concluded that LIF changes in the cervix reflect the gradual cervical softening (ripening) during pregnancy and the return to the rigid state of the cervix postpartum, and that cervical softening during pregnancy, as well as after sodium nitroprusside treatment, is associated with a decrease in cervical collagen cross-links.

**FORECASTING LABOR – CURRENT CLINICAL METHODS VS. EMG AND LIF**

From our own studies, as well as those of others, it is clear that for forecasting labor and delivery, the effectiveness of the technologies now generally accepted in clinical practice are limited, especially in relation to sensitivity and positive predictive value, as compared with EMG and LIF, as shown in Table 2 [38].

Intra-uterine pressure catheters cannot be used to predict labor. The invasive nature of the procedure involved can increase the risk of infection or cause serious complications. Such infections could be a risk factor for pre-term labor [39]. No real predictive capability exists for intrauterine pressure catheter devices because they are mainly used in cases where labor has already been diagnosed clinically, which is why they do not appear in the Table above.

Tocodynamometer devices are used in over 90% of all hospital births. Physicians have been quick to adopt these machines because they supply uterine contraction data with little risk. Ironically, most physicians also agree that these bulky force-transducer devices provide limited information on labor. The instruments are largely dependent upon the skill of the clinician, but have not changed treatments or improved outcomes following pre-term labor. The tocodynamometer generally cannot be used to predict true pre-term labor, as a recent study has shown [40]. That is because tocodynamometer devices are inaccurate. Many different variables affect the uterine external force measurement, such as instrument placement, amount of fat, and uterine wall...
pressure. Tocodynamometry of uterine contractions is essentially equivalent to measuring cardiac contractions and heart function with a contraction transducer placed on the chest. Clearly, 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 pre-term labor and decrease the frequency of pre-term birth [41]. However, HUAM has been shown to be no better in lowering the frequency of pre-term birth than weekly contact with a nurse [42]. The lack of significant clinical usefulness of HUAM is directly related to the inability of the tocodynamometer and its user to differentiate between false and true contractions (Fig. 14).

Contractions measured with the tocodynamometer can be large or small, and can occur with a similar number of contractions/unit time, regardless of whether the patient is in labor or not. The uterine EMG, in contrast, records different electrical signal amplitudes and frequencies (Fig. 15), depending upon the patient's labor or non-labor state.

Measuring the length of the cervix via endovaginal ultrasonography has been used to detect spontaneous pre-term labor [43, 44], with some degree of success. However, even in combination with other factors, with respect to positive predictive capabilities, there is a range of possible values reported, from around 50% to about 71%. And these results are obtained only after the onset of symptoms of spontaneous pre-term labor, so this method, too, is highly limited in its potential for early diagnosis and resulting treatment.

Cervicovaginal fetal fibronectin (FFN) has recently been suggested as a screening method for women at risk of spontaneous pre-term labor. Several studies [45, 46] have shown that FFN might be of benefit to predict spontaneous pre-term labor, but other studies indicate that FFN has limited value [47]. The main value of the FFN assay seems to be only in its high NPV (i.e. it has the ability to identify patients that are not at risk of spontaneous pre-term labor and pre-term birth, but can say nothing of the others). However, a high PPV is potentially important for the improved safety of the fetus.

Our most recent pilot study characterized differences in uterine EMG and cervical LIF parameters used in conjunction, for patients undergoing successful or failed induction. 12 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 non-invasively using EMG and LIF respectively, just prior to treatment with pitocin induction agent (standard start dose, 1MU), and then again approximately 4 hours later. Patients were divided into two

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### Table 2. Predictive Capability of Various Obstetric Technologies

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
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<tbody>
<tr>
<td>MPTLS</td>
<td>50.0</td>
<td>63.5</td>
<td>21.4</td>
<td>86.4</td>
</tr>
<tr>
<td>Ctx ≥ 4/hr</td>
<td>6.7</td>
<td>92.3</td>
<td>25.0</td>
<td>84.7</td>
</tr>
<tr>
<td>BS ≥ 4</td>
<td>32.0</td>
<td>91.4</td>
<td>42.1</td>
<td>87.4</td>
</tr>
<tr>
<td>Cx ≤ 25mm</td>
<td>40.8</td>
<td>89.5</td>
<td>42.6</td>
<td>88.8</td>
</tr>
<tr>
<td>CFFN +</td>
<td>18.0</td>
<td>95.3</td>
<td>42.9</td>
<td>85.6</td>
</tr>
<tr>
<td>EMG</td>
<td>75.0</td>
<td>93.3</td>
<td>88.0</td>
<td>93.0</td>
</tr>
<tr>
<td>LIF</td>
<td>59.0</td>
<td>100.0</td>
<td>78.9</td>
<td>80.0</td>
</tr>
</tbody>
</table>

MPTLS = Multiple pre-term labor symptoms
Ctx = Maximal uterine contractions (tocodynamometer - TOCO)
BS = Bishop Score
CFFN = Cervical fetal fibronectin test
Cx = Cervical length (measured with ultrasound)
EMG = Noninvasive transabdominal uterine electromyogram
LIF = Cervical Light-Induced Fluorescence

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Fig. (14). The tocodynamometer is ineffective at discerning between true and false labor, since contractions, as measured by this device, can be large or small in amplitude, long or short in duration, and can occur with the same frequency, regardless of whether the patient is in labor or not.

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Fig. (15). The tocodynamometer is ineffective at discerning between true and false labor, since contractions, as measured by this device, can be large or small in amplitude, long or short in duration, and can occur with the same frequency, regardless of whether the patient is in labor or not.
Fig. (15). Contraction electrical bursts, as measured by uterine EMG, are generally higher in amplitude and show higher action-potential frequencies during labor than during non-labor. This makes the device useful for prediction of labor and delivery.

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 hours of induction (although future studies will explore different cutoff points). A multivariate expression, namely EMG/LIF, was compared for G1 vs. G2 between pre-induction vs. post-induction measurements. A composite score, namely the average EMG/LIF activity of each patient including both before and after dosing, was then made using the mean of the pre- and post-induction values, and was compared between G1 and G2. Initially, one-way analysis of variance (ANOVA) was used, and post-hoc pair-wise comparisons were then made. T-test was used to compare the composite scores. P<.05 was considered significant.

For the multivariate expression EMG/LIF, the pre-induction measurement for G1 was significantly higher than either the pre- or post-induction measurements for G2 (0.48±0.20 vs. 0.31±0.12 and 0.24±0.08, respectively; Fig. 16A). The composite score was significantly higher for G1 compared to G2 (0.45±0.16 vs. 0.28±0.10; Fig. 16B).

In this pilot study, we only included patients who delivered spontaneously, and therefore c-section patients were excluded. As a result, we had to use a somewhat artificial criteria for determining successful vs. failed induction (i.e. delivery or not within 24 hours). In future studies, we will also consider c-section patients and cervical dilation in order to be more rigorous. For example, a woman who progressed to 9cm dilatation and had a C/S for fetal distress should not be classified as a failed induction. However, from this pilot study, we concluded that uterine EMG and cervical LIF, in the multivariate expression EMG/LIF, may be indicative of successful induction. Specifically, since the pre-pitocin EMG/LIF value was high in those who ultimately had effective treatment, the pre-treatment 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 four hours of dosing, and could aid clinicians in deciding on whether or not to continue the treatment.

CONCLUSIONS AND POTENTIAL BENEFITS OF EMG AND LIF

Uterine EMG and cervical LIF monitoring promise to be invaluable for many clinical situations during pregnancy in developed, as well as in developing, nations. In third-world countries, for example, one asset of accurate diagnosis of preterm labor would be the early transfer of women, where access to adequate facilities is greatly limited relative to the developed world. Medical intervention for pregnant women and their unborn fetuses under these conditions is most critical, since prenatal nutrition and care has probably already been sub-par for them by the time pre-term labor is diagnosed. An easy-to-use, portable system, which potentially provides an immediate, on-site diagnosis (such as uterine EMG and cervical LIF), could improve the pregnancy outcomes for these women. For the modern world, adoption of these technologies into standard pregnancy monitoring would also impact the field greatly therein.

The following is a description of some of the possible uses for combining EMG and LIF measurements, i.e. if made simultaneously on the same patients (Table 3):

Considering the tremendous need for (and potential benefits from) uterine EMG and cervical LIF technologies, joint implementation of them could likely improve patient management and classification, and could be expected to lead to a reduction in perinatal mortality and morbidity [48].
Fig. (16A,B). Comparison of EMG/LIF scores for 12 patients, 8 with successful induction and 4 with failed induction, as obtained both prior to pitocin treatment and after 4 hours of pitocin treatment: The pre-induction EMG/LIF for the patients with successful inductions was significantly higher than either the pre-induction or post-induction measurements for the patients who failed induction (ANOVA used, P < .05). A composite EMG/LIF score, using the average EMG/LIF value of the pre-induction and post-induction scores, indicated a significantly higher composite score for the patients having successful inductions compared to those who failed induction (t-test used, P < .05).

Table 3. Potential Uses of Simultaneous Uterine EMG and Cervical LIF Measurements

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Use</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum</td>
<td>Predict preterm delivery</td>
<td>Prevent preterm delivery and improve perinatal outcome</td>
</tr>
<tr>
<td>Early labor</td>
<td>Differentiate between false and true labor</td>
<td>Prevent unnecessary admissions</td>
</tr>
<tr>
<td>Preterm contractions</td>
<td>Determine need for tocolysis</td>
<td>Prevent unnecessary use of tocolytics and decrease cost</td>
</tr>
<tr>
<td>Induction of labor</td>
<td>Predict success of induction</td>
<td>Prevent unnecessary and prolonged inducions</td>
</tr>
<tr>
<td>Tocolysis</td>
<td>Predict success of tocolysis. More objective and accurate analysis of uterine activity. Improved method to monitor and adjust tocolytic therapy</td>
<td>Prevent complications from tocolytics. Decrease time on tocolytics</td>
</tr>
</tbody>
</table>

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REFERENCES


