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Complexity analysis of fetal heart rate preceding intrauterine demise

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Abstract

Background—Visual non-stress test interpretation lacks the optimal specificity and observer-agreement of an ideal screening tool for intrauterine fetal demise (IUFD) syndrome prevention. Computational methods based on traditional heart rate variability have also been of limited value. Complexity analysis probes properties of the dynamics of physiologic signals that are otherwise not accessible and, therefore, might be useful in this context.

Objective—To explore the association between fetal heart rate (FHR) complexity analysis and subsequent IUFD. Our specific hypothesis is that the complexity of the fetal heart rate dynamics is lower in the IUFD group compared with controls.

Study Design—This case-control study utilized cases of IUFD at a single tertiary-care center among singleton pregnancies with at least 10 minutes of continuous electronic FHR monitoring on at least 2 weekly occasions in the 3 weeks immediately prior to fetal demise. Controls delivered a live singleton beyond 35 weeks' gestation and were matched to cases by gestational age, testing indication, and maternal age in a 3 to 1 ratio. FHR data was analyzed using the multiscale entropy (MSE) method to derive their complexity index. In addition, pNNx, a measure of short-term heart rate variability, which in adults is ascribable primarily to cardiac vagal tone modulation, was also computed.

Results—211 IUFDs occurred during the 9-year period of review, but only 6 met inclusion criteria. The median gestational age at the time of IUFD was 35.5 weeks. Three controls were matched to each case for a total of 24 subjects, and 87 FHR tracings were included for analysis. The median gestational age at the first fetal heart rate tracing was similar between groups (median [1st– 3rd quartiles] weeks: IUFD cases: 34.7 (34.4–36.2); controls: 35.3 (34.4–36.1); $p=.94$). The

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median complexity of the cases' tracings was significantly less than the controls' (12.44 [8.9–16.77] vs. 17.82 [15.21–22.17]; $p<.0001$). Furthermore, the cases' median complexity decreased as gestation advanced whereas the controls' median complexity increased over time. However, this difference was not statistically significant [–0.83 (–2.03–0.47) vs. 0.14 (–1.25–0.94); $p=.62$]. The degree of short-term variability of FHR tracings, as measured by the pNN metric, was significantly lower ($p<0.005$) for the controls (1.1 [0.8–1.3]) than the IUFD cases (1.3 [1.1–1.6]).

Conclusions—FHR complexity analysis using multiscale entropy analysis may add value to other measures in detecting and monitoring pregnancies at the highest risk for IUFD. The decrease in complexity and short-term variability seen in the IUFD cases may reflect perturbations in neuroautonomic control due to multiple maternal-fetal factors.

INTRODUCTION

Identification and timely delivery of the compromised fetus remains a compelling, yet elusive goal of modern obstetrics. Recent data suggest that roughly 3.2 million cases of intrauterine fetal demise (IUFD) occur world-wide each year.¹ Controversy exists whether standard antepartum cardiotocography based on non-stress testing reduces stillbirth rates.² This approach is grounded in the understanding that the fetal heart rate (FHR) baseline fluctuations, as well as accelerations and decelerations, arise from the complex interplay of cortical regulatory centers (controlling sleep-wake cycles), the autonomic nervous system (through baroreceptors and chemoreceptors)³ and multiple other physiologic components. At various stages of pregnancy, certain FHR variability profiles have been interpreted as markers of fetal well-being and serve as the basis for contemporary non-stress testing strategies. However, visual interpretation of the cardiotocograph has been reported to lack sufficient specificity and observer-agreement to make it a reliable screening tool in preventing IUFD.^{4,5} Efforts at creating computerized systems for cardiotocographic analysis and interpretation have gained little clinical traction. Direct tests such as contraction-stress testing are not feasible or safe for routine antepartum use. These limitations motivate the search for more reliable and reproducible adjuncts to current cardiotocographic analysis. One promising approach expands the analysis of FHR time series by using measures derived from dynamical systems theory, also called nonlinear dynamics or complexity science.^{6–11}

Quantification of the complexity of various physiological signals is a relatively novel field¹² of research, and only a small number of studies have explored its applicability to various aspects of fetal monitoring.^{6–11} Biologic complexity arises from the interaction of myriad physiologic processes and regulatory feedback loops that operate over a wide range of temporal and spatial scales, enabling the organism to adapt to the stresses of everyday life.^{13–16} Complexity and variability are two distinct concepts. Complex signals are variable, but not all variable signals are complex.^{17–18} For example, uncorrelated random sequences, such as those that would arise from shuffling the words of a text or the sequence of mean heart rate values over the course of a day, are maximally entropic (variable), but not complex. A musical analogy may also help convey the difference between variability and complexity. For example, the noisy output produced by an infant randomly striking keys at a piano is highly unpredictable and variable but it is not complex or musical. In addition, the highly predictable output of robotically executed scales also lack musical complexity. A

captivating piece of music possesses a balance between the predictable and the unexpected that derives from its complex structure.

Complex signals, such as those generated by self-regulatory (homeostatic) physiologic systems, present spatial and/or temporal structures over a wide range of scales. Typically, these signals are nonlinear and non-stationary. Consequently, conventional signal analysis techniques, such as mean, standard deviation and higher order moments fail to fully characterize and quantify their properties.¹⁵

Complexity analysis was first applied to adult heart rate time series from healthy subjects of different ages and patients with a wide variety of conditions including heart failure, stroke, trauma and sepsis.^{19–24} Observations in these groups support the conceptual framework of complexity loss in aging and pathologic states.¹⁴ Subsequent applications of complexity analysis to FHR signals have shown promise in identifying intrauterine growth restriction and fetal acidemia in labor.^{3,7}

This pilot study focused on heart rate dynamics obtained from cardiotocographic recordings during non-stress tests in fetuses with subsequent intrauterine demise as compared to matched high-risk controls. Our specific hypothesis was that heart rate dynamics in the former group would have decreased complexity compared to those in the latter group.

METHODS

Subjects

This retrospective case-control study was performed at the Beth Israel Deaconess Medical Center from June, 2011 through June, 2013. Cases of IUFD were identified by review of the birth log of all deliveries occurring beyond 24 weeks of gestation at our center from January 2002 through January 2011. Only cases of IUFD among singleton pregnancies with at least 10 minutes of continuous electronic FHR monitoring on at least two occasions in the three weeks immediately prior to the date of the fetal demise were deemed eligible. Exclusion criteria included major fetal malformations, multiple gestation, intrapartum death, and gestational age (GA) less than 28 weeks at the time of antenatal testing. Controls were matched for GA (within 2 weeks), antenatal testing indication, and maternal age (within 5 years) to cases in a 3 to 1 ratio. Controls were identified by review of the antenatal testing unit schedule. Patients who underwent non-stress testing within 3 days of the cases and matched the above inclusions were selected. An additional criterion for the control group was delivery of a live born singleton at 36 weeks' gestation or greater. Subjects were assigned a unique study identification number, all personal health information was password protected, and informed consent was waived. We received approval for this study from the Institutional Review Board of the Beth Israel Deaconess Medical Center.

Fetal Heart Rate Recordings

All electronic FHR monitoring was performed for the purpose of antenatal non-stress testing on the Philips OB TraceVue® hardware and software platform (Philips Healthcare, Andover, MA). The raw FHR signals, sampled at 4 Hz, were exported using a program provided by

Philips Healthcare. The data were then analyzed using open-source software available at www.physionet.org.²⁵

Fetal Heart Rate Analysis

For each heart rate time series, the following measures were calculated: i) mean; ii) standard deviation (SD); iii) pNN_{1-20} ; and iv) degree of complexity. PNN_x , the percentage of differences between adjacent NN intervals that are greater than x ms, is a measure of short-term heart rate variability that, in adults, is ascribable primarily to cardiac vagal tone modulation.²⁶ To avoid selecting an arbitrary threshold, here we used pNN_{1-20} , the sum of PNN_x values for x ranging from 1 to 20 ms with increments of 1 ms. While SD quantifies the overall amount of variability, pNN_{1-20} is a measure of local (beat-to-beat) variability, less affected by the presence of trends and prolonged accelerations/decelerations.

To probe the multiscale dynamical properties of FHR time series we used the multiscale entropy (MSE) algorithm,¹⁷⁻¹⁸ which quantifies the degree of complexity of a signal. MSE comprises three steps: 1) construction of a set of coarse-grained time series, each of which represents the system's dynamics on a different time scale. The coarse-grained time series for scale s is obtained using a non-overlapping moving window of length s . 2) Quantification of the degree of irregularity of each of the coarse-grained time series using the sample entropy (SampEn) algorithm. SampEn is a conditional probability measure quantifying the likelihood that sequences of m consecutive data points $(x_j, x_{j+1}, \dots, x_{j+m-1})$ and $(x_j, x_{j+1}, \dots, x_{j+m-1})$ matching each other within a tolerance r , will still match when their length increases from m to $m + 1$ data points. 3) Calculation of the complexity index (unitless) by summing the SampEn values over a pre-defined range of time scales.⁷ The calculation of SampEn requires the definition of two parameters m and r ; here we used $m = 2$ and $r = 1.2$ bpm. In this study, we analyzed time scales ranging from 1 to 5 seconds.

Statistical Analysis

Changes in complexity with GA were assessed by linear regression (slope of best-fit line of complexity versus GA). Group summary statistics are presented as proportions and medians (interquartile ranges). Means were compared using the Mann-Whitney test considering a two-tailed p value < 0.05 to be significant.

RESULTS

Two hundred and eleven IUFDs occurred during the 9-year period of review, but only 6 were in full agreement with the strict inclusion and exclusion criteria. Many of the excluded IUFDs occurred among multiple gestations or without any prior antenatal testing. Table 1 describes the demographics of each case and lists the risk factors and presumed causes of mortality. The median GA at the time of IUFD was 35.5 weeks. Three controls were identified and matched to each case for a total of 18. The median number of fetal heart tracings among the cases was 3.5, and the median number of tracings among the controls was 4. Thus, a total of 24 subjects, 68 control and 19 case fetal heart rate tracings were included for analysis. The demographic characteristics of cases and controls were comparable except that the time interval between the first analyzed FHR tracing and the last

tracing was slightly greater among the cases (Table 2). In addition, the rate of macrosomia was greater among the cases than the controls (50% vs. 6%; $p=.035$). Summary statistics for the variables computed are presented in Table 3.

Examples of heart rate time series from an IUFD case and corresponding control are presented in Figure 1.

Mean heart rate was not different between the two groups. Standard deviation (SD) was significantly higher for the controls than the IUFD cases. PNN analysis (Figure 2) showed that, for all thresholds' values considered, short-term variability was lower for IUFD cases than controls. In addition, pNN_{1-20} was significantly lower for IUFD cases than controls. The complexity indexes as a function of GA for each case and its 3 corresponding controls are presented in Figure 3. The complexity index was significantly higher for the controls than the cases (Table 3). In addition, complexity tended to decrease with GA in cases and increase in controls, although these trends did not reach statistical significance. The coefficient of determination (R^2) of the correlation between the complexity index and SD was 0.33 for controls and 0.38 for IUFD cases. R^2 for the correlation between the complexity index and pNN_{1-20} was 0.51 for controls and 0.47 for IUFD cases. The number of days from the last recording to IUFD were: 1 for case D, 4 for cases A and F, 7 for cases B and C, and 8 for case E.

DISCUSSION

To our knowledge, this is the first report of an association between fetal heart rate complexity and IUFD. In addition to short-term reduced variability, we found a significant decrease in complexity among cases of IUFD syndrome in comparison to matched controls. Complexity and pNN_{1-20} as well as complexity and SD values were correlated. However, these measures quantify different properties of the time series. Complexity probes the temporal structure of a signal across multiple time scales. SD and pNN_{1-20} reflect the amplitude of the time series' fluctuations. Two time series with the same SD may have very different degrees of complexity. Consider a FHR time series and that obtained by shuffling the order of the FHR values. The shuffling procedure converts the physiologic time series into an uncorrelated random sequence of values. By construction, the original and the shuffled time series have the same SD. However, the complexity of the former is higher than the complexity of the latter.¹⁸ Although a decrease in complexity with gestational age was noted among the cases, the difference relative to the controls did not reach significance. These findings suggest that a decreased fetal heart rate complexity detectable on multiple time scales may be a dynamic biomarker of perturbed neuroautonomic control, impending asphyxia, and IUFD. Whether the pathophysiology involves a decline in complexity over time or a failure to achieve a gestation-age-appropriate level of complexity could not be determined from the limited number of subjects. Our findings do support previous studies,^{3,7-11} indicating that fetal maturation and well-being correlate with increased fetal heart rate complexity.

A retrospective case-control study by Ferrario *et al.* analyzed 59 antepartum fetal heart rate tracings from 3 groups of fetuses identified by the presence and severity of IUGR.³ Using

complexity measures, including multiscale entropy, the authors were able to identify the pathologic IUGR fetuses with a reported sensitivity of 77.8% and specificity of 82.4%. Our group recently published a report of complexity analysis on 148 intrapartum fetal heart tracings from singleton fetuses.⁷ The complexity over the two hours prior to delivery was significantly lower for acidemic fetuses than for non-acidemic fetuses. Other studies^{6, 8–11} also support the use of entropy-based complexity measures in assessing fetal health status during gestation and labor.

Obvious limitations of the present study include: 1) its retrospective nature, 2) the small sample size, attributable in part to the strict inclusion and exclusion criteria, 3) the fact that the time period between the last recording and fetal demise varied between 1 and 8 days, and 4) the lack of knowledge regarding the real-time clinical interpretation of the fetal heart rate data / non-stress test results. We did not explore whether clinicians expressed any clinical concerns about these tracings or whether they were deemed “reassuring.” Given that the implementation of an adjunctive measure to traditional fetal heart rate analysis would require the assertion of improved efficacy, knowledge of the clinical results of traditional analysis would have been helpful. Despite these limitations, the robust statistical differences in complexity observed between the cases of IUFD and matched controls are compelling and warrant, in our opinion, validation in larger studies.

CONCLUSIONS

This study suggests that fetal heart rate complexity analysis, in concert with other measures, has promise in differentiating high-risk pregnancies destined for IUFD from those at lower risk. The findings add to the growing body of evidence supporting the use of complexity measures, such as MSE, to assess neuroautonomic control over multiple time scales and fetal well-being. Larger studies are required to validate these suggestions and clarify the test characteristics and potential clinical implementations.

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REFERENCES

1. Lawn JE, Yakoob MY, Haws RA, Soomro T, Darmstadt GL, Bhutta ZA. 3.2 million stillbirths: epidemiology and overview of the evidence review. *BMC Pregnancy Childbirth*. 2009; 9(Suppl 1):S2. [PubMed: 19426465]
2. Haws RA, Yakoob MY, Soomro T, Menezes EV, Darmstadt GL, Bhutta ZA. Reducing stillbirths: screening and monitoring during pregnancy and labour. *BMC Pregnancy Childbirth*. 2009; 9(Suppl 1):S5. [PubMed: 19426468]
3. Ferrario M, Signorini MG, Magenes G. Complexity analysis of the fetal heart rate variability: early identification of severe intrauterine growth-restricted fetuses. *Med Biol Eng Comput*. 2009; 47:911–919. [PubMed: 19526262]
4. Figueras F, Albela S, Bonino S, Palacio M, Barrau E, Hernandez S, Casellas C, Coll O, Cararach V. Visual analysis of antepartum fetal heart rate tracings: inter- and intra-observer agreement and impact of knowledge of neonatal outcome. *J Perinat Med*. 2005; 33:241–245. [PubMed: 15914348]

5. Devoe L, Golde S, Kilman Y, Morton D, Shea K, Waller J. A comparison of visual analysis of intrapartum fetal heart rate tracings according to the new national institute of child health and human development guidelines with computer analyses by an automated fetal heart rate monitoring system. *Am J Obstet Gynecol*. 2000; 183:361–366. [PubMed: 10942470]
6. Goncalves H, Rocha AP, Ayres-de-Campos D, et al. Frequency domain and entropy analysis of fetal heart rate: appealing tools for fetal surveillance and pharmacodynamic assessment of drugs. *Cardiovasc Hematol Disord Drug Targets*. 2008; 8:91–98. [PubMed: 18537596]
7. Costa MD, Schnettler WT, Amorim-Costa C, Bernardes J, Costa A, Goldberger AL, Ayres-de-Campos D. Complexity-loss in fetal heart rate dynamics during labor as a potential biomarker of acidemia. *Early Hum Dev*. 2014; 90:67–71. [PubMed: 24290526]
8. Hoyer D, Nowack S, Bauer S, Tetschke F, Rudolph A, Wallwitz U, Jaenicke F, Heinicke E, Götz T, Huonker R, Witte OW, Schleussner E, Schneider U. Fetal development of complex autonomic control evaluated from multiscale heart rate patterns. *Am J Physiol Regul Integr Comp Physiol*. 2013; 304:R383–R392. [PubMed: 23269479]
9. Gieraltowski J, Hoyer D, Tetschke F, Nowack S, Schneider U, Zebrowski J. Development of multiscale complexity and multifractality of fetal heart rate variability. *Auton Neurosci*. 2013; 178:29–36. [PubMed: 23466040]
10. Choi WY, Hoh JK. Nonlinear analysis of fetal heart rate dynamics in fetuses compromised by asymptomatic partial placental abruption. *Placenta*. 2015; 36:1474–1479. [PubMed: 26602608]
11. Zaylaa A, Oudjemia S, Charara J, Girault JM. n-Order and maximum fuzzy similarity entropy for discrimination of signals of different complexity: Application to fetal heart rate signals. *Comput Biol Med*. 2015; 64:323–333. [PubMed: 25824414]
12. Beuter, A.; Glass, L.; Mackey, M.; Titcombe, MS. *Nonlinear dynamics in physiology and medicine*. New York: Springer-Verlag; 2003.
13. Goldberger AL, Peng CK, Lipsitz LA. What is physiologic complexity and how does it change with aging and disease? *Neurobiol Aging*. 2002; 23:23–26. [PubMed: 11755014]
14. Goldberger AL, Giles F. Filley lecture. Complex systems. *Proc Am Thorac Soc*. 2006; 3:467–471. [PubMed: 16921107]
15. Goldberger AL, Moody GB, Costa MD. Variability versus Complexity. <https://physionet.org/tutorials/cv/>.
16. Peng CK, Costa M, Goldberger AL. Adaptive data analysis of complex fluctuations in physiologic time series. *Adv Adap Data Anal*. 2009; 1:61–70.
17. Costa M, Goldberger AL, Peng CK. Multiscale entropy analysis of complex physiologic time series. *Phys Rev Lett*. 2002; 89:068102. [PubMed: 12190613]
18. Costa M, Goldberger AL, Peng C-K. Multiscale entropy analysis of biological signals. *Phys Rev E*. 2005; 71:021906.
19. Norris PR, Anderson SM, Jenkins JM, Williams AE, Morris JA Jr. Heart rate multiscale entropy at three hours predicts hospital mortality in 3,154 trauma patients. *Shock*. 2008; 30:17–22. [PubMed: 18323736]
20. Norris PR, Canter JA, Jenkins JM, Moore JH, Williams AE, Morris JA Jr. Personalized medicine: genetic variation and loss of physiologic complexity are associated with mortality in 644 trauma patients. *Ann Surg*. 2009; 250:524–530. [PubMed: 19730237]
21. Schulz S, Koschke M, Bär KJ, Voss A. The altered complexity of cardiovascular regulation in depressed patients. *Physiol Meas*. 2010; 31:303–321. [PubMed: 20086275]
22. Leistedt SJ-J, Linkowski P, Lanquart J-P, Mietus JE, Davis RB, Goldberger AL, Costa MD. Decreased neuroautonomic complexity in men during an acute major depressive episode: analysis of heart rate dynamics. *Transl Psychiatry*. 2011; 1:e27. [PubMed: 22832529]
23. Watanabe E, Kiyono K, Hayano J, Yamamoto Y, Inamasu J, Yamamoto M, Ichikawa T, Sobue Y, Harada M, Ozaki Y. Multiscale entropy of the heart rate variability for the prediction of an ischemic stroke in patients with permanent atrial fibrillation. *PLoS One*. 2015; 10:e0137144. [PubMed: 26325058]
24. Herlitz GN, Arlow RL, Cheung NH, Coyle SM, Griffel B, Macor MA, Lowry SF, Calvano SE, Gale SC. Physiologic variability at the verge of systemic inflammation: multiscale entropy of heart

rate variability is affected by very low doses of endotoxin. *Shock*. 2015; 43:133–139. [PubMed: 25526373]

25. Goldberger AL, Amaral LAN, Glass L, Hausdorff JM, Ivanov PCh, Mark RG, Mietus JE, Moody GB, Peng CK, Stanley HE. PhysioBank, PhysioToolkit, and PhysioNet: Components of a New Research Resource for Complex Physiologic Signals. *Circulation*. 101(23):e215–e220. [PubMed: 10851218]
26. Mietus JE, Peng C-K, Henry I, Goldsmith RL, Goldberger AL. The pNNx files: re-examining a widely used heart rate variability measure. *Heart*. 2002; 88:378–380. [PubMed: 12231596]

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Figure 1.

Heart rate time series from an intrauterine fetal demise case (left) and corresponding control (right).

Figure 2.

PNN analysis. Left panel: Percentage of differences between adjacent NN intervals greater than x ms (pNN_x). Symbols are group median values and error bars are the 1st and 3rd quartiles. Right panel: Median of the sum of the pNN values for thresholds 1 to 20 for each case and corresponding controls.

Figure 3.

Complexity index derived from multiscale entropy analysis of fetal heart rate time series for scales 1 to 5 s, for individual intrauterine fetal demise cases and corresponding controls as a function of gestational age. The red dotted line indicates the time of fetal demise.

Table 1

Demographics of the 6 cases of intrauterine fetal demise

Case	Age (years)	Gravidity	Parity	GA (Weeks)	Risk Factors	Cause of Death
A	39	2	1	35.6	Class C pregestational diabetes, advanced maternal age	Cardiomyopathy, diabetes and macrosomia
B	18	1	0	34.4	Bicornuate uterus, intra-uterine growth restriction, teen pregnancy	Unknown
C	26	7	2	35.4	Tobacco abuse, Human immuno-deficiency virus infection	Unknown
D	37	3	1	31.3	Prior child with congenital heart disease, current polyhydramnios, advanced maternal age	Marginal cord insertion, chronic hypoxia
E	36	6	4	37.3	Macrosomia, obesity, advanced maternal age, abnormal msAFP	Cord accident, macrosomia
F	25	2	1	36.6	Class B (Type 1) insulin-dependent diabetes, polyhydramnios, macrosomia	Hypoxia secondary to macrosomia

GA denotes gestational age. msAFP denotes maternal serum alpha-fetoprotein. Class refers to the modified White's classification system for diabetes in pregnancy.

Table 2

Demographics, IUFD risk factors and FHR recording information

Demographics	Cases (N=6)	Controls (N=18)	P Value
Maternal age (years)	26 (23.3 – 37.5)	31 (21.8 – 36)	0.91
Gravidity	2 (1.8 – 6.3)	2 (1 – 3)	0.33
Parity	1 (0.8 – 2.5)	1 (0 – 1)	0.23
FHR recording information			
Number of tracings	3.5 (2.3 – 4)	4 (3 – 4)	0.19
GA at the time of the 1 st FHR tracing (weeks)	34.7 (34.4 – 36.2)	35.3 (34.4 – 36.1)	0.94
Time between the 1 st and last tracings (weeks)	2 (2.0 – 2.9)	3 (2.9 – 3.6)	0.049
Time between the last tracing and IUFD (days)	5.5 (4.0 – 7.0)	n/a	n/a
Risk Factors			
Intrauterine growth restriction	1 (17%)	2 (11%)	0.99
Macrosomia	3 (50%)	1 (6%)	0.035
Abnormal amniotic fluid volume	3 (50%)	2 (11%)	0.08
Maternal tobacco use	1 (17%)	1 (6%)	0.99
Maternal Diabetes Mellitus	2 (33%)	5 (28%)	0.99
History of prior IUFD	2 (33%)	6 (33%)	0.99

Data are presented as medians (inter-quartile ranges) and total number (proportion as %).

Table 3

Time domain and complexity analysis results

Measure	Cases	Controls	P Value
Mean heart rate (bpm)	144.2 (132.1 – 149.9)	139.9 (137.0 – 144.8)	0.22
Standard deviation of heart rate (bpm)	21.2 (16.4 – 24.5)	29.5 (22.5 – 36.0)	0.0005
PNN _{1–20} (unitless)	1.1 (0.8 – 1.3)	1.3 (1.1 – 1.6)	0.0048
Complexity (unitless)	12.44 (8.90 – 16.77)	17.82 (15.21 – 22.17)	< 0.0001
Change in complexity (unitless)	−0.83 (−2.03 – 0.47)	0.14 (−1.25 – 0.94)	0.62

Data are presented as medians (inter-quartile ranges). GA denotes gestational age, FHR denotes fetal heart rate.