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CASE STUDY: Medical Device Solutions for Fetal and Maternal Health

Best Practices to Design an Inclusive Remote Pregnancy Monitoring Framework

Maria G. Signorini & Nicolò Pini

Dept of Electronics, Information and Bioengineering, DEIB, Politecnico di Milano, Italy

Department of Psychiatry, Columbia University Irving Medical Center & Division of Developmental Neuroscience, New York State Psychiatric Institute, New York, NY, USA

mariagabriella.signorini@polimi.it

np2600@cumc.columbia.edu

The multifaced challenges of pregnancy monitoring

Outcome

Measures in pregnancy: physiological meaning and usefulness

Fetal heart rate measurements and importance in the pregnancy monitoring

Case studies in Malawi and South Africa

Technical solution toward the improvement of the pregnancy monitoring (Tanzania, Guatemala)

Open challenges for Biomedical Engineers

Goal

The main goal of any kind of fetal (pregnancy) monitoring is
to **assess fetus and mother well-being:**

- **Minimize risks** of fetal morbidity and mortality
- Identify **at-risk fetuses** during pregnancy
- Evaluate the **optimal timing** of delivery

<u>Maternal health is also an ISSUE</u>

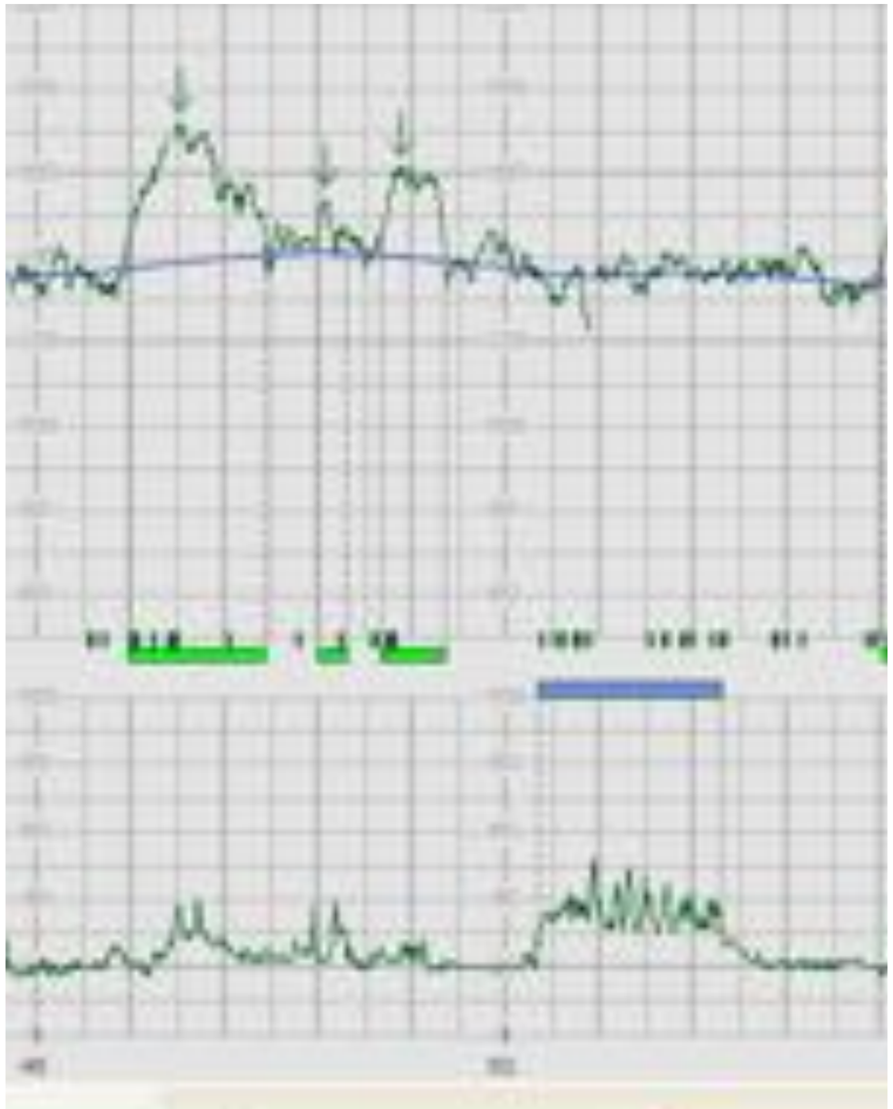
Quality of pregnancy influences neonatal and post-natal life

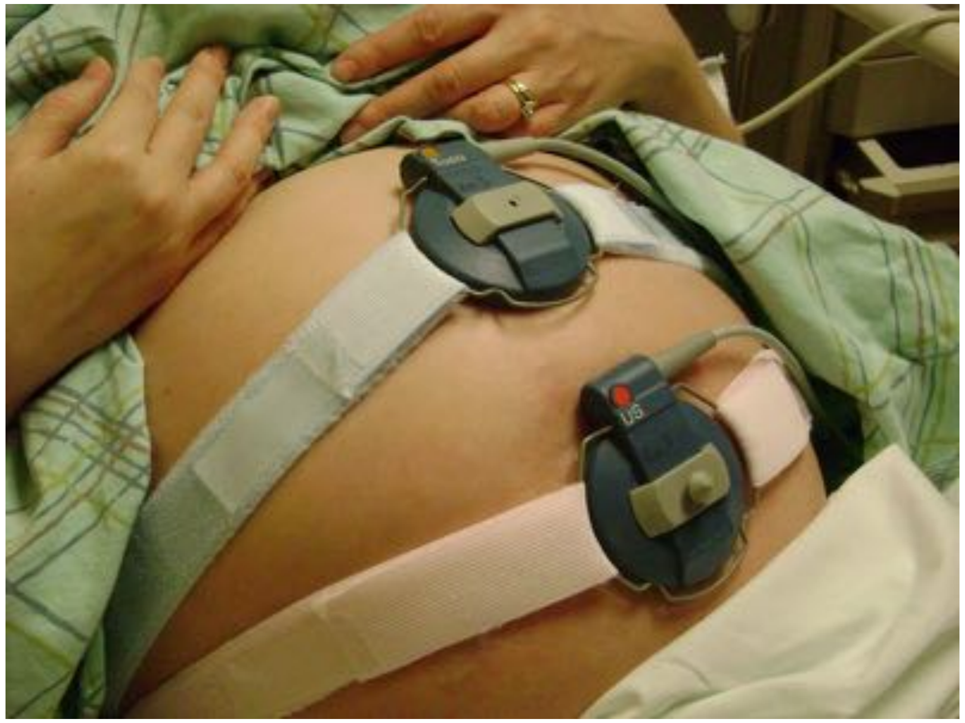
Pregnancy Monitoring (adopted approach)
Cardiotocograph and fetal heart rate variability

Cardiotocograph detects **contractions** and provides

fetal heart rate

by Ultrasound Doppler technique.

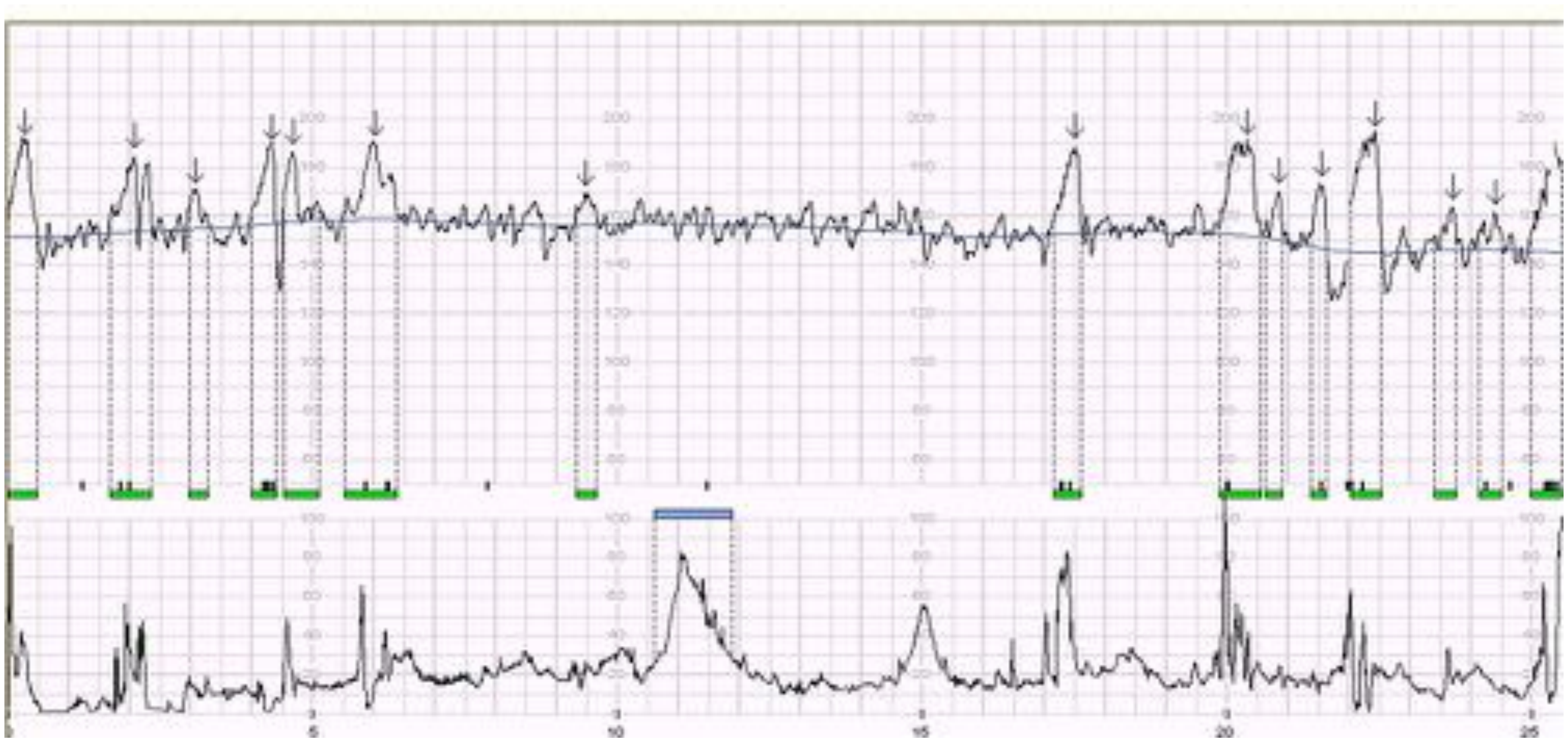




CTG fetal heart rate monitoring

adopted methods (traditional) come **from medical experience**

→ replicate performances of "eye inspection"



Question (by clinicians)

Improve **classification the FHR** signal

Fetal Monitoring

Main goal of of fetal monitoring (any kind):

to assess fetus well-being state

<u>Cardiotocography (CTG)</u>

the most used technique

Recording of **fetal heart rate** using Doppler ultrasound

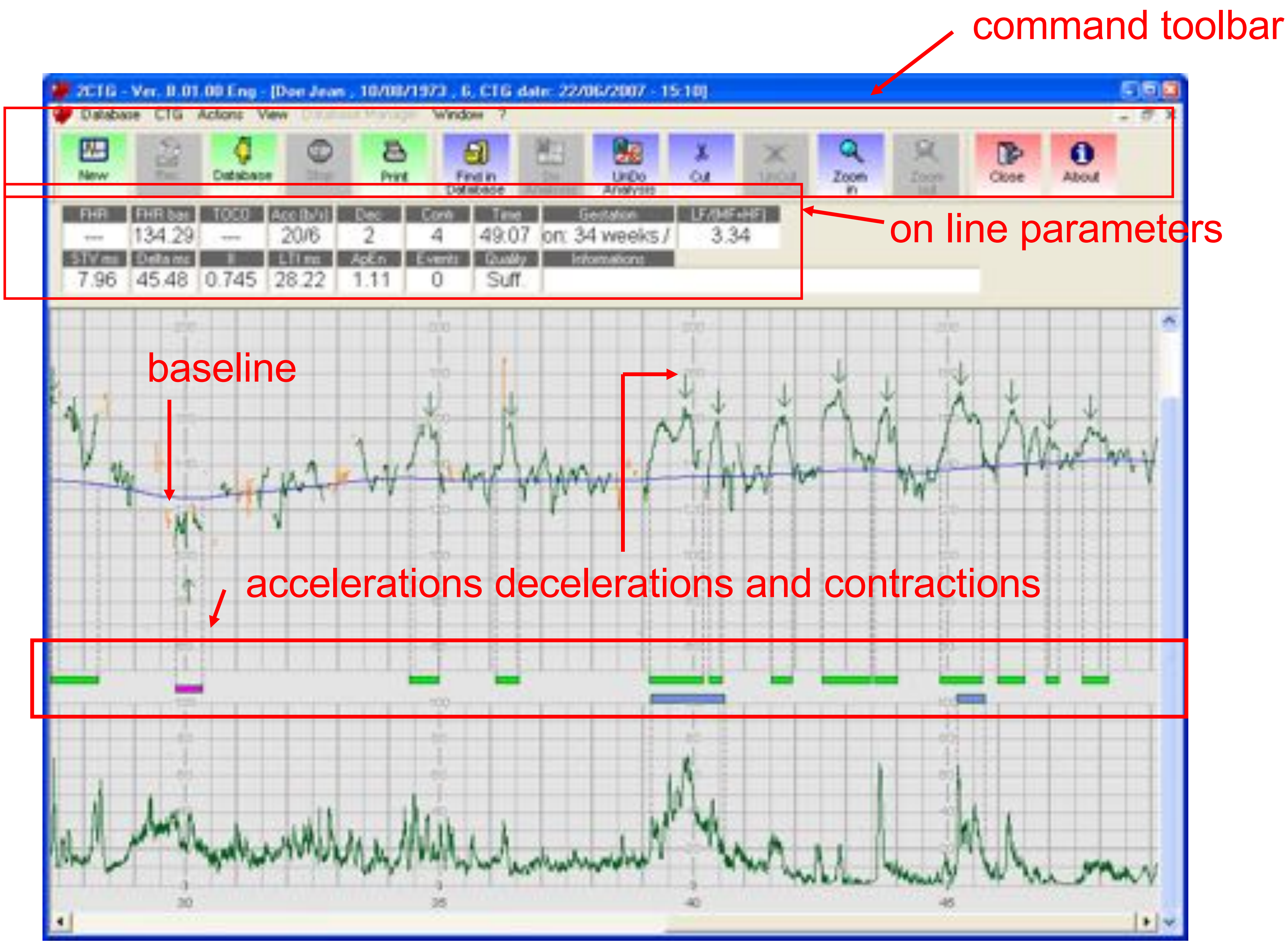
Recording of uterine contractions by a pressure sensor

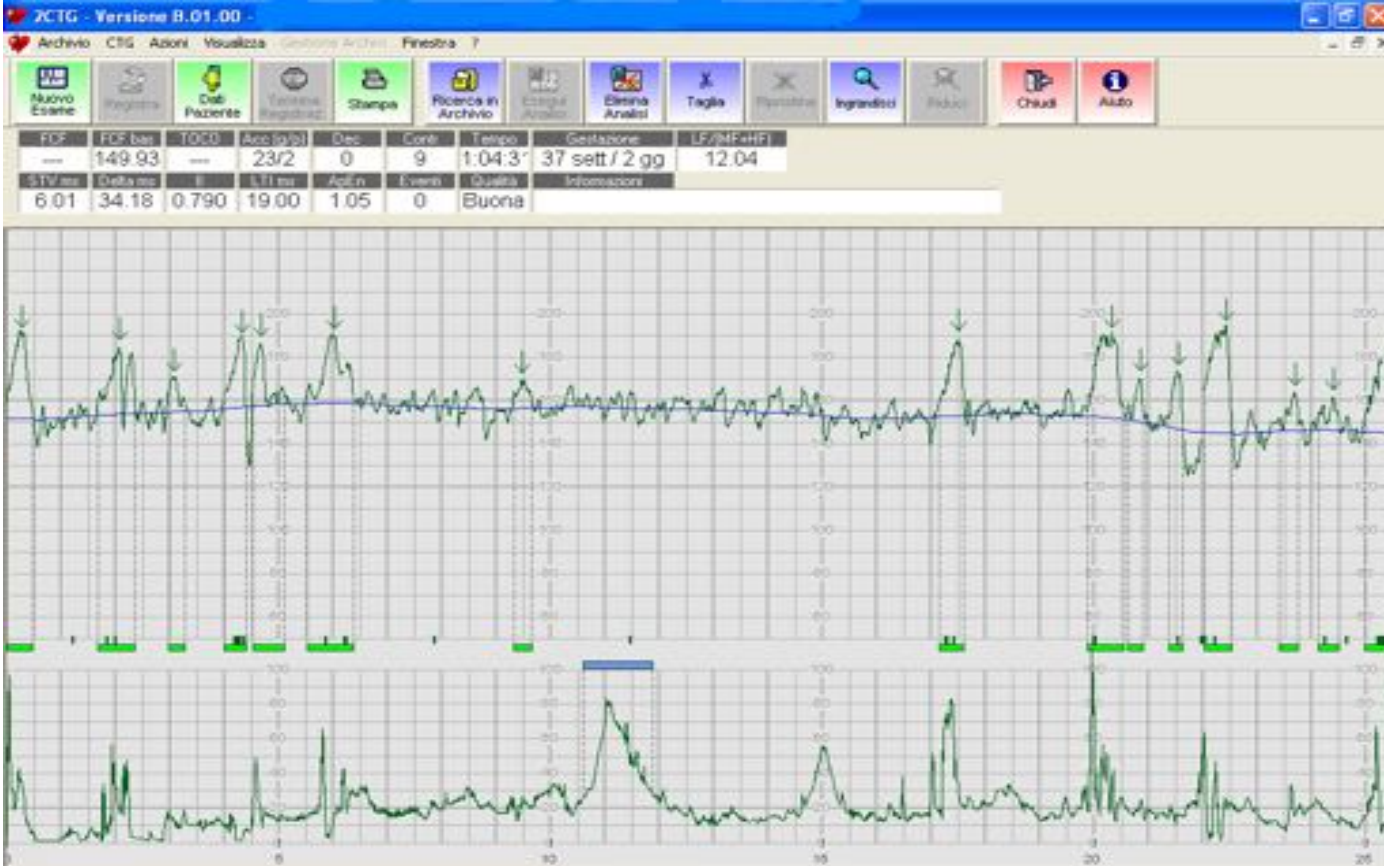
It requires

Expert personnel

Hospital – like context

Fetal Events



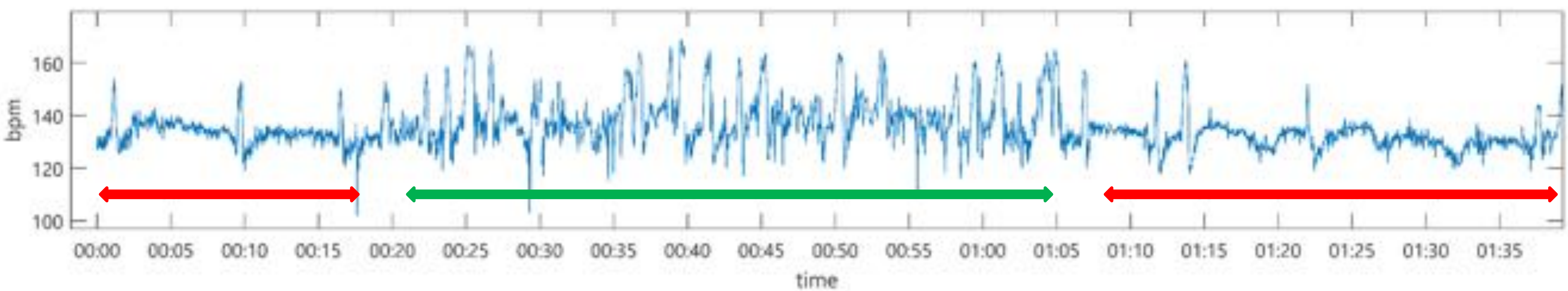


Extraction of parameters in Fetal Heart Rate with CTG. The action buttons of the program can be distinguished at the top, in the middle the calculated current parameters and at the bottom the tracks of FCF and uterine contractions.

The signal as a whole - challenge example

Fetus can experience **different states**
(even during labour stages)

FHR investigation → clear **comprehensive picture**
not limited to **single segments analysis**

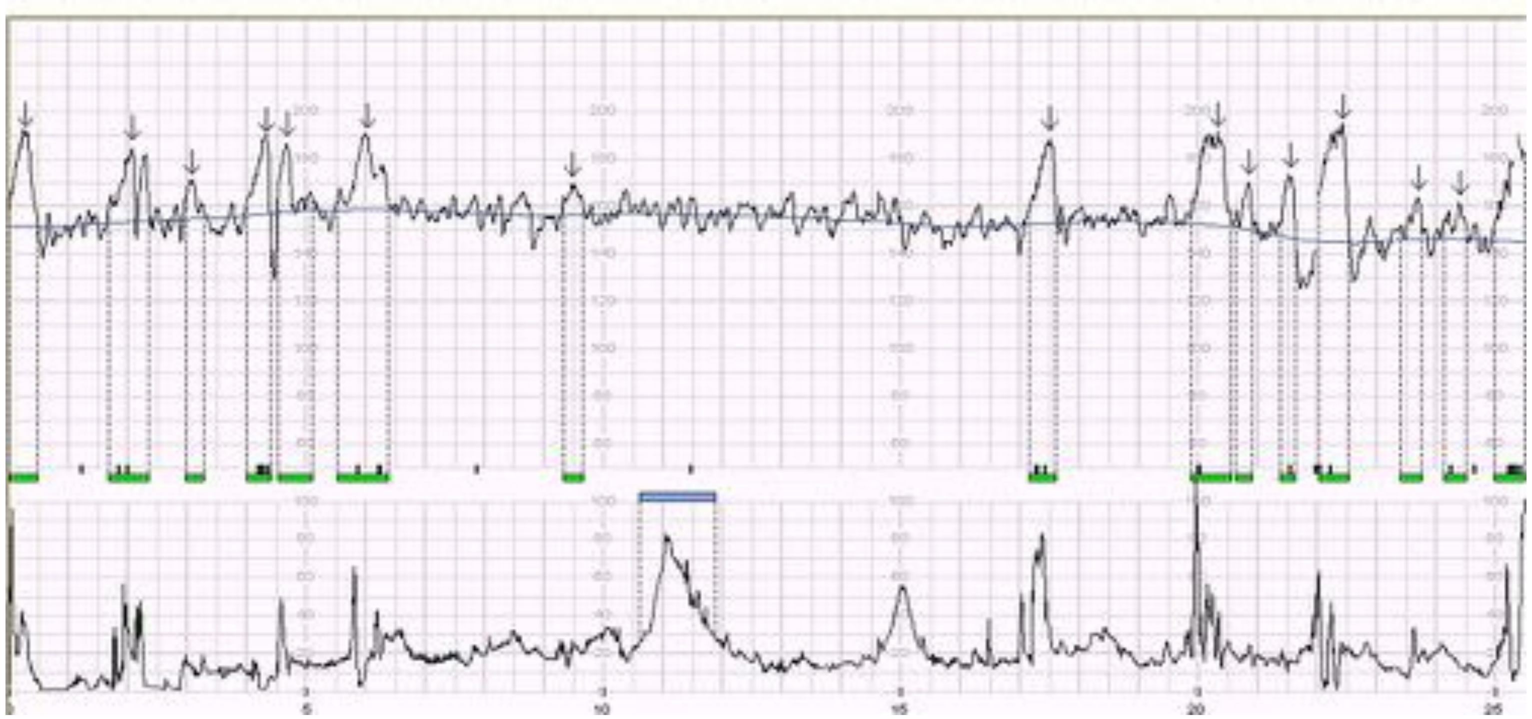


LOWER variability

HIGHER variability

LOWER variability

Monitoring Fetal Heart Rate



adopted methods (traditional) come **from medical experience**

→ replicate performances of "eye inspection"

New parameters: considered FHR time series as complex signals in which different, even nonlinear, mechanisms contribute.

New route to **classify the FHR** signal

Examples in two selected populations: **Normal Fetuses** and **Intra Uterine Growth Restricted (IUGR)** fetuses.

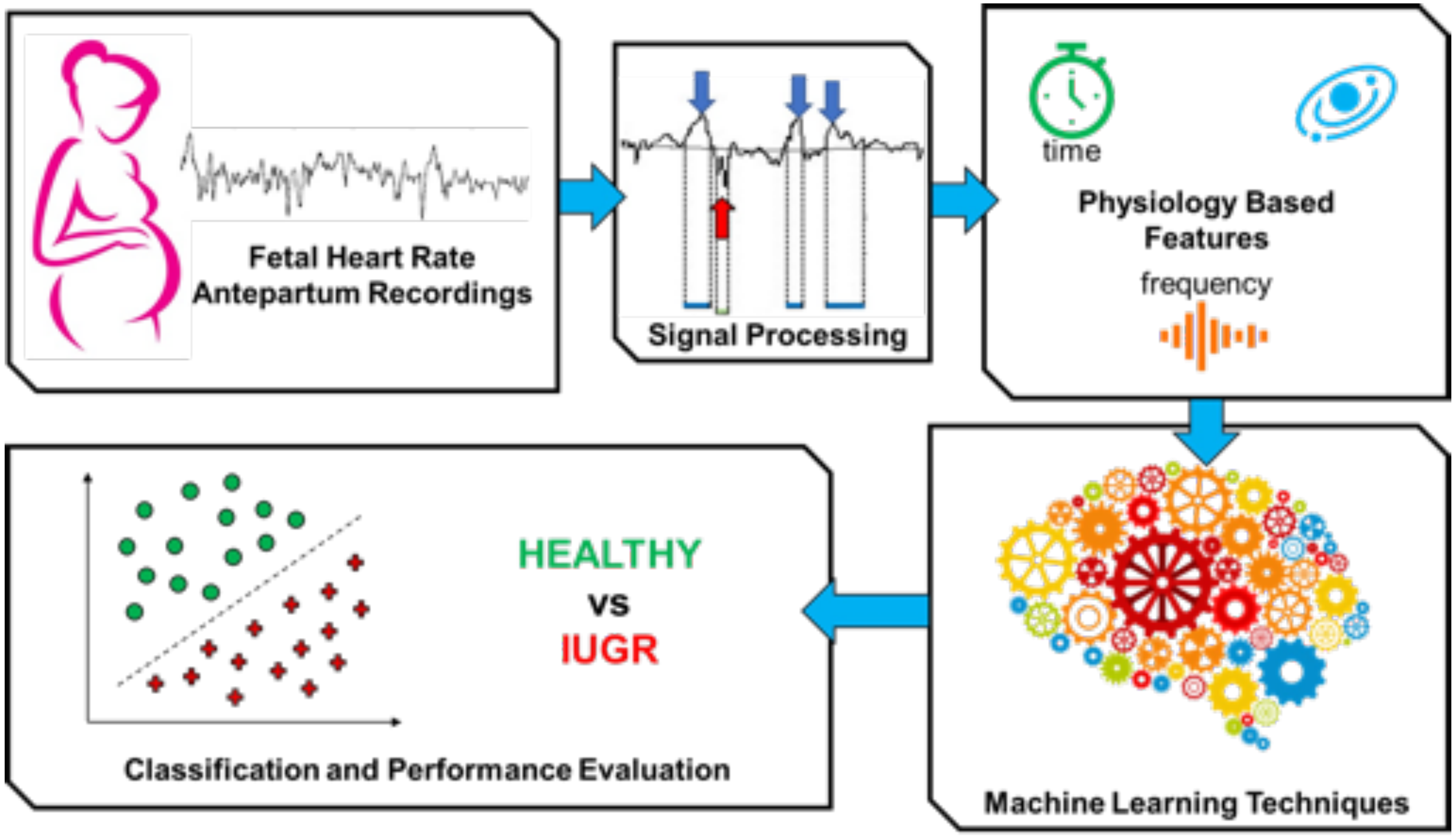
The biomedical engineer contribution

Set of new parameters

METHOD	PARAMETERS	SEQUENCE LENGTH	HYPOTHESIS
Frequency domain analysis AutoRegressive model estimation from data and measurement of spectral components in defined frequency bands.	% of spectral power ($msec^2$) in frequency bands: Low Frequency 0.03-0.15Hz Movement Frequency 0.15-0.5Hz High Frequency 0.5-1Hz LF/(MF+HF)	3 min 360 values	Quantification of the activity of the the autonomic nervous system.
Time domain analysis: morphological HR modification and variability	Delta (msec) STV (msec) II	1 min 120 values	Variability in the short period
	FHR avg (msec) LTI (msec)	3 min 360 values	Variability in the long period
Approximate Entropy	ApEn(1,0.2)	3 min 360 values	Presence of recurrent patterns in a single scale
Multiscale Entropy	MSE: entropy estimator as a function of a scale factor τ_{sf}	7000 values	Investigation of signal structure: repetitive patterns are present at different time scales.
Power Rectified Signal Averaging (PRSA)	Acceleration Phase Rectified Slope (APRS) and Deceleration Phase Rectified Slope (DPRS)	1200 values	Detection and quantification of quasi-periodic oscillations in nonstationary signals
Lempel Ziv Complexity (LZC)	LZC binary or ternary coding	7000 values	Rate of new patterns arising with the evolving of the signal

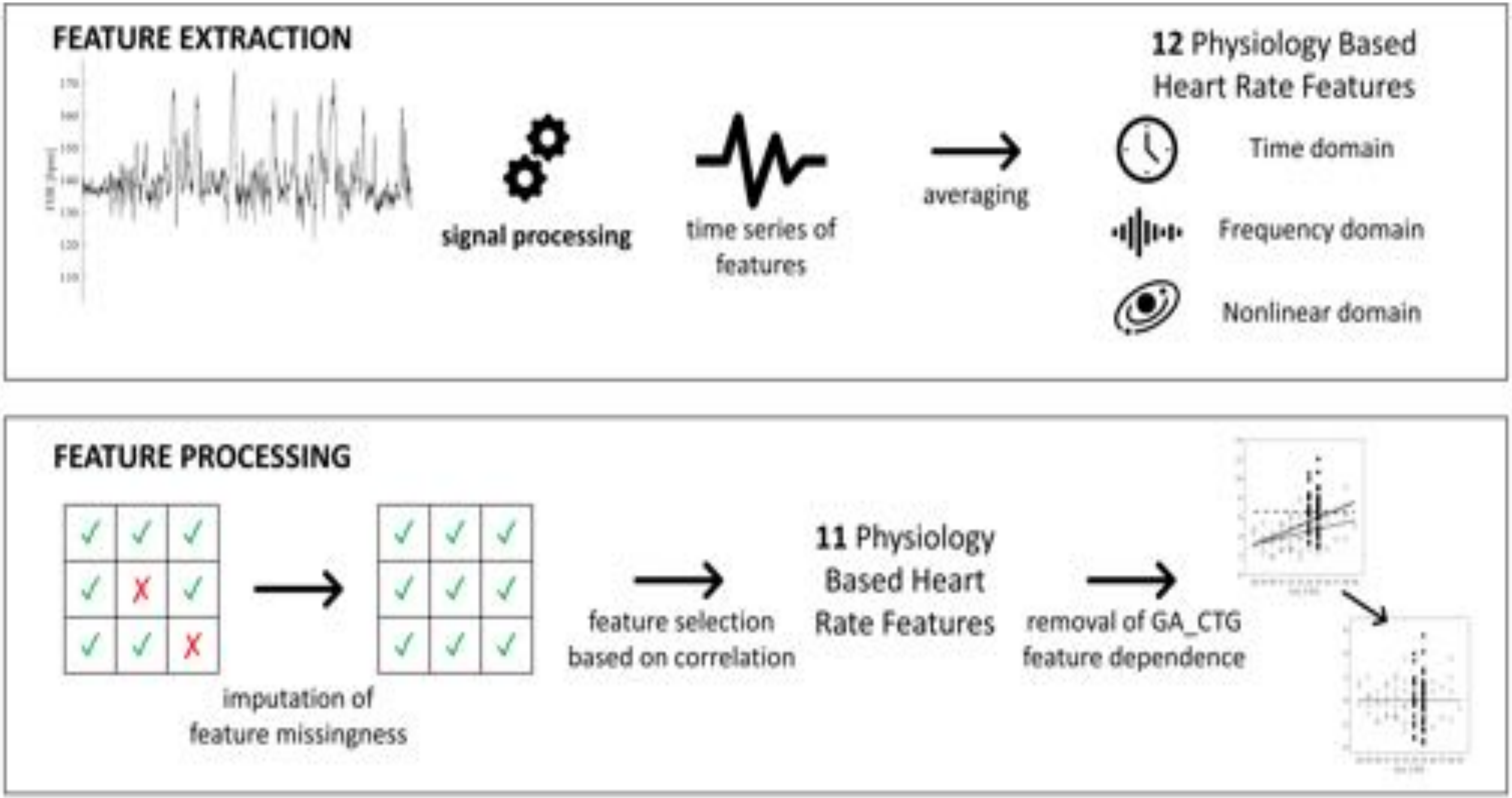
The biomedical engineer contribution

Pipeline of CTG analysis

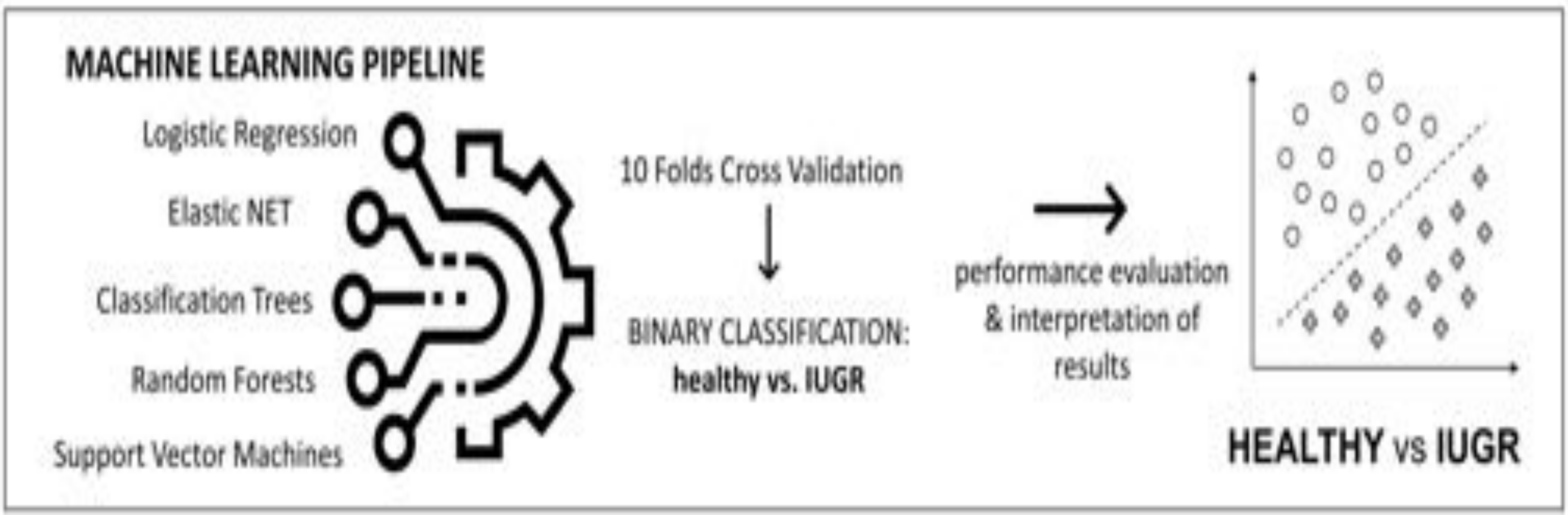


Signorini et al., 2020, Comp. Meth. & Programs in Biomedicine

Machine learning framework (I)



Machine learning framework (II)



M. G. Signorini, N. Pini, R. Bellazzi, A. Malovini, and G. Magenes. **"Integrating Machine Learning Techniques and Physiology Based Heart Rate Features for Antepartum Fetal Monitoring",** Computer Methods and Programs in Biomedicine, First published version available online: 17-OCT-2019 DOI: 10.1016/j.cmpb.2019.105015

Technical proposed solutions

Wearable INVU Solution

Good quality of maternal and fetal heart rate. 147 women. Remote solution for home monitoring

FIGURE 1
The Invu wearable belt is a self-administered device consisting of 8 electrical sensors and 4 acoustic sensors worn by the pregnant woman. The accompanying monitoring system also contains an algorithm that remotely analyzes the data for fetal heart rate (FHR) and maternal heart rate (MHR), and a data visualization layer, which can be accessed through 1 of 2 mobile apps that provide tailored information to either the healthcare provider or to the pregnant woman

Mhajna M, Schwartz N, Levit-Rosen L, et al. Wireless, remote solution for home fetal and maternal heart rate monitoring. Am J Obstet Gynecol MFM 2020;XX:x.ex-x.ex.

Moyo system Tanzania (intrapartum)

Regular fetal heart rate monitoring **during labor can drastically reduce** fresh stillbirths and neonatal mortality

An electronic strap-on fetal heart rate monitor called Moyo was introduced in Tanzania to improve intrapartum fetal heart rate monitoring

- *The electronic strap-on FHRM Moyo was perceived to make labor monitoring easier and to reduce stress among birth attendants, who, prior to the introduction of the device, described feeling overwhelmed by a high workload and an inability to adequately monitor each laboring woman.*

Tanzania

- **Moyo is a fetal heart rate (FHR) monitor designed for intermittent and prolonged monitoring in low-resource settings**

- A 9-crystal sensor accurately detects the fetal heart rate within seconds without needing to know the baby's position. Dual electrodes differentiate the maternal from the fetal heart rate which differs from a regular doppler. Moyo can be used continuously or intermittently.

Guatemala

- Limited funding for medical technology, low levels of education and poor infrastructure for delivering and maintaining technology severely limit medical decision support in low- and middle income countries.
- Perinatal and maternal mortality is of particular concern with millions dying every year from potentially treatable conditions.
- **Guatemala has one of the worst maternal mortality ratios, the highest incidence of intrauterine growth restriction (IUGR)**, and one of the lowest gross national incomes per capita within Latin America.

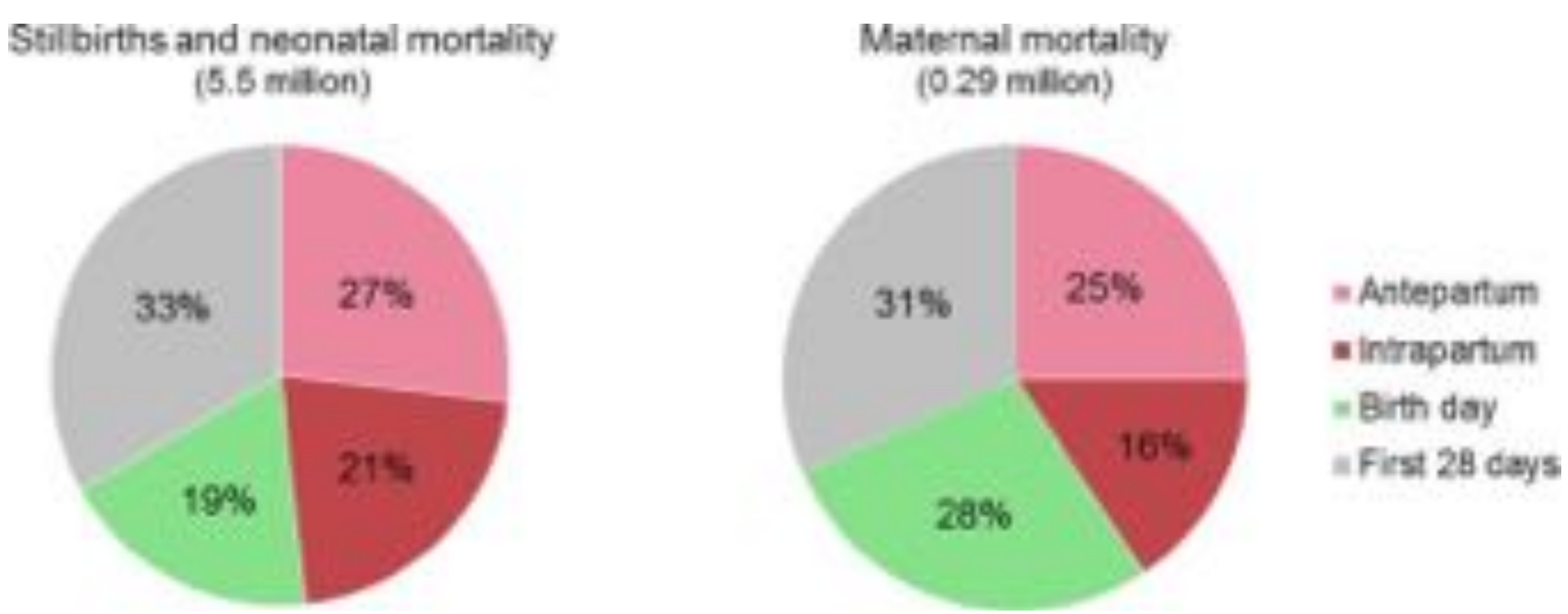
An mHealth monitoring system for traditional birth attendant-led antenatal risk assessment in rural Guatemala Dr Lisa Stroux, Dr Boris Martinez, Enma Coyote Ixen, Dr Nora King, Prof Rachel Hall-Clifford, Dr Peter Rohloff, Gari Clifford, Journal of Medical Engineering and Technology, Volume 40, Number 7-8, Publisher: Taylor & Francis | 2016-11-16, Pages 356-371 DOI: 10.1080/03091902.2016.1223196, Permanent URL: https://pid.emory.edu/ark:/25593/s5bjc

Guatemala Lisa Stroux

- **a smartphone-based system is proposed including peripheral sensors, such as a handheld Doppler for the identification of fetal compromise**.

- Designed for use by illiterate birth attendants, the system uses pictograms, audio guidance, local and cloud processing, SMS alerts and voice calling.

- The initial prototype was evaluated on 22 women in highland Guatemala. Results were fed back into the refinement of the system, currently undergoing RCT evaluation.



Maternal, fetal and early neonatal mortality rates as estimated globally, adapted from [4]. The majority of both maternal and perinatal deaths (close to 99%) occur in developing regions [1]. Perinatal estimates in particular are susceptible to error given discrepancies in death records [6], nevertheless they emphasise the high risk prevalent along the continuum of pregnancy and the often neglected post-partum period.

Guatemala technical solution

Traditional birth attendant with prototype equipment for recording fetal heart activity in a remote village in the Guatemalan highlands.

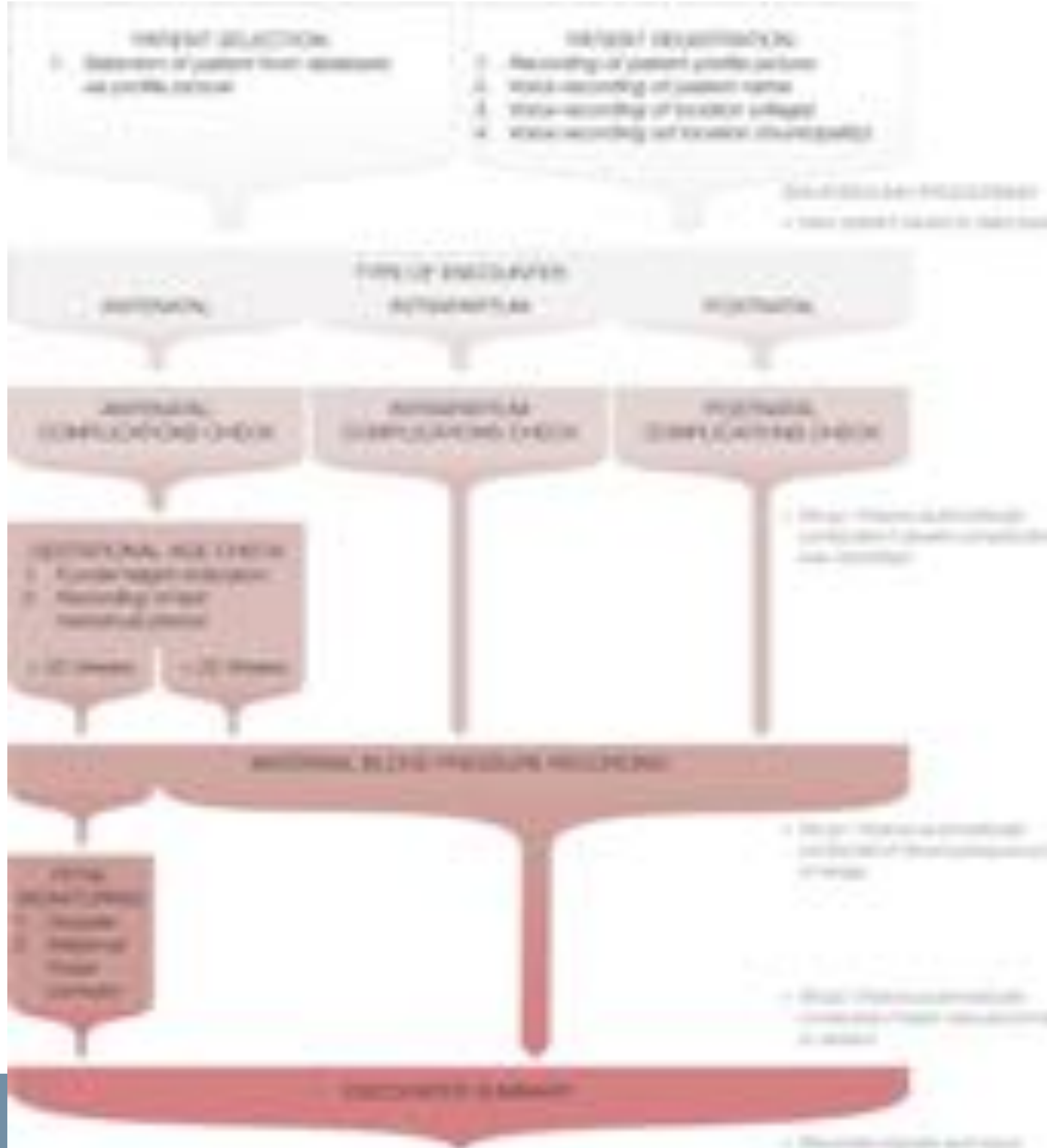
The separate components:

A: Smart phone,
B: Low-cost 1D Doppler,
C: Pulse oximeter
D: Speakers to enable both healthcare worker and patient to listen to the fetal cardiac signal.

Guatemala technical solution

Example screens of the mobile perinatal monitoring application. (a) Patient registration: In order to register a new patient the birth attendants is prompted to take a patient profile picture, guided by a positioning frame.
(b) Location information: The image provides a visual clue about the information to be collected, the loudspeaker button plays audio instructions if required, and the microphone button voice records the name of the patient’s home village provided by the midwife or patient.
(c) The physiological measurements are displayed real time to indicate successful recording. Signals are recorded for 30 minutes, the time elapsed is visualised by a progress wheel. Interface illustrations were produced for the specific use context, cLisa Stroux 2015, released under the creative commons license attribution 4.0 international (CC BY 4.0) Stroux et al. Page 28

Guatemala technical solution



OPEN CHALLENGES

Keywords and key questions

- **Technology** – how can we build technology able to be work efficiently in setting where resources are scarce (unstable powerline, low literacy, etc)?
- **Monitoring** – what role does scalability play in designing a piece of equipment/software?
- **Education** – how can we promote capacity building in low-middle income settings (acknowledging that everyone's background is different)?
- **Inclusion and Diversity** – think about your last published paper, did you report the breakdown of race and ethnicity in your sample/did you stratify your analysis by race and ethnicity?

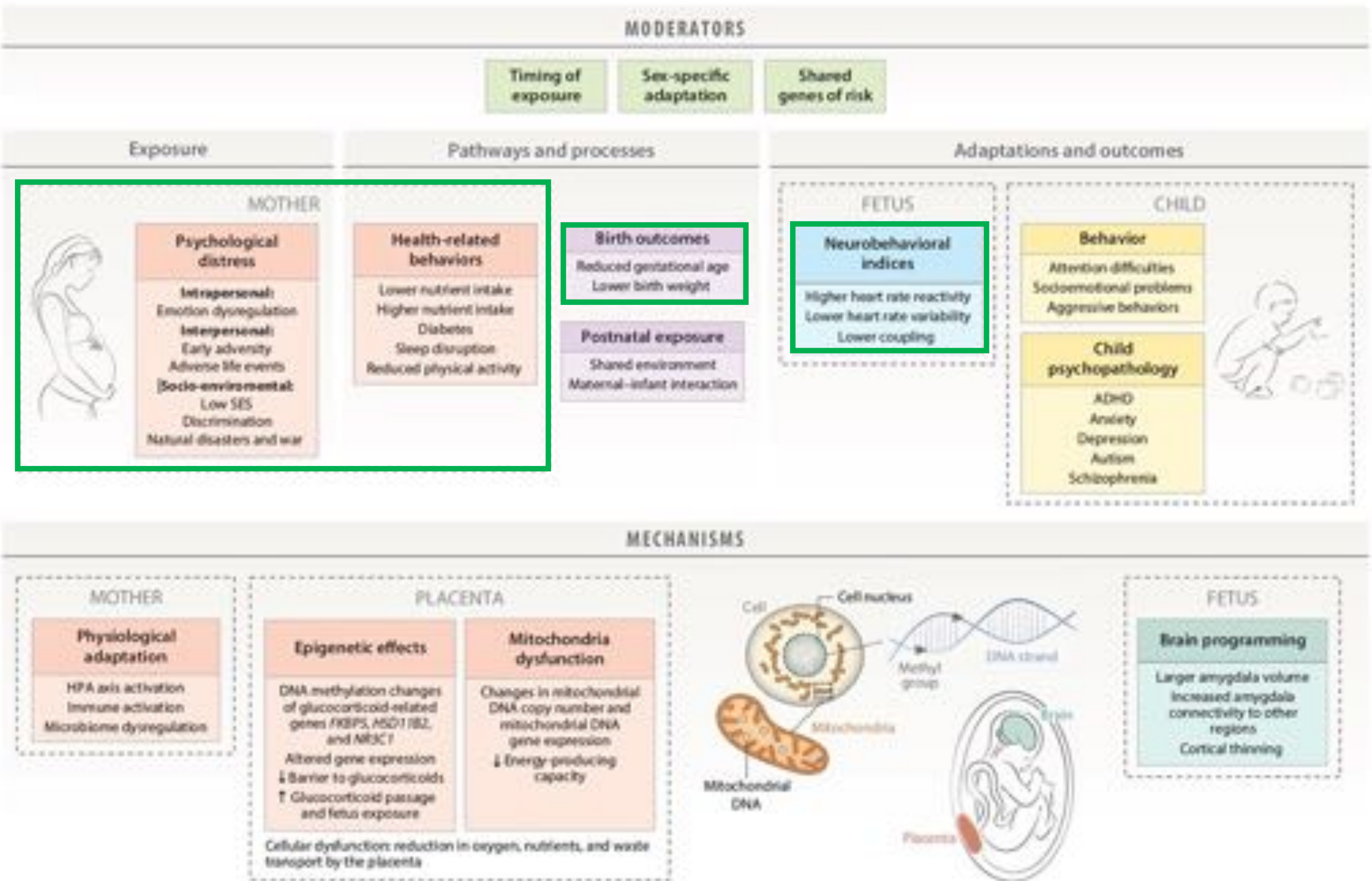
South Africa and Malawi in a snapshot

Contextual/environmental factors

- **59%** of mothers have at least finished high school
- **38%** of mothers are employed
- **70%** of mothers report monthly household income < $330
- **40%** of mothers are married or living with a partner
- **55%** of mothers live in shacks
- **18%** are at high risk for perinatal depression (EPDS)
- **41%** report having had inadequate financial resources to support or obtain food for their family
- **28%** feel unsafe in their neighborhood
- **91%** of mothers have heard gunshots while in their homes (SECV)
- **37%** have witnessed violence in their communities (SECV)
- **26%** have been physically attacked, with or without a weapon
- **22%** have been physically attacked by an intimate partner, with or without a weapon
- **41%** have experienced emotional abuse from an intimate partner (IPV)
- (At least) **17%** of mothers have been raped/sexually assaulted by an intimate partner (IPV)

What can we do to promote fetal (and maternal) wellbeing in low-middle income settings?

(while trying to raise the awareness of the importance of a comprehensive fetal monitoring throughout pregnancy to go beyond the primary outcome of a healthy delivery?)



Monk, C., Lugo-Candelas, C., & Trumpff, C. (2019). **Prenatal developmental origins of future psychopathology: mechanisms and pathways**. *Annual review of clinical psychology*, *15*, 317.

In-utero exposure to substance(s)

Original Investigation | Obstetrics and Gynecology
August 23, 2021

Association of Prenatal Exposure to Maternal Drinking and Smoking With the Risk of Stillbirth

Hein Odendaal, MD[1]; Kimberly A. Dukes, PhD[2,3,4]; Amy J. Elliott, PhD[5,6]; Marian Willinger, PhD[7]; Lisa M. Sullivan, PhD[3]; Tara Tripp, MA[2,4]; Coen Groenewald, MD[1]; Michael M. Myers, PhD[8,9]; William P. Fifer, PhD[8,9]; Jyoti Angal, MPH[5,6]; Theonia K. Boyd, MD[10]; Larry Burd, PhD[6]; Jacob B. Cotton, BS[10]; Rebecca D. Folkerth, MD[10]; Gary Hankins, MD[11]; Robin L. Haynes, PhD[10]; Howard J. Hoffman, MA[12]; Perri K. Jacobs, BS[10]; Julie Petersen, PhD[2,13]; Nicolò Pini, PhD[8]; Bradley B. Randall, MD[14]; Drucilla J. Roberts, MD[15]; Fay Robinson, MPH[2,16]; Mary A. Sens, MD, PhD[17]; Peter Van Eerden, MD[18]; Colleen Wright, MD[19]; Ingrid A. Holm, MD[20]; Hannah C. Kinney, MD[10]; for the Prenatal Alcohol in SIDS and Stillbirth (PASS) Network

> Author Affiliations | Article Information

JAMA Netw Open. 2021;4(8):e2121726. doi:10.1001/jamanetworkopen.2021.21726

Table 2. Associations Between Pregnancy Outcome and Exposure (Crude and Adjusted)

		Delivery at ≥28 weeks (n = 11 542)			Delivery at ≥20 weeks (n = 11 663)		
Exposure group	Pregnancies, No. (%) of total (n = 11 663)	Stillbirth, No. (%) (n = 82)	RR (95% CI)[a]	P value	Stillbirth, No. (%) (n = 145)	RR (95% CI)[a]	P value
Adjusted associations							
2-Level drinking and 2-level smoking (in model together)[d,e]							
Drinking (none/quit early)	8307 (73)	41 (0.5)	1 [Reference]	NA	87 (1)	1 [Reference]	NA
Drinking (continuous/quit late)	3096 (27)	40 (1)	1.87 (1.14-3.08)	.01	56 (2)	1.31 (0.90-1.90)[e]	.16
Smoking (none/quit early)	6810 (60)	31 (0.5)	1 [Reference]		64 (0.9)	1 [Reference]	
Smoking (continuous/quit late)	4593 (40)	50 (1)	1.45 (0.78-2.67)	.24	79 (2)	1.29 (0.86-1.93)[e]	.21
Primary: 4-level drinking and smoking[i,j]							
None/quit early	5806 (51)	21 (0.4)	1 [Reference]	NA	51 (0.9)	1 [Reference]	NA
Drinking only	1004 (9)	10 (1)	2.22 (0.78-6.18)	.06	13 (1)	1.26 (0.58-2.74)	.48
Smoking only	2501 (22)	20 (0.8)	1.60 (0.64-3.98)	.22	36 (1)	1.27 (0.69-2.35)	.35
Dual	2092 (18)	30 (2)	2.78 (1.12-6.67)	.005	43 (2)	1.75 (0.96-3.18)	.03

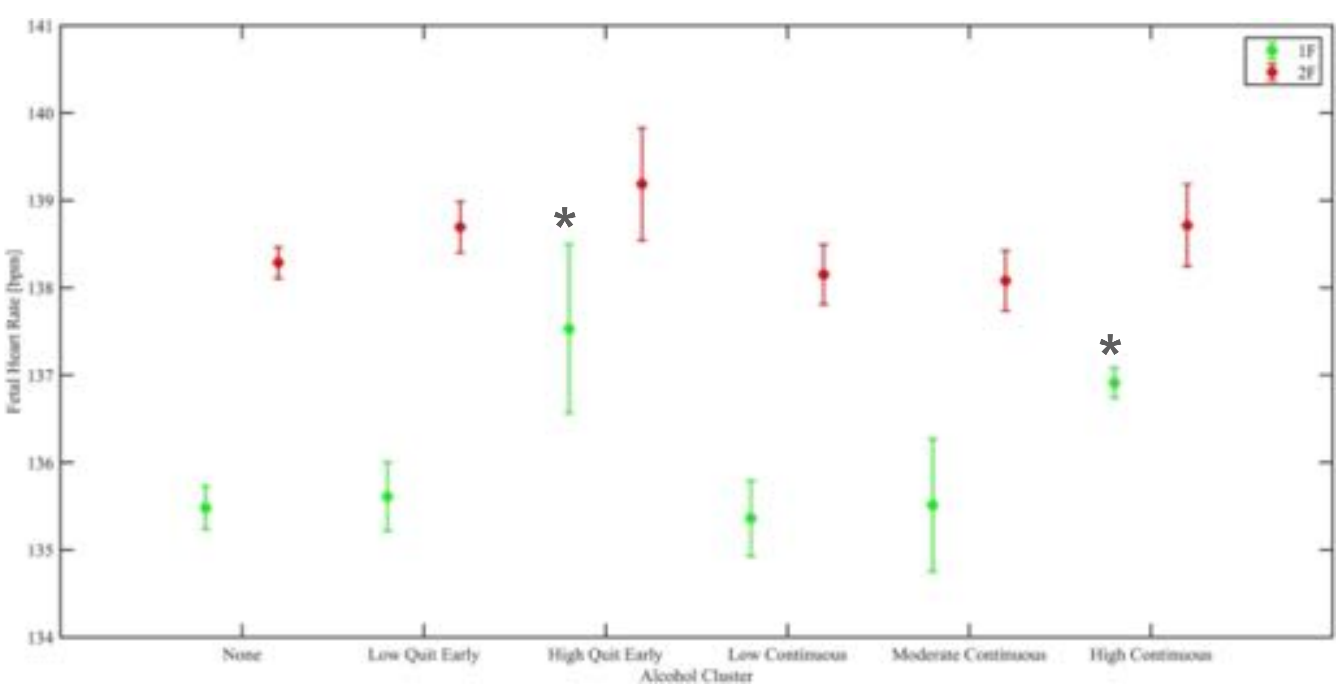
Findings – In this cohort study of 8,506 pregnant women (with 11,892 pregnancies) in Cape Town, South Africa, and the Northern Plains in the US, dual exposure to drinking and smoking after the first trimester of pregnancy had **2.78 times the risk** of late stillbirth compared with those with no exposure or who had quit before the end of the first trimester of pregnancy.

Odendaal, H., Dukes, K. A., Elliott, A. J., Willinger, M., Sullivan, L. M., Tripp, T., ... & Hereld, D. (2021). **Association of prenatal exposure to maternal drinking and smoking with the risk of stillbirth**. JAMA network open, 4(8), e2121726-e2121726.

frontiers in Physiology

Effects of Prenatal Exposure to Alcohol and Smoking on Fetal Heart Rate and Movement Regulation

Maristella Lucchini[1,2], Lauren C. Shuffrey[1,2], J. David Nugent[1,2], Nicoló Pini[1,2], Ayesha Sania[1], Margaret Shair[2], Lucy Brink[3], Carlie du Plessis[3], Hein J. Odendaal[3], Morgan E. Nelson[4,5], Christa Friedrich[4,5], Jyoti Angal[4,5], Amy J. Elliott[4,5], Coen A. Groenewald[5], Larry T. Burd[6], Michael M. Myers[1,2,7] and William P. Fifer[1,2,7] on behalf of the PASS Network*



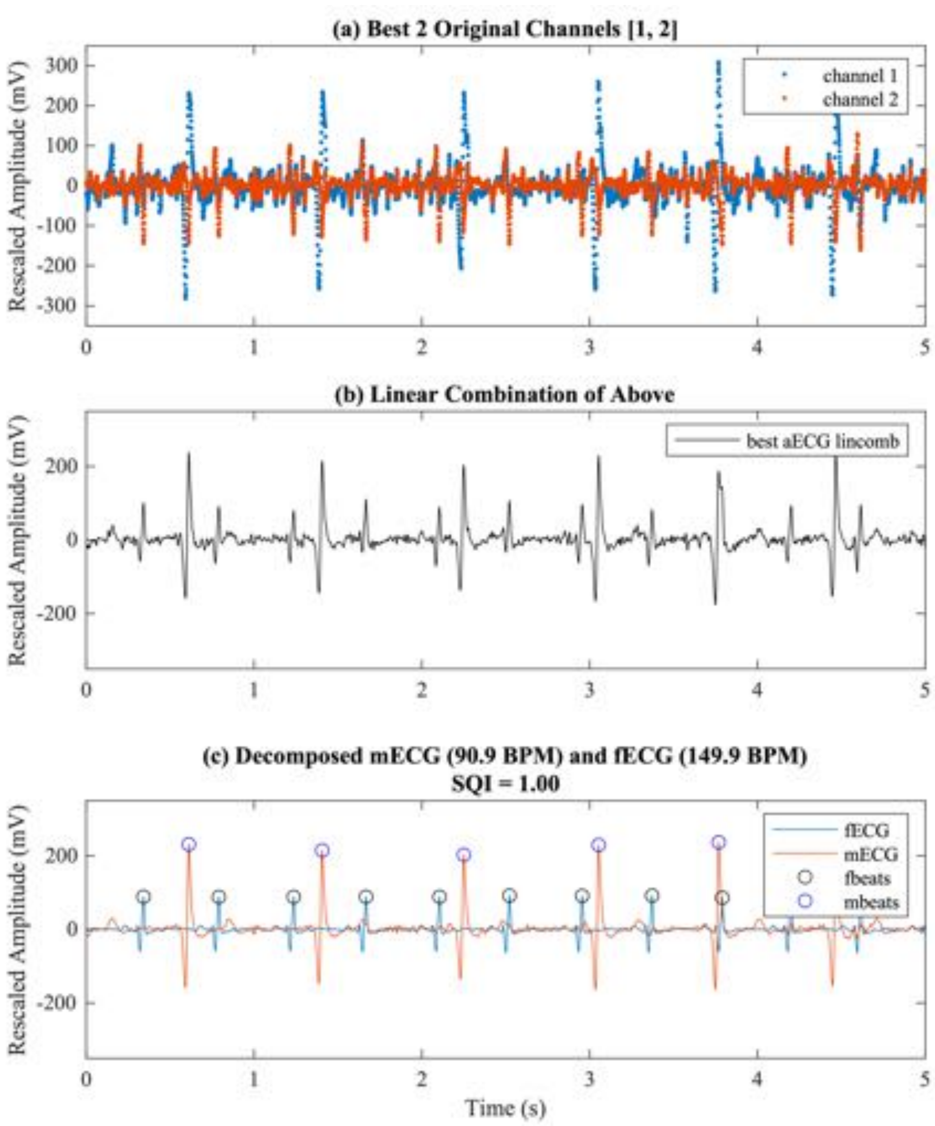
Findings – In this cohort study of 4,025 pregnant women in Cape Town, South Africa, high continuous drinking (irrespective of timing) was associated with higher fetal HR in 1F. The average increase in HR was ~2.1 bpm

PAE and PTE are risk factors for adverse fetal and neonatal outcomes such as IUGR, SIDS, and these same outcomes have been associated with altered ANS profiles

Lucchini, M., Shuffrey, L. C., Nugent, J. D., Pini, N., Sania, A., Shair, M., ... & Li, C. M. (2021). **Effects of Prenatal Exposure to Alcohol and Smoking on Fetal Heart Rate and Movement Regulation**. Frontiers in physiology, 1093.

44th Annual International Conference of the IEEE Engineering in Medicine and Biology Society
11-15 July 2022 Glasgow, Scotland, UK
IEEE EMB

In-utero exposure to GDM



- **In this cohort study of 108 pregnant women in Cape Town, South Africa, the average duration of fECG recordings was 59.33±5.54 min.**

- A comparable number of recordings for the three time points (F1, F2, F3) was analyzed.

- To validate the proposed algorithm, its performance was compared against the automatic extraction obtained via the Monica DK version 1.7 software.

- The resulting bias between the two measures was 16.55±4.38 BPM.

* This work has been carried out in collaboration with **Martin Frasch**

GDM as a risk factor (I)

In a linear regression model including FHR as the outcome measure:

- GDM fetuses had **5.72** BPM (CI [1.32 10.12]) <u>higher</u> FHR (wrt control fetuses) (p=0.0017)
  - Male fetuses had 6.05 BPM (CI [1.76 10.34]) higher FHR (wrt female fetuses) (p=0.0065)
  - Absence of significant gestational age dependency (narrow range of GA)
  - No association with maternal age, trauma, depression, anxiety, nor food insecurity

on the contrary…

In a linear regression model including RMSSD as the outcome measure:

- GDM fetuses had **25.69** ms (CI [6.11 45.27]) <u>lower</u> RMSSD (wrt control fetuses) (p=0.0087)
  - Male fetuses had 29.15 BPM (CI [2.07 56.23]) <u>lower</u> RMSSD (wrt female fetuses) (p=0.0025)
  - Absence of significant gestational age dependency (narrow range of GA)
  - No association with maternal age, trauma, depression, anxiety, nor food insecurity

GDM as a risk factor (II)

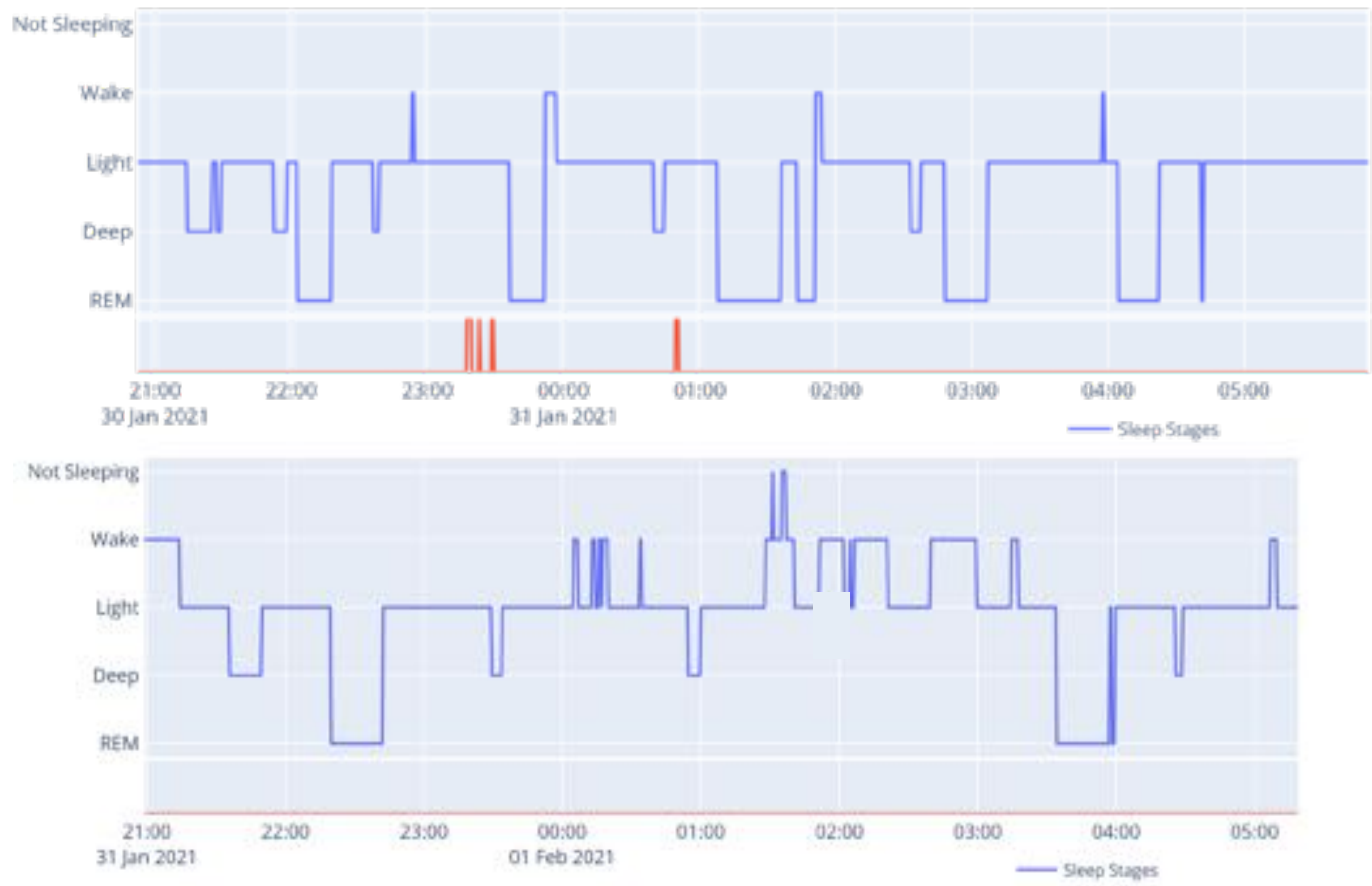
In a sex-stratify analysis, these reported effects were found more pronounced in **male fetuses**.

This ANS-derived risk profile has been previously reported in the **SIDS literature**:

- Higher risk for male infants via an underlying mechanisms of imbalanced ANS regulation

This speaks to the role of fetal life in shaping subsequent outcomes and to the role that fetal physiology could play in predictive models

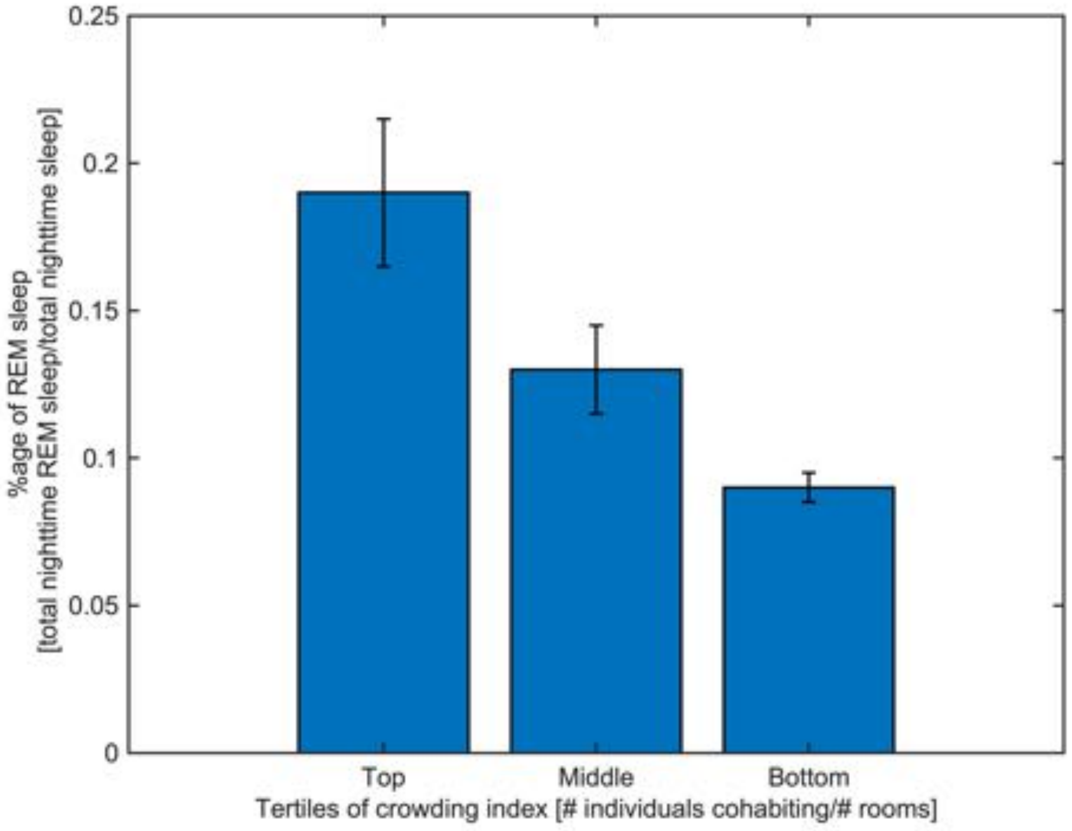
Sleep as biomarker



Today, I find out whether the baby is a boy or girl.
The thoughts surrounding this kept me from falling asleep and falling back asleep during the night.

https://www.frontiersin.org/articles/10.3389/fnins.2022.974192/full?utm_source=F-NTF&utm_medium=EMLX&utm_campaign=PRD_FEOPS_20170000_ARTICLE

Maternal REM sleep and Crowding Index



Results of ANOVA revealed a significant effect of CI on %age of REM sleep (p = .0025).

Corrected post hoc testing indicated significant differences for all of the pairwise comparisons

Pearson correlations revealed a significant association between CI and %age of REM sleep; r = .63, p =.007

how might this affect the fetus?

Lessons learned

- Contextual and/or environmental variables may play a crucial role in interpreting the fetal signal and may improve precision of the derived associations/relationships/predictions

- Wearables offer the opportunity to enable remote monitoring and complement more qualitative risk profiles predominantly derived from medical health records

- Research conducted in low-middle income settings presents far more opportunities than challenges (for the most part!)

- We are in this field together – we must partner to be able to answer the complex questions we want to address

Some Conclusions

- **importance of a multivariate approach** to investigate the variety of implications resulting from fetal heart rate analysis

- Computation of **different indices** on FHR signals, **either linear and non-linear**, can provide indications to **describe pathophysiological mechanisms** involved in the fetal heart rate control

- Advanced computation can be remotely performed even in rutral environnements and low resources contexts

- **Technological advanced solution** as **wearable and simplified monitoring** approaches can help the continuous fetal and maternal monitoring

Contribution of biomedical engineers can improve the fetal and maternal monitoring without reducing the level of the assistance **through novel approaches**

Thanks