THE NORMAL FETAL HEART RATE STUDY: ANALYSIS PLAN

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Abstract

Recording of fetal heart rate via CTG monitoring has been routinely performed as an important part of antenatal and subpartum care for several decades. The current guidelines of the FIGO (ref 1) recommend a normal range of the fetal heart rate from 110 to 150 bpm. However, there is no agreement in the medical community whether this is the correct range (ref 2). We aim to address this question by computerized analysis (ref 3) of a high quality database (HQDb, ref 4) of about one billion electronically registered fetal heart rate measurements from about 10,000 pregnancies in three medical centres over seven years. In the present paper, we lay out a detailed analysis plan for this evidence-based project in the vein of the validation policy of the Sylvia Lawry Centre for Multiple Sclerosis Research (ref 5) with a split of the database into an exploratory part and a part reserved for validation. We will perform the analysis and the validation after publication of this plan in order to reduce the probability of publishing false positive research findings (ref 6-7).

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1 INTRODUCTION

Recording of fetal heart rate via CTG monitoring has been routinely performed as an important part of antenatal and subpartum care for several decades. As stated by Massaniev (ref 2),

> "baseline rate provides valuable information
> on which we plan our further actions."

However, he also notes that

> "a survey of some well-established obstetric textbooks
> in Britain and abroad shows that there is no agreement
> on a normal term fetus's baseline heart rate."

The most frequently cited intervals are 110-150 bpm and 120-160 bpm, whereas 115-160 bpm and 110-160 bpm are used by a smaller number of clinicians. In the present study, we address this crucial issue from the point of view of clinical informatics, based on about one billion individual fetal heart rate measurements. Such an accurate definition of the normal fetal heart rate should allow to better detect abnormal fetal heart rates that may reveal bad condition of the fetus and necessitate intervention and to reduce the false alarm rate and the associated unnecessary interventions.

Previous research

Based on 250,000,000 individual fetal heart rate measurements, a preliminary study using the data from the hospital "Rechts der Isar" (Munich, Germany) for 2000 and 2001 revealed that the currently recommended normal ranges [110, 150 bpm] (ref 8) are inappropriate and should be shifted to [115, 160 bpm]. This might reduce the number of false alarms, a big problem in clinical practice. Our preliminary results were presented at the German Perinatal Congress (ref 9).

History of this analysis plan

This analysis plan is an improved version of an analysis plan draft written in March 2007. Besides small unimportant changes (typos, presentation, etc), the following substantial changes were carried out.

- It is now specified explicitly that confidence intervals are derived via the bootstrap method.
- The three validation data sets are now explicitly defined.
- Mixed models are now included.
- The analyses with the other parameters are now explained in more details.
- Separate analyses for each year are now included.

Criteria of inclusion of the CTGs

Only the CTGs of singleton pregnancies that are longer than 30 minutes will be included in the analysis.

Investigated variables

The following variables will be analyzed.

- Non-averaged raw fetal heart rate without accelerations and decelerations (FHR). Statistical unit = data point.
- Non-averaged baseline (BL) as computed by the CTG online algorithm (ref 3). Statistical unit = data point.
- Averaged raw fetal heart rate without accelerations and decelerations (AFHR). Statistical unit = CTG.
- Averaged baseline (ABL) as computed by the CTG online algorithm. Statistical unit = CTG.

Formulation of the normal fetal heart rate range

The main analysis will be based on the non-averaged baseline (BL). The normal interval for the fetal heart rate will be expressed as an interval of the form $[z_\alpha, z_{1-\alpha}]$, where z_α denotes the α-quantile. Values ending with 0 or 5 will considerably simplify

the practical application of the (new) normal heart rate range and improve its acceptance by clinicians. Because a width smaller than 40 bpm would further increase the false alarm rate and a width greater than 45 bpm would possibly put some fetuses in jeopardy, the admissible widths are 40 and 45 bpm.

Definition of the mathematical optimization problem

To sum up, we aim to find an interval of the form $[\tilde{z}_\alpha, \tilde{z}_{1-\alpha}]$ with:

- $\tilde{z}_\alpha$ and $\tilde{z}_{1-\alpha}$ ending with 0 or 5,
- $\tilde{z}_\alpha$ and $\tilde{z}_{1-\alpha}$ being as close as possible to the non-rounded quantiles z_α and $z_{1-\alpha}$, respectively,
- $\tilde{z}_{1-\alpha} - \tilde{z}_\alpha = 40$ or 45.

For $(z_-, z_+) \in \mathbb{R}_+^2$ and $\alpha < 0.5$, we define the optimality criterion $C(\alpha, z_-, z_+)$ as

$$C(\alpha, z_-, z_+) = (z_+ - z_{1-\alpha})^2 + (z_- - z_\alpha)^2.$$

For a fixed width W (e.g., $W = 40$ or $W = 45$), let ($\alpha^*(W)$,$z_-^*(W)$,$z_+^*(W)$) be the solution of the corresponding three-dimensional minimization problem:

$$C(\alpha^*(W), z_-^*(W), z_+^*(W)) = \min_{\alpha, z_-, z_+} (C(\alpha, z_-, z_+))$$

under the two following constraints:

1. $z_+^*(W) - z_-^*(W) = W$
2. $z_-^*(W)$ and $z_+^*(W)$ are multiples of 5.

It is to expect that this solution will be unique in practice. If not, we will choose the solution that is most similar to the FIGO recommendation (ref 1).

Finally, $C(\alpha^*(40), z_-^*(40), z_+^*(40))$ and $C(\alpha^*(45), z_-^*(45), z_+^*(45))$ will be compared. The width W^* yielding the minimal C will be selected as the final width and the normal fetal heart rate range will be defined as

$$[\, z_-^*(W^*)\, ,\ z_+^*(W^*)\,].$$

Training and validation

Validation of the results on an independent data set is a crucial step to avoid false research findings (ref 5-6). Both temporal validation (based on data collected later than the training data) and external validation (based on data collected in another medical center) are known to be important (ref 10). Hence, we adopt the following validation procedure.

Training data set

- data from the hospital "Rechts der Isar" (MRI), 2000-2004

Three validation data sets:

- data from the hospital "Rechts der Isar", 2005-2006 (temporal validation)
- data from the Marien-Hospital Witten (external validation, university hospital)
- data from the Achern hospital (external validation, non-university hospital)

First, all the analyses described below will be performed using the training data set only, without even opening the validation data sets. The main analysis (Part IA) will then be validated based on the three validation data sets. We will consider the results as completely validated if all three validation data sets yield the same range $[z^*_-(B^*), z^*_+(B^*)]$. If the result is different for at least one of the validation data sets, we will pool all four data sets and use them to suggest an interval (based on the same methodology) that will have to be validated in further research.

Part I: Estimation of the "normal" interval for the fetal hearth rate

A. Main analysis with BL

With BL only, we will determine the normal fetal heart rate range as described above using the following algorithm.

1. **Determining z_α and $z_{1-\alpha}$ for different values of α**
   For all $m \in \{100, \ldots, 125\}$, determine n such that

   $$\hat{F}(m-1) + \hat{F}(m) \;\approx\; (1 - \hat{F}(n)) + (1 - \hat{F}(n-1)),$$

   with $\hat{F}$ denoting the empirical distribution function of the fetal heart rate.

2. **Minimizing C for $W = 40$**
   For each pair of quantiles found in step 1, find the pair (z_-, z_+) of multiples of 5 minimizing C. Select the pair of quantiles yielding the smallest C and store the corresponding interval $[z_-^*(40), z_+^*(40)]$.

3. **Minimizing C for $W = 45$**
   Repeat step 2 for $W = 45$ instead of $W = 40$.

4. **Selecting the final range**
   Select the interval ($[z_-^*(40), z_+^*(40)]$ or $[z_-^*(45), z_+^*(45)]$) minimizing C as the final normal fetal heart rate.

The validation of this analysis will be performed as outlined in the introduction.

B. Complementary analyses

For FHR, BL, AFHR and ABL, the following analyses will be carried out based on the training data only.

1. Estimate of the 0.5%, 1%, 2.5%, 5%, 10%, 50%, 90%, 95%, 97.5%, 99%, 99.5% quantiles.

2. Estimate the 95% confidence interval and standard deviation of the 0.5%, 1%, 2.5%, 5%, 10%, 90%, 50%, 95%, 97.5%, 99%, 99.5% quantiles based on 100 (for FHR and BL) or 10000 bootstrap samples (for AFHR and ABL).

The validation of these analyses will be performed as follows. After all analyses with the training data are completed, step 1 will be repeated for all three validation data sets successively. A quantile computed with the training data will be considered as validated if the estimates based on all three validation data sets are located in the confidence interval derived from the training data set.

Part II: Association between fetal hearth rate and weeks of gestation

These analyses are based on the (comparatively small) subset of CTGs for which the week of gestation (WG) is known. Only training data are used.

1. Repeat the analyses from Part 1B for WG$<$28 (if there are more than 50 CTGs), WG in [28,31], WG in [32,36], WG$\geq$37.
2. Carry out linear regression with WG as predictor and AFHR or ABL as response (statistical unit = CTG).
3. Carry out linear regression with categorized WG (same thresholds as in A) as predictor and AFHR or ABL as response (statistical unit = CTG).
4. Carry out a mixed model analysis with WG as predictor and AFHR or ABL as response (statistical unit = CTG). This approach takes into account that some CTGs come from the same woman.

The validation of these analyses will be performed as follows. The models 2,3,4 will be fitted again to all three validation data sets successively. A significant p-value (i.e., p $<$0.05) obtained with the training data set will be considered as validated if it is also significant with all three validation data sets.

Part III: Association between fetal hearth rate and age of the mother

These analyses are based on the (comparatively small) subset of CTGs for which the age of the mother and the week of gestation (WG) are known. Only training data are used.

1. Carry out linear regression with age of the mother as predictor and AFHR or ABL as response (statistical unit = CTG).
2. Carry out a mixed model analysis with WG and age of the mother as predictors and averaged FHR and averaged BL as response (statistical unit = CTG). This approach takes into account that some CTGs come from the same woman.

These analyses will be validated using the approach outlined in Part II.

Part IV: Evolution of the fetal hearth rate

1. Perform the analyses from Part 1B with MRI data from 2000-2001 only (already published data).
2. Perform the analyses from Part 1B with MRI data for each year (2000,2001,2002,2003,2004) separately.

Appendix: Additional explorative analyses

Further questions related to the fetal heart rate may be investigated in future research, provided that the corresponding data are available. Among others:

1. Perform the analyses from Part 1B with ante partu CTGs only.
2. Perform the analyses from Part 1B with sub partu CTGs only.
3. Perform the analyses from Part 1B for all CTGs excepting fetuses with acidosis or amniotic infection.
4. Perform the analyses from Part 1B for sub partu CTGs with acidosis.
5. Perform the analyses from Part 1B for sub partu CTGs with amniotic infection.
6. Perform the analysis from Part 3 (1-2) with the sex of the fetus as additional predictor.

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