UCSF

UC San Francisco Previously Published Works

Title

Novel device to trend impedance and fluorescence of the cervix for preterm birth detection.

Permalink

<https://escholarship.org/uc/item/87n8p0ss>

Authors

Etemadi, Mozziyar
Chung, Philip
Heller, J Alex
et al.

Publication Date

2013

DOI

10.1109/embc.2013.6609466

Peer reviewed

Novel Device to Trend Impedance and Fluorescence of the Cervix for Preterm Birth Detection

Mozziyar Etemadi, *Student Member, IEEE*, Philip Chung, J. Alex Heller, *Student Member, IEEE*, Jonathan Liu, Rebecca Grossman-Kahn, Larry Rand, and Shuvo Roy, *Member, IEEE*

Abstract— Preterm birth is the leading cause of worldwide neonatal mortality. It follows a pathologically accelerated form of the normal processes that govern cervical softening and dilation. Softening and dilation occur due to changes in cervical collagen crosslinking, which can be measured non-invasively by changes in tissue fluorescence and impedance. We present a novel device designed specifically to take fluorescence and impedance measurements throughout pregnancy, with the end goal of fusing and trending these measurements to form an early diagnosis of preterm labor.

I. INTRODUCTION

Preterm birth results in 1 million neonatal deaths each year—35% of all neonatal mortality worldwide [1]. Those infants that survive preterm birth are commonly met with life-long morbidity and disabling illness [2]. In the United States, the total costs of preterm birth is over \$26 billion dollars [3]. Preterm birth by itself is not a disease, but a syndrome: many pathological mechanisms accelerating what would otherwise be the process of normal birth [4–6].

This process, whether or not it is accelerated, begins with firm cervical tissue, that is firm because the collagen within it is densely crosslinked [7–11]. The fetus develops behind this firm cervix, which prevents foreign bodies from entering the uterus, as well as preventing uterine contents from emerging. Days to weeks before (preterm) birth is to occur (see Figure 1), these tightly bound collagen fibers begin to unlink and become more disorganized [12–15].

After a period of microstructural changes in cervical collagen, the overall shape of the cervix begins to change. So-called “cervical shortening” is precisely the gold-standard diagnostic predictor of preterm birth measured today via transvaginal ultrasound. With this technique, a short cervix observed too early in gestational age is an indication of accelerated cervical changes that will ultimately result in preterm birth. Unfortunately, cervical shortening often occurs very close in time to the actual preterm delivery, and diagnostic results from ultrasound can be complicated by normal anatomic variability [16].

In an attempt to improve on the diagnostic ability of the macroscopic changes seen on ultrasound, researchers have attempted to measure the microscopic changes in collagen structure. Collagen crosslinks present in the cervix are autofluorescent, and its emission spectra has been shown to change throughout human pregnancy [17]. Collagenous tissue also exhibits a unique impedance spectrum, and has also been studied in the pregnant cervix [18–21].

Fluorescence and impedance are promising methods of preterm birth detection: they can be obtained very quickly and

Figure 1. The physiologic process that prepares the cervix for delivery can be brought about sooner by multiple pathologies, leading to preterm birth.

non-invasively. Also, due to recent advances in LED technology, both impedance and fluorescence detection can now be performed at low cost. Unfortunately, both cervical fluorescence [17], [22–26] and impedance [20], [21] have primarily been used only as “spot checks” to predict if labor will occur within 24 hours. We hypothesize that by fusion of multiple impedance and fluorescence measurements over time for a particular patient, an earlier detection of preterm labor can be achieved. Because many of the causes of preterm birth are reversible, an earlier detection would afford the time needed for treatment (i.e. antibiotics) to take effect. To test this hypothesis, we have created a novel cervical collagen interrogation device, specially designed for trending (monitoring changes in) impedance and fluorescence measurements across multiple time points, non-invasively in a clinical feasibility study.

II. BENCHTOP COLLAGEN MEASUREMENT

Bovine calf skin collagen (C3511, Sigma-Aldrich, St. Louis, MO) was prepared at various concentrations mimicking physiologic levels throughout the cervix during gestation. Impedance and fluorescence were measured using an impedance analyzer (Agilent 4294A, Agilent, Santa Clara, CA) and spectrophotometer (Tecan Infinite 200, Männedorf, Switzerland). Data from these instruments is shown in Figure 2 and was used to inform our design parameters.

*Research is supported by the Bill and Melinda Gates Foundation, the Vodafone Americas Foundation, and the FDA (2P50FD003793).

M. Etemadi, P. Chung, J. A. Heller, J. Liu, and Shuvo Roy are with the Department of Bioengineering and Therapeutic Sciences, University of

California, San Francisco, CA 94158 USA (415-514-9784; e-mail: Mozziyar.Etemadi@ucsf.edu).

L. Rand is with the Department of Obstetrics and Gynecology, University of California, San Francisco, CA.

Figure 2. In vitro collagen measurements made with gold-standard benchtop equipment.

III. DEVICE DESIGN

The device consists of a silicone vaginal probe embedded with six electrodes and an optical window to accept a fiber optic bundle. The fiber optic both transmits and receives light to determine fluorescence, and the electrodes are paired in sequence to perform two electrode impedance measurements, as detailed below. A block diagram is given in Figure 3, and a photo of the device used in the clinic is in Figure 4. The device was made using a 3D-printed silicone mold, which was injected with silicone in-house using standard laboratory air pressure. Design iterations were informed from direct physician and human subject feedback, increasing device usability and comfort.

A. Impedance Measurement System

Device electrodes are connected internally within the silicone to modified microUSB 3.0 cable. Electrode pairs are selected via a multiplexer and connected to an Op-Amp based voltage controlled current source. One electrode is fed the current (10 μ A AC at various frequencies) with the other connected to virtual ground. The resultant voltage, together with the drive signal, are fed into a gain/phase detector IC (AD 8302, Analog Devices), which outputs two voltages: one proportional to the gain ratio of drive voltage to output voltage, and the other proportional to the phase angle. These are converted to digital and fed over Bluetooth to a computer.

B. Fluorescence Measurement System

A specially arranged, commercially available fluorescence detection fiber bundle (QP600-025-UV, Ocean Optics) is passed down the length of a metal tube which is already molded in the silicone of the device, locking in place with a custom metal connector. The fiber bundle is designed such

Figure 3. Block diagram of combination fluorescence and impedance cervical interrogation system.

that excitation fibers minimally reflect their output upon emission fibers, as excitation and emission wavelengths are often close in wavelength and difficult to differentiate if excitation is too bright.

The excitation fibers are illuminated via a dual-LED light source (365nm & 385nm) that is first passed through a USB-operated wavelength selector (Optometrics). Emission fibers are fed into a low-cost, USB spectrometer (USB2000, Ocean Optics). Custom software controls the impedance and fluorescence measurement in synchrony, enabling rapid clinical setup and acquisition time.

IV. CLINICAL PROCEDURE

Under IRB approval, high-risk pregnant women are actively being recruited from the OB/GYN clinic at our institution. Following the regular prenatal visit, a sterile speculum is inserted into the vagina per the procedures of a standard sterile speculum exam. Excess cervical mucus is cleaned with a few milliliters of deionized water and a cotton swab. The device itself is brought to the clinic having been sterilized using hydrogen peroxide plasma (STERRAD). It is inserted through the speculum and a few, brief test measurements are taken to inform the physician as to how closely the device is contacting the cervix.

In practice, using these test measurements the physician is able to manually adjust the device to achieve contact on most if not all electrodes. A full measurement spanning all impedance frequencies and fluorescence wavelengths is then performed, which takes approximately 90 seconds. The device and speculum are removed, concluding the patient visit.

Figure 4. Photograph of novel cervical measurement device used in a clinical feasibility study at our institution. The cup shaped portion of the device is brought into contact with the cervix through a speculum.

V. PILOT DATA

Preliminary raw impedance and fluorescence data are seen in Figure 5 without post processing. There is general agreement with the raw collagen fluorescence data collected with gold-standard instruments seen in Figure 2. Of note, the impedance values shown in Figure 5 were computed from voltages proportional to impedance and phase (the outputs of the AD8302). Only a first-order conversion was applied, and thus could account for some discrepancies between gold-standard and patient-obtained impedance. Future work will more accurately calibrate and compare impedance to the gold standard across a wider frequency range, but the values here are still widely different from those obtained when there is no cervical contact (all electrodes $> 10\text{k}\Omega$), indicating that we are indeed measuring cervical tissue impedance.

A peak in fluorescence emission is seen at approximately 450nm for around 390nm of incident light. This peak is the result of a superposition of collagen crosslink fluorescence

and NADH fluorescence signals in the cervix [27], [28]. However, given that collagen is approximately 70% of cervical tissue, potential changes to this signal during pregnancy will be mostly attributed to collagen changes as the tissue microstructure rearranges [23], [29]. The use of LEDs centered at 365nm and 385nm as our light source limits the excitation range of our system to approximately 350-410nm, yet we have found results comparable to prior research which have used high-powered xenon arc lamps [17], [22–26]. An advantage to our approach is the ability to achieve substantially lower cost and portability. Use of 400nm and 420nm long-wave pass filters to remove excitation light from the measurement may slightly truncate the leading edge of the 450nm emission peak. Because the majority of the peak remains unfiltered, changes in fluorescence magnitude will still be visible as we continue data collection across gestation.

Impedance across the electrode pairs is similar except the face pair (electrodes C & D in Figure 5), which is relatively lower in magnitude. All impedance is within the range reported in the literature. Both magnitude and phase at high frequencies were relatively smaller and more tightly grouped. This has also been observed by other researchers and can be explained by greater ease of penetrating cell walls with high frequency signals [19–21]. Lower frequency signals have greater difficulty penetrating cell walls and injected current tends to follow extracellular paths. While data collection is ongoing, preliminary analysis shows good agreement of data from measurement to measurement for a particular patient. Future work will extract meaningful features from impedance and fluorescence data and correlate to birth outcome.

VI. CONCLUSION

In this work we have presented a novel cervical device to capture changes in tissue impedance and fluorescence concordant with preterm labor. We presented preliminary data from the device which is in agreement with published

Figure 5. Preliminary impedance and fluorescence data from one pregnant patient at one time point. Fluorescence is acquired at excitation wavelengths of every 10 nm between 320nm-420nm. Six combinations of electrode pairs used to acquire impedance include face of external os, lateral sides of the cervix, and a combination of face and side electrodes. Future work will trend this data over the course of pregnancy.

single measurements of fluorescence and impedance. Future work will capture trends in these measurements over the course of pregnancy, comparing features extracted from these trends to pregnancy outcome. Finally, knowing which features trend best with outcome will allow significant miniaturization of the device using embedded LEDs & photodiodes for the optics and miniaturized electronics for impedance, allowing the entire device to be contained within the cervical cup portion of the current prototype.

VII. ACKNOWLEDGEMENT

The authors would like to acknowledge the women who have volunteered so generously as subjects in our pilot study. We also thank Dr. Michael Harrison, Dr. Doug Miniati, Dr. Eveline Shue, and Dr. Samuel Schecter for their useful discussions and clinical advice. We also acknowledge Dr. Omer T. Inan for his technical advice in analog circuit design.

VIII. REFERENCES

- [1] H. Blencowe, S. Cousens, D. Chou, M. Z. Oestergaard, L. Say, A. Moller, M. Kinney, and J. Lawn, "15 million preterm births: priorities for action based on national, regional and global estimates," in *Born Too Soon - The Global Action Report on Preterm Birth*, C. P. Howson, M. V. Kinney, and J. E. Lawn, Eds. Geneva: World Health Organization, 2012, pp. 17–31.
- [2] D. Moster, R. T. Lie, and T. Markestad, "Long-term medical and social consequences of preterm birth.," *The New England journal of medicine*, vol. 359, no. 3, pp. 262–73, Jul. 2008.
- [3] R. E. Behrman and A. S. Butler, Eds., *Preterm Birth: Causes, Consequences, and Prevention*. Washington (DC): National Academies Press, 2007.
- [4] F. Gotsch, R. Romero, O. Erez, E. Vaisbuch, J. P. Kusanovic, S. Mazaki-Tovi, S. K. Kim, S. Hassan, and L. Yeo, "The preterm parturition syndrome and its implications for understanding the biology, risk assessment, diagnosis, treatment and prevention of preterm birth.," *The Journal of Maternal-Fetal and Neonatal Medicine*, vol. 22 Suppl 2, no. May, pp. 5–23, Jan. 2009.
- [5] R. L. Goldenberg, J. F. Culhane, J. D. Iams, and R. Romero, "Preterm Birth 1: Epidemiology and causes of preterm birth," *The Lancet*, vol. 371, pp. 75–84, 2008.
- [6] R. Romero, J. Espinoza, J. P. Kusanovic, F. Gotsch, S. Hassan, O. Erez, T. Chaiworapongsa, and M. Mazor, "The preterm parturition syndrome.," *BJOG : an international journal of obstetrics and gynaecology*, vol. 113 Suppl, pp. 17–42, Dec. 2006.
- [7] E. G. Canty and K. E. Kadler, "Procollagen trafficking, processing and fibrillogenesis.," *Journal of cell science*, vol. 118, no. Pt 7, pp. 1341–53, Apr. 2005.
- [8] Y. Mori, A. Ito, and K. Hirakawa, "The Change in Solubility of Type I Collagen in Human Uterine Cervix in Pregnancy at Term.," *Biochemical Medicine*, vol. 21, pp. 262–270, 1979.
- [9] J. C. Buckingham, R. Selden, and D. N. Danforth, "Connective Tissue Changes in the Cervix During Pregnancy and Labor," *Ann N Y Acad Sci*, vol. 97, pp. 733–742, 1962.
- [10] V. N. a Breeveld-Dwarkasing, J. M. te Koppele, R. a Bank, G. C. van der Weijden, M. a M. Taverne, and F. M. F. van Dissel-Emiliani, "Changes in water content, collagen degradation, collagen content, and concentration in repeated biopsies of the cervix of pregnant cows.," *Biology of reproduction*, vol. 69, no. 5, pp. 1608–14, Nov. 2003.
- [11] P. C. Leppert, "Anatomy and Physiology of Cervical Ripening," *Clinical obstetrics and gynecology*, vol. 38, no. 2, pp. 267–279, 1995.
- [12] R. Word, X. Li, M. Hnat, and K. Carrick, "Dynamics of cervical remodeling during pregnancy and parturition: mechanisms and current concepts," *Seminars in reproductive ...*, vol. 1, no. 212, pp. 69–79, 2007.
- [13] C. P. Read, R. A. Word, M. A. Ruschinsky, B. C. Timmons, and M. S. Mahendroo, "Cervical remodeling during pregnancy and parturition: molecular characterization of the softening phase in mice.," *Reproduction (Cambridge, England)*, vol. 134, no. 2, pp. 327–40, Aug. 2007.
- [14] P. G. Drewes, H. Yanagisawa, B. Starcher, I. Hornstra, K. Csiszar, S. I. Marinis, P. Keller, and R. A. Word, "Pelvic organ prolapse in fibulin-5 knockout mice: pregnancy-induced changes in elastic fiber homeostasis in mouse vagina.," *The American journal of pathology*, vol. 170, no. 2, pp. 578–89, Feb. 2007.
- [15] L. Granström, G. Ekman, U. Ulmsten, and A. Malmström, "Changes in the connective tissue of corpus and cervix uteri during ripening and labour in term pregnancy.," *British journal of obstetrics and gynaecology*, vol. 96, no. 10, pp. 1198–202, Oct. 1989.
- [16] V. Berghella, A. Roman, C. Daskalakis, A. Ness, and J. K. Baxter, "Gestational age at cervical length measurement and incidence of preterm birth.," *Obstetrics and gynecology*, vol. 110, no. 2 Pt 1, pp. 311–7, Aug. 2007.
- [17] D. Schlembach, L. Mackay, L. Shi, W. L. Maner, R. E. Garfield, and M. Holger, "Cervical ripening and insufficiency : From biochemical and molecular studies to in vivo clinical examination," *European Journal of Obstetrics & Gynecology and Reproductive Biology*, vol. 144S, pp. S70–S76, 2009.
- [18] M. P. O'Connell, N. J. Avis, B. H. Brown, S. R. Killick, and S. W. Lindow, "Electrical impedance measurements: an objective measure of prelabor cervical change.," *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, vol. 14, no. 6, pp. 389–91, Dec. 2003.
- [19] S. V. Gandhi, D. C. Walker, B. H. Brown, and D. O. C. Anumba, "Comparison of human uterine cervical electrical impedance measurements derived using two tetrapolar probes of different sizes.," *Biomedical engineering online*, vol. 5, p. 62, Jan. 2006.
- [20] R. P. Jokhi, B. H. Brown, and D. O. C. Anumba, "The role of cervical Electrical Impedance Spectroscopy in the prediction of the course and outcome of induced labour.," *BMC pregnancy and childbirth*, vol. 9, p. 40, Jan. 2009.
- [21] R. P. Jokhi, V. V. Ghule, B. H. Brown, and D. O. C. Anumba, "Reproducibility and repeatability of measuring the electrical impedance of the pregnant human cervix-the effect of probe size and applied pressure.," *Biomedical engineering online*, vol. 8, p. 10, Jan. 2009.
- [22] H. Maul, L. Mackay, and R. E. Garfield, "Cervical ripening: biochemical, molecular, and clinical considerations.," *Clinical obstetrics and gynecology*, vol. 49, no. 3, pp. 551–63, Sep. 2006.
- [23] R. E. Garfield, G. Saade, C. Buhimschi, I. Buhimschi, L. Shi, S.-Q. Shi, and K. Chwalisz, "Control and assessment of the uterus and cervix during pregnancy and labour," *Human Reproduction Update*, vol. 4, no. 5, pp. 673–695, 1998.
- [24] R. E. Garfield, W. L. Mader, L. Shi, S. Q. Shi, and G. R. Saade, "Uterine EMG and Cervical LIF - Promising Technologies in Obstetrics," *Current Women's Health Reviews*, vol. 2, pp. 207–221, 2006.
- [25] R. E. Garfield, H. Maul, W. Maner, C. Fittkow, G. Olson, L. Shi, and G. R. Saade, "Uterine EMG and Light Induced Fluorescence in the Management of Term and Preterm Labor.pdf," *J Soc Gynecol Investig*, vol. 9, pp. 265–75, 2002.
- [26] R. E. Garfield, "Instrumentation for the diagnosis of term and preterm labour," *J. Perinat. Med.*, vol. 26, no. 1998, pp. 413–436, 1998.
- [27] K. Sokolov, J. Galvan, A. Myakov, A. Lacy, R. Lotan, and R. Richards-Kortum, "Realistic three-dimensional epithelial tissue phantoms for biomedical optics," *Journal of Biomedical Optics*, vol. 7, no. 1, pp. 148–156, 2002.
- [28] R. Drezek and R. Richards-kortum, "Understanding the contributions of NADH and collagen to cervical tissue fluorescence spectra : Modeling , measurements , and implications," *Journal of Biomedical Optics*, vol. 6, no. 4, pp. 385–396, 2001.
- [29] P. C. Leppert and S. Y. Yu, "Three-dimensional structures of uterine elastic fibers: scanning electron microscopic studies.," *Connective tissue research*, vol. 27, no. 1, pp. 15–31, Jan. 1991.