Mini-commentary on BJOG-20-1394.R2: *What's pH got to do with it?*

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Fetal acidemia does not predict fetal brain injury. Were we chasing the wrong rabbit?

The growing recognition of detecting fetal cardiovascular decompensation (CVD) to prevent fetal brain injury by fetal heart rate (FHR) monitoring, is giving us new hope for electronic fetal monitoring (EFM) intrapartum.[1,2]

The relationship between pH and fetal brain injury is poor.[1,2] In contrast, a precipitous drop in the cerebral perfusion pressure (CPP) explains brain injury at birth in otherwise asymptomatic newborns.[3] Simply put, CVD, via dropping fetal systemic arterial blood pressure (ABP), translates into critical CPP decrease eventually leading to cerebral ischemia and cellular injury. Identifying fetal origins of CVD clinically is the subject of ongoing research. The clinical evidence of the contribution of head compression as the missing link in brain injury has reinforced this basic physiological concept.[3]

Since fetal ABP cannot be monitored, how is this insight clinically relevant?

This question has been addressed in several preclinical and clinical studies.[4–6]

In 30 near-term fetal sheep, modeling stages 1 and 2 of human labor using intermittent umbilical cord occlusions (UCO) of increasing severity, an anomaly detection algorithm applied to the widely-used FHR variability metric RMSSD (root mean square of successive differences of RR intervals of the fetal electrocardiogram, ECG) reliably detected the onset of CVD in the first or early second stages.[4,5] In 60 babies developing cerebral palsy and 360 controls, FHR pattern-based quantitative interpretation focused on the identification of CVD (Fetal Reserve Index) yielded more accurate predictions of cerebral palsy than traditional clinical interpretation.[6]

Georgieva *et al.* now add more evidence to this body of research.[4–7]

Using a similar preclinical model, they demonstrate that the ECG-based FHR metric phase rectified signal averaging (PRSA) predicts CVD. In a cohort of 18 animals, they show that the severity of fetal hypotension correlates with the PRSA metrics - deceleration area and capacity (DC). Important clinically, these metrics were altered ~2h in advance of severe hypotension.

Gold *et al.* predicted CVD using a machine learning algorithm derived from the *individual* RMSSD signal during the first stage of labor, so no group thresholds were required. In contrast, Georgieva *et al.* used conventional *group* statistical analysis to derive thresholds. As another translational limitation, this approach required data from the second stage of labor and of a duration exceeding the human average.

The DC metric is mathematically closely related to RMSSD. DC's dependence on UCO frequency needs to be studied rigorously and its physiological ability to detect CVD validated accordingly.

While the authors do not provide the positive and negative predictive values, they indicate that the computed thresholds resulted in recurring false positives and cannot be used for individualized anomaly detection. We need a solution for this repeated anomaly detection problem.

The cardiotocography (CTG), in contrast to ECG, suffers from low temporal precision in resolving FHR variability, especially at scales relevant to capturing its vagal modulation.[5,8] Clinical studies will test the performance of the various FHR variability metrics in identifying early CVD to provide actionable decision support during labor management using CTG- or ECG-based EFM.

References

1. Yeh P, Emary K, Impey L. The relationship between umbilical cord arterial pH and serious adverse neonatal outcome: analysis of 51,519 consecutive validated samples. BJOG [Internet]. 2012 Jun;119(7):824–31. Available from: http://dx.doi.org/10.1111/j.1471-0528.2012.03335.x

2. Jonsson M, Ågren J, Nordén-Lindeberg S, Ohlin A, Hanson U. Neonatal encephalopathy and the association to asphyxia in labor. Am J Obstet Gynecol [Internet]. 2014 Dec;211(6):667.e1–8. Available from: http://dx.doi.org/10.1016/j.ajog.2014.06.027

3. Jensen A, Holmer B. White Matter Damage in 4,725 Term-Born Infants Is Determined by Head Circumference at Birth: The Missing Link. Obstet Gynecol Int [Internet]. 2018 Feb 28;2018:2120835. Available from: http://dx.doi.org/10.1155/2018/2120835

4. Gold N, Frasch MG, Herry CL, Richardson BS, Wang X. A Doubly Stochastic Change Point Detection Algorithm for Noisy Biological Signals. Front Physiol [Internet]. 2017;8:1112. Available from: http://dx.doi.org/10.3389/fphys.2017.01112

5. Gold N, Herry CL, Wang X, Frasch MG. Fetal cardiovascular decompensation during labor predicted from the individual heart rate: a prospective study in fetal sheep near term and the impact of low sampling rate [Internet]. arXiv [q-bio.QM]. 2019. Available from: http://arxiv.org/abs/1911.01304

6. Evans MI, Eden RD, Britt DW, Evans SM, Schifrin BS. Re-engineering the interpretation of electronic fetal monitoring to identify reversible risk for cerebral palsy: a case control series. J Matern Fetal Neonatal Med [Internet]. 2019 Aug;32(15):2561–9. Available from: http://dx.doi.org/10.1080/14767058.2018.1441283

7. Georgieva A, Lear CA, Westgate JA, Kasai M, Miyagi E, Ikeda T, et al. Deceleration area and capacity during labour-like umbilical cord occlusions identify evolving hypotension: a controlled study in fetal sheep. BJOG. In press.

8. Li X, Xu Y, Herry C, Durosier LD, Casati D, Stampalija T, et al. Sampling frequency of fetal heart rate impacts the ability to predict pH and BE at birth: a retrospective multi-cohort study. Physiol Meas [Internet]. 2015 May;36(5):L1–12. Available from: http://dx.doi.org/10.1088/0967-3334/36/5/L1