EINDHOVEN UNIVERSITY OF TECHNOLOGY

Electrohysterography in pregnancy

Citation for published version (APA):
de Lau, H. (2017). *Electrohysterography in pregnancy: from technical innovation to clinical practice*. [Phd Thesis 1 (Research TU/e / Graduation TU/e), Electrical Engineering]. Technische Universiteit Eindhoven.

Document status and date:
Published: 02/10/2017

Document Version:
Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.tue.nl/taverne

Take down policy
If you believe that this document breaches copyright please contact us at:

openaccess@tue.nl

providing details and we will investigate your claim.

Download date: 08. Jul. 2024

Electrohysterography in pregnancy
from technical innovation to clinical application

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Technische Universiteit Eindhoven, op gezag van de rector magnificus prof.dr.ir. F.P.T. Baaijens, voor een commissie aangewezen door het College voor Promoties, in het openbaar te verdedigen op maandag 2 oktober 2017 om 16:00 uur

door

Hinke de Lau

geboren te Utrecht

Dit proefschrift is goedgekeurd door de promotoren en de samenstelling van de promotiecommissie is als volgt:

voorzitter:	prof.dr.ir. A.B. Smolders
1e promotor:	prof.dr. S.G. Oei
copromotor(en):	dr. C. Rabotti
	dr.ir. M. Mischi
leden:	prof.dr. W.J.E.P. Lammers (UAE University)
	prof.dr.ir. C.K. Marque (Université de Technologie de Compiègne)
	prof.dr.ir. J.W.M. Bergmans
	dr. A. Kwee (UMC Utrecht)
reserve:	dr. J. Hu PDEng MEng

Het onderzoek of ontwerp dat in dit proefschrift wordt beschreven is uitgevoerd in overeenstemming met de TU/e Gedragscode Wetenschapsbeoefening.

List of abbreviations

ADP	–	Adenosine DiPhosphate
ATP	–	Adenosine TriPhosphate
AUC	–	Area Under the Curve
BMI	–	Body Mass Index
CCI	–	Contractions Consistency Index
CTG	–	Cardio TocoGram
CV	–	Conduction Velocity
ECG	–	ElectroCardioGram
EHG	–	ElectroHysteroGram
eIUP	–	Estimated IntraUterine Pressure
FHR	–	Fetal Heart Rate
GA	–	Gestational Age
IUPC	–	IntraUterine Pressure Catheter
MVU	–	MonteVideo Units
PPROM	–	Preterm Prelabor Rupture Of Membranes
PSD	–	Power Spectral Density
PSDpf	–	Power Spectral Density Peak Frequency
RMS	–	Root Mean Square
ROC	–	Receiver Operating Characteristics
SNR	–	Signal to Noise Ratio
TOLAC	–	Trial Of Labor After previous Cesarean section
TVU CL	–	TransVaginal Ultrasonic Cervical Length
VBAC	–	Vaginal Birth After Cesarean section
Vrest	–	Resting potential

Contents

Chapter 1

Introduction and thesis outline

Introduction

Monitoring uterine contractions is an essential part of electronic fetal monitoring and is well established in high risk pregnancy and childbirth [1-4]. During pregnancy timely and accurate recognition of pathological preterm uterine contractions allows timely intervention [5-8]. During labor, frequency, regularity and duration of contractions needs to be closely monitored in order to establish the correct dosage of uterotonics and prevent hyperstimulation [9-11]. Furthermore, in order to assess the fetal condition, the temporal relationship of the fetal heart rate (FHR) pattern with uterine contractions needs to be reviewed [12, 13]. However, present methods for contraction monitoring leave room for improvement and new methods are needed. Imminent preterm delivery cannot be accurately established using current monitoring techniques, leading to both under treatment and, in particular, overtreatment of women presenting with preterm contractions; more than half of the patients admitted for preterm labor, deliver at term [14-18]. Monitoring contractions during term labor is challenging as well, and requires a tradeoff between the safety of the non-invasive external tocodynamometer and the accuracy of the invasive intrauterine pressure catheter (IUPC) [19-22]. Currently, inadequate tocogram tracings are accepted in favor of patient safety and comfort [23, 24].

The mechanical contractions of the uterus are preceded and initiated by the electrical activity of the myometrial cells in the form of intermittent bursts of action potentials [25-30]. It is well established that the patterns and characteristics of the electrical activity of the myometrium evolve in the course of pregnancy towards labor [26, 27, 31-34]. The myometrium changes from being quiescent in the beginning of pregnancy to producing regular, synchronous, high frequent and high amplitude bioelectrical bursts [27, 33, 35]. Electrohysterography involves the recording of this electrical activity of the myometrium [36-38]. Similar to the electrocardiogram (ECG), electrohysterography involves the recording of the propagating electrical activity underlying contractions rather than the mechanical output [29]. It is hard to imagine cardiology without the ECG. If one were to draw an analogy to obstetrics, only blood pressure and pulse would be used. Likewise, the Electrohysterogram (EHG) is a signal with great potential, unveiling information on the evolution of uterine activity and the onset of labor [27, 31-33, 39, 40], making it a promising tool for predicting imminent preterm delivery [38, 41-43]. In addition, the signal is relatively easy to obtain by placing electrodes on the abdomen [25, 44]. Therefore, it is also a candidate for replacing current methods for monitoring contractions during labor, combining accuracy and safety [45-48] and possibly providing additional information on the progress of labor [49, 50].

Electrohysterography is however far from new, the signal was first described in 1931 in Germany by dr Otto Bode using an electrocardiograph [51]. The author was convinced that he found a promising technique:

Ich bin überzeugt, daβ es gelingen wird, durch Verbesserung der Methodik weitere Feinheiten der physiologischen wie pathologischen Uteruskontraktion zur Darstellung zu bringen.[1]

Most probably, progress has been slower than he envisioned at the time. Over 85 years later, the EHG still has not found widespread use in clinical practice. While obtaining an EHG is relatively uncomplicated, the interpretation remains very challenging. The signal propagates through the intermediate tissue layers up to the abdominal surface where it is recorded. Its passage through multiple layers causes the signal to be diffused and filtered [52]. Tissue layers can vary in thickness and move mutually as well [42]. Artefacts can be introduced by either motion [53-55] or other bioelectrical signals [35, 53, 56]. A more thorough understanding is needed on the link between the action potentials originating in the myometrium and the resulting signal recorded at the abdominal surface for a better interpretation of the EHG [57]. Furthermore, algorithms need to be developed and tested in a clinical setting in order to make the analysis automated, and more importantly objective and reproducible. Finally, real time analysis is needed to make the final step towards a clinical application.

[1] I am convinced that, by improving the methodology, it will be possible to bring forth further intricacies of physiological and pathological uterine contractions.

Thesis outline

The objective of this thesis, is to contribute to the clinical introduction of the EHG. This comprises improving and developing automated EHG signal analysis methods, and exploring clinical applications for detecting preterm labor, monitoring term labor and detecting uterine rupture. The physiology underlying uterine contractions is no readily available knowledge for most clinicians and is presented in chapter 1, outlining the physiology of smooth muscle cells and the differences with striated muscle. An overview of the literature on the EHG is presented in chapter 2, ending with the current challenges for the clinical application of the EHG. Part 2 covers preterm labor detection, focusing on propagation analysis in the EHG. In chapter 3, we describe the results of a study in which a novel automated method for estimation of the conduction velocity was evaluated for detecting imminent delivery using a grid of 64 electrodes. Chapter 4 describes the study protocol of the PoPE study, which aimed to repeat the results of Lucovnik et al [41], employing a less complex electrode configuration of 4 monopolar electrodes in order to enable clinical application. Chapter 5 presents the results of the PoPE study, in which the conduction velocity was estimated in the EHG of pregnant women admitted for threatening preterm labor. In chapter 6, non-linear analysis as alternative approach for EHG analysis for preterm labor detection was evaluated in the cohort of patients of the PoPE study. Part 3 continues with term labor monitoring, chapter 7 starts off with a review on the tocogram changes that are visible in case of uterine rupture during trial of labor after a previous cesarean section. In chapter 8 propagation analysis in the EHG surrounding the uterine scar during trial of labor, was explored as novel method for detecting uterine rupture. Chapter 9 concludes with a study in which movement of uterus was continuously tracked by ultrasound during labor and correlated to an abdominally placed accelerometer, aiming to reduce movement induced artefacts in the EHG.

References

1. Meyer-Breiting P, Leuwer M: **[Fetal monitoring for anesthesiologists]**. *Der Anaesthesist* 1992, **41**(1):47-52.
2. Excellence NIfHaC: **Intrapartum care: Care of healthy women and their babies during childbirth**. 2007.
3. **ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles**. *Obstet Gynecol* 2009, **114**(1):192-202.
4. NVOG: **Intrapartum foetale bewaking à terme**. In.; 2013.
5. Amon E, Midkiff C, Winn H, Holcomb W, Shumway J, Artal R: **Tocolysis with advanced cervical dilatation**. *Obstet Gynecol* 2000, **95**(3):358-362.
6. Anotayanonth S, Subhedar NV, Garner P, Neilson JP, Harigopal S: **Betamimetics for inhibiting preterm labour**. *Cochrane Database Syst Rev* 2004(4):CD004352.
7. King J, Flenady V, Cole S, Thornton S: **Cyclo-oxygenase (COX) inhibitors for treating preterm labour**. *Cochrane Database Syst Rev* 2005(2):CD001992.
8. Papatsonis D, Flenady V, Cole S, Liley H: **Oxytocin receptor antagonists for inhibiting preterm labour**. *Cochrane Database Syst Rev* 2005(3):CD004452.
9. Bakker PC, Kurver PH, Kuik DJ, Van Geijn HP: **Elevated uterine activity increases the risk of fetal acidosis at birth**. *Am J Obstet Gynecol* 2007, **196**(4):313 e311-316.
10. Bakker PC, van Geijn HP: **Uterine activity: implications for the condition of the fetus**. *Journal of perinatal medicine* 2008, **36**(1):30-37.
11. Simpson KR, James DC: **Effects of oxytocin-induced uterine hyperstimulation during labor on fetal oxygen status and fetal heart rate patterns**. *Am J Obstet Gynecol* 2008, **199**(1):34 e31-35.
12. Parer JT, King T, Flanders S, Fox M, Kilpatrick SJ: **Fetal acidemia and electronic fetal heart rate patterns: is there evidence of an association?** *J Matern Fetal Neonatal Med* 2006, **19**(5):289-294.
13. Robinson B: **A Review of NICHD Standardized Nomenclature for Cardiotocography: The Importance of Speaking a Common Language When Describing Electronic Fetal Monitoring**. *Reviews in obstetrics and gynecology* 2008, **1**(2):56-60.
14. Fuchs IB, Henrich W, Osthues K, Dudenhausen JW: **Sonographic cervical length in singleton pregnancies with intact membranes presenting with threatened preterm labor**. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2004, **24**(5):554-557.
15. Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, Franks AL: **Hospitalizations during pregnancy among managed care enrollees**. *Obstet Gynecol* 2002, **100**(1):94-100.
16. King JF, Grant A, Keirse MJ, Chalmers I: **Beta-mimetics in preterm labour: an overview of the randomized controlled trials**. *Br J Obstet Gynaecol* 1988, **95**(3):211-222.
17. McPheeters ML, Miller WC, Hartmann KE, Savitz DA, Kaufman JS, Garrett JM, Thorp JM: **The epidemiology of threatened preterm labor: a prospective cohort study**. *Am J Obstet Gynecol* 2005, **192**(4):1325-1329; discussion 1329-1330.
18. Scott CL, Chavez GF, Atrash HK, Taylor DJ, Shah RS, Rowley D: **Hospitalizations for severe complications of pregnancy, 1987-1992**. *Obstet Gynecol* 1997, **90**(2):225-229.
19. Rood KM: **Complications associated with insertion of intrauterine pressure catheters: an unusual case of uterine hypertonicity and uterine perforation resulting in fetal distress after insertion of an intrauterine pressure catheter**. *Case reports in obstetrics and gynecology* 2012, **2012**:517461.
20. Thadepalli H, Appleman MD, Chan WH, Maidman JC, Davidson EC, Jr.: **Amniotic fluid contamination during internal fetal monitoring**. *J Reprod Med* 1978, **20**(2):93-96.
21. Trudinger BJ, Pryse-Davies J: **Fetal hazards of the intrauterine pressure catheter: five case reports**. *Br J Obstet Gynaecol* 1978, **85**(8):567-572.
22. Wilmink FA, Wilms FF, Heydanus R, Mol BW, Papatsonis DN: **Fetal complications after placement of an intrauterine pressure catheter: a report of two cases and review of the literature**. *J Matern Fetal Neonatal Med* 2008, **21**(12):880-883.
23. Bakker PC, Zikkenheimer M, van Geijn HP: **The quality of intrapartum uterine activity monitoring**. *Journal of perinatal medicine* 2008, **36**(3):197-201.
24. Reinhard J, Hayes-Gill BR, Schiermeier S, Loser H, Niedballa LM, Haarmann E, Sonnwald A, Hatzmann W, Heinrich TM, Louwen F: **Uterine activity monitoring during labour--a multi-centre, blinded two-way trial of external tocodynamometry against electrohysterography**. *Zeitschrift fur Geburtshilfe und Neonatologie* 2011, **215**(5):199-204.
25. Buhimschi C, Boyle MB, Saade GR, Garfield RE: **Uterine activity during pregnancy and labor assessed by simultaneous recordings from the myometrium and abdominal surface in the rat**. *Am J Obstet Gynecol* 1998, **178**(4):811-822.
26. Buhimschi C, Garfield RE: **Uterine contractility as assessed by abdominal surface recording of electromyographic activity in rats during pregnancy**. *Am J Obstet Gynecol* 1996, **174**(2):744-753.
27. Doret M, Bukowski R, Longo M, Maul H, Maner WL, Garfield RE, Saade GR: **Uterine electromyography characteristics for early diagnosis of mifepristone-induced preterm labor**. *Obstet Gynecol* 2005, **105**(4):822-830.
28. Lopes P, Germain G, Breart G, Reitano S, Le Houezec R, Sureau C: **Electromyographical study of uterine activity in the human during labour induced by prostaglandin F2 alpha**. *Gynecologic and obstetric investigation* 1984, **17**(2):96-105.
29. Marshall JM: **Regulation of activity in uterine smooth muscle**. *Physiological reviews Supplement* 1962, **5**:213-227.
30. Pajntar M, Roskar E, Rudel D: **Electromyographic observations on the human cervix during labor**. *Am J Obstet Gynecol* 1987, **156**(3):691-697.

31. Demianczuk N, Towell ME, Garfield RE: **Myometrial electrophysiologic activity and gap junctions in the pregnant rabbit**. *Am J Obstet Gynecol* 1984, **149**(5):485-491.
32. Kao CY: **Long-term observations of spontaneous electrical activity of the uterine smooth muscle**. *Am J Physiol* 1959, **196**(2):343-350.
33. Miller SM, Garfield RE, Daniel EE: **Improved propagation in myometrium associated with gap junctions during parturition**. *Am J Physiol* 1989, **256**(1 Pt 1):C130-141.
34. Parkington HC, Tonta MA, Brennecke SP, Coleman HA: **Contractile activity, membrane potential, and cytoplasmic calcium in human uterine smooth muscle in the third trimester of pregnancy and during labor**. *Am J Obstet Gynecol* 1999, **181**(6):1445-1451.
35. Buhimschi C, Boyle MB, Garfield RE: **Electrical activity of the human uterus during pregnancy as recorded from the abdominal surface**. *Obstet Gynecol* 1997, **90**(1):102-111.
36. Devedeux D, Marque C, Mansour S, Germain G, Duchene J: **Uterine electromyography: a critical review**. *Am J Obstet Gynecol* 1993, **169**(6):1636-1653.
37. Wolfs GM, van Leeuwen M: **Electromyographic observations on the human uterus during labour**. *Acta obstetricia et gynecologica Scandinavica Supplement* 1979, **90**:1-61.
38. Vinken MP, Rabotti C, Mischi M, Oei SG: **Accuracy of frequency-related parameters of the electrohysterogram for predicting preterm delivery: a review of the literature**. *Obstet Gynecol Surv* 2009, **64**(8):529-541.
39. Wolfs G, Rottinghuis H: **Electrical and mechanical activity of the human uterus during labour**. *Archiv fur Gynakologie* 1970, **208**(4):373-385.
40. Wolfs G, van Leeuwen M, Rottinghuis H, Boeles JT: **An electromyographic study of the human uterus during labor**. *Obstet Gynecol* 1971, **37**(2):241-246.
41. Lucovnik M, Maner WL, Chambliss LR, Blumrick R, Balducci J, Novak-Antolic Z, Garfield RE: **Noninvasive uterine electromyography for prediction of preterm delivery**. *Am J Obstet Gynecol* 2011, **204**(3):228 e221-210.
42. Marque CK, Terrien J, Rihana S, Germain G: **Preterm labour detection by use of a biophysical marker: the uterine electrical activity**. *BMC pregnancy and childbirth* 2007, **7 Suppl 1**:S5.
43. Rabotti C, Mischi M, Oei SG, Bergmans JW: **Noninvasive estimation of the electrohysterographic action-potential conduction velocity**. *IEEE Trans Biomed Eng* 2010, **57**(9):2178-2187.
44. Maul H, Maner WL, Olson G, Saade GR, Garfield RE: **Non-invasive transabdominal uterine electromyography correlates with the strength of intrauterine pressure and is predictive of labor and delivery**. *J Matern Fetal Neonatal Med* 2004, **15**(5):297-301.
45. Euliano TY, Nguyen MT, Darmanjian S, McGorray SP, Euliano N, Onkala A, Gregg AR: **Monitoring uterine activity during labor: a comparison of 3 methods**. *Am J Obstet Gynecol* 2013, **208**(1):66 e61-66.
46. Haran G, Elbaz M, Fejgin MD, Biron-Shental T: **A comparison of surface acquired uterine electromyography and intrauterine pressure catheter to assess uterine activity**. *Am J Obstet Gynecol* 2012, **206**(5):412 e411-415.
47. Jacod BC, Graatsma EM, Van Hagen E, Visser GH: **A validation of electrohysterography for uterine activity monitoring during labour**. *J Matern Fetal Neonatal Med* 2010, **23**(1):17-22.
48. Rabotti C, Mischi M, van Laar JO, Oei GS, Bergmans JW: **Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals**. *Physiol Meas* 2008, **29**(7):829-841.
49. Euliano TY, Marossero D, Nguyen MT, Euliano NR, Principe J, Edwards RK: **Spatiotemporal electrohysterography patterns in normal and arrested labor**. *Am J Obstet Gynecol* 2009, **200**(1):54 e51-57.
50. Garcia-Gonzalez MT, Charleston-Villalobos S, Vargas-Garcia C, Gonzalez-Camarena R, Aljama-Corrales T: **Characterization of EHG contractions at term labor by nonlinear analysis**. *Conf Proc IEEE Eng Med Biol Soc* 2013, **2013**:7432-7435.
51. Bode O: **Das Elektrohysterogramm**. *Archiv fur Gynakologie* 1931, **146**(1):123-128.
52. Rabotti C, Mischi M, Beulen L, Oei G, Bergmans JW: **Modeling and identification of the electrohysterographic volume conductor by high-density electrodes**. *IEEE Trans Biomed Eng* 2010, **57**(3):519-527.
53. Hassan M, Boudaoud S, Terrien J, Karlsson B, Marque C: **Combination of canonical correlation analysis and empirical mode decomposition applied to denoising the labor electrohysterogram**. *IEEE Trans Biomed Eng* 2011, **58**(9):2441-2447.
54. Hon EH, Davis CD: **Cutaneous and uterine electrical potentials in labor; an experiment**. *Obstet Gynecol* 1958, **12**(1):47-53.
55. Jezewski J, Horoba K, Matonia A, Wrobel J: **Quantitative analysis of contraction patterns in electrical activity signal of pregnant uterus as an alternative to mechanical approach**. *Physiol Meas* 2005, **26**(5):753-767.
56. Leman H, Marque C: **Rejection of the maternal electrocardiogram in the electrohysterogram signal**. *IEEE Trans Biomed Eng* 2000, **47**(8):1010-1017.
57. Marque C, Laforet J, Rabotti C, Alexandersson A, Germain G, Gondry J, Karlsson B, Leskosek B, Mischi M, Muszinski C *et al*: **A multiscale model of the electrohysterogram the BioModUE_PTL project**. *Conf Proc IEEE Eng Med Biol Soc* 2013, **2013**:7448-7451.

Chapter 2

Background: physiology and the current state of electrohysterography

2.1 Introduction

One of the main challenges in obstetrics, is the prevention and optimal management of preterm labor. It has been estimated that annually a total of 12,9 million babies are born preterm, before 37 weeks of gestation [1], approximately 75% of which are spontaneous: related to preterm labor or preterm premature rupture of the membranes [2]. Complications of preterm birth are the leading cause for neonatal mortality. Preterm birth ranges from 8,6% for the developed countries and 13,3% for southern Asia [3]. Addressing preterm birth is an important element for reaching Millennium Development Goal 4, calling for the reduction of child deaths by two-thirds by 2015 [3]. Prematurity is also associated with significant short term morbidity [4] as well as chronic conditions, including asthma and a subnormal cognitive function [5]. One of the key interventions to improve the neonatal outcome, is the antenatal administration of corticosteroids to the mother to induce fetal stress which provides a stimulus for fetal lung maturation. Corticosteroid administration is known to reduce both neonatal mortality and the incidence of the respiratory distress syndrome, intraventricular hemorrhage, and neonatal sepsis [6]. However, exposure to corticosteroids causes fetal as well as maternal side effects. Clinical data suggests that infants that are exposed to antenatal corticosteroids have reduced basal and stress-induced cortisol secretion [7] while maternal side effects include transient hyperglycemia, which can be severe in case of gestational diabetes [8]. In case of premature labor, tocolytic drug therapy is often used in order to delay delivery by at least 48 hours so that corticosteroids can achieve their maximum effect. Depending on the type of tocolytic agent used, tocolytic drug therapy frequently leads to maternal side effects such as palpitations, hypotension, headache and pulmonary edema [9-11]. These side effects can be severe and even lead to myocardial infarction and fetal death [12, 13].

Premature contractions are one of the most common reason for admission to an obstetrical ward early in pregnancy [14, 15]. Identifying the women who will actually deliver preterm, is an inexact process and the existing methods used for detecting preterm labor are subjective, inaccurate, and cannot predict the time to delivery. Intrauterine pressure measurement can provide quantitative information on contraction strength, but can only be used during labor and when the membranes have ruptured. External tocodynamometers are extensively used for pregnancy monitoring, but provide only quantification of the number of contractions per time unit, and frequently fail to show contractions even in term labor [16, 17]. Moreover, visible uterine contractions on the external tocogram is a poor predictor of preterm delivery [18-20]. Transvaginal ultrasonic cervical length (TVU CL) measurement is commonly used for predicting imminent preterm delivery, but sensitivity and specificity are moderate, especially for intermediate values for cervical length [21]. At present, the biochemical marker fetal fibronectin (fFN) is being introduced for short term prediction of preterm delivery. This test has a high negative predictive value, but it cannot be used to predict the time to delivery [22]. Finally, minor cervical changes can be hard to detect by digital cervical examination [23, 24], while advanced cervical dilatation is a late sign of imminent delivery and reduces the chance of successfully delaying delivery by 48 hours [25]. Overall, more than 50% of the patients admitted for imminent preterm labor deliver at term [14, 15, 26-28]. Current methods of detecting preterm labor are leading to overtreatment as well as undertreatment. Better methods of predicting preterm delivery are needed to prevent mother and child from being unnecessarily exposed to the potential side effects of tocolytics and corticosteroids as well as to initiate treatment when preterm labor is detected before the changes in uterine contractility are irreversible and treatment is ineffective. In addition, costs could potentially be substantially reduced by preventing unnecessary transport of pregnant women to perinatal centers and the associated treatment costs.

There is room for improvement in monitoring contractions during term labor as well [16]. Monitoring contractions currently only consists of measuring the mechanical output of the uterus by methods of varying accuracy. Most typically, an external tocodynamometer is used, which has the advantage of being non-invasive, easy to use, and safe. It provides information on contraction frequency and duration, but not on contraction strength. The device is a strain gauge and therefore dependent on the mechanical coupling between the transducer and the uterine muscle. It can fail to detect uterine contractions in some patients, especially in the growing obese population [17, 29, 30]. The most reliable approach is intrauterine pressure measurement, using a catheter to directly measure the pressure inside the uterus. It provides quantitative information on uterine contractions and is independent of the body habitus. The application is limited to women in active labor and ruptured membranes. Moreover, the use of an intrauterine pressure catheter (IUPC) is thought to be associated with a small risk of infection although more serious complications have been reported, even leading to fetal death [31-33]. Therefore the obstetrician’s dilemma is to choose between safety and accuracy. New methods are needed to improve both term labor monitoring and preterm labor prediction, and one such candidate is electrohysterography.

(Electro)physiology and EHG signals are closely linked. In order to understand the measured signal and the evolution of electrical activity towards labor, one must have a basic understanding of uterine electrophysiology. This first chapter of this thesis starts with the physiology related to uterine contractions, beginning with the anatomy of the myometrium and individual uterine smooth muscle cells. Subsequently, the activation of uterine myocytes on a cell level, the propagation of the electrical impulses on the organ level, and finally the excitation-contraction coupling. The second part of the chapter covers electrohysterography, starting with a summary of the technical aspects and recording techniques, followed by the studies on the various EHG parameters that are considered for predicting preterm delivery and finally EHG based estimation of the intrauterine pressure during term labor.

2.2 Physiology of contractions

2.2.1 The special characteristics of the myometrium

The uterus is an exceptional organ exerting diverse and contrasting functions. It undergoes dramatic physical and functional changes in the course of pregnancy to be able to nurture, protect and finally expel the fetus; Pregnancy starts with implantation of the fertilized ovum, which is mainly facilitated by the endometrium, although uterine contractility also appears to be of importance for both embryo transport and implantation [34, 35]. During pregnancy the uterus grows from weighing 60 g in the non-pregnant state, to over 1000 grams at full term whereby the volume of the uterine cavity increases from 10 ml to about 5000 ml [36, 37]. Fetal growth is supported by extensive adaptation of the uterine blood supply by the process of angiogenesis, which is necessary for an adequate supply of nutrients [38]. During this period the myometrium needs to remain electrically relatively quiescent while the cervix must remain rigid and closed in order to retain the pregnancy [39, 40]. At term on the other hand, the myometrium needs to contract forcefully in conjunction with remodeling of the cervix, in order to allow dilatation of the cervix and finally expulsion of the fetus [40-42]. Immediately after delivery, hemostasis is maintained by tonic contraction of the myometrium in combination with the anatomy of the vasculature [35, 43]. Following the immediate reduction in size, the uterus returns back to the normal non-pregnant size in approximately four to six weeks [37, 44]. In order to carry out all of these functions, the uterus requires specific anatomical and physiological properties.

The uterus mostly consists of smooth muscle cells, which differ in some important aspects from skeletal muscle cells [45]. In contrast to the understanding of skeletal and cardiac muscle, knowledge on smooth muscle cells is rudimentary. Smooth muscle cells are a heterogeneous collection of cells, highly plastic, and perform diverse functions. Unlike skeletal muscle, smooth muscle cells are present in organs which consist of more than only muscle tissue. The contractile apparatus inside smooth muscle cells has some basic similarities to that of skeletal muscle [46-48]. The way this contractile apparatus is triggered and contraction is maintained, is distinctly different though [47, 49-52]. This has important implications for the kinetics and energetics of uterine smooth muscle and enables slow but prolonged contraction at low energy expenditure [51]. Moreover, significant variations exist among the different types of smooth muscle cells with regard to cell activation and signaling principles [45]. Recent advances in the field of gastric and small intestinal electrophysiology have uncovered contractions patterns and a pacemaker site [53-55]. In the uterus, no pacemaker site has been identified to date and in fact many questions remain as regards to the physiology behind uterine contractions [35, 43, 56-58]; the cellular mechanism behind pacemaker activity remains unclear [52, 59-63], there is no complete understanding of the contribution of the various ion channels to cell depolarization and repolarization [35, 56-58, 63, 64], or the role of sarcoplasmic reticulum in cell contraction [52, 59, 60]. In addition, uncertainties remain with respect to pathways of cell to cell conduction of action potentials [65-68].

2.2.2 Anatomy of the myometrium

The uterus is a tubular organ originating from the müllerian ducts, which forms a single cavity (monkeys, humans) or two horns (rats, rabbits, ewes or human malformations) depending on the extent of the fusion [69]. The uterine wall can be divided into three layers: the inner endometrium, the myometrium and the outer serosa layer. During the first trimester of pregnancy, the uterine wall thickness increases from 10 mm to a maximum of 25 mm at the end of the first trimester, and then decreases to 5-10 mm at the end of pregnancy [70]. Initially, growth involves hyperplasia of the myocytes under the influence of among others estrogen [71-73]. This is followed by hypertrophic growth of the myocytes accompanied by angiogenesis and remodeling of the extracellular matrix, which is driven by distention of the wall by the growing fetus [38, 74-76]. This causes the myocytes to increase in length by a factor of ten.

The myometrium can be divided in three different layers of muscle cells: the outer stratum supravasculare, the stratum vasculare and the inner stratum subvasculare, also called the subendometrial myometrium. The cells are arranged in bundles, connected by connective tissue, running in different directions. The degree of organization and direction of the bundles in the human uterus remains a subject of debate, as well as the degree to which the different layers can be distinguished. Traditionally, the structure of the fibers has been described as two counter rotating networks, as is the case in non-primate species, with the inner stratum subvasculare consisting of circular fibers running perpendicular to the longitudinal axis, and the outer stratum supravasculare consisting of muscle fibers running in parallel with the longitudinal axis [77, 78]. Wetzstein and Renn however, described the same circular orientation in the stratum subvasculare, yet in the stratum vasculare observed fibers running in all directions [79, 80]. This was confirmed in a more recent study by magnetic resonance diffusion tensor imaging in non-pregnant uteri, where directional structures were only found in the inner layer [81]. This inner layer of the myometrium, the stratum subvasculare or subendometrial myometrium, is also thought to be of non-Müllerian origin which could explain the different arrangement [82]. In the pregnant uterus, the different layers appear to be less distinct [83]. In 3D structural analysis of the term pregnant uterus, bundles of fibers were identified of 1-2 mm in diameter, referred to as fasciculi [84]. These structures were found to intertwine and form a sheet like structure, with no prevailing direction, interweaving with the ample vasculature. It has been suggested that this configuration has an important hemostatic function in primates in preventing blood loss after delivery of the placenta [35].

In contrast to skeletal muscle cells, smooth muscle cells have a predominance of actin over myosin by a factor of six [85]. Three types of filaments form a dense network which functions as a motor: the thin filaments, mainly composed of two isomers actin [86], thick filaments, made of myosin and finally intermediate filaments. The actin and myosin filaments cause the cell contraction through a sliding interaction, initiated by phosphorylation of myosin. In this way the myosin filaments form the motor of the uterine myocytes. The actin filaments are connected to dense bodies, which in turn are interconnected by intermediate filaments. This network of filaments is anchored to the cell wall by dense bands. In this way, the force is transmitted to the outside of the cell and the cell shortens. The actin-myosin bundles are organized in a unstructured way, and therefore uterine myocytes do not have the characteristic striated appearance of skeletal muscle . Figure 1 shows the contractile apparatus of uterine myocytes: the network of filaments and a more detailed view of the actin-myosin complex.

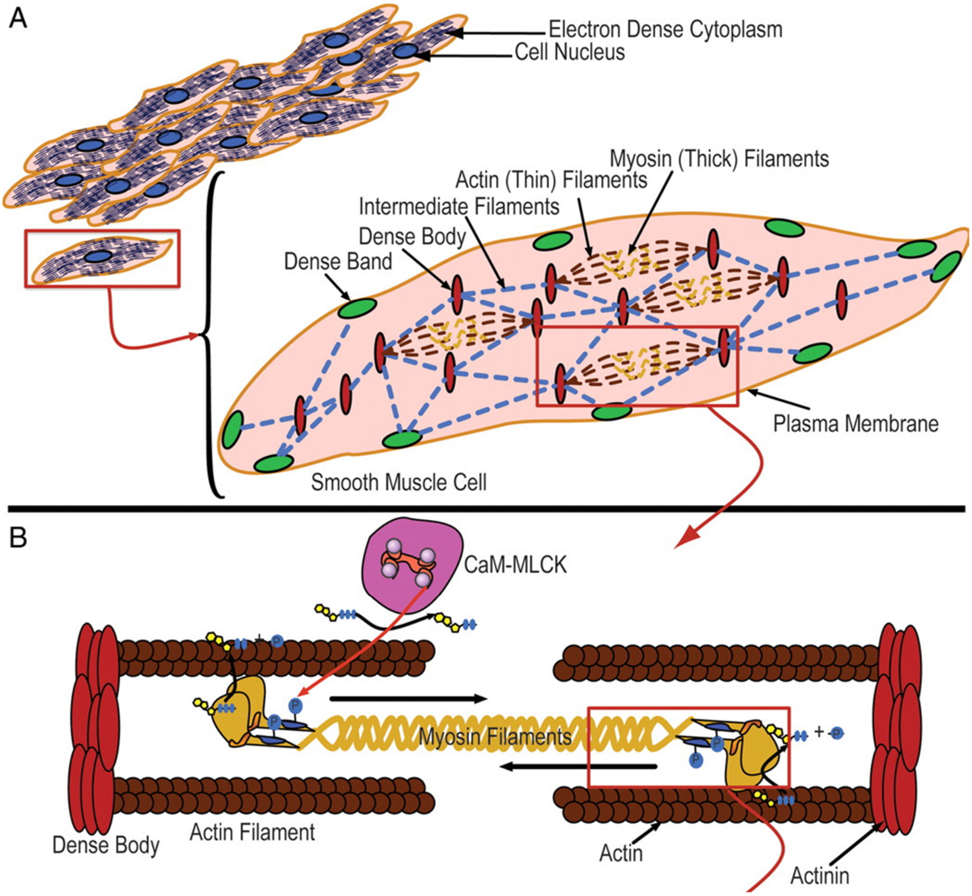

Figure 1: overview of the contractile apparatus of uterine myocytes. Part A shows the network of actin/myosin filaments, interconnected by intermediate filaments which are anchored to dense bodies and bands. Part B shows the complex of actin and myosin filaments in more detail. Courtesy of [35].

2.2.3 Electrical activation

Cell activation

Similar to skeletal muscle cells and nerve cells, uterine smooth muscle cells are activated by action potentials [87-92]. The depolarization of the cell membrane triggers a cascade of intracellular events leading to cell contraction. However, unlike in neurons and skeletal muscle cells, Ca^{2+} rather than Na^{2+} is the major charge carrier in membrane depolarization [57]. In addition, Ca^{2+} also serves as intracellular messenger triggering cell contraction. Therefore, the concentration of intracellular calcium (Ca^{2+}) is a key regulating factor in the contractile status of uterine myocytes [93, 94].

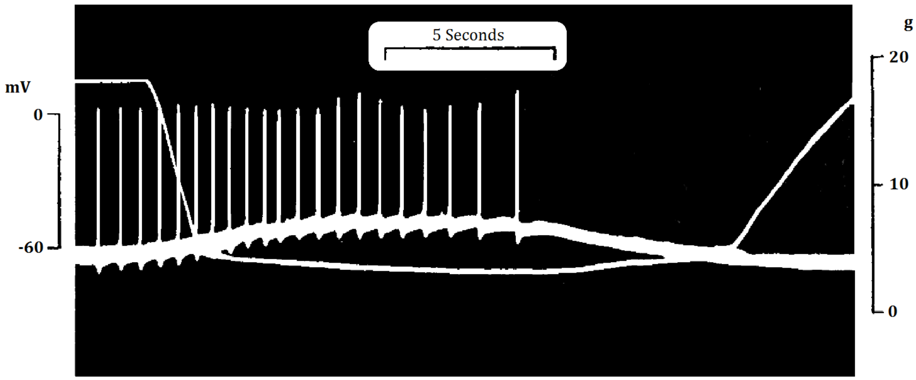

Figure 2: electrical activity of an individual muscle fiber of the rat uterus. The bottom trace shows the membrane potential showing a train of action potentials, which precedes the mechanical output (top trace). Redrawn from [95].

The plasma membrane potential is regulated by controlling ion movements across the cell membrane. Direction and magnitude of ion flux across the cell membrane is determined by gradient and ionic permeability. The plasma membrane itself is impermeable and ionic movements are mainly governed by specific ionic channels which all have different properties. The conductance of ionic channels may be influenced by numerous factors, including membrane potential [96-99], hormones [64, 95, 98, 100, 101], and pharmacological agents [97, 99, 102, 103].

The resting potential (V_{rest}) is determined by the distribution and conductance of Na^+, K^+ and Cl^-. However, similar to other cells, V_{rest} is mainly established by an outward current of K^+ and an electrochemical gradient which is maintained by ion pumps requiring adenosine triphosphate (ATP) [35, 56]. Furthermore, the efflux of K^+ repolarizes the membrane potential after depolarization. The main function of the various K+ channels is to reduce the excitability by hyperpolarizing and repolarizing the cell membrane. The K^+ channels therefore contribute to uterine quiescence during pregnancy [56, 57, 104]. K^+ channels operate based on the membrane potential, calcium concentration or ATP. However their relative contribution remains unclear [56, 104]. The relaxant effect of the ATPase K^+ pump is currently a target for pharmacological research [102]. In both animal [95, 101, 105] and human [106-108] *In vitro* experiments, V_{rest} ranged between -35 mV and -65 mV depending on the steroid hormonal status [95, 101]. However, in pregnant women, V_{rest} has been recorded as low as -80 mV [109]. V_{rest} is thought to depend on the gestational age (GA), increasing towards term and approaching the potential required for opening of the voltage operated calcium channels [52, 56, 57, 64].

In the resting state, Ca^{2+} shows by far the largest electrochemical gradient: the extracellular Ca^{2+} concentration is approximately 10^4 greater than the intracellular concentration, allowing for a rapid influx of Ca^{2+} ions upon opening of the calcium channels [57]. Multiple types of Ca^{2+} channels are present in human uterine myocytes [52, 63, 96, 97, 99]. The predominant type is the L type Ca^{2+} channel, which is voltage sensitive and is triggered at approximately -

40 mV [97-99]. The L-type channels have a slow action, allowing influx over a prolonged time. T-type Ca^{2+} channels have faster kinetics and are thought to promote opening of the L-type channels [96, 99]. Ca^{2+} is the main but not only charge carrier in creating action potentials; Na^{+} channels have been observed in human myometrial cells as well [110] and become more abundant approaching term [97, 98]. Na^{+} channels allow rapid influx of Na^{+} upon depolarization and contribute to the discharge frequency of myocytes [97, 98]. Chloride channels, triggered by Ca^{2+} have been observed in rat myometrium in which they appear to extend the depolarization [111-114]. However, their role in human myometrium has not been elucidated yet [43].

Uterine myocytes are able to depolarize without external input (neuronal or hormonal), referred to as myogenic activation [93, 115]. Measurements of isolated strips of myometrium, show spontaneous bursts of activity [95, 101, 105, 106, 108]. Although this does not necessarily imply that myometrial cells exhibit the same level of electrical activity *in vivo*, it does show that uterine myocytes carry the inherent ability of pacemaking. Nevertheless, the ionic currents underlying pacemaking in uterine myocytes have not been identified and different theories exist on possible cellular mechanisms behind pacemaking [57, 58]. One model that has been proposed is the membrane oscillator [45] or pre-potential [91, 95, 116], similar to cardiac pacemaking [117] or the activation of the smooth muscle cells in the urinary bladder [118]. This model entails a constant slow depolarization of the membrane potential. When the threshold is reached, the voltage operated calcium channels are triggered and which leads to an action potential, followed by repolarizing to a hyperpolarized state after which the cycle starts over by slow depolarization.

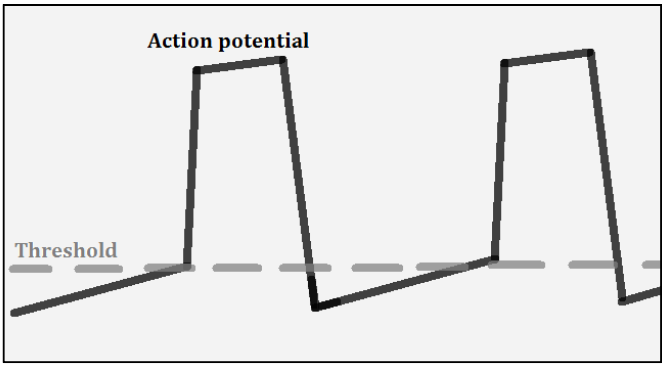

Figure 3: the membrane oscillator model showing a slow depolarization or pre-potential towards the threshold and a subsequent action potential. The cell then repolarizes to a hyperpolarized state after which the cycle repeats.

Alternatively, a pacemaker rhythm in the form of slow waves has been suggested [57, 119], which was found to be the mechanism that activates the smooth muscle cells of the small intestine [120] or stomach [121]. Although very low frequencies were observed in early abdominal measurements, it later appeared that they were caused by motion artefacts and did not reflect the uterine electrical activity [122, 123]. In the gastrointestinal tract, a pacemaker rhythm is generated and conducted by an interconnected network of Interstitial cells of Cajal [55]. More recently, Cajal like cells have also been observed in the human uterus [61, 124, 125]. However, their exact function remains unclear as they do not generate slow waves nor action potentials when depolarized [61]. To date, no specialized pacemaker cells have been identified in the myometrium [58]. This does not necessarily imply that no specific pacemaker region exists.

Extensive work has been performed in identifying a pacemaker region in the myometrium [61, 91, 95, 116, 119, 124-131]. *In vitro* experiments using longitudinal strips of rat myometrium, identified regions of pacemaking 2x4 mm in size [116]. These regions displayed a pre-potential, consistent with the findings of Marshall *et al.* [91, 95]. However, the location of these zones was not specified [116]. Some authors have reported a predominance of the ovarian end as source of uterine contractions [126, 130]. By means of simultaneous recording of the intra uterine pressure in different areas of the uterus in rats during term labor, a predominance of the ovarian end was observed [130]. Similarly, using laparoscopic video observations during labor in rats, the (mechanical) contractions appeared to originate in the ovarian end of the uterus [126]. However, *in vivo* experiments involving simultaneous measurement of the EHG in different sites of the uterus, have not revealed a consistent origin of the electrical activity [119, 128, 131, 132]. Kao *et al.* observed comparable electrical activity in the vaginal and ovarian end of the uterus utilizing implanted electrodes in rabbits [119]. Wolfs *et al.* analyzed human term labor using internal electrodes in the fundus, middle, and lower part of the uterus. Contractile activity was found to be equally distributed among those sites [131]. Parkington *et al.* found the electrical activity to be mostly independent during labor in ewes over distances of more than 3 cm and could not find a consistent origin [128]. Most authors have suggested that also in the whole organ, action potentials can start in any myometrial cell [119, 128, 129, 131, 132]. In short, it remains uncertain what mechanism and cells are responsible for pacemaking.

Propagation of electrical activity

The amplitude of uterine contractions depends on the number of myocytes simultaneously active and the frequency of the action potentials within a burst [91, 95]. Early in pregnancy or in a prelabor phase, local contractile activity can be measured which does not lead to a rise in intrauterine pressure [87, 88, 133, 134]. Uterine contractions depend on propagation of the electrical activity throughout the myometrium [66, 135, 136]. Propagation of action potentials from cell to cell has clearly been established *In vitro* [66, 136] and *in vivo* [128, 137].

Uterine myocytes excite neighboring cells by means of gap junctions [65, 66, 138]. Gap junctions are present in all smooth muscle cells [115] and have an important role in cell to cell signaling [45]. Gap junctions are specialized intercellular channels connecting the cytoplasm of two neighboring cells [139]. The main constituent is the connexin43 protein [140-142]. Different connexin proteins have been evidenced in the human myometrium, but they are not likely involved with delivery [140, 141]. The expression of connexin43 is regulated by progesterone (downregulation) and estrogen (upregulation) [143-145]. Connexin43 is scarcely present in early pregnancy, is strongly upregulated before the onset of labor, and declines quickly after delivery [138, 140, 141]. Six connexin43 proteins are formed into a channel, which docks to a similar channel of a neighboring cell, see Figure 4. These channels form low-resistance electrical connections which function to conduct action potentials to neighboring cells [65, 146, 147]. At term, electrical resistance is reduced by 33% by the formation of gap junctions while membrane resistance increases by 46% [147]. This change was based on a 33% decrease in internal resistance and an 46% increase in membrane resistance. Additionally, it has been suggested that these channels also form a metabolic connection by allowing communication of the intracellular calcium concentration [148].

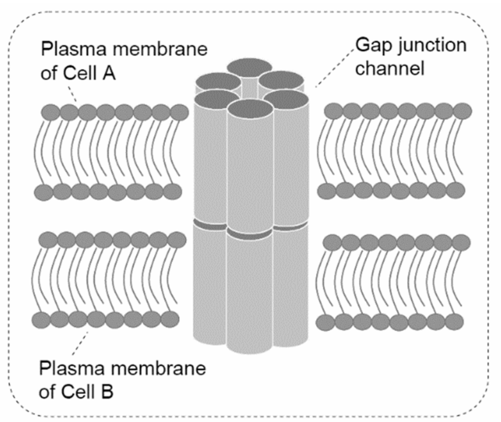

Figure 4: gap junctions. Hexamers of connexin43 proteins, lined up between cells which forms a channel allowing electrical and chemical communication between cells. Redrawn from [149].

Stretch receptors are thought to have an additional role in synchronizing the contractile activity of the uterus, termed mechanotransduction [43, 67, 150, 151]. In an experiment with two mechanically coupled but electrically and chemically isolated strips of myometrium, synchronous bursts of activity were observed [67]. The authors proposed that stretch induces a prolonged plateau phase of action potentials. On the organ level, synchronization of contractile activity could be established by communication via the intrauterine pressure [43, 67, 150, 151]. Despite the uncertain role of mechanotransduction, clearly the amount of gap junctions increases towards the end of pregnancy and this increased cell to cell coupling is essential for normal myometrial functioning [65, 66, 139, 147, 152-154]. This is evidenced by mutant mice carrying a mutation in the gene encoding connexin43 [142] or in which the expression of connexin43 was ablated [155]. The impaired gap junction formation resulted in reduced responsiveness to oxytocin, less forceful uterine contractions, a prolongation of pregnancy and suffocation of mouse fetuses [142, 155]. Defining normal patterns of propagation in the human uterus is challenging since there is no consistent starting point nor is there a fixed path of conduction [58, 136, 137]. Overall, even in physiological term labor, conduction patterns appears to be quite variable or even chaotic [128]. However, preterm propagation is distinctly different from term propagation [66, 136]. Individual spikes within the burst propagate further and with higher velocity at term compared to preterm, both spontaneous and when evoked [66]. Spontaneous activity in strips of myometrium of rats, showed a mean spike propagation velocity of 7,9 cm/s for preterm rats, compared to 13,5 cm/s for term rats during parturition. Evoked activity propagated at a comparable mean velocity of 9,2 cm/s and 10,5 cm/s for preterm and term rats, while the propagation distance was longer for term rats. Contributing to the impaired preterm conduction, is the reduced number of gap junctions [66, 138, 147, 152, 154, 155]. Yet the scarcity of gap junctions in preterm myocytes, is probably not the only factor in hampering the electrical communication among cells. In addition disparities exist in local excitability, manifesting as focal pacemaker activity as well as conduction blocks [136, 156]. Using high resolution multi-channel recordings with 240 electrodes, preterm propagation paths have been mapped in pregnant rats [135, 136, 156, 157]. Propagation paths were found to be highly variable, showing abrupt changes in direction or reversal of direction, both within single bursts and within contractions [136, 156, 157]. Contributing to this variability was either the fusion of multiple wave fronts, local conduction blocks, new wave fronts by local pacemaker activity or a combination of these effects [135]. In short, preterm propagation appears to be less organized and at lower velocities compared to term propagation.

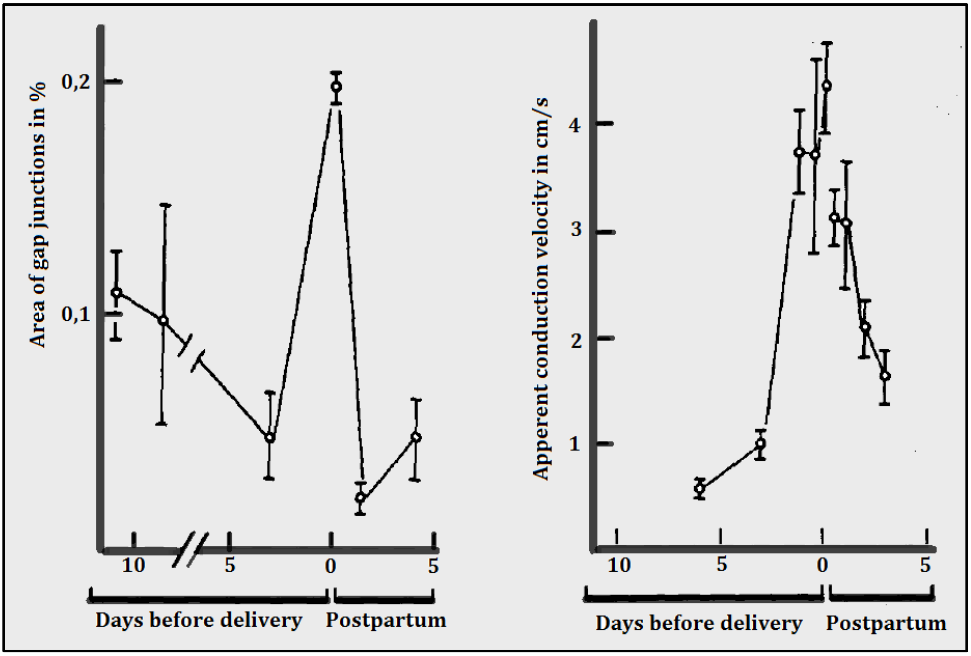

Figure 5: Left: marked increase in gap junctions preceding delivery in ewes. Right: accompanying rise in apparent conduction velocity, measured on the myometrial surface of ewes. The conduction velocity was measured in one direction only and therefore labeled as apparent conduction velocity. Redrawn from [138]

2.2.4 Excitation-contraction coupling

Skeletal and smooth muscle have different functions which lead to different kinetics and energetic requirements [49]. Skeletal muscle needs to contract quickly and with high power, while for smooth muscle maintaining force at little energy expenditure is more important. This is reflected in the different ways cell contraction is initiated [158, 159] and maintained [47, 49, 50].

Uterine myocytes control their contractile state by regulation of the intracellular Ca^{2+} concentration [52, 158, 160]. This can be divided in three processes: maintenance of basal concentration, the influx of Ca^{2+} causing cell contraction, and the return to the resting state. The influx of Ca^{2+} is dependent on the membrane potential by means of the voltage operated calcium channels as discussed in section 1.2.3. Extracellular Ca^{2+} is the main source; release of the intracellular stores of calcium in the sarcoplasmic reticulum (SER) alone, does not lead to cell depolarization [59, 100]. Only when opening of the L-type Ca^{2+} channels allows massive influx of Ca^{2+}, the cascade of intracellular events leading to contraction is initiated [57, 93]. The exact role of the SER in uterine smooth muscle contraction remains subject of debate [52, 59, 60, 63, 100]. Since inhibition of the calcium release of the SER does not reduce the amplitude of contractions [100], it has been suggested that the main function of the SER is to limit contractions via uptake op intracellular Ca^{2+} [52]. However, an alternative role cannot be ruled out [59].

Excitation-contraction coupling can be divided in four discrete steps (1) formation of the Ca^{2+}-calmodulin complex, (2) activation of the enzyme myosin light-chain kinase (MLCK), (3) phosphorylation of the light chain of myosin, (4) and finally binding of the myosin head to the actin filament and movement along the filament. This route for activation is very specific and inhibition of MLCK completely impedes smooth muscle cell contraction [161]. The first two steps, binding of intracellular Ca^{2+} to calmodulin and activation of MLCK, are distinctly different from the way skeletal and cardiac muscle cells initiate contraction [158]. In addition, they are thought to be the rate limiting steps in smooth muscle activation and introduce significant delay between Ca^{2+} influx and the ensuing contraction [52, 162].

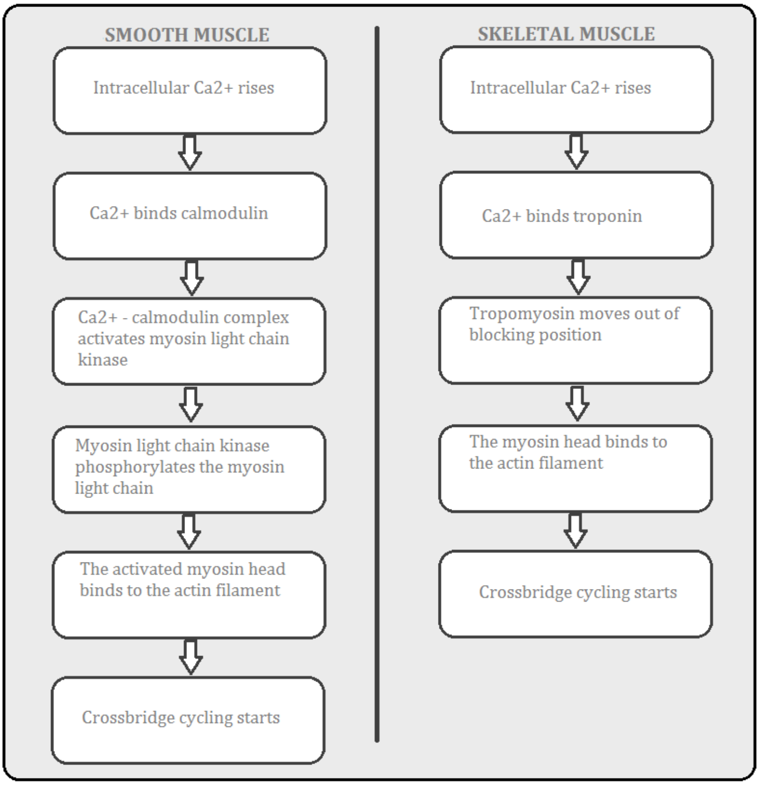

Figure 6: the list of steps involved in smooth (left) and skeletal (right) muscle in excitation-contraction coupling. Contraction is initiated in both types of muscle cells by a rise of intracellular Ca^{2+}, however all intermediate steps are different.

Activated MLCK phosphorylates the light chain of myosin, which is known as the regulatory light chain [159]. Upon activation, myosin interacts with actin filaments in what is known as the sliding filament model which is present in all muscle cells [48, 163, 164]. Phosphorylation of the regulatory light chain causes a conformational change of the neck region of myosin and allows the head to function as motor unit and drag along the actin filament over a distance of 10 nm. The neck and head of myosin form the cross-bridge which allows binding to actin filaments. The energy needed for the sliding interaction of myosin and actin filaments, is derived from degradation of ATP to ADP by the activated head of myosin [35, 50]. This process can be repeated multiple times and this is known as cross-bridge cycling [35, 50, 52].

Although similarities exist, cross-bridge cycling in smooth muscle cells differs in some very important aspects from skeletal muscle [47, 50, 51]. One marked difference, is the frequency of cross-bridge cycling which is much lower in smooth muscle cells [47, 49, 50]. This is reflected in the much lower amount of ATP consumed during prolonged contraction [51]. Different from skeletal muscle, smooth muscle can maintain contraction strength with little energy expenditure by means of slowly cycling cross-bridges, termed latch bridges [47].

Contrary to what the name suggests, latch bridges are not a different type of connection that lock myosin to actin, but rather the state of delayed release of myosin and actin initiated by dephosphorylation of the regulatory light chain [47, 49, 50]. The rate of cross-bridge cycling is therefore regulated by the ratio in activity of MLCK and its counterpart myosin light chain phosphatase (MLCP). The latch bridge phenomenon is what makes smooth muscle cells highly economical in sustained contraction, despite consuming more ATP than skeletal muscle cells for each cross-bridge cycle [51]. Only when all myosin lights chains are dephosphorylated by MLCP, relaxation ensues.

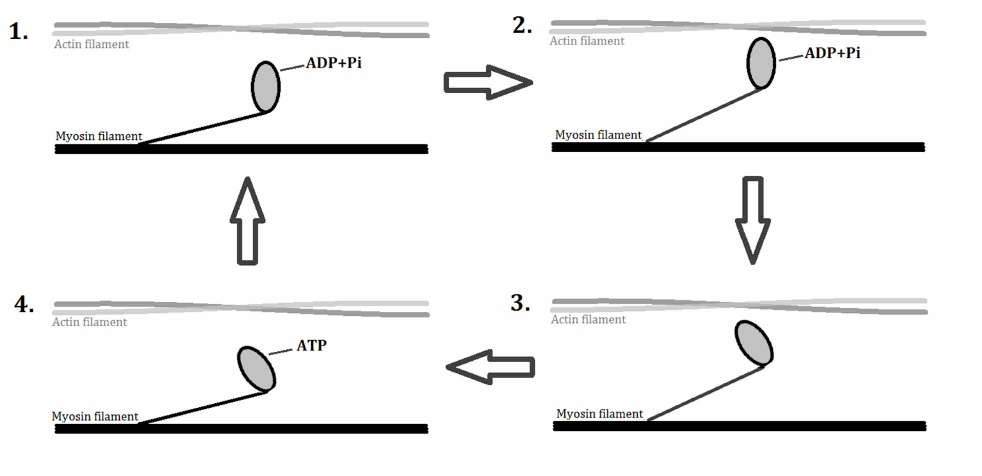

Figure 7: schematic drawing of the four steps of cross-bridge cycling. Upon phosphorylation (not shown) the myosin head binds to the actin filament (step 2). After release the head of myosin undergoes a conformational change creating tension: the power stroke (step 3). After binding a new molecule of ATP, myosin releases the actin filament (step 4). Energy from ATP serves to bring back the myosin head to the original state (step 1).

In short, contraction is initiated by the slow cascade of the Ca^{2+}-calmodulin complex and activation of MLCK and subsequent phosphorylation of the myosin light chain. The amount of phosphorylation determines the speed at which force is generated. However, force generation depends on phosphorylation to a much lesser extent and high forces can be generated when only a small fraction of the myosin filaments is phosphorylated [49]. Moreover, this low level of phosphorylation results in the latch state during which cross bridge cycling is low and force is maintained at low energy expenditure. This contrasts to skeletal muscle cells in which contraction is initiated by the much faster troponin complex and force is maintained through constant cross-bridge cycling, fitting the requirement of faster and high power action of skeletal muscle.

2.3 The current state of Electrohysterography

2.3.1 Electrohysterography

Considerable effort has been put into characterizing uterine contractions in the EHG. This chapter will give an overview of the studies reporting on the use of the EHG in clinical applications.

Electrohysterography, or uterine electromyography, uses a different modality for measuring uterine contractions than current mechanical based methods. The uterine electrical signal was first described in 1931 in Germany [78]. The signal is a representation of the changes in potential of the myometrial muscle cells. The first measurements were performed on the maternal abdomen targeting very low frequencies [165, 166]. By measuring directly on the uterine surface during cesarean section, it was later confirmed that the signals indeed originated from the uterus [166]. At a later stage, the validity of external recordings was confirmed by performing simultaneous measurements both on the abdominal surface and directly on the uterus in rats [87, 88], monkeys [134], and humans [131]. Synchronous activity was observed and the signals showed a good correlation in frequency as well as amplitude, although the abdominal recording was lower in amplitude, as to be expected. The signal at the abdominal surface is not only weaker, but the tissue layers between the myometrium and the abdominal surface (abdominal muscle, fascia, subcutaneous fat and skin) affect the signal by acting as low pass filter: higher frequencies in the signal are attenuated to a greater extent than the lower frequencies. This effect is dependent on the thickness of these layers [167, 168].

EHG measurements are not standardized and various recording techniques have been adopted regarding number, placement, and configuration of electrodes. Bipolar electrodes have the advantage of increasing the signal to noise ratio (SNR) by suppressing background common mode noise while monopolar electrodes offer better spatial resolution [169]. A single electrode pair can record the EHG, yet various multichannel setups have been used and proposed in the literature, including the use of two [19, 39, 170-172], three [173, 174] or four electrodes [29]. Also grids of electrodes have been used in order to study the propagation of electrical activity in more detail, containing 16 [175, 176] or even 64 electrodes [132, 177]. The electrodes are commonly placed near the median axis of the abdomen. Analysis of the influence of electrode position on the amplitude and frequency content of the EHG signal showed that moving away from the midline attenuates the signal, especially at higher frequencies [167]. Likewise, electrode positioning over the placental insertion results in a shifting towards lower frequencies.

Before analyzing the signal, it must be processed. A commonly used filter is a bandpass filter in order to remove noise and artefacts. The power spectrum of the EHG is situated <5Hz [122], with most energy concentrated <1 Hz in transabdominal recordings [172]. Originally, quite some attention was spent on the “slow wave” part of the spectrum in abdominal recordings, which was later attributed to artefacts [123] and not related to the EHG [122]. Typically, the signal is high passed at 0,3 Hz to remove artefacts caused by respiration, skin stretching and movement [174, 178]. The cut-off frequency for low passing varies, it can be set at 1 Hz for eliminating the influence of the maternal ECG [19, 29, 172, 179-181] or higher at 3 Hz to allow analysis of the higher frequency band [170, 182]. Figure 8 shows an example of EHG signals and their spectral content during term labor, showing the EHG (top graph) in the form of bursts coinciding with the contractions on the tocogram (bottom graph). Also motion artefacts are visible as short spikes in the EHG signal, and the influence of the maternal and even the fetal ECG can be clearly seen in the spectrogram (middle graph). This example shows the importance of employing various filtering techniques in order to extract the EHG and improve the SNR.

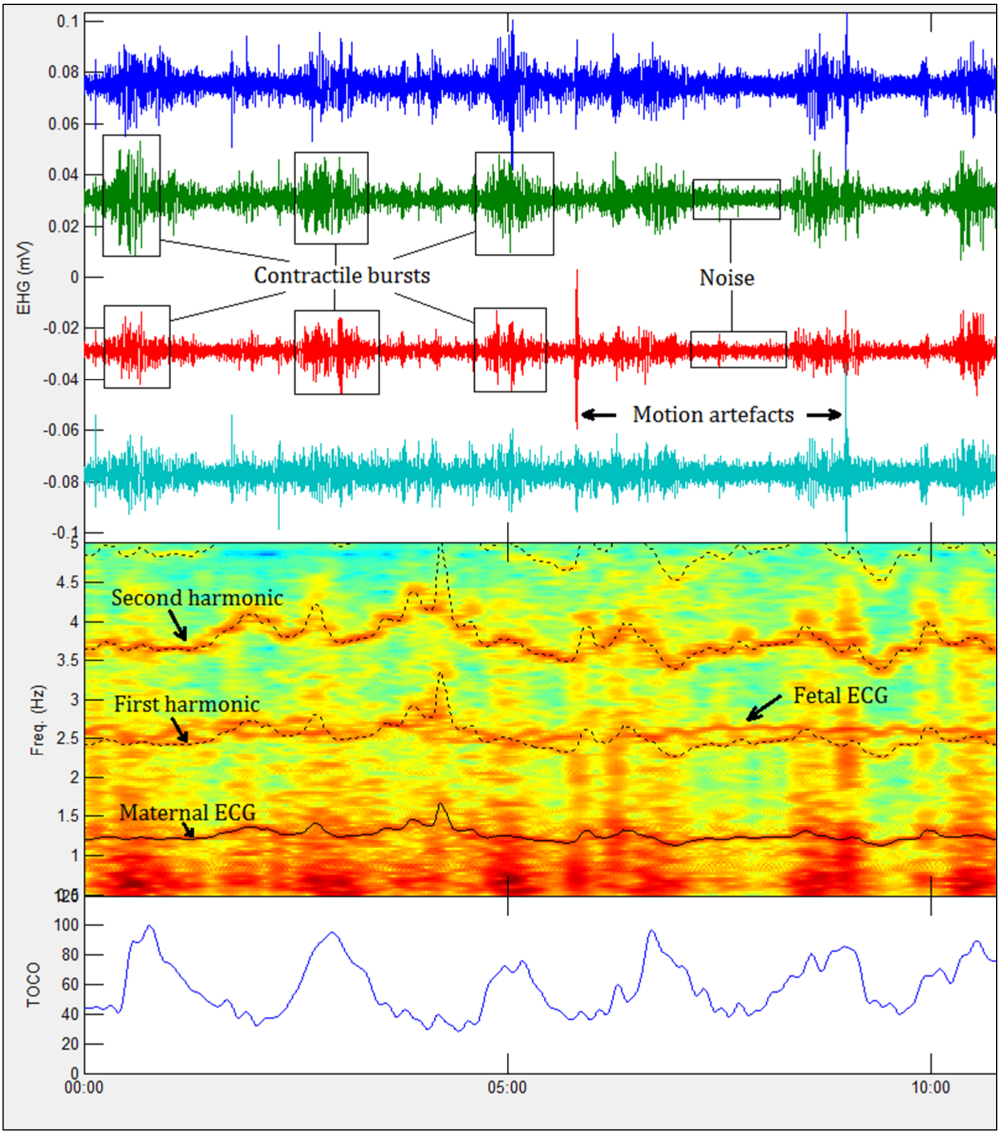

Figure 8: the EHG in term labor. The bottom graph shows the tocogram for reference. The top graph is the EHG signal, consisting of the EHG (bursts) with noise in between and motion artefacts (black arrows). The middle graph displays the spectrogram, revealing the contribution to the noise of the maternal ECG (black line) plus harmonics (dotted lines) and even the fetal ECG at 2,5 Hz (white arrow).

2.3.3 Preterm labor

The EHG represents the electrical activity triggering the mechanical contractions. The mechanical outcome of preterm contractions (cervical effacement, dilatation) which are currently used for establishing imminent preterm delivery are preceded by evolution of the electrical activity which causes the preterm contractions [39, 66]. Despite an incomplete understanding of the electrophysiology underlying uterine contractions [58], multiple parameters in the EHG have been identified which can be used to detect preterm labor.

Amplitude

It has long been established that uterine contractions are the result of the electrical activity in the uterine smooth muscle cells [91]. The myometrium is active to some extent at all times during pregnancy [119, 138, 183, 184]. In a human study, isolating electrical activity early in pregnancy proved challenging, yet electrical bursts could be observed as early as 19 weeks of GA [185]. In animal *in vivo* studies, bursts have been shown to appear with increasing frequency and amplitude when delivery approaches [64, 88, 89, 119, 138, 186]. Therefore, the amplitude of bursts has long been considered as predictive of preterm delivery. The amplitude has been expressed in various ways in clinical studies. The absolute value is influenced by the recording technique, the electrode type [187] and arrangement [188], and also patient specific factors [167, 168, 189]. This in part explains the striking differences in the absolute values found for the amplitude of the EHG in clinical studies [39, 190-192].

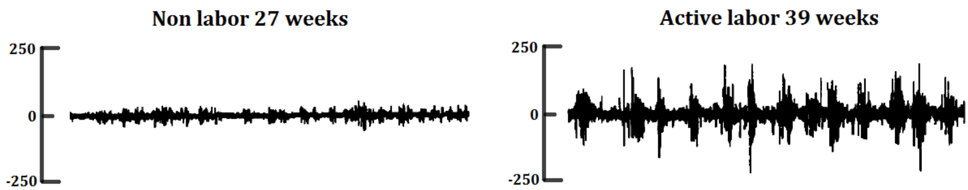

Figure 9: Surface EHG recording on the human uterus in the non-labor state at 27 weeks of GA (left) and during term labor (right), showing a rise in amplitude of the contractile bursts. Redrawn from [39].

Buhimshi *et al.* aimed at characterizing the electrical activity of both preterm contractions not leading to delivery and preterm labor [39]. Five preterm patients were included who were not in labor (GA 27-36 weeks) and compared to 4 patients in active preterm labor (GA 33-36 weeks). Exact inclusion criteria were not mentioned. The EHG was recorded using two bipolar electrode pairs, approximately 5 cm apart. The signal was bandpass filtered between 0,3 and 50 Hz. The spectral content, expressed as the power spectral density (PSD), was derived using Fast Fourier Transform (FFT) of at least three contractions bursts per patient. The peak amplitude of the PSD was compared and proved significantly higher in the preterm labor group compared to the non-labor group: 62,27 ±22,93 μV and 11,36 ±4,03 μV.

Thee prospective observation cohort studies, explored the mean root mean square (RMS) value as predictor of preterm delivery. Verdenik *et al.* included 47 patients in a tertiary care center that were admitted for preterm contractions but were not in active labor [192]. Therefore, cervical dilation of >2 cm was used as exclusion criterion. About 24% of the patients had visible contractions on the tocogram, and 36% of the patients delivered before term. The EHG was recorded using a single bipolar electrode pair and filtered in a relatively wide frequency band of 0,1 – 4 Hz. The mean RMS value of the entire EHG recording was derived and compared between the labor (delivery <37 weeks) and non-labor group (delivery >37 weeks). In addition, patients were screened for risk factors for preterm delivery. The mean RMS was 17,5 mV for the labor group compared to 12,2 mV for the non-labor group. Multivariate analysis showed the mean RMS value to be the strongest and independent predictor of preterm delivery, resulting in a modest sensitivity of 47% and a specificity of 90%.

Similarly, Most *et al.* included 87 women of GA 24 – 34 weeks admitted for preterm contractions, based on maternal perception [191]. The EHG was recorded using 9 electrodes and was bandpass filtered in a less common range of 1 – 1500 Hz. The average of the peak RMS value of contractions was derived and proved significantly higher for the labor group, 0,50 mV (delivery <14 days), compared to the non-labor group, 0,34 mV (delivery >14 days). In addition, an index score was calculated based on peak RMS value, frequency of contractions, and movement of the calculated center of electrical activity. This EHG index score was compared to traditional test and performed slightly better scoring a sensitivity of 42% and specificity of 92%, compared to cervical length by ultrasound (sensitivity 40%, specificity 83%) or fFN (sensitivity 34%, specificity 88%).

Kandill *et al.* used the mean amplitude of bursts in the EHG as predictor for preterm delivery [190]. In total 50 patients, of GA 28-34 weeks, were included admitted for imminent preterm labor, defined as contractions visible on the tocogram at least 1/10 min, cervical dilation of <2 cm and a cervical length of <25 mm. The EHG was recorded before initiating tocolytics therapy and patients were grouped in the labor and non-labor group according to delivery within two days or after more than two days. No details on the adopted EHG processing were specified. The mean amplitude of the EHG bursts was significantly higher in the group delivering within 2 days, 87,8 mV, compared to delivery between 2 – 14 days, 41,1 mV, and after 14 days, 21,0 mV. In addition, the authors concluded that the EHG could be used to predict the response to tocolytics as the EHG which was recorded post treatment showed less reduction in amplitude for the patients delivering within 2 days.

In the most recent study, Aviram et al. employed the Electrical Uterine Monitor, a commercial device, to measure the EHG amplitude in a population of 45 women admitted for imminent preterm labor at a mean gestational age of 30 weeks and of which 75% was treated by tocolytics and steroids [193]. The amplitude proved to be significantly higher in the preterm labor group and the ROC curve showed a modest AUC of 0,65 for delivery <34 weeks, a similar performance compared with cervical dilatation and effacement.

Spectral

Spectral parameters of the EHG have been frequently studied [39, 87, 89, 133, 134, 167, 171, 172, 179, 182, 194, 195]. The spectral content of the EHG is mainly determined by the frequency of action potentials within bursts [89, 186]. When labor approaches, changes in cell membrane permeability, which are not fully understood, allow the frequency of cell cycles of depolarization and repolarization to increase [57, 63]. Moreover, the frequency of the signal as measured at the abdominal surface, is influenced by the amount of myometrial cells simultaneously active underneath the electrode [172]. An upward shift in spectral content has been observed in both animal [87, 89, 133, 134] and human studies [39, 46, 167, 171, 172, 180, 192, 195] as delivery approaches. In rats, this shift was the earliest observable change in the EHG during the process leading up to (induced) preterm labor, see Figure 10 [89]. The spectral content can be expressed as the PSD: the energy content plotted against the frequency. Buhismhi *et al.* showed that this information can be extracted from recording directly on the uterus as well as on the abdominal surface [87]. Needless to say, in humans only abdominal recordings are available.

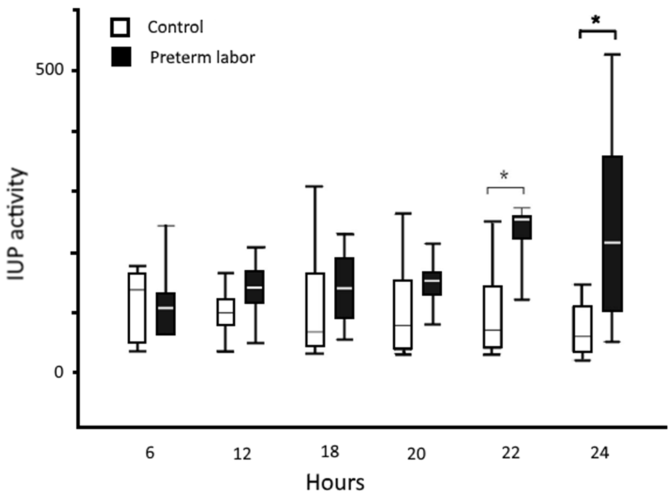

Figure 10: evolution of the spectral content (PSDpf) of the EHG in rats towards (induced) preterm labor and in an control group. A marked increase in the PSDpf is observed 18 hours prior to delivery. Adapted from [89].

Peak frequency

Efforts have mostly been concentrated on the peak frequency of the power density spectrum (PSDpf) [196]. Buhimshi *et al.* analyzed the spectral content of (at least three) contraction bursts in nine preterm patients, five not in labor and 4 in labor, based on FFT [39]. Among amplitude and periodic parameters, the PSDpf was compared between the preterm nonlabor and labor group, which was respectively 0,42 ±0,02 Hz and 0,78 ±0,06 Hz ($p<0,05$). In addition, term patients in active labor were included, and the PSDpf was interestingly found to be similar: 0,72 Hz.

Maner *et al.* included 42 preterm patients who were not in labor presenting with contractions [172]. Cervical dilation >2 cm or effacement >80%, multiple gestation, and rupture of membranes were all exclusion criteria. Similar to [39], two bipolar electrode pairs were used and contractile bursts were analyzed by FFT, the peak frequency was determined in the 0,3 – 1 Hz band. The PSDpf was analyzed as function of the measurement to delivery interval. A marked increase was observed 4 days prior to preterm delivery. On average, the PSDpf was found to be 0,39 ±0,01 Hz >4 days before delivery and 0,51 ±0,03 Hz ≤4 days within delivery. This resulted in a sensitivity of 60% and a specificity of 96,9%.

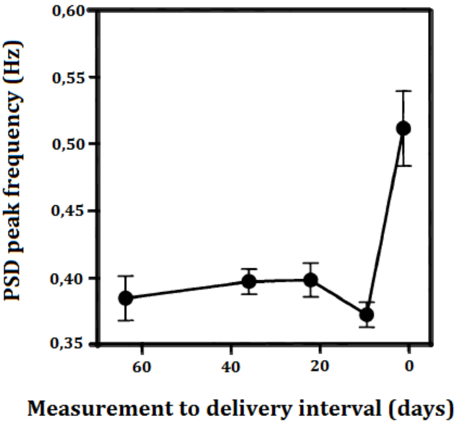

Figure 11: spectral content (PSDpf) as function of the measurement to delivery interval in preterm patients. The PSDpf was observed to rise 4 days prior to (preterm) delivery. Redrawn from [173]

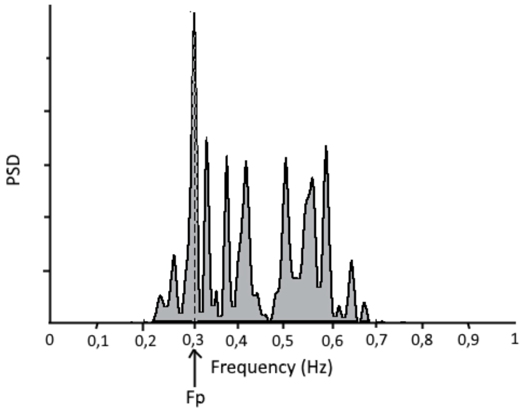

Figure 12: the peak frequency of the power density spectrum (PSDpf). Energy density is plotted on the y-axis and frequency on the x-axis, fP marks the peak frequency, in this case around 0,3 Hz.

In a follow up study using a similar approach, artificial neural networks classified preterm patients in labor and nonlabor, the best parameter being the PSDpf next to the standard deviation of bursts [171]. The PSDpf was 0,40 ±0,02 Hz in the nonlabor group (n=38) and 0,47 ±0,05 Hz in the labor group (n=13). Noteworthy is that the reference method used for classifying labor and nonlabor was based on clinical evaluation rather than the measurement to delivery interval, which resulted in mixing of the two groups as evidenced by the average measurement to delivery interval of 6,4 ±6,8 days in the preterm labor group. This method resulted in a sensitivity of 92,3% and specificity 71,1%.

Artificial networks were also used by Marque *et al.* in order to distinguish patients delivering preterm (<GA 37 weeks) or at term [167]. 111 Recordings were made in 107 hospitalized patients, inclusion criteria were singleton pregnancy, GA 18-37 weeks and the presence of uterine contractions. Signals were recorded in the median axis of the abdomen using a single bipolar electrode pair in a wide range of 0,05 – 16 Hz and the energy in two frequency bands was calculated, see Figure 13. Two algorithms were used for training the artificial neural networks. One algorithm performed better but was not able to classify all contractions, the other resulted in a sensitivity of approximately 80% and a specificity of 88% for predicting preterm delivery.

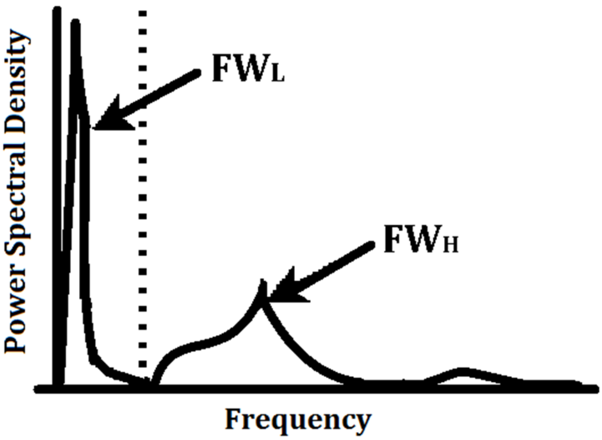

Figure 13: power density spectrum of an internally recorded EHG, showing two peaks, termed Fast Wave Low (FW_L) and High (FW_H). Redrawn from [167].

Median frequency

Verdenik *et al.*, in addition to the amplitude also analyzed the median frequency, in a population of 47 patients in a tertiary maternity care center, admitted for preterm contractions [192]. The whole EHG recording was analyzed, rather than just bursts of activity, which might render the method less sensitive. The method for deriving the spectral content was not mentioned. The patients were divided in a preterm and term group based on delivery before or after 37 weeks. No difference was found in the median frequency: 0,36 and 0,37 Hz. No analysis was made based on the measurement to delivery interval, which is probably more suitable since changes in spectral content are seen relatively close to delivery [89].

Propagation properties

Prelabor propagations patterns of preterm uterine activity have been found to be mostly chaotic [128, 135, 136, 157]. This is attributed to local differences in excitability [136] as well as a scarcity of gap junctions and therefore reduced electrical coupling between cells [66]. Approaching labor, an increase in propagation distance as well as velocity has been observed [66]. Mostly, propagation properties have been studied in isolated strips of myometrium or directly on the uterus in rats [66, 135, 136, 157, 183], guinea-pigs [137], rabbits [183] or sheep [128, 138]. The non-invasive measurement of propagation properties, has enabled its use in human studies aiming to detect preterm labor [132]. These studies mainly focused on the amplitude of the (averaged) vector of propagation: the conduction velocity (CV).

Methods of varying complexity have been proposed. In a more straightforward approach, the propagation in term parturients was characterized by use of three electrodes positioned in the median axis, analyzing the propagation of whole bursts of uterine activity [173]. The CV was found to be 1,53 cm/s and 2,15 cm/s depending on the electrode position. Both down- and up-ward propagation was observed. This is in line with the results from a similar study on six women in term labor, only using a 4x4 electrode grid allowing for estimation of propagation in two directions [197]. The CV was found to be 2,18 cm/s, again using the migration of whole bursts. The found CV values differ from values observed both *in vivo* and *In vitro* of single spike propagation, which are in the range of 3-15 cm/s [66, 128, 136, 137]. This could be explained by the employed method for analysis of the migration of whole bursts of activity. In term guinea-pigs, the CV of single spikes was found to be 6,8 cm/s, while migration of whole bursts occurred at a much lower velocity of 0,6 cm/s [137]. In rabbits, whole bursts migrated at a estimated velocity of 0,5 – 6 cm/s [183].

A very different approach is the use of magnetomyography, a technique which entails recording the magnetic fields in a magnetically shielded room which are a result of the currents flowing through the muscle cells [46, 198]. This method allows the non-invasive recording of very low frequency signals. In a case study, longitudinal measurements were performed on two pregnant women [199]. Four quadrants were defined and the CV was determined between burst of activities. The CV was found to be about 5-15 cm/s and a single measurement at term showed a marked increase as high as 50 cm/s. The influence of the method on the observed CV amplitudes becomes even more clear in a more recent study in which magnetomyography was employed as well [198]. Term pregnant women were enrolled that presented with contractions but who were not necessarily in labor. The conduction velocity was determined by first computing a "center of gravity" in each of 4 quadrants, representing the maximal activity on the magnetomyogram. The propagation delays among these 4 quadrants was determined by cross-correlation, excluding short delays. This method most closely resembles whole burst propagation and the observed conduction velocities ranged 1,3-9,5 cm/s. No comparison was made between those in labor and the women not in labor.

Only a single study has analyzed single spike propagation in the EHG for prediction of preterm delivery [19]. In this relatively large clinical prospective cohort study, 88 patients were included that were admitted for imminent preterm labor or preterm prelabor rupture of membranes (PPROM). The EHG was recorded using two bipolar electrode pairs allowing for estimating the amplitude of the CV vector in one direction only (vertical). This results in overestimation of the CV vector amplitude for propagation directions other than vertical [200]. By visual analysis of the processed EHG signals, peaks were identified and delays were obtained. Approximately 215 peaks were identified per patient and subsequently the average CV was compared between the group delivering within (labor) and after 7 days (non-labor). The CV was found to be significantly higher in the labor group, approximately 53 cm/s compared to 11 cm/s. These values are higher than what previously has been reported [66, 128, 138, 201] and this is possibly a result of the adopted method. However the accuracy of the estimation of the CV was not the goal of this study and the sensitivity and specificity of the method proofed to be excellent: 85% and 94% respectively. Adding the median frequency of the power density spectrum added little to the predictive value in this study.

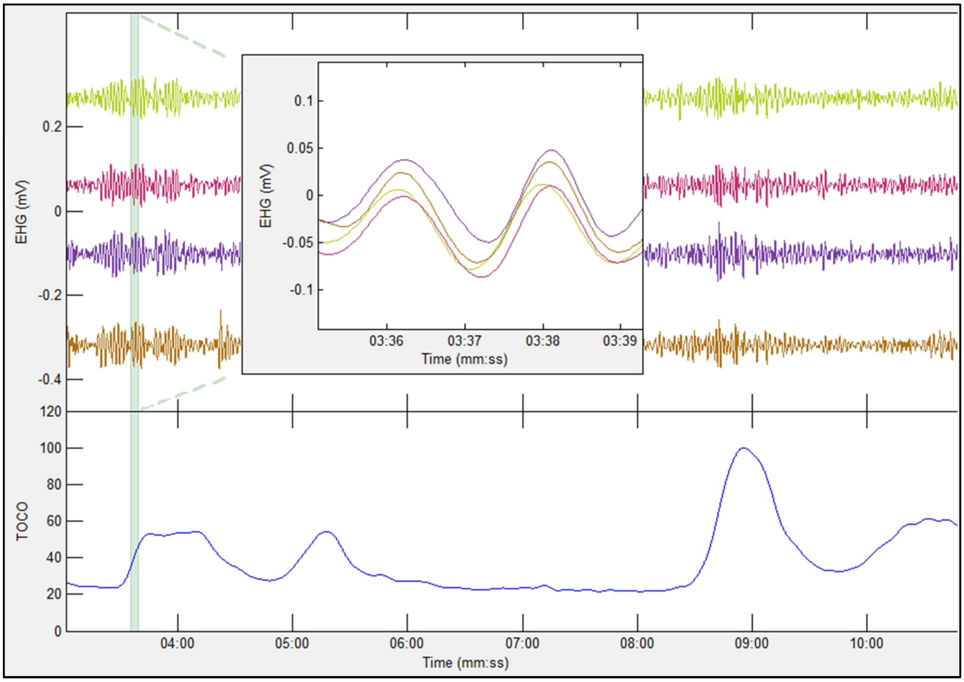

Figure 14: conduction velocity analysis in the EHG based on single spike propagation. Bottom graph shows the tocogram, coinciding with bursts in the EHG (top graph). The middle window shows an zoomed in view of the selected segment in which a small delay among channels is evident. Within these bursts, the conduction velocity can be estimated.

Recently, a more detailed method has been developed for analyzing propagation properties using an abdominally-placed electrode grid containing 64 electrodes with a high spatial resolution [132]. This configuration allows for the analysis of propagation of single spikes in two directions. In a case report, three consecutive measurements were performed on a women with a unicornuate uterus, showing an increase from 12 cm/s to 22 cm/s and finally 28 cm/s at a GA of 28+6, 29+3 and 29+6 weeks [177]. She delivered spontaneously at 34 weeks.

Non-linear analysis

All the aforementioned parameters of the EHG that have been discussed, are derived by linear methods, which entail either univariate (amplitude, spectral) or multivariate cross-correlation time series analysis. Linear methods build on the condition that the output is a linear combination of the input values [202]. However, based on physiology, non-linear behavior can be expected in the preterm myometrium. Preterm propagation patterns have been proven to be more chaotic and more localized compared to term [66, 128, 135, 136]. The propagation distance of single spike appears to be dependent on the GA [66] and activity is frequently detected in one electrode only in multichannel preterm recordings [128, 129, 131]. High resolution mapping of propagation patterns in preterm myometrium has revealed chaotic propagation patterns influenced by local variability in cell excitability [135-137]. The distance between electrodes is probably an important factor and the linear approximation might more likely be valid for shorter distances. For larger distances the connectivity between signals can be more complex, requiring nonlinear measures. For this reason non-linear multivariate analysis has been in use for over 20 years in various fields for analyzing biological signals [203], including monitoring the depth of anesthesia, sleep-wake research and detecting epilepsy. Likewise, various non-linear analysis methods have been employed for predicting (preterm) delivery [174-176, 204, 205].

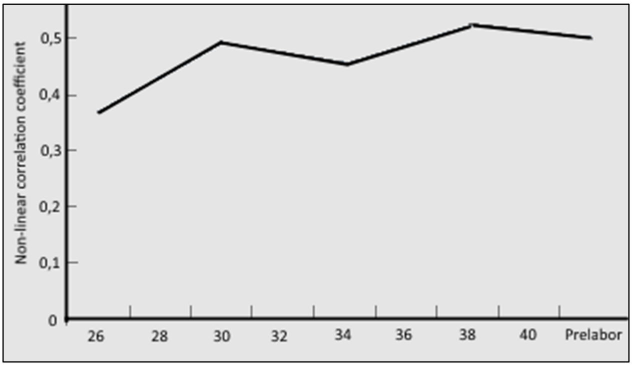

Figure 15: the evolution of the non-linear correlation during pregnancy of 16 low risk singleton pregnancies. The observered rise was not significant.

Fele-Žorž *et al.* tested a large number of parameters of the EHG in addition to different preprocessing filters on a large set of EHG records [174]. The patients, 300 in total, consisted of both normal uncomplicated pregnancies and patients admitted for premature contractions; their numbers were not specified. The EHG was recorded using four electrodes, combined into three bipolar pairs. Records were grouped based on the GA of recording (before or after 26 weeks) and preterm (262 records) or term delivery (38 records). Different bandpass filters were tested: 0,08–4 Hz, 0,3–4 Hz, and 0,3–3 Hz. Next to linear parameters, the amplitude and spectral analysis, various non-linear methods were applied: estimation of the maximal Lyapunov exponent, correlation dimension and sample entropy. All six possible combinations of the four groups of records were compared. In addition the analysis was performed separately on the three bipolar pairs. Of the linear parameters, the median frequency performed best and showed a significant difference between all preterm and all term deliveries. However, this difference was only found in one of the three signals and inconsistent with previous studies, a higher value was observed for patients delivering at term [39, 46, 87, 89, 167, 171, 172, 180, 192, 195]. Of the non-linear techniques, sample entropy was the most promising parameter and showed significant results in predicting preterm delivery for the majority of combinations of the three signals and bandpass filters. The other non-linear methods were less consistent. In general, differences among early and late recordings were more pronounced than between recordings of preterm and term deliveries. Similar to

[192], the entire recording was analyzed rather than the bursts of uterine activity, which could reduce the sensitivity of the analysis, especially in preterm patients with relatively scarce uterine activity [64, 88, 89, 119, 186].

Muszynski *et al.* studied non-linear correlation among channels in 12 channel recordings [175]. The authors tested the hypothesis that synchronization of electrical activity increases in the course of pregnancy, evidenced by an increase in non-linear correlation (h^2). This was tested in an observational clinical study. 16 low risk singleton pregnancies were included, seven of which were followed longitudinally from 24 weeks of gestation up until delivery. Two EHG recordings were made each month, using 16 electrodes formed into 12 bipolar pairs in order to reduce noise and filtered between 0,1 and 3 Hz, see Figure 16. The method for selecting the contraction segments in the EHG recordings was not specified. A non-significant rise in h^2 was observed in the course of pregnancy, see Figure 15. This could in part be explained by the small study group, which consisted of seven patients and in addition some data points were missing.

Hassan *et al.* focused on distinguishing contractions during uncomplicated pregnancy (36 patients), e.g. not leading to delivery, from contractions during term labor (13 patients) [176, 205, 206]. Similar to [175], a 4x4 grid of electrodes was used out of which 12 bipolar pairs were formed. Contractions were selected based on the external tocodynamometer. In the selected segments, the non-linear correlation coefficient h^2 was calculated among all possible combinations of channels and subsequently averaged. The performance of non-linear correlation was compared to two commonly employed spectral parameters, the peak and median frequency of the PSD.

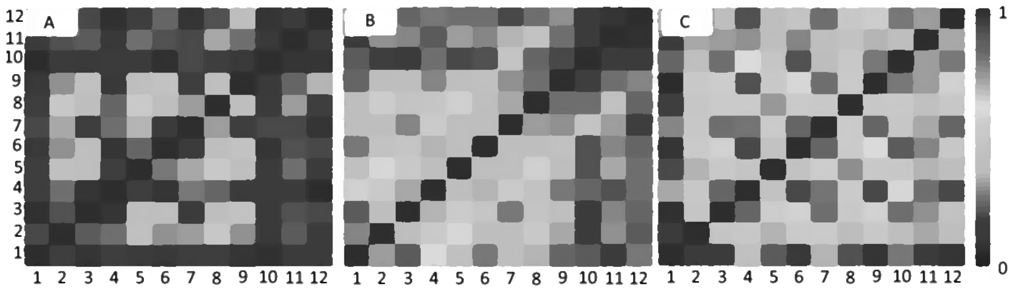

Figure 16: the evolution of the non-linear correlation coefficient (h^2) in the course of pregnancy in a single patient, from 33 wks (a) to 35 wks (b) and 37 wks (c). The maxtrix reprents the correlation between all combinations of the 12 channels of the EHG. Adapted from [177].

An increase in h^2 values was found from pregnancy to labor. Figure 16 shows the evolution of h^2 in a single patient at three gestational ages. Non-linear correlation had a sensitivity of 86% for distinguishing physiological from labor contractions at a specificity of 76%. This resulted in an area under the curve (AUC) of the receiver operating characteristics (ROC) of 0,66 for the peak frequency, 0,76 for the median frequency and 0,85 for non-linear correlation.

2.3.4 Term labor

Intra uterine pressure estimation

The close relation between electrical activation and the resulting mechanical output has long been established by simultaneous recording of the EHG and intrauterine pressure, using internal [88, 89, 131, 133, 134, 138, 186] or abdominal electrodes [39, 134, 166, 178, 207, 208]. In these studies, the contractions in the tocogram, have been observed to coincide with bursts of electrical activity. However, bursts can also be detected without leading to an appreciable rise in intra uterine pressure. This is frequently seen during pregnancy [87, 88, 133, 134] but also in the pre-labor phase [131, 138, 184]. Figure 17 shows an example of the pre-labor phase during mechanically induced labor. Frequent bursts were seen without close relation to the mechanical output (the IUP) [131]. When the same patient entered the first stage of labor, the electrical activity in between the (mechanical) contractions disappeared, see Figure 17.

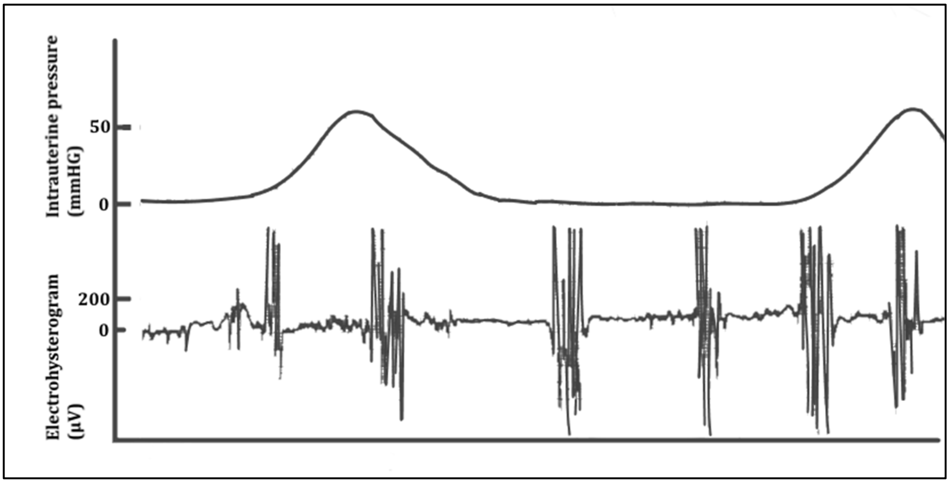

Figure 17: pre-labor contractions. Bursts of uterine activity appear frequently (lower trace) without clear correspondence to the mechanical acitivity (upper trace).

There is considerable time delay between the start of the electrical burst and the onset of the (mechanical) contraction, see Figure 18. This might be explained by the relatively slow excitation-contraction coupling of uterine myocytes [52, 162], previously discussed in section 1.2.4. In addition, the bursts disappear before the pressure has returned to the baseline, which could possibly be explained by the slow rate of cross-bridge cycling or latch bridges [47, 50].

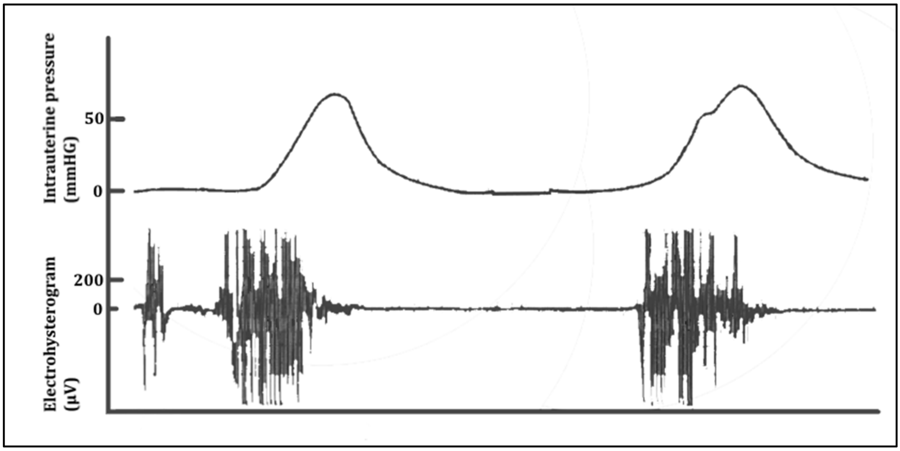

Figure 18: term labor contractions. The mechanical output (upper trace), i.e. the increase of intra uterine pressure, is preceded by a burst of electrical activity (lower trace).

Although the temporal relation is evident, the correlation in amplitude is more complicated. The amplitude of the EHG signal is dependent on the number of myocytes simultaneously active underneath the electrode [172]. This in turn relates to the magnitude of the mechanical contraction [91, 95]. However, the amplitude of the EHG as measured on the abdominal surface, can be influenced by multiple factors, including the electrode type [187] and arrangement [188], the impedance of the skin-electrode contact [189], and the thickness of the subcutaneous tissue [167]. Therefore, one must be cautious to interpret the amplitude of the (abdominal) EHG in an absolute way.

In order to be useful to the obstetrician, the EHG signal needs to be transformed into a recognizable tocogram signal. To this end, different processing methods have been developed [208-210]. Using the external tocogram as reference, Jezewski *et al.* used the RMS of the EHG after bandpass filtering [209]. This was combined with automatic detection of the baseline level by averaging the lowest 10% of the values. The EHG and external tocodynamometer were quite consistent in detecting contractions (91%), including their duration. In the study by Skowronski *et al.*, the EHG was recorded simultaneously with the IUPC in laboring women [210]. The EHG signal was normalized, lowpassed at 2 Hz, and rectified. A Wiener filter, using the IUPC as reference, was used to reduce noise and shape the processed EHG signal in order to mimic the intra uterine pressure. Another approach was developed by Rabotti *et al.*, aimed at a more precise estimation of the intra uterine pressure, again using the IUPC as reference [208]. The EHG was recorded using two bipolar electrode pairs and the signal was lowpass filtered at 5 Hz. A median filter was used to remove movement artefacts. The EHG was analyzed in the time frequency domain by a spectrogram. This method builds on the change in spectral content of the EHG caused by activated myocytes, and this can be depicted in a spectrogram. The IUP was estimated by using both the increase in EHG frequency and amplitude, therefore accounting for number of active myocytes (amplitude) and their connectivity (frequency). This estimation was further improved by adjusting the gain, offset, and time delay using the IUPC as a reference. This method was compared to the previously discussed methods [209] and [210].

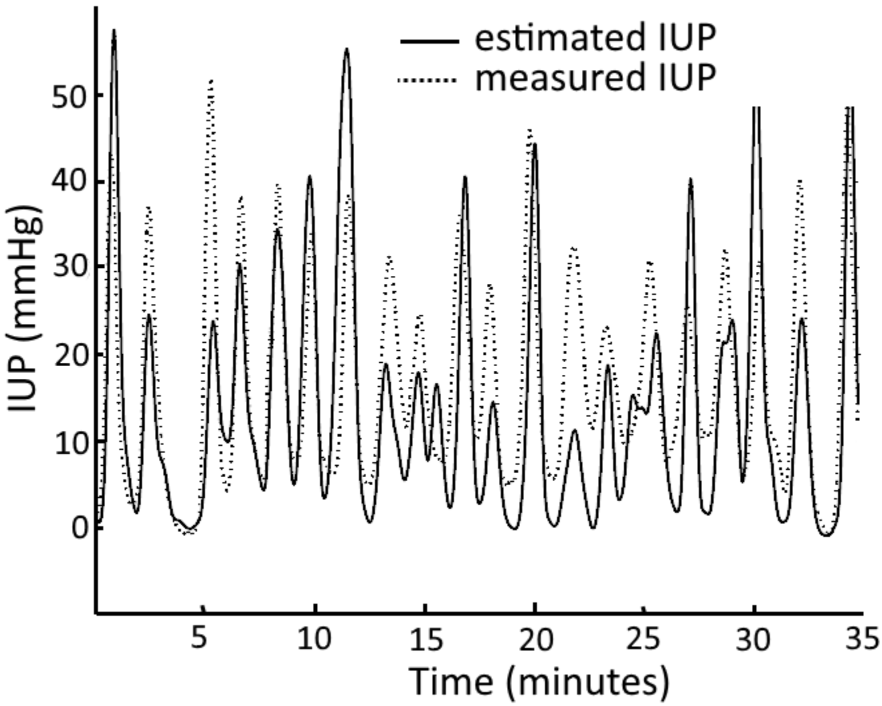

Figure 19: Example of estimation of the IUP based on the EHG during term labor. The dashed line represents the intra uterine pressure (IUP) as recorded by an IUPC. The uninterupted line shows the estimated IUP based on the EHG.

The method by Rabotti *et al.* showed the highest correlation to the IUPC (r=0.79), evidencing the ability to correctly identify the number of contractions. The method by Skowronski *et al.* had the lowest RMS error, meaning the closest relationship in amplitude. Recently, a new frequency-weighed energy estimator method was proposed for IUP estimation which is comparable to [208] in both the method and the accuracy of the estimation, but at much lower computational cost [211].

Electrohysterogram compared to current methods

Estimation of the IUP based on the EHG has enabled use of the EHG for monitoring contractions during term labor. The accuracy of EHG-based IUP estimation has been compared in clinical studies to the external tocodynamometer [212], the IUPC [213] or both [29], see Table 1. Reinhard *et al.* compared the EHG to the simultaneously recorded external tocodynamometer in 135 term laboring women in both the first and second stage of labor

[212]. The EHG was recorded using a single bipolar electrode pair and was processed by a commercial EHG recorder. Processing consisted of bandpass filtering in the range of 0,2 to 0,9 Hz and deriving the envelope of the energy of the signal. Analysis was performed offline in a blinded fashion by four observers who assessed the number of contractions, the ease of assessment, and the adequacy of the tracings, defined as a recognizable patterns of contractions. The EHG performed better in all three measures. The EHG tracings were all marked as adequate and more contractions were observed. They were found easier to assess, and had a lower intra-observer variability. The higher number of contractions that were detected by the EHG was attributed to an higher sensitivity of EHG based contraction monitoring. However, no IUPC recordings were available to confirm this.

In the study of Haran *et al.*, the EHG was compared to the IUPC in 47 parturients [213]. Patients were included if an IUPC was necessary for obstetrical reasons and without technical problems. The electrode configuration consisted of nine electrodes in a square around the umbilicus in combination with a commercial EHG recorder. The processing used by this recorder was not specified. Patients included both preterm and term and in "various" stages of labor, although the average GA was 39 weeks and the initial cervical dilatation amounted 4,7 cm. The EHG and the IUPC demonstrated a high agreement in start, end, and peak of contraction. Overall the Pearson correlation coefficient of the contraction length was 0,90. Moreover, the correlation in area under the curve of both modalities was also high (r=0,80).

In the most recent study, the EHG was compared to the external tocodynamometer using an IUPC as golden standard [29]. 73 patients in active labor were included with singleton pregnancy and cephalic presentation. 14 patients were excluded for various reasons, mostly technical failures. Although not mentioned as inclusion criterion, the study population had a mean body mass index (BMI) of 34,3 (range 23,1 – 61,4). The EHG was recorded by 4 monopolar electrodes, which were bandpass filtered between 0,2 and 1 Hz and combined based on their signal to noise ratio. The method to derive the estimated intrauterine pressure was not mentioned, other than that the combined signal was normalized to a 0 – 100 scale. To describe the performance of the EHG and external tocodynamometer with respect to the IUPC, the contractions consistency index (CCI) was used in addition to other descriptive statistics. This index is 1 if both modalities report the same number of contractions, but lower in case of false positives or negatives. The EHG outperformed the external tocodynamometer in most quality measures, with a CCI of 0,88 compared to 0,69 for the external tocodynamometer. The proportion of inadequate tocogram tracing (CCI <0,75) was also lower for the EHG, 16,7%, compared to 46,1% for the external tocodynamometer. This translated into a sensitivity of 0,89 for detecting contractions by the EHG and 0,62 of the external tocodynamometer. Interestingly, the performance of both modalities was also compared in relation to the BMI of the test subjects. The external tocodynamometer showed a negative correlation between sensitivity and maternal BMI of -0,26. The EHG showed a slight performance degradation as well in the obese group, but this difference was not significant. It should be noted that in this study, IUPC placement was based on obstetrical indications rather than purely for study reasons. A common indication for the use of an IUPC, as pointed out by the authors, was an inadequate (external) tocogram tracing. This could entail some selection bias. Moreover, the protocol states that the output of the external tocodynamometer (and the EHG as well) was blinded to the attending nurses. This means that there was no visual feedback on the quality of the tracing based on which the transducer could be repositioned or the belt fastened. These factors have possibly impaired the performance of the external tocodynamometer in this study to some extent, although the mediocre performance of the external tocodynamometer has also been established in several previous reports [16, 30].

Table 1: Overview of the clinical studies comparing the EHG to the external tocodynamometer, the IUPC or both.

Study	n	Inclusion	Electrode configuration	Processing	Comparison	Outcome
Reinhard 2011	144	All stages of labor, singleton, GA 35 – 42wks	1 bipolar pair	Bandpass filter 0,2 – 0,9 Hz	External tocodynamo meter	EHG detected more contractions, easier to asses, lower intra-observer variability
Haran 2012	47	GA >24wks, all stages of labor	9 electrodes	Not specified	IUPC	Duration r=0,94, amplitude r=0,80, overall r=0,81
Euliano 2013	73	Active labor, singleton, cephalic presentati on	4 monopolar electrodes	Bandpass filter 0,2 – 1 Hz, normalized	External tocodynamo meter and IUPC	CCI[1] external tocodynamometer 0,69 vs EHG 0,88

1 = Contractions consistency index, defined as the number of consistent contractions divided by the mean of the number of contractions detected by the IUPC and EHG.

2.4 Conclusions and challenges

There are several EHG parameters that can potentially be used for predicting imminent preterm delivery. The parameters relating to the amplitude of the EHG signal do not significantly differ from quantifying preterm contractions using an external tocodynamometer, although the EHG appears to be more sensitive in detecting contractile bursts than is possible using the tocogram [87, 88, 133, 134]. Amplitude parameters of the EHG have been shown to be moderately predictive of preterm delivery [191-193]. Patients specific factors affect the strength of the signal and complicate the use of amplitude related parameters of the EHG for preterm labor prediction [168, 171, 189]. The main focus of clinical research has been on spectral parameters [39, 87, 89, 133, 134, 167, 171, 172, 179, 182, 194, 195]. Evolution of spectral content has clearly been established preceding (preterm) labor, although changes occur relatively close to delivery [89]. This is reflected in the clinical studies and its ability to predict delivery appears to be restricted to only a few days before the event. In the end, analysis of the spectral content alone might not suffice to accurately distinguish physiological contractions from imminent preterm delivery.

Analysis of propagation patterns has only recently been considered for preterm labor prediction [19, 132, 177, 199]. Although physiological knowledge on propagation is far from complete, estimation of the velocity of single spike propagation in the EHG might be a powerful tool to quantify the increased cell to cell coupling in preparation to labor. However, this analysis is technically challenging and a variety of techniques has been adopted. These methods range from using a two channel setup [19] to 64 channels [132, 177], and from analyzing single spike propagation [19, 132, 177] to propagation of whole bursts [173, 197]. This has resulted in widely varying values for the conduction velocity. Moreover, to date visual review of signals has been necessary in the analysis of the EHG, hampering the objectivity and repeatability. For clinical applications, the use of validated automated methods is a prerequisite. This comprises two steps: automatic selection of contractile bursts in the EHG and automatic analysis of the conduction velocity.

The first step, the isolation of the EHG from noise and artefacts, is conditional to most EHG parameters which rely on analysis of the clean EHG rather than noise. However, it is also one of the most challenging steps in preterm EHG analysis as conventional methods cannot be used as golden standard. The relationship between EHG contractile bursts and mechanical output measured by an external tocodynamometer or IUPC is certain in one way only: contractions established in the tocogram are always accompanied by a contractile burst in the EHG, but not vice versa. Therefore preterm detection of contractile bursts will need to build on the established high correlation of the invasively measured and the abdominally derived EHG, in combination with well-developed detection of motion artefacts and rejection of other bioelectrical signals.

The second step, estimation of the conduction velocity, is not trivial either, as preterm propagation patterns appear to be highly variable [136, 156, 157]. Estimation of conduction velocity builds on the assumption of linear propagation. and this linear relation needs to be tested for, in order to get the most accurate estimate. Overall, a method needs to be developed which is objective and repeatable, and that is sensitive enough to distinguish high from low conduction velocities in order to timely predict imminent preterm delivery. The diagnostic accuracy of this method needs to be tested in a clinical setting.

Clinical application of the EHG in term labor is one step closer. Clinical studies have confirmed the limited accuracy and reliability of the external tocodynamometer on one hand [16, 17] and the potential of the EHG on the other hand [29, 208, 213, 214]. An important step towards clinical application as standard method will be the development of real time EHG processing to derive the estimate of the IUP. In addition, caution must be exercised in the use of EHG based monitoring during pregnancy and in the pre-labor phase as monitoring electrical activity will result in other information than measuring the mechanical output. This can also be seen as an opportunity, as this might disclose additional information on the evolution of the contractile activity during pregnancy and induction of labor, towards delivery.

References

1. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, Rubens C, Menon R, Van Look PF: **The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity.** *Bulletin of the World Health Organization* 2010, **88**(1):31-38.
2. Pennell CE, Jacobsson B, Williams SM, Buus RM, Muglia LJ, Dolan SM, Morken NH, Ozcelik H, Lye SJ, Relton C: **Genetic epidemiologic studies of preterm birth: guidelines for research**. *American journal of obstetrics and gynecology* 2007, **196**(2):107-118.
3. World Health Organization MoD, Partnership for Maternal, Newborn & Child Health, Save the Children: **Born too soon: the global action report on preterm birth**. In.; 2012.
4. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA *et al*: **Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network**. *Pediatrics* 2010, **126**(3):443-456.
5. Hack M, Schluchter M, Andreias L, Margevicius S, Taylor HG, Drotar D, Cuttler L: **Change in prevalence of chronic conditions between childhood and adolescence among extremely low-birth-weight children**. *JAMA : the journal of the American Medical Association* 2011, **306**(4):394-401.
6. Roberts D, Dalziel S: **Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth**. *Cochrane Database Syst Rev* 2006(3):CD004454.
7. Waffarn F, Davis EP: **Effects of antenatal corticosteroids on the hypothalamic-pituitary-adrenocortical axis of the fetus and newborn: experimental findings and clinical considerations**. *American journal of obstetrics and gynecology* 2012, **207**(6):446-454.
8. Bedalov A, Balasubramanyam A: **Glucocorticoid-induced ketoacidosis in gestational diabetes: sequela of the acute treatment of preterm labor. A case report**. *Diabetes care* 1997, **20**(6):922-924.
9. Ferguson JE, 2nd, Dyson DC, Schutz T, Stevenson DK: **A comparison of tocolysis with nifedipine or ritodrine: analysis of efficacy and maternal, fetal, and neonatal outcome**. *American journal of obstetrics and gynecology* 1990, **163**(1 Pt 1):105-111.
10. Bracero LA, Leikin E, Kirshenbaum N, Tejani N: **Comparison of nifedipine and ritodrine for the treatment of preterm labor**. *American journal of perinatology* 1991, **8**(6):365-369.
11. Gyetvai K, Hannah ME, Hodnett ED, Ohlsson A: **Tocolytics for preterm labor: a systematic review**. *Obstetrics and gynecology* 1999, **94**(5 Pt 2):869-877.
12. Oei SG, Oei SK, Brolmann HA: **Myocardial infarction during nifedipine therapy for preterm labor**. *N Engl J Med* 1999, **340**(2):154.
13. van Veen AJ, Pelinck MJ, van Pampus MG, Erwich JJ: **Severe hypotension and fetal death due to tocolysis with nifedipine**. *BJOG* 2005, **112**(4):509-510.
14. Scott CL, Chavez GF, Atrash HK, Taylor DJ, Shah RS, Rowley D: **Hospitalizations for severe complications of pregnancy, 1987-1992**. *Obstetrics and gynecology* 1997, **90**(2):225-229.
15. Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, Franks AL: **Hospitalizations during pregnancy among managed care enrollees**. *Obstetrics and gynecology* 2002, **100**(1):94-100.
16. Bakker PC, Zikkenheimer M, van Geijn HP: **The quality of intrapartum uterine activity monitoring**. *Journal of perinatal medicine* 2008, **36**(3):197-201.
17. Ray A, Hildreth A, Esen UI: **Morbid obesity and intra-partum care**. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology* 2008, **28**(3):301-304.
18. Dyson DC, Danbe KH, Bamber JA, Crites YM, Field DR, Maier JA, Newman LA, Ray DA, Walton DL, Armstrong MA: **Monitoring women at risk for preterm labor**. *N Engl J Med* 1998, **338**(1):15-19.
19. Lucovnik M, Maner WL, Chambliss LR, Blumrick R, Balducci J, Novak-Antolic Z, Garfield RE: **Noninvasive uterine electromyography for prediction of preterm delivery**. *American journal of obstetrics and gynecology* 2011, **204**(3):228 e221-210.
20. Iams JD, Newman RB, Thom EA, Goldenberg RL, Mueller-Heubach E, Moawad A, Sibai BM, Caritis SN, Miodovnik M, Paul RH *et al*: **Frequency of uterine contractions and the risk of spontaneous preterm delivery**. *N Engl J Med* 2002, **346**(4):250-255.
21. Sotiriadis A, Papatheodorou S, Kavvadias A, Makrydimas G: **Transvaginal cervical length measurement for prediction of preterm birth in women with threatened preterm labor: a meta-analysis**. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2010, **35**(1):54-64.
22. Sanchez-Ramos L, Delke I, Zamora J, Kaunitz AM: **Fetal fibronectin as a short-term predictor of preterm birth in symptomatic patients: a meta-analysis**. *Obstetrics and gynecology* 2009, **114**(3):631-640.
23. Phelps JY, Higby K, Smyth MH, Ward JA, Arredondo F, Mayer AR: **Accuracy and intraobserver variability of simulated cervical dilatation measurements**. *American journal of obstetrics and gynecology* 1995, **173**(3 Pt 1):942-945.
24. Tuffnell DJ, Bryce F, Johnson N, Lilford RJ: **Simulation of cervical changes in labour: reproducibility of expert assessment**. *Lancet* 1989, **2**(8671):1089-1090.
25. Amon E, Midkiff C, Winn H, Holcomb W, Shumway J, Artal R: **Tocolysis with advanced cervical dilatation**. *Obstetrics and gynecology* 2000, **95**(3):358-362.

26. King JF, Grant A, Keirse MJ, Chalmers I: **Beta-mimetics in preterm labour: an overview of the randomized controlled trials**. *British journal of obstetrics and gynaecology* 1988, **95**(3):211-222.
27. Fuchs IB, Henrich W, Osthues K, Dudenhausen JW: **Sonographic cervical length in singleton pregnancies with intact membranes presenting with threatened preterm labor**. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2004, **24**(5):554-557.
28. McPheeters ML, Miller WC, Hartmann KE, Savitz DA, Kaufman JS, Garrett JM, Thorp JM: **The epidemiology of threatened preterm labor: a prospective cohort study**. *American journal of obstetrics and gynecology* 2005, **192**(4):1325-1329; discussion 1329-1330.
29. Euliano TY, Nguyen MT, Darmanjian S, McGorray SP, Euliano N, Onkala A, Gregg AR: **Monitoring uterine activity during labor: a comparison of 3 methods**. *American journal of obstetrics and gynecology* 2013, **208**(1):66 e61-66.
30. Vanner T, Gardosi J: **Intrapartum assessment of uterine activity**. *Bailliere's clinical obstetrics and gynaecology* 1996, **10**(2):243-257.
31. Soper DE, Mayhall CG, Froggatt JW: **Characterization and control of intraamniotic infection in an urban teaching hospital**. *American journal of obstetrics and gynecology* 1996, **175**(2):304-309; discussion 309-310.
32. Wilmink FA, Wilms FF, Heydanus R, Mol BW, Papatsonis DN: **Fetal complications after placement of an intrauterine pressure catheter: a report of two cases and review of the literature**. *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 Obstet* 2008, **21**(12):880-883.
33. Rood KM: **Complications associated with insertion of intrauterine pressure catheters: an unusual case of uterine hypertonicity and uterine perforation resulting in fetal distress after insertion of an intrauterine pressure catheter**. *Case reports in obstetrics and gynecology* 2012, **2012**:517461.
34. MM IJ, Evers JL, Dunselman GA, Hoogland HJ: **Subendometrial contractions in the nonpregnant uterus: an ultrasound study**. *European journal of obstetrics, gynecology, and reproductive biology* 1996, **70**(1):23-24.
35. Aguilar HN, Mitchell BF: **Physiological pathways and molecular mechanisms regulating uterine contractility**. *Human reproduction update* 2010, **16**(6):725-744.
36. Robert K. Creasy RR, W.B Saunders: **Maternal-Fetal Medicine**, 4th edition edn; 1999.
37. Morrione TG, Seifter S: **Alteration in the collagen content of the human uterus during pregnancy and post partum involution**. *The Journal of experimental medicine* 1962, **115**:357-365.
38. Zygmunt M, Herr F, Munstedt K, Lang U, Liang OD: **Angiogenesis and vasculogenesis in pregnancy**. *European journal of obstetrics, gynecology, and reproductive biology* 2003, **110 Suppl 1**:S10-18.
39. Buhimschi C, Boyle MB, Garfield RE: **Electrical activity of the human uterus during pregnancy as recorded from the abdominal surface**. *Obstetrics and gynecology* 1997, **90**(1):102-111.
40. Gonzalez JM, Romero R, Girardi G: **Comparison of the mechanisms responsible for cervical remodeling in preterm and term labor**. *Journal of reproductive immunology* 2013, **97**(1):112-119.
41. Danforth DN: **The morphology of the human cervix**. *Clinical obstetrics and gynecology* 1983, **26**(1):7-13.
42. Timmons B, Akins M, Mahendroo M: **Cervical remodeling during pregnancy and parturition**. *Trends in endocrinology and metabolism: TEM* 2010, **21**(6):353-361.
43. Young RC: **Myocytes, myometrium, and uterine contractions**. *Annals of the New York Academy of Sciences* 2007, **1101**:72-84.
44. VanRees D, Bernstine RL, Crawford W: **Involution of the postpartum uterus: an ultrasonic study**. *Journal of clinical ultrasound : JCU* 1981, **9**(2):55-57.
45. Berridge MJ: **Cell Signalling Biology**; 2012.
46. Eswaran H, Govindan RB, Furdea A, Murphy P, Lowery CL, Preissl HT: **Extraction, quantification and characterization of uterine magnetomyographic activity--a proof of concept case study**. *European journal of obstetrics, gynecology, and reproductive biology* 2009, **144 Suppl 1**:S96-100.
47. Hai CM, Murphy RA: **Cross-bridge phosphorylation and regulation of latch state in smooth muscle**. *The American journal of physiology* 1988, **254**(1 Pt 1):C99-106.
48. Murphy RA: **Filament organization and contractile function in vertebrate smooth muscle**. *Annual review of physiology* 1979, **41**:737-748.
49. Murphy RA: **What is special about smooth muscle? The significance of covalent crossbridge regulation**. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 1994, **8**(3):311-318.
50. Murphy RA, Rembold CM: **The latch-bridge hypothesis of smooth muscle contraction**. *Canadian journal of physiology and pharmacology* 2005, **83**(10):857-864.
51. Paul RJ: **Smooth muscle energetics**. *Annual review of physiology* 1989, **51**:331-349.
52. Wray S, Jones K, Kupittayanant S, Li Y, Matthew A, Monir-Bishty E, Noble K, Pierce SJ, Quenby S, Shmygol AV: **Calcium signaling and uterine contractility**. *Journal of the Society for Gynecologic Investigation* 2003, **10**(5):252-264.
53. Du P, O'Grady G, Gao J, Sathar S, Cheng LK: **Toward the virtual stomach: progress in multiscale modeling of gastric electrophysiology and motility**. *Wiley interdisciplinary reviews Systems biology and medicine* 2013, **5**(4):481-493.
54. Lammers WJ, Ver Donck L, Stephen B, Smets D, Schuurkes JA: **Origin and propagation of the slow wave in the canine stomach: the outlines of a gastric conduction system**. *American journal of physiology Gastrointestinal and liver physiology* 2009, **296**(6):G1200-1210.

55. Cheng LK, O'Grady G, Du P, Egbuji JU, Windsor JA, Pullan AJ: **Gastrointestinal system**. *Wiley interdisciplinary reviews Systems biology and medicine* 2010, **2**(1):65-79.
56. Khan RN, Matharoo-Ball B, Arulkumaran S, Ashford ML: **Potassium channels in the human myometrium**. *Experimental physiology* 2001, **86**(2):255-264.
57. Sanborn BM: **Relationship of ion channel activity to control of myometrial calcium**. *Journal of the Society for Gynecologic Investigation* 2000, **7**(1):4-11.
58. Lammers WJ: **The electrical activities of the uterus during pregnancy**. *Reprod Sci* 2013, **20**(2):182-189.
59. Noble K, Matthew A, Burdyga T, Wray S: **A review of recent insights into the role of the sarcoplasmic reticulum and Ca entry in uterine smooth muscle**. *European journal of obstetrics, gynecology, and reproductive biology* 2009, **144 Suppl 1**:S11-19.
60. Gravina FS, Parkington HC, Kerr KP, de Oliveira RB, Jobling P, Coleman HA, Sandow SL, Davies MM, Imtiaz MS, van Helden DF: **Role of mitochondria in contraction and pacemaking in the mouse uterus**. *British journal of pharmacology* 2010, **161**(6):1375-1390.
61. Duquette RA, Shmygol A, Vaillant C, Mobasheri A, Pope M, Burdyga T, Wray S: **Vimentin-positive, c-kit-negative interstitial cells in human and rat uterus: a role in pacemaking?** *Biology of reproduction* 2005, **72**(2):276-283.
62. Parkington HC, Coleman HA: **Excitability in uterine smooth muscle**. *Frontiers of hormone research* 2001, **27**:179-200.
63. Wray S, Kupittayanant S, Shmygol A, Smith RD, Burdyga T: **The physiological basis of uterine contractility: a short review**. *Experimental physiology* 2001, **86**(2):239-246.
64. Parkington HC, Tonta MA, Brennecke SP, Coleman HA: **Contractile activity, membrane potential, and cytoplasmic calcium in human uterine smooth muscle in the third trimester of pregnancy and during labor**. *American journal of obstetrics and gynecology* 1999, **181**(6):1445-1451.
65. Garfield RE, Sims S, Daniel EE: **Gap junctions: their presence and necessity in myometrium during parturition**. *Science* 1977, **198**(4320):958-960.
66. Miller SM, Garfield RE, Daniel EE: **Improved propagation in myometrium associated with gap junctions during parturition**. *The American journal of physiology* 1989, **256**(1 Pt 1):C130-141.
67. Young RC, Goloman G: **Mechanotransduction in rat myometrium: coordination of contractions of electrically and chemically isolated tissues**. *Reprod Sci* 2011, **18**(1):64-69.
68. Lammers WJ, Stephen B, Al-Sultan MA, Subramanya SB, Blanks AM: **The location of pacemakers in the uteri of pregnant guinea pigs and rats**. *American journal of physiology Regulatory, integrative and comparative physiology* 2015, **309**(11):R1439-1446.
69. Teixeira J, Rueda BR, Pru JK: **Uterine stem cells**. In: *StemBook.* edn. Cambridge (MA); 2008.
70. Buhimschi CS, Buhimschi IA, Malinow AM, Weiner CP: **Myometrial thickness during human labor and immediately post partum**. *American journal of obstetrics and gynecology* 2003, **188**(2):553-559.
71. Reynolds LP, Redmer DA: **Growth and microvascular development of the uterus during early pregnancy in ewes**. *Biology of reproduction* 1992, **47**(5):698-708.
72. Jaffer S, Shynlova O, Lye S: **Mammalian target of rapamycin is activated in association with myometrial proliferation during pregnancy**. *Endocrinology* 2009, **150**(10):4672-4680.
73. Shynlova O, Tsui P, Jaffer S, Lye SJ: **Integration of endocrine and mechanical signals in the regulation of myometrial functions during pregnancy and labour**. *European journal of obstetrics, gynecology, and reproductive biology* 2009, **144 Suppl 1**:S2-10.
74. Csapo A, Erdos T, De Mattos CR, Gramss E, Moscowitz C: **Stretch-induced uterine growth, protein synthesis and function**. *Nature* 1965, **207**(5004):1378-1379.
75. Shynlova O, Kwong R, Lye SJ: **Mechanical stretch regulates hypertrophic phenotype of the myometrium during pregnancy**. *Reproduction* 2010, **139**(1):247-253.
76. White BG, MacPhee DJ: **Distension of the uterus induces HspB1 expression in rat uterine smooth muscle**. *American journal of physiology Regulatory, integrative and comparative physiology* 2011, **301**(5):R1418-1426.
77. Goerttler K: **[Structure of the human uterus wall]**. *Archiv fur Gynakologie* 1968, **205**(4):334-342.
78. Goerttler K: **Die archietektur der muscelwand des menschlichen uterus and ihre functinelle bedeutung**. *Jahrbuch Morph u Microsk Anat* 1931, **65**:45-128.
79. Wetzstein R: **[The myometrium: morphology]**. *Archiv fur Gynakologie* 1965, **202**:1-13.
80. Wetzstein R, Renn KH: **[Arrangement of smooth muscle in the human uterus]**. *Verhandlungen der Anatomischen Gesellschaft* 1970, **64**:461-468.
81. Weiss S, Jaermann T, Schmid P, Staempfli P, Boesiger P, Niederer P, Caduff R, Bajka M: **Three-dimensional fiber architecture of the nonpregnant human uterus determined ex vivo using magnetic resonance diffusion tensor imaging**. *The anatomical record Part A, Discoveries in molecular, cellular, and evolutionary biology* 2006, **288**(1):84-90.
82. Noe M, Kunz G, Herbertz M, Mall G, Leyendecker G: **The cyclic pattern of the immunocytochemical expression of oestrogen and progesterone receptors in human myometrial and endometrial layers: characterization of the endometrial-subendometrial unit**. *Hum Reprod* 1999, **14**(1):190-197.
83. Huszar G, Naftolin F: **The myometrium and uterine cervix in normal and preterm labor**. *N Engl J Med* 1984, **311**(9):571-581.
84. Young RC, Hession RO: **Three-dimensional structure of the smooth muscle in the term-pregnant human uterus**. *Obstetrics and gynecology* 1999, **93**(1):94-99.

85. Word RA, Stull JT, Casey ML, Kamm KE: **Contractile elements and myosin light chain phosphorylation in myometrial tissue from nonpregnant and pregnant women**. *The Journal of clinical investigation* 1993, **92**(1):29-37.

86. Draeger A, Amos WB, Ikebe M, Small JV: **The cytoskeletal and contractile apparatus of smooth muscle: contraction bands and segmentation of the contractile elements**. *The Journal of cell biology* 1990, **111**(6 Pt 1):2463-2473.

87. Buhimschi C, Boyle MB, Saade GR, Garfield RE: **Uterine activity during pregnancy and labor assessed by simultaneous recordings from the myometrium and abdominal surface in the rat**. *American journal of obstetrics and gynecology* 1998, **178**(4):811-822.

88. Buhimschi C, Garfield RE: **Uterine contractility as assessed by abdominal surface recording of electromyographic activity in rats during pregnancy**. *American journal of obstetrics and gynecology* 1996, **174**(2):744-753.

89. Doret M, Bukowski R, Longo M, Maul H, Maner WL, Garfield RE, Saade GR: **Uterine electromyography characteristics for early diagnosis of mifepristone-induced preterm labor**. *Obstetrics and gynecology* 2005, **105**(4):822-830.

90. Lopes P, Germain G, Breart G, Reitano S, Le Houezec R, Sureau C: **Electromyographical study of uterine activity in the human during labour induced by prostaglandin F2 alpha**. *Gynecologic and obstetric investigation* 1984, **17**(2):96-105.

91. Marshall JM: **Regulation of activity in uterine smooth muscle**. *Physiological reviews Supplement* 1962, **5**:213-227.

92. Pajntar M, Roskar E, Rudel D: **Electromyographic observations on the human cervix during labor**. *American journal of obstetrics and gynecology* 1987, **156**(3):691-697.

93. Wray S: **Uterine contraction and physiological mechanisms of modulation**. *The American journal of physiology* 1993, **264**(1 Pt 1):C1-18.

94. Word RA: **Myosin phosphorylation and the control of myometrial contraction/relaxation**. *Seminars in perinatology* 1995, **19**(1):3-14.

95. Marshall JM: **Effects of estrogen and progesterone on single uterine muscle fibers in the rat**. *The American journal of physiology* 1959, **197**:935-942.

96. Ohkubo T, Inoue Y, Kawarabayashi T, Kitamura K: **Identification and electrophysiological characteristics of isoforms of T-type calcium channel Ca(v)3.2 expressed in pregnant human uterus**. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology* 2005, **16**(4-6):245-254.

97. Sperelakis N, Inoue Y, Ohya Y: **Fast Na+ channels and slow Ca2+ current in smooth muscle from pregnant rat uterus**. *Molecular and cellular biochemistry* 1992, **114**(1-2):79-89.

98. Yoshino M, Wang SY, Kao CY: **Sodium and calcium inward currents in freshly dissociated smooth myocytes of rat uterus**. *The Journal of general physiology* 1997, **110**(5):565-577.

99. Young RC, Smith LH, McLaren MD: **T-type and L-type calcium currents in freshly dispersed human uterine smooth muscle cells**. *American journal of obstetrics and gynecology* 1993, **169**(4):785-792.

100. Kupittayanant S, Luckas MJ, Wray S: **Effect of inhibiting the sarcoplasmic reticulum on spontaneous and oxytocin-induced contractions of human myometrium**. *BJOG* 2002, **109**(3):289-296.

101. Goto M, Csapo A: **The effect of the ovarian steroids on the membrane potential of uterine muscle**. *The Journal of general physiology* 1959, **43**:455-466.

102. Hantooshzadeh S, Rezaeizadeh G, Nikfar S, Ghiasi S, Abdollahi M: **A systematic review of the uterine relaxant effect of potassium channel openers**. *Current drug discovery technologies* 2013, **10**(4):263-269.

103. Papatsonis D, Flenady V, Cole S, Liley H: **Oxytocin receptor antagonists for inhibiting preterm labour**. *Cochrane Database Syst Rev* 2005(3):CD004452.

104. Brainard AM, Korovkina VP, England SK: **Potassium channels and uterine function**. *Seminars in cell & developmental biology* 2007, **18**(3):332-339.

105. Casteels R, Kuriyama H: **Membrane Potential and Ionic Content in Pregnant and Non-Pregnant Rat Myometrium**. *The Journal of physiology* 1965, **177**:263-287.

106. Inoue Y, Nakao K, Okabe K, Izumi H, Kanda S, Kitamura K, Kuriyama H: **Some electrical properties of human pregnant myometrium**. *American journal of obstetrics and gynecology* 1990, **162**(4):1090-1098.

107. Pressman EK, Tucker JA, Jr., Anderson NC, Jr., Young RC: **Morphologic and electrophysiologic characterization of isolated pregnant human myometrial cells**. *American journal of obstetrics and gynecology* 1988, **159**(5):1273-1279.

108. Nakajima A: **Action potential of human myometrial fibers**. *American journal of obstetrics and gynecology* 1971, **111**(2):266-269.

109. Kumar D, Barnes AC: **Studies in human myometrium during pregancy. II. Resting membrane potential and comparative electrolyte levels**. *American journal of obstetrics and gynecology* 1961, **82**:736-741.

110. George AL, Jr., Knittle TJ, Tamkun MM: **Molecular cloning of an atypical voltage-gated sodium channel expressed in human heart and uterus: evidence for a distinct gene family**. *Proceedings of the National Academy of Sciences of the United States of America* 1992, **89**(11):4893-4897.

111. Jones K, Shmygol A, Kupittayanant S, Wray S: **Electrophysiological characterization and functional importance of calcium-activated chloride channel in rat uterine myocytes**. *Pflugers Archiv : European journal of physiology* 2004, **448**(1):36-43.
112. Kaya T, Guvenal T, Karadas B, Cetin A, Soydan AS: **Effects of 5-nitro-2-(3-phenylpropylamino) benzoic acid, anthracene-9-carboxylate, and zaprinast on endothelin-1-induced contractions of pregnant rat myometrium**. *European journal of obstetrics, gynecology, and reproductive biology* 2002, **105**(2):114-119.
113. Yarar Y, Cetin A, Kaya T: **Chloride channel blockers 5-nitro-2-(3-phenylpropylamino) benzoic acid and anthracene-9-carboxylic acid inhibit contractions of pregnant rat myometrium in vitro**. *Journal of the Society for Gynecologic Investigation* 2001, **8**(4):206-209.
114. Young RC, Bemis A: **Calcium-activated chloride currents prolongs the duration of contractions in pregnant rat myometrial tissue**. *Reprod Sci* 2009, **16**(8):734-739.
115. Hanani M, Brading AF: **Electrical coupling in smooth muscles. Is it universal?** *Journal of basic and clinical physiology and pharmacology* 2000, **11**(4):321-330.
116. Lodge S, Sproat JE: **Resting membrane potentials of pacemaker and non pacemaker areas in rat uterus**. *Life sciences* 1981, **28**(20):2251-2256.
117. Tsien RW, Carpenter DO: **Ionic mechanisms of pacemaker activity in cardiac Purkinje fibers**. *Federation proceedings* 1978, **37**(8):2127-2131.
118. Hashitani H, Bramich NJ, Hirst GD: **Mechanisms of excitatory neuromuscular transmission in the guinea-pig urinary bladder**. *The Journal of physiology* 2000, **524 Pt 2**:565-579.
119. Kao CY: **Long-term observations of spontaneous electrical activity of the uterine smooth muscle**. *The American journal of physiology* 1959, **196**(2):343-350.
120. Lee HT, Hennig GW, Fleming NW, Keef KD, Spencer NJ, Ward SM, Sanders KM, Smith TK: **The mechanism and spread of pacemaker activity through myenteric interstitial cells of Cajal in human small intestine**. *Gastroenterology* 2007, **132**(5):1852-1865.
121. Ordog T, Takayama I, Cheung WK, Ward SM, Sanders KM: **Remodeling of networks of interstitial cells of Cajal in a murine model of diabetic gastroparesis**. *Diabetes* 2000, **49**(10):1731-1739.
122. Devedeux D, Marque C, Mansour S, Germain G, Duchene J: **Uterine electromyography: a critical review**. *American journal of obstetrics and gynecology* 1993, **169**(6):1636-1653.
123. Hon EH, Davis CD: **Cutaneous and uterine electrical potentials in labor; an experiment**. *Obstetrics and gynecology* 1958, **12**(1):47-53.
124. Popescu LM, Ciontea SM, Cretoiu D: **Interstitial Cajal-like cells in human uterus and fallopian tube**. *Annals of the New York Academy of Sciences* 2007, **1101**:139-165.
125. Popescu LM, Vidulescu C, Curici A, Caravia L, Simionescu AA, Ciontea SM, Simion S: **Imatinib inhibits spontaneous rhythmic contractions of human uterus and intestine**. *European journal of pharmacology* 2006, **546**(1-3):177-181.
126. Crane LH, Martin L: **In vivo myometrial activity during early pregnancy and pseudopregnancy in the rat**. *Reproduction, fertility, and development* 1991, **3**(3):233-244.
127. Fuchs AR: **Uterine activity in late pregnancy and during parturition in the rat**. *Biology of reproduction* 1969, **1**(4):344-353.
128. Parkington HC, Harding R, Sigger JN: **Co-ordination of electrical activity in the myometrium of pregnant ewes**. *Journal of reproduction and fertility* 1988, **82**(2):697-705.
129. Wolfs G, van Leeuwen M, Rottinghuis H, Boeles JT: **An electromyographic study of the human uterus during labor**. *Obstetrics and gynecology* 1971, **37**(2):241-246.
130. Fuchs AR, Poblete VF, Jr.: **Oxytocin and uterine function in pregnant and parturient rats**. *Biology of reproduction* 1970, **2**(3):387-400.
131. Wolfs G, Rottinghuis H: **Electrical and mechanical activity of the human uterus during labour**. *Archiv fur Gynakologie* 1970, **208**(4):373-385.
132. Rabotti C, Mischi M, Oei SG, Bergmans JW: **Noninvasive estimation of the electrohysterographic action-potential conduction velocity**. *IEEE transactions on bio-medical engineering* 2010, **57**(9):2178-2187.
133. Hsu HW, Figueroa JP, Honnebier MB, Wentworth R, Nathanielsz PW: **Power spectrum analysis of myometrial electromyogram and intrauterine pressure changes in the pregnant rhesus monkey in late gestation**. *American journal of obstetrics and gynecology* 1989, **161**(2):467-473.
134. Mansour S, Devedeux D, Germain G, Marque C, Duchene J: **Uterine EMG spectral analysis and relationship to mechanical activity in pregnant monkeys**. *Medical & biological engineering & computing* 1996, **34**(2):115-121.
135. Lammers WJ, el-Kays A, Arafat K, el-Sharkawy TY: **Wave mapping: detection of co-existing multiple wavefronts in high-resolution electrical mapping**. *Medical & biological engineering & computing* 1995, **33**(3 Spec No):476-481.
136. Lammers WJ, Arafat K, el-Kays A, el-Sharkawy TY: **Spatial and temporal variations in local spike propagation in the myometrium of the 17-day pregnant rat**. *The American journal of physiology* 1994, **267**(5 Pt 1):C1210-1223.
137. Lammers WJ, Mirghani H, Stephen B, Dhanasekaran S, Wahab A, Al Sultan MA, Abazer F: **Patterns of electrical propagation in the intact pregnant guinea pig uterus**. *American journal of physiology Regulatory, integrative and comparative physiology* 2008, **294**(3):R919-928.
138. Verhoeff A, Garfield RE, Ramondt J, Wallenburg HC: **Electrical and mechanical uterine activity and gap junctions in peripartal sheep**. *American journal of obstetrics and gynecology* 1985, **153**(4):447-454.

139. Sakai N, Tabb T, Garfield RE: **Modulation of cell-to-cell coupling between myometrial cells of the human uterus during pregnancy**. *American journal of obstetrics and gynecology* 1992, **167**(2):472-480.
140. Orsino A, Taylor CV, Lye SJ: **Connexin-26 and connexin-43 are differentially expressed and regulated in the rat myometrium throughout late pregnancy and with the onset of labor**. *Endocrinology* 1996, **137**(5):1545-1553.
141. Ou CW, Orsino A, Lye SJ: **Expression of connexin-43 and connexin-26 in the rat myometrium during pregnancy and labor is differentially regulated by mechanical and hormonal signals**. *Endocrinology* 1997, **138**(12):5398-5407.
142. Tong D, Lu X, Wang HX, Plante I, Lui E, Laird DW, Bai D, Kidder GM: **A dominant loss-of-function GJA1 (Cx43) mutant impairs parturition in the mouse**. *Biology of reproduction* 2009, **80**(6):1099-1106.
143. Di WL, Lachelin GC, McGarrigle HH, Thomas NS, Becker DL: **Oestriol and oestradiol increase cell to cell communication and connexin43 protein expression in human myometrium**. *Molecular human reproduction* 2001, **7**(7):671-679.
144. Lye SJ, Nicholson BJ, Mascarenhas M, MacKenzie L, Petrocelli T: **Increased expression of connexin-43 in the rat myometrium during labor is associated with an increase in the plasma estrogen:progesterone ratio**. *Endocrinology* 1993, **132**(6):2380-2386.
145. MacKenzie LW, Garfield RE: **Hormonal control of gap junctions in the myometrium**. *The American journal of physiology* 1985, **248**(3 Pt 1):C296-308.
146. Miyoshi H, Boyle MB, MacKay LB, Garfield RE: **Voltage-clamp studies of gap junctions between uterine muscle cells during term and preterm labor**. *Biophysical journal* 1996, **71**(3):1324-1334.
147. Sims SM, Daniel EE, Garfield RE: **Improved electrical coupling in uterine smooth muscle is associated with increased numbers of gap junctions at parturition**. *The Journal of general physiology* 1982, **80**(3):353-375.
148. Young RC, Hession RO: **Intra-and intercellular calcium waves in cultured human myometrium**. *Journal of muscle research and cell motility* 1996, **17**(3):349-355.
149. Nakano T, Suda T, Koujin T, Haraguchi T, Hiraoka Y: **Molecular communication through gap junction channels: System design, experiments and modeling**. In: *Bio-Inspired Models of Network, Information and Computing Systems, 2007 Bionetics 2007 2nd: 2007*: IEEE; 2007: 139-146.
150. Csapo AI, Jaffin H, Kerenyi T, Lipman JI, Wood C: **Volume and activity of the pregnant human uterus**. *American journal of obstetrics and gynecology* 1963, **85**:819-835.
151. Takeda H: **Generation and Propagation of Uterine Activity in Situ**. *Fertility and sterility* 1965, **16**:113-119.
152. Garfield RE, Blennerhassett MG, Miller SM: **Control of myometrial contractility: role and regulation of gap junctions**. *Oxford reviews of reproductive biology* 1988, **10**:436-490.
153. Garfield RE, Hertzberg EL: **Cell-to-cell coupling in the myometrium: Emil Bozler's prediction**. *Progress in clinical and biological research* 1990, **327**:673-681.
154. Garfield RE, Merrett D, Grover AK: **Gap junction formation and regulation in myometrium**. *The American journal of physiology* 1980, **239**(5):C217-228.
155. Doring B, Shynlova O, Tsui P, Eckardt D, Janssen-Bienhold U, Hofmann F, Feil S, Feil R, Lye SJ, Willecke K: **Ablation of connexin43 in uterine smooth muscle cells of the mouse causes delayed parturition**. *Journal of cell science* 2006, **119**(Pt 9):1715-1722.
156. Lammers WJ, Hamid R: **The initiation, continuation, and termination of spontaneous episodes of circus movements in the pregnant myometrium of the rat**. *American journal of obstetrics and gynecology* 1998, **179**(6 Pt 1):1515-1526.
157. Lammers WJ: **Circulating excitations and re-entry in the pregnant uterus**. *Pflugers Archiv : European journal of physiology* 1997, **433**(3):287-293.
158. Takashima S: **Phosphorylation of myosin regulatory light chain by myosin light chain kinase, and muscle contraction**. *Circulation journal : official journal of the Japanese Circulation Society* 2009, **73**(2):208-213.
159. Gorecka A, Aksoy MO, Hartshorne DJ: **The effect of phosphorylation of gizzard myosin on actin activation**. *Biochemical and biophysical research communications* 1976, **71**(1):325-331.
160. Filo RS, Bohr DF, Ruegg JC: **Glycerinated Skeletal and Smooth Muscle: Calcium and Magnesium Dependence**. *Science* 1965, **147**(3665):1581-1583.
161. Longbottom ER, Luckas MJ, Kupittayanant S, Badrick E, Shmigol T, Wray S: **The effects of inhibiting myosin light chain kinase on contraction and calcium signalling in human and rat myometrium**. *Pflugers Archiv : European journal of physiology* 2000, **440**(2):315-321.
162. Somlyo AP, Somlyo AV: **Flash photolysis studies of excitation-contraction coupling, regulation, and contraction in smooth muscle**. *Annual review of physiology* 1990, **52**:857-874.
163. Huxley AF, Niedergerke R: **Structural changes in muscle during contraction; interference microscopy of living muscle fibres**. *Nature* 1954, **173**(4412):971-973.
164. Huxley H, Hanson J: **Changes in the cross-striations of muscle during contraction and stretch and their structural interpretation**. *Nature* 1954, **173**(4412):973-976.
165. Bode O: **Das Elektrohysterogramm**. *Archiv fur Gynakologie* 1931, **146**(1):123-128.
166. Steer CM, Hertsch GJ: **Electrical activity of the human uterus in labor; the electrohysterograph**. *American journal of obstetrics and gynecology* 1950, **59**(1):25-40.
167. Marque CK, Terrien J, Rihana S, Germain G: **Preterm labour detection by use of a biophysical marker: the uterine electrical activity**. *BMC pregnancy and childbirth* 2007, **7 Suppl 1**:S5.

168. Rabotti C, Mischi M, Beulen L, Oei G, Bergmans JW: **Modeling and identification of the electrohysterographic volume conductor by high-density electrodes**. *IEEE transactions on bio-medical engineering* 2010, **57**(3):519-527.
169. Hassan M, Boudaoud S, Terrien J, Karlsson B, Marque C: **Combination of canonical correlation analysis and empirical mode decomposition applied to denoising the labor electrohysterogram**. *IEEE transactions on bio-medical engineering* 2011, **58**(9):2441-2447.
170. Leman H, Marque C, Gondry J: **Use of the electrohysterogram signal for characterization of contractions during pregnancy**. *IEEE transactions on bio-medical engineering* 1999, **46**(10):1222-1229.
171. Maner WL, Garfield RE: **Identification of human term and preterm labor using artificial neural networks on uterine electromyography data**. *Ann Biomed Eng* 2007, **35**(3):465-473.
172. Maner WL, Garfield RE, Maul H, Olson G, Saade G: **Predicting term and preterm delivery with transabdominal uterine electromyography**. *Obstetrics and gynecology* 2003, **101**(6):1254-1260.
173. Mikkelsen E, Johansen P, Fuglsang-Frederiksen A, Uldbjerg N: **Electrohysterography of labor contractions: propagation velocity and direction**. *Acta obstetricia et gynecologica Scandinavica* 2013, **92**(9):1070-1078.
174. Fele-Zorz G, Kavsek G, Novak-Antolic Z, Jager F: **A comparison of various linear and non-linear signal processing techniques to separate uterine EMG records of term and pre-term delivery groups**. *Medical & biological engineering & computing* 2008, **46**(9):911-922.
175. Muszynski C, Terrien J, Drean Y, Chkeir A, Hassan M, Marque C, Gondry J: **[Evolution of electrohysterogram signals synchronization according to term of pregnancy: interest for preterm labor diagnosis]**. *Gynecologie, obstetrique & fertilite* 2012, **40**(6):344-349.
176. Hassan M, Terrien J, Muszynski C, Alexandersson A, Marque C, Karlsson B: **Better pregnancy monitoring using nonlinear correlation analysis of external uterine electromyography**. *IEEE transactions on bio-medical engineering* 2013, **60**(4):1160-1166.
177. van 't Hooft J, Rabotti C, Oei SG: **Electrohysterographic evaluation of preterm contractions in a patient with a unicornuate uterus**. *Acta obstetricia et gynecologica Scandinavica* 2013, **92**(6):730-733.
178. Maul H, Maner WL, Olson G, Saade GR, Garfield RE: **Non-invasive transabdominal uterine electromyography correlates with the strength of intrauterine pressure and is predictive of labor and delivery**. *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 Obstet* 2004, **15**(5):297-301.
179. Garfield RE, Maner WL, MacKay LB, Schlembach D, Saade GR: **Comparing uterine electromyography activity of antepartum patients versus term labor patients**. *American journal of obstetrics and gynecology* 2005, **193**(1):23-29.
180. Schlembach D, Maner WL, Garfield RE, Maul H: **Monitoring the progress of pregnancy and labor using electromyography**. *European journal of obstetrics, gynecology, and reproductive biology* 2009, **144 Suppl 1**:S33-39.
181. Rabotti C, Mischi M, van Laar JO, Oei GS, Bergmans JW: **Inter-electrode delay estimators for electrohysterographic propagation analysis**. *Physiological measurement* 2009, **30**(8):745-761.
182. Marque C, Duchene JM, Leclercq S, Panczer GS, Chaumont J: **Uterine EHG processing for obstetrical monitoring**. *IEEE transactions on bio-medical engineering* 1986, **33**(12):1182-1187.
183. Csapo AI, Takeda H: **Effect of Progesterone on the Electric Activity and Intrauterine Pressure of Pregnant and Parturient Rabbits**. *American journal of obstetrics and gynecology* 1965, **91**:221-231.
184. Wolfs GM, van Leeuwen M: **Electromyographic observations on the human uterus during labour**. *Acta obstetricia et gynecologica Scandinavica Supplement* 1979, **90**:1-61.
185. Gondry J, Marque C, Duchene J, Cabrol D: **Electrohysterography during pregnancy: preliminary report**. *Biomedical instrumentation & technology / Association for the Advancement of Medical Instrumentation* 1993, **27**(4):318-324.
186. Demianczuk N, Towell ME, Garfield RE: **Myometrial electrophysiologic activity and gap junctions in the pregnant rabbit**. *American journal of obstetrics and gynecology* 1984, **149**(5):485-491.
187. Searle A, Kirkup L: **A direct comparison of wet, dry and insulating bioelectric recording electrodes**. *Physiological measurement* 2000, **21**(2):271-283.
188. Lynn PA, Bettles ND, Hughes AD, Johnson SW: **Influences of electrode geometry on bipolar recordings of the surface electromyogram**. *Medical & biological engineering & computing* 1978, **16**(6):651-660.
189. Hewson DJ, Hogrel JY, Langeron Y, Duchene J: **Evolution in impedance at the electrode-skin interface of two types of surface EMG electrodes during long-term recordings**. *Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology* 2003, **13**(3):273-279.
190. Kandil MA, Abdel-Sattar MM, Abdel-Salam SM, Saleh S, Khalafallah MM: **Abdominal electromyography may predict the response to tocolysis in preterm labor**. *European journal of obstetrics, gynecology, and reproductive biology* 2012, **160**(1):18-21.
191. Most O, Langer O, Kerner R, David GB, Calderon I: **Can myometrial electrical activity identify patients in preterm labor?** *American journal of obstetrics and gynecology* 2008, **199**(4):378 e371-376.
192. Verdenik I, Pajntar M, Leskosek B: **Uterine electrical activity as predictor of preterm birth in women with preterm contractions**. *European journal of obstetrics, gynecology, and reproductive biology* 2001, **95**(2):149-153.

193. Aviram A, Hiersch L, Ashwal E, Yogev Y, Hadar E: **The association between myometrial electrical activity and time to delivery in threatened preterm labor**. *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 Obstet* 2016, **29**(18):2897-2903.
194. Vinken MP, Rabotti C, Mischi M, van Laar JO, Oei SG: **Nifedipine-induced changes in the electrohysterogram of preterm contractions: feasibility in clinical practice**. *Obstet Gynecol Int* 2010, **2010**:325635.
195. Diab MO, Marque C, Khalil M: **An unsupervised classification method of uterine electromyography signals: classification for detection of preterm deliveries**. *The journal of obstetrics and gynaecology research* 2009, **35**(1):9-19.
196. Vinken MP, Rabotti C, Mischi M, Oei SG: **Accuracy of frequency-related parameters of the electrohysterogram for predicting preterm delivery: a review of the literature**. *Obstetrical & gynecological survey* 2009, **64**(8):529-541.
197. Lange L, Vaeggemose A, Kidmose P, Mikkelsen E, Uldbjerg N, Johansen P: **Velocity and directionality of the electrohysterographic signal propagation**. *PloS one* 2014, **9**(1):e86775.
198. Escalona-Vargas D, Govindan RB, Furdea A, Murphy P, Lowery CL, Eswaran H: **Characterizing the Propagation of Uterine Electrophysiological Signals Recorded with a Multi-Sensor Abdominal Array in Term Pregnancies**. *PloS one* 2015, **10**(10):e0140894.
199. Furdea A, Preissl H, Lowery CL, Eswaran H, Govindan RB: **Conduction velocity of the uterine contraction in serial magnetomyogram (MMG) data: event based simulation and validation**. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference* 2011, **2011**:6025-6028.
200. Rabotti C, Oei SG, van 't Hooft J, Mischi M: **Electrohysterographic propagation velocity for preterm delivery prediction**. *American journal of obstetrics and gynecology* 2011, **205**(6):e9-10; author reply e10.
201. Rabotti C, Bijloo R, Oei G, Mischi M: **Vectorial analysis of the electrohysterogram for prediction of preterm delivery: a preliminary study**. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference* 2011, **2011**:3880-3883.
202. Elbert T, Ray WJ, Kowalik ZJ, Skinner JE, Graf KE, Birbaumer N: **Chaos and physiology: deterministic chaos in excitable cell assemblies**. *Physiological reviews* 1994, **74**(1):1-47.
203. Jansen BH: **Quantitative analysis of electroencephalograms: is there chaos in the future?** *International journal of bio-medical computing* 1991, **27**(2):95-123.
204. Garcia-Gonzalez MT, Charleston-Villalobos S, Vargas-Garcia C, Gonzalez-Camarena R, Aljama-Corrales T: **Characterization of EHG contractions at term labor by nonlinear analysis**. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference* 2013, **2013**:7432-7435.
205. Hassan M, Terrien J, Alexandersson A, Marque C, Karlsson B: **Nonlinearity of EHG signals used to distinguish active labor from normal pregnancy contractions**. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference* 2010, **2010**:2387-2390.
206. Hassan M, Terrien J, Karlsson B, Marque C: **Spatial analysis of uterine EMG signals: evidence of increased in synchronization with term**. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference* 2009, **2009**:6296-6299.
207. Jacod BC, Graatsma EM, Van Hagen E, Visser GH: **A validation of electrohysterography for uterine activity monitoring during labour**. *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 Obstet* 2010, **23**(1):17-22.
208. Rabotti C, Mischi M, van Laar JO, Oei GS, Bergmans JW: **Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals**. *Physiological measurement* 2008, **29**(7):829-841.
209. Jezewski J, Horoba K, Matonia A, Wrobel J: **Quantitative analysis of contraction patterns in electrical activity signal of pregnant uterus as an alternative to mechanical approach**. *Physiological measurement* 2005, **26**(5):753-767.
210. Skowronski MD, Harris JG, Marossero DE, Edwards RK, Euliano TY: **Prediction of intrauterine pressure from electrohysterography using optimal linear filtering**. *IEEE transactions on bio-medical engineering* 2006, **53**(10):1983-1989.
211. Rooijakkers MJ, Rabotti C, Oei SG, Aarts RM, Mischi M: **Low-complexity intrauterine pressure monitoring by Teager energy estimation**. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference* 2013, **2013**:7424-7427.
212. Reinhard J, Hayes-Gill BR, Schiermeier S, Loser H, Niedballa LM, Haarmann E, Sonnwald A, Hatzmann W, Heinrich TM, Louwen F: **Uterine activity monitoring during labour--a multi-centre, blinded two-way trial of external tocodynamometry against electrohysterography**. *Zeitschrift fur Geburtshilfe und Neonatologie* 2011, **215**(5):199-204.

213. Haran G, Elbaz M, Fejgin MD, Biron-Shental T: **A comparison of surface acquired uterine electromyography and intrauterine pressure catheter to assess uterine activity**. *American journal of obstetrics and gynecology* 2012, **206**(5):412 e411-415.
214. Alberola-Rubio J, Prats-Boluda G, Ye-Lin Y, Valero J, Perales A, Garcia-Casado J: **Comparison of non-invasive electrohysterographic recording techniques for monitoring uterine dynamics**. *Medical engineering & physics* 2013, **35**(12):1736-1743.

Chapter 3

Automated conduction velocity analysis in the electrohysterogram for prediction of imminent delivery: a preliminary study

Published in Computational and Mathematical Methods 2013.

de Lau H, Rabotti C, Bijloo R, Rooijakkers MJ, Mischi M, Oei SG

Abstract

Background: analysis of the electrohysterogram (EHG) is a promising diagnostic tool for preterm delivery. For the introduction in the clinical practice, analysis of the EHG should be reliable and automated to guarantee reproducibility.

Study goal: investigating the feasibility of automated analysis of the EHG conduction velocity (CV) for detecting imminent delivery.

Materials and methods: twenty-two patients presenting with uterine contractions (7 preterm) were included. An EHG was obtained non-invasively using a 64-channel high-density electrode grid. Contractions were selected based on the estimated intrauterine pressure derived from the EHG, the tocodynamometer and maternal perception. Within the selected contractions, the CV vector was identified in two dimensions.

Results: nine patients delivered within 24 hours and were classified as labor group. 64 contractions were analyzed; the average amplitude of the CV vector was significantly higher for the labor group, 8.65cm/s ±1.90, compared to the non-labor group, 5.30cm/s ±1.47 ($p<0{,}01$).

Conclusion: the amplitude of the CV is a promising parameter for predicting imminent (preterm) delivery. Automated estimation of this parameter from the EHG signal is feasible and should be regarded as an important prerequisite for future clinical studies and applications.

Introduction

Preterm delivery, defined as delivery before 37 weeks of gestation, constitutes a major problem in terms of neonatal mortality, morbidity, and healthcare costs [1-3]. Timely intervention and treatment with tocolytics and corticosteroids improves neonatal outcome [4]. However, the diagnostics currently used lack both sensitivity and specificity leading to both under- as well as over-treatment [5, 6]. A potential new diagnostic tool is the electrohysterogram (EHG), which is a noninvasive abdominal measurement of the electrical activity underlying uterine contractions.

The sequence of contraction and relaxation of the uterus results from a cyclic depolarization and re-polarization of its smooth muscle cells in the form of action potentials (AP). APs occur in bursts; they arise in cells that act as pacemakers and propagate from cell to cell through gap junctions [7-9]. Labor and delivery are preceded by two physiological phenomena: increased excitability and increased connectivity among the cells resulting in increased propagation of APs and more synchronized firing [10]. These changes are reflected in the recorded EHG.

Previous literature demonstrated that the EHG has great potential for monitoring labor, predicting labor time and discriminating between physiological uterine activity and contractions leading to (preterm) delivery. Therefore, analysis of the EHG can support timely treatment of preterm labor [11-16]. To this end, several studies have focused on analyzing the spectral content of the EHG using either the peak frequency of the power density spectrum [15, 17-19] or the ratio between a high and low frequency band [11]. Another parameter from the EHG that has been proposed for predicting imminent preterm labor, is the non-linear correlation among channels in a multichannel recording [16].

Prior to delivery, the increased connectivity among cells also increases propagation, which can be assessed by estimating the conduction velocity (CV) from the EHG [20-22]. Differently from skeletal muscles, which are striated and present an anatomical direction of propagation parallel to the fiber orientation, the direction of propagation of the uterine APs is a priori unknown [23, 24]. Due to lack of evidence [25], many authors also concluded that no classical linear propagation of single APs could be assumed for the uterus, and that only global propagation of the whole burst envelop could be measured [23, 25]. However, more recently, measurements of the electrical activity of the guinea pig uterus using a grid of extracellular electrodes clearly demonstrated that also for the uterus, similarly to the myocardium, a linear propagation of single APs can be measured [26]. However, direction and speed of AP propagation can change even within the same bursts.

Previous research mainly focused on the methods for measuring the CV [27-31]. Recently, the prognostic value of the CV for predicting imminent preterm delivery was investigated by visual inspection of the EHG signal [15]. Despite the very promising results presented in this clinical study, the employed visual approach has the disadvantage of not being reproducible. For use as a clinical tool, it would be desirable to rely on a fully automated CV analysis.

However, automated CV analysis entails a number of scientific challenges, namely, automatic detection of contractions, estimation of amplitude and direction of the CV vector, and exclusion of signals that are not related to propagating APs.

This study investigates the feasibility of a new automated approach for the analysis of the EHG CV for detecting imminent delivery. Our approach integrates previously validated EHG-based methods for contraction detection and automated analysis of the CV in two dimensions using a high density electrode grid.

Materials and Methods

Study protocol

A prospective observational cohort study was performed at the Máxima Medical Center Veldhoven, the Netherlands. Approval from the local medical ethical board was obtained and all the included women, provided written informed consent for study participation. Patients with singleton pregnancies were enrolled, presenting with at least 3 contractions in 30 minutes, which were either perceived by the patient or visible on the external tocogram. Both term patients (Gestational age 37+0 – 41+6) and preterm patients (Gestational age 24+0 – 36+6) were included. Exclusion criteria were oxytocin or prostaglandin administration prior to or during the measurement, induction of labor within 24 hours after the measurement, and known uterine malformation.

Measurements from all enrolled patients were obtained using a measurement setup as shown in Figure 1. A 64 channel high-density (HD) electrode grid with external reference electrode on the hip was used in conjunction with a bipolar electrode pair (1 cm diameter, variable inter-electrode distance) to record the EHG. Due to the a priori unknown AP direction of propagation, the bi-dimensional arrangement of the electrodes on the grid (8x8) permits to estimate all the possible CV directions along the abdominal plane parallel to the abdominal surface. The bipolar signal initially used to allow recording other signals (such as the fetal ECG) was eventually employed to derive the contraction timing and trigger the CV vector estimation. The HD electrode grid could also be suitable, but the larger surface of the bipolar sensors offered better results for this specific purpose.

Recording of these signals was performed using a Refa multichannel amplifier (TMS International, Enschede, The Netherlands), with a patient ground on the hip. Simultaneously, a tocodynamometer was used as reference for contraction detection. For the same reason, the time instants at which the patient felt a contraction were annotated.

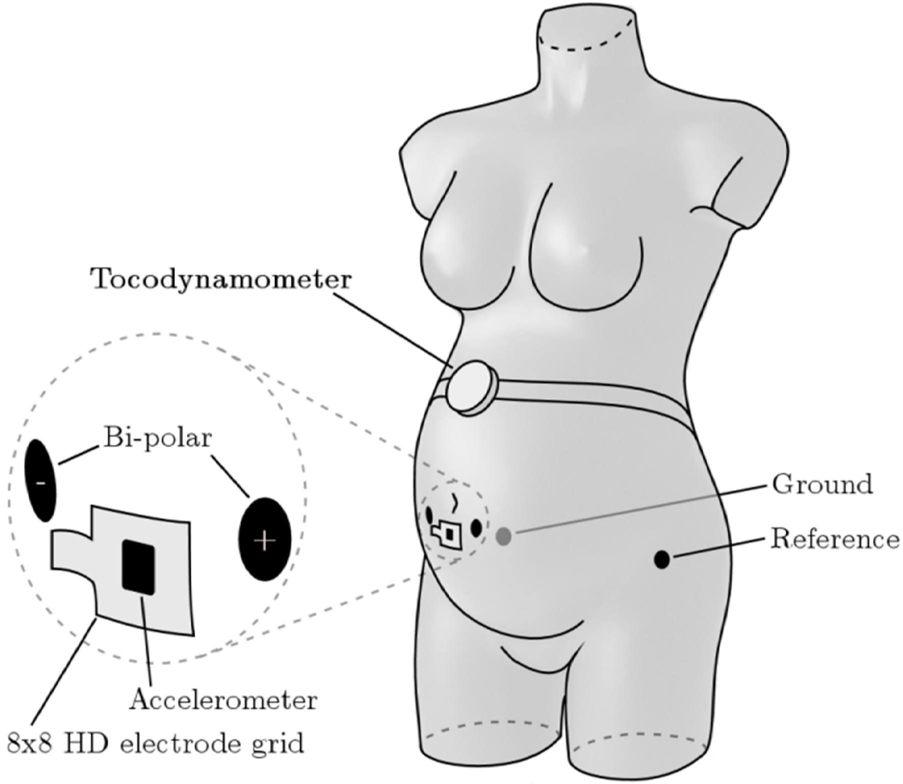

Figure 1: Measurement setup showing the position of all abdominal sensors.

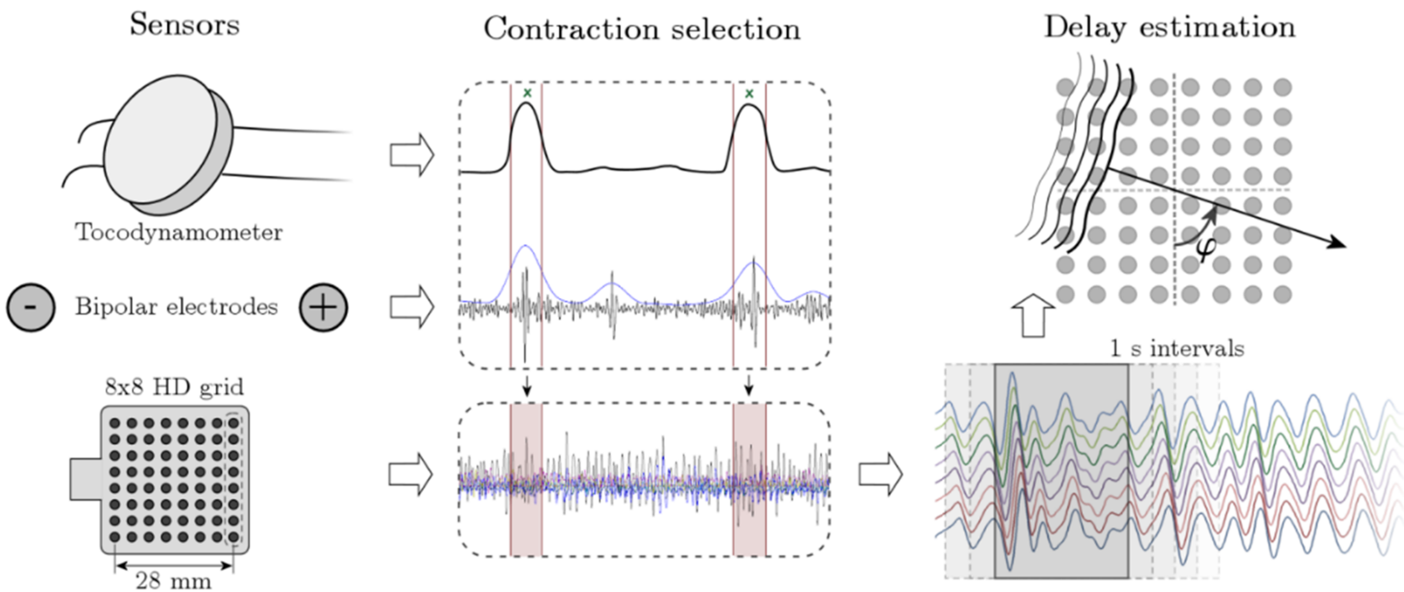

Figure 2: Schematic representation of the method

Signal analysis

Here, a synthetic overview of the methodology used for the analysis is given. For further details we refer to [32] and [31].

The CV vector was identified during the contraction periods. Differently from previous studies, where contractions were annotated manually, we automatically derived an initial estimation of onset and duration of contractions. To this end, an estimate of the internal uterine pressure (IUP) was derived from the bipolar EHG signal. Based on a validated method [32], indicated by n and f the discrete time and frequency variables, respectively, the unnormalized first statistical moment $\Psi(n)$ of the bipolar EHG Spectrogram, $\rho(n, f)$ was calculated in a selected frequency band, $[f_{min}, f_{max}]$, i.e.,

$$\Psi(n) = \sum_{f=f_{min}}^{f_{max}} f\rho(n, f), \tag{1}$$

with $f_{min} = 0{,}3$ Hz and $f_{max}. = 0{,}8$ Hz. An adaptive threshold was then used to detect onset and duration of each contraction in 60 s overlapping windows [33]. Differently from our previous work [3], no modeling was used to improve the estimation accuracy of the IUP amplitude. A more accurate estimation of the IUP, which was out of the scope of the present work, would not significantly improve the accuracy of the thresholding procedure used to assess onset and duration of contractions.

Of the contractions selected by EHG signal analysis, only those that were visible on the external tocogram or concurred with annotations of contractions as felt by the patient were eventually selected for further analysis.

In the signal segments selected as contractions, the CV vector was identified in two dimensions from the 8x8 HD electrode grid in overlapping segments (5 s overlap). Following the schematic representation of Figure 2, we describe the EHG propagation by a CV vector *v*. The vector has an amplitude and an incidence angle θ ($\theta \in [-\pi\ \pi]$) with respect to the vertical axis of the electrode grid. The signal is detected by N_r rows and N_c columns of electrodes. Assuming that the same signal shape $s(n)$ is measured at each channel, the signal $x_{r,c}$easured at the channel (r, c) in the r^{th} row and c^{th} column of the electrode grid can be modeled as

$$x_{rc}\,(n) = s\,(n - (r-1)\tau_r - (c-1)\tau_c) + w_{r,c}\,(n), \tag{2}$$

where *n* indicates the time sample ($n = [1,2 \dots N]$) and $w_{r,c}\,(n)$, is the white Gaussian noise which is present at the channel (r, c). As from (2), we assume linear propagation of the AP, i.e., in each channel (r, c) the reference signal shape $s(n)$ is delayed by τ_r and τ_c time samples relative to the previous row and column, respectively. Identification of the vector *v* requires estimation of (τ_r, τ_c), which we obtain using a maximum likelihood approach, i.e., by maximization of the probability density function $p\big((\tau_r, \tau_c)\big|x_{rc}(n), s(n)\big)$. In the frequency domain, where τ_r and $\tau_c$can be estimated without resolution limits. Under the assumption of white Gaussian noise, the maximum likelihood approach is equivalent to the minimization of the cost function E^2 defined as

$$E^2\,(\tau_r, \tau_c) = \frac{2}{N}\sum_{r=1}^{N_r}\sum_{c=1}^{N_c}\sum_{f=0}^{\frac{N}{2}-1}[X_{rc}(f) - S(f)e^{-j2\pi f[(r-1)\tau_r-(c-1)\tau_c]}] \tag{3}$$

indicated by f the discrete frequency, $X_{rc}(f)$ and $S(f)$ are the Fourier transforms of the signal recorded at the channel (r, c) and of the reference shape, respectively. Following the description in Figure 2, for an inter-electrode distance equal to d it follows that τ_r and τ_c are related to the CV amplitude and to the incidence angle θ by

$$\tau_r = \frac{d\ \cos\theta}{CV}$$
$$\tau_c = \frac{d\ \sin\theta}{CV}. \tag{4}$$

The use of different weighting strategies of the derived cost function was introduced in [31] to deal with poor interchannel signal similarity due to the presence of noise. The weights are inversely proportional to the estimated channel noise. Of the different weighting strategies proposed in [31], we chose the weighted cost function with the best estimation accuracy.

Segments with a calculated CV value above 30 cm/s, which are significantly higher than the physiological values reported in the literature [23, 26], were considered as outliers and excluded.

Statistical analysis

Patients delivering within 24 hours after the measurement were classified as labor group and those delivering outside this time window, as non-labor group. CV and propagation path were compared between these groups. In order to be independent of the number of analyzed segments and contractions per patient, an average CV vector was identified for each analyzed contraction and subsequently the average CV vector for each patient was determined. The Shapiro–Wilk test was used to test for a normal distribution of the estimated values of CV vector amplitude. Levene's test was applied to test for equal variances in the labor and non-labor group. Finally an independent samples t-test was used to test for a significant difference in amplitude of the CV between both groups. The alpha was set to 0.05 for all statistical tests.

Results

Twenty-two patients were included in the study, of which 7 were preterm. Nine patients delivered within 24 hours and were classified as labor group. Table 1 shows the baseline characteristics of the labor and non-labor group. An example of a downward propagating wave of uterine activity during a contraction visualized by the adopted high-density grid of 64 electrodes, can be seen in Figure 3.

Table 1: patient characteristics

	Labor	Non labor
Number of patients	9	13
Gestational age (weeks+days)[1]	31+1 – 40+4 (37+2)	26+2 – 41+3 (36+1)
Preterm	2	5
Nulliparous	4	8
Age[1]	17 – 36 (27.9)	16 – 36 (27.8)
BMI[1]	22 – 42 (28.2)	24 – 34 (26.8)
Hours to delivery[1]	1 – 10 (6)	27 – 1488 (255)

1. Mean value in parentheses

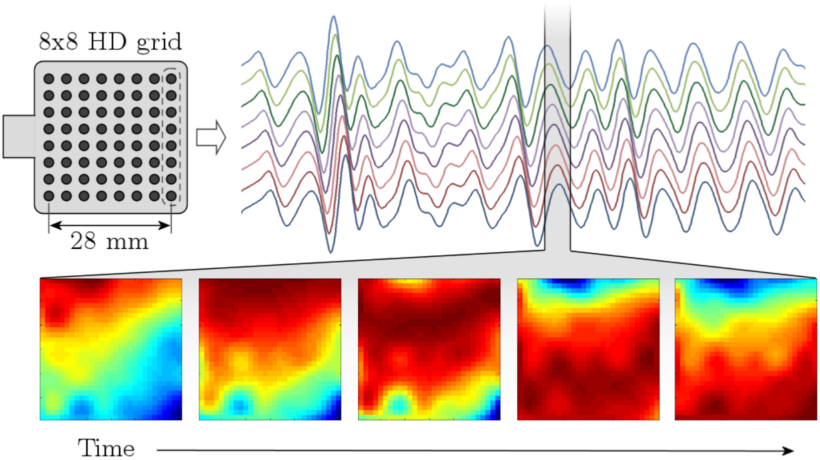

Figure 3: Next to the HD electrode grid, the EHG signals of eight electrodes (one column) are shown during a contraction. The five images at the bottom show an interpolated 2D representation of a single EHG pulse propagating from top to bottom.

In total, 64 contractions were analyzed. Figure 4 shows the boxplot of the mean CV for the patients in the labor and the non-labor group; the median values of the CV of the groups as a whole are indicated as a horizontal line. The Shapiro–Wilk test was insignificant, supporting the nul hypothesis that the data is derived from a normally distributed population. Similarly Levene's test showed an insignificant result, supporting equal variances in the labor and non-labor group. The average amplitude of the CV vector was significantly higher for the labor group, 8.65cm/s ±1.90, compared to the non-labor group, 5.30cm/s ±1.47 ($p<0{,}01$). The angle of propagation showed a high variability among patients in both the labor as non-labor group, even within the same contraction.

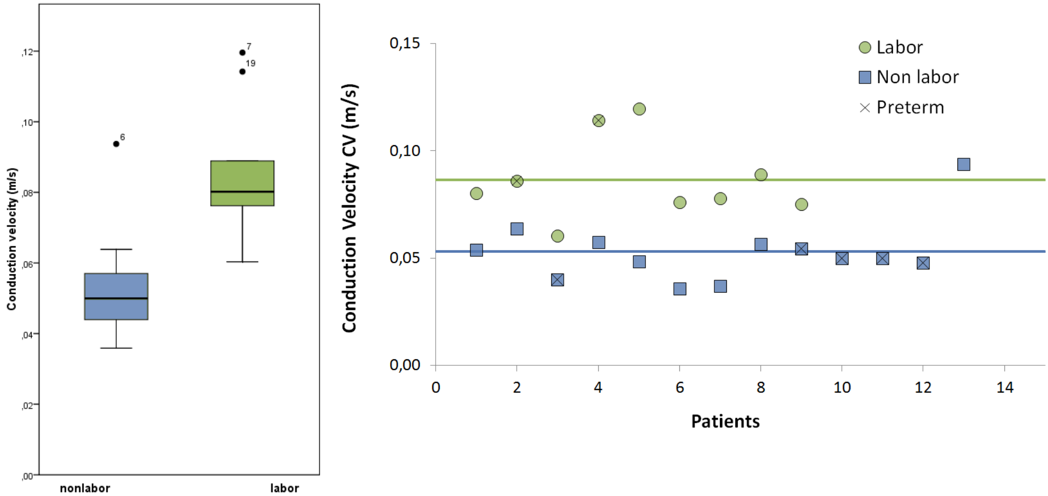

Figure 1: on the left a boxplot showing the average amplitude of the CV vector for the labor and non-labor group. The median value is displayed with a horizontal line. On the right a scatter plot showing the individual average amplitudes of the CV vector for both groups. The horizontal lines represent the average value for the labor and non-labor group.

Discussion

This study investigates the feasibility of a new automated approach for the analysis of the EHG CV for detecting imminent delivery. Our approach integrates validated EHG-based methods for contraction detection and automated analysis of the CV in two dimensions using a high density electrode grid [31]. The patients in this study presented with uterine contractions and were classified as labor group or non-labor group based on delivery within or after 24 hours, respectively. The results show a significantly higher amplitude of the CV vector in the labor group.

The measurements were performed in a diverse group of patients featuring both term and preterm patients admitted for varying reasons. The common denominator was that all patients had palpable and measurable contractions. The emphasis was placed on investigating the feasibility of automated CV analysis and open the way to future clinical studies and applications based on this parameter as diagnostic tool for imminent (preterm) birth. The assumption here is that comparable changes in conduction properties can be observed in contractions leading to preterm and term delivery. In follow-up studies it will be important to have a consistent group of patients presenting with premature contractions and who are considered for treatment with tocolytics based on gestational age and clinical parameters.

In this study additional data other than the EHG signal was used for detecting contractions, namely, an external tocodynamometer and annotations of subjectively perceptible contractions by the patient. This was chosen to achieve a more robust distinction between uterine activity and measurement artifacts. In future work a fully automated selection of contraction segments and analysis of CV should be pursued. However, while an automated method ensures reproducibility and should therefore be preferred for everyday clinical use, visual inspection might be required in a preliminary phase for discriminating uterine activity from noise and excluding from the analysis artifacts and signals that do not propagate linearly.

Noteworthy, identification of the EHG CV vector using the present methods implies the assumption that the signal does propagate and that propagation is linear. While it is reasonable to hypothesize that the linearity of the propagation could be a discriminative parameter for predicting imminent delivery in itself, several aspects related to the evolution from pregnancy to labor are not yet fully understood and need further dedicated research [34]. Therefore, we excluded spikes propagating non linearly from the analysis as we expected those cases to be outliers, i.e., to have a CV outside the physiological range reported by previous literature [26, 35]. Only [15] reported values higher than 30 cm/s; these values cannot be considered as a physiological reference due to the specific measurement setup, which allows for information on only a projection of the CV vector [36].

Finally, another novelty of this study is the use of a 64 channel high-density electrode grid for recording the EHG. Due to the a priori unknown AP direction of propagation, the bi-dimensional arrangement of the electrodes on the grid permits to estimate all the possible CV directions along the abdominal plane parallel to the abdominal surface. Furthermore, due to the grid dimensions, planar wave propagation could be assumed and the small inter electrode distance enables following the same spike (action potential) from one electrode to the other [29]. In the present study we intended to use the conduction velocity as an independent predictor of imminent delivery reflecting the increased propagation of action potentials between myometrial cells. Therefore we chose a high density grid with relatively small dimension. However uterine activity throughout the whole uterus might provide additional information on imminent delivery and for that purpose we would consider a larger grid preferable. Ideally, a combination of local propagation and global synchronicity should be pursued, and this will be possibly considered in our future studies. Moreover, in order to improve user friendliness and simplify signal analysis, a reduced number of electrodes could be used, and depending on the chosen electrode configuration, different hypothesis (e.g., point source) may be considered for propagation.

Conclusion

In agreement with previous studies, our results show that the CV vector amplitude is a promising parameter for predicting imminent (preterm) delivery. Automated estimation of this parameter from the EHG signal is feasible and should be regarded as an important prerequisite for future clinical studies and applications in this context. Therefore, these results open the way to future studies on the accuracy of EHG parameters, such as the CV, for timely and accurate diagnosis of imminent preterm delivery.

References

1. Green NS, Damus K, Simpson JL, Iams J, Reece EA, Hobel CJ, Merkatz IR, Greene MF, Schwarz RH: **Research agenda for preterm birth: recommendations from the March of Dimes**. *Am J Obstet Gynecol* 2005, **193**(3 Pt 1):626-635.
2. Mathews TJ, MacDorman MF: **Infant mortality statistics from the 2005 period linked birth/infant death data set**. *National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System* 2008, **57**(2):1-32.
3. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA *et al*: **Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network**. *Pediatrics* 2010, **126**(3):443-456.
4. Roberts D, Dalziel S: **Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth**. *Cochrane Database Syst Rev* 2006(3):CD004454.
5. King JF, Grant A, Keirse MJ, Chalmers I: **Beta-mimetics in preterm labour: an overview of the randomized controlled trials**. *Br J Obstet Gynaecol* 1988, **95**(3):211-222.
6. Goldenberg RL, Culhane JF, Iams JD, Romero R: **Epidemiology and causes of preterm birth**. *Lancet* 2008, **371**(9606):75-84.
7. Garfield RE, Merrett D, Grover AK: **Gap junction formation and regulation in myometrium**. *Am J Physiol* 1980, **239**(5):C217-228.
8. Garfield RE, Blennerhassett MG, Miller SM: **Control of myometrial contractility: role and regulation of gap junctions**. *Oxford reviews of reproductive biology* 1988, **10**:436-490.
9. Garfield RE, Hertzberg EL: **Cell-to-cell coupling in the myometrium: Emil Bozler's prediction**. *Progress in clinical and biological research* 1990, **327**:673-681.
10. Lammers WJ: **The electrical activities of the uterus during pregnancy**. *Reprod Sci* 2013, **20**(2):182-189.
11. Marque C, Duchene JM, Leclercq S, Panczer GS, Chaumont J: **Uterine EHG processing for obstetrical monitoring**. *IEEE Trans Biomed Eng* 1986, **33**(12):1182-1187.
12. Garfield RE, Maul H, Shi L, Maner W, Fittkow C, Olsen G, Saade GR: **Methods and devices for the management of term and preterm labor**. *Ann N Y Acad Sci* 2001, **943**:203-224.
13. Euliano TY, Marossero D, Nguyen MT, Euliano NR, Principe J, Edwards RK: **Spatiotemporal electrohysterography patterns in normal and arrested labor**. *Am J Obstet Gynecol* 2009, **200**(1):54 e51-57.
14. Vinken MP, Rabotti C, Mischi M, Oei SG: **Accuracy of frequency-related parameters of the electrohysterogram for predicting preterm delivery: a review of the literature**. *Obstet Gynecol Surv* 2009, **64**(8):529-541.
15. Lucovnik M, Maner WL, Chambliss LR, Blumrick R, Balducci J, Novak-Antolic Z, Garfield RE: **Noninvasive uterine electromyography for prediction of preterm delivery**. *Am J Obstet Gynecol* 2011, **204**(3):228 e221-210.
16. Hassan M, Terrien J, Muszynski C, Alexandersson A, Marque C, Karlsson B: **Better pregnancy monitoring using nonlinear correlation analysis of external uterine electromyography**. *IEEE Trans Biomed Eng* 2013, **60**(4):1160-1166.
17. Buhimschi C, Boyle MB, Garfield RE: **Electrical activity of the human uterus during pregnancy as recorded from the abdominal surface**. *Obstet Gynecol* 1997, **90**(1):102-111.
18. Maner WL, Garfield RE, Maul H, Olson G, Saade G: **Predicting term and preterm delivery with transabdominal uterine electromyography**. *Obstet Gynecol* 2003, **101**(6):1254-1260.
19. Maner WL, Garfield RE: **Identification of human term and preterm labor using artificial neural networks on uterine electromyography data**. *Ann Biomed Eng* 2007, **35**(3):465-473.
20. Miller SM, Garfield RE, Daniel EE: **Improved propagation in myometrium associated with gap junctions during parturition**. *Am J Physiol* 1989, **256**(1 Pt 1):C130-141.
21. Miyoshi H, Boyle MB, MacKay LB, Garfield RE: **Gap junction currents in cultured muscle cells from human myometrium**. *Am J Obstet Gynecol* 1998, **178**(3):588-593.
22. Garfield RE, Maner WL: **Physiology and electrical activity of uterine contractions**. *Semin Cell Dev Biol* 2007, **18**(3):289-295.
23. Devedeux D, Marque C, Mansour S, Germain G, Duchene J: **Uterine electromyography: a critical review**. *Am J Obstet Gynecol* 1993, **169**(6):1636-1653.
24. Lammers WJ: **The Electrical Activities of the Uterus During Pregnancy**. *Reprod Sci* 2012.
25. J. Duchˆene CM, and S. Planque: **Uterine EMG signal: propagation analysis**. *IEEE EMBS Proc Int Conference* 1990:pp 831–832.
26. Lammers WJ, Mirghani H, Stephen B, Dhanasekaran S, Wahab A, Al Sultan MA, Abazer F: **Patterns of electrical propagation in the intact pregnant guinea pig uterus**. *Am J Physiol Regul Integr Comp Physiol* 2008, **294**(3):R919-928.
27. Rabotti C, Mischi M, van Laar J, Oei G, Bergmans J: **On the propagation analysis of electrohysterographic signals**. *Conf Proc IEEE Eng Med Biol Soc* 2008, **2008**:3868-3871.
28. Mischi M, Rabotti C, Vosters LJ, Oei SG, Bergmans JM: **Electrohysterographic conduction velocity estimation**. *Conf Proc IEEE Eng Med Biol Soc* 2009, **2009**:6934-6937.
29. Rabotti C, Mischi M, van Laar JO, Oei GS, Bergmans JW: **Inter-electrode delay estimators for electrohysterographic propagation analysis**. *Physiol Meas* 2009, **30**(8):745-761.
30. Rabotti C, Mischi M: **Two-dimensional estimation of the electrohysterographic conduction velocity**. *Conf Proc IEEE Eng Med Biol Soc* 2010, **2010**:4262-4265.

31. Rabotti C, Mischi M, Oei SG, Bergmans JW: **Noninvasive estimation of the electrohysterographic action-potential conduction velocity**. *IEEE Trans Biomed Eng* 2010, **57**(9):2178-2187.
32. Rabotti C, Mischi M, van Laar JO, Oei GS, Bergmans JW: **Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals**. *Physiol Meas* 2008, **29**(7):829-841.
33. Jezewski J, Horoba K, Matonia A, Wrobel J: **Quantitative analysis of contraction patterns in electrical activity signal of pregnant uterus as an alternative to mechanical approach**. *Physiol Meas* 2005, **26**(5):753-767.
34. Laforet J, Rabotti C, Terrien J, Mischi M, Marque C: **Toward a multiscale model of the uterine electrical activity**. *IEEE Trans Biomed Eng* 2011, **58**(12):3487-3490.
35. Lammers WJEP, Stephen B, Hamid R, Harron DWG: **The effects of oxytocin on the pattern of electrical propagation in the isolated pregnant uterus of the rat**. *Pflügers Archiv European Journal of Physiology* 1999, **437**(3):363-370.
36. Rabotti C, Oei SG, van 't Hooft J, Mischi M: **Electrohysterographic propagation velocity for preterm delivery prediction**. *Am J Obstet Gynecol* 2011, **205**(6):e9-10; author reply e10.

Chapter 4

Study protocol: PoPE- Prediction of Preterm delivery by Electrohysterography

Published in BMC Pregnancy Childbirth 2014.

de Lau H, Rabotti C, Oosterbaan HP, Mischi M, Oei GS.

Abstract

Background: Traditional methods used for prediction of preterm delivery are subjective and inaccurate. The Electrohysterogram (EHG) and in particular the estimation of the EHG conduction velocity, is a relatively new promising method for detecting imminent preterm delivery. To date the analysis of the conduction velocity has relied on visual inspection of the signals. As a next step towards the introduction of EHG analysis as a clinical tool, we propose an automated method for EHG conduction velocity estimation for both the speed and direction of single spike propagation.

Methods / design: The study design will be an observational cohort study. 100 pregnant women, gestational age between 23+5 and 34 weeks, admitted for threatening preterm labor or preterm prelabor rupture of membranes, will be included. The length of the cervical canal will be measured by transvaginal ultrasound. The EHG will be recorded using 4 electrodes in a fixed configuration. Contractions will be detected by analysis of the EHG and using an estimation of the intra uterine pressure. In the selected contractions, the delays between channels will be estimated by cross-correlation, and subsequently, the average EHG conduction velocity will be derived. Patients will be classified as labor group and non-labor group based on the time between measurement and delivery. The average conduction velocity and cervical length will be compared between the groups. The main study endpoints will be sensitivity, specificity, and area under the ROC curve for delivery within 1,2,4,7, and 14 days from the measurement.

Discussion: In this study, the diagnostic accuracy of EHG conduction velocity analysis will be evaluated for detecting preterm labor. Visual and automatic detection of contractions will be compared. Planar wave propagation will be assumed for the calculation of the CV vector.

1. Background

Traditional methods for detecting preterm labor

Preterm labor and subsequent preterm birth occur in about 10% of all pregnant patients in developed countries and are the leading cause of neonatal mortality and morbidity [1-3]. Antenatal treatment with tocolytics and corticosteroids can be used to improve the neonatal outcome of preterm birth [4]. However, traditional methods used for predicting preterm delivery are subjective and cannot accurately predict when labor will occur. Intrauterine pressure measurement is invasive and cannot be used for pregnancy monitoring. External tocography, being noninvasive, is extensively used for pregnancy monitoring, but provides only quantification of the number of contractions per time unit [5]. Transvaginal ultrasonic cervical length (TVU CL) measurement is widely used in patients presenting with preterm contractions, but it has only a moderate sensitivity and specificity, especially for intermediate values for cervical length [6]. A relatively new biochemical marker, fetal fibronectin, is currently being introduced for short term prediction of preterm delivery. Its strength lies in ruling out imminent preterm delivery, but it cannot be used to predict when labor will occur [7]. Cervical dilatation is a late sign of imminent delivery and the change of successfully delaying delivery using tocolytics is inversely related to the cervical dilatation [8]. Overall more than 50% of the patients admitted for threatening preterm labor, deliver at term [9-11].

The electrohysterogram and preterm labor

Labor and delivery are preceded by two physiological phenomena: increased excitability and increased connectivity among the myometrial cells resulting in increased propagation of the action potentials that underlie uterine contractions [12-14]. These changes are reflected in the electrohysterogram (EHG), which is a noninvasive abdominal measurement of the uterine electrical activity. As a relatively new diagnostic tool, the EHG has been shown to have potential for monitoring contractions during labor [15-19], as well as detecting pathological contractions leading to preterm delivery [5, 20-28]. Various ways of characterizing the EHG have been proposed, including the spectral content using either the peak frequency [5, 22-24] or median frequency [28, 29] of the power density spectrum, or the ratio between a high and low frequency band [30]. Alternatively, the non-linear correlation among signals in multichannel EHG recordings has been proposed to predict (preterm) delivery [31, 32]. The propagation speed of the electrical activity, referred to as conduction velocity (CV), has been quantified by analyzing either the propagation of whole bursts of uterine electrical activity [33, 34], or single spikes within a burst [5, 21, 35, 36] Different physiological phenomena could possibly underlie changes in these types of propagation [37, 38]. Recently, the estimated CV based on single spike propagation, has been suggested to be a discriminative parameter of imminent preterm delivery [5].

Towards automated analysis of the CV

To date, analysis of the CV in preterm patients has relied on visual selection of uterine contractile bursts and spikes within these bursts. Despite the promising results that have been presented using this approach, it would be desirable to rely on an automatic approach in order to make the method reproducible and suitable for clinical use. However, automated estimation of the CV entails a number of challenges, namely, automatic detection of uterine contractile bursts, exclusion of signals that are not related to propagating action potentials, and finally calculation of the amplitude and direction of the CV vector. In previous work, we showed automatic calculation of the CV vector within the selected contractile bursts to be feasible [21]. As a next step towards fully automated analysis of the CV in the EHG, we propose an automated method for selecting contractile bursts based on the estimated intrauterine pressure (eIUP) which is derived from the EHG signal [18, 21]. Since invasive methods are not available in preterm patients, visual review of the signals will be adopted to refine the automatic burst selection. Furthermore, in order to reduce the complexity and standardize the measurement for use as a clinical tool, a patch with a fixed configuration of five electrodes will be used. This configuration will allow estimating both the speed and direction of the CV amplitude.

In this study protocol we propose an observational study evaluating EHG CV analysis as clinical tool for diagnosing imminent preterm labor using an automated analysis.

2. Methods and design

Study population

The population will consist of patients admitted to the obstetrical ward of the Máxima Medical Center Veldhoven and the Jeroen Bosch hospital for threatening preterm labor or preterm prelabor rupture of membranes and who are eligible for treatment with tocolytics and corticosteroids. The decision on treatment will be based on the standard diagnostic tests and local protocol. Administration of tocolytics will be registered: type and dosage, time of administration.

Ethics

The study has been approved by the research ethics committee of the Máxima Medical Center and is registered under ISRCTN07603227 in the current controlled trial register.

Inclusion criteria

- Gestational age between 23+5 and 34+0 weeks.
- Clinically evaluated symptoms of preterm labor: at least 6 contractions in 60 minutes based on the external tocogram and/or maternal perception.
- Both singleton and multiple gestations will be included.

Exclusion criteria

- Patients in active labor: cervical dilatation >3cm
- Signs of infection: baseline fetal heart rate >160 and/or maternal temperature ≥38,0
- Signs of fetal distress: the following cardiotocogram (CTG) characteristics [39]
    - Baseline heart frequency <100 or >170
    - Reduced variability: <5bpm during >60min
    - Complicated variable decelerations, duration >60sec
    - Repeated late uniform decelerations

Inclusion and measurement

After written informed consent is acquired, patients will be enrolled in the study. In accordance with local protocol, a CTG registration of at least 30 minutes will be performed and maternal temperature will be measured for all patients. In case of intact membranes a TVU CL measurement will be performed as standard diagnostic test. The length of the cervical canal will be measured in a straight line, the shortest of three measurements will be recorded. Simultaneous with the CTG, the EHG will be recorded using a patch containing 4 monopolar electrodes in a diamond shaped pattern and a ground electrode (Nemo Healthcare B.V.). This patch is placed on the middle of the abdomen, just below the umbilicus. A reference electrode is placed on the left anterior superior iliac spine, see Figure 1. Minimal recording length is 30 minutes. The signals will be amplified and stored on the Porti amplifier (Twente Medical Systems International B.V.). The Porti amplifier will be used in a configuration that does not provide any visible reading of the measurement and the data will be stored directly on its flash memory. All diagnostic tests will be performed within 24 hours after admission.

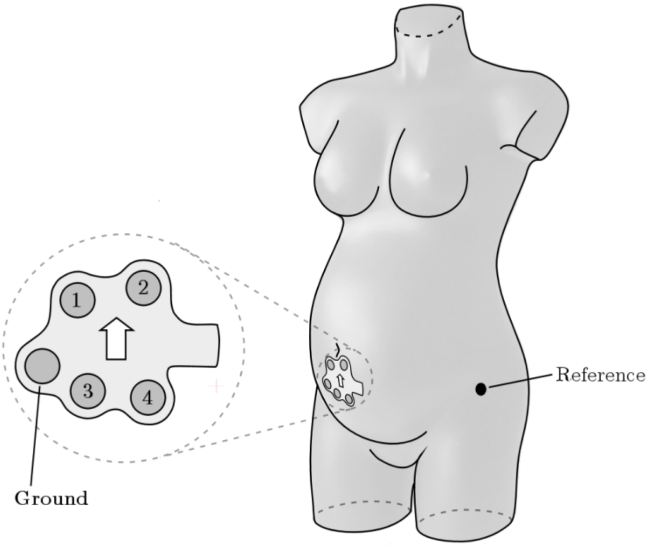

Figure 1: schematic drawing of the patch containing four electrodes in a diamond shaped pattern plus a ground electrode. The patch is placed just underneath the umbilicus in the midline of the maternal abdomen. A reference electrode is placed on the left anterior superior iliac spine.

EHG signal analysis

All signal processing and analysis will be performed afterwards offline without knowledge of the pregnancy outcome. Identifying the CV vector will consist of three steps: selection of the contraction segments, estimating the time delays between the channels and calculating the CV vector, see Figure 2. The automatic selection of contractions will be based on the estimate of the internal uterine pressure (eIUP) which is derived from the EHG signal [18]. The algorithm used for the eIUP, as well as the algorithm used for detection of onset and duration of contractions, will be adapted to be suitable for the unpredictable nature of premature and non-labor contractions. Prior to the CV analysis, visual review of the signals will be used to optimize the automatic burst selection.

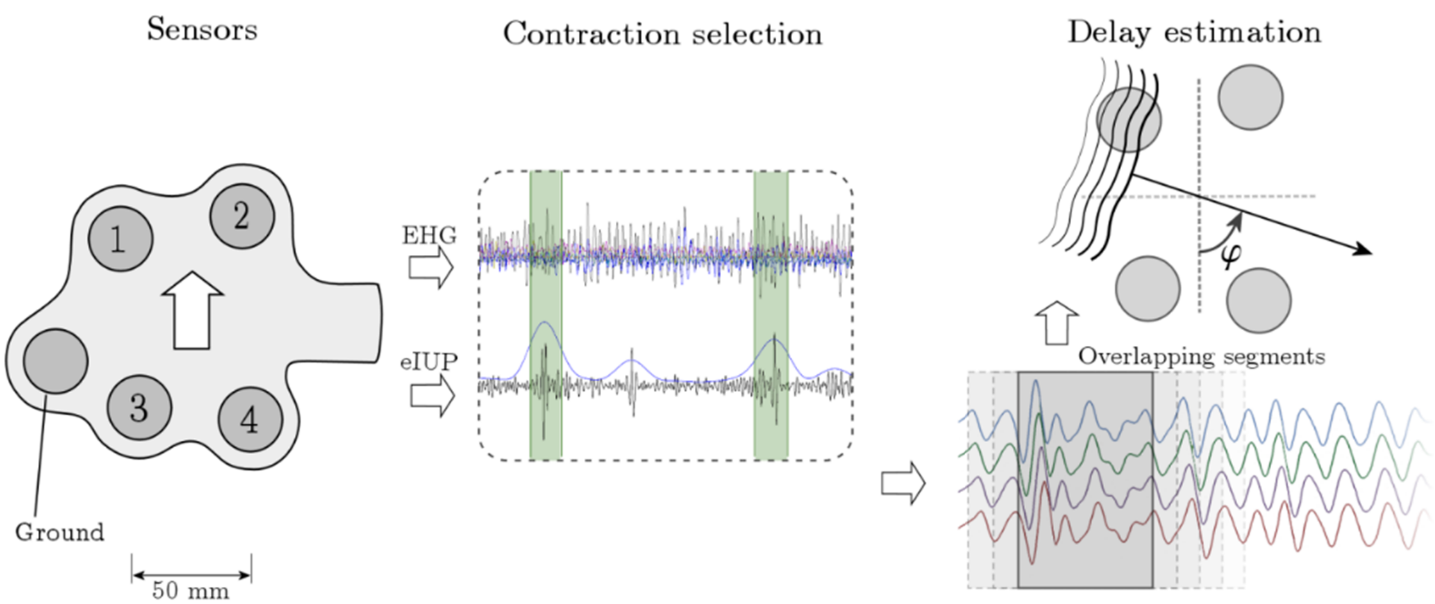

Figure 2: the method for analyzing the EHG CV. The EHG is recorded using a fixed configuration of four electrodes plus ground and reference electrodes. The eIUP is derived from the EHG signal and is used for selecting contraction segments. Finally, the delays are estimated in overlapping windows using cross-correlation.

In the signal segments selected as contractions, the CV will be determined in overlapping windows. The length of these windows will be fixed to a value to allow single spikes to be included. Cross-correlation will be used for estimation of the time delay between channels. We will describe the EHG propagation by a CV vector. This CV vector has an amplitude and an incidence angle with respect to the vertical axis. Based on statistical analysis, a threshold value will be determined for the CV vector amplitude. Values above this threshold will be considered to be artefacts and discarded.

Study parameters/endpoints

Patients will be classified as labor group and non-labor group based on the interval between measurement and delivery. The cutoff points will be delivery within 1, 2, 7, and 14 days of the measurement. As primary outcome the EHG parameters will be compared between these groups in terms of amplitude and angle of the CV. In order to be independent of the number of analyzed segments and contractions per patient, the average CV vector will be identified for each analyzed contraction and subsequently the average CV vector for each patient will be determined. As secondary analysis the TVU CL will be compared between the labor and non-labor group. The sensitivity and specificity will be calculated for the EHG parameters and TVU CL for predicting preterm delivery within 1, 2, 7, and 14 days. In order to be independent on arbitrarily chosen cutoff points, the area under the curve of the receiver operating characteristics will be determined.

Sample size

During the year 2010, a total of 150 patients were admitted to the obstetrical ward of the Máxima Medical Center for threatening preterm labor which met the inclusion criteria. Approximately 40% of these patients delivered within 7 days. A sample size can be calculated based on an observed difference in test characteristics between the standard diagnostics and the EHG analysis using a fixed allocation ratio of 40 – 60% for the positive and negative group respectively. In the study by Lucovnik et al an area under the curve of the receiver operating characteristics (ROC) of 0,96 was observed for the EHG analysis and 0,72 for the Bishop score (the best performing test among the standard diagnostics) [5].

A sample of 7 from the positive group and 11 from the negative group achieve 82% power, assuming an area under the ROC curve of 0,95 for EHG CV analysis and 0,70 for the standard diagnostics and using a two-sided z-test at a significance level of 0.05. This means a minimal number of 20 patients will need to be included. However, this observed difference is based on a single study. In order to increase the likelihood of detecting a difference in case of a lower observed difference or different allocation ratio, we propose to include a total of 100 patients.

Statistical analysis

Baseline characteristics will be determined for the labor and non-labor group. Differences will be tested for statistical significance using a fisher exact test for dichotomized variables and a non-paired t-test for continuous variables. We will evaluate the influence of significant differences in background variables on the outcome using a multivariate logistical regression model.

The Shapiro–Wilk test will be applied to test for a normal distribution of the estimated values of the CV vector amplitude. Levene's test will be applied to test for equal variances in the labor and non-labor group. An independent samples t-test will be used to test for a significant difference in amplitude of the CV between both groups. The alpha will be set to 0.05 for all statistical tests. Using contingency tables, the sensitivity and specificity of the EHG and standard diagnostics will be determined.

Discussion

The study aims to evaluate CV analysis of the EHG as clinical tool for the diagnosis of imminent preterm delivery. In an observational cohort study the EHG will be recorded in patients admitted for threatened preterm labor. The CV will be estimated in the EHG using a fully automated analysis. This automated approach entails a novel automatic selection of contractions based on the eIUP and automatic delay estimation. The diagnostic accuracy will be expressed in terms of sensitivity, specificity and area under the ROC curve for delivery within 1,2,7, and 14 days from the measurement.

Similar to [5], part of the patients will already be treated with tocolytics at the time of the measurement. This could influence the amount of contractions and possibly the CV as well. Using logistic regression, the administration of tocolytics will be tested as possible confounding factor. The EHG CV analysis will be evaluated as diagnostic tool for predicting imminent spontaneous preterm delivery. Although it is not a common scenario in patients admitted for threatened preterm labor, patients within the labor group in which labor is induced will not be included in the final analysis.

Perhaps the biggest challenge and also an essential step in accurate estimation of the CV is recognizing contractions amongst noise and artifacts in the EHG. Different from term patients in labor, preterm patients admitted for threatened preterm labor have mostly an irregular pattern of uterine contractions of a varying frequency as well as duration. Therefore, the detection algorithm cannot assume a regular pattern and fixed duration. Furthermore an external tocodynamometer can fail to show contractions in some patients [40, 41]. Therefore, for use as independent clinical tool, the EHG CV analysis cannot rely on the external tocodynamometer as reference. Hence the analysis will be mainly based on the electrical signal recorded on the skin.

Our methods will entail filtering in a narrow frequency band (0,3 – 0,8 Hz) in order to suppress signals other than uterine activity, including (abdominal) striated muscle activity and the maternal electrocardiogram. The eIUP will be used in order to distinguish uterine activity from the background noise. Visual review of the data is envisaged to evaluate the performance of the automatic algorithm.

Unlike in our previous work, the time delays between channels will be estimated using cross-correlation. The maximum likelihood method previously proposed, will not be used for this study since it is more suitable when more electrodes are used. Furthermore, given the need for a short time window, no frequency based method can be applied on account of loss of resolution. In addition, it would also increase the complexity and therefore computing time of the algorithm, impeding the use as clinical tool. Using cross-correlation, the resolution in time is dictated by the sampling frequency of the recording and therefore we will use a relatively high sampling frequency of 1000Hz.

The four electrodes of the patch enable the CV vector to be estimated in all the possible directions along the abdominal plane. By using different triangles of electrodes depending on the direction of propagation, the problem of action potentials originating from within the electrodes is mostly solved. Since the dimensions of the electrodes patch are relatively small compared to the whole uterine surface, planar wave propagation will be assumed for the calculation of the CV vector. To explore uterine propagation patterns in detail, an electrode grid containing more electrodes and of a relatively big size would be needed. However this falls beyond the scope of this project, which has the objective to test a clinical application for distinguishing low from high CVs in order to timely recognize imminent preterm labor.

To summarize, in this study the diagnostic accuracy of EHG CV analysis will be evaluated for detecting preterm labor. By employing a fully automated analysis of the EHG without the use of external reference signals, this project aims to make the next step towards introducing the EHG CV analysis as clinical tool.

References

1. Goldenberg RL, Culhane JF, Iams JD, Romero R: **Epidemiology and causes of preterm birth**. *Lancet* 2008, **371**(9606):75-84.
2. World Health Organization MoD, Partnership for Maternal, Newborn & Child Health, Save the Children: **Born too soon: the global action report on preterm birth**. In.; 2012.
3. Lawn JE, Gravett MG, Nunes TM, Rubens CE, Stanton C: **Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data**. *BMC pregnancy and childbirth* 2010, **10 Suppl 1**:S1.
4. Roberts D, Dalziel S: **Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth**. *Cochrane Database Syst Rev* 2006(3):CD004454.
5. Lucovnik M, Maner WL, Chambliss LR, Blumrick R, Balducci J, Novak-Antolic Z, Garfield RE: **Noninvasive uterine electromyography for prediction of preterm delivery**. *American journal of obstetrics and gynecology* 2011, **204**(3):228 e221-210.
6. Sotiriadis A, Papatheodorou S, Kavvadias A, Makrydimas G: **Transvaginal cervical length measurement for prediction of preterm birth in women with threatened preterm labor: a meta-analysis**. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2010, **35**(1):54-64.
7. Sanchez-Ramos L, Delke I, Zamora J, Kaunitz AM: **Fetal fibronectin as a short-term predictor of preterm birth in symptomatic patients: a meta-analysis**. *Obstetrics and gynecology* 2009, **114**(3):631-640.
8. Amon E, Midkiff C, Winn H, Holcomb W, Shumway J, Artal R: **Tocolysis with advanced cervical dilatation**. *Obstetrics and gynecology* 2000, **95**(3):358-362.
9. Scott CL, Chavez GF, Atrash HK, Taylor DJ, Shah RS, Rowley D: **Hospitalizations for severe complications of pregnancy, 1987-1992**. *Obstetrics and gynecology* 1997, **90**(2):225-229.
10. Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, Franks AL: **Hospitalizations during pregnancy among managed care enrollees**. *Obstetrics and gynecology* 2002, **100**(1):94-100.
11. McPheeters ML, Miller WC, Hartmann KE, Savitz DA, Kaufman JS, Garrett JM, Thorp JM: **The epidemiology of threatened preterm labor: a prospective cohort study**. *American journal of obstetrics and gynecology* 2005, **192**(4):1325-1329; discussion 1329-1330.
12. Garfield RE, Blennerhassett MG, Miller SM: **Control of myometrial contractility: role and regulation of gap junctions**. *Oxford reviews of reproductive biology* 1988, **10**:436-490.
13. Miller SM, Garfield RE, Daniel EE: **Improved propagation in myometrium associated with gap junctions during parturition**. *The American journal of physiology* 1989, **256**(1 Pt 1):C130-141.
14. Lammers WJ: **The electrical activities of the uterus during pregnancy**. *Reprod Sci* 2013, **20**(2):182-189.
15. Euliano TY, Marossero D, Nguyen MT, Euliano NR, Principe J, Edwards RK: **Spatiotemporal electrohysterography patterns in normal and arrested labor**. *Am J Obstet Gynecol* 2009, **200**(1):54 e51-57.
16. Euliano TY, Nguyen MT, Darmanjian S, McGorray SP, Euliano N, Onkala A, Gregg AR: **Monitoring uterine activity during labor: a comparison of 3 methods**. *American journal of obstetrics and gynecology* 2013, **208**(1):66 e61-66.
17. Haran G, Elbaz M, Fejgin MD, Biron-Shental T: **A comparison of surface acquired uterine electromyography and intrauterine pressure catheter to assess uterine activity**. *American journal of obstetrics and gynecology* 2012, **206**(5):412 e411-415.
18. Rabotti C, Mischi M, van Laar JO, Oei GS, Bergmans JW: **Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals**. *Physiological measurement* 2008, **29**(7):829-841.
19. Reinhard J, Hayes-Gill BR, Schiermeier S, Loser H, Niedballa LM, Haarmann E, Sonnwald A, Hatzmann W, Heinrich TM, Louwen F: **Uterine activity monitoring during labour--a multi-centre, blinded two-way trial of external tocodynamometry against electrohysterography**. *Zeitschrift fur Geburtshilfe und Neonatologie* 2011, **215**(5):199-204.
20. Vinken MP, Rabotti C, Mischi M, Oei SG: **Accuracy of frequency-related parameters of the electrohysterogram for predicting preterm delivery: a review of the literature**. *Obstetrical & gynecological survey* 2009, **64**(8):529-541.
21. de Lau H, Rabotti C, Bijlo R, Rooijakkers MJ, Mischi M, Oei SG: **Automated conduction velocity analysis in the electrohysterogram for prediction of imminent delivery: a preliminary study**. *Computational and Mathematical Methods in Medicine* 2013, **2013**:7.
22. Buhimschi C, Boyle MB, Garfield RE: **Electrical activity of the human uterus during pregnancy as recorded from the abdominal surface**. *Obstetrics and gynecology* 1997, **90**(1):102-111.
23. Maner WL, Garfield RE: **Identification of human term and preterm labor using artificial neural networks on uterine electromyography data**. *Ann Biomed Eng* 2007, **35**(3):465-473.
24. Maner WL, Garfield RE, Maul H, Olson G, Saade G: **Predicting term and preterm delivery with transabdominal uterine electromyography**. *Obstetrics and gynecology* 2003, **101**(6):1254-1260.

25. Marque CK, Terrien J, Rihana S, Germain G: **Preterm labour detection by use of a biophysical marker: the uterine electrical activity**. *BMC pregnancy and childbirth* 2007, **7 Suppl 1**:S5.
26. Kandil MA, Abdel-Sattar MM, Abdel-Salam SM, Saleh S, Khalafallah MM: **Abdominal electromyography may predict the response to tocolysis in preterm labor**. *European journal of obstetrics, gynecology, and reproductive biology* 2012, **160**(1):18-21.
27. Most O, Langer O, Kerner R, David GB, Calderon I: **Can myometrial electrical activity identify patients in preterm labor?** *American journal of obstetrics and gynecology* 2008, **199**(4):378 e371-376.
28. Verdenik I, Pajntar M, Leskosek B: **Uterine electrical activity as predictor of preterm birth in women with preterm contractions**. *European journal of obstetrics, gynecology, and reproductive biology* 2001, **95**(2):149-153.
29. Fele-Zorz G, Kavsek G, Novak-Antolic Z, Jager F: **A comparison of various linear and non-linear signal processing techniques to separate uterine EMG records of term and pre-term delivery groups**. *Medical & biological engineering & computing* 2008, **46**(9):911-922.
30. Marque C, Duchene JM, Leclercq S, Panczer GS, Chaumont J: **Uterine EHG processing for obstetrical monitoring**. *IEEE transactions on bio-medical engineering* 1986, **33**(12):1182-1187.
31. Hassan M, Terrien J, Muszynski C, Alexandersson A, Marque C, Karlsson B: **Better pregnancy monitoring using nonlinear correlation analysis of external uterine electromyography**. *IEEE transactions on bio-medical engineering* 2013, **60**(4):1160-1166.
32. Muszynski C, Terrien J, Drean Y, Chkeir A, Hassan M, Marque C, Gondry J: **[Evolution of electrohysterogram signals synchronization according to term of pregnancy: interest for preterm labor diagnosis]**. *Gynecologie, obstetrique & fertilite* 2012, **40**(6):344-349.
33. Lange L, Vaeggemose A, Kidmose P, Mikkelsen E, Uldbjerg N, Johansen P: **Velocity and directionality of the electrohysterographic signal propagation**. *PloS one* 2014, **9**(1):e86775.
34. Mikkelsen E, Johansen P, Fuglsang-Frederiksen A, Uldbjerg N: **Electrohysterography of labor contractions: propagation velocity and direction**. *Acta obstetricia et gynecologica Scandinavica* 2013, **92**(9):1070-1078.
35. Rabotti C, Mischi M, Oei SG, Bergmans JW: **Noninvasive estimation of the electrohysterographic action-potential conduction velocity**. *IEEE transactions on bio-medical engineering* 2010, **57**(9):2178-2187.
36. van 't Hooft J, Rabotti C, Oei SG: **Electrohysterographic evaluation of preterm contractions in a patient with a unicornuate uterus**. *Acta obstetricia et gynecologica Scandinavica* 2013, **92**(6):730-733.
37. Lammers WJ, Mirghani H, Stephen B, Dhanasekaran S, Wahab A, Al Sultan MA, Abazer F: **Patterns of electrical propagation in the intact pregnant guinea pig uterus**. *American journal of physiology Regulatory, integrative and comparative physiology* 2008, **294**(3):R919-928.
38. Parkington HC, Harding R, Sigger JN: **Co-ordination of electrical activity in the myometrium of pregnant ewes**. *Journal of reproduction and fertility* 1988, **82**(2):697-705.
39. Westerhuis ME, van Horen E, Kwee A, van der Tweel I, Visser GH, Moons KG: **Inter- and intra-observer agreement of intrapartum ST analysis of the fetal electrocardiogram in women monitored by STAN**. *BJOG* 2009, **116**(4):545-551.
40. Vanner T, Gardosi J: **Intrapartum assessment of uterine activity**. *Bailliere's clinical obstetrics and gynaecology* 1996, **10**(2):243-257.
41. Bakker PC, Zikkenheimer M, van Geijn HP: **The quality of intrapartum uterine activity monitoring**. *Journal of perinatal medicine* 2008, **36**(3):197-201.

Chapter 5

PoPE- Prediction of Preterm delivery by Electrohysterography

Submitted to the American Journal of Obstetrics and Gynecology

de Lau H, Rabotti C, Rooijakkers MJ, Bajlekov G, van der Hout B, Oosterbaan HP, Mischi M, Oei SG

Abstract

Background: Various parameters of the electrohysterogram have been explored for predicting imminent preterm delivery. Estimation of the velocity of electrical propagation, the conduction velocity, has shown promising results.

Objective: Validation of conduction velocity for detecting preterm labor based on automated estimation of the conduction velocity in 4 channel recordings.

Study design: Patients admitted for threatening preterm labor or preterm prelabor rupture of membranes, gestational age between 23+5 and 34+0 weeks, were included in this study. The electrohysterogram was recorded with a patch using 4 monopolar channels in a fixed pattern. All recordings were independently reviewed and manually segmented by two experts in contractions and noise, using a predefined set of visual criteria. The algorithm for conduction velocity estimation included cross correlation for obtaining the delays among channels. A plane wave propagation front was assumed.

Results: 81 patients were included for the analysis, 16 patients delivered within 7 days and were allocated to the labor group. The mean conduction velocity was 10.22 cm/s in the non-labor group and 12.21 cm/s in the labor group (p=0.27). Propagation was predominantly vertical for both the labor and non-labor group. The observed differences found in conduction velocity amplitude and angle were not significant.

Conclusion: The results could not confirm conduction velocity analysis as diagnostic tool for imminent preterm delivery. As future perspective, a smaller inter-electrode distance or more complex propagation models could be considered.

Introduction

Prevention and management of preterm labor is one of the main challenges is obstetrics, with an estimated 1 million neonatal deaths each year related to preterm delivery [1, 2]. Premature contractions are among the most common reasons for admission to an obstetrical ward early in pregnancy [3, 4]. Identifying those women who will actually deliver preterm, however, is challenging and traditional methods used for detecting preterm labor are inaccurate and cannot predict the time to delivery. This is reflected in the fact that overall more than 50% of the patients admitted for imminent preterm labor ultimately deliver at term [3-7]. More accurate methods of predicting preterm delivery are needed to reduce overtreatment with tocolytics and corticosteroids [8-14], as well as to initiate treatment before the changes in uterine contractility are irreversible and treatment becomes ineffective [15].

The physical result of preterm contractions (cervical effacement, dilatation) is preceded by evolution of the electrical activity underlying the preterm contractions [16, 17]; the increasing excitability and connectivity among the myometrial cells lead to increased propagation of the action potentials through the myometrium, both in distance as well as velocity [17-19]. These changes are reflected in the electrohysterogram (EHG), which is the noninvasive abdominal measurement of the uterine electrical activity. EHG based contraction monitoring is finding its way into clinical practice for term labor [20-22], and has also shown great potential for detecting imminent preterm delivery [16, 23-31]. Considerable effort has been invested in characterizing the EHG of contractions leading to preterm delivery. Various parameters of the EHG have been considered, including signal amplitude [16, 29-31], spectral parameters [16, 26-28, 32-39] and more recently non-linear parameters in multichannel EHG recordings have been proposed [40, 41]. These parameters have been shown to be moderately predictive of imminent delivery; however, alone they do not suffice to accurately and timely distinguish physiological contractions from imminent preterm delivery.

Estimation of the conduction velocity of propagating electrical activity by multichannel EHG recordings has recently been considered for preterm labor detection [24, 42-44]; however, accurate estimation of the conduction velocity in the EHG is technically challenging and a variety of approaches have been adopted, ranging from a two channel setup [24] to 64 channels [42, 43], and from analyzing single spike propagation [24, 42, 43, 45] to propagation of whole bursts [46, 47]. This has resulted in a wide range of values found for the conduction velocity [24, 45-47]. Very promising results were found in a relatively large clinical study using only two channels [24]. The resulting reduced complexity of the measurement and related computations fulfills the needs for clinical use of conduction velocity estimation for preterm labor detection.

In this study, the use of 4 monopolar channels rather than 2 bipolar pairs allows reproducing the method in [24] and it enables a more accurate 2-dimensional estimation of the conduction velocity vector in two dimensions [48]. Moreover, the EHG was analyzed by visual review of the recorded signals, limiting repeatability of the study. For clinical applications, the use of validated automated methods is a prerequisite. This comprises both an algorithm for selection of contractile bursts in the EHG and automated estimation of the conduction velocity. Nevertheless, manual annotation of contractile bursts is still required as a reference method since the relationship between EHG contractile bursts and mechanical output measured by an external tocodynamometer or an internal uterine pressure catheter (IUPC) is certain in one direction only: contractions established in the tocogram are always accompanied by a contractile burst in the EHG, but not vice versa [49, 50].

The primary goal of this study was to validate conduction velocity analysis for detecting imminent preterm labor based on automated estimation of the conduction velocity vector in 4 channel recordings. As a first step, manual annotation of contractile bursts was used as reference.

Materials and Methods

Study protocol

The study protocol has been previously described in full detail [51]. An observational cohort study was performed at the Máxima Medical Center Veldhoven and the Jeroen Bosch Hospital, the Netherlands. Approval from the local medical ethical board was obtained and all the included women provided written informed consent for study participation. Patients were enrolled that were admitted to the obstetrical ward for threatening preterm labor or preterm prelabor rupture of membranes (PPROM) and who were eligible for treatment with tocolytics and corticosteroids: gestational age between 23+5 and 34+0 weeks and clinically evaluated symptoms of preterm labor: at least 6 contractions in 60 minutes based on the external tocogram and/or maternal perception. Decision on treatment was based on a local protocol. Both singleton and multiple gestations were included. Patients in active labor, or with signs of intra uterine infection or fetal distress, were excluded.

In case of intact membranes, the cervical length was measured by ultrasound as the standard diagnostic test. The EHG recordings from all enrolled patients were obtained using a fixed patch containing 4 electrodes in a diamond shaped pattern plus a ground electrode (Nemo Healthcare B.V.), having an center-to-center interelectrode distance ranging from 4.5 cm to 7.5 cm. The patch was positioned in the midline of the abdomen, just below the umbilicus. A reference electrode was placed on the left anterior superior iliac spine. Following the results of previous work [52], an 3D accelerometer was added to the study protocol in the course of the study. Minimal recording length was 30 minutes. All signals were stored on the Porti amplifier (Twente Medical Systems International B.V) without providing any visible reading of the measurement. All diagnostic tests were performed within 24 hours after admission.

Contraction selection

Based on a two-step procedure, a protocol was developed for manual contraction selection. In the first step, the signal-to-noise ratio was optimized by optimizing the signal processing settings for the EHG using a high quality external tocogram signal as reference. All combinations of band-pass filters with different bandwidth, electrode configurations, and algorithms for removal of the maternal ECG were tested for the best fit between the power of the EHG signal and the simultaneously recorded tocogram. Removal of the maternal ECG was realized by an linear prediction algorithm [53], which allowed the use of a wider frequency band. Although the majority of the energy of the EHG is situated beneath 1 Hz, a wider frequency band retains better visibility of the EHG signal in the presence of low-frequency noise. The optimal fit was found for the frequency range of 0,3 – 5 Hz after removal of the maternal ECG and using a bipolar electrode configuration of two vertical and two horizontal pairs. Secondly, a set of visual criteria for selection of contractions and artefacts were formulated based on recordings of term and preterm contractions as well as self-induced artefacts; contractions were defined as a rise in the estimated intra uterine pressure [54] (eIUP) above twice the baseline at a minimum duration of 20 seconds, without visible movement in the accelerometer or high-frequency content in the EHG signal. These criteria served as a guideline for manual contraction selection by the observers.

All recordings were independently reviewed and manually segmented by two experts without knowledge of the pregnancy outcome. Low concordance between observers necessitated a consensus meeting for 39 cases, in order to reduce dissimilarity in segmentation. Segments selected by the two observers were used for the analysis.

Signal analysis

To exclude interference from breathing and the maternal heart rate, the EHG signal was band-pass filtered in the range of 0.35 - 0.8 Hz. Since the overall pattern of propagation is unpredictable, it is important to detect the propagation vector over a two dimensional surface without prior assumptions on the direction of propagation. Moreover, analysis of propagation direction requires the phase of the propagating EHG signal to be unaffected. Since the direction of propagation is a priori unknown, this requires the use of a monopolar electrode configuration. To this end, 4 monopolar signals were derived by subtracting the external reference channel. The time difference between every electrode pair was determined by maximizing the normalized cross-correlation between the two corresponding signals. By using interpolation, discrete time offsets were mitigated, therefore increasing the temporal resolution. The cross correlation was calculated on running time window. A window size of 3 seconds was chosen to cover one wavelength at the lowest frequency in the passband: 0.35 Hz [25]. The range of offsets was chosen based on the distance between the electrode pair and on the assumption of a minimum velocity of 3 cm/s. Also due to the periodicity of the signal, incorrect cross correlation peaks can be identified in the presence of noise. Therefore, weighting was applied to the cross correlation favoring the peak closest to an offset of zero.

An apparent-velocity vector was calculated for each pair of electrodes from their time difference and positions. This vector is a projection of the actual conduction velocity on the line connecting the respective electrode pair. The accuracy decreases as the projection approaches a perpendicular angle. Therefore, the delays were limited to a range corresponding to a velocity between 3 cm/s and 30 cm/s for propagation within an arc of 120° around the direction of all possible electrode pairs. The resulting 6 vectors provide redundant information for the calculation of the conduction velocity; this is used to improve the accuracy in the presence of noise.

For calculation of the conduction velocity, planar wave front propagation was assumed. Based on this assumption, a propagation front was fitted through the individual vectors estimated from the estimated apparent velocities, as shown in Figure 1. The fitting error of the individual vectors to the optimal wave front was used as a measure of the error in the conduction velocity estimation. Individual vectors were considered as outliers if the error exceeded 2 standard deviations and therefore discarded. The average fitting error is equivalent to the variance in the observed velocity due to the presence of noise affecting the result of the delay estimation by cross correlation. High variance in the observed velocity is more likely caused by noise rather than a propagating wave front. Fits based on less than 3 vectors were discarded as well. As an additional analysis, a bimodal curve fit was applied to the observed distribution of conduction velocity values in order to improve the robustness to noise.

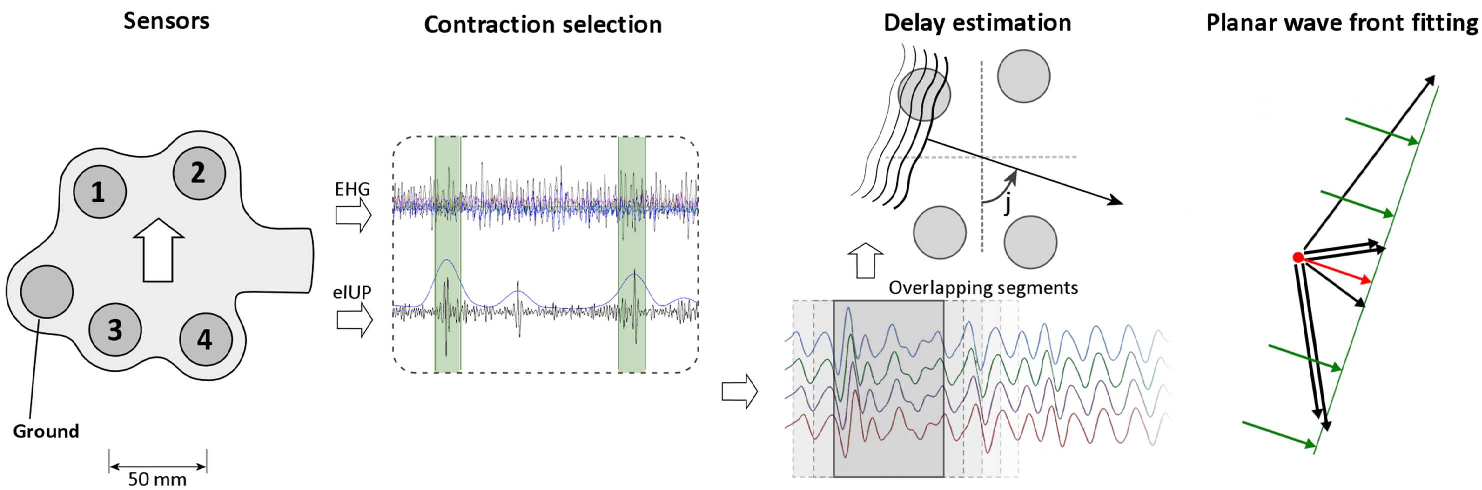

Figure 1: summary of the method for estimation of the conduction velocity. Firstly, uterine contractile bursts were selected in the EHG signal by two observers. Secondly, the delays among the 4 EHG channels were estimated by cross-correlation. Finally, a planar wavefront was fitted to the individual vectors of all possible electrode pairs.

Statistical analysis

Differences in baseline characteristics between the labor and non-labor group were tested for statistical significance using a fisher exact test for dichotomized variables and an independent samples t-test for continuous variables. Levene's test was applied to test for equal variances in the labor and non-labor group. An independent samples t-test was used to test for a significant difference in amplitude of the conduction velocity between both groups, using an alpha of 0.05 for all statistical tests. The area under the curve (AUC) of the receiver operating characteristics (ROC) of the EHG and standard diagnostics were determined.

Results

120 patients met the inclusion criteria of which 39 patients were excluded because of technical failure (27 cases of cable faults in at least 1 channel and 12 corrupt files). As a result, 81 patients were included for the analysis, of which 9 patients were admitted for PPROM. In total, 16 patients delivered within 7 days and were allocated to the labor group. The patients characteristics are outlined in Table 1.

Table 1: patient characteristics

	Non-Labor (>=7days)	Labor (<7days)	p
N	65 (80%)	16 (20%)	
PPROM	3	6	<0,0011
Gestational age	208 (169 – 280)	208 (176 – 237)	0.962
Parity	0.67 (0 – 3)	0.5 (0 – 2)	0.452
Fetal cephalic presentation	82%	78%	0.801
Previous preterm delivery	15%	19%	0.741
BMI	24.2 (16.48 – 39.8)	24.7 (18.0 – 32.7)	0.712
Caucasian	86%	93%	0.451
Tocolytics	57%	87%	0.0231
Contractions (EHG)	15 (1 - 85)	17 (3 - 122)	0.662
Interval to delivery	48 (7,5 - 102)	2 (0.05 - 4,5)	<0.0012
Vaginal delivery	84%	87%	0.781

1 = Pearson chi square
2 = t-test for independent samples

In total, 1259 contraction segments were analyzed, on average 15 in the non-labor group and 17 in the labor group. The mean overlap between observers in contraction segmentation was 59%. The mean cervical length was 26 mm in the non-labor group compared to 8 mm in the labor group (p=0,001). As shown in Table 2 and Figure 2, the mean conduction velocity was 10.22 cm/s in the non-labor group and 12.21 cm/s in the labor group (p=0.27). Levene's test showed a significant outcome and therefore equal variance could not be assumed in both groups. The observed difference in mean conduction velocity was not significant (p=0.27), also after exclusion of the erroneous low conduction-velocity values caused by noise, 16.14 cm/s vs. 18.97 cm/s (p=0.12). The AUC of the ROC curve was 0.86 for cervical length measurement by vaginal ultrasound, compared to 0.58 for the conduction velocity. When a smaller measurement-to-delivery interval of 2 days was considered, the observed mean conduction velocity was 10.25 cm/s for the non-labor group and 13.93 cm/s for the labor group (p=0.27). Figure 3 shows a scatter plot of the conduction velocity as function of the time-to-delivery interval. Table 2 shows all results for the conduction velocity.

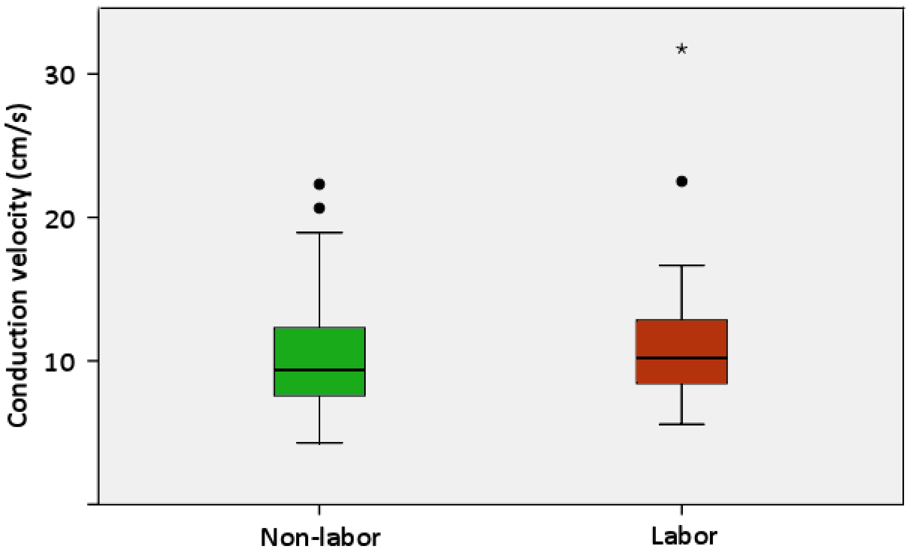

Figure 2: boxplot of the conduction velocity in the labor group (delivery <7days) and non-labor group (delivery >7 days). The boxes represent the 1st to 3rd quartile of the data, while the line marks the median value. Outliers are shown as dots and asterix. The mean conduction velocity (not shown) was 12.21 cm/s in the labor group and 10.22 cm/s in the non-labor group (p=0.27).

The distribution of conduction velocity angles was predominantly vertical for both the labor and non-labor group, 61.4% compared to 62.5% (p=0.70). Upward propagation was slightly more common in the non-labor group, while downward propagation was more frequent in the labor group. All observed differences were not significant. See table 3 for all results on conduction velocity angles.

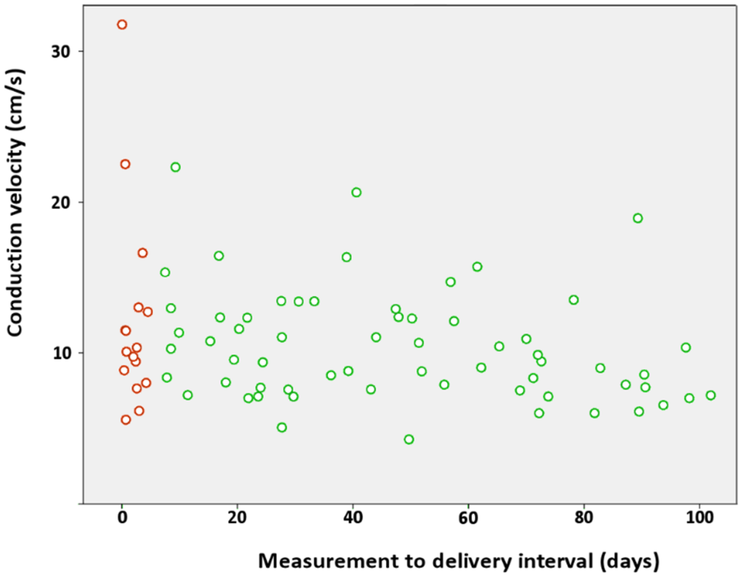

Figure 3: the conduction velocity as function of the measurement-to-delivery interval. The x-axis shows the time between the measurement and delivery, while the y-axis shows the mean conduction velocity per patient. The women delivering within 7 days were allocated to the labor group and are shown in red. The observed conduction velocities show a similar distribution for the labor and non-labor group.

Table 2: results on conduction velocity

	Non-labor (>=7days)	Labor (<7days)	P	AUC ROC
Cervical length	26 (0 - 54)	8 (0 - 33)	0.001	0.86
Mean conduction velocity	10.22 cm/s	12.21 cm/s	0.27	0.58
Mean conduction velocity high	16.14 cm/s	18.97 cm/s	0.12	0.62
Vertical propagation	62.5%	61.4%	0.70	na
	Non-labor (>=2days)	Labor (<2days)	P	AUC ROC
Cervical length	24.8 (0 - 54)	5 (0 - 24)	0.01	0.88
Mean conduction velocity	10.25 cm/s	13.93 cm/s	0.27	0.62
Mean conduction velocity high	16.31 cm/s	20.28 cm/s	0.24	0.62
Vertical propagation	62.3%	62.9%	0.88	na

Table 3: results on conduction velocity angle

Propagation direction	Non-labor (>=7days)	Labor (<7days)	P
Upward	33.1%	27.4%	0.46
Downward	29.5%	34.0%	0.22
Left	18.4%	21.1%	0.47
Right	19.0%	17.7%	0.74
Propagation direction	Non-labor (>=2days)	Labor (<2days)	P
Upward	32.4%	28.4%	0.45
Downward	30.0%	34.5%	0.35
Left	18.8%	19.6%	0.87
Right	18.8%	17.8%	0.83

Comment

In this study, the conduction velocity analysis in the EHG was evaluated for the diagnosis of imminent preterm labor. In pregnant women admitted for threatened preterm labor, the EHG was recorded using 4 monopolar electrodes. Within the manually annotated contraction segments, the conduction velocity was estimated in a sliding window using a cross-correlation method. The mean conduction velocity amplitude and angle were compared between the labor and non-labor group, defined as delivery within or after 7 days respectively. The mean conduction velocity was 10.22 cm/s in the non-labor group and 12.21 cm/s in the labor group ($p=0.27$). Propagation was predominantly vertical for both the labor and non-labor group. The differences observed in conduction velocity amplitude and direction were not significant.

The current method proved susceptible to noise. Considerable effort was made to reduce the influence of signals other than the EHG. To this end, the signal was bandpass filtered and the maternal ECG was removed. Time differences were limited to a range corresponding to a velocity between 3 cm/s and 30 cm/s for propagation within an arc of 120° around the direction of each electrode pair. Furthermore, the agreement between the velocity vectors from all possible electrode pairs with respect to the optimal (planar) wave front, expressed as the mean fitting error, was used to reject erroneous values. However, in simulated EHG signals the presence of uncorrelated noise clearly resulted in an underestimation of the conduction velocity amplitude. This was further evidenced by a bimodal distribution of the observed conduction velocity amplitudes. On the contrary, the presence of common noise among the channels results in an overestimation of the conduction velocity amplitude. The net influence of these opposing effects possibly varied from patient to patient and might have reduced the observed difference in conduction velocity.

Although the conduction velocity vector was estimated by an automated algorithm, segmentation of contraction segments still required manual annotation. This is also one of the most challenging steps in preterm EHG analysis as conventional methods cannot be used as golden standard. Contractile bursts visible in the EHG have been shown to be more frequent than concomitant mechanical output as measured by an external tocodynamometer or IUPC just prior to labor [49, 50]. A possible explanation is that depolarization can be local and therefore does not lead to measurable contractions. The actual golden standard, invasive measurement of the EHG, was deemed unethical. Moreover, preterm contractions lack the periodicity of term contractions and generally have a smaller amplitude [16, 55]. Differentiating EHG from background noise requires high quality recordings. The difficulty in the annotation of contraction segments was further evidenced by the low concordance between the two observers.

The outcome of this study disagrees with some published results [24]. Both this study and the study performed by Lucovnik et al were of comparable size and both were performed in an obstetric high care unit in a mixed population of patients with and without tocolytics. A similar four electrode setup was employed. Noteworthy was the use of two bipolar pairs by Lucovnik et al, allowing for estimation of the conduction velocity (its projection) in one direction only. It is conceivable that the observed increase in conduction velocity amplitude by Lucovnik et al might have been related to a change in propagation direction resulting in an apparent rise in conduction velocity amplitude [48]. However, the results of our study show a predominance of vertical propagation in both the labor and non-labor group, and no significant shift in propagation angle was observed. We have followed the method of Lucovnik et al [24] as closely as possible while we have also elaborated the method aiming for future clinical application. Nevertheless, using this approach, we could not confirm conduction velocity analysis as diagnostic tool for imminent preterm delivery.

In the present study, the aim was to detect a rise in conduction velocity as a predictor of imminent preterm delivery, rather than producing the most accurate estimation of the conduction velocity amplitude. In order to be suitable for clinical use, the number of electrodes was reduced. The inter-electrode distance was chosen to be comparable with the configuration used by Lucovnik et al [24]. Although the propagation distance of single spikes is not precisely known for the human myometrium, both a reduced propagation distance [17] and incoherent electrical activity during non-labor contractions have been reported [49, 50]. The present method implies the assumption of a linear propagation with a planar wave front. When the inter-electrode distance exceeds the propagation distance, non-propagating signals might be incorrectly be identified as propagating signals, confounding the result. A smaller inter-electrode distance might be required in order to meet the criterion of linear propagation in the case of preterm propagation. Moreover, a smaller electrode grid may result in a more reliable planar wave-front approximation. Alternatively, nonlinear measures should also be considered to interpret the connectivity between EHG signals measured at different locations.

In conclusion, no significant change in conduction velocity amplitude or angle was observed approaching preterm delivery. These results cannot validate the estimation of the conduction velocity for prediction of preterm delivery using a reduced number of electrodes. In future studies, a smaller inter-electrode distance and electrode grid, or alternatively nonlinear analysis, should be considered for more accurate estimation of preterm propagation.

References

1. Lawn JE, Gravett MG, Nunes TM, Rubens CE, Stanton C: **Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data**. *BMC pregnancy and childbirth* 2010, **10 Suppl 1**:S1.
2. World Health Organization MoD, Partnership for Maternal, Newborn & Child Health, Save the Children: **Born too soon: the global action report on preterm birth**. In.; 2012.
3. Scott CL, Chavez GF, Atrash HK, Taylor DJ, Shah RS, Rowley D: **Hospitalizations for severe complications of pregnancy, 1987-1992**. *Obstetrics and gynecology* 1997, **90**(2):225-229.
4. Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, Franks AL: **Hospitalizations during pregnancy among managed care enrollees**. *Obstetrics and gynecology* 2002, **100**(1):94-100.
5. King JF, Grant A, Keirse MJ, Chalmers I: **Beta-mimetics in preterm labour: an overview of the randomized controlled trials**. *British journal of obstetrics and gynaecology* 1988, **95**(3):211-222.
6. Fuchs IB, Henrich W, Osthues K, Dudenhausen JW: **Sonographic cervical length in singleton pregnancies with intact membranes presenting with threatened preterm labor**. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2004, **24**(5):554-557.
7. McPheeters ML, Miller WC, Hartmann KE, Savitz DA, Kaufman JS, Garrett JM, Thorp JM: **The epidemiology of threatened preterm labor: a prospective cohort study**. *American journal of obstetrics and gynecology* 2005, **192**(4):1325-1329; discussion 1329-1330.
8. Ferguson JE, 2nd, Dyson DC, Schutz T, Stevenson DK: **A comparison of tocolysis with nifedipine or ritodrine: analysis of efficacy and maternal, fetal, and neonatal outcome**. *American journal of obstetrics and gynecology* 1990, **163**(1 Pt 1):105-111.
9. Bracero LA, Leikin E, Kirshenbaum N, Tejani N: **Comparison of nifedipine and ritodrine for the treatment of preterm labor**. *American journal of perinatology* 1991, **8**(6):365-369.
10. Gyetvai K, Hannah ME, Hodnett ED, Ohlsson A: **Tocolytics for preterm labor: a systematic review**. *Obstetrics and gynecology* 1999, **94**(5 Pt 2):869-877.
11. Oei SG, Oei SK, Brolmann HA: **Myocardial infarction during nifedipine therapy for preterm labor**. *N Engl J Med* 1999, **340**(2):154.
12. van Veen AJ, Pelinck MJ, van Pampus MG, Erwich JJ: **Severe hypotension and fetal death due to tocolysis with nifedipine**. *BJOG* 2005, **112**(4):509-510.
13. Waffarn F, Davis EP: **Effects of antenatal corticosteroids on the hypothalamic-pituitary-adrenocortical axis of the fetus and newborn: experimental findings and clinical considerations**. *American journal of obstetrics and gynecology* 2012, **207**(6):446-454.
14. Bedalov A, Balasubramanyam A: **Glucocorticoid-induced ketoacidosis in gestational diabetes: sequela of the acute treatment of preterm labor. A case report**. *Diabetes care* 1997, **20**(6):922-924.
15. Amon E, Midkiff C, Winn H, Holcomb W, Shumway J, Artal R: **Tocolysis with advanced cervical dilatation**. *Obstetrics and gynecology* 2000, **95**(3):358-362.
16. Buhimschi C, Boyle MB, Garfield RE: **Electrical activity of the human uterus during pregnancy as recorded from the abdominal surface**. *Obstetrics and gynecology* 1997, **90**(1):102-111.
17. Miller SM, Garfield RE, Daniel EE: **Improved propagation in myometrium associated with gap junctions during parturition**. *The American journal of physiology* 1989, **256**(1 Pt 1):C130-141.
18. Lammers WJ, Arafat K, el-Kays A, el-Sharkawy TY: **Spatial and temporal variations in local spike propagation in the myometrium of the 17-day pregnant rat**. *The American journal of physiology* 1994, **267**(5 Pt 1):C1210-1223.
19. Verhoeff A, Garfield RE, Ramondt J, Wallenburg HC: **Electrical and mechanical uterine activity and gap junctions in peripartal sheep**. *American journal of obstetrics and gynecology* 1985, **153**(4):447-454.
20. Euliano TY, Nguyen MT, Darmanjian S, McGorray SP, Euliano N, Onkala A, Gregg AR: **Monitoring uterine activity during labor: a comparison of 3 methods**. *American journal of obstetrics and gynecology* 2013, **208**(1):66 e61-66.
21. Haran G, Elbaz M, Fejgin MD, Biron-Shental T: **A comparison of surface acquired uterine electromyography and intrauterine pressure catheter to assess uterine activity**. *American journal of obstetrics and gynecology* 2012, **206**(5):412 e411-415.
22. Reinhard J, Hayes-Gill BR, Schiermeier S, Loser H, Niedballa LM, Haarmann E, Sonnwald A, Hatzmann W, Heinrich TM, Louwen F: **Uterine activity monitoring during labour--a multi-centre, blinded two-way trial of external tocodynamometry against electrohysterography**. *Zeitschrift fur Geburtshilfe und Neonatologie* 2011, **215**(5):199-204.
23. Vinken MP, Rabotti C, Mischi M, Oei SG: **Accuracy of frequency-related parameters of the electrohysterogram for predicting preterm delivery: a review of the literature**. *Obstetrical & gynecological survey* 2009, **64**(8):529-541.

24. Lucovnik M, Maner WL, Chambliss LR, Blumrick R, Balducci J, Novak-Antolic Z, Garfield RE: Noninvasive uterine electromyography for prediction of preterm delivery. *American journal of obstetrics and gynecology* 2011, 204(3):228 e221-210.
25. de Lau H, Rabotti C, Bijlo R, Rooijakkers MJ, Mischi M, Oei SG: Automated conduction velocity analysis in the electrohysterogram for prediction of imminent delivery: a preliminary study. *Computational and Mathematical Methods in Medicine* 2013, 2013:7.
26. Maner WL, Garfield RE: Identification of human term and preterm labor using artificial neural networks on uterine electromyography data. *Ann Biomed Eng* 2007, 35(3):465-473.
27. Maner WL, Garfield RE, Maul H, Olson G, Saade G: Predicting term and preterm delivery with transabdominal uterine electromyography. *Obstetrics and gynecology* 2003, 101(6):1254-1260.
28. Marque CK, Terrien J, Rihana S, Germain G: Preterm labour detection by use of a biophysical marker: the uterine electrical activity. *BMC pregnancy and childbirth* 2007, 7 Suppl 1:S5.
29. Kandil MA, Abdel-Sattar MM, Abdel-Salam SM, Saleh S, Khalafallah MM: Abdominal electromyography may predict the response to tocolysis in preterm labor. *European journal of obstetrics, gynecology, and reproductive biology* 2012, 160(1):18-21.
30. Most O, Langer O, Kerner R, David GB, Calderon I: Can myometrial electrical activity identify patients in preterm labor? *American journal of obstetrics and gynecology* 2008, 199(4):378 e371-376.
31. Verdenik I, Pajntar M, Leskosek B: Uterine electrical activity as predictor of preterm birth in women with preterm contractions. *European journal of obstetrics, gynecology, and reproductive biology* 2001, 95(2):149-153.
32. Mansour S, Devedeux D, Germain G, Marque C, Duchene J: Uterine EMG spectral analysis and relationship to mechanical activity in pregnant monkeys. *Medical & biological engineering & computing* 1996, 34(2):115-121.
33. Vinken MP, Rabotti C, Mischi M, van Laar JO, Oei SG: Nifedipine-induced changes in the electrohysterogram of preterm contractions: feasibility in clinical practice. *Obstet Gynecol Int* 2010, 2010:325635.
34. Doret M, Bukowski R, Longo M, Maul H, Maner WL, Garfield RE, Saade GR: Uterine electromyography characteristics for early diagnosis of mifepristone-induced preterm labor. *Obstetrics and gynecology* 2005, 105(4):822-830.
35. Diab MO, Marque C, Khalil M: An unsupervised classification method of uterine electromyography signals: classification for detection of preterm deliveries. *The journal of obstetrics and gynaecology research* 2009, 35(1):9-19.
36. Garfield RE, Maner WL, MacKay LB, Schlembach D, Saade GR: Comparing uterine electromyography activity of antepartum patients versus term labor patients. *American journal of obstetrics and gynecology* 2005, 193(1):23-29.
37. Hsu HW, Figueroa JP, Honnebier MB, Wentworth R, Nathanielsz PW: Power spectrum analysis of myometrial electromyogram and intrauterine pressure changes in the pregnant rhesus monkey in late gestation. *American journal of obstetrics and gynecology* 1989, 161(2):467-473.
38. Buhimschi C, Boyle MB, Saade GR, Garfield RE: Uterine activity during pregnancy and labor assessed by simultaneous recordings from the myometrium and abdominal surface in the rat. *American journal of obstetrics and gynecology* 1998, 178(4):811-822.
39. Marque C, Duchene JM, Leclercq S, Panczer GS, Chaumont J: Uterine EHG processing for obstetrical monitoring. *IEEE transactions on bio-medical engineering* 1986, 33(12):1182-1187.
40. Hassan M, Terrien J, Muszynski C, Alexandersson A, Marque C, Karlsson B: Better pregnancy monitoring using nonlinear correlation analysis of external uterine electromyography. *IEEE transactions on bio-medical engineering* 2013, 60(4):1160-1166.
41. Muszynski C, Terrien J, Drean Y, Chkeir A, Hassan M, Marque C, Gondry J: [Evolution of electrohysterogram signals synchronization according to term of pregnancy: interest for preterm labor diagnosis]. *Gynecologie, obstetrique & fertilite* 2012, 40(6):344-349.
42. Rabotti C, Mischi M, Oei SG, Bergmans JW: Noninvasive estimation of the electrohysterographic action-potential conduction velocity. *IEEE transactions on bio-medical engineering* 2010, 57(9):2178-2187.
43. van 't Hooft J, Rabotti C, Oei SG: Electrohysterographic evaluation of preterm contractions in a patient with a unicornuate uterus. *Acta obstetricia et gynecologica Scandinavica* 2013, 92(6):730-733.
44. Furdea A, Preissl H, Lowery CL, Eswaran H, Govindan RB: Conduction velocity of the uterine contraction in serial magnetomyogram (MMG) data: event based simulation and validation. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference* 2011, 2011:6025-6028.
45. de Lau H, Rabotti C, Bijloo R, Rooijakkers MJ, Mischi M, Oei SG: Automated conduction velocity analysis in the electrohysterogram for prediction of imminent delivery: a preliminary study. *Comput Math Methods Med* 2013, 2013:627976.

46. Lange L, Vaeggemose A, Kidmose P, Mikkelsen E, Uldbjerg N, Johansen P: **Velocity and directionality of the electrohysterographic signal propagation**. *PloS one* 2014, **9**(1):e86775.
47. Mikkelsen E, Johansen P, Fuglsang-Frederiksen A, Uldbjerg N: **Electrohysterography of labor contractions: propagation velocity and direction**. *Acta obstetricia et gynecologica Scandinavica* 2013, **92**(9):1070-1078.
48. Rabotti C, Oei SG, van 't Hooft J, Mischi M: **Electrohysterographic propagation velocity for preterm delivery prediction**. *American journal of obstetrics and gynecology* 2011, **205**(6):e9-10; author reply e10.
49. Wolfs G, Rottinghuis H: **Electrical and mechanical activity of the human uterus during labour**. *Archiv fur Gynakologie* 1970, **208**(4):373-385.
50. Wolfs G, van Leeuwen M, Rottinghuis H, Boeles JT: **An electromyographic study of the human uterus during labor**. *Obstetrics and gynecology* 1971, **37**(2):241-246.
51. de Lau H, Rabotti C, Oosterbaan HP, Mischi M, Oei GS: **Study protocol: PoPE-Prediction of Preterm delivery by Electrohysterography**. *BMC pregnancy and childbirth* 2014, **14**:192.
52. de Lau H, Rabotti C, Haazen N, Oei SG, Mischi M: **Towards improving uterine electrical activity modeling and electrohysterography: ultrasonic quantification of uterine movements during labor**. *Acta obstetricia et gynecologica Scandinavica* 2013, **92**(11):1323-1326.
53. Vullings R, Peters C, Mischi M, Oei G, Bergmans J: **Maternal ECG removal from non-invasive fetal ECG recordings**. *Conf Proc IEEE Eng Med Biol Soc* 2006, **1**:1394-1397.
54. Jezewski J, Horoba K, Matonia A, Wrobel J: **Quantitative analysis of contraction patterns in electrical activity signal of pregnant uterus as an alternative to mechanical approach**. *Physiological measurement* 2005, **26**(5):753-767.
55. Wolfs GM, van Leeuwen M: **Electromyographic observations on the human uterus during labour**. *Acta obstetricia et gynecologica Scandinavica Supplement* 1979, **90**:1-61.

Chapter 6

Dedicated entropy measures for early assessment of pregnancy progression from single-channel electrohysterography

Published in Transactions on Biomedical Engineering 2017.

Mischi M, Chen C, Ignatenko T, de Lau H, Ding B, Oei SG, Rabotti C

Abstract

Objective: Preterm birth is a large-scale clinical problem involving over 10% infants. Diagnostic means for timely risk assessment are lacking and the underlying physiological mechanisms unclear. To improve the evaluation of pregnancy before term, we introduce dedicated entropy measures derived from a single-channel electrohysterogram (EHG).

Methods: The estimation of Approximate Entropy (ApEn) and Sample Entropy (SampEn) is adjusted to monitor variations in the regularity of single-channel EHG recordings, reflecting myoelectrical changes due to pregnancy progression. In particular, modifications in the tolerance metrics are introduced for improving robustness to EHG amplitude fluctuations. An extensive database of 58 EHG recordings with 4 monopolar channels in women presenting with preterm contractions was manually annotated and used for validation. The methods were tested for their ability to recognize the onset of labor and the risk of preterm birth. Comparison with the best single-channel methods according to the literature was performed.

Results: The reference methods were outperformed. SampEn and ApEn produced the best prediction of delivery, although only one channel showed a significant difference ($p < 0.04$) between labor and non labor. The modified ApEn produced the best prediction of preterm delivery, showing statistical significance ($p < 0.02$) in 3 channels. These results were also confirmed by the area under the receiver operating characteristic curve and 5-fold cross-validation. Conclusion: The use of dedicated entropy estimators improves the diagnostic value of EHG analysis earlier in pregnancy.

Significance: Our results suggest that changes in the EHG might manifest early in pregnancy, providing relevant prognostic opportunities for pregnancy monitoring by a practical single-channel solution.

Introduction

Birth occurring before completing the 37th week of gestation (preterm), accounts for 75% of perinatal mortality and more than half of birth-related long-term morbidity [1]. With the exception of births induced for medical reasons before the 37th week, preterm birth is spontaneous and the most common precursor is uterine activity in the form of painful contractions. Timely administration of tocolytics can be used to delay preterm birth, often in combination with corticosteroids in order to improve the respiratory function after birth [2].

Unfortunately, timely intervention is hindered by the lack of diagnostic tools. In fact, there is no method able to discriminate, at the onset of the first symptoms, between contractions that represent a real threat of imminent preterm birth and physiological uterine activity triggered e.g. by environmental causes. Accurate distinction between these two types of uterine activity is crucial because, while threatening contractions need to be promptly suppressed by medical intervention, rest is often sufficient to sedate physiological, harmless uterine activity [3]. Eventually, about half of the women hospitalized due to premature contractions deliver at term, even without treatment [4]; this evidences the limits of the available diagnostic tools, often causing overdiagnosis and overtreatment.

Only few options are nowadays available for characterizing the uterine activity. Among these options, intrauterine pressure measurement is the most reliable; however, due to the need for catheterization, it cannot be used for pregnancy monitoring before labor [5]. External tocography, being non-invasive, is extensively used, but it provides only quantification of contraction frequency and duration. Furthermore, tocography has been demonstrated not to be able to predict delivery. Even cervical changes may not be an accurate indicator of labor alone, as a large percentage of women with established cervical changes do not deliver preterm, even without treatment [4].

Impending preterm delivery is likely associated with a change in uterine cell excitability, favoring conduction of electrical activity across the uterine muscles, the myometrium. Analysis of the electrohysterogram (EHG), which is the non- invasive measurement of the uterine electrical activity, has therefore been investigated as a potential method for pregnancy monitoring and early diagnosis of preterm birth [6-22].

Previous research on EHG-signal analysis has mainly addressed the diagnosis of preterm birth, with focus on either one of two distinct objectives. The first objective is to predict the delivery time irrespective of its occurrence before (preterm) or after (at term) the 37th week of gestation (prediction of delivery). This translates into the recognition of contractions related to imminent delivery [18], e.g., by evaluating the correlation between the evaluated features and the measurement- to-delivery interval. The second objective focuses on early differentiation between those pregnancies that will eventually reach the 37th week of gestation and those that will end with a preterm delivery, irrespective of the measurement-to-delivery time interval (diagnosis of preterm birth).

While the first objective allows inclusion of measurements at any gestational age, the latter necessarily requires the availability of EHG measurements early in pregnancy, i.e., from patients with preterm contractions. The challenge here is that not only are these patients more difficult to recruit, but preterm measurements are also difficult to annotate and process, due to the poor signal-to-noise ratio (SNR) and the lack of a golden standard for contraction assessment. Furthermore, extending the results obtained in term patients for the prediction of the delivery time to the diagnosis of preterm birth underlies the hypothesis that the pathogenesis of preterm delivery coincides with an earlier evolution of the physiological process leading to a delivery at term. Despite its viability, this hypothesis has not been proven yet.

Motivated by the lack of insight into the physiology underlying the onset of labor and the exact mechanism underpinning spontaneous preterm birth, a number of different features extracted from the EHG have been proposed for (preterm) delivery prediction, both on single- and multi-channel signals. Promising single-channel features are related to the frequency content of the EHG signal. In particular, an increase in the peak frequency extracted from the signal power spectral density (PSD) seems to be an indicator of approaching labor both at term and preterm, when measured within 1-7 days to delivery [8], [10], [23-29]. A significant distinction between term and preterm EHG measurements has been shown in [10] by estimation of the median frequency.

Studies on parameters related to EHG signal amplitude and energy show more controversial results [10], [17], [28], [30]. A number of studies report an increase in the power spectrum amplitude just prior to delivery both by analyzing the whole signal as well as each individual burst separately, and a significant difference in root mean squares between recordings performed before and after the 26th week of gestation [10], [24]. However, a number of studies failed to show a significant correlation of amplitude-related parameters with gestational age or with the measurement-to-delivery time [18], [28], [30]. The use of nonlinear features such as entropy, time reversibility, and maximal Lyapunov exponent [10], [16], has also been tested for prediction of labor. Among the methods evaluated for the estimation of EHG nonlinear features, the use of time reversibility accurately separated pregnancy and labor contractions on a dataset of 12 women, processing manually selected contraction segments [17]. Time reversibility can therefore be considered as a potential method for the prediction of delivery [17].

The initiation of labor is likely related to altered levels of myometrial cell connectivity that induce changes in the regularity of the measured EHG signal [31]. In line with this hypothesis, Sample Entropy (SampEn) measured early in pregnancy provided the best separation between term and preterm delivery in a large cohort of preterm women when compared to a number of other linear and nonlinear features [10]. Noteworthy, these results have been obtained by analyzing the whole EHG recording without distinction between contractile and quiescent segments. While very advantageous for the clinical implementation of the method, this approach does not discriminate between the contribution of quiescent and contractile signal segments to the final results.

More recently, estimation of the EHG conduction velocity has been proposed to predict (preterm) delivery [14], [32]. Physiologically, this approach hypothesizes a relation between the increased amount of gap-junctions observed with approaching delivery and changes in the conduction properties of the myometrial cells, which can be reflected in variations of the

EHG conduction velocity [14], [31], [33], [34]. To this end, multichannel EHG recordings have been used and a number of algorithms proposed for the analysis. Promising results have been shown by visual analysis and selection of EHG signal collected in a large population with preterm contractions [18]

Beyond the approximation of the EHG as resulting from propagating plane waves, additional connectivity measures, such as nonlinear correlation, have been tested and evaluated for their ability to reflect the underlying uterine activity [16]. The use of graph theory is also being investigated as method to assess connectivity (spatial dependency) and detect labor [35].

In this paper, we propose new dedicated methods for preterm birth diagnosis from single-channel EHG signals that are based on entropy features. The use of a single channel facilitates the clinical uptake of the methods, requiring the application of two or three (reference plus ground) electrodes only. With the aim of detecting variations in signal regularity, the proposed methods are based on a modification of the traditional calculation of Approximate Entropy (ApEn) and Sample Entropy (SampEn).

ApEn [36] and SampEn [37] are signal features derived from information theory. They reflect the regularity of a time series and, therefore, have been extensively used for analysis and characterization of physiological signals. The available methods for entropy estimation are more accurate for time series with moderate fluctuations of their mean and standard deviation [36], [38]. Due to the occurrence of uterine action potentials in bursts and to the progressive recruitment often observed at the beginning and at the end of each burst [39], the EHG signal typically shows large amplitude fluctuations that may weaken the hypothesis of stationarity. This may explain the poor results reported for the use of ApEn in order to estimate labor in a small cohort of 7 patients [17].

Here we revisited and adjusted the derivation of ApEn and SampEn in order to propose dedicated methods for EHG signal analysis that aim at suppressing the influence of amplitude fluctuations on the estimation of the signal entropy. A dataset containing EHG measurements on 81 patients with preterm contractions was available for validation. These patients were recruited at the Maxima Medical Center (MMC) in Veldhoven (the Netherlands) and included in a clinical study referred to as PoPE [40]. Based on this dataset, the proposed methods were evaluated on both the possible objectives: 1) the ability of classifying each patient as in labor or not and 2) the accuracy in the diagnosis of preterm birth. Only contraction periods were considered for the analysis. For comparison, previously proposed statistical methods based on single channel EHG analysis were also tested on our dataset. In particular, we selected those two methods that have shown, according to the literature, the best classification performance in each of the two classification objectives; these are Time Reversibility and SampEn, respectively.

Materials and methods

Data acquisition

Data were collected at the MMC within the PoPE study, approved by the ethical medical committee of the hospital. After signing an informed consent, 120 women admitted to the hospital for preterm contractions underwent multichannel EHG recording. An electrode patch containing five sensors (Nemo Healthcare, Veldhoven, the Netherlands), including a ground electrode, was placed in the middle line of the abdomen [41], as shown Fig. 1. An additional reference electrode was placed on the right hip to obtain monopolar derivations. A multichannel Porti system (Twente Medical Systems Inter national, Enschede, the Netherlands) was used to amplify and digitize the data at a sampling frequency of 500 Hz. Out of the 120 included women, 39 were originally excluded from the PoPE study because of technical failure with the acquisition. The duration of the remaining recordings ranged from 20 minutes to 60 minutes. Of the included 81 patients, 18 had a synchronized registration with a tocodynamometer.

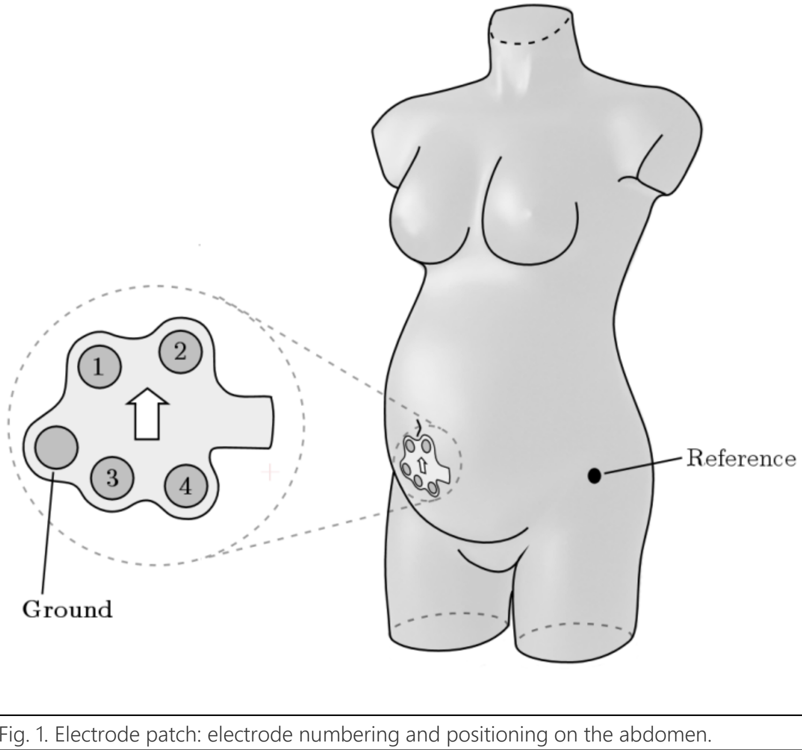

Fig. 1. Electrode patch: electrode numbering and positioning on the abdomen.

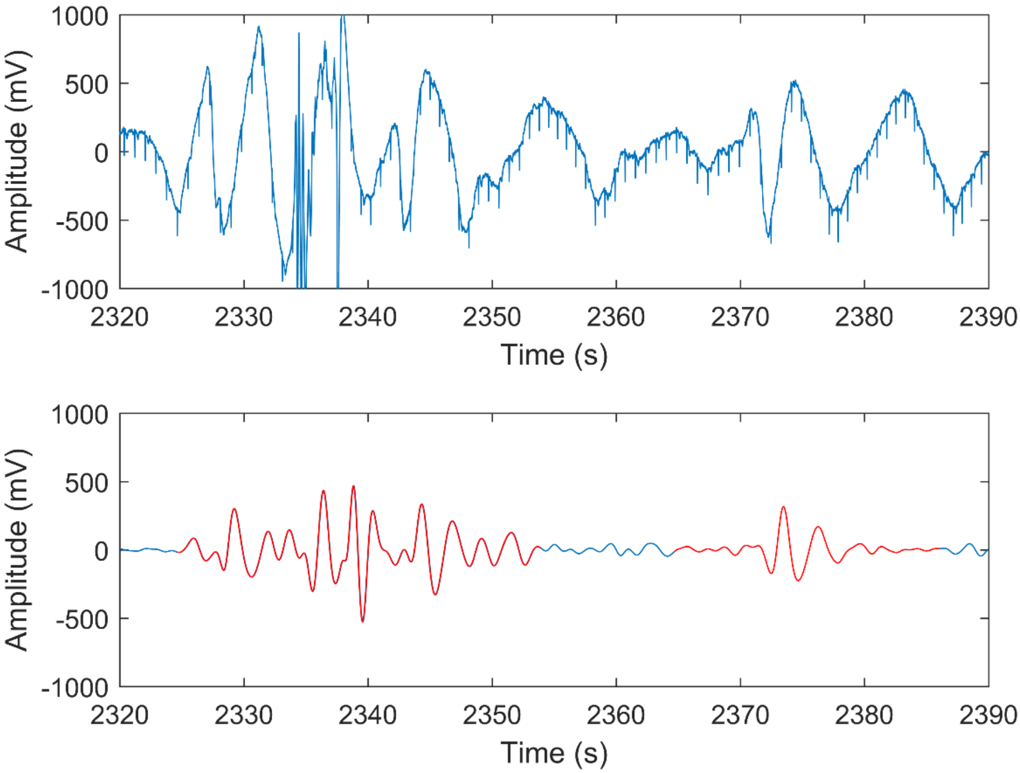

Fig. 2. EHG signal reflecting two contractions (red segments according to the experts' annotations) before (upper plot) and after (lower plot) bandpass filtering between 0.3 and 0.8 Hz. A clear improvement in the SNR with enhancement of the contraction segments can be noticed. For visualization purposes, the upper signal is detrended by highpass filtering at 0.1 Hz.

Two independent clinical experts annotated manually the contraction periods on the full dataset after training on six patients with synchronized tocodynamometer measurement. The contraction periods were identified as bursts of uterine electrical spikes with the additional support of the contraction estimates by the method described in [11] and [20]. In order to reinforce our choice to limit the analysis to contractile activity, only contraction segments recognized by all experts, and confirmed by the automatic selection method, were retained for further analysis. Of the remaining dataset, to ensure sufficient data for the following analysis, only recordings with at least 5 min of annotated contraction time were considered, resulting in a final validation dataset comprising the recordings of 58 patients.

Pre-processing

For each recording, the contraction segments were concatenated to form a new sequence. Similar to previous studies [14] [20] [25], the recorded signals were bandpass filtered within the frequency range from 0.3 to 0.8 Hz in order to suppress the main noise components due to respiration, motion artifacts, and maternal ECG. After filtering, downsampling to 20 Hz was applied.

The literature on the choice of unipolar or bipolar derivations for EHG signal analysis is rather controversial. Although bipolar derivations offer a better SNR due to the suppression of common mode components, unipolar derivations should be preferred when the spatial properties of the signal in terms of origin and direction of propagation are a priory unknown and may impact bipolarization in an unpredictable way [39]. Therefore, we performed our analysis independently on the 4 unipolar signals of the electrode patch.

Entropy features

Approximate Entropy

ApEn, originally formalized in [36], is a family of statistics that provides a measure of regularity, closely related to the Kolmogorov entropy; it can be applied to typically short and noisy clinical data [36] [43] [44]. When this statistic is used to compare time series for similar epochs, more frequent and more similar epochs lead to lower values of ApEn [37]. Therefore, we consider ApEn to be particularly suitable for revealing EHG changes in relation to pregnancy progression and labor.

For a description of ApEn, we refer to a time series, $u(j)$, with $j = 1, \ldots, N$. In order to estimate its ApEn, we subdivide $u(j)$ in epochs of length m, forming $N - (m + 1)\tau$ vectors $x_m(i)$, with $x_m(i) = \{u(i + k\tau) : 0 \leq k \leq m - 1\}, \{i | 1 \leq i \leq N - \tau(m - 1)\}$, and τ an integer time delay. A tolerance, r, is defined for accepting matches among the epochs. This tolerance is typically defined based on the vectors' Euclidean distance or on the maximum difference of their scalar components, namely, $lx_m(i) - x_m(j)l2 \leq r$ or $maxk\, |u(i + k\tau) - u(j + k\tau)| \leq r$, respectively [41]. In this work, as the signals are already pre-filtered and down-sampled based on the EHG bandwidth, no additional downsampling is applied for the definition of the epochs, i.e., $\tau = 1$. Moreover, due to the large amplitude fluctuations of the EHG, the Euclidian's distance is used to define the tolerance r. This results in a definition of tolerance that is less sensitive to the presence of spikes and large fluctuations in EHG recordings. Given tolerance r, let Bi be the number of vectors $x_m(j)$ within r of $x_m(i)$. The empirical probability $Cm(r)$ that a vector $x_m(j)$ is within r of $x_m(i)$ can be estimated by

$$C_m^i\,(r) = \frac{B_i}{(N-m+1)} \quad (1)$$

After introducing $\phi_m^N(r)$ given as

$$\Phi_m^N(r) = \frac{\sum_{i=1}^{N-m+1} \ln\lfloor C_i^m(r) \rfloor}{N-m+1}, \quad (2)$$

ApEn can be defined [38] as

$$ApEn\,(m,r) = \lim_{n\to\infty}[\phi_m^N(r) - \phi_{m+1}^N(r)] \quad (3)$$

which, for a finite time series, is estimated as

$$ApEn\,(m,r,N) = \phi_m^N(r) - \phi_{m+1}^N(r) \quad (4)$$

This estimated ApEn(m, r, N), for fixed parameters m, N, and r, provides a measure of regularity and complexity [36]. Theoretically, a perfectly regular time series would show ApEn close to 0, while a perfectly irregular time series would show ApEn close to 2 [42].

Sample Entropy

SampEn is a family of statistics that has been specifically proposed to reduce the bias caused by self-matching counts introduced in the calculation of ApEn by the occurrence of *ln(0)*. Based on the same definitions used for ApEn, and making the same choices for τ and *r*, $C_i^m(r)$ is defined as the template wise probability that $x_m(j)$ is located within the tolerance *r* of $x_m(i)$, with $j \neq i$, to exclude self-matches in the epoch comparison. The average of $C_i^m(r)$, given as

$$C_a^m(r) = \frac{1}{N-m+1}\sum_{i=1}^{N-m+1} C_i^m(r)\ , \quad (5)$$

is then used as the overall probability to approximate the entropy as

$$SampEn(m,r,N) = -\ln\left[\frac{C_a^{m+1}(r)}{C_a^m(r)}\right], C_a^m(r), C_a^{m+1}(r) \neq 0 \quad (6)$$

Notice that, although the definitions of ApEn and SampEn look similar, Eq. 6 represents a conditional entropy, different from the entropy rate represented by Eq. 4.

Modified distance metrics

In general, more accurate entropy estimation is obtained when the mean and standard deviation of the analyzed signal shows limited variation over time. Therefore, the presence of large amplitude fluctuations and spikes, typical of EHG signals [39], may affect the estimated ApEn and SampEn more than signal regularity. This makes direct application of entropy measures unsuitable for most EHG applications, hampering the possibility to perform accurate classification [17], [36], [43]. To overcame this problem, we propose a modification of the original distance metrics aiming at limiting the tolerance dependency on large amplitude fluctuations and spikes.

In particular, we modify the tolerance and define it by angular metrics, i.e., the tolerance ρ, -1 < ρ < 1, is defined based on the angle between the vectors $x_m(i)$ and $x_m(j)$, $\Phi(x_m(i);x_m(j))$ expressed by:

$$cos\left(\theta\left(\boldsymbol{xm}(i), \boldsymbol{xm}(j)\right)\right) = \frac{\boldsymbol{x_m}(i)\cdot \boldsymbol{x_m}(j)}{l\boldsymbol{x_m}(i)l2l\boldsymbol{x_m}(j)l_2} \geq \rho\ , \quad (7)$$

where · denotes the inner product of two vectors. We can then use the estimated entropy measures (ApEn and SampEn) based on this new tolerance to compare epochs that are scaled in amplitude. We can observe that the proposed entropy analysis with modified tolerance is equivalent to the analysis of the original entropy applied to normalized data. In fact, for the vectors $x'_m(i) = \frac{x_m(i)}{[\![x_m(i)]\!]2}$ and $x'_m(j) = \frac{x_m(j)}{[\![x_m(j)]\!]2}$ with a unit length, it holds that

$$[\![x'_m(i) - x'_m(j)]\!]_2^2 = 2(1 - \cos(\Theta(x'_m(i).x'_m(j)))) \ . \ (8)$$

Therefore, defining B_i for this normalized data, we obtain

$= \#j: [\![x'_m(i) - x'_m(j)]\!]_2 \leq r$

$= \#j: [\![x'_m(i) - x'_m(j)]\!]_2^2 \leq r^2$

$= \#j: 2(1 - \cos(\Theta(x'_m(i).x'_m(j)))) \leq r^2$

$= \#j: \cos(\Theta(x'_m(i).x'_m(j)))) \geq 1 - r^2/2 \triangleq \rho$,

where # denotes number of elements. Because of the similarity in their definition, SampEn and ApEn are often interchanged and compared for analysis of physiological signals [42], [43]. Therefore, the proposed modified tolerance metrics based on angular distance was applied to both entropy features.

Validation strategy

Classification objectives

All the features, namely, ApEn, SampEn, Modified ApEn,and Modified SampEn, were evaluated for their classification ability in the two identified, relevant scenarios.

1) Prediction of delivery within 1 week from the measurement, irrespectively of being at term or preterm. For preterm cases, 1 week is a common cut-off to separate pregnancy from labor.
2) Diagnosis of preterm birth, i.e., for distinguishing between real and false threat among women who were prospectively classified at risk of preterm delivery.

According to the literature, SampEn provides the best results for the prediction of labor (first scenario) [10]. However, the best results for the second scenario are provided by the assessment of Time Reversibility [17]. Therefore, for completeness, this method was also implemented and compared.

Time Reversibility

A stochastic process is defined as time-reversible if it is invariant under the reversal of the time scale [44]. An example of time-reversible process is a linear Gaussian random process. Since Time Reversibility can be a strong signature of nonlinearity, in [22] it has been proposed as feature to distinguish between pregnancy and labor contractions. A common measure of Time Reversibility is the third-order quantity

$$Tr(\tau) = \frac{1}{N-\tau} \sum_{n=\tau+1}^{N} (S_n - S_n - \tau)^3 \ (9)$$

where S is a signal with N samples, and t = 1 [44], [45]. According to the original study, 99 surrogate data are created by iterative amplitude-adjusted Fourier transform in order to match the same PSD of the original signal [45]. The value of Time Reversibility Tr(t) of the original time series is tested in order assess whether it is likely to be drawn, within a confidence level, from the distribution of values of the surrogates. Comparatively different values for the original series lead to the rejection of the null hypothesis and the original series is considered to be nonlinear. To this end, the Rank test is adopted, and the discriminative statistics of the original signal is used as feature for classification.

To accurately reproduce the original study, different from ApEn and Sample Entropy, assessment of Time Reversibility was based on separate contractions rather than on sliding windows. Since decimation to 20 Hz has been demonstrated not to degrade the performance of Time Reversibility for EHG signal analysis, 20 Hz sampling frequency was used also in this study [46]. Although all features were estimated on monopolar derivations, for the estimation of Time Reversibility only, some additional tests on bipolar derivations were also performed to fully reproduce the original study [17].

Statistics

The classification ability of each feature was assessed on the average values extracted from each woman data sequence in each electrode. The average of the results for the 4 electrodes was also considered.

The Wilcoxon rank sum test was adopted to evaluate the discrimination ability of the selected features in both scenarios. This statistic was chosen to account for the non-Gaussian distribution of the data and unbalanced classes [47]. The feature ability to provide correct classification was also assessed by the area under the receiver operating characteristic (ROC) curve, derived over the full dataset of 58 patients.

In addition, 5-fold cross-validation was performed in order to evaluate sensitivity, specificity, and accuracy of all the features for classification in both scenarios. To this end, the data were subdivided in 5 patient groups. The optimal threshold was then determined by ROC curve analysis (point closest to the upper-left corner) on 4 groups and applied to the remaining group to evaluate the classification performance, rounding in a way that all groups would undergo classification. This procedure was repeated for 50 random subdivisions in 5 groups.

Adopted parametrization

Prior to the proposed statistical analysis, the parametrization for the implemented methods was determined. In line with the literature, ApEn and SampEn were estimated using m = 3 and r equal to 0.15 the standard deviation of the signal [10], [36], [42], [43]. For the modified metrics, these parameters were chosen to optimize the classification performance on the subset of annotated EHG signals for which the external tocogram was also available. Classification aimed at differentiating between contraction and quiescent periods as annotated by the experts with the support of the tocogram and additional automatic detection algorithms [11], [20]. The estimation of modified ApEn and SampEn was therefore performed with $m = 3$ and $\rho = cos(\pi/18)$ "" 0.98.

Based on the same optimization, all entropy features were estimated employing an 80-s sliding windows with 40-s overlap. For each patient, the average over all windows was considered in our statistical analysis. All signals were analyzed after preprocessing, including the concatenation of the contraction segments. For completeness, SampEn was also calculated on the whole signal, without contraction selection, in line with the original study described in [10]. All the analysis was implemented in Matlabr (The MathWorks, Natick, MA) running on a windows system with Intel(R) Core(TM) i7-4710MQ and 8 GB RAM. With this implementation, the computational time for the measurement of entropy using the Euclidian distance metrics was 10-s per window, and 16-s per window using the modified distance metrics.

Results

In total, 58 women with preterm contractions were analyzed, of which 34 delivered preterm. Nine of the women who delivered preterm were measured at less than one week to delivery (labour). The gestational age at delivery versus the measurement-to-delivery interval is shown in Fig. 3. We analyzed a total number of 804 contractions which were distributed across the included 58 subjects as shown in Fig. 4.

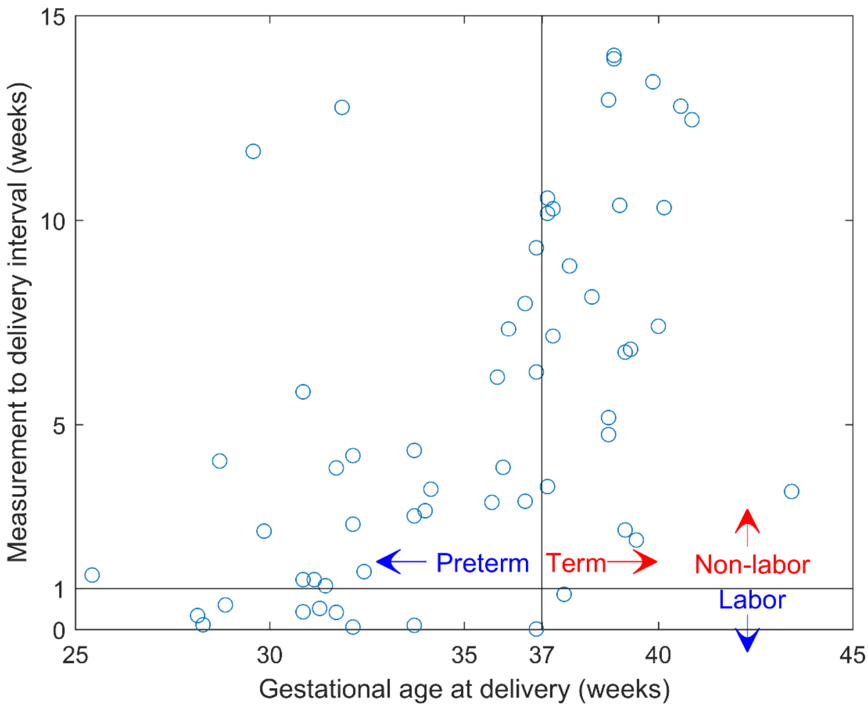

Fig. 3. Measurement-to-delivery time interval vs. gestational age at delivery in the study population.

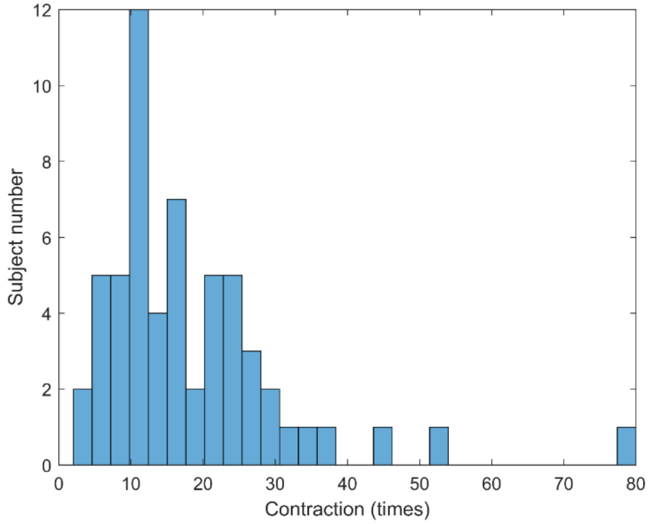

Fig. 4. Distribution of the measured contractions over the population included in the study.

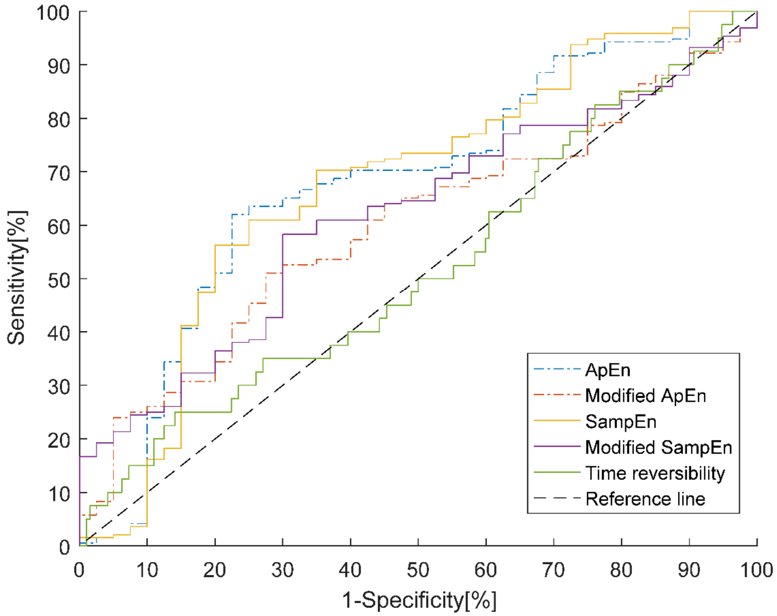

Fig. 5. Prediction of delivery: ROC curve obtained for each of the evaluated features based on all the electrodes.

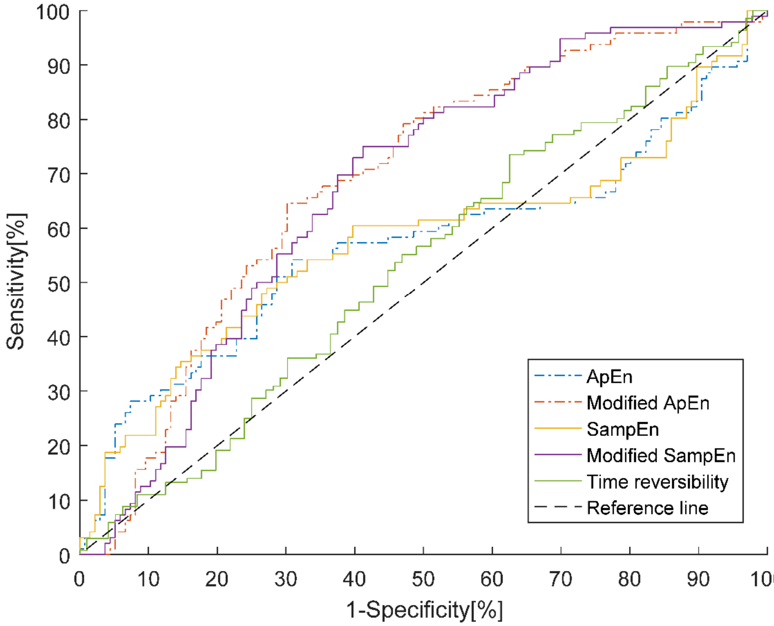

Fig. 6. Diagnosis of preterm birth: ROC curve obtained for each of the evaluated features based on all the electrodes.

Prediction of delivery

Focussing on the classification of each women as being in labor or not, the left side of Table I shows the average values of all the features together with the statistical significance (p-value) of the difference between non-labor and labor condition. The results are reported for each monopolar electrode and for the average values of all the electrodes, estimated for each woman. The best results are obtained by SampEn and ApEn, with minor differences between the two; women in labor showed lower values (average SampEn=0.312 and average ApEn=0.364) compared to those who were not in labor (average SampEn=0.403 and average ApEn=0.442). Significant differences, however, are obtained only with electrode 1 (E1 in Fig. 1). These results are also confirmed by the ROC curve areas, also reported in Table I. The full ROC curves are shown in Fig. 5, where all the electrodes are considered independently to derive an average value of each feature per woman.

Table 1 Feature difference between preterm/term and between non-labour/labor groups

Non-labor/Labor						Preterm/Term			
Method	Electrode	Non-labor	Labor	p-value	ROC area	Preterm	Term	p-value	ROC area
ApEn	1	0.451±0.097	0.353±0.150	0.039	0.710	0.438±0.106	0.429±0.125	0.641	0.537
	2	0.437±0.105	0.345±0.157	0.086	0.675	0.422±0.112	0.421±0.131	0.543	0.599
	3	0.437±0.100	0.373±0.147	0.198	0.631	0.423±0.108	0.430±0.116	0.482	0.573
	4	0.441±0.093	0.385±0.122	0.093	0.671	0.421±0.091	0.447±0.112	0.087	0.652
	average	0.442±0.092	0.364±0.139	0.054	0.696	0.426±0.098	0.431±0.115	0.372	0.593
Modified ApEn	1	0.250±0.008	0.259±0.006	0.943	0.508	0.249±0.008	0.251±0.005	0.193	0.602
	2	0.250±0.007	0.570±0.006	0.339	0.598	0.247±0.006	0.252±0.005	0.001	0.754
	3	0.250±0.008	0.249±0.004	0.198	0.631	0.248±0.007	0.252±0.007	0.009	0.705
	4	0.250±0.008	0.247±0.006	0.141	0.650	0.248±0.008	0.252±0.005	0.015	0.690
	average	0.250±0.007	0.248±0.005	0.237	0.621	0.248±0.007	0.251±0.005	0.004	0.728
SampEn	1	0.413±0.120	0.301±0.156	0.023	0.731	0.391±0.121	0.398±0.151	0.453	0.559
	2	0.397±0.127	0.294±0.168	0.072	0.683	0.374±0.126	0.387±0.159	0.435	0.561
	3	0.397±0.127	0.315±0.162	0.153	0.646	0.376±0.129	0.392±0.147	0.502	0.553
	4	0.405±0.121	0.340±0.146	0.191	0.633	0.377±0.115	0.417±0.142	0.120	0.621
	average	0.403±0.117	0.312±0.150	0.054	0.696	0.380±0.115	0.398±0.143	0.356	0.572
Modified SampEn	1	0.244±0.009	0.241±0.006	0.371	0.592	0.242±0.010	0.246±0.005	0.026	0.674
	2	0.245±0.009	0.241±0.008	0.299	0.606	0.242±0.009	0.247±0.007	0.015	0.689
	3	0.245±0.010	0.243±0.007	0.382	0.590	0.243±0.010	0.247±0.008	0.051	0.652
	4	0.245±0.009	0.240±0.009	0.106	0.665	0.242±0.010	0.248±0.007	0.021	0.680
	average	0.245±0.008	0.241±0.007	0.184	0.635	0.242±0.009	0.247±0.006	0.020	0.681
Time Reversibility	1	9.463±6.303	10.792 ±5.854	0.360	0.585	9.865±5.071	9.446±7.631	0.280	0.594
	2	8.269±5.324	8.161±5.253	0.894	0.500	8.270±5.355	8.223±5.251	1.000	0.515
	3	9.315±4.744	8.716±4.064	0.877	0.542	8.835±4.306	9.745±5.047	0.586	0.517
	4	8.991±6.553	12.937 ±12.419	0.765	0.567	10.797 ±9.199	8.077±5.272	0.390	0.531
	average	9.009±4.089	10.152 ±5.336	0.673	0.540	9.441±4.430	8.873±4.174	0.608	0.544

The assessment of the classification performance by 5-fold cross-validation is reported in Table II (left side). The best classification results are achieved with SampEn and ApEn, with differences depending on the classification objective: higher sensitivity for SampEn (63% vs. 54%) and higher specificity for ApEn (77% vs. 57%). The classification results for the modified ApEn are also very close. When the statistical analysis was performed on Time Reversibility extracted by bipolar derivations, as presented in the original work, no statistical difference could be found.

Diagnosis of preterm birth

Following the same statistical analysis as for the prediction of labor, the right side of Table I shows the average values of all the features together with the statistical significance (p-value) of the difference between term and preterm deliveries.

The results show a significant improvement in the classification performance when the modified distance metrics is adopted. In particular, the best results are obtained by the modified ApEn (average p-value of 0.004); women who eventually delivered at term showed higher values of modified ApEn (0:251) compared to those who delivered preterm (0:248). This result is also confirmed by the ROC curve areas, reported in Table I. The full ROC curves are shown in Fig. 6, where all the electrodes are considered independently to derive an average value of each feature per woman.

The assessment of the classification performance by 5-fold cross-validation is reported in Table II (right side). Again, a clear advantage by Modified ApEn is evidenced by the results, especially in terms of specificity and accuracy. For completeness, SampEn was also calculated on the whole signal, without contraction selection, following the same procedure reported in [10]. This solution led to a deterioration of the classification performance by SampEn in both classification scenarios.

Table 2 Classification performance based on 5-fold cross-validation

Non-labor/Labor					Preterm/Term		
Method	Electrode	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
ApEn	1	0.59±0.17	0.64±0.46	0.62±0.14	0.46±0.23	0.66±0.23	0.57±0.14
	2	0.60±0.17	0.59±0.39	0.63±0.14	0.47±0.24	0.68±0.19	0.59±0.14
	3	0.58±0.18	0.69±0.44	0.60±0.14	0.51±0.20	0.65±0.16	0.59±0.12
	4	0.61±0.18	0.66±0.42	0.63±0.13	0.54±0.22	0.70±0.14	0.63±0.10
	average	0.54±0.13	0.77±0.42	0.59±0.11	0.45±0.22	0.67±0.19	0.58±0.14
Modified ApEn	1	0.62±0.15	0.66±0.37	0.63±0.13	0.58±0.23	0.81±0.10	0.72±0.10
	2	0.54±0.15	0.50±0.38	0.55±0.12	0.68±0.23	0.82±0.18	0.75±0.13
	3	0.57±0.15	0.65±0.33	0.60±0.13	0.60±0.23	0.81±0.10	0.72±0.11
	4	0.63±0.14	0.60±0.37	0.64±0.12	0.61±0.24	0.82±0.17	0.73±0.14
	average	0.56±0.17	0.65±0.43	0.60±0.15	0.61±0.20	0.83±0.11	0.73±0.12
SampEn	1	0.66±0.18	0.60±0.33	0.65±0.14	0.50±0.28	0.69±0.16	0.60±0.15
	2	0.65±0.13	0.60±0.44	0.65±0.11	0.41±0.26	0.65±0.16	0.56±0.13
	3	0.62±0.17	0.39±0.37	0.59±0.13	0.52±0.24	0.67±0.15	0.61±0.11
	4	0.62±0.15	0.56±0.40	0.62±0.13	0.51±0.20	0.63±0.18	0.58±0.12
	average	0.63±0.17	0.57±0.36	0.63±0.13	0.51±0.25	0.66±0.15	0.60±0.14
Modified SampEn	1	0.56±0.17	0.55±0.43	0.57±0.13	0.63±0.21	0.59±0.22	0.62±0.11
	2	0.58±0.16	0.58±0.43	0.57±0.14	0.71±0.25	0.56±0.19	0.63±0.13
	3	0.57±0.17	0.48±0.45	0.57±0.13	0.54±0.26	0.71±0.24	0.60±0.14
	4	0.50±0.21	0.60±0.40	0.54±0.15	0.58±0.24	0.79±0.19	0.61±0.11
	average	0.56±0.21	0.56±0.42	0.57±0.15	0.63±0.27	0.56±0.19	0.64±0.13
Time Reversibility	1	0.50±0.14	0.51±0.42	0.52±0.12	0.55±0.20	0.42±0.24	0.49±0.13
	2	0.48±0.20	0.31±0.37	0.47±0.18	0.47±0.23	0.46±0.25	0.47±0.13
	3	0.54±0.17	0.40±0.38	0.50±0.12	0.56±0.25	0.42±0.28	0.50±0.13
	4	0.48±0.17	0.38±0.39	0.47±0.13	0.59±0.25	0.44±0.25	0.53±0.14
	average	0.48±0.17	0.35±0.40	0.46±0.15	0.53±0.22	0.47±0.24	0.50±0.11

Discussion

In current diagnosis of preterm birth, both sensitivity and specificity represent critical issues. Overall, over 50% of the patients admitted for threatening preterm delivery, deliver at term, some even without treatment [4]. On the other hand, although tocolytics prolong pregnancy, they have not been shown to improve perinatal or neonatal outcomes, and most efforts aimed at arresting preterm labor once it has started have failed [48], [49]. Indeed, a high sensitivity towards the first signs of a preterm delivery threat would allow prompt intervention and improvement of pregnancy outcome.

With the final objective of introducing new diagnostic and prognostic tools for early assessment of pregnancy progression, the entropy measures ApEn and SampEn are revisited and tailored to the characteristics of the EHG signal for a more accurate quantification of the signal complexity. To this end, the distance metrics is redefined emphasizing the angular difference rather than the amplitude difference between two vectors. This modification aims at defining a tolerance threshold such that the effects of large EHG amplitude fluctuations on the entropy estimation is mitigated.

The methods have been tested on an extended in-house dataset of annotated preterm EHG measurements and compared to the best single-channel methods for EHG signal analysis based on the literature. In particular, focussing independently on two related but different objectives, namely prediction of delivery and diagnosis of preterm birth, we selected those methods that have been shown to provide the best classification performance in each of these two scenarios, Time Reversibility and Sample Entropy.

The results on the prediction of delivery, based on the differentiation between labor and non-labor condition, show SampEn and ApEn as providing the best classification performance. This result is confirmed by all figures, namely, p-value, area under the ROC curve and, although to a lesser extent, the results of the 5-fold cross validation. Instead, the modified metrics, as well as the reference method from the literature, Time Reversibility, resulted in lower performance. The ApEn improvement compared to the results reported in the literature [17] may relate to the use of the Eucledian's metrics, which is more robust than the maximum distance in the case of low SNR.

The results on the prediction of preterm delivery show the modified metrics to outperform the standard definitions of ApEn and SampEn. This is confirmed by all statistical figures. In particular, the modified ApEn results in the most accurate prediction and best differentiation between the two groups. This result suggests that while approaching labor is reflected in amplitude changes in the signal, signs related to the risk of preterm labor are independent of the signal amplitude and are mainly related to the regularity of the normalized EHG time series. This would support the hypothesis that preterm delivery cannot be simply regarded as early idiopathic activation of the normal labor process. In general, although the mechanisms underlying term and preterm delivery are poorly understood, the EHG seems to offer an important tool for early assessment of preterm risk, as well as for revealing relevant changes in the uterine activity during pregnancy.

Our study reveals a decrease in signal entropy, both ApEn and SampEn, for women who are in labor compared to women who are not in labor. This result is also in line with the results obtained with the modified measures of entropy for the assessment of the risk of preterm birth. Women that are at risk show a significant lower value of modified entropy, both ApEn and SampEn. Physiologically, a decrease in the signal entropy may be expected as a result of increased coordination among cells at the myometrial level. However, different underlying mechanisms may be reflected by the different distance metrics employed for the entropy estimation.

In general, when single electrodes are evaluated, each method shows the best results for different positions. This result, in line with previous studies [50], may be due to the complex spatial distribution of the EHG characteristics, which may affect differently each feature depending on the electrode position. In our measurements, E1 (upper right electrode in Fig. 1) provided the best results for the detection of labor, while it provided the worst results for the prediction of preterm delivery. This result may again relate to the different physiological mechanisms in pregnancies leading to term or preterm delivery.

In the pregnant uterus, contractions occur in bursts of action potentials. Recently, the approach towards the analysis of the EHG has polarized toward processing the whole signal regardless of the alternation between active bursts and quiescent periods. Indeed, the detection of contractions is a critical preprocessing step, particularly preterm, and the lack of annotations on the publicly available databases does not allow for validation. Sample Entropy has been previously evaluated on the whole signal and Time Reversibly on manually segmented contraction segments. In this study, we focused on an in-house dataset, where only validated contractions segments were used for the analysis. The aim was to focus on the contribution of the uterine activity only, while neglecting factors such as contraction frequency or duration. For completeness, to fully reproduce the results reported in the literature, SampEmp was additionally applied to the whole signal, including the quiescent periods. However, these results showed lower classification performance. We may therefore hypothesize that most entropy information for the characterization of pregnancy relates to the contraction phase, while the remaining signal introduces noise in the measurement.

Time Reversibility had been previously presented as a measure of signal nonlinearity that shows significant increase with approaching delivery. Our results did not evidence the same performance. The reason for this discrepancy may relate to the different strategy adopted in the original study [17], averaging the results based on the contractions in the entire groups, without distinction between subjects. This way, the results are influenced by the number of contractions recorded per women, which are highly variable and dependent, among other factors, on the time to delivery. Therefore, we opted to evaluate the average value per woman. Importantly, the use of monopolar derivations may have also affected the estimation of the Time Reversibility due to the bias introduced by the common mode. However, additional tests using bipolar derivations did not show any significant improvement.

In general, although the use of a single EHG channel is desirable for practical use and the obtained results are promising, the obtained classification accuracy shows room for improvement. In order improve the obtained results on single channel recordings, multiple features reflecting different aspects of the underlying physiological phenomena may be combined in the future. Alternative entropy measures, such as correlation and variance entropy, could therefore be investigated for their ability to provide additional, complementary information. Machine-learning techniques could then be employed to achieve ranking and optimal combination of all the available features and information [51]. In addition, multichannel analysis, possibly coupled with advanced multiscale 9 modeling of the uterine electrical activation [52-54], may provide additional features that are valuable to elucidate the role of cell activity and connectivity in relation to the onset of labor and preterm labor.

Conclusion

Entropy measures have been revisited and adjusted with the objective of achieving noninvasive prediction of delivery and diagnosis of preterm birth by analysis of single-channel EHG signals. On an extended database of in-house preterm EHG measurements, the estimated ApEn and SampEn have shown the best prediction of delivery, while the modified ApEn has shown a clear advantage for early diagnosis of delivery. These results prove the value of EHG entropy analysis as a tool for early, prognostic evaluation of pregnancy.

References

1. Iams JD: **Prediction and early detection of preterm labor**. *Obstetrics & Gynecology* 2003, **101**:402-412.
2. Vogel JP, Souza JP, Gülmezoglu AM, Mori R, Lumbiganon P, Qureshi Z, Carroli G, Laopaiboon M, Fawole B, Ganchimeg T *et al*: **Use of antenatal corticosteroids and tocolytic drugs in preterm births in 29 countries: an analysis of the WHO Multicountry Survey on Maternal and Newborn Health**. *The Lancet* 2014, **384**:1869-1877.
3. Goldenberg RL, Culhane JF, Iams JD, Romero R: **Epidemiology and causes of preterm birth**. *Lancet* 2008, **371**:75-84.
4. Linhart J, Olson G, Goodrum L, Rowe T, Saade G, Hankins G: **Preterm labor at 32 to 34 weeks� gestation: effect of a policy of expectant management on length of gestation**. *American Journal of Obstetrics & Gynecology* 1990, **178**:S179.
5. Garfield RE, Maul H, Maner W, Fittkow C, Olson G, Shi L, Saade GR: **Uterine electromyography and light-induced fluorescence in the management of term and preterm labor**. *Journal of the Society for Gynecologic Investigation* 2002, **9**:265-275.
6. Euliano TY, Nguyen MT, Marossero D, Edwards RK: **Monitoring contractions in obese parturients: electrohysterography compared with traditional monitoring**. *Obstetrics & Gynecology* 2007, **109**:1136-1140.
7. Rooijakkers MJ, Rabotti C, Oei SG, Aarts RM, Mischi M: **Low-complexity intrauterine pressure estimation using the Teager energy operator on electrohysterographic recordings**. *Physiological measurement* 2014, **35**:1215.
8. Leman H, Marque C, Gondry J: **Use of the electrohysterogram signal for characterization of contractions during pregnancy**. *IEEE Transactions on Biomedical Engineering* 1999, **46**:1222-1229.
9. Jezewski J, Horoba K, Matonia A, Wrobel J: **Quantitative analysis of contraction patterns in electrical activity signal of pregnant uterus as an alternative to mechanical approach**. *Physiological Measurement* 2005, **26**:753.
10. Fele-Žorž G, Kavšek G, Novak-Antolič Ž, Jager F: **A comparison of various linear and non-linear signal processing techniques to separate uterine EMG records of term and pre-term delivery groups**. *Medical & biological engineering & computing* 2008, **46**:911-922.
11. Rabotti C, Mischi M, Van Laar JOEH, Oei GS, Bergmans JWM: **Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals**. *Physiological Measurement* 2008, **29**:829-841--.
12. Euliano TY, Marossero D, Nguyen MT, Euliano NR, Principe J, Edwards RK: **Spatiotemporal electrohysterography patterns in normal and arrested labor**. *American Journal of Obstetrics and Gynecology* 2009, **200**:54.e51--54.e57.
13. Rabotti C, Mischi M, Van Laar JOEH, Oei GS, Bergmans JWM: **Inter-electrode delay estimators for electrohysterographic propagation analysis**. *Physiological Measurement* 2009, **30**:745-761.
14. Rabotti C, Mischi M, Oei SG, Bergmans JWM: **Noninvasive estimation of the electrohysterographic action-potential conduction velocity**. *IEEE Transactions on Biomedical Engineering* 2010, **57**:2178-2187.
15. Jacod BC, Graatsma EM, Van Hagen E, Visser GHA: **A validation of electrohysterography for uterine activity monitoring during labour**. *Journal of Maternal-Fetal and Neonatal Medicine* 2010, **23**:17-22--.
16. Hassan M, Boudaoud S, Terrien J, Karlsson B, Marque C: **Combination of canonical correlation analysis and empirical mode decomposition applied to denoising the labor electrohysterogram**. *IEEE Transactions on Biomedical Engineering* 2011, **58**:2441-2447.
17. Hassan M, Terrien J, Marque C, Karlsson B: **Comparison between approximate entropy, correntropy and time reversibility: Application to uterine electromyogram signals**. *Medical engineering & physics* 2011, **33**:980-986.
18. Lucovnik M, Maner WL, Chambliss LR, Blumrick R, Balducci J, Novak-Antolic Z, Garfield RE: **Noninvasive uterine electromyography for prediction of preterm delivery**. *American Journal of Obstetrics and Gynecology* 2011, **204**:228.e221--228.e210.
19. Rabotti C, Oei SG, Van 'T Hooft J, Mischi M: **Comment to Electrohysterographic propagation velocity for preterm delivery prediction**. *American Journal of Obstetrics and Gynecology* 2011, **205**:e9-e10.
20. De Lau H, Rabotti C, Bijloo R, Rooijakkers MJ, Mischi M, Oei SG: **Automated conduction velocity analysis in the electrohysterogram for prediction of imminent delivery: A preliminary study**. *Computational and Mathematical Methods in Medicine* 2013, **2013**:7.
21. Van'T Hooft J, Rabotti C, Oei SG: **Electrohysterographic evaluation of preterm contractions in a patient with a unicornuate uterus**. *Acta Obstetricia et Gynecologica Scandinavica* 2013, **92**:730-733--.
22. Hassan MM, Terrien J, Muszynski C, Alexandersson A, Marque C, Karlsson B: **Better pregnancy monitoring using nonlinear correlation analysis of external uterine electromyography**. *IEEE Transactions on Biomedical Engineering* 2013, **60**:1160-1166.
23. Doret M, Bukowski R, Longo M, Maul H, Maner WL, Garfield RE, Saade GR: **Uterine electromyography characteristics for early diagnosis of mifepristone-induced preterm labor**. *Obstetrics & Gynecology* 2005, **105**:822-830.

24. Buhimschi C, Boyle MB, Garfield RE: Electrical activity of the human uterus during pregnancy as recorded from the abdominal surface. *Obstetrics & Gynecology* 1997, 90:102-111.
25. Maner WL, Garfield RE, Maul H, Olson G, Saade G: Predicting term and preterm delivery with transabdominal uterine electromyography. *Obstetrics & Gynecology* 2003, 101:1254-1260.
26. Buhimschi C, Boyle MB, Saade GR, Garfield RE: Uterine activity during pregnancy and labor assessed by simultaneous recordings from the myometrium and abdominal surface in the rat. *American journal of obstetrics and gynecology* 1998, 178:811-822.
27. Garfield RE, Maner WL, Maul H, Saade GR: Use of uterine EMG and cervical LIF in monitoring pregnant patients. *BJOG: An International Journal of Obstetrics & Gynaecology* 2005, 112:103-108.
28. Maner WL, Garfield RE: Identification of human term and preterm labor using artificial neural networks on uterine electromyography data. *Annals of biomedical engineering* 2007, 35:465-473.
29. Vinken MPGC, Rabotti C, Mischi M, Guid Oei S: Accuracy of frequency-related parameters of the electrohysterogram for predicting preterm delivery: A Review of the literature. *Obstetrical and Gynecological Survey* 2009, 64:529-541.
30. Verdenik I, Pajntar M, Leskošek B: Uterine electrical activity as predictor of preterm birth in women with preterm contractions. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2001, 95:149-153.
31. Lammers WJEP: The electrical activities of the uterus during pregnancy. *Reproductive Sciences* 2013, 20:182-189.
32. Lucovnik M, Kuon RJ, Chambliss LR, Maner WL, SHI SQ, Shi L, Balducci J, Garfield RE: Use of uterine electromyography to diagnose term and preterm labor. *Acta Obstetricia et Gynecologica Scandinavica* 2011, 90:150-157.
33. Garfield RE: Is knowledge of the pattern of electrical activity in the pregnant uterus helpful to our understanding of uterine function? Focus on" Patterns of electrical propagation in the intact pregnant guinea pig uterus" by Lammers et al. *American journal of physiology Regulatory, integrative and comparative physiology* 2008, 63:R917-R918.
34. Lammers WJEP, Mirghani H, Stephen B, Dhanasekaran S, Wahab A, Al Sultan MAH, Abazer F: Patterns of electrical propagation in the intact pregnant guinea pig uterus. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* 2008, 294:R919--R928.
35. Nader N, Hassan M, Falou W, Diab A, Al-Omar S, Khalil M, Marque C: Classification of pregnancy and labor contractions using a graph theory based analysis. In: *Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE.* 2015: 2876-2879.
36. Pincus SM: Approximate entropy as a measure of system complexity. *Proceedings of the National Academy of Sciences* 1991, 88:2297-2301.
37. Richman JS, Moorman JR: Physiological time-series analysis using approximate entropy and sample entropy. *American Journal of Physiology-Heart and Circulatory Physiology* 2000, 278:H2039--H2049.
38. Kantz H, Schreiber T: Nonlinear time series analysis. 2004, 7.
39. Rabotti C, Mischi M: Propagation of electrical activity in uterine muscle during pregnancy: a review. *Acta Physiologica* 2015, 213:406-416.
40. de Lau H, Rabotti C, Oosterbaan HP, Mischi M, Oei GS: Study protocol: PoPE-Prediction of preterm delivery by electrohysterography. *BMC pregnancy and childbirth* 2014, 14:192.
41. Grassberger P, Procaccia I: Estimation of the Kolmogorov entropy from a chaotic signal. *Physical review A* 1983, 28:2591.
42. Yentes JM, Hunt N, Schmid KK, Kaipust JP, McGrath D, Stergiou N: The appropriate use of approximate entropy and sample entropy with short data sets. *Annals of biomedical engineering* 2013, 41:349-365.
43. Molina-Picó A, Cuesta-Frau D, Aboy M, Crespo C, Miró-Mart\'\inez P, Oltra-Crespo S: Comparative study of approximate entropy and sample entropy robustness to spikes. *Artificial intelligence in medicine* 2011, 53:97-106.
44. Weiss G: Time-reversibility of linear stochastic processes. *Journal of Applied Probability* 1975:831-836.
45. Schreiber T, Schmitz A: Surrogate time series. *Physica D: Nonlinear Phenomena* 2000, 142:346-382.
46. Diab A, Hassan M, Karlsson B, Marque C: Effect of decimation on the classification rate of non-linear analysis methods applied to uterine EMG signals. *IRBM* 2013, 34:326-329.
47. Wilcoxon F: Individual comparisons by ranking methods. *Biometrics bulletin* 1945, 1:80-83.
48. Goldenberg RL: The management of preterm labor. *Obstetrics & Gynecology* 2002, 100:1020-1037.
49. Gyetvai K, Hannah ME, Hodnett ED, Ohlsson A: Tocolytics for preterm labor: a systematic review. *Obstetrics & Gynecology* 1999, 94:869-877.
50. Rooijakkers MJ, Song S, Rabotti C, Oei SG, Bergmans JWM, Cantatore E, Mischi M: Influence of electrode placement on signal quality for ambulatory pregnancy monitoring. *Computational and mathematical methods in medicine* 2014, 2014.

51. Bishop CM: **Pattern recognition**. *Machine Learning* 2006, **128**:1-58.
52. Rabotti C, Mischi M, Beulen L, Oei G, Bergmans JWM: **Modeling and identification of the electrohysterographic volume conductor by high-density electrodes**. *IEEE Transactions on Biomedical Engineering* 2010, **57**:519-527.
53. Laforet J, Rabotti C, Terrien J, Mischi M, Marque C: **Toward a multiscale model of the uterine electrical activity**. *IEEE Transactions on Biomedical Engineering* 2011, **58**:3487-3490.
54. Marque C, Laforet J, Rabotti C, Alexandersson A, Germain G, Gondry J, Karlsson B, Leskosek B, Mischi M, Muszinski C *et al*: **A multiscale model of the electrohysterogram the BioModUE_PTL project**. In: *Engineering in Medicine and Biology Society (EMBC), 2013 35th Annual International Conference of the IEEE.* 2013: 7448-7451.

Chapter 7

Tocogram characteristics of uterine rupture: systematic review

Published in Archives of Gynecology and Obstetrics 2017.

Vlemminx M, de Lau H, Oei SG

Abstract

Purpose: timely diagnosing a uterine rupture is challenging. based on the pathophysiology of complete uterine wall separation, changes in uterine activity are expected. The primary objective is to identify tocogram characteristics associated with uterine rupture during trial of labor after cesarean. The secondary objective is to compare the external tocodynamometer with intra-uterine pressure catheters.

Methods: MEDLINE, EMBASE and the Cochrane library were systematically searched for eligible records. Moreover, clinical guidelines were screened. Studies analyzing tocogram characteristics of uterine rupture during trial of labor after cesarean section were appraised and included by two independent reviewers. Due to heterogeneity, a meta-analysis was only feasible for uterine hyperstimulation.

Results: thirteen studies were included. Three tocogram characteristics were associated with uterine rupture; 1) Hyperstimulation was more frequently observed compared to controls during the entire delivery (38% versus 21% and 58% versus 53%, and in the last two hours prior to birth (19% versus 4%). Results of meta-analysis: OR 1.65; 95% CI 0.95-2.85; p=0.08). 2) Decrease of uterine activity was observed in 14-40%, and 3) an increasing baseline in 10-20%. Five studies documented no changes in uterine activity or Montevideo units. A direct comparison between external tocodynamometer and intra-uterine pressure catheters was not feasible.

Conclusions: uterine rupture can be preceded or accompanied by several types of changes in uterine contractility including hyperstimulation, reduced number of contractions, increased or reduced baseline of the uterine tonus. While no typical pattern has been repeatedly reported, close follow-up of uterine contractility is advised and hyperstimulation should be prevented.

Introduction

There is a worldwide increasing incidence of cesarean sections (CS) [1,2]. Subsequently, there will be a growing number of pregnant women with a previous uterine scar. The high success (76%) of vaginal birth after cesarean section (VBAC) and the degree of maternal and neonatal safety have encouraged physicians and midwives to be supportive of women attempting trial of labor after previous cesarean section (TOLAC) [3,4]. Moreover, VBAC is advocated as a means to control the increasing rates of operative delivery [5]. Despite the excellent outcome, every physician should keep in mind the risk of a uterine rupture. Unfortunately, the incidence of uterine rupture has not declined in the last decades [6]. Women opting for TOLAC have a less than one percent chance on a complete uterine rupture, which is associated with an estimated 10% risk of perinatal mortality [7,8,4,9,10].

The number of repeat CS needed to prevent one uterine rupture is very high [11]. Alternatively, intrapartum monitoring of women during TOLAC could be improved. The classical symptoms of uterine rupture are described as fetal heart rate abnormalities, the onset of severe abdominal pain persisting between contractions, scar tenderness, abnormal vaginal bleeding, hematuria, cessation of previously efficient uterine activity, loss of station of the presenting part and maternal hypotension or shock [12]. Timely diagnosing a uterine rupture remains challenging as these symptoms can appear at a late stage or may not be present at all [13,3,14,15]. In the end, the diagnosis will have to be confirmed or rejected during an emergency CS.

Clinical guidelines concerning TOLAC mainly focus on fetal heart rate abnormalities and clinical signs [16,12]. However, based on the pathophysiology of complete uterine wall separation, changes in the uterine activity can be expected. A defect in the uterine wall reduces wall tension and can therefore lead to a decrease or clipping of intrauterine pressure [17]. Moreover, reduced tension can diminish contractility and influence contraction frequency and/or amplitude [18]. Therefore, uterine activity patterns, monitored by an intra-uterine pressure catheter (IUPC), external tocodynamometer (TOCO) or electrohysterogram (EHG), could potentially provide warning signs of uterine rupture [19].

This systematic review aims to summarize the tocographic characteristics related to uterine rupture during TOLAC. The primary goal is to identify changes in the tocogram preceding or occurring during this emergency event. The secondary goal is to compare TOCO with IUPC.

Material and methods

Sources

This systematic review was conducted according to the PRISMA guidelines. The MEDLINE, EMBASE and the Cochrane library have been systematically searched in September 2016 using the following standardized medical subject headings (MeSH): uterine rupture, obstetric labor, trial of labor, vaginal birth after cesarean, uterine contraction, uterine monitoring, fetal monitoring, cardiotocography, tocogram and related terms presented in the title and abstract. No limits have been used. The full electronic search strategy is available in Appendix 1. Furthermore, the references of paragraphs on intrapartum monitoring during TOLAC available in national and international guidelines (NVOG, ACOG, RCOG, SOGC), as well as the references of the selected articles have been included. To assess eligibility of the studies, two authors (MV, HdL) independently appraised and cross-checked the extracted studies. In case of disagreement, the two reviewers reconsidered the article and made the final decision.

Study selection

A total of 175 articles have been systematically identified after removing duplicates. Table 1 shows a flowchart of the search strategy and selection. We selected studies that featured an analysis of the uterine activity during TOLAC, in term pregnant women with a complete uterine rupture confirmed during CS or during postpartum complications. In each study population, there should be a minimum of 5 cases and at least 50% of the women should have a previous cesarean scar. Articles not in English, case reports, reviews and guidelines were excluded. Because of the limited amount of available evidence, the critical appraisal was restricted to study design, patient selection and analysis of the tocogram. After reading the 46 full-text articles, the reviewers excluded two reports based on patient selection. Since a minority of the women had a previous CS, the case-control study of Sheiner et al. and the study of Chen et al. have been excluded [20,21]. The quality of the articles were assessed using the Newcastle–Ottawa Scale (NOS), which is a quality assessment tool for non-randomized studies for meta-analysis. The NOS contains eight items, which are categorized into three themes: selection (four stars), comparability (two stars), and exposure (three stars). High quality studies achieve seven stars or more, medium quality studies between four and six stars and poor-quality studies less than four stars.

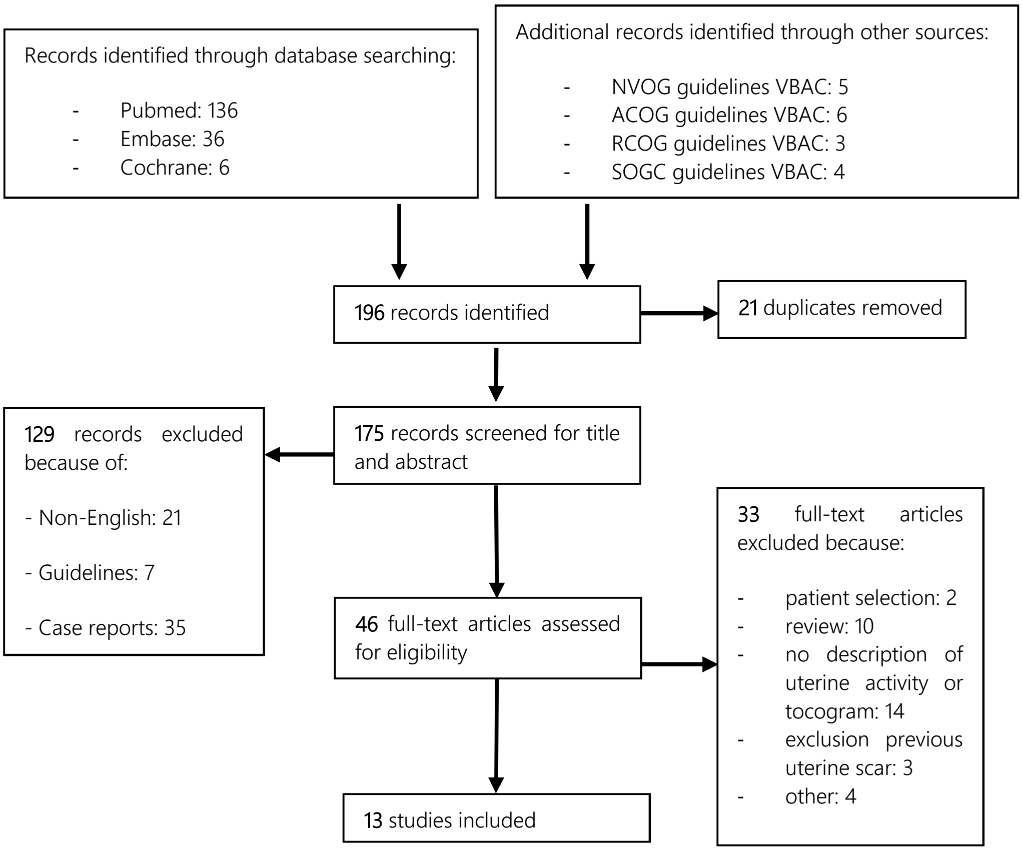

Figure 1: flowchart of the reviewing process

Statistical analysis

Data of all included studies have been extracted and subdivided into a variety of characteristics related to uterine rupture. If not provided, odds ratios and 95% confidence interval (95% CI) was calculated using contingency tables when possible. A meta-analysis was only considered feasible for uterine hyperstimulation during the entire delivery due to the heterogeneity of the included studies with regard to the study design and the observed tocogram characteristics. For one study in the meta-analysis (Goetzl 2001), controls were matched by birth weight, year of delivery and whether labor was induced or augmented. Using the published data, we were not able to correct for matching when calculating the odds ratios. Yet, the effect on the outcome is expected to be minor due to the heterogeneity of the study population in this study. We performed the meta-analysis in RevMan (Revision Manager 5.3 for Windows, Utrecht; Cochrane The Netherlands) and applied a random effects model. Inter-studies heterogeneity was tested using… A p-value of <0.05 was considered statistical significant.

Results

Thirteen studies have been included in this systematic review: one prospective cohort study, six case-control studies and six retrospective cohort studies. The results could be categorized into five main themes: hyperstimulation, decrease in uterine activity, increased baseline, Montevideo units or no changes in tocogram characteristics. An overview of the included studies and their results are shown in Table 1.

Hyperstimulation

The frequency of contractions prior to uterine rupture has been examined in three case-control studies. In the study by Goetzl et al., uterine rupture was more often preceded by an episode of hyperstimulation (defined as >5 contractions per 10 minutes, that resulted in reduced administration of oxytocin) compared to controls: 37.5% and 20.8%, p=0.05, which is on the margin of significance [22]. Odds ratios were not provided. Craver et al. studied hyperstimulation at more than 4, 2-4 and less than 2 hours prior to delivery. Hyperstimulation (defined as >5 contractions per 10 minutes) was more common during the two hours prior to birth: 19% and 4%, p<0.05 (OR 5.9, CI 1.2-28.6) [23]. In contrast, a more recent study of Andersen et al. showed no significant difference in uterine hyperstimulation (>5 contractions per 10 minutes) during labor: 58% in the rupture group versus 53% in controls, p=0.74 [24]. Sub analyses in first/second stage and induced/augmented labor also showed no significant differences. All three case-control studies did not report how the uterine activity patterns were monitored.

Meta-analysis of hyperstimulation

A meta-analysis was performed based on three studies evaluating uterine hyperstimulation during TOLAC in relation to the risk of uterine rupture (see Figure 2). Uterine hyperstimulation during the delivery showed a trend in relation to the risk of uterine rupture: OR 1.64 [95% CI 0.95-2.85] p=0.08. Heterogeinity…. (nog beschrijven i.o.m. Dieleman)

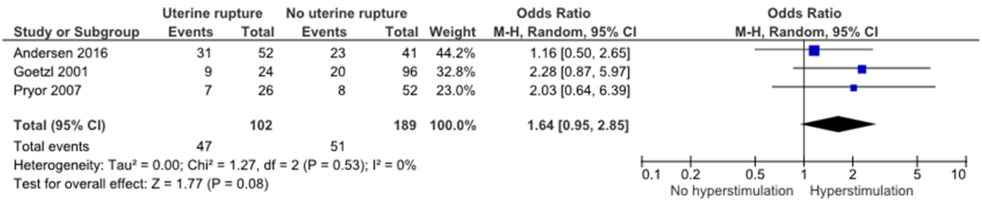

Figure 2:
Review: Tocogram characteristics related to uterine rupture
Comparison: No hyperstimulation and hyperstimulation during trial of labor after previous cesarean section.
Outcome: Risk of uterine rupture

Table 1: Overview of the included studies analyzing tocogram characteristics of uterine rupture during TOLAC. The studies are categorized according to five themes: hyperstimulation, decrease of uterine activity, increasing baseline, Montevideo units and no changes in uterine activity.

Decrease in uterine activity

Study	Design	Population	Toco	Findings	Study characteristics
Zwart 2009	Prospective cohort Netherlands 2004-2006	-Case* N=210, 87% scarred -In 358.874 deliveries	ND	13.6% (25/184) acute absence of contractions	+ Complete uterine rupture + Large nationwide prospective study
Ridge-way 2004	Case-control USA&Sweden 1984-2001	-Case* N=36, 100% scarred -Control N=100, VBAC -In 45.113 deliveries.	ND	Loss of uterine tone: - 1st stage(n=36); 3% (n=1) vs. 0% p=0.27 - 2nd stage(n=14); 0% vs. 0% p= n.a.	+ Complete uterine rupture + 3 independent examiners + Blinded
Arulku-maran 1992	Retrospective cohort Singapore 1985-1990	-Case* N=9, 100% scarred 5/9 complete rupture. -In 722 during TOL	IUPC: 56%	33% (3/9) showed decrease in uterine activity, all registered with IUPC and in absence of other symptoms or signs.	+/- Incomplete and complete uterine rupture. -- Incomplete = intact serosa
Beckley 1991	Retrospective cohort England 1982-1988	-Case* N=10, 100% scarred -In 1.740 during TOL.	IUPC 100%	40% (4/10) show marked fall in uterine activity; 'clipping' off of the pressure peaks.	+ Complete uterine rupture.

Hyperstimulation

Study	Design	Population	Toco	Findings	Study characteristics
Pryor 2007	Case-control USA 1995-2000	-Case* N=26, 100% scarred -Control N=52, VBAC -In 1.896 during TOL.	ND	More hyperstimulation <2h prior to delivery ($p<0.05$): - 19% vs. 4%, OR 5.9 (1.2-28.6), $p<0.05$. Not significant for <4h and 2-4h.	+ Complete uterine rupture + Hyperstimulation = >5/10min -- No correction for significant differences in oxytocin use.
Goetzl 2001	Case-control USA 1984-1996	-Case* N=24, 100% scarred -Control N=96, VBAC -All oxytocin use -In 1.650 primiparas during TOL.	ND	Cases were more likely to have an episode of uterine hyperstimulation. - Overall; 37.5% vs. 20.8%, p=0.05 - Induction; 38.5 vs. 30.8%, p=0.42 - Augmentation; 36.4% vs. 9.1%,p=0.05	+ Hyperstimulation= >5/10 min + Matching cases and controls for induction/augmentation. + Extensive analysis of oxytocin use: no significant difference

Increasing baseline pressure

Study	Design	Population	Toco	Findings	Study characteristics
Zwart 2009	Prospective cohort Netherlands 2004-2006	-Case* N=210, 87% scarred -In 358.874 deliveries	ND	20.2% (38/188) hypertonia	+ Complete uterine rupture + Large nationwide prospective study -- Hypertonia not clearly defined
Rodri-guez 1989	Retrospective cohort USA 1979-1988	-Case* N=76, 79% scarred -In 138.853 deliveries	IUPC: 51%	Increase of baseline uterine tone in 10.2% (4/39) using an IUPC. Decrease of uterine activity was not observed.	+ Complete uterine rupture

No change in uterine activity

Study	Design	Population	Toco	Findings	Study characteristics
Meni-han 1998	Retrospective cohort USA 1990-1995	-Case* N=11, 100% scarred -In 3.353 during TOL.	IUPC: 36%	All normal uterine activity before onset of bradycardia. Decrease or cessation of uterine tone was not observed.	+ Complete uterine rupture
Leung 1993	Retrospective cohort USA 1983-1992	-Case* N=86, 100% scarred -In 11.179 during TOL.	ND	Decrease of uterine tone or cessation of uterine activity has not been observed.	+ Complete uterine rupture + Complete, partial or no fetal extrusion.

* = number of patients with a uterine rupture
- Case* = uterine rupture
- Method = uterine monitoring technique
- + = positive study characteristic
- ~ = negative study characteristic

Decrease in uterine activity

In a large nationwide Dutch prospective cohort study of Zwart et al., acute absence of contractions was reported in 13.6% (25/184) of the cases of uterine rupture [10]. They did not describe the applied uterine monitoring techniques. A smaller case-control study of Ridgeway et al. focused on changes in the fetal heart rate pattern, and in addition described a loss of uterine tone during first stage in a single case (1/36) [14]. Two small retrospective studies of Arulkumaran et al. and Beckley at al. found a decrease of the uterine contraction amplitude in respectively 33% (3/9) and 40% (4/10) of the uterine ruptures, which were all monitored by IUPC [25,26]. Finally, Phelan et al. observed a significantly (p=0.03) lower amount of contractions per hour in ruptures (15.8/hour) compared to VBAC (19.7/hour) [27]. Most of their cases had external fetal monitoring.

Increasing baseline

Zwart et al. observed hypertonia in 20% (38/188) of the uterine ruptures in their large nationwide prospective study [10]. They did not describe their definition of hypertonia nor which uterine monitoring technique (i.e. TOCO or IUPC) was applied. The retrospective study of Rodriguez et al. detected an increased baseline uterine pressure in 10% (n=4) of the cases (n=39) which were monitored with an IUPC [28].

Montevideo units

Montevideo units (MVU) can only be calculated in the presence of an IUPC. In the case-control study of Maggio et al., cases of uterine rupture (n=9) have been compared to successful VBAC (n=48) and failed TOLAC (n=35). They found no association between MVU and uterine rupture in pregnant women undergoing TOLAC. Buhimschi et al. retrospectively reported MVU of uterine ruptures for the comparison of women who received prostaglandins/oxytocin versus oxytocin alone [29]. The average amount of MVU was 205 (range 160-300) per 10 minutes in the oxytocin group compared to 247 (range 140-380) per 10 minutes in the prostaglandin/oxytocin group, during at least one hour prior to rupture [27]. These results were not compared with controls.

No change in uterine activity

Uterine activity patterns of uterine ruptures resulting in permanent severe brain injury have been examined by Phelan et al. [27]. No significant difference in the occurrence of hyperstimulation or tetanic episodes was found. A retrospective study of Menihan et al. focused on both features of fetal heart rates and uterine activity patterns in 11 cases of uterine upture with 36% (4/11) IUPC monitoring; no change in uterine activity was found [30]. Leung et al. analyzed uterine activity amongst numerous other features, and observed no decrease of uterine tone or cessation of contractions in 86 hospitalized cases of uterine rupture. The tocographic method was not described. [31].

Discussion

In this systematic review of the literature, several changes in uterine activity have been identified to be associated with uterine rupture: hyperstimulation, decrease in uterine activity, an increased or reduced baseline tonus. Of these tocogram characteristics, only hyperstimulation could be evaluated in a meta-analysis. showing an increased risk of uterine rupture in case of hyperstimulation, on the margin of significance (p=0.08). Furthermore, in a large prospective study hypertonia was reported in 20% of the cases and acute absence of contractions in 14% [10].

We are aware that the majority of the included studies are of retrospective design (12 out of 13). Since uterine rupture is a relatively rare event, retrospective study designs are commonly used. However, this carries the risk of selection bias. For example, Phelan et al. identified their cases within the National Registry of Brain Injured Babies, including only those uterine ruptures resulting in severe perinatal morbidity or 'silent' uterine ruptures potentially leading to selection bias [27]. The size of the retrospective study populations also showed a strong variation, from 9 up to 86 cases of uterine rupture. The two large retrospective studies showed dissimilar results compared to the single prospective study: Leung et al. (n=86) and Rodriguez et al. (n=39) observed no decrease of uterine activity [31,28], while Zwart et al. revealed acute absence of contractions in 14% of uterine rupture cases (25 out of 184) in their prospective study [10]. Furthermore, our systematic search identified multiple large studies regarding uterine ruptures in which information on the tocogram was not provided. For example, Al-Zirqi et al. (n=94) and Kwee et al. (n=98) identified a total of 192 uterine ruptures, yet both studies did not analyze uterine activity patterns [32,8]. And we excluded the study of Kayani et al. because there was no uterine activity description, while they do report that 'the intrauterine pressure catheters recording have contributed to the diagnosis of uterine rupture' [33]. This could entail publication bias.

In this systematic review, we are interested in tocogram characteristics of complete uterine rupture during TOLAC. Uterine rupture concerns a challenging diagnosis. This is reflected in the diverse definitions of uterine rupture in the included studies. A complete uterine rupture, defined as disruption of all the layers of the uterine wall resulting in direct communication between the uterine cavity and peritoneal cavity, might result in different symptoms than dehiscence of the uterine scar, in which case the serosa is still intact leading to minimal intra-abdominal bleeding and often few or no symptoms. Several studies identified their cases based on the International Classification of Diseases (ICD-9) coding for uterine rupture during labor, which does not discriminate between a complete rupture or dehiscence [23,30,14]. Furthermore, we are aware that not all cases of the included studies concerned women with a previous uterine scar (79% up to 100%). Finally, uterine activity parameters have not been clarified in some studies. For example, Zwart et al. described hypertonia in 20% of the uterine rupture cases, but did not define hypertonia [10]. Whereas studies examining a decrease in uterine activity did not provide a percentage in decrease. Therefore, our systematic review might consist of a mix of both complete and incomplete uterine ruptures, scarred and unscarred uteri, and uterine activity characteristics might be indistinct.

Continuous electronic fetal monitoring is recommended during TOLAC, whilst there is no consensus about the method for monitoring contractions [12,16]. International guidelines concerning TOLAC do not recommend routine use of IUPC's as they do not assist in the diagnosis of uterine rupture [12,16]. Yet, compared to TOCO, an IUPC has the advantage of providing quantitative measurement of uterine resting tone as well as the intensity and MVU of contractions, possibly contributing to the diagnosis of a uterine rupture. Unfortunately, in this systematic review half of the studies do not document their tocographic method, impeding the comparison of the two modalities used for monitoring uterine contractions. Two features of the tocogram however, a decrease in contraction amplitude and increasing baseline pressure, are only observed using an IUPC. Rodriguez et al. noticed an increase of baseline uterine tone in 4 out of 39 women monitored IUPC, while not visible in the 29 women monitored with TOCO [28]. This might indicate that an IUPC is needed to observe these subtle changes in the tocogram. The use of IUPC during TOLAC is not supported by Maggio et al. who found no differences in MVU between uterine ruptures and VBAC [34]. Devoe et al. also revealed no change in uterine tone and peak uterine pressure 2.5 minutes after uterine incision for CS [35]. Possibly, the observed changes can also be influenced by localization of the catheter [25]. The results of this review do not provide solid evidence for the standard use of an IUPC. Nevertheless, this does not negate the need for adequate uterine monitoring during TOLAC.

The observed association of hyperstimulation and uterine rupture have no trivial relation. The relationship could be causal in nature in the sense that hyperstimulation by oxytocin administration leads to increased stress on the uterine scar and eventually failure. Alternatively, failure of the scar could cause an increase in contraction frequency due intra-abdominal causing excitation of the myometrium, in this way preceding a complete rupture. However, based on the physiology of uterine contractions, a decrease rather than an increase in contraction frequency caused by a loss of wall tension is to be expected [36,18]. The combination is also conceivable and could explain why both changes in contraction frequency were observed: hyperstimulation causing rupture of the scar and then leading to a cessation of uterine contractions. It is remarkable that the only study of ruptures with severe neonatal brain injury showed significant less contractions in the uterine rupture group, which might indicate that the disastrous event has already occurred [27]. Finally, it could also be a confounding factor, associated with for instance prolonged deliveries, abnormal fetal presentation or macrosomia. The information available does not permit further analysis of this relationship.

In literature, fetal heart rate abnormality is the most common sign associated with uterine rupture, which has been reported in up to 70% of the cases of uterine rupture [16]. Andersen et al., even revealed that none of the uterine rupture cases had a completely normal CTG according to the International Federation of Gynaecology and Obstetrics (FIGO) guidelines. Only a great number of severe variable decelerations, fetal bradycardia or preterminal CTG were significant pathologic fetal heart pattern to differentiate uterine rupture from successful VBAC [14,24]. We calculated the positive predictive values of several fetal heart rate and uterine activity patterns in the study Ridgeway et al., based on a contingency table and corrected for an estimated uterine rupture prevalence of 1.0%. For example, the estimated positive predictive value for bradycardia in second stage was 8.3%. In addition, the positive predictive value of mild-moderate and severe variable decelerations in first stage was respectively 1.2% and 4.0% [14]. Andersen et al. showed comparable low diagnostic values. This compares to the predictive value of uterine hyperstimulation of 4.8% less than two hours prior to delivery evaluated in the study of Pryor et al. [23]. Hence, an abnormal CTG cannot be considered as a strong predictor of uterine rupture [24]. Physician decision-making should therefore be based on monitoring clinical signs, fetal heart rate patterns and uterine activity during TOLAC [24].

International guidelines report a two- to three-fold increased risk of uterine rupture during induction and augmentation of labor [12,24,37]. This could be related to the increased risk of uterine hyperstimulation due to oxytocin usage. In the study of Craver et al., uterine rupture cases experienced a significant longer duration of oxytocin and maximum dose of oxytocin compared to controls [23]. However, no significant differences in oxytocin were reported by Goetzl et al.[22]. These somewhat contradictory results support to at least closely monitor the use of oxytocin in order to prevent hyperstimulation. Both Craver and Goetzl showed more hyperstimulation (>5 contractions per 10 minutes) in case of uterine rupture compared to VBAC controls [23,22]. Therefore, special attention should be paid to the contraction frequency and to correct the frequency pattern as necessary. Unfortunately, a proper assessment of the uterine activity could not be made in 28% of the cases in last hour prior to uterine rupture in the study of Andersen et al., suggesting substandard care. Moreover, current guidelines do not recommend a strict contraction frequency. Based on our results, we would advise to aim for 3 to 5 contractions per 10 minutes. More than 5 contractions per 10 minutes should be corrected with oxytocin reduction or tocolytic drugs. And if no adequate tocogram can be obtained with TOCO, alternative tocographic techniques like an IUPC or an EHG based method should be considered in order to guarantee adequate uterine monitoring and prevent hyperstimulation [38,39].

Conclusion

Uterine rupture can be preceded or accompanied by several types of changes in uterine contractility including hyperstimulation, reduced number of contractions, increased or reduced baseline tonus. While no typical pattern has been repeatedly reported, we advise close follow-up of uterine contractility for early detection of atypical changes and to prevent hyperstimulation.

References

1. Betran AP, Merialdi M, Lauer JA, Bing-Shun W, Thomas J, Van Look P, Wagner M (2007) **Rates of caesarean section: analysis of global,regional and national estimates.** *Paediatric and perinatal epidemiology* 2007, 21 (2):98-113. doi:10.1111/j.1365-3016.2007.00786.x
2. Gibbons L, Belizán JM, Lauer JA, Betrán AP, Merialdi M, Althabe F **The Global Numbers and Costs of Additionally Needed and Unnecessary Caesarean Sections Performed per Year: Overuse as a Barrier to Universal Coverage.** 2010.
3. Kwee A, Bots ML, Visser GH, Bruinse HW **Obstetric management and outcome of pregnancy in women with a history of caesarean section in the Netherlands.** *European journal of obstetrics, gynecology, and reproductive biology* 2007, 132 (2):171-176. doi:10.1016/j.ejogrb.2006.07.017
4. Landon MB, Hauth JC, Leveno KJ, Spong CY, Leindecker S, Varner MW, Moawad AH, Caritis SN, Harper M, Wapner RJ, Sorokin Y, Miodovnik M, Carpenter M, Peaceman AM, O'Sullivan MJ, Sibai B, Langer O, Thorp JM, Ramin SM, Mercer BM, Gabbe SG **Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery.** *The New England journal of medicine* 2004, 351 (25):2581-2589. doi:10.1056/NEJMoa040405
5. Christmann-Schmid C, Raio L, Scheibner K, Muller M, Surbek D **Back to "once a caesarean: always a caesarean"? A trend analysis in Switzerland.** *Archives of gynecology and obstetrics* 2016, doi:10.1007/s00404-016-4055-4
6. Hofmeyr GJ, Say L, Gulmezoglu AM **WHO systematic review of maternal mortality and morbidity: the prevalence of uterine rupture.** *BJOG : an international journal of obstetrics and gynaecology* 2016, 112 (9):1221-1228. doi:10.1111/j.1471-0528.2005.00725.x
7. de Lau H, Gremmels H, Schuitemaker NW, Kwee A **Risk of uterine rupture in women undergoing trial of labour with a history of both a caesarean section and a vaginal delivery.** *Archives of gynecology and obstetrics* 2011, 284 (5):1053-1058. doi:10.1007/s00404-011-2048-x
8. Kwee A, Bots ML, Visser GH, Bruinse HW **Uterine rupture and its complications in the Netherlands: a prospective study.** *European journal of obstetrics, gynecology, and reproductive biology* 2006, 128 (1-2):257-261. doi:10.1016/j.ejogrb.2006.02.005
9. Landon MB, Leindecker S, Spong CY, Hauth JC, Bloom S, Varner MW, Moawad AH, Caritis SN, Harper M, Wapner RJ, Sorokin Y, Miodovnik M, Carpenter M, Peaceman AM, O'Sullivan MJ, Sibai BM, Langer O, Thorp JM, Ramin SM, Mercer BM, Gabbe SG **The MFMU Cesarean Registry: factors affecting the success of trial of labor after previous cesarean delivery.** *American journal of obstetrics and gynecology* 2005, 193 (3 Pt 2):1016-1023. doi:10.1016/j.ajog.2005.05.066
10. Zwart JJ, Richters JM, Ory F, de Vries JI, Bloemenkamp KW, van Roosmalen J **Uterine rupture in The Netherlands: a nationwide population-based cohort study.** *BJOG* 2009, 116 (8):1069-1078; discussion 1078-1080. doi:10.1111/j.1471-0528.2009.02136.x
11. Guise JM, McDonagh MS, Osterweil P, Nygren P, Chan BK, Helfand M (2004) **Systematic review of the incidence and consequences of uterine rupture in women with previous caesarean section.** *BMJ* 2004, 329 (7456):19-25. doi:10.1136/bmj.329.7456.19
12. **RCOG Guideline: Birth after previous caesarean birth 2007**. *Royal College of Obstetricians and Gynaecologists Londen, United Kingdom*
13. Ayres AW, Johnson TR, Hayashi R **Characteristics of fetal heart rate tracings prior to uterine rupture.** *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2001, 74 (3):235-240
14. Ridgeway JJ, Weyrich DL, Benedetti TJ **Fetal heart rate changes associated with uterine rupture.** *Obstet Gynecol* 2004, 103 (3):506-512. doi:10.1097/01.AOG.0000113619.67704.99
15. Tutschek B, Bender HG, Henrich W **Silent uterine rupture during vaginal delivery successfully managed conservatively.** *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2005, 26 (2):199-200. doi:10.1002/uog.1931
16. ACOG **Practice bulletin no. 115: Vaginal birth after previous cesarean delivery.** *Obstet Gynecol* 2010, 116 (2 Pt 1):450-463. doi:10.1097/AOG.0b013e3181eeb251
17. Gee H, Taylor EW, Hancox R **A model for the generation of intra-uterine pressure in the human parturient uterus which demonstrates the critical role of the cervix.** *Journal of theoretical biology* 1988, 133 (3):281-291
18. Young RC, Goloman G **Mechanotransduction in rat myometrium: coordination of contractions of electrically and chemically isolated tissues.** *Reprod Sci* 2011, 18 (1):64-69. doi:10.1177/1933719110379637
19. de Lau H, Yang KT, Rabotti C, Vlemminx M, Bajlekov G, Mischi M, Oei SG **Toward a new modality for detecting a uterine rupture: electrohysterogram propagation analysis during trial of labor after cesarean.** *J Matern Fetal Neonatal Med* 2016:1-6. doi:10.1080/14767058.2016.1178227
20. Sheiner E, Levy A, Ofir K, Hadar A, Shoham-Vardi I, Hallak M, Katz M, Mazor M **Changes in fetal heart rate and uterine patterns associated with uterine rupture.** *The Journal of reproductive medicine* 2004, 49 (5):373-378

21. Chen KC, Hsieh TT **Rupture of gravid uterus: a eight-year clinical analysis and review of the literature.** *Changgeng yi xue za zhi / Changgeng ji nian yi yuan = Chang Gung medical journal / Chang Gung Memorial Hospital* 1992 15 (1):15-22
22. Goetzl L, Shipp TD, Cohen A, Zelop CM, Repke JT, Lieberman E **Oxytocin dose and the risk of uterine rupture in trial of labor after cesarean.** *Obstetrics and gynecology* 2001 97 (3):381-384
23. Craver Pryor E, Mertz HL, Beaver BW, Koontz G, Martinez-Borges A, Smith JG, Merrill D **Intrapartum predictors of uterine rupture.** *Am J Perinatol* 2007, 24 (5):317-321. doi:10.1055/s-2007-981433
24. Andersen MM, Thisted DL, Amer-Wahlin I, Krebs L **Can Intrapartum Cardiotocography Predict Uterine Rupture among Women with Prior Caesarean Delivery?: A Population Based Case-Control Study.** *PloS one* 2016 11 (2):e0146347. doi:10.1371/journal.pone.0146347
25. Arulkumaran S, Chua S, Ratnam SS **Symptoms and signs with scar rupture--value of uterine activity measurements.** *The Australian & New Zealand journal of obstetrics & gynaecology* 1992, 32 (3):208-212
26. Beckley S, Gee H, Newton JR **Scar rupture in labour after previous lower uterine segment caesarean section: the role of uterine activity measurement.** *British journal of obstetrics and gynaecology* 1991, 98 (3):265-269
27. Phelan JP, Korst LM, Settles DK **Uterine activity patterns in uterine rupture: a case-control study.** *Obstetrics and gynecology* 1998, 92 (3):394-397
28. Rodriguez MH, Masaki DI, Phelan JP, Diaz FG **Uterine rupture: are intrauterine pressure catheters useful in the diagnosis?** *American journal of obstetrics and gynecology* 1989, 161 (3):666-669
29. Buhimschi CS, Buhimschi IA, Patel S, Malinow AM, Weiner CP (2005) **Rupture of the uterine scar during term labour: contractility or biochemistry?** *BJOG* 2005, 112 (1):38-42. doi:10.1111/j.1471-0528.2004.00300.x
30. Menihan CA **Uterine rupture in women attempting a vaginal birth following prior cesarean birth.** *Journal of perinatology : official journal of the California Perinatal Association* 1998, 18 (6 Pt 1):440-443
31. Leung AS, Leung EK, Paul RH **Uterine rupture after previous cesarean delivery: maternal and fetal consequences.** *American journal of obstetrics and gynecology* 1993, 169 (4):945-950
32. Al-Zirqi I, Stray-Pedersen B, Forsen L, Vangen S **Uterine rupture after previous caesarean section.** *BJOG : an international journal of obstetrics and gynaecology* 2010, 117 (7):809-820. doi:10.1111/j.1471-0528.2010.02533.x
33. Kayani SI, Alfirevic Z **Uterine rupture after induction of labour in women with previous caesarean section.** *BJOG* 2005, 112 (4):451-455. doi:10.1111/j.1471-0528.2004.00336.x
34. Maggio L, Forbes J, Carey LL, Sangi-Haghpeykar H, Davidson C **Association of Montevideo units with uterine rupture in women undergoing a trial of labor.** *J Reprod Med* 2014, 59 (9-10):464-470
35. Devoe LD, Croom CS, Youssef AA, Murray C **The prediction of "controlled" uterine rupture by the use of intrauterine pressure catheters.** *Obstetrics and gynecology* 1992, 80 (4):626-629
36. Lammers WJ **The Electrical Activities of the Uterus During Pregnancy.** *Reprod Sci 2012.* doi:10.1177/1933719112446082
37. Rossi AC, Prefumo F **Pregnancy outcomes of induced labor in women with previous cesarean section: a systematic review and meta-analysis.** *Archives of gynecology and obstetrics* 2015, 291 (2):273-280. doi:10.1007/s00404-014-3444-9
38. Euliano TY, Nguyen MT, Darmanjian S, McGorray SP, Euliano N, Onkala A, Gregg AR **Monitoring uterine activity during labor: a comparison of 3 methods.** *Am J Obstet Gynecol* 2013, 208 (1):66 e61-66. doi:10.1016/j.ajog.2012.10.873
39. Vlemminx MW, de Lau H, Vullings R, Peters CH, Oei SG **Electrohysterography. A promising alternative for monitoring contractions.** *Nederlands tijdschrift voor geneeskunde* 2015, 159 (0):A8535

Chapter 8

Towards a new modality for detecting a uterine rupture: electrohysterogram propagation analysis during trial of labor after cesarean

Published in the Journal of Maternal-Fetal and Neonatal Medicine 2017.

de Lau H, Yang KT, Rabotti C, Vlemminx M, Bajlekov G, Mischi M, Oei SG

Abstract

Objective: observational cohort study which aimed to explore the potential of electrohysterogram analysis for detecting a uterine rupture during trial of labor after cesarean. The electrohysterogram propagation characteristics surrounding the uterine scar of six patients with a previous cesarean section were compared to a control group of five patients without a scarred uterus.

Methods: the electrohysterogram was recorded during the first stage of labor using a high-resolution 64 channel electrode grid positioned on the maternal abdomen across the cesarean scar. Based on simulations, the inter-channel correlation and propagation direction were adopted as electrohysterogram parameters for evaluating possible disruption of electrical propagation by the uterine scar.

Results: no significant differences in inter-channel correlation or propagation direction were observed between the group of patients with an intact uterine scar and the control group. A strong predominance of vertical propagation was observed in one case, in which scar rupture occurred.

Conclusions: the results support unaffected propagation of electrical activity through the intact uterine scar tissue suggesting that changes in the electrohysterogram might only occur in case of rupture.

Introduction

Uterine rupture is a rare but serious complication which is closely related to a previous caesarean section (CS) [1-3]. Establishing a uterine rupture is a very challenging diagnosis since the symptoms can be late signs or even completely absent [4-7]. Currently, intrapartum monitoring during trial of labor is limited to assessing the fetal condition and uterine activity by cardiotocography, which is not reliable for detecting a uterine rupture [2, 3, 6]. Reducing the risks involved with attempting trial of labor after CS requires improved monitoring methods during trial of labor. A potential alternative modality is the electrohysterogram (EHG), which entails noninvasive abdominal measurement of the depolarizations of uterine smooth muscle cells. Synchronized uterine contraction arises from cell to cell propagation of action potentials through the myometrium [8]. The presence of scar tissue or rupture of this scar could interrupt propagation of action potentials or locally change the propagation direction by disruption of the vertical propagation pathway.

Little is known about the physiological propagation patterns in the unscarred lower uterine segment and the conductive properties of scar tissue in the myometrium. In cardiac muscle, scar tissue created by surgical incisions is used as a method for interrupting propagation, in order to prevent macro reentry circuits [9]. Smooth muscle, on the other hand, is considered to have considerable regenerative capacity and histological studies of scar tissue after CS have found the normal tissue architecture to be mostly restored [10]. The EHG has been demonstrated to have great potential for characterizing electrical propagation [11]. In previous work, we analyzed propagation patterns by means of a grid of 64 closely spaced electrodes [12-14]. The square arrangement of the electrodes in this grid allows estimation in all possible directions [15]. In addition, a small inter-electrode distance permits tracking the course of electrical propagation through the electrode grid.

This study aimed at exploring the potential of electrohysterogram propagation analysis for detecting a uterine rupture. The primary goals were to determine the feasibility of EHG recording over the lower uterine segment and to study the baseline propagation characteristics of an intact uterine scar during trial of labor after cesarean in comparison with a control group.

Methods

Study protocol

A prospective observational cohort study was performed at the Máxima Medical Center Veldhoven, the Netherlands. Approval from the local medical ethical board was issued the 8th of May 2013 under registration number NL43294.015.13. All the included women provided written informed consent for study participation. Six patients with a single previous caesarean section and five patients without uterine scar as control were enrolled.

Inclusion criteria were:

- first stage of labor: fully effaced cervix, dilatation ≥ 1 cm, ≥ 3 contractions / 10 minutes
- singleton pregnancy
- epidural analgesia
- foley bladder catheter

As an additional inclusion criterion for the group with a previous CS, the gestational age of the previous CS had to be within two weeks of the current delivery in order to avoid differences in position of the uterine scar. Operation techniques other than a horizontal incision in the lower uterine segment were excluded. Furthermore, patients with previous multiple gestations were excluded.

Measurements from all enrolled patients were obtained using a high-density electrode grid of 62 by 62 mm, containing 64 monopolar electrodes. The scar on the skin was the reference to determine the location of the uterine scar underneath. The grid was positioned in the midline of the abdomen and centered over the scar, see figure 1. A reference electrode was positioned on the left hip. Additionally an 3D accelerometer was used to record maternal movement plus an external tocodynamometer for contraction detection. All signals were recorded using a Refa multichannel amplifier (TMS International, Enschede, The Netherlands).

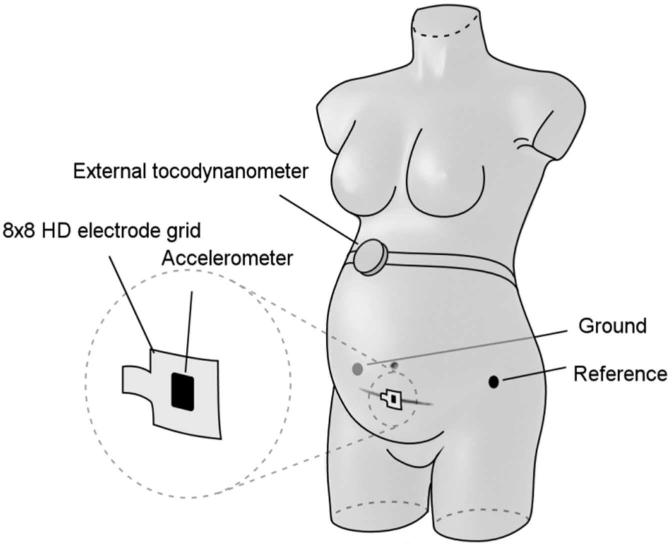

Figure 1: positioning of the sensors on the maternal abdomen. The 64 channel electrode grid was positioned in the midline of the abdomen and centered over the scar. An external reference electrode was positioned on the left hip. In addition, an accelerometer was attached to the electrode grid and an external tocodynamometer was used.

Signal analysis

As a first step, simulated EHG signals were constructed that emulated different scenarios of altered electrical propagation caused by the presence of non-conducting uterine scar tissue. A wave front propagating through a 64 channel electrode grid was simulated, either interrupted midway by the scar tissue or circulating around the uterine scar. In addition, a simulation of a horizontally travelling wave front was included which was not impeded by the virtual scar tissue. These simulated signals served to test multiple EHG parameters in their ability to detect altered propagation caused by a conduction block. Both in simulations of an interrupted or a circulating wave front, the signals of the channels on each side of the simulated scar tissue were less correlated in the time domain. The correlation between vertical pairs of adjacent electrodes was found to be most sensitive for detecting interruption of propagation. However, only estimation of the conduction velocity (CV) vector could correctly identify a horizontal propagation direction. Based on these simulations, two EHG parameters were adopted for signal analysis: inter-channel linear correlation in the time domain and CV analysis based on single spike propagation [12]. We hypothesized that an conduction block caused by the presence of scar tissue would result in the inter-channel correlation to be lower for the middle area of the electrode grid and the propagation direction to be predominantly horizontal rather than variable.

Analysis of propagation direction requires the phase of the propagating EHG signal to be unaffected, necessitating a monopolar electrode configuration. To this end, all 64 monopolar signals were referred to an external reference channel not containing EHG signal. In order to minimize the influence of maternal respiration and ECG, all EHG signals were band-pass filtered between 0,35 and 0,8 Hz and downsampled to 20 Hz [16]. Figure 2 shows an overview of the sensors used, the selection of contraction segments and the multi-channel analysis of the EHG. Segments containing artefacts were identified based on the accelerometer and removed from the analysis. Contractions were manually selected based on either the external tocodynamometer, when available, or the estimated intra uterine pressure (eIUP). The method for deriving the eIUP was a root mean square based method similar to the one described by Jezewski et al. [17, 18], only using the frequency band 0,35 – 0,80 Hz. A minimum of three and a maximum of four contractions were selected for each patient.

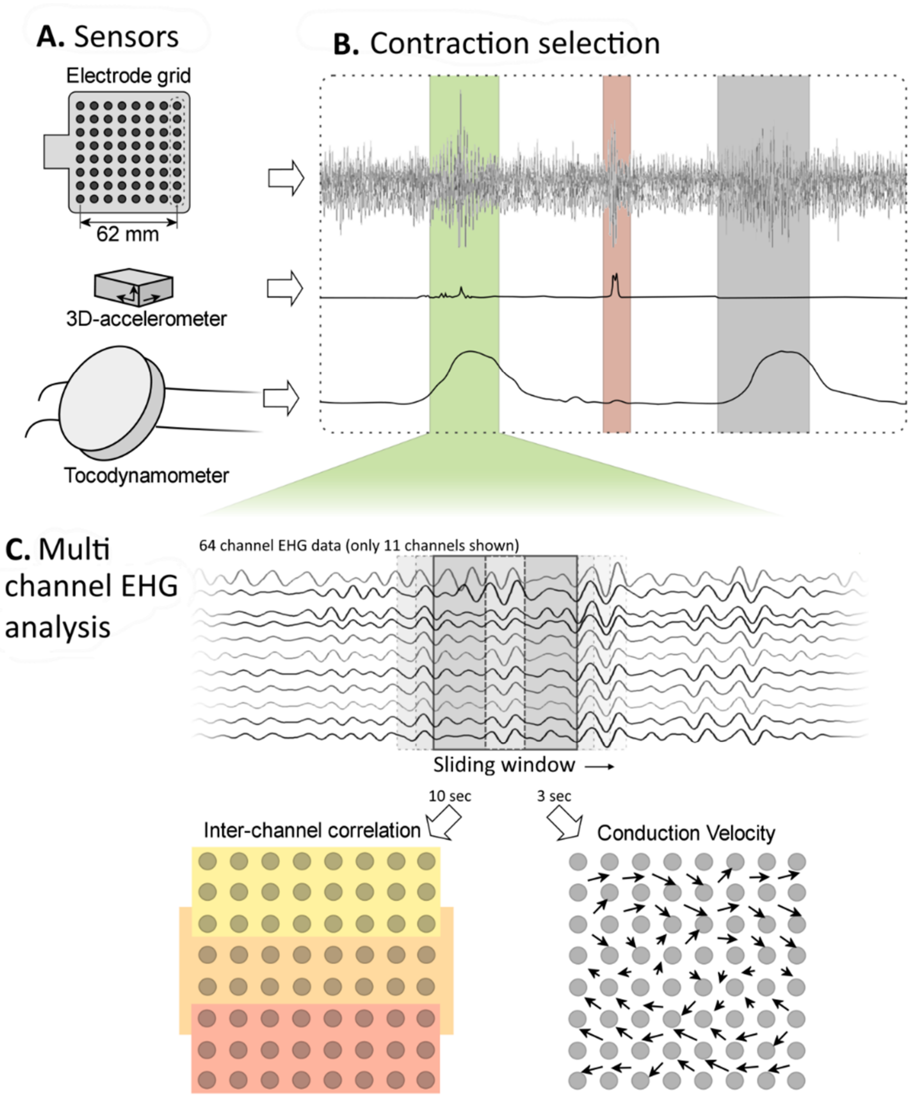

Figure 2:
Schematic representation of the methods for signal analysis. The EHG was recorded using a 64 channel electrode grid (A. Sensors). The external tocodynamometer was used for identifying contractions, while the accelerometer recorded maternal movement (B. Contraction selection). Within the selected contraction segments, the mean correlation between vertical and horizontal adjacent electrode pairs was calculated for three areas of the grid, shown as the yellow, orange and red zones. The conduction velocity was calculated in squares of four adjacent electrodes, resulting in 49 vectors (C. Multi channel EHG analysis). Subsequently, the amplitude and angles of these vectors were averaged and the propagation was categorized as horizontal or vertical.

The inter-channel correlation was calculated in a sliding window of 10 seconds by means of the Pearson product-moment correlation coefficient between horizontal or vertical pairs of two adjacent electrodes, thereby obtaining two sets of 56 values per window. Channels containing large artefacts or with a low signal-to-noise ratio were discarded. In case of one neighboring missing channel, the correlation with the next electrode was calculated. In case of two or more missing channels, the channels were discarded. The electrode grid was divided in three areas, corresponding to the electrodes above, over, and below the uterine scar. The mean inter-channel correlation was calculated for all three areas of the grid, both for the horizontal and vertical pairs of electrodes.

The CV vector was estimated in each square of four adjacent electrodes, resulting in 49 values sampled every 50 ms. The time difference between every channel pair was determined by maximizing the normalized cross-correlation between two offset signals in a sliding window of 3 s. A shorter time window was used to account for a highly variable direction of propagation. The time differences were limited to a range corresponding to a velocity between 3 cm/s and 30 cm/s for propagation within an angle of 120° around the direction of each electrode pair. Along each pair, a vector of observed velocity was calculated from their time difference and electrode positions. A plane wave propagation front was fitted through these individual vectors, resulting in a CV vector. The root mean square error of the fit was used to discard observations with an error exceeding the amplitude of the CV. Fits based on less than three vectors were discarded as well. The CV amplitude and angle were averaged independently over all 49 observations for each time step, preserving the CV amplitude in a noisy signal. Finally, the resulting CV angle was categorized as horizontal or vertical depending whether it was within 45 degrees of the horizontal or vertical axis.

Statistical analysis

Mean values of inter-channel correlation for the three areas of electrodes were derived. Furthermore, the mean CV amplitude and the distribution of horizontal and vertical propagation was calculated for each patient. Levene's test was applied to test for equal variances in the scar and control group. An one way ANOVA was used to test for significant differences in the results on inter-channel correlation between groups of electrodes, within the scar and control group. Differences between CV amplitude and propagation direction were also tested for significance, comparing the results from the scar and control group using one way ANOVA. A sample size of 10 patients resulted in a power ($1 - \beta$) of 0.80 to detect an effect size of 1.72, allowing for a type I error rate (α) of 0.05. This effect size was based on the inter-channel correlation of simulated EHG signals circulating around the uterine scar. A worst case estimate of the standard deviation was assumed, considering the correlation of channels containing white noise only. The alpha was set to 0,05 for all statistical tests.

Results

In total, 11 patients in the first stage of labor were included in the study: six patients with a previous CS and five patients without scarred uterus as control. Rupture of the uterine scar occurred in one patient that was part of five pilot measurements which were recorded just prior to inclusion of the main body of patients. Uterine rupture entailed complete separation of the uterine wall with clinical symptoms [3]. This patient had a history of a CS and labor was induced at term by amniotomy and administration of oxytocin. Two hours prior to the measurement, the medical record states complaints of increased abdominal pain despite previously adequate pain relief by epidural analgesia. Approximately an hour following the measurement, decelerations were noted in the fetal heart rate tracing. The decision was made for a secondary CS for arrest of labor at 7 cm despite an adequate and regular contraction rate of 3-4 contractions per 10 minutes. Approximately three hours after the measurement, a uterine rupture was found during the CS: the peritoneal cavity was filled with hemorrhagic amniotic fluid and a 2-3 cm defect was visible at the left side of the location of the uterine scar. Supplemental digital content s1 shows a brief outline of the patient characteristics.

Table 1: Patient characteristics. Mean values are shown for both groups plus the uterine rupture case. The range is shown in parentheses.

	Intact scar	Control	Uterine rupture
Gestational age	41+2 (40+0 – 42+2)	40+1 (38+3 – 41+6)	40+2
Maternal age	33 (29 – 38)	32 (27 – 37)	35
BMI	27,8 (21,2 – 37,7)	22,4 (19,2 – 31,6)	22,7
Parity	1,2 (1 – 2)	0,4 (0 – 1)	1
Years since previous CS	2,64 (1,4 – 4,2)	NA	2,69
Augmention of labor	5 (100%)	3 (60%)	Yes
Secondary CS	60%	20%	Yes
Fetal birth weight	3649 gram (3230 – 4380)	3850 gram (2990 – 4485)	3145 gram

Two examples of recorded EHG signals, in which bursts of activity are visible that correspond to contractions in the tocogram, are shown in figure 3. In total, 40 contractions were analyzed. Levene's test did not show significance in any of the outcomes, thereby supporting equal variances in the intact scar and control group. Based on the observed standard deviation, the post hoc analysis showed sufficient achieved power. In both groups, the inter-channel correlation in the middle area was similar to the upper- and lower areas of electrodes (figure 4, upper panel). All observed differences were non-significant.

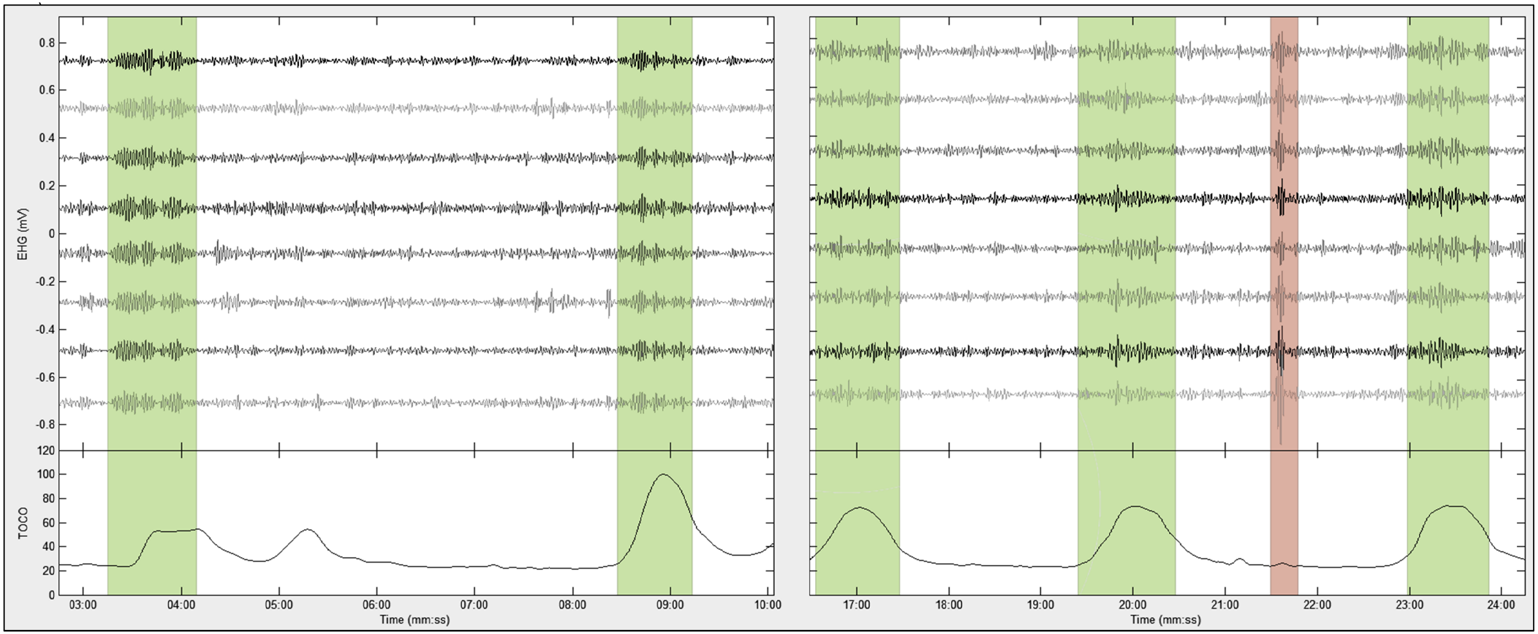

Figure 3: two examples of measured EHG signals. The left panel shows part of a recording of a women with a previous CS. The recording in the right panel is from a patient of the control group. In the top graph, the EHG signals of one row of (eight) electrodes are shown. Signals are filtered between 0.35 – 0.80 Hz. The bottom graph shows the corresponding tocogram (external tocodynamometer). Bursts of activity are visible in the EHG signals that correspond to the contractions in the tocogram. The signal amplitude during contractions is approximately 0,1 mV p-p. The green bars indicate the contraction segments that were selected for calculation of the inter-channel correlation and the conduction velocity. The red bar in the right panel indicates a movement artefact.

The average amplitude of the CV vector was similar for the intact scar and control group as well as in the case of uterine rupture (figure 4, lower panel). The small difference between the intact scar and control group was non-significant. The angle of the CV vector was evenly distributed in patients of both groups between horizontal and vertical direction. In the EHG signal of the patient in which uterine rupture occurred, an abnormal propagation pattern was observed showing a strong predominance of vertical propagation.

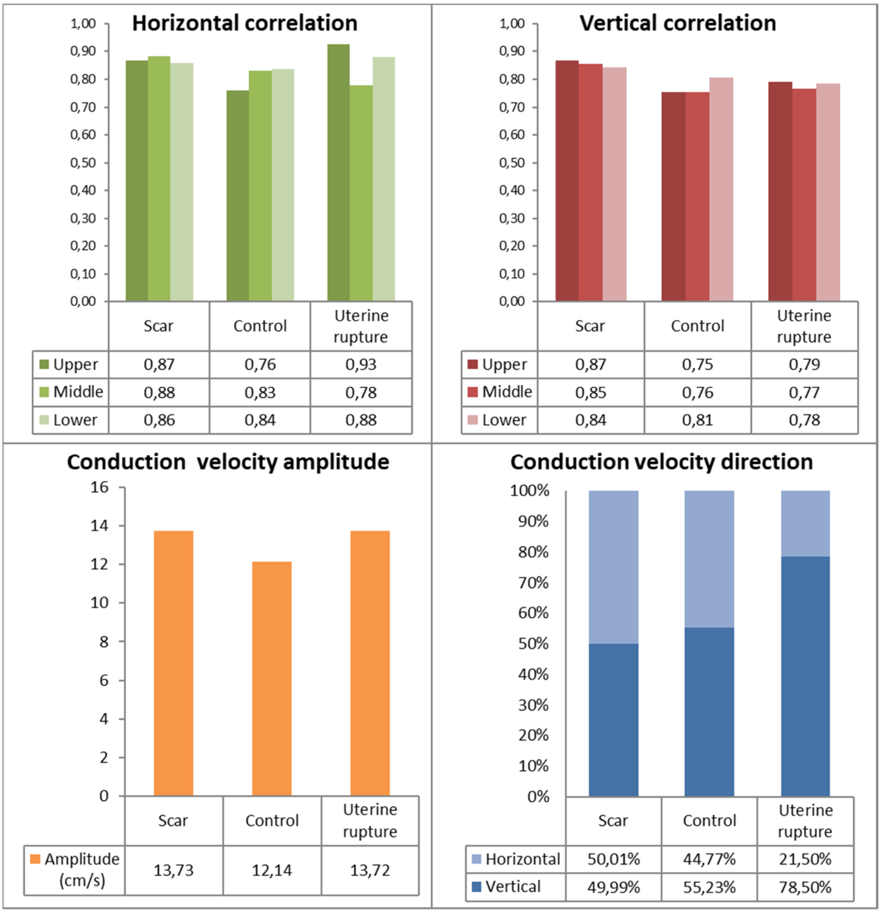

Figure 4: Upper panel: results of inter-channel correlation in the time domain using horizontal and vertical pairs of electrodes. Results are averaged in three areas of the grid, corresponding to the electrodes above, over and below the uterine scar respectively. Observed differences between the different areas, were non-significant within both groups. Lower panel: Results on conduction velocity amplitude and angle. The mean amplitude of the CV vector per group is shown in the left panel. The estimated CV vector angles were categorized as horizontal and vertical and the mean distribution is shown on the right. Results were compared between the scar and control group and the observed differences were non-significant.

Discussion

This study aimed to explore the potential of EHG propagation analysis for detecting a uterine rupture during trial of labor. The baseline propagation characteristics of an intact uterine scar were studied and compared to a control group to understand the effect of scar tissue on electrical propagation. The EHG was recorded using a high-resolution electrode grid positioned over the lower uterine segment across the scar. Based on simulations, inter-channel correlation and the CV vector were adopted as EHG parameters for evaluating possible disruption of electrical propagation. The measurements show that EHG signals can be recorded in the lower uterine segment. No significant differences in inter-channel correlation or propagation direction were observed between the group of patients with an intact uterine scar and the control group. Therefore, the results support unaffected propagation of electrical activity by the intact uterine scar tissue. In contrast, a strong predominance of vertical propagation was observed in the uterine rupture case.

In line with EHG signals recorded at other locations of the uterus during term labor, the signals obtained from the lower uterine segments showed typical bursts of activity alternated by quiescent periods. These bursts clearly corresponded to the contractions visible in the tocogram and showed a good inter-channel correlation. The signal within these bursts was found to propagate through the electrode grid at a velocity that was in the range of values found in electrophysiological [19-22] and previous clinical studies [14, 16]. However, recording the EHG from the lower uterine segment is challenging especially considering the gradual thinning of the lower uterine segment during the first stage of labor. This requires extra care for obtaining an optimal electrode-skin contact to ensure optimal signal quality.

The results on inter-channel correlation showed comparable values for the three areas of the grid in all cases. Based on simulations, in case of interruption of electrical activity by the scar, the results on correlation were expected to be lower for the middle area of electrodes representing the electrical activity of the uterine scar tissue. However, this effect on correlation by the scar tissue might be local and therefore sensitive to placement of the electrode grid. In order to achieve an optimal approximation of the location of the uterine scar underneath, the scar on the skin was used as reference for placement of the electrode grid over the uterine scar. Moreover, to avoid differences in scar height, all patients in the scar group had a previous transverse incision in the lower uterine segment at a gestational age within two weeks of the gestational age at the time of recording. Finally, to account for possible remaining inaccuracy in positioning the electrode grid, the middle area of the grid spanned multiple rows of electrodes. A local effect by the scar tissue in inter-channel correlation may have been reduced by using multiple rows. However, also in the individual results of electrode pairs on correlation, no trend indicating lower correlation in the middle was evident.

Analysis of the local propagation direction might be less sensitive for misplacement of the electrode grid over the uterine scar and therefore more suitable for a clinical application of detecting failure of a uterine scar during labor. The propagation direction proved to be variable in both the scar and control group and was evenly distributed between a horizontal and vertical direction of propagation. This is in line with previous analysis of propagation direction [16, 19, 23] and consistent with previous studies on the electrophysiology of the uterus in which no fixed pacemaker location has been identified [13, 22, 24-26]. This finding, in combination with the results on the inter-channel correlation, does not show any disruption of propagation by an intact uterine scar implicating that EHG changes might only occur in case of rupture. However, in a follow up study the sample size should be adequate in order to discern possible inter-patient variation in wound healing [27].

In order to explore the propagation pattern preceding failure of a uterine scar, one case of uterine rupture was included. The diagnosis was confirmed over three hours after the measurement during CS; therefore, the exact status of the uterine scar during the measurement could not be fully ascertained. However, the observed clinical signs (arrest of labor, increased abdominal pain despite epidural analgesia, and decelerations in the fetal heart rate tracing) suggest that the scar might already have ruptured at the time of the measurement. In this recording, a strong predominance of vertical propagation was found. Horizontal propagation is to be expected if the rupture would be located underneath the electrodes. Moreover, no lower values for inter-channel correlation were found in the middle rows using vertical pairs. It should be noted that only 16 channels out of 64 were recorded for this case, resulting in an interelectrode distance of 17,7 mm. The lower spatial resolution may have reduced the sensitivity for detecting interruption of propagation. During the surgery, it was established that the uterine scar had ruptured on the left side and therefore was possibly located entirely next to the electrode grid. This could have resulted in local conduction to be predominantly vertical in this case by propagation fronts circumventing or circulating around the defect in the uterine scar. In general, rupture can occur in any part of the uterine scar and can result in an oval shaped defect. Therefore, any dominant direction of propagation might indicate a uterine rupture. Since the intact uterine scar tissue does not appear to influence the propagation of electrical activity, and an abnormal propagation pattern was found in case of uterine rupture, EHG changes might only occur in case of rupture of the uterine scar.

In order to reliably detect a change in propagation direction caused by failure of the scar during labor, the size of the electrode grid should be adapted to cover a larger part of the uterine scar. This study was limited to the use of linear propagation models of cell to cell propagation. In addition, non-linear models can be considered as these might provide more accurate results [28-30].

Conclusion

The observed propagation patterns in the lower uterine segment support unaffected propagation of electrical activity through the intact uterine scar suggesting that changes in the EHG might only occur in case of failure of the scar. This study motivates further research in a larger group of patients since advanced analysis of the EHG propagation pattern could potentially provide detection of scar rupture during trial of labor after cesarean.

References

1. Lydon-Rochelle M, Holt VL, Easterling TR, Martin DP: **Risk of uterine rupture during labor among women with a prior cesarean delivery**. *N Engl J Med* 2001, **345**(1):3-8.
2. Zwart JJ, Richters JM, Ory F, de Vries JI, Bloemenkamp KW, van Roosmalen J: **Uterine rupture in The Netherlands: a nationwide population-based cohort study**. *BJOG* 2009, **116**(8):1069-1078; discussion 1078-1080.
3. Kwee A, Bots ML, Visser GH, Bruinse HW: **Uterine rupture and its complications in the Netherlands: a prospective study**. *European journal of obstetrics, gynecology, and reproductive biology* 2006, **128**(1-2):257-261.
4. Ayres AW, Johnson TR, Hayashi R: **Characteristics of fetal heart rate tracings prior to uterine rupture**. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2001, **74**(3):235-240.
5. Kwee A, Bots ML, Visser GH, Bruinse HW: **Obstetric management and outcome of pregnancy in women with a history of caesarean section in the Netherlands**. *European journal of obstetrics, gynecology, and reproductive biology* 2007, **132**(2):171-176.
6. Ridgeway JJ, Weyrich DL, Benedetti TJ: **Fetal heart rate changes associated with uterine rupture**. *Obstet Gynecol* 2004, **103**(3):506-512.
7. Tutschek B, Bender HG, Henrich W: **Silent uterine rupture during vaginal delivery successfully managed conservatively**. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2005, **26**(2):199-200.
8. Lammers WJ: **The electrical activities of the uterus during pregnancy**. *Reprod Sci* 2013, **20**(2):182-189.
9. Cox JL, Schuessler RB, D'Agostino HJ, Jr., Stone CM, Chang BC, Cain ME, Corr PB, Boineau JP: **The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure**. *The Journal of thoracic and cardiovascular surgery* 1991, **101**(4):569-583.
10. Schwarz OH, Paddock R: **The cesarean scar**. *American Journal of Obstetrics & Gynecology* 1925, **10**(2):153-171.
11. Rabotti C, Mischi M: **Propagation of electrical activity in uterine muscle during pregnancy: a review**. *Acta Physiol (Oxf)* 2015, **213**(2):406-416.
12. de Lau H, Rabotti C, Bijloo R, Rooijakkers MJ, Mischi M, Oei SG: **Automated conduction velocity analysis in the electrohysterogram for prediction of imminent delivery: a preliminary study**. *Comput Math Methods Med* 2013, **2013**:627976.
13. Rabotti C, Mischi M, Oei SG, Bergmans JW: **Noninvasive estimation of the electrohysterographic action-potential conduction velocity**. *IEEE Trans Biomed Eng* 2010, **57**(9):2178-2187.
14. van 't Hooft J, Rabotti C, Oei SG: **Electrohysterographic evaluation of preterm contractions in a patient with a unicornuate uterus**. *Acta obstetricia et gynecologica Scandinavica* 2013, **92**(6):730-733.
15. Rabotti C, Oei SG, van 't Hooft J, Mischi M: **Electrohysterographic propagation velocity for preterm delivery prediction**. *Am J Obstet Gynecol* 2011, **205**(6):e9-10; author reply e10.
16. de Lau H, Rabotti C, Bijlo R, Rooijakkers MJ, Mischi M, Oei SG: **Automated conduction velocity analysis in the electrohysterogram for prediction of imminent delivery: a preliminary study**. *Computational and Mathematical Methods in Medicine* 2013, **2013**:7.
17. Jezewski J, Horoba K, Matonia A, Wrobel J: **Quantitative analysis of contraction patterns in electrical activity signal of pregnant uterus as an alternative to mechanical approach**. *Physiol Meas* 2005, **26**(5):753-767.
18. Rooijakkers MJ, Rabotti C, Oei SG, Aarts RM, Mischi M: **Low-complexity intrauterine pressure estimation using the Teager energy operator on electrohysterographic recordings**. *Physiol Meas* 2014, **35**(7):1215-1228.
19. Lammers WJ, Arafat K, el-Kays A, el-Sharkawy TY: **Spatial and temporal variations in local spike propagation in the myometrium of the 17-day pregnant rat**. *Am J Physiol* 1994, **267**(5 Pt 1):C1210-1223.
20. Lammers WJ, Mirghani H, Stephen B, Dhanasekaran S, Wahab A, Al Sultan MA, Abazer F: **Patterns of electrical propagation in the intact pregnant guinea pig uterus**. *Am J Physiol Regul Integr Comp Physiol* 2008, **294**(3):R919-928.
21. Miller SM, Garfield RE, Daniel EE: **Improved propagation in myometrium associated with gap junctions during parturition**. *Am J Physiol* 1989, **256**(1 Pt 1):C130-141.
22. Parkington HC, Harding R, Sigger JN: **Co-ordination of electrical activity in the myometrium of pregnant ewes**. *Journal of reproduction and fertility* 1988, **82**(2):697-705.
23. Mikkelsen E, Johansen P, Fuglsang-Frederiksen A, Uldbjerg N: **Electrohysterography of labor contractions: propagation velocity and direction**. *Acta obstetricia et gynecologica Scandinavica* 2013, **92**(9):1070-1078.
24. Wolfs G, van Leeuwen M, Rottinghuis H, Boeles JT: **An electromyographic study of the human uterus during labor**. *Obstet Gynecol* 1971, **37**(2):241-246.
25. Kao CY: **Long-term observations of spontaneous electrical activity of the uterine smooth muscle**. *Am J Physiol* 1959, **196**(2):343-350.
26. Wolfs G, Rottinghuis H: **Electrical and mechanical activity of the human uterus during labour**. *Archiv fur Gynakologie* 1970, **208**(4):373-385.

27. Buhimschi CS, Zhao G, Sora N, Madri JA, Buhimschi IA: **Myometrial wound healing post-Cesarean delivery in the MRL/MpJ mouse model of uterine scarring**. *The American journal of pathology* 2010, **177**(1):197-207.
28. Diab A, Hassan M, Marque C, Karlsson B: **Performance analysis of four nonlinearity analysis methods using a model with variable complexity and application to uterine EMG signals**. *Medical engineering & physics* 2014, **36**(6):761-767.
29. Diab A, Hassan M, Boudaoud S, Marque C, Karlsson B: **Nonlinear estimation of coupling and directionality between signals: application to uterine EMG propagation**. *Conf Proc IEEE Eng Med Biol Soc* 2013, **2013**:4366-4369.
30. Hassan M, Terrien J, Muszynski C, Alexandersson A, Marque C, Karlsson B: **Better pregnancy monitoring using nonlinear correlation analysis of external uterine electromyography**. *IEEE Trans Biomed Eng* 2013, **60**(4):1160-1166.

Chapter 9

Towards improving uterine electrical activity modeling and electrohysterography: ultrasonic quantification of uterine movements during labor

Published in Acta Obstetricia et Gynecologica Scandinavica 2013.

de Lau H, Rabotti C, Haazen N, Oei SG, Mischi M

Abstract

The electrohysterogram is a potential new tool for diagnosing preterm labor. The parameters derived from the electrohysterogram may be influenced by movement of the uterus. An observational study was performed quantifying uterine movement during labor as a first step towards improving the analysis of the electrohysterogram for predicting preterm labor. The uterine wall was continuously tracked by ultrasound imaging during the first stage of labor while an accelerometer recorded external abdominal accelerations. Recordings from 6 women were used for analysis. In all patients a cyclic cranial-caudal movement of the uterine wall, caused by maternal respiration, was observed. This movement was reported and quantified in this study for the first time. The average frequency, amplitude, and peak speed were 0.27 ±0.07 Hz, 0.68 ±0.84 cm, and 1.04 ±1.20 cm/s, respectively. The signal recorded by the accelerometer placed on the abdomen correlates with the uterine movement and therefore can possibly provide a reference for removing movement induced artifacts. The next step will be to model and measure the effect of uterine movement on the electrohysterogram parameters and finally make the measurements more robust to movement artifacts.

Introduction

The electrohysterogram (EHG) is a noninvasive measurement of the electrical activity underlying uterine contractions. The EHG can be measured by electrodes placed on the abdomen; each electrode records the electrical activity of the myometrium underneath the electrode. Previous literature demonstrated that the EHG is a potential new diagnostic tool for monitoring labor, discriminating between physiological and pathological contractions, thereby supporting timely treatment of preterm labor [1-5].

Unfortunately, the introduction in the clinical practice of diagnostic tools based on the EHG is hampered by a lack of understanding of the link between the action potentials initiating (preterm) labor and the EHG signal recorded on the skin surface. The propagation of action potentials originating in myometrial cells and the resulting EHG signal measured on the skin surface builds on several complex processes; the signal propagates from cell to cell within the myometrium [6] and through the tissue layers underneath the skin [7]. Furthermore, tissue layers can vary in thickness and move mutually as well. All these factors affect the measured EHG signal and make its interpretation challenging.

The international BioMod UE_PTL project (Biophysical Modeling of the Uterine Electromyogram for understanding and preventing Preterm Labor [8]) focuses on multi-scale modeling to understand the link between the electrical activity at the cell level and the EHG signal recorded on the skin [9]. The ultimate objective is providing the necessary knowledge for a new EHG-based tool for the diagnosis of preterm labor.

As part of the BioMod UE_PTL project, this study focuses, for the first time, on continuous measurement of the mechanical activity of the myometrium by abdominal ultrasound (US). Our primary objective is to observe myometrial changes and movements during labor as a first step to improve in the future the interpretation of the EHG signal measured on the skin surface during pregnancy and labor.

Patients and Methods

An observational study was performed. Approval was obtained by the local medical ethical board and written informed consent was acquired. The study was conducted according to the principles of the Declaration of Helsinki (59th WMA General Assembly, October 2008). Inclusion criteria were women in the first stage of labor, singleton pregnancy, a gestational age of at least 37 weeks, and finally epidural analgesia. Only women with epidural analgesia were included due to the need to remain still in order to obtain high quality US images. The target inclusion size was 10 patients. It was not possible to perform a power analysis. The mechanical activity of the myometrium was continuously assessed by abdominal US measurements. An Aloka SSD 100 US scanner (Hitachi Aloka Medical, Tokyo, Japan) was used in B-mode (2D mode) in combination with a 6 MHz abdominal convex probe. The US probe was placed perpendicular to the skin. A position was chosen just below the umbilicus and close to the midline of the abdomen in order to obtain optimal contrast between the uterine wall and the surrounding tissues and to measure the myometrium underneath our standard position for EHG electrode placement [10]. Both sagittal and transversal US recordings were obtained for a minimum of 3 contractions for each patient. A tocodynamometer was positioned above the umbilicus to record contractions and provide a reference by the standard clinical monitoring method. Finally, a 3D accelerometer was placed on the maternal abdomen close to the US probe, enabling the measurement of the accelerations of the abdominal surface, thereby indirectly capturing movement of the abdominal surface in three directions, x, y, and z. The B-Mode US recordings, digitized at 25 frames/s, the tocodynamometer, and the measured accelerations were stored on a computer for further analysis.

Uterine movement was analyzed by the following procedure. US data were first visually inspected to exclude frames that contained out-of-plane probe movements. In order to estimate uterine movement, selected portions of the US image were followed over time using a speckle tracking algorithm based on 2D cross correlation, see [11] for a more detailed description. Based on the assumption that subcutaneous tissue does not move relative to the skin, the displacement of both uterus and subcutaneous tissue were tracked in order to compensate for small movements of the probe. The speckle tracking algorithm was independently applied to the subcutaneous tissue layer and to the uterine layer. The uterine movement U(t) was estimated by subtracting the displacement of the subcutaneous tissue layer from the displacement of the uterus. For each participant the peak frequency and the average amplitude of the uterine movement were calculated. The peak speed was then derived based on a sinusoidal movement.

The z-axis, perpendicular to the skin surface, of the 3D accelerometer was used in order to correlate the amplitude of the measured abdominal acceleration, A(t), and the amplitude of the uterine movement, U(t). The correlation between A(t) and U(t) was quantified by the maximum of the normalized cross-correlation function, ρ. The correlation between A(t) and U(t) was calculated also in the frequency domain. Oscillatory uterine movements were observed in all patients which were considered to be induced by maternal respiration. Therefore band-pass filtering was applied to U(t) in the frequency band corresponding to respiration frequencies [0.17 Hz- 0.67 Hz]. The Pearson correlation coefficient, r, between the power density spectra of U(t) and A(t) was calculated. Finally, the peak frequency of both signals was compared and the Wilcoxon signed-rank test was used to test for statistical significance.

Results

A total of nine women were enrolled into the study, of them three were excluded from further analysis. One measurement was stopped upon request of the women, one measurement was stopped because fetal bradycardia was detected during the measurement and, finally, one measurement could not be analyzed because of inadequate US quality. The gestational age ranged from 37+5 to 40+5, the body mass index from 22,0 to 25,6 and the cervical dilatation from 2 to 9 cm. Five women were nulliparous and one patient had a history of a cesarean delivery. After excluding all US segments affected by out-of-plane movements or large translational movements, 110 minutes of US recordings were analyzed, with an average of 19±7 minutes per patient.

As shown in Table 1, in all subjects, a cyclic cranial – caudal movement of the uterine wall with respect to the skin was detected in the US data. Based on observation, this movement had a sinusoidal pattern, here simply referred to as uterine movement. The average amplitude of this movement (calculated as the full motion divided by two) showed a high inter-patient variability, from 0.03 cm to 2.49 cm. In each subject, the average period (duration of one cycle) ranged from 2.7 s to 5.3 s, corresponding to oscillation frequencies from 0.19 Hz to 0.37 Hz and to a peak speed of the uterine wall between 0.04 and 3.60 cm/s. On average, values of 0.27±0.07 Hz, 0.68±0.84 cm, and 1.04±1.20 cm/s were found for the frequency, amplitude, and speed of the uterine movement, respectively. The analysis of the correlation between the accelerometer signal amplitude, A(t), and the uterine movement, U(t), shows an average correlation $\rho = 0.51 \pm 0.08$. No significant difference ($p<0.05$) was found in the peak frequency. The correlation coefficient of the power density spectra was $r = 0.85 \pm 0.06$.

Table 1. Uterine movement.

Case	Oscillation frequency [Hz]	Average amplitude [cm]	Peak speed [cm/s]
2	0.37	0.05	0.12
3	0.21	0.03	0.04
6	0.23	2.49	3.60
7	0.19	0.63	0.75
8	0.31	0.35	0.68
9	0.32	0.53	1.07
Mean ±SD	0.27±0.07	0.68±0.84	1.04±1.20

The hypothesis that the uterine movement was due to respiration was confirmed by an additional measurement on a pregnant woman (35 weeks gestational age) who was not in labor and was without epidural analgesia, see Figure 1. Similar to the measurements in patients in labor, an accelerometer was placed on the abdomen and the uterine movement was measured by US. When this woman stopped breathing for a short period, uterine movement and abdominal acceleration were no longer detected.

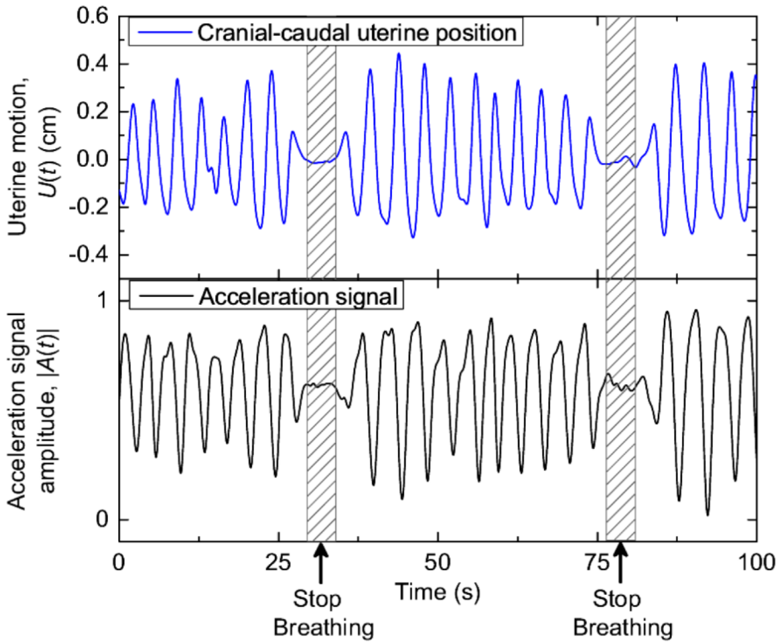

Figure 1. An additional measurement showing the uterine movement to be induced by maternal respiration. The uterine movement (top) and abdominal acceleration (bottom) were no longer detected when the woman held her breath for a short period.

Discussion

This research aimed at observing the mechanical activity of the uterus during labor, in order to improve interpretation and measurement of the abdominally derived electrohysterogram. For the first time the uterine movement was quantified and correlated to abdominal acceleration.

In all subjects, a cyclic movement of the uterine wall underneath the abdominal surface was observed in the vertical direction (caudal – cranial). An additional dedicated measurement, in which this vertical movement disappeared when the woman held her breath, confirmed this movement to be caused by maternal respiration. Since this movement was not observed in the tissues above the uterus, i.e., skeletal muscle and subcutaneous tissue, our hypothesis is that the organs lying in the abdominal cavity within the peritoneum, including the uterus, are displaced by the diaphragm during respiration relatively to the abdominal layers outside the peritoneum. The observed high inter-patient variability could be due to individual differences in type of breathing: chest or diaphragmatic breathing. Following our hypothesis, diaphragmatic breathing would lead to a higher amplitude of the uterine movement.

The correlation between the uterine movement and the detected acceleration was calculated by the maximum of the normalized cross correlation, rather than by the Pearson correlation coefficient, in order to have a measure of correlation which is independent of the synchronization accuracy between the signals. Although the uterine movement has the same frequency as detected by the accelerometer, the signals have only a modest correlation in the time domain. We can deduce that, in this domain, nonlinear effects, presumably in the phase of the equivalent transfer function between the signals, play a dominant role. These effects are likely to result from the complex mechanical system linking abdominal accelerations and uterine movements. A system identification approach should therefore be employed to process the signals prior to performing any correlation analysis. This approach is being considered for future research.

The uterine movement due to respiration was present in all patients and with a frequency approximately in the frequency range used for EHG analysis [5]. Our findings have pressing implications for the models currently under development for signal propagation and the interpretation of the abdominally derived EHG [9]. Firstly, it implies movement of the signal source; the electrodes of the EHG record the signal at that specific location with a continuously moving myometrium underneath. Therefore, EHG parameters previously proposed for characterization of uterine contractions during pregnancy and for prediction of labor, e.g., frequency content [5] and conduction velocity [3, 4], may be affected by uterine movement induced by respiration. Secondly, abdominal movement can cause measurement artifacts due to variations in the electrode-to-skin contact. The interpretation should therefore be adjusted by taking uterine movement into account. The main question that arises relates to the extent of the influence of respiration on the observed variations in EHG parameters.

Since the EHG propagation properties have been recently suggested as the most promising indicators for preterm labor prediction (8), understanding the effect of uterine movement on the measured EHG conduction velocity would be particularly relevant. In this study, the uterine movement had a peak velocity of 1.04 cm/s. Being this value is much smaller than the values of EHG conduction velocity previously reported in the literature: 4.9 - 53 cm/s [3, 4, 6], we may infer that the effect of respiration-induced artifacts on the analysis of the EHG conduction velocity is negligible. However, due to the yet unclear mechanism underlying EHG signal propagation [4], further research is needed to thoroughly understand and quantify the effect of uterine movement on the parameters derived from EHG signal analysis in order to avoid misinterpretation of clinical results.

Future work will focus on understanding and modeling the effects of the observed uterine movements on the EHG signal, possibly leading to new improved methods for EHG analysis that are robust to respiration-induced artifacts [12]. Understanding and modeling the link between respiration and EHG is essential for a reliable use of the EHG for prediction of preterm labor.

References

1. Euliano TY, Marossero D, Nguyen MT, Euliano NR, Principe J, Edwards RK: Spatiotemporal electrohysterography patterns in normal and arrested labor. *Am J Obstet Gynecol* 2009, **200**(1):54 e51-57.
2. Garfield RE, Maul H, Shi L, Maner W, Fittkow C, Olsen G, Saade GR: Methods and devices for the management of term and preterm labor. *Ann N Y Acad Sci* 2001, **943**:203-224.
3. Lucovnik M, Maner WL, Chambliss LR, Blumrick R, Balducci J, Novak-Antolic Z, Garfield RE: Noninvasive uterine electromyography for prediction of preterm delivery. *Am J Obstet Gynecol* 2011, **204**(3):228 e221-210.
4. Rabotti C, Mischi M, Oei SG, Bergmans JW: Noninvasive estimation of the electrohysterographic action-potential conduction velocity. *IEEE Trans Biomed Eng* 2010, **57**(9):2178-2187.
5. Vinken MP, Rabotti C, Mischi M, Oei SG: Accuracy of frequency-related parameters of the electrohysterogram for predicting preterm delivery: a review of the literature. *Obstet Gynecol Surv* 2009, **64**(8):529-541.
6. Miller SM, Garfield RE, Daniel EE: Improved propagation in myometrium associated with gap junctions during parturition. *Am J Physiol* 1989, **256**(1 Pt 1):C130-141.
7. Rabotti C, Mischi M, Beulen L, Oei G, Bergmans JW: Modeling and identification of the electrohysterographic volume conductor by high-density electrodes. *IEEE Trans Biomed Eng* 2010, **57**(3):519-527.
8. Biophysical Modeling of the Uterine Electromyogram for understanding and preventing Preterm Labor [http://www.erasysbio.net/index.php?index=268]
9. Laforet J, Rabotti C, Mischi M, Marque C: Improved multi-scale modeling of uterine electrical activity. *IRBM* 2013, **34**(1):38-42.
10. Rabotti C, Mischi M, van Laar JO, Oei GS, Bergmans JW: Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals. *Physiol Meas* 2008, **29**(7):829-841.
11. Rabotti C, de Lau H, Haazen N, Oei S, Mischi M: Ultrasound analysis of the uterine wall movement for improved electrohysterographic measurement and modeling. *35th Annual International Conference of the IEEE EMBS* 2013.
12. Xu L, Rabotti C, Mischi M: Novel vibration-exercise instrument with dedicated adaptive filtering for electromyographic investigation of neuromuscular activation. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society* 2013, **21**(2):275-282.

Summary

Electrohysterography in pregnancy: from technical innovation to clinical application

Imminent preterm delivery cannot be accurately established using current monitoring techniques, leading to both under treatment and, in particular, overtreatment of women presenting with preterm contractions; more than half of the patients admitted for preterm labor, eventually deliver at term [1-5]. The electrohysterogram (EHG) can potentially provide insight in the evolution of uterine activity and the onset of (preterm) labor. The objective of this thesis was to contribute to the development of the EHG as objective and repeatable tool for preterm labor detection and to explore new applications for EHG propagation analysis for term labor monitoring. This thesis is subdivided in 5 parts: part 1 provides background information, part 2 focuses on preterm labor detection, part 3 covers term labor monitoring and part 4 concludes with a general discussion. Part 5 contains a list of publications, a curriculum vitae and acknowledgements.

Part 1: Physiology and electrohysterography

Chapter 1 entails a general introduction to electrohysterography and states the objective of this thesis. The first part of chapter 2 provides the relevant physiology for understanding the processes that underlie the EHG signals. The topics covered are the uterus and its myocytes, the generation and propagation of action potentials and finally coupling of the action potential to contraction in smooth muscle cells. Electrical propagation of action potentials in uterine smooth muscle is dependent on cell to cell coupling by gap junctions, the presence of which is dependent on the stage of the pregnancy [6-8]. Labor and delivery is preceded by an increase in propagation speed and distance [9-11]. Smooth muscle cell physiology differs in some important respects from skeletal muscle cell function: the pattern of propagation is continuously changing and lacking a fixed pacemaker region [12, 13]. Furthermore, the contraction of smooth muscle cells is much slower in onset and relaxation and more energy efficient as a consequence of slow cross-bridge cycling. Electrohysterography involves the recording of the electrical activity of the myometrium. In the second part of chapter 2 various techniques that are used for recording the EHG are set out, and an overview of the literature on electrohysterography for detecting preterm labor and monitoring term labor is provided. Linear parameters can be further subdivided in parameters regarding signal amplitude [14-17], the spectral content [14, 17-21] or signal propagation [22-25]. Signal amplitude has shown considerable variability among patients, limiting its usability for preterm labor detection. While spectral parameters have been shown to be predictive for preterm delivery, they lack accuracy to be used as a standalone method. The increased connectivity among cells prior to delivery increases propagation speed and distance, which can be quantified by estimating the conduction velocity from the EHG. However, considerable variability exists in methods for estimating the conduction velocity [22, 23, 26-28]. Alternatively, non-linear parameters have been proposed [29-33], among others non-linear propagation and sample entropy. Characteristic for preterm contractions is a more variable and shorter propagation path of action potentials [9, 10, 34]. Non-linear methods could provide an alternative when the conditions for linear propagation are not met.

Part 2: Preterm labor detection

Part 2 covers the subject of preterm labor detection focusing on propagation analysis in the EHG. Previously, analysis of the conduction velocity in preterm patients has relied on visual selection of uterine contractile bursts and/or spikes within these bursts. Despite the promising results that have been presented using this approach [22], clinical application requires a method that is reproducible and objective. However, automated estimation of the conduction velocity entails a number of challenges, namely, automatic detection of uterine contractile bursts, exclusion of signals that are not related to propagating action potentials, and finally derivation of the mean conduction velocity vector.

As a first step, a new automated approach for derivation of the conduction velocity vector in a multi-channel EHG recording was investigated for detecting imminent delivery. A grid of 64 closely spaced electrodes allowed for bidirectional estimation of the conduction velocity vector by a 2-step process: estimation of time delays in the frequency domain and derivation of an average conduction velocity vector based on a maximum likelihood method. Chapter 3 describes the results of an observational cohort study of 16 term and 6 preterm pregnant patients presenting with pre-labor contractions. This study aimed to detect imminent delivery based on the conduction velocity. The average amplitude of the conduction velocity vector was significantly higher for the labor group (8.63cm/s) compared to the non-labor group (4.89cm/s). This confirmed linear propagation as promising tool for (pre)term labor detection. Noteworthy was that external reference by an external tocodynamometer combined with annotations of maternal perception was still required to confirm the initial selection of contractions by the estimated intra uterine pressure (eIUP). Furthermore, the 64 channel setup was complex in use and calculations required considerable computational time.

The PoPE study (Prediction of Preterm delivery by the Electrohysterogram) aimed to address these challenges and to validate conduction velocity analysis for preterm labor detection using a method similar to Lucovnik et al [22]. A method of reduced complexity was adopted using 4 monopolar EHG channels in a fixed configuration. This electrode configuration could replicate a bipolar electrode configuration comparable to the aforementioned study, while also enabling conduction velocity estimation in two directions using 4 channels, which allows estimation of the angle of propagation as well as reduce overestimation of the conduction velocity amplitude [35]. The method for automated derivation of the conduction velocity vector was adapted to the 4 channel setup and optimized in order to make it more robust to (white) noise. Time delays among channels were estimated by cross-correlation. Subsequently, a planar wave front was fitted through the individual vectors of electrode pairs. The mean fitting error was employed as measure of observed variance in conduction velocity and observations with high variance were not considered as linear propagation and therefore discarded. The PoPE study also envisioned to add automatic selection of contraction segments using a derivative of the eIUP in a second stage. In the absence of an absolute reference for detecting uterine contractile bursts, manual segmentation of contraction segments was considered as a reference.

In Chapter 4 we describe the study protocol of the PoPE study testing the hypothesis that the conduction velocity would be higher of preterm contractions leading to (preterm) delivery within 7 days. Similarly to [22], the PoPE study aimed to enroll approximately 100 patients presenting with either clinical symptoms of threatening preterm labor or preterm prelabor rupture of membranes at a gestational age between 23+5 and 34+0 weeks. Manual contraction selection was protocoled by a two step process: the signal to noise ratio of the EHG was increased by optimizing filter settings and removal of the maternal ECG using a high quality external tocogram as reference. Secondly, a set of visual criteria for selection of contractions and artefacts were formulated based on recordings of term and preterm contractions as well as self-induced artefacts. In chapter 5, the results of the PoPE study are presented. Selection of contraction segments proved to be challenging, evidenced by a low concordance between observers. This necessitated a consensus meeting for 39 cases, in order to reduce dissimilarity in segmentation. The resulting overlap in contraction segmentation amounted to 59%. Furthermore, the method for conduction velocity estimation proved susceptible to both common mode and non-common mode noise, apparent in the binominal distribution of observed conduction velocity values. No significant differences were observed in conduction velocity amplitude and direction between the preterm labor and non-labor group. Using the method of the PoPE study, no rise in conduction velocity could be detected preceding preterm delivery. Conduction velocity as EHG parameter has shown inconsistent results. In the PoPE study, using only four electrodes and a distance of approximately 5-8 cm between electrodes, no rise in conduction velocity was apparent preceding preterm delivery. In a more complex approach using 64 electrodes spaced 4 mm apart, the conduction velocity was almost twice as high in the labor group consisting of both term and preterm patients. The distance between electrodes is a possible explanation for this discrepancy, since the linear approximation might more likely be valid for shorter distances.

In chapter 6 an alternative approach for EHG analysis for preterm labor detection was evaluated in the cohort of patients of the PoPE study. 58 from the 81 patients were selected who had at least 5 minutes of contractions during the recording. A modified version of approximate entropy and sample entropy in single EHG channels during contractions was compared to reference non-linear EHG parameters: standard sample entropy and approximate entropy plus time-reversibility. The modified algorithm for approximate entropy and to a lesser extent, sample entropy, outperformed the reference methods in predicting preterm delivery. Noteworthy was that the modified versions of approximate entropy and sample entropy were not able to recognize imminent onset of labor. However, these parameters showed statistically different values in the EHG recordings when performed at least 4 weeks in advance of preterm delivery. Therefore, changes in the EHG might be manifest early in pregnancy and dedicated entropy measures could provide early risk assessment for preterm delivery.

Part 3: Term labor monitoring

Part 3 continues with term labor monitoring, with special focus on uterine rupture detection. While the days of “once a cesarean, always a cesarean” are over, diagnosing a uterine rupture remains challenging. While guidelines mainly focus on changes in the fetal heart rate pattern [36, 37], changes in the tocogram are expected based on the pathophysiology of complete separation of the uterine wall. Chapter 7 reviews the tocogram characteristics associated with uterine rupture during trial of labor after cesarean section. In 13 studies diverse changes in uterine contractility were observed preceding uterine rupture. Hyperstimulation was observed more frequently preceding uterine rupture, which might be a factor leading to uterine rupture or alternatively hyperstimulation could be an indicator of obstructed labor. In the largest prospective cohort study, sudden absence of contractions was reported in 14% of cases of uterine rupture. In addition, hypertonia was observed in 20%. The method for monitoring uterine activity was not specified. No direct comparison could be made between the external tocodynamometer and intrauterine pressure catheters. 5 studies did not report observed changes in the tocogram. Chapter 7 concluded that tocogram changes associated with uterine rupture are diverse and can be absent in some cases.

In chapter 8 we explored propagation characteristics in the EHG as alternative modality for detecting a uterine scar rupture during trial of labor, the most common scenario of uterine rupture. The presence of uterine scar tissue could potentially impede electrical propagation, or alternatively, only disrupt propagation in case of rupture. The latter scenario could potentially serve as basis for detecting a uterine rupture. As a first step, the aim was to establish the baseline propagation characteristics of the intact uterine scar during trial of labor. To this end a 64 electrode grid was positioned above the uterine scar allowing for high spatial resolution data on propagation surrounding the uterine scar. Simulated EHG signals were constructed that emulated different scenarios of propagation in the presence of non-conducting uterine scar tissue. Based on these simulations, inter-channel correlation and propagation direction were adopted as EHG parameters suitable for evaluating possible disruption of electrical propagation by the uterine scar. Propagation was compared between 5 women with an intact uterine scar and 5 women without scarred uterus during the first stage of labor. Both inter-channel correlation and propagation direction proved similar, supporting unaffected propagation in case of an intact uterine scar. Additionally, a single case of uterine rupture occurred as part of pilot measurements. An abnormal propagation pattern was observed in the EHG, showing other than expected, a strong predominance of vertical propagation. This direction was possibly related to the rupture location being to the left of the electrode grid. The results of this study suggest that changes in propagation might become apparent in the EHG in case of uterine scar rupture.

The abdominal EHG signal depends on propagation of action potentials through the layers in between the skin and uterus which can potentially move mutually or vary in thickness. The aim of chapter 9 was to observe changes and movement of the myometrium during labor, in order to improve the interpretation and measurement of the abdominally derived EHG. The myometrium was continuously monitored by ultrasound and an accelerometer. A clear caudal-cranial cyclic movement was present which was confirmed to be caused by respiration. A similar oscillation was observed In the accelerometer, showing a modest correlation in amplitude and a high correlation in frequency. Therefore, the accelerometer can possibly provide a reference for removing movement induced artifacts.

Future directions

Capturing uterine contractile bursts and distinguishing them from background noise, is one of the main challenges in preterm EHG analysis. Recently, research on EHG analysis has moved towards processing the whole signal. Although challenging, distinguishing contractile bursts from background noise is a critical step as extracting EHG parameters such as conduction velocity on signals other than originating from uterine myocytes has little meaning. Moreover, especially preterm the ratio of contractile bursts and quiescent periods is variable, therefore also the influence of these quiescent periods on the outcome of EHG parameters is variable. This notion is further supported by the observation that the classification performance of sample entropy is improved when applied on manually segmented contractions rather than processing the whole signal in the above-mentioned study. Therefore, the method for automated detection of uterine contractions in the externally recorded EHG will need to be further developed. Since a non-invasive gold standard for detecting uterine contractions is lacking, validation of this method will continue to rely on visual inspection of the EHG signals. The goal of this method should be to either reliably match manual segmentation, or alternatively aim to distinguish values obtained during contractions from those related to noise based on the outcome of the EHG parameter.

In order to come to a verdict on conduction velocity as EHG parameter for preterm labor detection, the conditions for linear propagation analysis should be optimal in a follow up study. This includes a small inter-electrode distance and a group of preterm patients clearly showing contractions. Furthermore, an accelerometer should be included as a reference for maternal respiration and other movement artefacts. Conduction velocity can be compared to non-linear entropy parameters. This comparison could guide future research on preterm labor detection towards either linear or non-linear analysis of the EHG.

Connectivity among uterine myocytes could be a factor in successful induction of term labor as well. Quantifying this connectivity at the start of induction by linear propagation analysis or non-linear methods, could potentially discriminate pregnant patients who have a successful vaginal delivery from those who will have obstructed labor. In an observational study the hypothesis could be tested that a lower connectivity, either a lower conduction velocity or a higher entropy, is associated with an increased risk of a cesarean section.

Follow up on uterine rupture detection by EHG propagation analysis, should build on the recommendations from chapter 8; the grid of electrodes should cover the entire uterine scar. Furthermore, non-linear analysis could be considered in addition to linear propagation analysis. Finally the sample size should be appropriate for the low incidence of uterine rupture.

References

1. Fuchs IB, Henrich W, Osthues K, Dudenhausen JW: **Sonographic cervical length in singleton pregnancies with intact membranes presenting with threatened preterm labor**. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2004, **24**(5):554-557.
2. Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, Franks AL: **Hospitalizations during pregnancy among managed care enrollees**. *Obstet Gynecol* 2002, **100**(1):94-100.
3. King JF, Grant A, Keirse MJ, Chalmers I: **Beta-mimetics in preterm labour: an overview of the randomized controlled trials**. *Br J Obstet Gynaecol* 1988, **95**(3):211-222.
4. McPheeters ML, Miller WC, Hartmann KE, Savitz DA, Kaufman JS, Garrett JM, Thorp JM: **The epidemiology of threatened preterm labor: a prospective cohort study**. *Am J Obstet Gynecol* 2005, **192**(4):1325-1329; discussion 1329-1330.
5. Scott CL, Chavez GF, Atrash HK, Taylor DJ, Shah RS, Rowley D: **Hospitalizations for severe complications of pregnancy, 1987-1992**. *Obstet Gynecol* 1997, **90**(2):225-229.
6. Orsino A, Taylor CV, Lye SJ: **Connexin-26 and connexin-43 are differentially expressed and regulated in the rat myometrium throughout late pregnancy and with the onset of labor**. *Endocrinology* 1996, **137**(5):1545-1553.
7. Ou CW, Orsino A, Lye SJ: **Expression of connexin-43 and connexin-26 in the rat myometrium during pregnancy and labor is differentially regulated by mechanical and hormonal signals**. *Endocrinology* 1997, **138**(12):5398-5407.
8. Verhoeff A, Garfield RE, Ramondt J, Wallenburg HC: **Electrical and mechanical uterine activity and gap junctions in peripartal sheep**. *Am J Obstet Gynecol* 1985, **153**(4):447-454.
9. Lammers WJ, Arafat K, el-Kays A, el-Sharkawy TY: **Spatial and temporal variations in local spike propagation in the myometrium of the 17-day pregnant rat**. *Am J Physiol* 1994, **267**(5 Pt 1):C1210-1223.
10. Lammers WJ, Hamid R: **The initiation, continuation, and termination of spontaneous episodes of circus movements in the pregnant myometrium of the rat**. *Am J Obstet Gynecol* 1998, **179**(6 Pt 1):1515-1526.
11. Miller SM, Garfield RE, Daniel EE: **Improved propagation in myometrium associated with gap junctions during parturition**. *Am J Physiol* 1989, **256**(1 Pt 1):C130-141.
12. Lammers WJ: **The electrical activities of the uterus during pregnancy**. *Reprod Sci* 2013, **20**(2):182-189.
13. Lammers WJ, Stephen B, Al-Sultan MA, Subramanya SB, Blanks AM: **The location of pacemakers in the uteri of pregnant guinea pigs and rats**. *Am J Physiol Regul Integr Comp Physiol* 2015, **309**(11):R1439-1446.
14. Buhimschi C, Boyle MB, Garfield RE: **Electrical activity of the human uterus during pregnancy as recorded from the abdominal surface**. *Obstet Gynecol* 1997, **90**(1):102-111.
15. Kandil MA, Abdel-Sattar MM, Abdel-Salam SM, Saleh S, Khalafallah MM: **Abdominal electromyography may predict the response to tocolysis in preterm labor**. *European journal of obstetrics, gynecology, and reproductive biology* 2012, **160**(1):18-21.
16. Most O, Langer O, Kerner R, David GB, Calderon I: **Can myometrial electrical activity identify patients in preterm labor?** *Am J Obstet Gynecol* 2008, **199**(4):378 e371-376.
17. Verdenik I, Pajntar M, Leskosek B: **Uterine electrical activity as predictor of preterm birth in women with preterm contractions**. *European journal of obstetrics, gynecology, and reproductive biology* 2001, **95**(2):149-153.
18. Eswaran H, Govindan RB, Furdea A, Murphy P, Lowery CL, Preissl HT: **Extraction, quantification and characterization of uterine magnetomyographic activity--a proof of concept case study**. *European journal of obstetrics, gynecology, and reproductive biology* 2009, **144 Suppl 1**:S96-100.
19. Maner WL, Garfield RE: **Identification of human term and preterm labor using artificial neural networks on uterine electromyography data**. *Ann Biomed Eng* 2007, **35**(3):465-473.
20. Maner WL, Garfield RE, Maul H, Olson G, Saade G: **Predicting term and preterm delivery with transabdominal uterine electromyography**. *Obstet Gynecol* 2003, **101**(6):1254-1260.
21. Marque CK, Terrien J, Rihana S, Germain G: **Preterm labour detection by use of a biophysical marker: the uterine electrical activity**. *BMC pregnancy and childbirth* 2007, **7 Suppl 1**:S5.
22. Lucovnik M, Maner WL, Chambliss LR, Blumrick R, Balducci J, Novak-Antolic Z, Garfield RE: **Noninvasive uterine electromyography for prediction of preterm delivery**. *Am J Obstet Gynecol* 2011, **204**(3):228 e221-210.
23. Mikkelsen E, Johansen P, Fuglsang-Frederiksen A, Uldbjerg N: **Electrohysterography of labor contractions: propagation velocity and direction**. *Acta obstetricia et gynecologica Scandinavica* 2013, **92**(9):1070-1078.
24. Rabotti C, Mischi M: **Two-dimensional estimation of the electrohysterographic conduction velocity**. *Conf Proc IEEE Eng Med Biol Soc* 2010, **2010**:4262-4265.
25. van 't Hooft J, Rabotti C, Oei SG: **Electrohysterographic evaluation of preterm contractions in a patient with a unicornuate uterus**. *Acta obstetricia et gynecologica Scandinavica* 2013, **92**(6):730-733.
26. Furdea A, Preissl H, Lowery CL, Eswaran H, Govindan RB: **Conduction velocity of the uterine contraction in serial magnetomyogram (MMG) data: event based simulation and validation**. *Conf Proc IEEE Eng Med Biol Soc* 2011, **2011**:6025-6028.

27. Lange L, Vaeggemose A, Kidmose P, Mikkelsen E, Uldbjerg N, Johansen P: **Velocity and directionality of the electrohysterographic signal propagation**. *PloS one* 2014, **9**(1):e86775.
28. Rabotti C, Mischi M, Oei SG, Bergmans JW: **Noninvasive estimation of the electrohysterographic action-potential conduction velocity**. *IEEE Trans Biomed Eng* 2010, **57**(9):2178-2187.
29. Diab A, Hassan M, Marque C, Karlsson B: **Performance analysis of four nonlinearity analysis methods using a model with variable complexity and application to uterine EMG signals**. *Medical engineering & physics* 2014, **36**(6):761-767.
30. Fele-Zorz G, Kavsek G, Novak-Antolic Z, Jager F: **A comparison of various linear and non-linear signal processing techniques to separate uterine EMG records of term and pre-term delivery groups**. *Medical & biological engineering & computing* 2008, **46**(9):911-922.
31. Hassan M, Terrien J, Alexandersson A, Marque C, Karlsson B: **Nonlinearity of EHG signals used to distinguish active labor from normal pregnancy contractions**. *Conf Proc IEEE Eng Med Biol Soc* 2010, **2010**:2387-2390.
32. Hassan M, Terrien J, Muszynski C, Alexandersson A, Marque C, Karlsson B: **Better pregnancy monitoring using nonlinear correlation analysis of external uterine electromyography**. *IEEE Trans Biomed Eng* 2013, **60**(4):1160-1166.
33. Muszynski C, Terrien J, Drean Y, Chkeir A, Hassan M, Marque C, Gondry J: **[Evolution of electrohysterogram signals synchronization according to term of pregnancy: interest for preterm labor diagnosis]**. *Gynecologie, obstetrique & fertilite* 2012, **40**(6):344-349.
34. Lammers WJ: **Circulating excitations and re-entry in the pregnant uterus**. *Pflugers Archiv : European journal of physiology* 1997, **433**(3):287-293.
35. Rabotti C, Oei SG, van 't Hooft J, Mischi M: **Electrohysterographic propagation velocity for preterm delivery prediction**. *Am J Obstet Gynecol* 2011, **205**(6):e9-10; author reply e10.
36. **ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles**. *Obstet Gynecol* 2009, **114**(1):192-202.
37. (RCOG) RCoOaG: **Birth after previous caesarean birth**. In. London; 2012.

Nederlandse samenvatting

Elektrohysterografie tijdens de zwangerschap: van technische innovatie naar de klinische praktijk

Dit proefschrift draait om elektrohysterografie: het opnemen van de elektrische signalen die gepaard gaan met weeën. Met behulp van deze signalen worden nieuwe methoden beschreven voor het voorspellen of vroeggeboorte op gang gaat komen (deel 1) en het vaststellen van het uitscheuren van een litteken van een eerdere keizersnede (deel 2).

Deel 1: hoe de baarmoeder werkt en elektrohysterografie

Hoofdstuk 1 beschrijft het doel van dit proefschrift; toepassingen voor elektrohysterografie ontwikkelen die geschikt zijn voor gebruik in ziekenhuizen. Er is nog veel werk te doen om de zorg rondom vroeggeboorte te verbeteren. Huidige methoden schieten te kort in vaststellen wie er te vroeg gaat bevallen en wanneer het "loos alarm" is. Dit blijkt uit het feit dat ruim de helft van de vrouwen die opgenomen wordt voor "dreigende vroeggeboorte", uiteindelijk pas na 37 weken zwangerschap bevalt. Voor het vaststellen van het uitscheuren van het litteken van een eerdere keizersnede, bestaan momenteel geen gespecialiseerde methoden. Daarom moet worden gebruik gemaakt van indirecte signalen zoals tekenen van foetale nood of het wegvallen van de weeën; vaak late tekenen waarbij het kwaad reeds geschied is.

In hoofdstuk 2 wordt beschreven hoe de spiercellen van de baarmoeder (samen)werken. Dit is belangrijk om de elektrische signalen van de spiercellen die gemeten worden met elektrohysterografie, te kunnen begrijpen. De baarmoeder bestaat uit zogenaamde gladde spiercellen, die anders dan dwarsgestreepte spiercellen (zoals bijvoorbeeld de spieren van je armen of benen), niet bewust aangestuurd kunnen worden. Spiercellen trekken samen als gevolg van elektrische ontlading, waarbij de ontlading van cel naar cel springt en als een stroompje door de baarmoeder heen loopt. Het belangrijke verschil met dwarsgestreepte spieren, is dat in het gladde spierweefsel van de baarmoeder de elektrische ontladingen zich in een chaotisch patroon verspreiden; het wisselt continu waar de ontlading begint en welke richting deze op verloopt. Eénmaal ontladen, duurt het relatief lang voordat de samentrekking van de spiercel begint en vervolgens kan deze samentrekking zonder veel energie in stand worden gehouden. Met behulp van elektroden op de buikhuid kunnen deze elektrische ontladingen worden gemeten. De methoden hiervoor lopen enorm uitéén en kunnen bestaan uit een enkele elektrode of een veelvoud, bijvoorbeeld 64 elektroden in een vierkant. Het signaal kan op verschillende manieren beschreven worden, bijvoorbeeld de grootte van signaal of de frequentie inhoud. Als voorbereiding op de bevalling wordt de verbinding tussen de spiercellen beter en lopen de elektrische ontladingen sneller door de baarmoeder. Nieuwe methoden voor het voorspellen van vroeggeboorte richten zich op het meten van de snelheid van voortgeleiding van de elektrische ontladingen.

Een alternatieve manier om het signaal van de baarmoeder te analyseren, is met non-lineaire methoden. Hiervoor zijn onder meer non-lineaire correlatie en sample entropy voorgesteld. Een eigenschap van vroegtijdige weeën, is een kortere afstand van voortgeleiding van elektrische ontladingen. Non-lineaire analyse kan een alternatief vormen wanneer niet aan de voorwaarde van lineaire voortgeleiding wordt voldaan.

Deel 2: het voorspellen van vroeggeboorte

Voor het bepalen van de snelheid van voortgeleiding, is tot op heden gebruik gemaakt van visuele inspectie van de signalen. Dit kent zijn beperkingen, want de uitkomst hiervan is niet door anderen te controleren. Om deze methode objectief en bruikbaar te maken voor gebruik in het ziekenhuis, is het nodig dat het meten van de voorgeleiding geautomatiseerd gebeurt. Echter, kent dit een aantal uitdagingen: het automatisch herkennen van weeën, het uitsluiten van stoor signalen en uiteindelijk het berekenen van de voortgeleidingssnelheid. Dit laatste wordt hoofdstuk 3 beschreven. Hiervoor werd het elektrohysterogram opgenomen met 64 dichtbij elkaar gelegen elektroden. De tijdsverschillen tussen de elektroden werden bepaald aan de hand van de fase van het signaal en met behulp van een statistische methode werd de gemiddelde voortgeleidingsrichting en snelheid bepaald. Deze methode werd getest in een studie met 22 patiënten: 6 zwangere vrouwen met een dreigende vroeggeboorte en 16 vrouwen met weeën die al voorbij de 37 weken zwangerschap waren. De voortgeleidingssnelheid was hoger voor de vrouwen die kort na de meting bevielen (8.63 cm/s) vergeleken met de vrouwen die later bevielen (4.89 cm/s). Deze studie liet zien dat geautomatiseerde meting van de voortgeleidingssnelheid bruikbaar kan zijn voor het vaststellen welke zwangeren binnen korte tijd zullen bevallen. Het nadeel van de methode was dat er veel rekentijd van de computer voor nodig was en dat er nog extra metingen nodig waren voor het vaststellen van begin en eind van de weeën.

De PoPE studie werd opgezet om deze problemen het hoofd te bieden. Tevens werd in deze studie gepoogd de resultaten te bevestigen van eerder onderzoek door een vergelijkbare opzet te kiezen. In hoofdstuk 4 wordt de werkwijze van de PoPE studie beschreven. De hypothese was dat bij vrouwen met een aanstaande vroeggeboorte een hogere voortgeleidingssnelheid zou worden gezien vergeleken met vrouwen die pas later bevallen (na 7 dagen of langer). Vergeleken met de studie uit hoofdstuk 3, werd nu een simpelere meetopstelling gebruikt met 4 elektroden voor het meten van het elektrohysterogram. Een aangepaste methode werd ontwikkeld voor het automatisch berekenen van de voortgeleidingssnelheid, gebruik makend van 4 elektroden. Met behulp van cross-correlatie werden de tijdsverschillen tussen de 4 kanalen bepaald. De voortgeleidingssnelheid werd tussen alle mogelijke combinaties van de 4 elektroden bepaald; als de gemiddelde fout hiervan te hoog was werd die individuele waarneming als te onnauwkeurig beschouwd. Dit had als doel de waarnemingen als gevolg van ruis weg te gooien en zo de nauwkeurigheid te verhogen van de meting.

Voor het kunnen herkennen van de weeën in het signaal, werd een afschatting gemaakt van de druk in de baarmoeder: een maat voor de weeën kracht. Dit gebeurde aan de hand van het elektrohysterogram na uitgebreide voorbewerking van het signaal, waaronder het wegfilteren van het signaal van het hart van de moeder. Aan de hand van een aantal vooropgestelde criteria, werden de weeën in het signaal geselecteerd door 2 onderzoekers.

In hoofdstuk 5 worden de resultaten van de PoPE studie beschreven. In totaal 81 patiënten die werden opgenomen voor dreigende vroeggeboorte of vroegtijdig gebroken vliezen deden aan de studie mee. De zwangerschapsduur bedroeg tussen de 24 en 34 weken. Bij al deze zwangeren werd een elektrohysterogram opgenomen en naderhand werd de voortgeleidingssnelheid bepaald tijdens de weeën die gemeten werden. De invloed van ruis bleek nog significant, resulterend in foutief lage en hoge waarden. Er werd geen verschil gevonden in voortgeleidingssnelheid tussen de groep zwangeren die binnen 7 dagen na de meting beviel en de groep die pas na meer dan 7 dagen beviel. Hiermee konden de resultaten uit eerder onderzoek en de hypothese van een hogere voortgeleidingssnelheid als teken van een naderende vroeggeboorte, niet worden bevestigd. Een mogelijke verklaring voor de discrepantie met eerder gevonden resultaten met 64 elektroden, is de grotere afstand tussen de elektroden bij de 4 kanaals methode waarbij mogelijk niet altijd aan de voorwaarde van lineaire voortgeleiding wordt voldaan. Onze aanbeveling voor een vervolgstudie van voortgeleidingssnelheid voor het voorspellen van vroeggeboorte, is dan ook om de afstand tussen elektroden te verkleinen.

In hoofdstuk 6 worden een alternatieve non-lineaire methoden onderzocht voor het voorspellen van vroeggeboorte. Bestaande algoritmen voor entropie, een maat voor de mate van wanorde in een signaal, werden aangepast voor het monitoren van de regelmatigheid van het signaal. Tevens werden de algoritmen meer bestand gemaakt tegen de grote fluctuaties en korte pieken in amplitude die kenmerkend zijn voor elektrohysterogram signalen. Deze aangepaste algoritmes voor approximate entropy en sample entropy, werden vergeleken met de originele algoritmen en time revsersibility, als referentie non-lineaire parameters voor het elektrohysterogram. 58 van de 81 patiënten uit de PoPE studie Alhoewel de standaard algoritmen de beste voorspelling gaven van vroeggeboorte binnen 7 dagen, gaven de aangepaste approximate entropy en in iets mindere mate sample entropy, de beste voorspelling welke zwangeren uiteindelijk voor de 37 weken zwangerschap bevielen. Concluderend betekent dit dat veranderingen in het elektrohysterogram mogelijk al vroeg in de zwangerschap waarneembaar zijn en dit biedt mogelijkheden voor risico inschatting van een vroeggeboorte.

Deel 3: monitoren van weeën tijdens de bevalling

Het laatste deel houdt zich bezig met het monitoren van de baarmoeder tijdens de bevalling, met speciale aandacht voor het uitscheuren van het litteken van een eerdere keizersnede: een zogenaamde uterus ruptuur. Ooit betekende een keizersnede dat alle erop volgende bevallingen ook middels een keizersnede moesten plaatsvinden. Tegenwoordig is duidelijk dat aan herhaalde keizersnedes risico’s zitten en dat natuurlijk bevallen vaak goed mogelijk is. Echter blijft er een risico bestaan op een uterus ruptuur, en het diagnosticeren hiervan is een grote uitdaging. De huidige richtlijnen voor het herkennen van een uterus ruptuur, hebben het meeste aandacht voor veranderingen in het hartslag patroon bij de ongeboren baby. Echter, zijn deze veranderingen aspecifiek en bovendien vaak een laat teken van deze ernstige complicatie. Op basis van het mechanisme van het volledige doorscheuren van de wand van de baarmoeder, zijn er ook veranderingen in het weeën patroon te verwachten. In hoofdstuk 7 is een overzicht gemaakt van alle veranderingen die beschreven worden in de bestaande literatuur. In totaal 13 studies werden hiervoor gebruikt, waarin verschillende veranderingen in het weeën patroon werden waargenomen. Hyperstimulatie werd vaker gezien voorafgaand aan een uterus ruptuur, een uiting van ofwel de oorzaak van de ruptuur dan wel een teken van een niet vorderende baring. In de grootste studie werd een plotse afwezigheid van weeën in 14% van de gevallen van uterus ruptuur gezien. Tevens werd een verhoogde druk in de baarmoeder tussen de weeën geobserveerd bij 20% van de gevallen.

Er kon op basis van deze overzicht studie, niet bepaald worden of de inwendige druklijn beter geschikt is voor het vaststellen van een uterus ruptuur dan de uitwendige meting van weeën.

In hoofdstuk 8 is de analyse van voortgeleiding met behulp van het elektrohysterogram onderzocht voor het detecteren van een uterus ruptuur tijdens de bevalling. Het uitscheuren van het litteken na een eerdere keizersnede, is de meest voorkomende oorzaak van een uterus ruptuur. Het ontstaan van een uterus ruptuur geeft mogelijk een verandering in voortgeleiding van de elektrische ontladingen die van buitenaf te meten is in het elektrohysterogram. Hiervoor was het nodig om eerst de voortgeleiding rond het litteken gemeten zou worden rond het litteken als het nog intact is. Om dit te bepalen, is tijdens de bevalling bij 5 vrouwen een grid van 64 elektroden gepositioneerd boven het keizersnede litteken. Ter vergelijk is op gelijke wijze gemeten bij 5 vrouwen zonder een eerdere keizersnede. In de meting werd gekeken naar de richting van voortgeleiding van de elektrische ontladingen van de spiercellen van de baarmoeder. Daarnaast werd de correlatie bepaald tussen de signalen van boven en onder het litteken in het elektrohysterogram. Tussen de vrouwen met en zonder keizersnede litteken, werd geen verschil in voortgeleidingsrichting en correlatie gevonden, wijzend op een ongestoorde voortgeleiding van elektrische ontladingen door het littekenweefsel. Een enkel geval van een uterus ruptuur ontstond tijdens een proefmeting voorafgaande aan de hiervoor genoemde 10 patiënten. Bij deze vrouw werd kort na de meting een uterus ruptuur vastgesteld tijdens een spoedkeizersnede, waarbij de linkerzijde van het litteken was uitgescheurd. Ten tijde van de meting bestond de ruptuur mogelijk al, en in de meting werd een sterk overheersende verticale voortgeleiding gezien, dit werd bij geen van de vrouwen met een intact litteken gezien. Mogelijk hing deze richting samen met dat de ruptuur die niet onder het elektroden grid ontstond, maar links ervan. Een verandering in voortgeleidingsrichting van variabel naar een overheersende richting zou derhalve kunnen wijzen op een uterus ruptuur tijdens de bevalling. In een vervolgonderzoek is het aanbevelingswaardig om een nog groter grid te gebruiken en in een grotere groep zwangeren te meten tijdens een bevalling na een eerdere keizersnede.

In hoofdstuk 9 wordt een studie beschreven die als doel had veranderingen en beweging van de baarmoederwand in beeld te brengen, ten einde de meting en interpretatie te verbeteren. Hiervoor werd de baarmoederwand gevolgd met behulp van echo tijdens de bevalling van 6 vrouwen in de ontsluitingsfase. Hierin was een duidelijk ritmische beweging gezien, waarvan werd bevestigd dat deze verzaakt werd door de ademhaling. Deze beweging werd ook gemeten met een versnellingsmeter op de buikhuid, waarbij de overéénkomst in frequentie van de beweging goed was en minder wat betreft grootte van de beweging. Een versnellingsmeter kan mogelijk wel als referentie dienen voor het verwijderen van artefacten in de meting als gevolg van de ademhaling.

Dankwoord

22 februari 2011 had ik een afspraak met Prof. Oei in Veldhoven, in het Maxima Medisch Centrum. Enthousiast geraakt door zijn optreden in een promotiecommissie voor een proefschrift waarin het afschatten van de intra-uteriene druk werd behandeld, heb ik op de bonnefooi een afspraak gemaakt. Vol met ideeën voor nieuw onderzoek, werd ik meegenomen in zijn enthousiasme en al snel kon ik starten in het Maxima medisch Centrum als arts-onderzoeker. Het voelde als een warm welkom in het zuiden en het was de start van een prachtige periode waarin ik de mogelijkheid heb gekregen mij op wetenschappelijk en persoonlijk vlak te ontwikkelen.

Beste Prof. Oei, beste Guid, ik ben je enorm dankbaar dat je een sprong in het diepe hebt genomen met iemand die je nog niet kende. Ik heb enorme waardering voor jouw tomeloze energie. Zo herinner ik me nog een gezamenlijke dienst, voor mij de drukste nachtdienst ooit maar voor jou 24 uur aan één stuk werken. En jij vertelde ’s ochtends dat je nog even een halve marathon ging lopen. Jouw eindeloze stroom ideeën en onverslaanbare optimisme waren wat ik nodig had om dit project tot een goed einde te brengen. Tot het einde aan toe heb je me in alles gesteund en vertrouwen gehouden in een goede afloop. Ik ben trots dat ik onder jouw begeleiding heb mogen promoveren.

Beste Chiara, mijn promotie is grotendeels gedragen door jouw intensieve begeleiding. Je stimuleerde me altijd om mijn eigen draai te geven aan mijn onderzoek in onze wekelijkse besprekingen. Jouw oog voor detail hebben mijn artikelen de kwaliteit gegeven die ze nodig hadden. Ik heb genoten van je mooie Italiaanse karakter. Dank voor je geduld en je energie. Dit proefschrift komt je toe.

Beste Massimo, jouw kennis en kritische blik hebben richting gegeven aan mijn onderzoek. Als jij je goedkeuring ergens aan gaf, dan wist je dat het goed zat. Ongeacht het tijdstip, vakantie of weekend, je kreeg altijd direct antwoord op vragen. Bovendien was het commentaar altijd raak en behulpzaam. Je was een voorbeeld voor mij en ik denk vele anderen op de TUe.

Geachte leden van de leescommissie: prof.dr. Lammers, prof.dr.ir. Marque, prof.dr.ir. Bergmans, dr. Kwee, hartelijk dank voor uw kritische beoordeling van mijn proefschrift en ik voel me vereerd dat u bereid bent zitting te nemen in de promotiecommissie.

Beste Beatrijs, tijdens de moeilijkste momenten van de PoPE, wist jij het project vlot te trekken. Jouw ervaring en betrouwbaarheid waren erg prettig om op terug te kunnen vallen.

Beste Michiel, partner van het begin tot en met het einde. Een belangrijk deel van dit proefschrift komt uit jouw hand. Naast een intensieve samenwerking, werd jij ook een goede vriend. Ik heb genoten van alle gezelligheid samen en wil je nogmaals bedanken voor de gastvrijheid. Een mooier toeval kon niet dan toen bleek dat we exact gelijk ons proefschrift af zouden ronden en onze promotie op dezelfde dag konden organiseren.

Beste Galin, ik ben onder de indruk van je kennis en wat jij met signaal analyse kan. Eindeloze stromen grafieken en analyses van problemen waren er voor nodig om de PoPE analyse tot een goed einde te brengen.

Dear Kai Tao, you came to my aid when the need was high. You put an enormous effort in the SCAR study and with good effect. It was very pleasant working with you.

Beste Nicole, een zeer slimme techneut, heel exact en georganiseerd. Ik vond het een prettige samenwerking en ik hoop dat het je goed gaat.

Nanette, dank voor de gastvrijheid om elke keer weer alle jonge onderzoekers van de onderzoeksgroep over de vloer te krijgen voor de uitstekend verzorgde FUN meetings.

In de loop van mijn onderzoek zijn er een heel aantal semi-artsen die ik graag nog zou willen bedanken voor hun bijdrage: Joris, Olenka, Kim, Noortje en Andreea. Dank voor het werk wat jullie geleverd hebben en succes met jullie carrière.

Ik heb warme herinneringen aan mijn tijd in de kliniek van het Maxima Medisch Centrum. Het was bij tijd een hectische werkplek, maar altijd in een goede sfeer. Met daarbij een mooi gezelschap aan assistenten en supervisors: een fanatieke en kundige club, maar ook sociaal en enorm gezellig. Het ski weekend in Oostenrijk vond ik tekenend hiervoor, niet eerder een gezelschap met zo over elkaar heen buitelende mensen meegemaakt, iedereen die het hoogste woord wilde hebben plus nog grappiger dan de voorgaande spreker. En Annemarie, bedankt voor je gezelschap en al die keren dat ik mocht logeren na een late dienst. En natuurlijk dat ene briefje met de tekst bedoeld voor Tesse dat "Hinke altijd mocht blijven logeren". En beste dr ter Haar, beste Sylvia. Dank voor je uitstekende begeleiding in het MMC. Als mentor wist ik precies wat ik aan je had wat ik erg prettig vond.

Al het personeel van de verloskamers en de obstetrische high care van het Maxima medisch centrum ook het Jeroen Bosch ziekenhuis, bedankt voor jullie bijdrage voor het includeren van patiënten en het helpen te combineren van de dagelijkse patiëntenzorg met het uitvoeren van onderzoek. Dank aan de mensen van Nemo voor het leveren van materialen.

Beste vrienden, heel anders en toch ook zo gelijkgestemd. In jullie aanwezigheid kan ik helemaal mezelf zijn zoals nergens anders. Bovendien bieden jullie me een wereldwijde blik en verdieping die verder gaat dan de binnenkant van het ziekenhuis die ik doorgaans zie. Ik ben erg blij dat ik jullie gekke filosofen en aanverwanten heb leren kennen, en ik hoop dat we nog lang een hechte vriendengroep blijven!

Beste Robin, slim en zelfverzekerd, en heel erg goed in het deel waar ik weinig kaas van heb gegeten: statistiek. Niet alleen heb je een belangrijke bijdrage geleverd in de totstandkoming van dit proefschrift, ook ben ik je dankbaar mij bij te staan op deze dag. Dat we nog maar lang vrienden mogen zijn, nog veel festivals samen aflopen met hele harde basmuziek!

Lieve Michelle, beste zus, wat een prachtig mens ben jij. Jouw onbaatzuchtigheid en zorgzaamheid is ongeëvenaard. In veel opzichten een voorbeeld, ook al heb ik dat misschien nooit zo uitgesproken. Een betere paranimf kan ik mij niet wensen!

Lieve Suze, beste mamma, resoluut, doortastend en zorgzaam; jij was de beste moeder die ik me kon wensen. Lieve Wim, beste pappa, een genetische kopie is nog een understatement wat betreft onze gelijkenis. Een half woord is doorgaans genoeg en jij begrijpt mij zoals niemand dat kan. Lieve Simone, jij staat altijd voor iedereen klaar in raad en daad. Met jou heb ik een 2e moeder erbij gekregen. Lieve Githa en Jo en Rik, een cadeau om jullie erbij te hebben gekregen.

Lieve Tesse, wat ben ik blij dat ik jou heb ontmoet! Ik ben apetrots dat jij mijn vriendinnetje bent. Jij vult mijn "realisme" aan met een ongebreideld optimisme. Ik vind je fantastisch en hoop dat ik je nog tot in het oneindige mijn vriendinnetje mag noemen!

List of author publications

1. Mischi M, Chen C, Ignatenko T, de Lau H, Ding B, Oei GS, Rabotti C. Dedicated entropy measures for early assessment of pregnancy progression from single-channel electrohysterography. *IEEE Trans Biomed Eng. 2017 Jul 10.*
2. Vullings R, Verdurmen KMJ, Hulsenboom ADJ, Scheffer S, de Lau H, Kwee A, Wijn PFF, Amer-Wåhlin I, van Laar JOEH, Oei SG. The electrical heart axis and ST events in fetal monitoring: A post-hoc analysis following a multicentre randomised controlled trial. *PLoS One. 2017 Apr 14;12(4).*
3. Vlemminx MW, de Lau H, Oei SG. Tocogram characteristics of uterine rupture: a systematic review. Arch Gynecol Obstet. 2017 Jan;295(1):17-26.
4. de Lau H, Yang KT, Rabotti C, Vlemminx M, Bajlekov G, Mischi M, Oei SG. Towards a new modality for detecting a uterine rupture: electrohysterogram propagation analysis during trial of labor. *The Journal of Maternal-Fetal & Neonatal Medicine. 2016 May 10:1-6.*
5. Rooijakkers M, Rabotti C, de Lau H, Oei S, Bergmans J, Mischi M. Feasibility study of a new method for low-complexity fetal movement detection from abdominal ECG recordings. *IEEE J Biomed Health Inform. 2015 Jul 2.*
6. Vlemminx MW, de Lau H, Vullings R, Peters CH, Oei SG. Electrohysterography. A promising alternative for monitoring contractions. *Ned Tijdschr Geneeskd. 2015;159:A8535.*
7. Rooijakkers MJ, de Lau H, Rabotti C, Oei SG, Bergmans JW, Mischi M. Fetal movement detection based on QRS amplitude variations in abdominal ECG recordings. *Conf Proc IEEE Eng Med Biol Soc. 2014 Aug;2014:1452-5. doi: 10.1109/EMBC.2014.6943874.*
8. de Lau H, Rabotti C, Oosterbaan HP, Mischi M, Oei GS. Study protocol: PoPE-Prediction of Preterm delivery by Electrohysterography. *BMC Pregnancy Childbirth. 2014 Jun 5;14:192.*
9. de Lau H, Rabotti C, Bijloo R, Rooijakkers MJ, Mischi M, Oei SG. Automated conduction velocity analysis in the electrohysterogram for prediction of imminent delivery: a preliminary study. *Comput Math Methods Med. 2013;2013:627976. Epub 2013 Dec 29.*
10. de Lau H, Rabotti C, Haazen N, Oei SG, Mischi M. Towards improving uterine electrical activity modeling and electrohysterography: ultrasonic quantification of uterine movements during labor. *Acta Obstet Gynecol Scand. 2013 Nov;92(11):1323-6.*
11. Rabotti C, de Lau H, Haazen N, Oei G, Mischi M. Ultrasound analysis of the uterine wall movement for improved electrohysterographic measurement and modeling. *Conf Proc IEEE Eng Med Biol Soc. 2013;2013:7436-9.*
12. de Lau H, Depmann M, Laeven YJ, Stoutenbeek P, Pistorius LR, van Beek E, Schuitemaker NW. Group counselling for the second trimester ultrasound: can group counselling be an alternative for individual counselling? *Ned Tijdschr Geneeskd. 2013;157(23):A5935.*
13. de Lau H, Gremmels H, Schuitemaker NW, Kwee A. Risk of uterine rupture in women undergoing trial of labour with a history of both a caesarean section and a vaginal delivery. *Arch Gynecol Obstet. 2011 Nov;284(5):1053-8.*

Curriculum vitae

Hinke de Lau was born on June 24th 1981 in Utrecht, the Netherlands. He graduated from the Utrechts Stedelijk Gymnasium in 1999. Having a strong interest in medical as well as technical subjects, he started a medical study in Utrecht only to switch to Electrical Engineering in 2000. Soon hereafter he continued his career working as an audio engineer in the Stadsschouwburg Utrecht in 2001. In 2003, he started over with studying medicine which he finished in 2009. He combined medical school with working as an audio engineer in the Stadsschouwburg Utrecht, and later as a freelance technician for a variety of other clients as well. In addition to audio as a hobby, he spent his spare time on long distance running.

During his study, he gained an interest for the discipline of Obstetrics and Gynecology and became an Obstetrics and Gynecology resident at the Diakonessenhuis in Utrecht. During the PhD defense of one of his colleagues, the PhD candidate commented on the gap between medical professionals and technicians. This remark inspired him to meet Prof. Dr. Oei, one of the committee members, which resulted in a PhD project at the Technical University of Eindhoven and the Maxima Medical Center at Veldhoven. This research project was part of the BioModUE_PTL program, an European collaboration project aiming to model the uterine electromyogram for understanding and preventing preterm labor. Working at the Technical University under supervision of Dr. IR. Rabotti and Dr. IR. Mischi, allowed him to pursue his medical as well as his technical interests and the results are presented in this thesis.

After three years at the Maxima Medical center, he applied for the training for anesthesiologist in the Antonius hospital, led by Dr Bruins. Anesthesiology proved to be an optimal combination of a medical and technical profession. Hinke de Lau is currently in his second year of training under the supervision of Drs Cornelissen at the Jeroen Bosch Hospital.