Longitudinal Analysis of Fetal Ventricular Rate for Risk Stratification in Immune Congenital Heart Block

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Abstract

Objectives: To assess the perinatal risks of immune complete congenital heart block (iCCHB) based on the longitudinal analysis of fetal heart rate. ***Methods:*** Retrospective analysis of a cohort of grade III congenital heart block diagnosed in utero, in the absence of associated cardiac defect, with positive maternal serum antibodies. Longitudinal measurements of the fetal heart rate were used to estimate the average slope of ventricular rate as a function of gestational age. We then defined the following prognostic stratification based on longitudinal follow-up observations: the high-rate (HR) group included cases for which all prenatal ventricular rate measurements were above the age-specific mean of our population of iCCHB and the low-rate (LR) group included those with at least one observation below the mean during follow-up. The 2 groups were compared to analyze the potential relationship between prenatal ventricular rate and adverse neonatal outcome defined by in utero or peri- natal death, neonatal heart rate <50 bpm, or hemodynamic failure requiring emergency pacing. ***Results:*** Forty-four cases were studied. Overall, the average heart rate significantly decreased during gestation from 65 bpm at 20 weeks to 55 bpm at 38 weeks. The HR and LR groups included 18 (41%) and 26 (59%) cases, respectively. Adverse perinatal outcome occurred in 1/18 (6%) and 22/26 (85%) cases in the HR and LR groups, respectively ($p < 0.001$). In the HR group, 33% of cases remained nonpaced at >6 months. The positive predictive values and negative predictive values for adverse perinatal outcome in the LR group were 85% (22/26) and 94% (17/18), respectively (100 and 80% <30 weeks and 88 and 78% at ≥30 weeks). ***Conclusions:*** The prognostic classification we developed based on longitudinal heart rate assessment may be used in the late 2nd or early 3rd trimester to identify iCCHB cases at high risk of adverse perinatal outcome. This prognostic stratification should help refine counseling and perinatal management earlier in pregnancy instead of waiting for late gestation or predelivery assessment.

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Introduction

Immune complete congenital heart block (iCCHB) is a severe, potentially life-threatening disease defined by a complete interruption of atrioventricular conduction [1], with normal cardiac anatomy and the presence of maternal antinuclear antibodies, most often of the anti-Ro (SSA) or anti-La (SSB) type [2–4]. Women with anti-SSA/Ro and anti-SSB/La autoantibodies have a risk of 1–5% of developing heart block in the fetus [5, 6] and a risk of recurrence of 14–16% following a first case of iCCHB [6, 7]. The condition usually develops between 16 and 24 weeks of gestation and is almost always irreversible when third-degree block has developed [8].

iCCHB is associated with a perinatal mortality rate of 16% [7, 9]. In neonatal survivors, 70% of cases will require permanent pacing with a survival rate of 86% at 10 years [7]. Risk factors for adverse perinatal outcome include endocardial fibroelastosis and dilated cardiomyopathy, low fetal heart rate, fetal hydrops, and early gestational age at diagnosis [7, 10, 11]. However, prenatal assessment remains ill-defined: early and standardized methods for prognostic assessment are lacking for counseling and planning perinatal management. In this study, we present an assessment of perinatal risk based on the longitudinal analysis of fetal heart rate in a cohort of pregnancies complicated with iCCHB defined by the presence of a grade III congenital heart block (CHB) diagnosed in utero, in the absence of associated cardiac defect, with positive maternal serum antibodies [2].

Materials and Methods

Patients and Follow-Up

We retrospectively reviewed all consecutive cases with an antenatal diagnosis of CHB followed in our center from 2009 to 2017. We excluded all cases with grade 1 or 2 CHB ($n = 9$) or associated congenital heart defect ($n = 13$). We also excluded cases for which maternal antibody status was either unknown or negative ($n = 3$). Termination of pregnancy could be performed in the most severe cases upon maternal request. Prenatal follow-up comprised monthly ultrasound and echocardiography up until 28 weeks, and weekly thereafter. In our unit, delivery is typically planned by cesarean section, at around 36 weeks to avoid the remaining risk of in utero fetal demise [12]. Cardiologic postnatal follow-up was at least 6 months in all cases.

Procedures

Autoimmunity Assay

Maternal anti-SSA/Ro and/or anti-SSB/La antibodies were detected using quantitative radioligand assays either because of a known pre-existing maternal condition or following the diagnosis of a CHB.

Echocardiography

Fetal echocardiographic examinations were performed by a pediatric cardiologist using standardized anatomical planes including pulsed-wave and color Doppler imaging. M-mode and Doppler recordings of the mitral valve/aorta, as well as of the superior vena cava/aorta, were used. Complete CHB was diagnosed in the presence of complete dissociation of atrial and ventricular contractions, with normal atrial rate but slow ventricular escape rate.

Antenatal Therapy

In utero treatment by using steroids varied over the time of the study and was left at the discretion of the cardiologist, using either dexamethasone (4 mg/day) or betamethasone (4–8 mg/day). The treatment was generally started following the diagnosis of iCCHB and continued until delivery. Sympathomimetics could also be used in some cases at the discretion of the cardiologist.

Neonatal Management

Neonatal cardiologic assessment for emergency pacemaker (PM) implantation was performed immediately at birth in all cases. Indications for PM placement in our institution were a neonatal ventricular escape rate of ≤50 beats per minute (bpm) and neonatal hemodynamic failure. For a ventricular escape rate between 50 and 60, PM implantation may be delayed, depending on neonatal hemodynamical assessment. When the neonatal heart rate was above 60 bpm, PM implantation was usually delayed.

Data and Outcomes

Prenatal records were reviewed for gestational age at the time of diagnosis, presence and type of maternal antibodies, effusion of one single serous cavity, occurrence of fetal hydrops (defined by the association of 2 of the following symptoms: pericardial effusion, pleural effusion, ascites, and skin edema), fetal ventricular rate on each follow-up visit, and in utero steroidal therapy. Postnatal charts were reviewed for neonatal outcomes: gestational age at birth, birth weight and umbilical artery pH, initial cardiologic assessment (including neonatal heart rate and evaluation of left ventricular function by echocardiography), survival, and the need for emergency neonatal pacing.

Standard pediatric cardiological follow-up was longer than 6 months in all cases and included assessment of ventricular rates by electrocardiogram and Holter monitoring and evaluation of left ventricular function by echocardiography. Indications for PM implantation complied with international guidelines for pacing therapy in pediatric patients with congenital heart disease [13, 14]. We defined an adverse perinatal outcome as any of the following: a neonatal heart rate of <50 bpm [14], hemodynamic failure requiring emergency rescue neonatal pacing, in utero fetal death, or neonatal death.

Definition of Study Groups and Statistical Analysis

We investigated several models describing the longitudinal evolution of ventricular escape rate throughout gestation: a simple linear polynomial model was compared to linear mixed modeling. The resulting models did not differ substantially; we therefore resorted to use simple linear regression to describe the trend of ventricular escape throughout gestation.

Based on this average model of ventricular rate, all cases were classified in 2 groups based on their longitudinal evolution: the high-rate group included cases for which all prenatal ventricular

Fig. 1. Flowchart of the population and outcomes. CHD, congenital heart defect; CHB, congenital heart block; TOP, termination of pregnancy; iCCHB, immune complete congenital heart block; IUFD, intrauterine fetal demise; PM, pacemaker.
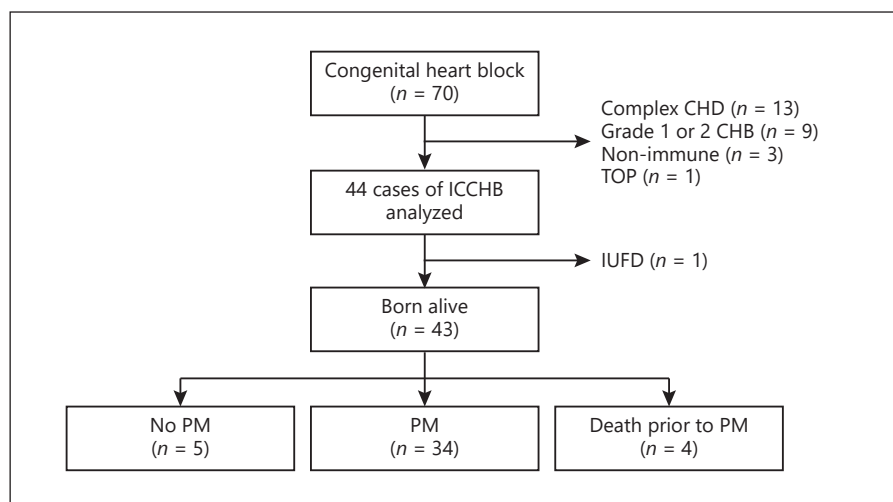
rate measurements were above the age-specific mean heart rate of our population of iCCHB and the low-rate group included those with at least one observation below the mean. The 2 groups were compared to analyze the potential relationship between the prenatal evolution of ventricular rate assessment and adverse neonatal outcome.

The prognostic performance of this classification was further assessed by calculating positive and negative predictive values for adverse perinatal outcome. Because we hypothesized that the prognostic performance of our classification could depend on gestational age at echocardiographic assessment, we evaluated the prognostic performance of our model in 2 groups of gestational age at assessment: <30 weeks and ≥30 weeks. In each group of gestational age, we computed positive and negative predictive values of a low escape rate (i.e., below the age-specific average) for an adverse perinatal outcome.

Cumulative probabilities for PM implantation were calculated as a function of age and compared between the high-rate and low-rate groups using a log-rank test in the absence of competing events. All analyses were conducted using R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Population and Outcomes

Seventy cases of CHB were referred to our unit between 2009 and 2017 (Fig. 1). Following exclusion of cardiac defects, nonimmune CHB, grade 1 or 2 CHB, and 1 TOP upon maternal request, 44 cases were analyzed. The baseline characteristics and outcomes of this population are presented in Table 1. For 39 patients, this was the first case of iCCHB, for 2 of them there was 1 recurrence and 2 recurrences, respectively. Overall, 14 women were pretreated with hydroxychloroquine. The median gestational age at diagnosis was 22 (IQR = 22–23.5) weeks. The

Table 1. Baseline antenatal findings

Maternal age, years, median (IQR)	31 (29.0–35.3)
Nulliparity, n (%)	17 (38.6)
Maternal clinical symptoms, n (%)	
Lupus	13 (29.5)
Others	5 (11.4)
None/unknown	26 (59.1)
Type of antibodies, n (%)	
SSA	18 (40.9)
SSB	1 (2.3)
SSA/SSB	25 (56.8)
Previous infant with iCCHB, n (%)	5 (11.3)
GA at diagnosis, weeks, median (IQR)	22.0 (22.0–23.5)
Fetal heart rate at diagnosis, bpm, median (IQR)	67.0 (58.0–75.0)
Lowest fetal heart rate, bpm, median (IQR)	45 (42–46)
Antenatal treatment, n (%)	18 (41)
Dexamethasone	4 (9.1)
Betamethasone	14 (31.9)
Effusion of 1 serous cavity, n (%)	9 (20.4)
Fetal hydrops, n (%)	3 (6.8)
IUFD, n (%)	1 (2.3)
GA at delivery, weeks, median (IQR)	36.5 (35.6–37.2)
Birth weight, grams, median (IQR)	2,555 (2,120–2,743)
Heart rate at birth, bpm, median (IQR)	60 (50–80)
Umbilical artery pH, median (IQR)	7.3 (7.27–7.35)
PM, n (%)	34 (77.2)
PM in the first week of life, n (%)	18 (40.9)
Emergency rescue neonatal pacing, n (%)	13 (38.2)
Late PM, n (%)	16 (36.3)
Neonatal death <28 days, n (%)	4 (9.1)
Infant death >28 days, n (%)	1 (2.3)

Data are reported as median (interquartile range) and frequencies. iCCHB, immune complete congenital heart block; GA, gestational age; IUFD, intrauterine fetal demise; bpm, beats per minute; PM, pacemaker.

Fig. 2. Ventricular rate as a function of gestational age in the 184 longitudinal measurements from 44 fetuses. The dashed line represents the fiftieth percentile. The line in red represents cases with an adverse perinatal outcome. The line in blue represents those without an adverse perinatal outcome.
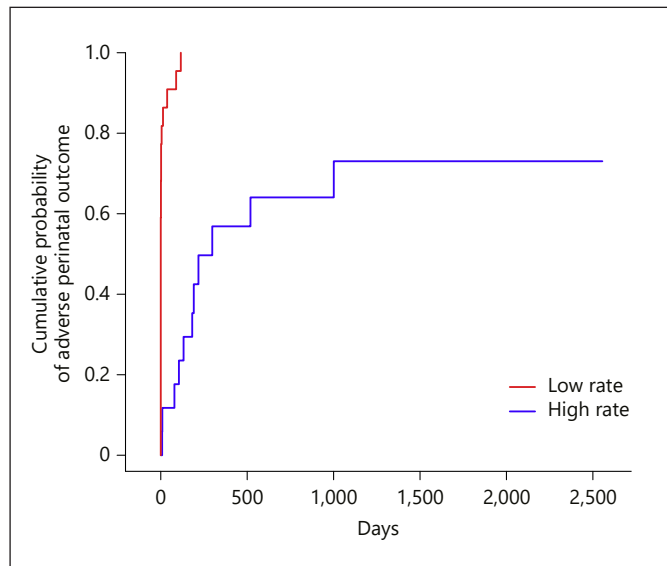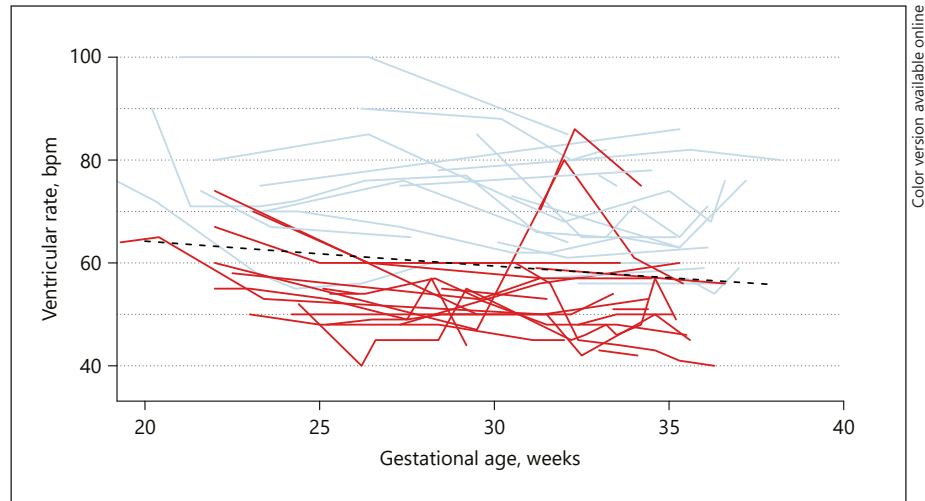
Fig. 3. Cumulative probability of adverse perinatal outcome according to the prenatal longitudinal heart rate model.

median ventricular heart rate at diagnosis was 67 (IQR = 58–75) bpm. Three (7%) fetuses developed fetal hydrops, while 9 (20.4%) other fetuses showed fluid accumulation in a single compartment: 7 with pericardial effusions, 1 with mild skin edema, and 1 with isolated ascites. In the hydropic fetuses, intrauterine fetal demise (IUFD) occurred in 1 case at 36 weeks: treatment by using steroids had been initiated at diagnosis and the last recorded ventricular rate was 51 bpm. Overall, 18 fetuses (41%) were treated in utero with fluorinated corticosteroids and 2 (4.5%) fetuses were treated by sympathomimetics. No

difference was found in the pretreatment characteristics, nor in the postnatal outcomes between cases treated (n = 18) and not treated (n = 26) by fluorinated steroids: the rate of fetal hydrops was 1/18 (5.6%) and 2/26 (7.7%), respectively (p = 1); the rate of pacing in the first week of life was 7/18 (38.9%) and 10/26 (38.5%), respectively (p = 1). However, neonatal death was 3-fold higher in the treated group (3/18, 16.7%) than in the untreated group (1/26, 3.8%), although this difference did not reach statistical significance (p = 0.29).

The overall rate of adverse perinatal outcome was 52% (23/44 cases). Within the 43 live born neonates, 4 (9.3%) died in the neonatal period, 3 of them before 2 h of life. These 3 neonates had ventricular rates of 46, 45, and 44 bpm before birth, 1 had pericardial effusion and 2 had developed hydrops. The fourth case died at 3 days of life of cardiogenic failure despite the absence of hydrops or dilated cardiomyopathy during pregnancy and a ventricular rate of 80 bpm at birth.

Overall, a PM was implanted in 34 (77%) cases: 18/34 (53%) in the neonatal period, within the first week, and 16/34 (47%) beyond 1 week of life. Within cases requiring neonatal pacing, emergency pacing was required immediately after birth in 13/18 cases and within 2 days following birth in the remaining 5 cases. When pacing was required beyond the neonatal period, the median age at pacing was 116 (IQR = 58–205) days.

Longitudinal Analysis of Prenatal Ventricular Rate and Comparison of Study Groups
Longitudinal measurements of fetal ventricular escape rates obtained from the population of 44 fetuses yielded a total of 184 measurements. The average number of mea-

Table 2. Baseline antenatal findings based on the longitudinal heart rate group

	High-rate group $n = 18$	Low-rate group $n = 26$	p value
Maternal age, years, median (IQR)	32 (29–34)	30 (29–37)	0.84
Nulliparity, n (%)	9 (50)	8 (30.8)	0.23
Lupus, n (%)	7 (38.9)	12 (46.2)	0.76
Type of antibodies, n (%)			
SSA and SSB	10 (55.6)	9 (34.6)	0.22
SSA/SSB	8 (44.4)	17 (65.4)	
Hydroxychloroquine, n (%)	6 (33.3)	8 (30.7)	1
GA at diagnosis, weeks, median (IQR)	23 (21–24)	22 (21.7–23)	0.69

Fetuses were included in the high-rate group if all fetal heart rate measurements were above fiftieth percentile during pregnancy and in the low-rate group if at least one fetal heart rate measurement was below fiftieth percentile. Data are reported as median (interquartile range) and frequencies. GA, gestational age; IUFD, intrauterine fetal demise; HR, heart rate; PM, pacemaker; bpm, beats per minute.

Table 3. Perinatal outcomes based on the longitudinal heart rate group

	High-rate group $n = 18$	Low-rate group $n = 26$	p value
Single serosal effusion, n (%)	2 (11)	7 (27)	0.27
Hydrops, n (%)	1 (6)	2 (8)	1
GA at birth, weeks, median (IQR)	36.7 (35.7–37.3)	36.1 (35.6–37)	0.41
HR at birth, bpm, median (IQR)	80 (73.7–90)	50 (44.5–60)	<0.001
Adverse perinatal outcome, n (%)	1 (6)	22 (85)	<0.001
IUFD, n (%)	0 (0)	1 (4)	1
Neonatal death, n (%)	1 (6)	3 (12)	0.63
Neonatal heart rate <50, bpm	0 (0)	15 (58)	<0.001
Emergency rescue neonatal pacing, n (%)	0 (0)	13 (50)	<0.001

Fetuses were included in the high-rate group if all fetal heart rate measurements were above fiftieth percentile during pregnancy and in the low-rate group if at least one fetal heart rate measurement was below fiftieth percentile. Data are reported as median (interquartile range) and frequencies. GA, gestational age; IUFD, intrauterine fetal demise; HR, heart rate; PM, pacemaker; bpm, beats per minute.

surements was between 4 and 5 per fetus. The ventricular escape rate decreased with gestational age ($p < 0.001$): The model and parameter estimate for the mean and standard deviation (SD) for ventricular escape rate as a function of gestational age was the following: log(rate) = 4.3191582–0.007831177 × GA and SD = 0.1991254. Figure 2 presents the evolution of ventricular rate as a function of gestational age for cases with adverse perinatal outcome compared to cases without it.

Based on the individual evolution of fetal ventricular rate during prenatal follow-up, the population was divided into 2 groups: 18 (41%) cases were included in the high-rate group when the observations were all above the mean during follow-up and 26 (59%) in the low-rate group when at least one measurement was found below the mean (Fig. 2, dotted line). In 33/44 (75%) of cases, follow-up observations were consistently either above or below the mean throughout follow-up. In 11/44 (25%) of cases, at least one measurement crossed the mean; therefore, they were included in the low-rate group. However, this change did not occur more frequently at any given gestation (data not shown).

No difference was found in the baseline characteristics between the high-rate group and the low-rate group (Table 2). Table 3 compares the perinatal outcomes between the high-rate group and the low-rate group. No difference

was found between the high-rate group and the low-rate group for gestational age at diagnosis and gestational age at birth. Neonatal heart rate was significantly higher in the high-rate group (80 [73.7–90] vs. 50 [44.5–60] bpm, $p < 0.001$). The rates of adverse perinatal outcome were 1/18 (6%) in the high-rate group and 22/26 (85%) in the low-rate group ($p < 0.001$). None of the high-rate cases required early neonatal pacing, whereas 69% of cases in the low-rate group were implanted within the first week of life (18/26 vs. 0/18, $p < 0.001$), half of which required immediate neonatal emergency pacing (13/26, 50%). Conversely, in the high-rate group, none required early neonatal pacing and 33% of cases remained nonpaced at >6 months.

The positive predictive value (PPV) and negative predictive value (NPV) for adverse perinatal outcome in the low-rate group (i.e., the NPV and PPV for the high-rate group) were 85% (22/26) and 94% (17/18), respectively. The prognostic performance of our model did not change with gestational age; rather, the prognostic value of ventricular escape rate was higher in earlier gestation, with a PPV = 100% and NPV = 80% at <30 weeks compared to 88 and 78%, respectively, at ≥30 weeks.

Figure 3 presents the cumulative probability of adverse perinatal outcome as a function of time. There was a significant difference between the high-rate and low-rate groups ($p < 0.001$): in the low-rate group, all cases had been paced by 4 months, whereas in the high-rate group, the median time to pacing was 6 months (i.e., half the group have been paced by 6 months) together with a 25% probability of remaining nonpaced in the long term.

Discussion

In this retrospective study, we describe the prenatal longitudinal follow-up and outcomes in a cohort of fetuses diagnosed with iCCHB. We have shown that the overall ventricular escape rate significantly decreases during gestation in this population. Using a simple classification of the prenatal longitudinal evolution of the ventricular escape rate, we have defined a group at high risk of adverse perinatal outcome when the ventricular rate drops below the average at least once during follow-up (Fig. 2). Furthermore, we have shown that this classification does not depend on gestational age at assessment and may be used in the 2nd trimester, without waiting for late 3rd trimester assessment.

For example, a patient with iCCHB and a ventricular rate of 70 bpm at 20 weeks that drops to 60 bpm at 24 weeks is at high risk of adverse neonatal event. Conversely, a fetus with ventricular rates of 80, 70, and 60 bpm at 22, 30, and 36 weeks is at low risk of adverse event, despite the significant reduction in heart rate during pregnancy.

The perinatal mortality rate in our population is within ranges reported by previous studies: between 4 and 14% for early neonatal death [2, 15, 16], between 0 and 8% for late postnatal death (>28 days) [15–17], and between 2% [18] and 12% for IUFD [18, 19]. The predictive factors of poor outcome in CHB differ between reports, and the only consistent factor for mortality is an associated congenital heart disease [19, 20]. The remarkably small number of fetal and neonatal deaths in our study precludes analyses of risk factors for that. In survivors, PM implantation remains the only treatment. Overall, 70% of our cases required pacing, 40% of which within the first year, which is similar to recent published cohorts [7, 9, 21].

Several prognostic markers have been associated with iCCHB: the presence of fetal hydrops [7, 9, 22], endocardial fibroelastosis [7], preterm birth [9, 22], and early gestational age at diagnosis have been [21] associated with poor fetal and neonatal outcome. In this study, we provide a unified approach for prognostic assessment of iCCHB based on the longitudinal follow-up of fetal heart rate from 2nd trimester diagnosis to term. The nadir of fetal ventricular escape rate has been studied by several authors, but with conflicting results, whereas Izmirly et al. [7] report a strong correlation with postnatal outcome, Levesque et al. [9] found similar outcomes in cases with a nadir of <50 bpm compared to cases with a nadir of >50 bpm, and others describe a 5-fold increase in the rate of intrauterine demise in case of fetal ventricular rate ≤50 bpm [21]. Compared to these studies, our study offers several novelties: (i) the population we consider is based on a strict definition of iCCHB, thus excluding associations with heart defects and lower grade blocks; (ii) we consider both prenatal and early postnatal outcomes, which encompass perinatal mortality and immediate postnatal pacing; and (iii) the prognostic model we developed may be used at any gestational age. Indeed, the prognostic value of our model showed high positive and negative predictive values throughout gestation: the PPV for perinatal death or early pacing was 100% when the escape rate was below the mean before 30 weeks with a NPV of 80%, suggesting that counseling and perinatal management can accurately be planned in the late 2nd or early 3rd trimester instead of waiting for late gestation or pre-delivery assessment. However, fetuses with a high rate remain at risk of pacing, but at an older age.

To our knowledge, this is the first study to assess the prognostic value of longitudinal follow-up of fetal heart rate in iCCHB. Although the strict inclusion criteria for iCCHB led to a significant reduction in the initial sample size, we believe the prognostic model developed in this homogeneous group is more easily generalizable to other centers and future patients with iCCHB.

However, we were not able to reliably assess and quantify the presence of endocardial fibroelastosis and in a lesser extent dilated cardiomyopathy, both of which have been associated with poor prognosis in the neonate [23]. We also acknowledge that a significant proportion of our cases were treated by using steroids. Although the decision for treatment was not based on a predefined protocol, no differences were found in the pretreatment characteristics between treated and untreated fetuses, nor in postnatal outcomes. This makes the use of corticosteroids unlikely to bias the results.

Conclusions

Most of the perinatal prognosis of iCCHB can be approached by the longitudinal assessment of the fetal heart rate. The prognostic model we developed could refine prenatal counseling and help standardize perinatal management protocols and optimize resource allocation: cases identified at high risk warrant close follow-up and active perinatal management; on the contrary, those at low risk could benefit from less aggressive management.

Statement of Ethics

Deidentified data were collected from 2 digital databases that are regularly updated by cardiologists and obstetricians. The analysis of the data was completed in one protected spreadsheet. The framework used by the APHP oversees the information given to patients regarding the use of their data for research purposes. It provides the right to oppose. This right has not been exercised in the context of this study. The study was structured in accordance with the principles of the Helsinki Declaration and obtained approval from the institutional review board of the Ethics Committee at AP-HP, Paris, France (IRB registration 00011928).

Conflict of Interest Statement

The authors declare they have no conflicts of interest.

Funding Sources

There are no funders to report for this submission.

Author Contributions

Ayla Shokrzadeh, Alice Maltret, and Julien Stirnemann contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. Nathalie Morel, Nathalie Costeadoat, and Marine Driessen contributed to the implementation of the research. Damien Bonnet, Olivier Raisky, and Yves Ville supervised the findings of this work.

References

1 Sonesson SE, Acharya G. Hemodynamics in fetal arrhythmia. Acta Obstet Gynecol Scand. 2016;95(6):697–709.

2 Brucato A, Jonzon A, Friedman D, Allan LD, Vignati G, Gasparini M, et al. Proposal for a new definition of congenital complete atrioventricular block. Lupus. 2003;12(6):427–35.

3 Ho SY, Esscher E, Anderson RH, Michaëlsson M. Anatomy of congenital complete heart block and relation to maternal anti-Ro antibodies. Am J Cardiol. 1986 Aug 1;58(3):291–4.

4 Villain E, Coastedoat-Chalumeau N, Marijon E, Boudjemline Y, Piette JC, Bonnet D. Presentation and prognosis of complete atrioventricular block in childhood, according to maternal antibody status. J Am Coll Cardiol. 2006 Oct 17;48(8):1682–7.

5 Brucato A, Frassi M, Franceschini F, Cimaz R, Faden D, Pisoni MP, et al. Risk of congenital complete heart block in newborns of mothers with anti-Ro/SSA antibodies detected by counterimmunoelectrophoresis: a prospective study of 100 women. Arthritis Rheum. 2001 Aug;44(8):1832–5.

6 Costedoat-Chalumeau N, Amoura Z, Lupoglazoff JM, Huong DL, Denjoy I, Vauthier D, et al. Outcome of pregnancies in patients with anti-SSA/Ro antibodies: a study of 165 pregnancies, with special focus on electrocardiographic variations in the children and comparison with a control group. Arthritis Rheum. 2004 Oct;50(10):3187–94.

7 Izmirly PM, Saxena A, Kim MY, Wang D, Sahl SK, Llanos C, et al. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. Circulation. 2011 Nov 1;124(18):1927–35.

8 Friedman DM, Rupel A, Glickstein J, Buyon JP. Congenital heart block in neonatal lupus: the pediatric cardiologist's perspective. Indian J Pediatr. 2002 Jun;69(6):517–22.

9 Levesque K, Morel N, Maltret A, Baron G, Masseau A, Orquevaux P, et al. Description of 214 cases of autoimmune congenital heart block: results of the French neonatal lupus syndrome. Autoimmun Rev. 2015 Dec; 14(12):1154–60.

10 Sonesson S-E. Diagnosing foetal atrioventricular heart blocks. Scand J Immunol. 2010 Sep; 72(3):205–12.

11 JMPJ B, Kapusta L, Stoutenbeek P, Visser GHA, van den Berg P, Meijboom E-J. Isolated congenital atrioventricular block diagnosed in utero: natural history and outcome. J Matern-Fetal Neonatal. 2008 Jul;21(7):469–76.

12 Doti PI, Escoda O, Cesar-Díaz S, Palasti S, Teixidó I, Sarquella-Brugada G, et al. Congenital heart block related to maternal autoantibodies: descriptive analysis of a series of 18 cases from a single center. Clin Rheumatol. févr 2016;35(2):351–6.

13 Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices) developed in collaboration with the American Association for Thoracic Surgery and society of thoracic surgeons. J Am Coll Cardiol. 2008 May 27; 51(21):e1–62.

14 European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA); Brignole M, Auricchio A, Brignole M, Auricchio A, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013 Aug;15(8): 1070–118.

15 et al C, Geipel A, Kohl T, Breuer J, Germer U, Krapp M, et al. Atrioventricular block detected in fetal life: associated anomalies and potential prognostic markers. Ultrasound Obstet Gynecol. 2005 Jul;26(1):4–15.

16 Rosenthal E, Gordon PA, Simpson JM, Sharland GK. Letter regarding article by Jaeggi et al, "transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease". Circulation. 2005 May 10; 111(18):e287–8.

17 Groves AM, Allan LD, Rosenthal E. Outcome of isolated congenital complete heart block diagnosed in utero. Heart. 1996 Feb;75(2): 190–4.

18 Kuleva M, Le Bidois J, Decaudin A, Villain E, Costedoat-Chalumeau N, Lemercier D, et al. Clinical course and outcome of antenatally detected atrioventricular block: experience of a single tertiary centre and review of the literature. Prenat Diagn. 2015 Apr;35(4):354–61.

19 Jaeggi ET, Hornberger LK, Smallhorn JF, Fouron JC. Prenatal diagnosis of complete atrioventricular block associated with structural heart disease: combined experience of two tertiary care centers and review of the literature. Ultrasound Obstet Gynecol. 2005 Jul;26(1):16–21.

20 Maeno Y, Himeno W, Saito A, Hiraishi S, Hirose O, Ikuma M, et al. Clinical course of fetal congenital atrioventricular block in the Japanese population: a multicentre experience. Heart. 2005 Aug;91(8):1075–9.

21 Eliasson H, Sonesson SE, Sharland G, Granath F, Simpson JM, Carvalho JS, et al. Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. Circulation. 2011 Nov 1;124(18): 1919–26.

22 Ho A, Gordon P, Rosenthal E, Simpson J, Miller O, Sharland G. Isolated complete heart block in the fetus. Am J Cardiol. 2015 Jul; 116(1):142–7.

23 Eronen M, Sirèn MK, Ekblad H, Tikanoja T, Julkunen H, Paavilainen T. Short- and long-term outcome of children with congenital complete heart block diagnosed in utero or as a newborn. Pediatrics. 2000 Jul;106(1 Pt 1): 86–91.