Author's response to reviews

Title: Study protocol: PoPE- Prediction of Preterm delivery by Electrohysterography

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Author's response to reviews: see over
Dear Dr O'Donovan and reviewers,

Thank you for considering our manuscript. Below you can find our answers to the comments of the review reports.

**Comment:** The only part of the protocol that needs clarification is, in my opinion, how will contractions be chosen. This is essential since conduction velocity will only be measured during contractions (not the whole EHG recording). The authors state: “Contractions will be detected by analysis of the EHG and using an estimation of the intra uterine pressure.” How will intrauterine pressure be estimated is not clear to me. Analysis of EHG recording in order to find contractions, on the other hand, implies visual inspection of signals. This is again both time consuming and subjective, which may limit the clinical usefulness of the method studied. Many groups have used root mean square to convert EHG signals to resemble contraction tracings. This could, perhaps, be helpful in identifying uterine contractions to be analyzed by this method also.

We agree that automatic selection of contraction segments is a very important step for clinical usefulness and objectivity of the method. However, we think visual selection is still needed for validating an automatic selection algorithm in preterm patients, as it is the only available method which can be used as reference.

**Comment:** The hypothesis of "planar wave propagation" seems to be very strong, why not circular? Is there is any computational modelling or experimental based analysis validating this hypothesis? This point is in direct relation with the electrodes position/number used in the protocol.

Estimating the conduction velocity based on planar wave assumption has been shown to be an accurate parameter for detecting imminent preterm delivery by Lucovnik et al [1], using a two channel configuration and a comparable inter electrode distance. In this study two channels have been added to further improve conduction velocity estimation. However, studying propagation patterns in more detail falls beyond the scope of this clinical application.

**Comment:** It has been reported that the increase of electrodes number can dramatically increase the analysis of the correlation between signals. In this project, the authors reduce their previous montage from 8x8 grid to only four electrodes! This may directly affect the results of the CV. A comparison between both montage in crucial before proposing the new system.

We agree with the reviewer that increasing the inter-electrode distance can possibly decrease the correlation among channels. However, linear correlation has been previously shown on a large scale using a large inter-electrode distance [2]. Moreover, a clinical application necessitates the use of a reduced number of electrodes.
Comment: The filtering between 0.3-0.8 Hz is a crucial parameter in the processing. Refer to Terrien et al. 2011 ("Synchronization between EMG at different uterine locations investigated using time-frequency ridge reconstruction: comparison of pregnancy and labor" EURASIP journals on). The analysis of the correlation (linear or nonlinear) is preferred to be done in low frequencies (0.1-0.3) and not in the high frequencies (>0.3) where they are based on the physiological hypothesis that the uterine propagation is more related to the low frequencies and the cell excitabilities are more related to the high frequencies. As the conduction velocity is a measure of propagation (computed from a correlation measure), how authors can comment about that? I suggest looking for the propagation/velocity/correlation in Low range 0.1-0.4, high range 0.4-0.8 and broad band 0.1-0.8 to identify the best frequency band to be used in the estimation of CV.

To the best of our knowledge, the concept of a slow wave for synchronizing myocyte depolarization has not been established in the uterus. In our experience, the low frequencies are susceptible to artefacts induced by maternal respiration, which can seriously affect the signal in that frequency range. We have therefore chosen to use a frequency band which minimizes the influence of maternal respiration and the maternal ECG on the accuracy of conduction velocity estimation.

Comment: Cross correlation function assume that the relationship between uterine bursts is linear (i.e. the uterine generation model is linear) which is not totally true. The presence of nonlinear behavior in the EHG signals has been reported in many studies. Also the methods that explore the nonlinear relationships between signals showed higher performance than linear ones to analyze uterine electrical activity propagation. Authors should take this crucial aspect in account or at least comment about it.

We agree with the reviewer that the concept of conduction velocity implies linearity. Linear conduction of action potentials has been shown in previous work [2-4]. A threshold will be applied to the correlation among channels in order to reject signals showing non-linear or poor connectivity. We agree that non-linear correlation might be a valuable alternative to conduction velocity and it will be considered in future work.

Comment: "the analysis of the conduction velocity has relied on visual inspection of the signals". This sentence is unclear. If the 'visual inspection' is related to the segmentation of the uterine bursts, several segmentation algorithms have been proposed in the literature. Also the computation of CV has been automatically computed. I recommend to the authors to clarify this point.

We believe that segmentation of uterine bursts is different in preterm patients compared to term. Correct automatic identification of contractile bursts is a challenging as well as essential step. Therefore, prior to the CV analysis, visual review of the signals is used to optimize the automatic burst selection. We have clarified the role of visual inspection in the background chapter.
**Comment:** Authors have to explain the originality of the proposed project comparing to other previous studies used velocity parameter such as (Eva Mikkelsen et al; 2013 “Electrohysterography of labor contractions: propagation velocity and direction” Acta Obstetricia et Gynecologica Scandinavica) and (Lange L, Vaeggemose A, Kidmose P, Mikkelsen E, Uldbjerg N, et al. (2014) Velocity and Directionality of the Electrohysterographic Signal Propagation. PLoS ONE).

We have added a short description of whole burst propagation to the background chapter, referring to the studies mentioned by the reviewer.