Summary

Characterization of uterine activity by electrohysterography

A growing number of pregnancies is complicated by miscarriage, preterm delivery, and birth defects, with consequent health problems later in life. It is therefore increasingly important to monitor the health status of mother and fetus, so as to permit timely medical intervention when acute health risks are detected. For timely recognition of complications, quantitative assessment of uterine activity can be fundamental during both pregnancy and delivery.

During pregnancy, timely prediction of preterm delivery can improve the effectiveness of the required treatments. Unfortunately, the prognostic techniques employed in current obstetrical practice, namely, uterine contraction measurements using an elastic belt (external tocography), cervical change evaluation, and the use of biomarkers like fetal fibronectin, have been demonstrated to be inaccurate for the prediction of preterm delivery. In the last stage of pregnancy and during labor, contractions are routinely monitored. Especially when complications occur, e.g., when labor shows poor progress, quantitative assessment of uterine activity can guide the physician to choose a uterine contraction induction or augmentation, a cesarean section, or other therapies. Furthermore, monitoring the fetal heart response to the uterine activity (cardiotography) is widely used as a screening test for timely recognition of fetal distress (e.g. asphyxia). However, in current obstetrical practice, accurate quantitative assessment of the uterine contractions can be provided only invasively and during labor. The current golden standard for contraction monitoring, which is based on the direct internal uterine pressure (IUP) measurement by an intrauterine catheter, can be risky and its use is generally limited to very complicated deliveries.

The contractile element of the uterus is the myometrium, which is composed of smooth muscle cells. Uterine contractions are caused by electrical activity in the form of action potentials (AP) that propagate through the myometrium cells. Electrohysterography is the measurement of the uterine electrical activity and can be performed by electrodes placed on the abdomen. Electrohysterographic (EHG) measurements

are inexpensive and noninvasive. Moreover, it has been demonstrated that the noninvasively recorded EHG signal is representative of those APs that, by propagating from cell to cell, are the root cause of a uterine contraction. Therefore, in view of the limitation of current obstetrical practice, significant benefits could be expected from the introduction of EHG signal analysis for routine contraction monitoring.

Previous studies highlighted the potential prognostic and diagnostic value of EHG signal analysis, but did not investigate the possibility of accurately estimating the IUP from noninvasive EHG recordings. Moreover, important issues like the effect of the tissues interposed between the uterus and the skin (volume conductor) on EHG recordings have not been studied. Besides, EHG signal interpretation has been typically based on single-channel measurements, while the use of multiple electrodes conveys additional information (e.g., distribution and dynamics of the electrical activation) that can possibly be predictive of delivery.

In this thesis, we focus on the analysis of the EHG signal as an alternative to existing techniques for predicting preterm delivery and monitoring uterine contractions during both pregnancy and delivery. The main goal of this work is to contribute to the technical basis which is required for the introduction of electrohysterography in everyday clinical practice.

A major part of this thesis investigates the possibility of using electrohysterography to replace invasive IUP measurements. A novel method for IUP estimation from EHG recordings is developed in the first part of this thesis. The estimates provided by the method are compared to the IUP invasively recorded on women during delivery and result in a root mean squared error (RMSE) with respect to the reference invasive IUP recording as low as 5 mmHg, which is comparable to the accuracy of the invasive golden standard.

Another important objective of this thesis work is to contribute to the introduction of novel techniques for timely prediction of preterm delivery. As the spreading of electrical activity at the myometrium is the root cause of coordinated and effective contractions, i.e., contractions that are capable of pushing the fetus down into the birth canal ultimately leading to delivery, a multichannel analysis of the spatial propagation properties of the EHG signal could provide a fundamental contribution for predicting delivery. A thorough study of the EHG signal propagation properties is therefore carried out in this work. Parameters related to the EHG that are potentially predictive of delivery, such as the uterine area where the contraction originates (pacemaker area) or the distribution and dynamics of the EHG propagation vector, can be derived from the delay by which the signal is detected at multiple locations over the whole abdomen.

To analyze the propagation of EHG signals on a large scale (cm), a method is designed for calculating the detection delay among the EHG signals recorded by multiple electrodes. Relative to existing interelectrode delay estimators, this method improves the accuracy of the delay estimates for interelectrode distances larger than 5-10 cm. The use of a large interelectrode distance aims at the assessment of the EHG propagation properties through the whole uterine muscle using a limited number of sensors. The method estimates values of velocity within the physiological range and highlights the upper part of the uterus as the most frequent (65%) pacemaker area during labor. Besides, our study suggests that more insight is needed on the effect that tissues interposed between uterus and skin (volume conductor) have on the EHG signal.

With the aim of improving the current interpretation and measurement accuracy of EHG parameters with potential clinical relevance, such as the conduction velocity (CV), a volume conductor model for the EHG signal is introduced and validated. The intracellular AP at the myometrium is analytically modeled in the spatial domain by a 2-parameter exponential in the form of a Gamma variate function. The unknown atomical parameters of the volume conductor model are the thicknesses of the biological tissues interposed between the uterus and the abdominal surface. These model parameters can be measured by echography for validation. The EHG signal is recorded by an electrode matrix on women with contractions. In order to increase the spatial resolution of the EHG measurements and reduce the geometrical and electrical differences among the tissues below the recording locations, electrodes with a reduced surface and smaller interelectrode distance are needed relative to the previous studies on electrohysterography. The EHG signal is recorded, for the first time, by a 64-channel (8×8) high-density electrode grid, comprising 1 mm diameter electrodes with 4 mm interelectrode distance. The model parameters are estimated in the spatial frequency domain from the recorded EHG signal by a least mean square method. The model is validated by comparing the thickness of the biological tissues recorded by echography to the values estimated using the mathematical model. The agreement between the two measures (RMSE = 1 mm and correlation coefficient, $R = 0.94$) suggests the model to be representative of the underlying physiology.

In the last part of this dissertation, the analysis of the EHG signal propagation focuses on the CV estimation of single surface APs. As on a large scale this parameter cannot be accurately derived, the propagation analysis is here carried out on a small scale (mm). Also for this analysis, the EHG signal is therefore recorded by a 3×3 cm^2 high-density electrode grid containing 64 electrodes (8×8). A new method based on maximum likelihood estimation is then applied in two spatial dimensions to provide an accurate estimate of amplitude and direction of the AP CV. Simulation results prove the proposed method to be more robust to noise than the standard techniques used for other electrophysiological signals, leading to over 56% improvement of the RMS CV estimate accuracy. Furthermore, values of CV between 2 cm/s and 12 cm/s, which are in agreement with invasive and *in-vitro* measurements described in the literature, are obtained from real measurements on ten women in labor.

In conclusion, this research provides a quantitative characterization of uterine contractions by EHG signal analysis. Based on an extensive validation, this thesis indicates that uterine contractions can be accurately monitored noninvasively by dedicated analysis of the EHG signal. Furthermore, our results open the way to new clinical studies and applications aimed at improving the understanding of the electrophysiological mechanisms leading to labor, possibly reducing the incidence of preterm delivery and improving the perinatal outcome.