SLOW HEART REGISTRY

A PROSPECTIVE OBSERVATIONAL COHORT STUDY OF FETAL IMMUNE-MEDIATED HIGH-DEGREE HEART BLOCK

Study PI:

Edgar Jaeggi, MD, FRCP(C)

Head, Fetal Cardiac Program

The Hospital for Sick Children

555 University Avenue, Toronto, ON, Canada M5G 1X8

Tel: +1-416-813-6142 ext.2

Study-related communications: slow.heart@sickkids.ca

1. INTRODUCTION

Complete 3rd-degree heart block (CAVB) is defined as the complete failure of electrical impulse propagation from the atriums through the AV node and to the ventricles. In the fetus with a structurally normal heart, CAVB typically develops between 18 and 24 gestational weeks and results from the fetal exposure to a high amount of maternal anti-Ro/SSA antibodies. Immune-mediated CAVB (ICAVB) occurs in about 1 in 10,000 pregnancies. In comparison, seronegative CAVB is very rare and accounts for <5% of all isolated congenital AV block cases. The clinical diagnosis of ICAVB is based on the serological confirmation of maternal auto-antibodies and the demonstration of a complete failure of AV conduction by fetal echocardiography, with atriums and ventricles that beat independently at their own intrinsic pacemaker rates. While the fetal atrial rate typically remains normal between 130-150 bpm, the ventricular rate ranges between 50-60 bpm or slower. The condition carries a significant mortality risk as the fetus needs to overcome the sudden drop in ventricular rate, the loss of normal atrial systolic contribution to ventricular filling, and perhaps concomitant myocardial inflammation and fibrosis. Prenatal management options of ICAVB include: 1) no transplacental treatment, 2) treatment targeting more severely affected fetuses, and 3) routine treatment from the start of diagnosis to birth. Available medication, if treatment is elected, include oral fluorinated steroids (dexamethasone, betamethasone), intravenous infusion of gamma globulin (IVIG), or both to reduce or limit fetal cardiac inflammation/damage. Maternal oral β-sympatho-mimetics may be used to increase the fetal heart rate, if required. Yet, in the absence of prospective data, the optimal management of ICAVB remains unclear, including clear indications for the use anti-inflammatory and beta-mimetic transplacental treatment. Moreover, the benefit and risks of prenatal treatment vs no treatment on survival, postnatal pacing and myocardial performance is unclear. In the absence of prospectively collected scientific evidence, there is currently no consensus for the optimal management of ICAVB.

Incomplete AV block (IAVB) refers to AV conduction anomalies with delayed (1st degree AVB) or incomplete (2nd degree AVB) propagation of normal atrial events to the ventricles. Immune-mediated IAVB may preceed the development of ICAVB although, due to the rapid progress from normal AV conduction to complete block, this diagnosis is only rarely made by fetal echocardiography.[1] First degree AV block does not present with a slow heart rate but with prolonged AV conduction. In 2nd degree AVB Mobitz type I (Wenckebach), the non-conducted atrial event is preceded by progressive AV lengthening while in Mobitz type II the AV conduction is either normal or blocked. In both forms of 2nd degree block, the cardiac rhythm is irregular ± slowed due to skipped ventricular beats. In 2:1 AV block, the atriums beat completely regular at a normal rate but every second atrial beat fails electrical propagation to the ventricles. As a result, the ventricular rate will be exactly half of the atrial rate, usually between 60 and 80 bpm. Finally, in 2nd to 3rd degree AV block, there will be episodes of complete AV dissociation. Data on the outcome of 2nd degree fetal IAVB is scarce, including the role of anti-inflammatory prenatal medication to prevent ICAVB. Second degree AVB Mobitz type 2 and intermittent ICAVB is most likely secondary to antibody-mediated AV nodal inflammation and may then benefit from anti-inflammatory treatment to prevent progression to permanent ICAVB.[2] On the other hand, 2nd degree AVB type 1 and 2:1 AVB may also be secondary to transient QT prolongation and then could resolve spontaneously.[1, 2]

The ***SLOW HEART REGISTRY*** is a *multi-centered prospective observational study* that will address the knowledge gap to guide future management of high-degree immune-mediated AVB to the best of care. The study seeks to

establish an international database of the management and outcome of affected fetuses, to be used to publish information on the results of currently available prenatal care and to evaluate the need for additional research.

The ***study aims*** are to document the outcome of patients diagnosed prenatally with **immune-mediated 2nd or 3rd degree AVB** irrespective of the primary choice of prenatal care.

The ***primary objective*** will be to determine the rate of transplant-free survival to 1 year of life of fetuses with AVB based on the prenatal management decision:

- **Cohort 1:** Fetuses not treated with fluorinated glucocorticoids
- **Cohort 2:** Fetuses treated with fluorinated glucocorticoids from the time of immune-mediated AVB diagnosis.

Secondary objectives will be to determine: a) the evolution of clinical findings from AVB diagnosis to birth (AV conduction; fetal heart rate; other NL manifestations; fetal growth; effusions/hydrops) between cohorts; b) the need of new/additional treatment (steroids; beta-mimetics; IVIG) to birth; c) gestational age and weight at birth; d) postnatal management (pacing; steroids; IVIG); and e) clinical evolution from birth to 1-3 years of life (cardiac function; developmental milestones; infant growth; health). Prevalence of relevant fetal-maternal events and complications (death; IUGR; morbidity) between the study cohorts will also be determined.

All management is decided by the treating center and physicians in accordance to institutional guidelines and clinical findings. Participation in this prospective observational cohort study requires site REB approval and an executed legal contract with the primary investigator/SickKids Hospital, Toronto.

2. STUDY BACKGROUND AND RATIONALE

2.1 ETIOLOGY AND MANIFESTATIONS OF CARDIAC NEONATAL LUPUS (NL)

The cardiac manifestations of NL are strongly associated with the fetal exposure to a very high amount of maternal anti-Ro antibodies.[3] The vast majority of pregnant women carrying these antibodies is healthy and unaware about their antibody-status and their potential risks. The current understanding of the cardiac NL mechanism is that the maternal anti-Ro antibodies increasingly cross the placenta to the fetus during mid-gestation, where they may interact with fetal Ro ribonucleoproteins and initiate cardiac inflammation in the susceptible fetus. Subsequent replacement of the inflamed cardiac tissue with fibrosis and calcification may then manifest as heart block, sinus node dysfunction, AV valve disease, endocardial fibroelastosis (EFE), and/or dilated cardiomyopathy.[4-9] ICAVB, the most frequently observed cardiac NL manifestation, develops predominantly sometimes between 18 and 24 gestational weeks and probably within a few hours to days of a normal echocardiogram.[2, 10] Its prenatal diagnosis is based on the echocardiographic demonstration of a complete failure of AV conduction, with atriums and ventricles that beat independently at their own intrinsic rates. The prevalence and severity of other cardiac pathology associated with AVB may be underestimated by ultrasound imaging[7, 11] although it is now well established that acute and chronic diseases of the working myocardium including carditis, EFE and dilated cardiomyopathy are often part of the disease spectrum. Indeed, histological findings of a more generalized process of inflammation and scarring are frequently present in other

areas of the heart.[11] The concept of more generalized inflammation has been substantiated by the demonstration of immunoglobulin G, complement, and fibrin deposition on the fetal myocardium.[12, 13] Moreover, at least 20% of fetal AVB cases display ultrasound findings indicative of more generalized cardiac inflammation and damage, such as reduced ventricular contractility, valvar regurgitation, sinus bradycardia, pericardial effusion, and patchy echogenicity of myocardial tissues.[5, 14, 15]

2.2 PROGNOSIS OF UNTREATED AND TREATED IMMUNE-MEDIATED AVB

The cardiac output of the fetus with ICAVB is negatively affected by the slowed ventricular rate, the loss of the normal atrial contribution to ventricular filling, and, if present, by concomitant myocardial inflammation and damage.[4, 16] While the slow heart rate is frequently well tolerated to birth, the condition carries a significant risk of perinatal mortality at the severe end of the NL spectrum. Risk factors associated with perinatal demise include a younger gestational age at AVB diagnosis, fetal hydrops, carditis, EFE, and a slow ventricular rate.

Management of newly diagnosed CAVB often differs significantly among centers and countries. While some offer prenatal anti-inflammatory medication to most mothers with fetal AVB,[16] others do not use medication at all or are considering prenatal treatment only for severely affected fetuses, when additional cardiac disease manifestations are present or subsequently develop.[17] Irrespective whether or not treatment is used, AVB once complete is irreversible although transient improvement to 1:1 AV conduction has rarely been reported with high-dose steroids.[18] Unlike, there is some evidence that incomplete high-degree AV block may still improve or not progress with steroids although long-term data is missing.[2, 19, 20] Whether fetal and postnatal outcomes improve with fetal treatment remain unclear: most of the retrospective experiences with inconsistent prenatal treatment showed no benefit in early survival with steroids vs no steroids, although the treated vs untreated patient cohorts appeared clinically comparable.[16, 17, 21-24] In study cohorts of predominantly untreated patients (number of patients: 51 – 198; steroid-treated: 11%-39%; beta-mimetic treated: 16-33%), neonatal survival rates with CAVB were highly variable, ranging from 66% to 93%.[4, 17, 21-25] Finally, 7%-19% of fetal survivors in these experiences developed “late-onset” cardiomyopathy mainly during infancy or early childhood, despite apparently normal cardiac function at birth.[9, 17, 23, 24] Neonates with CAVB and slow ventricular rates often undergo their first permanent pacemaker implant already early after birth.[15] Whether prenatal anti-inflammatory treatment influences the risk of cardiomyopathy and/or improves ventricular escape rates, e.g. delaying the need of postnatal pacing, is unknown.

2.3 PERINATAL MANAGEMENT OPTIONS INCLUDING CURRENT GUIDELINES

Possible prenatal management options of **immune-mediated AVB** include:

- No treatment
- Treatment targeting more severely affected fetuses; and
- Routine treatment usually to birth

Available medication options, if transplacental treatment is elected, include daily oral fluorinated steroids, intermittent IVIG in intervals of 2-3 weeks, or both, to reduce fetal cardiac inflammation/damage as well as daily oral β-sympathomimetics to increase the fetal cardiac output.

Postnatal permanent pacemaker implantation is recommended in the infant with a ventricular rate <55 bpm (class 1 indication) according to AHA/ACC guidelines.[15, 26] Postnatal antiinflammatory treatment is usually reserved for those newborns with CAVB and additional NL manifestations (carditis; EFE) or with incomplete AVB.

Guidelines. In the absence of universally accepted protocols, management recommendations of fetal IAVB often vary between centers. Nonetheless, recommendations recently published by the American Heart Association may be used to guide the prenatal management of AVB.[27]

The AHA recommends the following approach (with the caution that prospective studies will be necessary to establish definitive treatment recommendations):

- The use of **β-Sympathomimetics** (terbutaline; salbutamol) is considered reasonable with *fetal heart rates <55 bpm or* with higher rates if there are *symptoms of heart failure or hydrops* (evidence level IIa/c).
- Treatment with **dexamethasone** of fetuses with *ICAVB and no heart failure* may be considered with the goal of improving survival or reducing the incidence of dilated cardiomyopathy (IIb/B), although its usefulness has not been established given that studies to date have been retrospective and nonrandomized and have had incomplete follow-up. Dexamethasone use is recommended for *immune-mediated 2nd degree AVB*, as it may halt progression to CAVB (IIb/B). Reported benefits of dexamethasone (4–8 mg/d) include reduction of inflammation, reversal or stabilization of IAVB, and improvement or resolution of hydrops or EFE.[2, 16 19] Important complications of dexamethasone include growth restriction, oligohydramios, ductal constriction, maternal diabetes, and central nervous system side effect.
- **IVIG**, usually co-administered with dexamethasone, may be considered (IIb/C) given that it improved survival of ICAVB when *EFE or systolic dysfunction* was present.[28] Steroids and IVIG (1 g/kg maternal weight up to a maximal dose of 70 g every 2-3 weeks) were also successfully used to treat *incomplete AVB*.[2] The optimal timing of administration and intervals of repeat dosing is unknown. Risks of IVIG treatment are mainly exposure to blood products and allergic reactions.
- **Idiopathic sero-negative isolated AVB** is considered to have a better prognosis than sero-positive AVB and can be managed without anti-inflammatory fetal treatment.

2.4 PHARMACOTHERAPY

The following summary provides an overview on the use, results and risks of transplacental pharmacotherapy for cardiac NL:

- **BETA-SYMPATHOMIMETIC AGENTS.** The β_1-adrenergic action of salbutamol and terbutaline increases the fetal cardiac output by an increase in heart rate and a decrease in systemic vascular resistance.[29, 30]
  Results: When given orally to the mother at or close to the maximal recommended daily doses, salbutamol (10 mg q 8h; maximal: 40 mg/day)[16] and terbulatin (2.5–7.5 mg q 4 -6 h; maximal 30 mg/day)[31] will typically increase the ventricular rate by 5 to 10 bpm. The chronotropic effect usually persists for weeks and often allows the pregnancy to continue to a more viable gestational age for delivery and postnatal pacing.
  Adverse Drug Reactions: Adrenergic maternal effects include tremor, palpitations and sweating that usually improve or resolve with the duration of drug therapy. Maternal serious adverse events (SAE) or intolerable symptoms that required a change or cessation in drug treatment have not been reported and were also not

observed by us with oral salbutamol. Beta-agonists should however be used cautiously in mothers with diabetes, hypertension, hyperthyroidism, or tachyarrhythmias.

- **DEXAMETHASONE and BETAMETHASONE** are potent synthetic glucocorticoids that are only minimally metabolized by the placenta and easily pass to the fetus, making these agents useful for direct fetal treatment. Dexamethasone is often preferred as it can be given as a single daily oral dose.
  The ***SickKids Protocol*** recommends starting dexamethasone at the time of high-degree/complete AVB diagnosis, initially at a dose of 8 mg/day for two weeks that is then reduced to 4 mg/day at around 28-30 weeks and to 2 mg/day for the remainder of pregnancy.[15] If the maternal anti-Ro/La antibody test results turns out to be negative, dexamethasone is discontinued, which applies to about 5% of isolated CAVB. For treated cases with anti-Ro antibodies, lowering the dexamethasone dose to 2 mg/day during the last trimester is recommended to reduce the risk of progressive oligohydramnios before birth. Maternal **IVIG** (1 g/kg every 3 weeks; maximal 70 g per dose) is added if we detect EFE, cardiac dysfunction, and/or AVB is incomplete.[2, 28] We would not offer prenatal treatment but close observation for a late pregnancy referral >32 gestation weeks with isolated ICAVB, ventricular rates >55 bpm and no obvious evidence of EFE and/or heart failure, because survival to birth is expected without significant disease progression.
  Results. Benefits of transplacental dexamethasone ± IVIG include reduction of cardiac inflammation, reversal or stabilization of incomplete heart block, as well as improvement or resolution of AV valvar regurgitation, effusions, fetal hydrops, and/or EFE.[2, 3, 16, 19, 28, 32-34] There has been an immediate improvement in outcome since 1996, coinciding with the introduction of perinatal dexamethasone for ICAVB, in a Canadian multicenter study.[16] Including deaths unrelated to NL, current survival rates of treated CAVB patients in Toronto exceed 95% at 1 month and 90% at 10 years of life, which is significantly improved from our historical outcome data and when compared with predominantly untreated patient cohorts reported by others.[15-17, 22-24] However, none of the other retrospective studies have shown a similar survival benefit with prenatal steroids.
  Precautions. Dexamethasone given at doses greater than 1.5 mg/day suppresses the hypothalamic-pituitary-adrenal function. Gradual weaning in maternal steroid dosing (including after birth) is therefore required if dexamethasone has been given for more than 2 weeks.
  Adverse Drug Reactions. Possible maternal drug-mediated effects are numerous and include changes in mood (irritability, euphoria, mania, depression, anxiety), insomnia, increased weight gain, fluid retention, arterial hypertension, glucose intolerance, hirsutism, strias, impaired wound-healing, and stomach irritation. Nonetheless, significant adverse reactions are rare: we have not observed any SAEs in our Toronto experience of more than 80 treated mothers that would have required discontinuing using steroids apart for one mother with significant mood changes with 8 mg/day of dexamethasone. Her symptoms improved once dexamethasone was reduced and resolved after birth once the steroids were discontinued. Elliason et al reported a case of maternal psychosis that was attributed to the prenatal use of steroids.[17] Possible effects of prolonged high-dose dexamethasone administration on the pregnancy include oligohydramnios and fetal growth restriction[16 35] alhough no other serious fetal effects have been reported. No negative longterm effects on the physical, mental and neurological performance of children have been reported following the prenatal exposure to steroids. This includes prenatally treated school-age children with CAVB.[36-41]

3. OUTLINE OF THE SLOW HEART REGISTRY

3.1 STUDY DURATION AND ENROLMENT

The "Slow Heart Registry" is an observational cohort study of pregnant mothers and their fetus with a new diagnosis of 2nd or 3rd degree AVB. Eligible participants will be prospectively recruited over a 5-year period (January 2020 to December 2025). At SickKids, we encounter 5-10 patients/year with ICAVB. Overall, we expect to be able to enroll 50 ICAVB cases/year in this multicenter study and overall >100 cases in each of two possible study arms based on the initial management decision at ICAVB diagnosis: Group 1: untreated; Group 2: steroid treated. Up to 350 participants will be enrolled in the study in total. Outcome data will be collected until the postnatal neurodevelopmental assessment by ASQ-3 has been completed (latest December 2027).

3.2 GOALS

To determine the role and impact of prenatal care of high-degree AVB to ≥1 year of life.

3.3 PARTICIPATION

Study enrolment of an eligible participant is possible ***within ≤8 days of AVB diagnosis***. Irrespective whether a mother elects study participation or not, all management decisions will be decided by the primary physician in accordance with institutional guidelines and good clinical practice.

3.4 STUDY WITHDRAWAL

A participant is free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice. If the participant withdraws, data that has already been collected up to that point in time will be kept (as indicated in the patient informed consent). Entry of study data in REDCap after a withdrawal will be disabled.

3.5 SERO-NEGATIVE SUBJECTS

Subjects known to be anti-Ro antibody negative at the time of AVB diagnosis are not eligible and are not to be approached for study participation as treatment with steroids is not expected to change the outcome. Nonetheless, anti-Ro/La antibody test results are rarely known at the time of a new AVB diagnosis, when first management decisions are made. Serological confirmation of the maternal anti-Ro/La antibody status, which in 95% will be positive if a fetus has isolated AVB, then usually takes a few days. If a patient has been approached and agreed to Registry enrolment but is eventually tested negative for anti-Ro/La antibodies, all data that has already been collected in REDCap will be kept up to the time the negative antibody test result becomes known (as indicated in the patient informed consent). Further data entry in REDCap will be disabled once the negative antibody test result is entered in the database.

4. STUDY CONDUCT

4.1 PATIENT IDENTIFICATION

The site investigator and/or a qualified delegate will be responsible for identifying, recruiting and enrolling participants, and conducting the study at his/her center.

4.2 ELIGIBILITY CRITERIA

Participants are eligible for study participation if they meet the following inclusion and none of the exclusion criteria.

INCLUSION CRITERIA:

- Written informed maternal consent to participate in the Slow Heart Registry
- High-degree (2^{nd}; 2:1; 2^{nd}-3^{rd} or 3^{rd} degree) AVB diagnosed ≤ 32+0 weeks *with or without* hydrops
- Enrolment within maximally 8 days of high-degree AVB diagnosis
- Positive or pending anti-Ro/SSA and anti-La/SSB antibody test results at the time of enrolment

EXCLUSION CRITERIA:

- AVB associated with major CHD, including left atrial isomerism and congenitally corrected transposition
- AVB with known negative anti-Ro and anti-La antibody test result at the time of enrolment
- 1^{st} degree AVB (normal atrial and ventricular rate with prolonged AV time intervals)
- Sinus bradycardia with normal 1:1 AV conduction
- Blocked atrial bigeminy (irregular atrial rate with failure of AV conduction of the premature atrial beat)
- Primary delivery for postnatal treatment
- Maternal-fetal conditions (other than cardiac NL) associated with high odds of premature delivery or death (e.g. renal failure, significant infectious diseases, major extracardiac anomalies, PROM, etc.)
- Preexisting maternal mental disorder (e.g. bipolar, mania, severe depression, substance abuse)
- Poorly controlled insulin-dependent diabetes (HbA1c >7%) at CAVB diagnosis
- Oligohydramnios (deepest/maximal vertical pocket <2 cm)
- Severe IUGR (estimated fetal weight <3^{rd} percentile)

4.3 INFORMED CONSENT

The consent process at each site will be performed as approved per institutional practices. The study is explained to the patient in detail, including the option of non-participation, and any questions are answered prior to signing the consent form. The person obtaining consent must co-sign the form with date (and time, depending on institutional policies). A copy of the consent form must be given to the patient.

4.4 DATA COLLECTION

4.4.1 Database

REDCap (**Research Electronic Data Capture**) is a browser-based, metadata-driven EDC software solution and workflow methodology for designing clinical and translational research databases. It is a network of more than 3,000 institutional partners in over 120 countries. The SLOW HEART REGISTRY Database is deployed through a secured/encrypted server at SickKids. REDCap is available anytime, anywhere in the world, is completely automated and will allow new patient input into the Database once a center becomes eligible to participate. The password-protected REDCap data management system (www.project-redcap.org) will be used to enter de-identified patient data by the participating sites. Credentialing to access REDCap is managed centrally by the study team at SickKids. Individual access will be limited to data from individual sites. The Database will be managed by the study sponsor in collaboration with experienced Clinical Research and Database managers. Study data is automatically backed-up on daily basis in REDCap.

The site investigator is responsible for ensuring accurate and complete data entry into REDCap. Regular updates of key findings will be requested from the site investigator up to postnatal outcome between 1 and 3 years of life. Once completed, participant data will be verified for completeness and validity by the research team, and any queries will be sent to the site investigator.

The SLOW HEART REGISTRY Database is structured in chronological order of events (see 4.4.2 to 4.4.10). It is recommended to *enter data in a chronological order, ideally immediately following a patient visit.*

4.4.2 Baseline Data

To protect patient privacy an individual ID code is assigned by REDCap at first data entry to be used for any patient-related communication with the study site and to submit de-identified information into REDCap. Completion of the enrolment process of an eligible patient requires the site investigator to submit baseline information into the participant's electronic REDCap form. SickKids functions as Core Lab and will review de-identified baseline echocardiographic findings to confirm the AVB diagnosis and associated findings. Upload of baseline echo imaging in REDCap for Core Lab review is requested ***within ≤7 days of study enrolment***.

At the time of enrolment the following baseline information is collected in REDCap:

- Name and institution of the site investigator, including contact information
- Checklist of eligibility criteria for participation
- Baseline maternal health information
- Baseline fetal echocardiographic findings
- Management decisions at AVB diagnosis

Separate consent will be obtained at the time of Registry enrolment to allow contacting eligible study participants for future REB-approved research e.g. to determine the patient outcome beyond 3 years of life. No contacts will be made to any patient recruited by a site without local REB approval and involvement.

4.4.3 File Uploads

Within ≤7 days of patient enrollment the following information and uploads are requested in REDCap:

- Confirmation of a positive anti-Ro 60 and/or anti-Ro 52 and/or anti-La antibody test result (Form 3)
- Imaging Uploads (Form 2):
  a) Mandatory:
     - ***Rhythm Tracing I (still or clip):*** SVC/aorta Doppler (preferable) or PV/PA Doppler or simultaneous atrio-ventricular M-mode recording, demonstrating the AVB
     - ***Cardiac function (clip):*** Cardiac 4-chamber view
  b) Optional (still or clip):
     - ***Rhythm Tracing II***
     - ***EFE***
     - ***Other significant findings***

Preferred format for still images is jpeg, tiff, or bmp. Moving clips up to 32 MB can be uploaded as avi, mp4, or mov files. If de-identification is not possible by the site, images and clips can be send to SickKids via secure file transfer. The Core Lab team will then de-identify the images prior to storage in REDCap.

4.4.4 Maternal Anti-Ro/La Antibody Status (Form 3)

Confirmation of positive maternal anti-Ro or anti-La antibody titers will be required to participate in the Slow Heart Study and to enable any further pre- and postnatal data entry (see 3.5 for more information).

4.4.5 Core Lab Review (Form 8)

Differentiation of high-degree or complete AVB from other bradycardia causes (e.g. sinus bradycardia, blocked premature atrial beats) and "hydrops vs. non-hydrops" is essential to confirm the diagnosis/study eligibility and the disease severity.

The Core Lab will review uploads within ≤7 working days. Once completed, a confirmation e-mail will be issued to the site investigator. Participants with a different diagnosis from high-degree AVB will be excluded from the study. This approach will avoid inaccuracies in diagnosis and interpretation of main findings.

4.4.6 Patient Management

All management decisions including the choice and dosages of medication will be at the discretion of the primary physicians and should not differ from that of a non-study participant with the same clinical findings at the same center. The responsible physician will at any time be free to add, reduce or cease medication or to deliver a fetus based on his/her own clinical judgment. Analysis will be based on the initial plan to use or not use steroids at the time of diagnosis of immune-mediated AVB, irrespective whether steroids were added or removed later in pregnancy. Hospitalization for prenatal pharmacotherapy, if elected, is usually not required unless there is a clinical need e.g. to more closely monitor the maternal-fetal well-being.

All *perinatal management decisions* including timing/mode of delivery and the postnatal treatment (pacing, steroids, IVIG, other) will also be decided by physicians involved in the primary care of the child.

4.4.7 Prenatal Encounters (Form 4)

Upon the baseline data entry at the time of enrolment it will be possible to document the result of up to 30 prenatal encounters in REDCap (from Day 1 of management to birth or in-utero fetal demise). *Serial (about 1-2 weekly) fetal echocardiography* to delivery is recommended to monitor the evolution of fetal heart rate, cardiac function and wellbeing throughout the pregnancy. More frequent visits may be required for more severily affected pregnancies. It is recommended to *enter this data in a chronological order, ideally immediately following a patient visit.*

Information that will be captured at each encounter include:

- Date of encounter → gestational age at encounter
- Maternal findings: weight, new symptoms (as identified in questionnaire); new diagnoses; adverse events
- Fetal echocardiogram: AVB; atrial/ventricular rate; effusions/hydrops; cardiac function, AV regurgitation; EFE; deepest vertical amniotic fluid pocket; fetal growth (BPD, FL)
- Current medication, total days of treatment and treatment recommendations to next encounter
- Rationale of treatment modifications
- File uploads of major new findings (de-identified)

4.4.8 Birth and Delivery (Form 5)

REDCap form 5 captures:

- Pregnancy outcomes including date and gestational age at birth or demise
- Mode and indication of delivery
- Sex, weight, height and head circumference (live births)

4.4.9 Neonatal Period (0-30 days: Form 6)

Form 6 captures the outcome of live-born babies to hospital discharge or 30 days postpartum.

- Neonatal treatment
- Neonatal complications
- Neonatal exams: ECG and Echocardiogram
- Outcome to hospital discharge or 30 days postpartum:
  - Date of discharge from hospital → length of in-hospital care (delivery to discharge)
  - Date and cause of death

4.4.10 Outcome to Study End (12-36 months; Form 7)

Findings collected in Form 7 will be obtained at the first visit ≥ 1 year of life, corrected for gestational age, *ideally between 12 and 18 months and no later that 36 months of life*. Study end is projected by December 31st 2027 at which stage every infant survivor with AVB will be older than 12 months corrected age.

Collected variable include:

- Date, patient age, body weight and height at last visit
- Outcome
- Cardiac variables:
  Surgical procedures after neonatal period: PM implant and mode, other
  Echocardiogram
  Heart Failure: Ross Score, medication

  The **Ross Heart Failure Score** is best suited to quantify the functional capacity in younger children.[42] It will be obtained at the first visit >1 year of life to classify the heart failure severity.

Class of Symptoms	Symptoms Noted on History
I	Asymptomatic
II	Infants: mild tachypnea or diaphoresis with feeding; no growth failure Older children: dyspnea on moderate exertion
III	Infants: marked tachypnea or diaphoresis with feeding; growth failure Older children: dyspnea on mild or minimal exertion
IV	Tachypnea, diaphoresis or respiratory distress at rest

- Non-cardiac conditions
- Neurodevelopmental assessment by ASQ-3 Questionnaires between 12 and 18 months of life

  Ages & Stages Questionnaires®, 3rd Edition (ASQ®-3) is a developmental screening tool designed for use by early educators and health care professionals.[43] It relies on parents as experts, is easy-to-use, and creates the snapshot to assess milestones and catch delays. The aim is a single assessment by ASQ-3 at 12, 14, 16 or 18 months. Forms in English are attached in the appendix and in Form 3. Forms are also available in French, Spanish, Chinese, Arabic, and Vietnamese. Completion of the questionnaire by a parent takes 10—15 minutes and 2-3 minutes for health professionals to score. ASQ-3 is considered a valid, reliable, accurate and cost-effective measure of development and also available for older patients if an assessment is missed between 12 and 18 months.

  Age-appropriate questionnaires can be downloaded in REDCap Form 7. Once completed by the parents, the forms should be re-uploaded for review by an experienced developmental specialist who has no knowledge of the patient's medical history (treatment vs no treatment). Total scores will be calculated for 5 different areas of child development (communication; gross motor; fine motor; problem solving; personal social; 0 – 60 per area) and entered into the ASQ-3 scoring sheet and REDCap. The result of the completed assessment will be communicated to the submitting site.

4.5 MEDICATION-RELATED PROCEDURES

4.5.1 Supply of Medication

The care of the participant is the responsibility of the primary physician. The sponsor has no involvement and no obligations in this process including in the prescription of medication.

4.5.2 Accountabilty, Compliance and Adherence

Accountability procedures are not required for the study participants, however non-compliance should be addressed if suspected.

4.6 CENTERS

Requirements to participate in the Slow Heart Registry include:

- The site provides the primary perinatal care from the time of AVB diagnosis to study end
- Ascertainment of fetal and neonatal outcomes to hospital discharge or 30 days post birth
- Ascertainment of postnatal outcomes to at least 12 corrected months of age
- The site investigator/site have the experience, commitment, and infrastructure to conduct this research
- REB/IRB approval has been obtained including, if applicable, for affiliated institutions
- Data share agreements between the Sponsor and Study Site have been finalized.

4.7 OUTCOME MEASURES

The following outcome measures will be used for Registry participants in Group 1 vs Group 2.

PRIMARY OUTCOME

- Freedom from cardiac death ≥1 year of life

SECONDARY OUTCOME

- Proportion of participants with fetal and neonatal death and their causes/factors
- Proportion of participants with change in prenatal treatment
- Proportion of secondarily treated patients (initially untreated group 1 cases)
- Proportion of serious pregnancy outcomes (IUFD, IUGR <3rd percentile, delivery <35 weeks)
- Proportion of patients/group with progression from incomplete to complete AVB by 1 year
- Proportion of maternal SAEs and outcomes
- Average gestational age at birth
- Average birth weight
- Neonatal ventricular rate
- Freedom from permanent pacemaker implantation from birth to 1 year of life
- Prevalence of significant heart failure (HF score, echo, HF treatment) at 1 year of life

- Proportion of children with moderate/severe neurodevelopmental delay at 12-18 months

The primary outcome measure is absolute (alive at 1 year without heart transplant) with no room for interpretation. Secondary outcomes will be freedom from permanent pacing, heart failure and significant neurodevelopmental challenges at >1 year of life. Fetal demise, development of fetal hydrops, delivery <35 weeks and/or progression from incomplete to complete AVB will be considered prenatal management failure.

4.8 QUALITY AND ETHICAL STANDARDS

Investigators will ensure that this Registry is conducted in accordance with the principles of the Declaration of Helsinki, and that the Registry is conducted in full conformity with Guidelines for GCP and this protocol. The protocol and informed consent forms will be submitted to the appropriate Research Ethics Committees, including the host and affiliated institutions for written approval. The site investigator will submit and, where necessary, obtain approval from the above parties for amendments to the original approved documents. The Registry staff will ensure that the participants' anonymity is maintained. Each participant will be assigned a unique study ID number to be used in the REDCap database and for communications between the study site and the Registry sponsor. All identifiable documents will be stored securely by the site investigator and will only be accessible by authorized personnel at the study site. Safety and accuracy of all equipment used in this study, such as ultrasound systems, is the responsibility of the study site where the equipment is used. REDCap files will be regularly monitored for any accidental upload of documents or images containing personal health information. All accidentially uploaded identifiers will be immediately removed by the sponsor.

4.9 AGREEMENTS AND POLICIES

Data share agreements will be made between the SLOW HEART REGISTRY Sponsor (Edgar Jaeggi; The Hospital for Sick Children) and the Primary Site Investigator and respective Institution(s). The primary physician and care center will be medically and legally responsible for all patient care decisions. The Registry is a non-funded initiative and, unless funding becomes available at a later stage, ***no financial contributions are foreseen*** to compensate site investigators and participants for costs of medicine, equipment, exams, visits, REB approval and data entry into the Registry. Each participant will be receiving standard of care that will not require extra time or extra-visits. The sponsor team will provide all possible assistance to sites with the study setup.

5. STUDY SAFETY

5.1 SAFETY PROCEDURES

The SLOW HEART REGISTRY will assess *prenatal management* that may be used because the fetus suffers from a potentially life-threatening cardiac condition. Perinatal demise is not an unexpected outcome of ICAVB, even with prenatal treatment. Drug-related maternal AEs are not infrequent, although SAEs owing to transplacental steroid, beta-mimetic and/or IVIG therapy are exceptional events. Still, the risk of serious events likely increases with some preexisting fetal-maternal conditions, such as a diagnosis or history of a significant maternal mental

disorders or placental failure, for which the use of high dose steroids is not advised and contraindicated (see Form 1A: exclusion criteria).

5.2 ADVERSE EVENT DOCUMENTATION

DOCUMENTATION OF AES. Assessment of patient safety is study objective and relevant pregnancy- and treatment-related AEs should be documented in REDCap. Sources of information include assessment of symptoms by questionnaire at baseline and each encounter for changes in reported symptoms and severity from baseline. At study enrollment, a thorough medical history is recommended to document all preexisting maternal symptoms, complaints and health concerns and entered in Form 1B in REDCap. AEs are defined as new or more severe symptoms and diagnosis from baseline recorded during prenatal encounters (Form 4B). The questionnaires can be directly downloaded in REDCap (Maternal Baseline: Form 1B; Maternal Follow-up: Form 4B) and will be used to compare the frequency and severity of maternal symptoms and diagnosis to birth, irrespective of the prenatal use of medication.

CLASSIFICATION OF EVENTS. It will be the responsibility of the site investigator to identify, and classify the severity and frequency of any AE.

- Events will be considered MILD if signs/symptoms are mild, clinical relevance is marginal, laboratory findings are asymptomatic and no specific medical intervention is required,
- Events will be considered MODERATE if they require minimal, local, or non-invasive intervention only.
- Events will be considered SEVERE if they interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.
- Events will be considered SERIOUS (SAE) if they result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent/significant disability/incapacity, or in congenital abnormalities or birth defect

6. DATA MANAGEMENT & RESPONSIBILITIES

6.1 DATA MANAGEMENT

The password-protected REDCap data management system will be used to enter de-identified patient data by the participating sites. Credentialing to access REDCap will be managed the study PI/SickKids. Individual access will be limited to data from individual sites. Regular updates of key findings will be requested from the site investigator to study end. data will be verified for completeness and validity by the Registry team, and any queries will be sent to the site investigator. Once the record is deemed complete/valid, it will be locked so that further edits will not be possible to ensure highest data quality.

6.2 STEERING COMMITTEE

The clinical research aspect of the Slow Heart Registry is conducted under the supervision of a multidisciplinary team of experts, including maternal-fetal medicine, cardiology, neonatology, and rheumatology. Committee members include *Edgar Jaeggi (PI, Toronto)*, *Nico Blom (Amsterdam/Leiden, NL), Bettina Cuneo (Denver, USA), Joanna Dangel (Warsaw, Poland), Hakan Eliasson (Stockhom, Sweden)*, *Linda Hiraki (Toronto), Lisa Hornberger (Edmonton, Canada), Ed Kelly (Toronto), Owen Miller (London, UK), Orhan Uzun (Cardiff, UK), and Tim van Mieghem (Toronto).* Steering Committee Members will assist with the interpretation of study data and with the development of practice guidelines and interdisciplinary knowledge transfer.

6.3 GOVERNANCE OF REGISTRY

Study data will be maintained by the PI, Edgar Jaeggi. In the event that Dr Jaeggi becomes unable to fulfill this role, the Steering Committee will appoint a suitable PI to take over the study. The Steering Committee will control the use of study data for purposes not defined in this Protocol. Researchers from internal and external sites may apply for use of the Registry data. The Steering Committee will review applications for data use, and approve the use of data based on the scientific merit of the individual research proposals. Approval of data use will be based on a majority vote by Steering Committee members. The use of study data will also be contingent upon proof of REB approval and the execution of a data transfer agreements. If studies require additional follow-up data that is not present in the Registry data set, only the participants who consented to be contacted in the future, as indicated on their signed consent form, will be contacted for consent for any additional research studies.

6.4 CONFIDENTIALITY AND PRIVACY

Identifying patient information will be kept separate from the study data in an enrollment log which will be stored behind two types of electronic protection. Participants will be identified by a unique study ID in the study database. Study data will be securely stored in the SickKids REDCap database and the data will be accessible only to members of the study.

6.5 RECORD RETENTION AND DESTRUCTION

Study records will be retained for 7 years after the last publication as per SickKids guidelines. All digital data will then be destroyed by contacting the SickKids HelpDesk.

7. STATISTICAL ANALYSES

PRIMARY OUTCOME

- Freedom from cardiac death ≥1 year of life

SECONDARY OUTCOME

- Proportion of participants with fetal and neonatal death and their causes
- Proportion of participants with change in prenatal treatment
- Proportion of secondarily treated patients (initially untreated group 1 cases)
- Proportion of serious pregnancy outcomes (IUFD, IUGR <3rd percentile, delivery <35 weeks)
- Proportion of patients/group with progression from incomplete to complete AVB by 1 year
- Proportion of maternal SAEs and outcomes
- Average gestational age and weight at birth
- Neonatal ventricular rate
- Freedom from postnatal permanent pacemaker implantation at 1 year of life
- Prevalence of significant heart failure (Ross HF score, echo, HF treatment) at ≥ 1 year of life
- Proportion of children with moderate/severe neurodevelopmental delay based on ASQ-3 score

All data analyses will be performed by qualified personel at SickKids. Study findings will be summarized using descriptive statistics. Continous variables, will be summarized using mean ± standard deviation or median and inter-quartile range, as appropriate. Dichotomous and polytomous variables will be summarized using frequencies. Between-group differences in continuous variables will be assessed using either t-tests or Wilcoxon rank sum tests. Differences in dichotomous or polytomous variables will be assessed using Fisher's exact tests.

The **PRIMARY OUTCOME** will be assessed using time-to-event analysis. Specifically, the outcome, to the end of the follow-up or the time that a patient withdraws consent, will be assessed using a competing risk model, with non-cardiac death as the competing risk. The proportion of patients who die of cardiac causes will be estimated from the competing risk model. Between-group differences will be assessed using Gray's test.

SECONDARY OUTCOME: Dichotomous and polytomous variables (e.g. demise) will be summarized using frequencies. Continouous variables (e.g. birth weight) will be reported as mean ± standard deviation or median with inter-quartile range, as appropriate. Between-group differences will be assessed using Fisher's exact test for dichotomous and polytomous variables and t-tests for continouous variables. For pacemaker implants, competing risk analysis will be applied with all-cause mortality as the competing risk. Between-group differences will be assessed using Gray's tests.

8. DISSEMINATION OF RESULTS AND PUBLICATION GUIDELINES

Dissemination of results will be decided by the PI and Steering Committee. Publication policy for the SLOW HEART REGISTRY will be included in the study agreement. It is expected that study results will be published in several papers by Writing Committees to be determined by the Committee. Individual authorship will be based on the investigator's contribution to study components and journal guidelines of authorship as well as the institution's contributions to patient enrolments. Authorship on a publication will usually be limited to 1-2 investigators per study site. Investigators from institutions with less than 3 patient enrolments to study end do not qualify for authorship.

As per the International Committee of Medical Journal Editors authorship of qualified investigators will be based on these 4 criteria (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html): a) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; b) Drafting the work or revising it critically for important intellectual content; c) Final approval of the version to be published; AND d) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Submission of case materials alone does not satisfy the ICMJE authorship requirement. Study Investigators and Collaborators who have significantly contributed to the Registry but are not included as authors on a manuscript will be listed under "SLOW HEART REGISTRY Participants" which is a searchable designation in PubMed.

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