Published in final edited form as:

Cardiol Young. 2016 January ; 26(1): 84–89. doi:10.1017/S1047951114002686.

Electrocardiographic Intervals in Fetuses with Congenital Heart Disease

Betul Yilmaz¹, Hari K. Narayan¹, Abigail Wilpers², Christina Wiess¹, William P. Fifer^{1,2}, and Isme A. Williams¹

¹Department of Pediatrics, Columbia University Medical Center, Morgan Stanley Children's Hospital, New York, United States

²Department of Psychiatry, Columbia University, New York, United States

Abstract

Objectives—To assess fetal electrocardiographic intervals across gestational age among fetuses with and without congenital heart disease and to investigate differences between groups.

Design—A prospective observational cohort study.

Setting—Center for Prenatal Pediatrics, Morgan Stanley Children's Hospital of New York-Presbyterian.

Population or Sample—Singleton pregnancies, 92 subjects; 41 with normal anatomy, 51 with congenital heart disease.

Methods—Using a maternal abdominal monitor, fetal electrocardiogram was obtained serially from fetuses with and without congenital heart disease at 20–24 weeks (F1), 28–32 weeks (F2), and 34–38 weeks (F3) gestational age. A signal-averaged waveform was calculated and PR, QRS, and QT intervals were measured. Intervals from controls were compared with gestational age-norms. Using Pearson's correlation coefficient, we analyzed the relationship between gestational age and fetal electrocardiographic intervals. Intervals from control and congenital heart disease fetuses were compared by student's t test.

Results—PR ($r=0.333$, $p=0.02$) and QRS ($r=0.248$, $p=0.05$) intervals correlated with gestational age only among controls. QRS intervals in fetuses with congenital heart disease were significantly longer than controls at F1 (63 ± 6 vs. 52 ± 5 ms, $p<0.001$), F2 (61 ± 8 vs. 56 ± 7 ms, $p=0.02$), and F3 (64 ± 10 vs. 56 ± 9 ms, $p=0.007$).

Conclusions—PR and QRS intervals lengthen across gestational age among fetuses with normal cardiac anatomy but not among congenital heart disease fetuses. As early as 20 weeks gestational

Corresponding author for proofs and reprints: Isme A. Williams, MD, MS, Department of Pediatrics, Division of Pediatric Cardiology, Morgan Stanley Children's Hospital of New York-Presbyterian, 3959 Broadway, MS-CHONY 2 North, New York, NY 10032, iib6@columbia.edu, Phone: 212-342-1560, FAX: 212-342-1563.

Conflicts of Interest: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript, or other conflicts of interest to disclose.

Details of Ethics Approval: The Columbia University Medical Center Institutional Review Board approved this study. Reference number: IRB-AAAD3454. Date of approval: 9/24/2008.

age, differences between fetuses with and without congenital heart disease are discernible with congenital heart disease fetuses demonstrating longer QRS intervals compared with controls.

Keywords

Fetal electrocardiography; congenital heart disease; electrocardiographic intervals

Introduction

Fetal electrocardiographic (ECG) intervals follow a predictable pattern among healthy fetuses.¹⁻⁵ In normal pregnancies PR and QRS intervals lengthen and parallel the weight gain of the fetal heart and increase in ventricular mass. It has been proposed that the duration of cardiac intervals could be used as an index of the size and development of the fetal heart and aid in the identification of fetal growth restriction.²⁻⁵ In the setting of congenital heart disease, resultant changes in ventricular mass presenting as ventricular hypertrophy or hypoplasia were also reported to be associated with increased or decreased interval length, respectively.⁵ It is, however, not known whether fetal ECG intervals change across gestation in fetuses with congenital heart disease or if differences in fetal ECG intervals exist between congenital heart disease and non-congenital heart disease fetuses. The goal of this project was to characterize and compare fetal ECG intervals across gestational ages among fetuses with and without structural heart defects. We hypothesized fetal ECG intervals would lengthen across gestation and differences would be observed between groups. These findings could have the potential to impact prenatal screening for congenital heart disease, especially in the third world where ultrasound technology and expertise is limited.

Materials and Methods

We conducted a prospective observational cohort study of fetuses with and without congenital heart disease. The Columbia University Medical Center Institutional Review Board approved this study. Subjects consisted of pregnant women and fetuses referred to the Morgan Stanley Children's Hospital of New York-Presbyterian's Center for Prenatal Pediatrics for fetal echocardiogram with a diagnosis of either normal cardiac anatomy or congenital heart disease consisting of Hypoplastic Left Heart Syndrome, Tetralogy of Fallot, or Transposition of the Great Arteries. We chose these three lesions because they are commonly diagnosed prenatally at our center and they have distinct anatomic and physiologic features that could potentially impact ECG intervals in important ways.

Exclusion criteria for this study included multiple gestation, fetal genetic anomalies, and fetal rhythm abnormalities. Fetal electrocardiograms were obtained using the Monica AN24 maternal abdominal fetal ECG monitor (Monica Healthcare Ltd., Nottingham, UK). The use of the Monica AN24 has been previously described.⁵ In brief, the Monica AN24 has 5 electrodes and non-invasively records both maternal and fetal electrocardiographic signals. Recorded data were processed via the Monica DK V1.8 (Monica Healthcare Ltd) software which separates maternal ECG from fetal ECG and filters artifact from maternal abdominal contractions or movement, thereby allowing direct analysis of the fetal electrocardiogram.

Other groups have reported success using this monitor to record and analyze fetal heart rate but not in fetuses with congenital heart disease.⁹⁻¹³

Fetal ECGs were obtained at three gestational ages: 20-24 weeks (F1), 28-32 weeks (F2), and 34-38 weeks (F3). Study duration was 45 minutes. Fetal R waves were identified and beat-to-beat fetal HR in a range of 60-200 beats per minute (bpm) was calculated via automated analyses. Any value out of this heart rate range was excluded from further analysis. The signal-averaged waveform was calculated from tracings where at least 10% of fetal beats were detected. At least two physicians (IW and either BY or HN) reviewed each sample independently to rate tracing quality as poor, moderate, or good and calculate PR, QRS, and QT interval length. Only fetal ECG tracings of moderate to good quality were used in the final analysis (Figure 1). Therefore, success was defined first by obtaining a good quality fetal ECG recording with a detectable fetal ECG signal, and second, by obtaining a high quality signal-averaged waveform with readily identifiable P, QRS, and T waves.

Statistical Analysis

Gestational ages for each group (F1 vs. F2 vs. F3) are reported as means (SD). Pearson's correlation coefficient was used to analyze the relationship between gestational age and fetal ECG interval length. Intervals from controls were compared with GA-normed published values.¹ Comparisons between gestational age periods were assessed using ANOVA and paired t-test. Comparisons between congenital heart disease and non-congenital heart disease fetuses were made using Student's t-test. Interobserver variability was calculated using the intraclass correlation coefficient (ICC) and the ICC for PR and QRS were 0.85 ($P<0.001$) and 0.78 ($P<0.001$) respectively. Alpha level was set at $p = 0.05$.

Results

We enrolled 92 subjects, 41 with normal cardiac anatomy and 51 with congenital heart disease. A total of 177 fetal ECGs were obtained across gestation with a mean gestational age of 23 ± 1.6 weeks at F1, 31 ± 1.3 weeks at F2, and 35 ± 3.6 weeks at F3. Sufficient data quality to create a signal-averaged waveform was seen in 132 (75%) fetal ECGs from 74 (80%) subjects. Of these 74 subjects, 33 (45%) were controls and 41 (55%) had congenital heart disease. Of the congenital heart disease subjects, 15 had the diagnosis of hypoplastic left heart syndrome, 12 had transposition of the great arteries, and 14 had tetralogy of Fallot. Of the 132 fetal ECGs, tracing quality was adequate to calculate PR in 102 (77%), QRS in 129 (98%), and QT in 39 (30%). Signal quality for interval analysis was highest at 20-24 weeks and 34-38 weeks of gestation. While waveform success rate did not change statistically across gestation for calculation of PR and QRS intervals, the least success was seen in F2. T waves appeared to become more detectable with increasing GA though even late in pregnancy T wave identification was limited (Table 1).

Fetal ECG Intervals of Control Fetuses and Gestational Age

Among fetuses without structural heart disease, 88% of PR intervals, 87% of QRS intervals, and 86% of QT intervals fell within 2 standard deviations of previously reported norms.

Among these control fetuses, PR ($r=0.333$, $p=0.02$) and QRS ($r=0.248$, $p=0.05$) intervals demonstrated a mild to modest correlation with gestational age (Figure 2 and 3). Using paired t-test, differences in PR interval were seen between F1 and F2 as well as between F1 and F3 (Table 2), however unlike in the correlation analysis, in the paired analyses no significant differences were observed in QRS across gestational age periods. Due to the low success of QT measurement, we did not compare QT intervals between groups or across gestation.

Fetal ECG Intervals of Congenital Heart Disease Fetuses and Gestational Age

Among fetuses with structural heart defects, there was no correlation between PR, QRS, and QT intervals and gestational age. Using paired analyses, we were not able to identify any significant differences in PR, QRS, and QT intervals among congenital heart disease fetuses at F1, F2, and F3.

Fetal ECG Comparisons between Control and Congenital Heart Disease Fetuses

Fetuses with congenital heart disease demonstrated longer QRS intervals at F1, F2, and F3 compared with fetuses with normal cardiac anatomy (Table 3). While PR intervals were longer in congenital heart disease fetuses compared with fetuses without structural heart defects, these differences were not statistically significant (Table 3).

In subgroup analyses among fetuses with congenital heart disease, fetuses with tetralogy of Fallot demonstrated the longest PR interval at F1 (Table 4). There was no significant difference in QRS interval found at any gestational age between subgroups, but each congenital heart disease subtype had longer QRS intervals than fetuses without structural heart disease (Table 4).

Discussion

Heart rate and ECG intervals are known to change over time from fetal life to adulthood⁶, though there is limited data on the ECG intervals of the fetuses and newborns with congenital heart disease. In previously reported small series, PR and QRS intervals were shown to be prolonged in newborns with hypoplastic left heart syndrome as compared with age matched controls. It was proposed that these changes might be due to changes in the conduction system, including focal degeneration and increased connective tissue in the His bundle and other bundle branches.⁷ Our study is the first prospective investigation to assess ECG intervals of congenital heart disease fetuses across gestation and to compare these intervals with those of fetuses with normal cardiac anatomy. Similar to previous reports, we found healthy fetuses demonstrated lengthening of PR and QRS intervals across gestational ages. In both correlation and paired t test analyses, PR was shown to lengthen. While QRS demonstrated a significant, positive correlation with gestational age, we did not see a significant difference in QRS interval in paired analyses likely due to limited sample size¹⁻⁵ However, among fetuses with congenital heart disease, there was no correlation between fetal ECG intervals and gestational age, suggesting an abnormal developmental trajectory for these intervals. Furthermore, we observed as early as 20-24 weeks gestational age that fetuses with congenital heart disease demonstrated longer QRS intervals compared with

controls. Although our sample size within individual diagnostic groups was limited, there was no significant difference in QRS interval found at any gestational age between congenital heart disease subgroups.

As opposed to previously proposed hypotheses^{2-5,7} it is unclear whether the increased interval length in the congenital heart disease group resulted from ventricular hypertrophy, increased ventricular mass, or conduction abnormalities, given that congenital heart disease subgroups had different anatomical and physiological characteristics. Differences in fetal ECG intervals may be explained by underlying differences in RR interval or baseline heart rate. In a separate analysis to investigate autonomic function utilizing heart rate variability measures, we found congenital heart disease fetuses demonstrated longer RR intervals compared with controls from 20 to 34 weeks gestational age.⁸ Reasons for differences in autonomic variability remain speculative and include perturbation of brain stem development due to alterations in fetal blood flow secondary to structural cardiac anomalies. Although the exact underlying mechanism is unknown, these findings suggest structural heart defects impact the normal progression of electrocardiographic development of the fetus.

Our rate of signal separation success was slightly lower compared with the success rates of 82-85% found in the literature^{1,9}, however, our rate of fetal ECG measurement was comparable to the previous reports.^{1,3} Taylor et al., in a study using a different fetal ECG monitor, reported PR and QRS interval measurement success in 80% of 250 fetal ECG recordings. Of the 250 recordings, 15% were deemed failures due to insufficient separation of the maternal and fetal signal, 84% of which occurred between 27-36 weeks gestational age.¹ Chia et al., in a study using another fetal ECG monitor reported success rates for detecting the P and QRS waves of 74% and 91%, respectively. Similar to these reports, we observed increased identification of T waves after 34 weeks gestation, which was likely due to advancing fetal maturity. However, whereas both of these reports identified T waves in 78-79% of tracings, we experienced a lower success rate for QT interval calculation. Differences between the fetal ECG systems likely explain the disparate results. Taylor et al. used a fetal ECG monitor with 12 to 16 electrodes, whereas the Monica AN24 has 5 electrodes including the grounding electrode. It is important to note that the monitor cited in Taylor's paper was developed for research purposes only and is not widely available for clinical use.¹

Graatsma et al. used the same monitor, the Monica AN24, only for heart rate monitoring and not for electrocardiographic interval analysis. Good quality signal, defined as >60% of fetal ECG detection over a 15-hour study, was observed in 123 out of 150 (82%) women between 20 and 40 weeks gestation.⁹ The signal quality of the fetal ECG was reported to be highest between 20-26 weeks of gestation, while the lowest quality was found between 26-34 weeks, similar to the previous reports and presumed to be due to interference of the vernix caseosa.^{1,3,9} In our study, the recording time was 45 minutes or less, shorter than that of Graatsma's group, which likely explains the difference in tracing quality. Since completion of our study, we have altered our protocol to include overnight studies and have noticed a pronounced improvement in fetal ECG signal quality.

Limitations

Our study was from a single center. While we attempted to record fetal ECG at the same gestational age periods in each individual, subject availability varied. For these reasons, sample size was limited and subgroup analyses may have lacked sufficient power to discern statistical differences. In addition, a percentage of fetal ECG recordings demonstrated suboptimal quality. Changes to the protocol, including lengthening recording duration and performing overnight studies, as well as improvements in filtering and signal processing are ongoing and have significantly increased fetal ECG signal detection.

Conclusion

PR and QRS intervals in fetuses with congenital heart disease do not lengthen across gestation as they do in normal fetuses. Differences between congenital heart disease and normal fetuses were detected as early as 20-24 weeks of pregnancy with congenital heart disease fetuses demonstrating longer QRS intervals. Additional studies are warranted to investigate differences between specific congenital heart disease subtypes and test mechanistic hypotheses as to why these differences exist. Advances in fetal ECG monitor use, including automated interval calculation, may widen the applicability of this monitor and will ultimately determine the role of fetal ECG in routine care and obstetrical screening, especially in areas of the world where access to ultrasound is limited.

Acknowledgments

Financial Support: I.A. Williams received support from Grant No. 1K23HD061601 from the National Institute of Child Health & Human Development of the National Institutes of Health. This publication was also supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number UL1 TR000040. The contents of this paper are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Clinical Trial Registration NCT00115934.

References

1. Taylor MJ, Smith MJ, Thomas M, et al. Non-invasive fetal electrocardiography in singleton and multiple pregnancies. *BJOG*. 2003; 110(7):668–78. [PubMed: 12842058]
2. Brambati B, Pardi G. The intraventricular conduction time of fetal heart in uncomplicated pregnancies. *Br J Obstet Gynaecol*. 1980; 87(11):941–8. [PubMed: 7437367]
3. Chia EL, Ho TF, Rauff M, Yic WC. Cardiac time intervals of normal fetuses using noninvasive fetal electrocardiography. *Prenat Diagn*. 2005; 25(7):546–552. [PubMed: 16032763]
4. Pardi G, Marconi AM, Ferrazzi E. The intraventricular conduction time of fetal heart in pregnancies with suspected fetal growth retardation. *BR J Obstet Gynaecol*. 1986; 93(3):250–4. [PubMed: 3964600]
5. Pardi G, Ferrazzi E, Cetin I, et al. The clinical relevance of the abdominal fetal electrocardiogram. *J Perinat Med*. 1986; 14(6):371–7. [PubMed: 3546668]
6. Mehta, Chetan; Dhillon, Rami. Understanding Paediatric ECGs. *Current Paediatrics*. 2004; 14(3): 229–236.
7. Lev M, Killian ST. Hypoplasia of the aorta without transposition with electrocardiographic and histopathologic studies of the conduction system. *American Heart Journal*. 1942; 24:794–806.
8. Siddiqui S, Wilpers A, Weiss C, Fifer WP, Williams IA, et al. Autonomic Regulation in Fetuses with Congenital Heart Disease. *Congenit Heart Dis*. 2013; 8:457. (abstract).
9. Graatsma EM, Jacod BC, van Egmond LA, Mulder EJ, Visser GH. Fetal electrocardiography: feasibility of long-term fetal heart rate recordings. *BJOG*. 2009; 116(2):334–7. discussion 337-338. [PubMed: 19076966]

10. Graatsma EM, Miller J, Mulder EJ, Harman C, Baschat AA, Visser GH. Maternal body mass index does not affect performance of fetal electrocardiography. *Am J Perinatol*. 2010; 27:573–7. [PubMed: 20195954]
11. Reinhard J, Hayes-Gill B, Yi Q, Hatzmann H, Schiermeier S. Comparison of non-invasive fetal electrocardiogram to Doppler cardiotocogram during the 1st stage of labor. *J Perinat Med*. 2010; 38:179–85. [PubMed: 20121540]
12. Reinhard J, Hayes-Gill BR, Schiermeier S, et al. Intrapartum signal quality with external fetal heart rate monitoring: a two way trial of external Doppler CTG ultrasound and the abdominal fetal electrocardiogram. *Arch Gynecol Obstet*. 2012; 286:1103–7. [PubMed: 22714064]
13. Reinhard J, Hayes-Gill BR, Schiermeier S, Hatzmann H, Heinrich TM, Louwen F. Intrapartum Fetal and Maternal Heart Rate Ambiguity- a Comparison of Doppler Ultrasound CTG and the Abdominal Fetal Electrocardiogram with Maternal Electrocardiogram. *Gynecol Obstet Invest*. 2013; 75:101–8. [PubMed: 23328351]

Figure 1.

An example of a signal-averaged waveform obtained from each recording channel where 1,000 fetal QRS complexes were averaged. Tracings obtained from channels (CH) 1, 2, and 3 were analyzed independently to calculate PR, QRS, and QT interval length. Note that the T wave detection was poor on this subject.

Figure 2.

PR interval correlates positively with gestational age among non-CHD fetuses indicating PR interval lengthens as pregnancy progresses.

Figure 3. QRS interval correlates positively with gestational age among non-CHD fetuses indicating QRS interval lengthens as pregnancy progresses.

Table 1

Fetal ECG interval calculation success at different gestational age (GA) periods.

Total N=132 studies	F1	F2	F3
GA (mean)	23±1.6wks	31±1.3wks	35±3.6wks
# studies	38 (29%)	47 (36%)	47 (36%)
PR success	31/38 (81%)	33/47 (70%)	38/47 (81%)
QRS success	37/38 (97%)	46/47 (98%)	46/47 (98%)
QT success	11/38 (29%)	10/47 (21%)	18/47 (38%)

Table 2

PR, QRS and QT intervals among non-CHD fetuses during the different GA periods with ANOVA p-values. Using paired t test, differences in PR interval between F1 and F2 (N=11, P=0.007) and F1 and F3 (N=8, P=0.02) were seen. While QRS intervals appeared to lengthen, differences between GA periods were not statistically significant in paired analyses.

Non-CHDs (N=64 studies)	F1	F2	F3	P value
Mean GA (weeks)	23±1.6	31±1.3	35±3.6	
PR interval (ms)	93±12 (n=19)	102±15 (n=13)	109±18 (n=16)	p=0.01*
QRS interval (ms)	52±5 (n=22)	56±7 (n=22)	56±9 (n=19)	p=0.13
QT interval (ms)	240±15 (n=7)	231±41 (n=6)	233±43 (n=8)	P=0.87

Table 3

CHD vs. Non-CHD QRS and PR intervals in different GA periods. Fetuses with CHD consistently demonstrated longer QRS intervals compared with controls. Fetuses with CHD also demonstrated longer PR intervals compared with controls however these differences were not statistically significant.

QRS interval (ms)	F1	F2	F3
Controls	52±5 (n=22)	56±7 (n=22)	56±9 (n=19)
CHD	63±6 (n=15)	61±8 (n=24)	64±10 (n=27)
P value	<0.001*	0.02*	0.007*
PR interval (ms)	F1	F2	F3
Controls	93±12 (n=19)	102±15 (n=13)	109±18 (n=16)
CHD	99±20 (n=12)	107±13 (n=20)	110±21 (n=22)
P value	0.28	0.3	0.87

Table 4

CHD subtypes (Hypoplastic Left Heart Syndrome (HLHS) vs. Transposition of the Great Arteries (TGA) vs. Tetralogy of Fallot (TOF)) vs. non-CHD PR and QRS intervals at different gestational age (GA) periods using t-test. Although the sample size within the individual CHD diagnostic groups was limited, fetuses with TOF had the longest PR interval at F1. There was no significant difference in QRS interval found across GA, but within CHDs, each subtype had longer QRS than the fetuses without structural heart disease.

PR interval (ms)	F1	F2	F3
Controls	93±12 (n=19)	102±15 (n=13)	109±18 (n=16)
HLHS	97±16 (n=6)	113±12 (n=7)	120±21 (n=6)
TGA	92±21 (n=4)	101±10 (n=5)	101±20 (n=9)
TOF	119±29 (n=2) (p=0.02*)	105±14 (n=8)	113±21 (n=7)
QRS interval (ms)	F1	F2	F3
Controls	52±5 (n=22)	56±7 (n=22)	56±9 (n=19)
HLHS	66±6 (n=8) (p=0.000*)	62±7 (n=7) (p=0.05*)	61±16 (n=8) (p=0.3)
TGA	60±2 (n=4) (p=0.006*)	64±9 (n=7) (p=0.025*)	64±8 (n=10) (p=0.03*)
TOF	61±3 (n=3) (p=0.004*)	59±9 (n=10) (p=0.3)	67±5 (n=9) (p=0.02*)