Analysis of uterine activity in nonpregnant women by electrohysterography: a feasibility study

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Abstract—With an overall effectiveness below 30%, in vitro fertilization (IVF) is in urgent need for improvements, especially in view of the increasing trend in postponing childbirth in developed societies. Abnormal contraction of the uterus may underlie impaired fertility and unsuccessful IVF. However, currently, there is no method for quantitative assessment of uterine activity and guidance of dedicated intervention. Analysis of the electrohysterogram (EHG) has been extensively used in pregnancy for quantifying uterine contractions. In this paper, we evaluate, for the first time, the use of EHG analysis for characterizing contractions in women in two different phases of the menstrual cycle, when the uterus is expected to be active and quiescent. In this preliminary study, by estimating the time evolution of the EHG signal energy, we derive the contraction frequency, $f_C$, as a possible marker for quantifying the activity of the uterus and discriminate between active and quiescent status. Ultrasound (US) image sequences are simultaneously recorded and visually analyzed for a qualitative validation of the results. The high correlation (0.91) between $f_C$ obtained by EHG and US analysis and the measured different values of $f_C$ in the two phases motivate further research to confirm the value of EHG analysis for contraction quantification in nonpregnant women.

I. INTRODUCTION

Nowadays up to 20% of couples have difficulties conceiving [1]. These rates are expected to increase because of the well-known trend in postponing childbirth in developed societies [2], [3]. Approximately 50% of infertile couples seek medical care services and recur to assisted reproductive technology. In spite of major efforts to improve assisted reproductive technology over the past 20 years, the overall effectiveness remains below 30% per treatment cycle even for the most advanced technique, which is in vitro fertilization (IVF) [4].

Most IVF failures remain unexplained and infertile couples often undergo a series of unsuccessful IVF treatments with devastating emotional, societal, and economical implications. Together with embryo quality, uterine receptivity is crucial for successful conception in natural as well as in IVF treatments and could be pointed out as a potential responsible factor for the unexplained failure of IVF. In fact, there is strong evidence of a major involvement of uterine contractions in infertility as well as in IVF failure [5]. Uterine contractions of the nonpregnant human uterus have been so far investigated by using invasive intrauterine pressure catheters, magnetic resonance imaging (MRI), and histerosalphingoscintigraphy (HSSG) [6], [7], [8], [9]. Similar studies have been conducted by analyzing ultrasound (US) image sequences visually or deriving anatomical Motion-Mode images.

Although the employed methods are suboptimal for a clinical tool in everyday practice, these studies suggested the functional role of uterine activity in normal menstrual cycles to promote fertilization. For example, the uterus is quiescent in the postfollicular (luteal) phase to favor embryo nidation, while in the late follicular phase upward contractions are expected to facilitate sperm transport toward the distal end of the tubes [7]. The disruption of these natural properties may be the cause of a number of dysfunctions, including subfertility. Furthermore, in IVF treatments, during and after embryo transfer, the presence of uterine contractions or specific features of contractions, such as direction, may hamper implantation and even expel the embryo from the uterine cavity [5].

As compared to the invasiveness of an intraventricular catheter, or to the practical drawbacks of using MRI and HSSG during IVF procedures and weekly (or even daily) check-ups, US-based techniques have been more extensively used due to their limited invasiveness and availability. However, the analysis methods employed so far are subjective or provide only partial information, limiting the possibility of capturing the complex and largely unknown mechanisms underlying uterine contractility.

The lack of a method for an objective characterization of uterine activity outside pregnancy hampers the possibility of understanding the role of uterine contractions in infertility and evaluate possible counteracting measures by large clinical trials.

The electrohysterogram (EHG) measures the electrical activity that triggers and drives the mechanical contraction of the uterus [10]. It can be recorded by electrodes placed on the abdominal skin. During pregnancy, EHG measurement has been proven to allow for accurate estimation of amplitude, frequency, direction, and velocity of uterine contractions, even outperforming the diagnostic value of methods currently used in clinical practice [11], [12]. The EHG potentially allows for a complete characterization of contractions in terms of amplitude, frequency, direction, and velocity, with the
additional advantage of being noninvasive, cost effective, and particularly suitable for long-term measurements. However, the EHG has never been recorded on a non-pregnant human uterus.

In this paper, we propose, for the first time, the use of EHG analysis for characterizing the contractions of the non-pregnant uterus. The EHG is recorded noninvasively in three women with regular menstrual cycle. In this preliminary study, we focus on estimating the contraction frequency in order to assess the level of activity of the uterus at the time of recording and possibly discriminate between active and nonactive status. Therefore, recordings were performed on the same subject in two different phases of the cycle, when the uterus was expected to be active and quiescent. US image sequences were simultaneously recorded and used for a qualitative validation of the results.

II. METHODOLOGY

A. Dataset

The study was approved by the relevant medical ethical committee. After signing an informed consent, three women with regular menstrual cycle were enrolled in the study and measured in different phases. In this study, the late follicular (LF) and late luteal (LL) phases were considered. The LF phase, expected between day 11 and 13 of the cycle, was established based on US estimates of the follicle size. The measurements were performed only when one of the follicle size was larger than 16 mm, in order to be immediately before ovulation, when the uterus is expected to be the most active. The second measurement was performed in the late luteal (LL) phase, 7 days after ovulation, when the uterus should be quiescent in order to promote embryo nidation. Blood tests were performed in order to test hormone (e.g., progesterone) levels and exclude any hormonal unbalance which may contribute to dysfunctional uterine activity [7].

During each phase, 4-min data were acquired in which US and EHG measurements were performed simultaneously. An US scanner Accuvix 20 (Samsung-Medison) equipped with a transvaginal EC4-9IS probe was employed for the acquisition of US image sequences. For this preliminary study, only 2D analysis was implemented. The acquisition frame rate was 25 frames/s, which is amply sufficient to meet the Nyquist condition given the limited bandwidth of uterine movement. After skin preparation for contact impedance reduction, the EHG signal was recorded by a high-density electrode grid placed on the pubic bone. The correct placement of the abdominal grid was guided by US in order to maximize coverage of the uterus. The EHG was recorded and digitized at a sampling frequency of 1024 Hz using a Refa system (TMS International, Enschede, the Netherlands), a multichannel amplifier for electrophysiological signals.

B. Preprocessing

In this study, we aim at estimating the frequency of uterine contractions, i.e. the number of contractile events per unit time, by following time variations of the EHG signal energy. For this purpose, which does not require high spatial resolution, the signal-to-noise ratio (SNR) is improved by averaging neighboring electrodes and simulating larger sensing surfaces. Eight sensing areas, A1, A8 were then obtained as shown in Fig. 1 by averaging the corresponding electrodes. Finally, 4 bipolar signals were derived by subtracting areas in the 4 directions, i.e., Bip1 = A1 − A5, Bip2 = A2 − A6, Bip3 = A3 − A7, and Bip4 = A4 − A8.

C. Signal analysis

As demonstrated during pregnancy, an estimate of the contraction pattern can be derived by calculating the EHG signal energy. Three standard methods for EHG energy estimation in pregnancy were adapted to this novel application, namely, the unnormalized first statistical moment (UMF), the absolute value (AV), and the root mean squared (RMS) value, and applied independently to the 4 bipolar signals obtained as described above [13] [14].

To calculate the UMF, the time-frequency representation $\rho [n, f]$ of the EHG signal, $x[n]$, is first obtained based on the squared magnitude of the short-time Fourier transform with a Hanning window $w[m]$ of length 8 s as defined by

$$\rho [n, f] = \sum_{m=1}^{M} x[m] \cdot w[m-n] \cdot e^{-j2\pi fm}. \quad (1)$$

A frequency-weighted energy of the EHG is then derived by the UFM in a chosen frequency band $[f_{\text{min}}, f_{\text{max}}]$, i.e.,

$$\Psi[n] = \sum_{f=f_{\text{min}}}^{f_{\text{max}}} f \cdot \rho [n, f]. \quad (2)$$

In line with the frequency content of the EHG signal in pregnancy, a frequency band $[f_{\text{min}}, f_{\text{max}}] = [0.3 \text{ Hz}, 5 \text{ Hz}]$ was chosen. However, while in previous studies in pregnancy a lower $f_{\text{max}}$ was set to reject the heart rate, here the adopted small interelectrode distance reduces the possible effect of interferences form the cardiac activity around 1 Hz and allows for higher $f_{\text{max}}$ and improved SNR. Therefore, prior to calculation of the other two parameters, the EHG signal was first filtered by a fourth-order Butterworth band-pass filter with cut-off frequencies at 0.3 and 5 Hz. An example of the signal recorded in Bip1 during the LF phase is reported in Fig 2.

The RMS value was obtained by

$$\text{RMS}[n] = \sqrt{\frac{\sum_{m=0}^{M-1} x[m+n]^2 \cdot w[m]}{\sum_{m=0}^{M-1} w[m]}}. \quad (3)$$

Fig. 1. High-density electrode grid and electrode surfaces (A1-A8) derived for estimation of the EHG signal energy.
where $w[m]$ is a rectangular window of length $M = 3$ s.

The AV is also computed on the band-pass filtered signal independently for the 4 bipolar derivations obtained from the electrode grid. For all three estimators, an average signal was obtained by the mean of the energy estimated independently in the four bipolar channels.

D. Peak detection

Based on the assumption that an increase in the EHG signal energy corresponds to a contraction, a threshold-based peak-detection algorithm was used to derive an estimate of the contraction frequency. The peak detection was performed on the average energy estimate obtained by each method. For each of the six 4-minute recordings, the threshold was experimentally set at 40% above the standard deviation (STD) of the estimated energy in that recording, after removal of the average value. Based on a maximum contraction frequency of 5/min, peaks detected within 12 s from a larger peak were rejected. Prior to peak detection, a fourth-order Butterworth band-pass filter with cut-off frequencies at 0.02 Hz and 0.2 Hz was used to remove baseline and high-frequency oscillations, respectively. The number of contraction per minute, $f_C$, was then estimated for each recording based on the number of detected peaks per recording.

E. Validation

Visual inspection of the recorded US image sequence was used as comparison method for the $f_C$ estimated by EHG signal analysis. After recording, off-line analysis was performed at high speed (four times) replay and focussed on detecting tissue displacements that could indicate the onset of a uterine contraction. Two independent experts performed the US visual analysis. For each recording, $f_C$ was calculated, after consensus was reached, as the ratio between the number of detected events and the duration of the recording.

III. RESULTS

In Fig. 3, the average $f_C$ is reported with its standard deviations for the three different methods used for EHG signal analysis and for the visual inspection of the US image sequence. The results are reported separately for the LF and for the LL phase.

When comparing the three EHG analysis methods with visual inspection of US, correlation coefficients equal to 0.91, 0.58, and 0.73 were found for the UFM, the RMS and the AV estimator, respectively. The agreement between the EHG-based analysis and US visual inspection was evaluated by a Bland-Altman plot, focussing on the UFM estimator, which showed the highest correlation with US. A comparison between the contraction frequency $f_C$ obtained by these two modalities is summarized in Fig. 4, where the difference between the value of $f_C$ obtained by the UFM and by US are plotted against the average $f_C$ between the two methods [15].

Finally, an example of energy estimate obtained by the UFM method is reported in Fig. 5 for the same recording as in Fig. 2, acquired during the LF phase.

IV. DISCUSSION AND CONCLUSIONS

In this paper, for the first time, the feasibility of EHG analysis for the assessment of uterine activity in nonpregnant
women is proposed. Previous work, suggesting the crucial role of uterine activity on subfertility and IVF success rate, mainly relies on visual inspection of US image sequences. Although subjective and prone to inter- and intra-observer variability, visual analysis of US image sequences is currently the most used and suitable method, and it is therefore used as reference for this preliminary study. Three established approaches for estimating the energy of muscular biopotentials and quantifying contractions from EHG signals during pregnancy are here evaluated and adapted to this novel application aiming at deriving an estimate of the uterine contraction frequency in two different phases of the menstrual cycle.

Our results consistently show, on average, a higher frequency in the LF phase as compared to the LL in all the methods, including US visual inspection. This trend is in line with the literature that identifies these two phases as the most active and the most quiet, respectively, and is more evident when processing the EHG signal using the UFM estimator. In fact, the UMF-based EHG analysis method also shows the highest correlation with the values of $f_c$ obtained by visual inspection of US and, in this sense, outperforms the other energy estimators considered here. The Bland-Altman analysis, however, reveals some discrepancy in the two methods. This could be ascribed to the different nature of the two measures and require further investigation.

In general, the uterus is a very complex organ and even in pregnancy, when it has been studied more extensively also by biopotential measurements, many aspects remain unclear. For example, the spatiotemporal properties of both the electrical activation and the mechanical dynamics of a contraction in the 3D space are poorly understood. This complexity represents an additional reason for which the use of 2D US visual analysis can be considered a valuable reference only for qualitative assessment of uterine activity. Further research (combined with 3D US) is needed to understand the electromechanical dynamics underlying the uterine contraction and to define a validation strategy for quantitative analysis of biopotentials.

To conclude, based on the estimated frequency of contraction, the proposed new methods for uterine activity assessment by EHG signal analysis of the nonpregnant human uterus show a good agreement with visual inspection of US image sequences and are promising to discriminate active and non active phase of the uterus. Our preliminary results motivate further research for validating the use of EHG signal analysis in nonpregnant women.

Future work will focus on evaluating EHG signal analysis methods, tailored to this novel application. A quantitative validation strategy will be investigated on an extended database in order to increase our understanding of the physiological processes underlying uterine contractions and to be able to quantify their role in fertilization.

**REFERENCES**


