

Measurement of the cardiac time intervals of the fetal ECG utilising a computerised algorithm: A retrospective observational study

JRSM Cardiovascular Disease
Volume 11: 1–11
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/20480040221096209
journals.sagepub.com/home/cvd



SC Chivers^{1,4} , T Vasavan¹, M Nandi⁵ , BR Hayes-Gill⁶,
IA Jayawardane⁶ , JM Simpson⁴, C Williamson¹, WP Fifer^{2,3}
and M Lucchini^{2,3}

Abstract

Objective: Establish whether the reliable measurement of cardiac time intervals of the fetal ECG can be automated and to address whether this approach could be used to investigate large datasets.

Design: Retrospective observational study.

Setting: Teaching hospitals in London UK, Nottingham UK and New York USA.

Participants: Singleton pregnancies with no known fetal abnormality.

Methods: Archived fetal ECG's performed using the MonicaAN24 monitor. A single ECG (PQRST) complex was generated from 5000 signal-averaged beats and electrical cardiac time intervals measured in an automated way and manually.

Main Outcome measure: Validation of a newly developed algorithm to measure the cardiac time intervals of the fetal ECG.

Results: 188/236 (79.7%) subjects with fECGs of suitable signal:noise ratio were included for analysis comparing manual with automated measurement. PR interval was measured in 173/188 (92%), QRS complex in 170/188 (90%) and QT interval in 123/188 (65.4%). PR interval was 107.6 (12.07) ms [mean(SD)] manual vs 109.11 (14.7) ms algorithm. QRS duration was 54.72(6.35) ms manual vs 58.34(5.73) ms algorithm. QT-interval was 268.93 (21.59) ms manual vs 261.63 (36.16) ms algorithm. QTc was 407.5(32.71) ms manual vs 396.4 (54.78) ms algorithm. The QRS-duration increased with gestational age in both manual and algorithm measurements.

Conclusion: Accurate measurement of fetal ECG cardiac time intervals can be automated with potential application to interpretation of larger datasets.

Keywords

Fetal, ECG, pregnancy, abdominal fetal ECG, cardiac time intervals, algorithm, signal to noise ratio

Date received: 23 January 2022; Revised 4 April 2022; accepted: 5 April 2022

Introduction

Non-invasive fetal ECG (fECG) acquired by signals generated using maternal abdominal electrodes is not utilised routinely in clinical practice for assessment of suspected arrhythmia or measurement of the electrical cardiac time intervals (CTI).^{1–8} Signal to noise ratio remains the main barrier to clinical application. Current guidelines recommend fetal echocardiography but acknowledge interest in emerging technologies, including fECG.⁹

Echocardiography is the dominant non-invasive modality used to assess fetal heart structure, function and rhythm. This has the advantage of convenience, but uses mechanical

¹Department of Women and Children's Health, King's College London, London, UK

²Department of Pediatrics, Columbia University Medical Center, Morgan Stanley Children's Hospital, New York, USA

³Department of Psychiatry, Columbia University, New York, USA

⁴Department of Fetal cardiology, Evelina London Children's Hospital, London, UK

⁵School of Cancer and Pharmaceutical Sciences, King's College London, London, UK

⁶Faculty of Engineering, University of Nottingham, Nottingham, UK

Corresponding author:

Dr Maristella Luccinni, Columbia University Medical Center, New York State Psychiatric Institute, 1051 Riverside Dr, Unit 40, New York, NY 10032

Email: ml3551@cumc.columbia.edu



rather than electrical events to assess rhythm, limiting information on the electrical cardiac time intervals and cardiac repolarisation. Alternative techniques including magnetocardiography (fMCG) are not widely available, expensive and require magnetic shielding. A further drawback is an inability to monitor fetal cardiac rhythm over prolonged periods where paroxysmal arrhythmias or response to prenatal therapy could be assessed.

A device that accurately separates the fECG from the dominant maternal ECG (mECG) signal would be valuable in clinical practice in the management of the fetus with arrhythmia, congenital heart disease (CHD) and conditions predisposing to stillbirth, through longitudinal community/home monitoring. Optimal application would be similar to the use of the Holter monitor. The fECG could inform management and identify red flags that may signify or prevent disease progression.

Advances in signal processing, powerful real time microprocessors and low noise analogue electronics have increased availability of non-invasive portable devices with the ability to isolate the fECG signal independently of the mECG. Refining the signal with filtering, processing and amplification techniques produces a complex where fetal P, QRS and T components may be identified. These techniques have sparked renewed interest with several papers looking at the CTI and heart rate variability.^{1–8,10}

The current “gold standard” for ECG interpretation is manual analysis, but this requires expertise and is not feasible for large datasets. This study therefore aimed to establish whether fetal CTI measurement can be automated. Automated measurement is in place in postnatal practice and would have the potential to improve utility of this approach before birth. Additionally, the technique may reduce operator bias or skewed interpretation. We report the results of such a comparison.

Design and setting

This retrospective observational study investigated the fECG from 236 participants recruited from Guy’s and St Thomas’ Hospital NHS Foundation Trust and Queen Charlotte’s and Chelsea Hospital (London, UK) (REC approvals:15/WM/0017,16/LO/0839). Nottingham University Hospital (Nottingham, UK) (REC approval: 08/H0707/21). Midland office, Rapid City and Sanford Health, Sioux Falls (South Dakota, USA⁽⁷⁾). Ethical approval was obtained from Sanford Health, the Indian Health Service, and New York State Psychiatric Institute (NYSPI) (IRB approvals: CR00000266,5338). NYSPI approval was obtained to analyse de-identified data collected at Sanford Health. Data was collected between November 2007 and March 2011 in Nottingham, March 2015 and November 2018 in Guy’s and St Thomas’ Hospital and April 2015 and December 2017 in Queen Charlotte’s and Chelsea hospital. Data was collected between December 2011 and August 2015 in the USA.

Participants

Participants provided either a 30–60 min clinic recording or 12–16 h overnight recording whilst at home/as a hospital inpatient. Inclusion criteria were singleton pregnancies with gestational age (GA) 20–40 weeks (median 34.9 weeks, IQR 32.1–36.0 weeks) in women aged ≥ 18 years. Exclusion criteria were multifetal pregnancies and known fetal CHD.

The majority of participants had healthy pregnancies (68.6%, 162/236). The remainder had a medical/obstetric history including: intrahepatic cholestasis of pregnancy, diabetes mellitus, hypertension, hyperthyroidism, hypothyroidism, antiphospholipid antibody, renal disease, history of fetal CHD, history of cancer and previous deep vein thrombosis. Subgroup analysis based on the presence of coexistent condition was not undertaken as the focus was validation of the algorithm.

Signal acquisition and processing

The fECG was recorded using the MonicaAN24 monitor and analysed using the MonicaDKv1.9 program (Monica Healthcare Limited., Nottingham, UK.). The device recorded for 30 min to 16 h and was fitted in the standardised manner by skin preparation and placement of five electrodes across the maternal abdomen.⁸ The AN24 fECG is hardware filtered from approximately 0.2–110 Hz then passed into the analogue to digital converter sampling at 900 Hz. Suitable regions of recording (30–200 min) were qualitatively examined for continuous fetal signal, stable heart rate and absence of non-physiological artefacts and extracted for analysis. A signal-averaged fECG complex was generated via MonicaDKv1.9 from the fetal signal (following extraction from the mECG by MonicaDKv1.9) using a heart rate range of 120–160 beats per minute (bpm). Where there were multiple areas of usable fECG acquisition, several sections with good acquisition as defined above were assessed, and one signal-averaged complex with the clearest points of interest visually was chosen for analysis. The steps for signal acquisition and processing are shown in Figure 1. The mixed mECG/fECG signals are shown in Figures 5C/6A and the signal averaged fECG complexes are shown in Figures 2/5A/6B.

A script was created using MATLABR2020a (Mathworks Inc., Natick, MA, USA) to measure CTI from the fECG complex generated from the MonicaDK software. The script is an adaptation of Aalizade et al.¹¹ which identifies the fiducial points of an ECG signal. The newly developed script processed the fECG complex with a lowpass Butterworth filter at 100 Hz and high pass filter at 0.2 Hz. Successively, the signal was processed with a derivative filter, squared, normalised and processed with a moving average filter. The R-peak of the processed fECG complex was identified and used as a reference point to determine

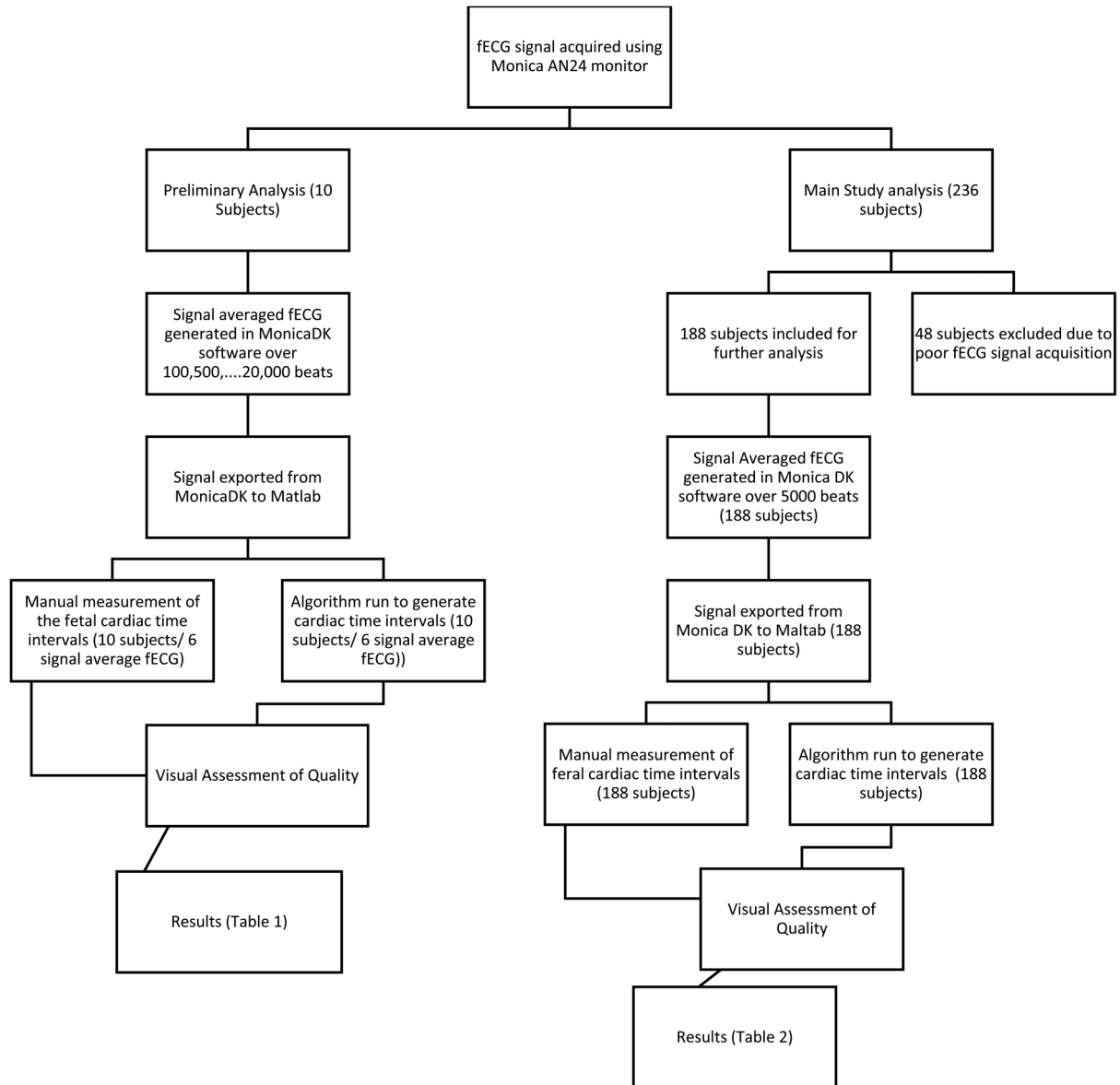


Figure 1. Flowchart delineating the process from data acquisition to result generation in preliminary study and main study.

peaks of the P and T wave alongside troughs of the QRS-complex. Two methods were implemented to identify the start of the P wave since the fECG may include additional baseline wander. Firstly, a change in concavity of the baseline prior to the P-peak (PRStart_A) and secondly, local minimum prior to the P-peak (PRStart_B). The end of the T-wave was identified as the local minimum after the T-peak. Following identification of each element of the fECG complex, the CTI were measured and converted to milliseconds (ms). The PR-interval was calculated in two ways. Firstly, using PRStart_A as the starting point, generating PRAI_g_A and secondly using PRStart_B as a starting point, generating PRAI_g_B.

Signal quality assessment and fiducial points (P, QRS_{start}, Q, R, S, QRS_{end}, T_{end}) were marked manually in 188 subjects by two independent observers skilled in

ECG interpretation (SC/TV). Quality of the averaged complex was assessed by SC/TV and rated as good or poor by the observer. A poor rating was given if there was inability to locate a point of interest due to baseline wander, poor delineation of onset/offset of a wave, additional deflections within a wave or noise such that points of interest could not be defined visually. Where there was an inadequacy, the waveform was assessed to see which CTI would be appropriate to measure and consensus agreed between SC/TV. Inter-observer reliability between manual measurements of the investigators (SC/TV) was calculated, with an intraclass coefficient of 0.97 for the PR-interval, 0.89 for the QRS-duration and 0.79 for the QT-interval. Because there was agreement between observers, measurements from SC were subsequently used to

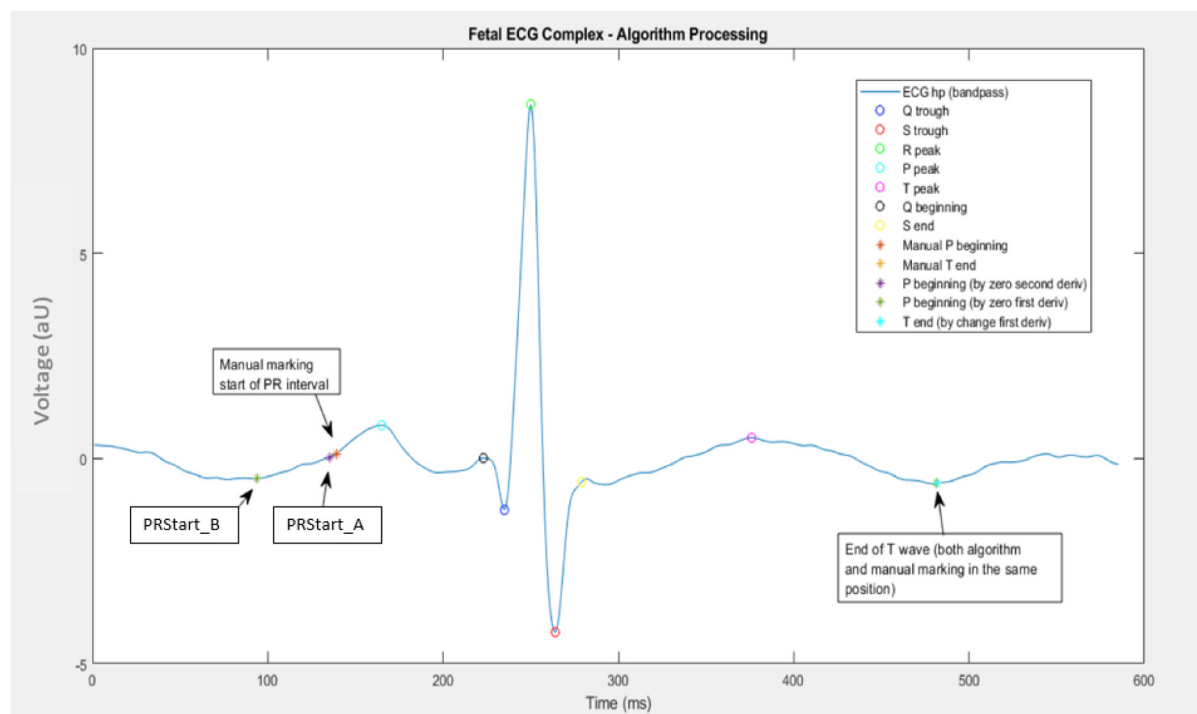


Figure 2. Example of fECG complex plotted with markings after being processed by the algorithm. The markings of the algorithm can be compared with manual observations (as shown) or plotted alone. (PRStart_A and PRStart_B are algorithm derived measures delineating the start of the P wave).

compare manual and algorithm measurements. The corrected QT interval (QTc) was calculated from the QT-interval using Bazett's formula as used in other non-invasive fECG studies and commonly used in clinical practice.^{4,5}

Preliminary assessment was undertaken to investigate the effect of signal averaging on the quality of the complex and ability to measure the fetal CTI. Ten subjects were randomly chosen, and an average complex generated using 100, 500, 1000, 5000, 10,000 and 20,000 beats from the same starting position on the recording. The quality of the signal was assessed and CTI measured as described below.

Statistical analysis

Statistical analysis was performed using SPSS statistics 26 (SPSS Inc., Chicago, IL, USA.). Results were normally distributed and are presented as population means with standard deviation in parentheses and 95% confidence intervals (CI) in brackets. Statistical significance was set at $p < 0.05$. Inter-observer reliability was calculated using the interclass coefficient. Bland-Altman plots were used to assess agreement between manual measurement of CTI and those generated by the algorithm. The correlation between CTI measurements and GA was assessed using linear regression. Regression coefficients (β) have been presented.

Results

Of the 236 recruited participants, 188 provided fECG data suitable for analysis with median GA 34.9 weeks, IQR 32.1–36.0 weeks. Overall, 48 out of 236 participants were excluded due to poor/no fECG signal or significant noise, where the points of interest could not be visually identified. 20/37 (54%) of the 30–55 min recordings and 28/199 (14%) of the >12 h recordings were rejected prior to analysis. Each complex was analysed for calculation of the fetal CTI. An example of the algorithm's output is shown in Figure 2.

Signal-averaged complexes were optimal when generated from 5000 beats; with highest visual quality according to the criteria described in methods and greatest agreement of manual and automated measurements (Table 1). At 100 and 500 averaged beats the quality of the complex was poor in several cases such that the points of interest could not be identified by the automated process.

The PR-interval was measured in 173/188 (92%), QRS-duration in 170/188 (90%) and QT-interval in 123/188 (65.4%) subjects by operator agreement (SC/TV) for inclusion in further analysis.

Measurement of the fetal cardiac time intervals

The PR-interval was 107.60 ms (12.07 ms) [95%CI: 105.79–109.41 ms] manual measurement and 118.54 ms (23.21 ms) [95%CI: 115.05–122.02 ms] algorithm measurement of

Table 1. Preliminary assessment demonstrating the effect of signal averaging on the cardiac time intervals of the fetal ECG in ten random? subjects.

| Number of Signal averaged complexes | 100 | 500 | 1000 | 5000 | 10,000 | 20,000 |
|-------------------------------------|---------|---------|---------|---------|---------|---------|
| PR Manual (ms) | 99.67 | 101.67 | 104.33 | 101.56 | 100.11 | 100.44 |
| [Mean (SD)] | (11.34) | (9.53) | (11.14) | (8.53) | (8.58) | (9.58) |
| PRAI _g _A (ms) | 123.78 | 103.58 | 100.49 | 105.22 | 105.89 | 108.22 |
| [Mean (SD)] | (26.35) | (33.31) | (28.89) | (7.93) | (10.42) | (9.45) |
| PRAI _g _B (ms) | 108.44 | 97.90 | 99.38 | 107.11 | 112.56 | 116.33 |
| [Mean (SD)] | (27.10) | (29.47) | (34.59) | (13.62) | (17.72) | (26.60) |
| QRS Manual (ms) | 50 | 52.89 | 54.11 | 54.11 | 55.44 | 54.00 |
| [Mean (SD)] | (5.88) | (6.18) | (5.08) | (2.96) | (4.07) | (3.40) |
| QRS Algorithm (ms) | 54.22 | 59.01 | 57.41 | 56.00 | 56.56 | 56.11 |
| [Mean (SD)] | (3.46) | (6.05) | (6.11) | (5.30) | (5.53) | (5.30) |
| QT Manual (ms) | 216.33 | 237.33 | 242.78 | 244.67 | 250.78 | 251.22 |
| [Mean (SD)] | (43.47) | (32.61) | (46.11) | (32.73) | (30.79) | (29.81) |
| QT Algorithm (ms) | 245.33 | 230.62 | 220.25 | 233.44 | 240.22 | 239.56 |
| [Mean (SD)] | (40.81) | (38.43) | (37.96) | (23.63) | (28.72) | (27.90) |

Table 2. Cardiac time intervals of the fetal ECG (all subjects) using a complex derived from 5000 signal averaged beats.

| | N | Mean (ms) | SD (ms) | 95% CI (ms) |
|----------------------|-----|-----------|---------|---------------|
| PR Manual | 173 | 107.60 | 12.07 | 105.79–109.41 |
| PRAI _g _A | 173 | 109.11 | 14.70 | 106.91–111.32 |
| PRAI _g _B | 173 | 118.54 | 23.21 | 115.05–122.02 |
| QRS Manual | 170 | 54.72 | 6.35 | 53.76–55.68 |
| QRS Algorithm | 170 | 58.34 | 5.73 | 57.47–59.21 |
| QT Manual | 123 | 268.93 | 21.59 | 265.08–272.79 |
| QT Algorithm | 123 | 261.63 | 36.16 | 255.17–268.08 |
| QTc Manual | 123 | 407.48 | 32.71 | 401.64–413.31 |
| QTc Algorithm | 123 | 396.40 | 54.78 | 386.62–406.18 |

PRAI_g_B and 109.11 ms (14.70 ms) [95%CI: 106.91–111.32 ms] algorithm measurement of PRAI_g_A (n = 173, Table 2). The QRS-duration was 54.72 ms (6.35 ms) [95%CI: 53.76–55.68 ms] manual measurement and 58.34 ms (5.73 ms) [95%CI: 57.47–59.21 ms] algorithm measurement (n = 170, Table 2). The QT-interval was 268.93 ms (21.59 ms) [95%CI: 265.08–272.79 ms] manual measurement and 261.63 ms (36.16 ms) [95%CI: 255.17–268.08 ms] algorithm measurement (n = 123, Table 2). The QTc-interval (Bazett formula) was 407.5 ms (32.71 ms) [95%CI: 401.64–413.31 ms] manual measurement and 396.40 ms (54.78 ms) [95%CI: 386.62–406.18 ms] algorithm measurement (n = 123, Table 2).

Bland-Altman assessment demonstrated that PR/PRAI_g_B measurements had a bias of –10.94 ms and limits of agreement (LOA) of 29.29 and –51.17 ms. PR/PRAI_g_A measurements showed a bias of –1.52 ms and LOA of 19.94 and –22.97 ms. QRS/QRSAlg measurements showed a bias of –3.62 ms and LOA of 5.33 and –12.57 ms. QT/QTAI_g-interval measurements showed a bias of 7.31 ms and LOA of 67.02 and –52.4 ms (Figure 3).

The amplitude of the P and T waves was greater in averaged complexes accepted for analysis based on quality than rejected. Accepted complexes had larger amplitude

measurements of (mean/SD) 0.39 arbitrary units(au)/0.4 au for PRAI_g_A, 0.46 au/0.33 au for PRAI_g_B and 0.5 au/0.4 au for T. Rejected complexes had amplitude measurements of (mean/SD) 0.21 au/0.17 au for PRAI_g_A, 0.25 au/0.19 au for PRAI_g_B and 0.22 au/0.35 au for T.

Measurement of the fetal cardiac time intervals and gestational Age

The CTI according to GA groups are shown in Table 3/ Figure 4. Linear regression analysis showed the manual PR-interval measurements were significantly positively correlated with GA ($\beta=0.170$, $p=0.03$). Algorithm-derived PRAI_g_B ($\beta=0.110$, $p=0.190$) and PRAI_g_A ($\beta=0.100$, $p=0.220$) measurements did not significantly correlate with GA. QRS-duration significantly positively correlated with GA both by manual measurement ($\beta=0.190$, $p=0.02$) and by algorithm measurement ($\beta=0.210$, $p=0.01$). QT-interval was not correlated with GA by manual measurements ($\beta=0.550$, $p=0.560$) or algorithm measurements ($\beta=0.800$, $p=0.390$). There was no correlation between amplitude of P wave ($\beta=-0.001$, $p=0.991$) and T wave ($\beta=0.177$, $p=0.058$) with GA.

Ability to measure the PR interval increased as gestation progressed. At GA ≤ 32 weeks, it was 86%(38/44), 32–36 + 6 weeks 94%(102/109) and 95%(20/21) at >37 weeks of gestation. Ability to measure the QT interval also increased as gestation progressed. At GA ≤ 32 weeks, it was 39%(17/44), 32–36 + 6 weeks 72%(79/109) and 81%(17/21) at >37 weeks of gestation. Ability to measure the QRS-duration remained constant throughout gestation.

Notable cases

One fetus developed sudden onset tachycardia lasting twenty minutes with altered morphology of the

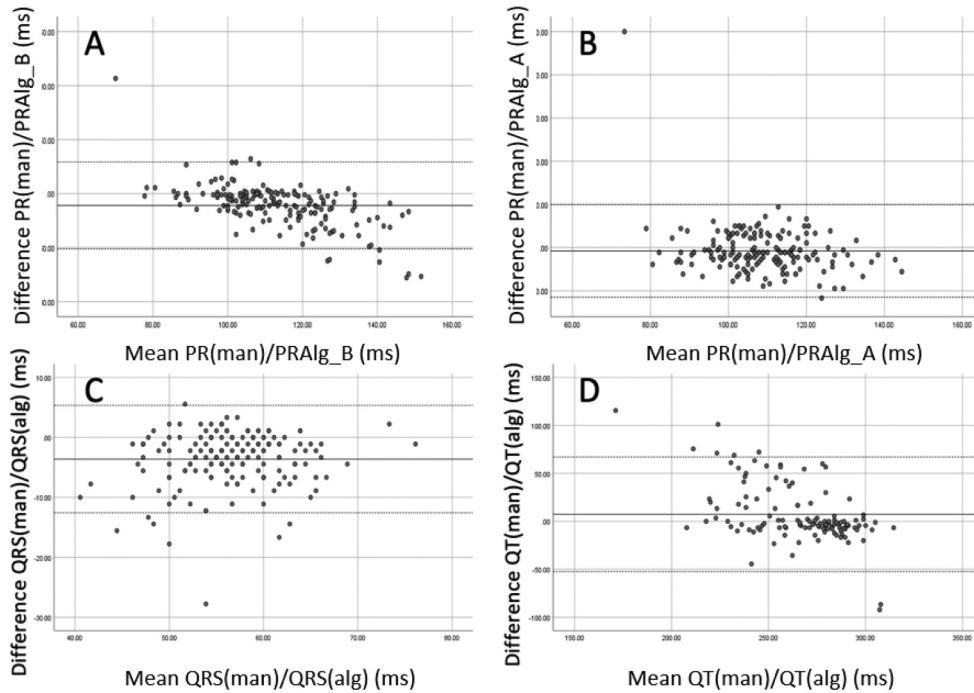


Figure 3. Bland Altman plots demonstrating agreement between manual and algorithm measurements of (A) manual PR interval and algorithm derived PR I, (B) manual PR interval and algorithm derived PR, (C) manual QRS interval and algorithm derived QRS, and (D) manual QT interval and algorithm derived QT.

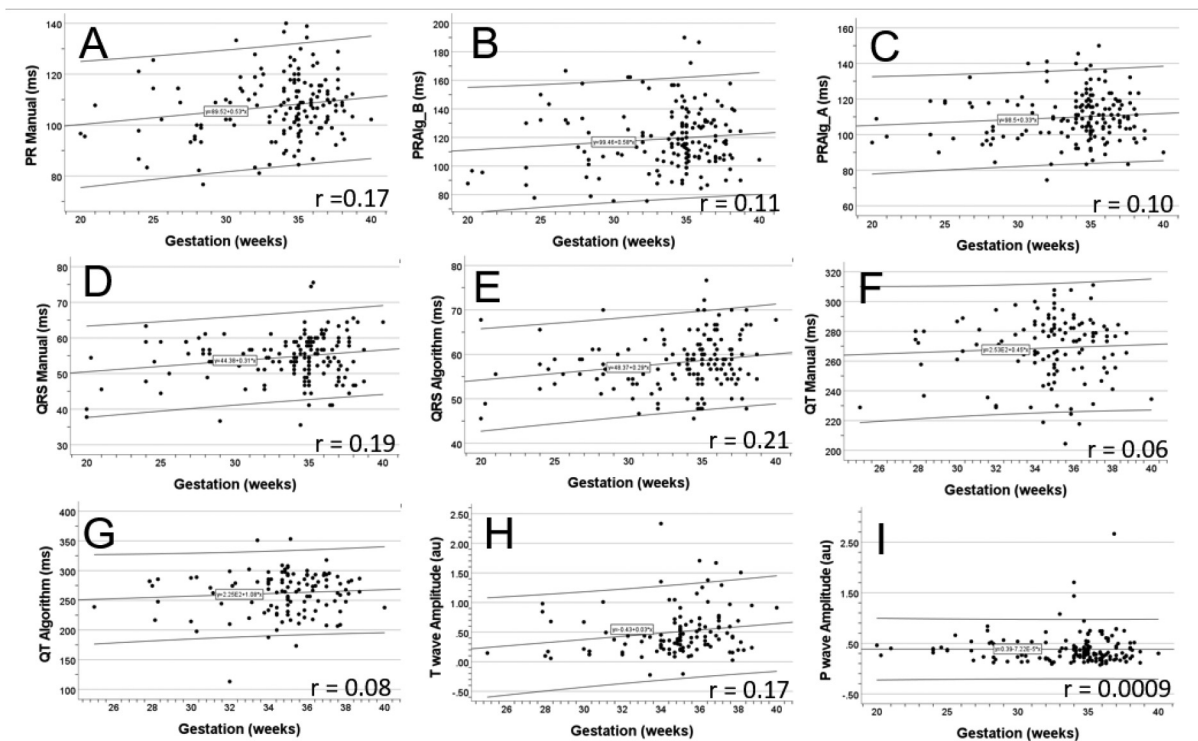


Figure 4. Linear regression demonstrating the correlation between gestation and measurements of the fetal cardiac time intervals: (A) PR Manual and GA, (B) PRAIlg_B and GA, (C) PRAIlg_A and GA, (D) QRSMan and GA, (E) QRSAIlg and GA, (F) QTMan and GA, (G) QTAIlg and GA, (H) T-Amplitude and GA, (I) P amplitude and GA.

Table 3. Cardiac time intervals of the fetal ECG according to gestation derived from 5000 signal averaged beats.

| | <32 weeks | | | 32 + ¹ -36 + ⁶ weeks | | | >37 weeks | | |
|----------------------|-----------|-----------|---------|--|-----------|---------|-----------|-----------|---------|
| | N | Mean (ms) | SD (ms) | N | Mean (ms) | SD (ms) | N | Mean (ms) | SD (ms) |
| PR Manual | 38 | 104.56 | 13.13 | 98 | 108.70 | 12.57 | 26 | 107.56 | 8.37 |
| PRAI _g _A | 38 | 108.42 | 15.14 | 98 | 110.87 | 13.18 | 26 | 107.64 | 10.93 |
| QRS Manual | 40 | 52.78 | 6.27 | 94 | 55.33 | 6.16 | 25 | 55.02 | 6.87 |
| QRS Algorithm | 40 | 55.83 | 5.37 | 94 | 58.91 | 5.49 | 25 | 59.33 | 6.29 |
| QT Manual | 17 | 263.20 | 22.79 | 76 | 270.22 | 22.34 | 23 | 268.16 | 18.78 |
| QT Algorithm | 17 | 248.04 | 46.99 | 76 | 265.41 | 34.25 | 23 | 262.13 | 29.77 |
| QTc Manual | 17 | 398.79 | 34.54 | 76 | 409.42 | 33.85 | 23 | 406.31 | 28.45 |
| QTc Algorithm | 17 | 375.81 | 71.21 | 76 | 402.13 | 51.88 | 23 | 397.16 | 45.10 |

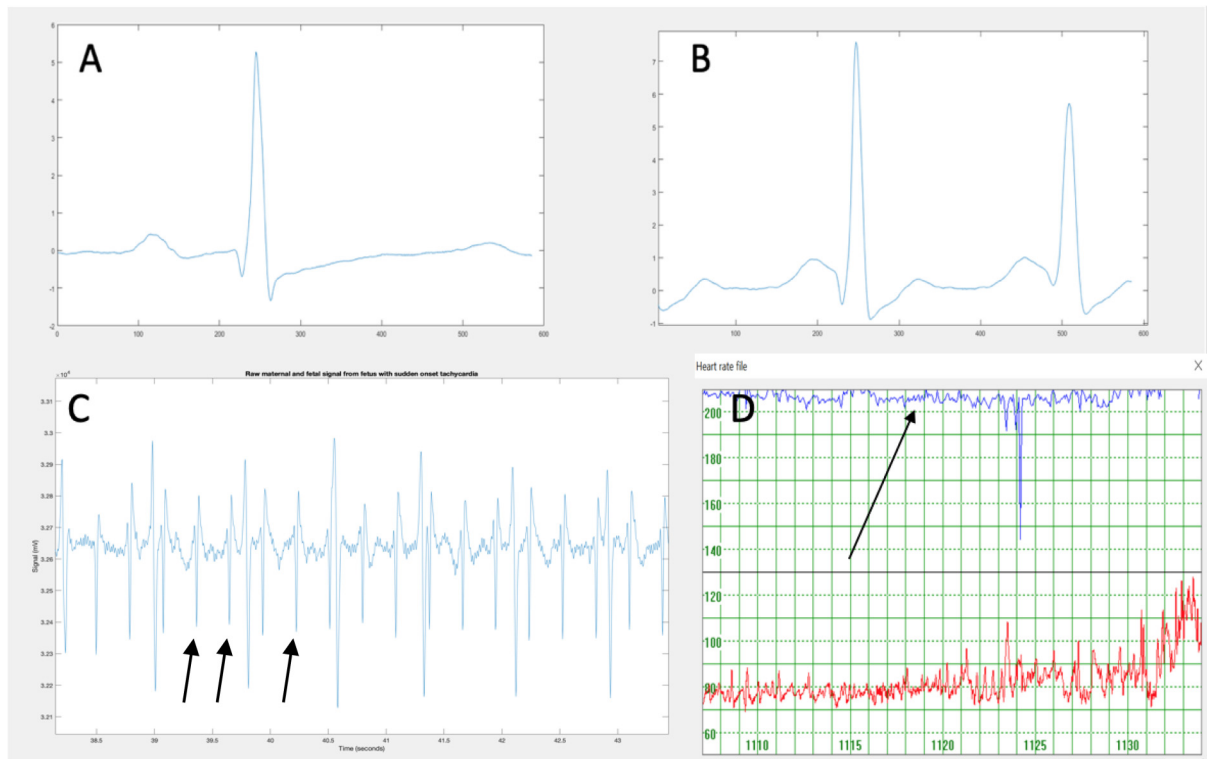


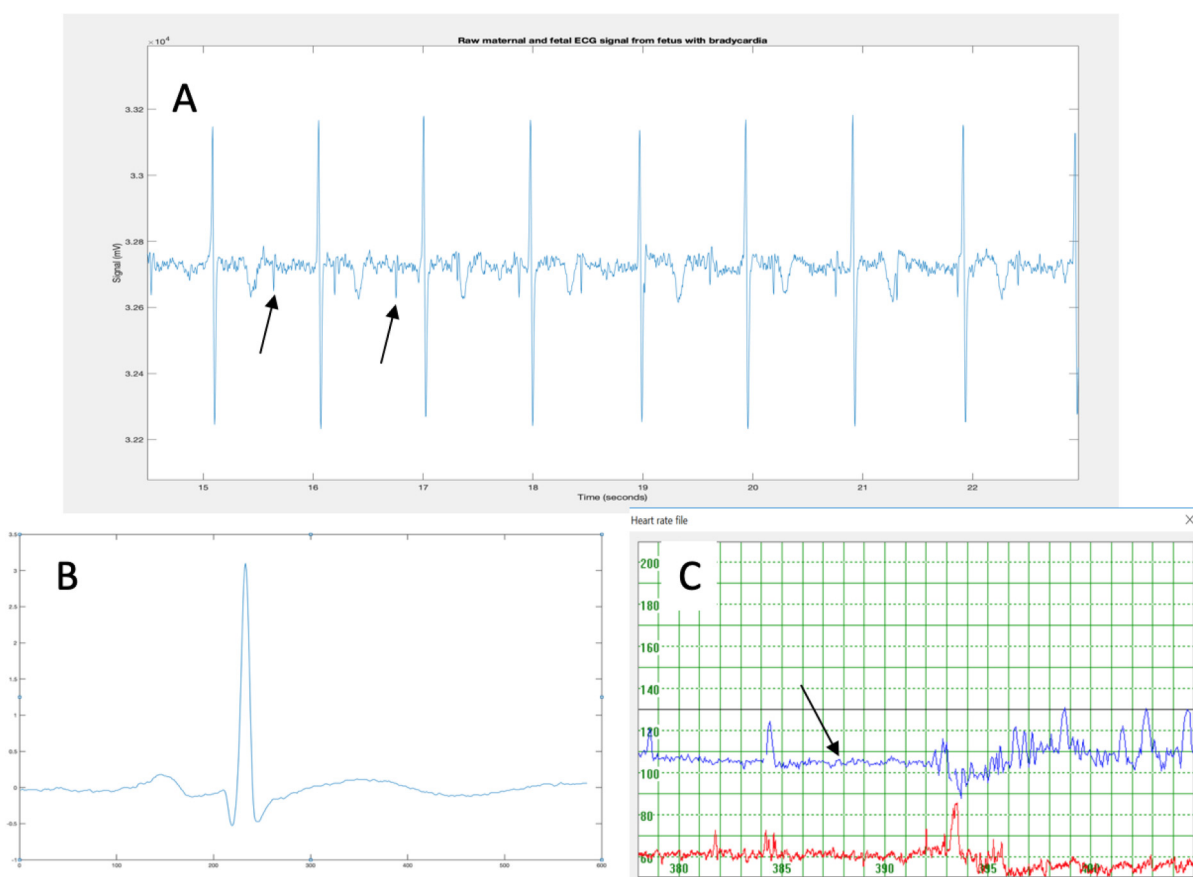
Figure 5. Fetus with sudden onset tachycardia. (A) Signal average complex from period of normal heart rate showing normal PR interval and QRS duration, (B) Signal average complex from period of sudden onset tachycardia showing a change in the P wave and T wave morphology, (C) Raw maternal and fetal ECG signal with fetal QRS complexes shown with arrow and confirming that the fetal ventricular rate is over 200 beats per minute, (D) Heart rate files showing fetal heart rate greater than 200 beats per minute (arrow) and maternal heart rate 80–120 beats per minute.

signal-averaged complex (Figure 5). A heart rate of 211 beats per minute was demonstrated within the raw signal. Given the altered morphology, sudden onset tachycardia and heart rate this was likely to represent a supraventricular tachycardia, rather than physiological sinus tachycardia. Given the retrospective data analysis, it was not possible to validate this with fetal echocardiography or postnatal ECG. The algorithm identified a significantly shorter PR-interval during tachycardia. Automated detection of these abnormal measurements could thus prompt clinician review.

One 38 + 5 week fetus had bradycardia throughout the recording. Baseline heart rate was 105–130 bpm (Figure 6). There was no known maternal or fetal disease. The PR-interval was shorter both by manual (103.33 ms) and algorithm (97.78 ms) measurements and the QRS and QT-intervals were within normal limits when compared to published values (Table 4). Multiple measurements demonstrated consistent results. Importantly, the QT/QTc-interval was not prolonged (manual-265.56/358.86 ms, algorithm-264.44/

Table 4. Cardiac time intervals (measured in ms) according to gestation compared with other published literature.

| Study | Year | N | <32 weeks | | | 32 + ¹ -36 + ⁶ weeks | | | >37 weeks | | | |
|------------------------------------|------|-----------|-----------|-----|-----|--|-----|-----|-----------|-----|-----|-----|
| | | | PR | QRS | QT | PR | QRS | QT | PR | QT | QT | |
| Abboud et al. ⁶ | 1990 | 21 | | | | 107 | 46 | 255 | | | | |
| Taylor et al. ¹ | 2003 | 199 | | | | 102 | 47 | 251 | 105 | 55 | 259 | |
| Chia et al. ⁵ | 2005 | 178 | | | | 110 | 51 | 235 | 110 | 53 | 243 | |
| Taylor et al. ⁷ | 2005 | 15 | 93 | 62 | 255 | 104 | 56 | 256 | | | | |
| Hayashi et al. ⁸ | 2009 | 48 | | | | | 57 | | | 52 | | |
| Arya et al. ³ | 2015 | 13 | 133 | 96 | | 128 | 85 | | 135 | 76 | | |
| Yilmaz et al. ² | 2015 | 64 | 98 | 54 | 236 | 109 | 56 | 233 | | | | |
| Wacker Gussman et al. ⁴ | 2017 | 117 | | | | 107 | 54 | 253 | 108 | 53 | 250 | |
| Chivers et al. | 2022 | Manual | 188 | 105 | 53 | 263 | 109 | 55 | 270 | 108 | 55 | 268 |
| | | Algorithm | 188 | 108 | 56 | 248 | 110 | 59 | 265 | 108 | 59 | 262 |

**Figure 6.** Fetus with Bradycardia. (A) Raw maternal and fetal ECG signal with fetal QRS complexes shown with arrow confirming that the fetal heart rate is 110 beats per minute, (B) Signal averaged complex generated in Matlab at fetal heart rate of 110 beats per minute for measurement of the cardiac time intervals, (C) Heart rate file demonstrating fetal heart rate (arrow) over time. Maternal heart rate shown in this trace as 50–60 beats per minute.

357.35 ms) because fetal bradycardia may signify fetal long-QT-syndrome. Other possible explanations for this presentation of regular bradycardia include physiological sinus bradycardia, bradycardia secondary to circulating maternal Ro/La antibodies and low atrial rhythm.

Discussion

In this study we found that automated classification can reliably measure fetal CTI and showed good agreement with manual measurements and previously reported literature (Table 4).^{1–8} In addition, we were able to measure the

QT-interval in a higher proportion of cases compared to previous studies, likely secondary to use of longer recordings with greater signal generation therefore leading to greater opportunity to select high quality signal for analysis.

Of the fetal CTI, PR-interval was most closely correlated between algorithm and manual measurements. Using the change in concavity of the signal from baseline (PRStart_A) provided greater accuracy compared with assessment of the local minimum of the signal (PRStart_B). PRAI_g_A measurements had a greater mean amplitude of the P wave than PRAI_g_B suggesting that a greater deflection from baseline improved measurability. Other studies also noted that larger P-wave amplitudes correlated with greater measurement success.⁴

QRS-duration was successfully measured in a high proportion of cases but was longer by automated assessment compared to manual measurement, which showed a stronger correlation with published literature (Table 4).^{1–8} The difference between the mean measurement was 3.6 ms (Table 2) which is negligible when compared to the QRS-duration associated with CHD, where mean QRS-duration of 62 and 64 ms have been seen in patients with hypoplastic left heart syndrome and transposition of the great arteries respectively.²

The proportion of signal deemed acceptable for measurement of the QT-interval showed lowest inclusion for analysis, but was higher than many previous studies.^{2,4} There was good agreement between manual measurement of QT-interval and published literature.^{1–8} As with the P wave, T waves with a smaller amplitude were more likely to be rejected. Low amplitude T waves led to interpretation difficulty in other studies of both the fECG and fMCG.^{2,4,12} Alternate options to measure QT-interval have been assessed in other studies including using the peak of the R wave to model the T wave as the discharging phase of a capacitor showing good correlation with fetal scalp electrode measurements.¹³

Signal to noise ratio remains an obstacle with contributing factors including: superimposition of the mECG, movement artefact, electromyogram/ambient electromagnetic interference, instrumentation electronic noise and vernix caseosa insulation.¹² Additionally, the electrical axis changes according to fetal position. The intrauterine scalp electrode and the fMCG also produce a fECG complex^{12,14} but have drawbacks as they are invasive, non-portable and unable to record for prolonged periods. Both fMCG and intrauterine scalp electrodes have shown similar measurements for the CTI's to that of the non-invasive fECG^{15–17} One study simultaneously measured fECG utilising a scalp electrode and non-invasive fECG (Mindchild Medical, North Andover, MA) during labour in 22 women and demonstrated close agreement between the measurement of QT intervals.¹⁵

Recordings >12 h provided interpretable signal more frequently than short recordings. Of the recordings

performed over 30–55 min, 20/37 (54%) were rejected prior to initial analysis compared with 28/199 (14%) of >12 h recordings. Longer recordings had more periods where fetal movement and variation in heart rate was minimised, improving signal quality. Additional information could also be quantified, including overall assessment of heart rate and heart rate variability, duration of tachycardia/bradycardia and ectopic beats. As many arrhythmias are paroxysmal, longer recordings are advantageous.

The positive correlation between GA and QRS-duration was consistent with previous literature.^{2,5} There was also a positive correlation between PR-interval and GA when measured manually but not when measured via the algorithm. The QT-interval showed no correlation with GA. Some studies have proposed that fetal CTI increase with GA due to increasing cardiac mass^{5,18} whilst others reported no correlation.^{3,4} A number of previous studies demonstrated difficulty in fECG detection at 27–32 weeks gestation^{2,5} in keeping with this study where ability to measure the CTI was lowest ≤ 32 weeks gestation. Potential causes include vernix caseosa insulation and a smaller fetal electrical signal due to lower cardiac mass.¹⁹

This study did not assess the impact of fetal/maternal disease, and the incidental findings of sudden onset tachycardia and bradycardia for the duration of the recording occurred in uncomplicated pregnancies. Studies that assessed use of the fECG in fetuses with CHD demonstrated a lack of change in the CTI as gestation increased and difference in the cardiac axis in comparison to control pregnancies (when measured with 12 leads).^{2,20} Other studies demonstrated significantly longer QT-interval in the fECG with confirmed long-QT-syndrome diagnosed postnatally.^{3,21}

Further benefits of automation are rapid measurements on large datasets flagging up areas of concern whilst removing subjective bias and human error. Reference ranges require large sample sizes to account for variabilities within populations. Whilst algorithms may give swift results, caution and attention should be applied to ensure accuracy. This algorithm rapidly provides output measurements but manual pre-processing and quality assessment of the fECG is still currently required. In this study, assessment of the recording for suitable areas for analysis and generation of a signal averaged complex took up to 5 min per subject. The time taken to extract regions of recording suitable for analysis, and the qualitative nature of this process could impact the interpretation of large datasets in future studies. Newer devices with higher quality signal or automated extraction will streamline this process.

Other automation methods have been developed to process and analyse the fECG. The Physionet Computing in Cardiology Challenge 2013 aimed to improve limitations posed by scientists and clinicians related to the fECG by answering whether fetal heart rate and QT-interval can be accurately measured by the non-invasive fECG. It led to development of an annotated public database and range of

approaches to interpretation. It additionally provided open source code to scientists and clinicians with interest in this area. The scientific outputs were published in a special edition of *Physiological Measurement*.^{22,23} This special edition included articles focussing on extraction of the fECG from the mixed maternal/fetal signal and on QRS detection and quantification of fetal heart rate. The other CTI's were not assessed in this edition and therefore our algorithm builds on the work from this challenge.

Further to this challenge, one study assessed an automated approach in 19 participants and was able to measure PR-interval and QRS-durations with results comparable to ours.³ This study had lower overall success rate but utilised short recordings. Other studies report that it is feasible to use an algorithm to assess fetal cardiac disease with one study finding that an event detection algorithm was able to identify an abnormality in 12 participants using the raw fECG signal and that the abnormality correlated with echocardiographic findings in all but one subject.²⁴

Strengths

This study had a higher success rate in terms of included complexes than comparable studies on the fECG of measuring the CTI. It adds to the published literature on the use of algorithms assessing the fECG indicating real time extraction feasibility and, to date, is the largest study utilising such an automate approach to provide fECG measurements. It adds to the growing literature on reference ranges for the fetal CTI in normal pregnancy.

Limitations

The study was not adequately powered to assess the fetus with known or suspected arrhythmia. It would be beneficial to assess the algorithm in the fetus at risk of disease. Larger studies are needed to confirm the normal reference intervals fECG.

Overall, this study has demonstrated the utility of a novel algorithm generated by our group to reliably automatically measure the CTI's of the fECG. Overnight recordings had higher signal quality and gave additional information on heart rate. Clinical application below 32 weeks may be limited due to signal acquisition at lower gestations. This study and the presence of the MonicaAN24 device in the obstetric armory adds to the literature on potential practical application of automatically analysing the non-invasive fECG.

Contribution to authorship

SC, ML: conceptualisation, planning and carrying out, analysing and write up of the study. TV: planning, carrying out and write up of the study. JMS, CW, MN, WPF: planning and write up of the study. BRHG, IAJ: write up of the study.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval

In the UK ethical approval was obtained to collect data at Guy's and St Thomas' Hospital NHS Foundation Trust and Queen Charlotte's and Chelsea Hospital (London, UK) (REC approvals:15/WM/0017, 16/LO/0839). Nottingham University Hospital (Nottingham, UK) (REC approval: 08/H0707/21). In the USA ethical approval was obtained to collect data from Midland office, Rapid City and Sanford Health, Sioux Falls (South Dakota, USA). Ethical approval was obtained from Sanford Health, the Indian Health Service, and New York State Psychiatric Institute(NYSPI) (IRB approvals: CR00000266 and 5338).


Funding


The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Tommy's, NIHR Biomedical Research Centre, Guy's and St Thomas' NHS trust, Madeleine Steel Charitable Fund, John Coates Charitable trust, NIHR Senior Investigator Award, (grant number IS-BRC-1215-20006, N/A).


Supplementary information

Readers can request supplementary information related to the study by email to the corresponding author.

ORCID iDs

SC Chivers  <https://orcid.org/0000-0002-4060-2714>

M Nandi  <https://orcid.org/0000-0001-8585-5363>

IA Jayawardane  <https://orcid.org/0000-0001-6568-8035>

References

1. Taylor MJ, et al. Non-invasive fetal electrocardiography in singleton and multiple pregnancies. *BJOG* 2003; 110: 668–678.
2. Yilmaz B, Narayan HK, Wilpers A, et al. Electrocardiographic intervals in fetuses with congenital heart disease. *Cardiol Young* 2016; 26: 84.
3. Arya B, Govindan R, Krishnan A, et al. Feasibility of non-invasive fetal electrocardiographic monitoring in a clinical setting. *Pediatr Cardiol* 2015; 36: 1042–1049.
4. Wacker-Gussmann A, Plankl C, Sewald M, et al. Fetal cardiac time intervals in healthy pregnancies—an observational study by fetal ECG (Monica Healthcare System). *J Perinat Med* 2018; 46: 587–592.
5. Chia EL, Ho TF, Rauff M, et al. Cardiac time intervals of normal fetuses using noninvasive fetal electrocardiography. *Prenat Diagn* 2005; 25: 546–552.
6. Abboud S, Barkai G, Mashiach S, et al. Quantification of the fetal electrocardiogram using averaging technique. *Comput Biol Med* 1990; 20: 147–155.
7. Taylor MJ, et al. Non-invasive intrapartum fetal ECG: preliminary report. *BJOG* 2005; 112: 1016–1021
8. Hayashi R, Nakai K, Fukushima A, et al. Development and significance of a fetal electrocardiogram recorded by signal-averaged high-amplification electrocardiography. *Int Heart J* 2009; 50: 161–171.
9. Donofrio MT, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. *Circulation* 2014; 129: 2183–2242.

10. Dukes KA, et al. The safe passage study: design, methods, recruitment, and follow-up approach. *Paediatr Perinat Epidemiol* 2014; 28: 455–465.
11. Aalizade N. ECG P QRS T wave detecting matlab code MATLAB central file exchange. 2020. Available from: <https://www.mathworks.com/matlabcentral/fileexchange/66098-ecg-p-qrs-t-wave-detecting-matlab-code> (accessed 01/02/2021).
12. Strand SA, Strasburger JF and Wakai RT. Fetal magnetocardiogram waveform characteristics. *Physiol Meas* 2019; 40: 035002.
13. Widatalla N, Kasahara Y, Kimura Y, et al. Model based estimation of QT intervals in non-invasive fetal ECG signals. *PLoS One* 2020; 15: e0232769.
14. Leuthold A, Wakai RT and Martin CB. Noninvasive in utero assessment of PR and QRS intervals from the fetal magnetocardiogram. *Early Hum Dev* 1999; 54: 235–243.
15. Behar J, et al. Evaluation of the fetal QT interval using non-invasive fetal ECG technology. *Physiol Meas* 2016; 37: 1392.
16. Horigome H, Takahashi MI, Asaka M, et al. Magnetocardiographic determination of the developmental changes in PQ, QRS and QT intervals in the foetus. *Acta Paediatr* 2000; 89: 64–67.
17. Stinstra J, et al. Multicentre study of fetal cardiac time intervals using magnetocardiography. *BJOG* 2002; 109: 1235–1243.
18. Pervolaraki E, et al. Antenatal architecture and activity of the human heart. *Interface Focus* 2013; 3: 20120065.
19. Sameni R and Clifford GD. A review of fetal ECG signal processing; issues and promising directions. *Open Pacing Electrophysiol Ther J* 2010; 3: 4–20.
20. Lempersz C, et al. The standardized 12-lead fetal electrocardiogram of the healthy fetus in mid-pregnancy: a cross-sectional study. *PLoS One* 2020; 15: e0232606.
21. Sethi N, et al. Noninvasive fetal electrocardiography in the diagnosis of long QT syndrome: a case series. *Fetal Diagn Ther* 2020; 47: 711–716.
22. Clifford GD, Silva I, Behar J, et al. Non-invasive fetal ECG analysis. *Physiol Meas* 2014; 35: 1521.
23. Focus issue: non-invasive fetal ECG. *Physiol Measure* 2014; 35.
24. Behar JA, Bonnemains L, Shulgin V, et al. Noninvasive fetal electrocardiography for the detection of fetal arrhythmias. *Prenat Diagn* 2019; 39: 178–187.