**Specific Aims**

Fetal complete AV block (CAVB) is associated with high morbidity and mortality. The most common cause of CAVB is injury to the conduction system secondary to maternal anti-SSA (Sjogren) antibodies. These antibodies cross the placenta at ~ 18 weeks of gestation and cause inflammation and fibrosis of the fetal AV node, usually by 26 weeks gestation (1). The disease burden of CAVB is considerable (2, 3). For example, the 35% of affecteds who die is a much higher mortality than the 11% cited for all congenital anomalies together. If the CAVB fetus survives to birth, almost all require life-long cardiac pacing. Furthermore, in addition to perinatal morbidity and mortality, individuals with CAVB are subjected to complications associated with long-term cardiac pacing (4, 5).

CAVB develops in ~4% of anti-SSA antibody + pregnancies. CAVB risk is greater if a previous offspring had CAVB (recurrence is ~20%), and if maternal anti-SSA antibody levels are > 100 U/ml (CAVB event rate 57%) (6). CAVB is irreversible, resulting in either fetal demise or life-long pacemaker dependence. Clinical evidence suggests there is a ~ 24 hour period when an irregular fetal heart rhythm (FHR) signals the emergence of CAVB as the rhythm transitions from normal to CAVB. This transition period is referred to as “emergent” CAVB (eCAVB). Identification of eCAVB is critically important because anti-inflammatory treatment during this period has been reported to restore sinus rhythm (3, 6-11). **However, reports of successful treatments are only anecdotal because standard surveillance of anti-SSA + pregnancies by weekly fetal echo fails to detect eCAVB since eCAVB develops in ~24 hours.** Thus, most cases of CAVB are detected after the fact and after the time when treatment can be ineffective. An important barrier to progress in this field is lack of a FHR surveillance method to detect eCAVB. A dependable method to detect eCAVB would allow design of studies to test efficacy of therapy to prevent progression to irreversible CAVB. Continuous FHR surveillance would be the true “gold standard” to detect eCAVB, but this is not feasible.

To overcome this barrier to progress, we propose that pregnant anti-SSA antibody + mothers use a commercially available Doppler FHR monitor at home 2x/day to detect the irregular FHR of eCAVB. Since eCAVB develops in ~ 24 hrs, 2x/day monitoring will provide 2 opportunities to detect eCAVB. We previously demonstrated that anti-SSA antibody + mothers can detect eCAVB using the FHR monitor at home (11). In a multicenter recruitment of 140 mothers, we found that 94% of eligible subjects enrolled and 96% completed monitoring with a false positive rate < 2%. No eCAVB went undetected (12). Together, these **findings demonstrate 1) home-based FHR monitoring is feasible, 2) mothers can recognize irregular FHR in the ambulatory setting and 3) eCAVB can be detected by this technique.** The over-arching goal of this study is to build on our preliminary results and compare the specificity/sensitivity of eCAVB detection between 2 methods of FHR surveillance: 2x/day home FHR monitoring (**home monitoring**) and the current standard of care, weekly FHR monitoring by echocardiography (**office monitoring**). We propose a multicenter clinical observational trial of anti-SSA + pregnancies in which the 2 interventions will be compared to determine which intervention is more successful in detecting eCAVB. We propose 2 specific aims.

**Specific Aim 1:** **To compare the success of detection and the sensitivity/specificity for identifying eCAVB between home monitoring versus office monitoring.** We hypothesize that eCAVB will be more frequently detected by 2x/day home monitoring than by standard office monitoring. To test this hypothesis, we will compare the detection (diagnostic rate), and the sensitivity/specificity for identifying eCAVB between the two surveillance techniques (interventions). **Each mother will serve as her own control as both interventions will be performed in each mothe**r. Assuming 4/100 fetuses will develop eCAVB, a sample size of 500 mothers will provide ~90% power at 5% significance to show that 2x/day maternal ambulatory FHR monitoring will more frequently detect eCAVB than fetal echo surveillance.

**Specific Aim 2:**  **To** **risk stratify development of fetal eCAVB by maternal anti-SSA antibody levels**. We hypothesize that since maternal anti-SSA antibodies levels are higher in fetuses who develop CAVB, levels will be higher in fetuses that develop eCAVB. If so, maternal anti-SSA levels can be used in the future to risk stratify anti-SSA positive pregnancies allowing for personalized surveillance. To test this hypothesis we will analyze the strength of the association with maternal antibody levels and the development of fetal eCAVB using ROC from logistic regression. With a sample size of 500 subjects (Aim 1), there will be 80% power at 5% significance to show C-statistics > 0.8 if the true C-statistic is 0.95.

**Impact:** Our study is based on the stalwart obstetrical method of assessing fetal well-being, but it is innovative as mothers rather than obstetricians will monitor FHR outside the obstetrical suite. Our study is highly significant because identifying a robust method to detect eCAVB is the first step to designing a clinical trial to test effective therapies that prevent the devastating and lifelong consequences of fetal CAVB.

Experimental Design and Methods

**Subjects:** We will recruit pregnant women at 16-18 6/7 weeks of gestation with anti-SSA or anti-SSA/anti-SSB antibodies documented during the current pregnancy by antibody screening or antibody titers. We will exclude anti-SSB + women, pregnancies> 18 6/7 weeks of gestation and pregnancies in which there is already emergent or CAVB or a prolonged AV interval indicative of 1° AVB (≥170 ms) (14). We will contact rheumatologists, maternal fetal medicine physicians and their obstetrical care providers of anti- SSA + pregnant women by phone and email to inform them of our study. We will provide IRB-approved advertisement for their offices. We also have an IRB approved website (heartsoundsathome.com) with links to local and national Rheumatology organizations, the Heart Rhythm Society, the Fetal Heart Society, The Pediatric Arrhythmia and Congenital Electrophysiological Society and the Lupus Foundation.

**Design:** Patients will be followed and monitored until week 26. The study is an international prospective observational randomized trial using an FDA approved commercial device. We have chosen this a randomized trial design because each research subject undergoes 2 interventions (office and home monitoring) and each serves as their own control. We feel this is appropriate as the occurrence of CAVB is rare and it would be difficult for physicians to be in equipoise given the promising preliminary data and the minimal to no risk of the home monitoring intervention.

**Participating Centers: To date, 14 centers in the United States, Europe and Canada are participating in the study.** The research protocol will be approved by the Institutional Review Boards at the participating centers. Based on previous clinical practice patterns and the scope of participating centers, we plan to recruit 150 mothers/year.

**Table 2: Core and Participating Sites and Personnel**

|  |  |
| --- | --- |
| 1. **Core Site**: Children’s Hospital Denver CO | PI: Bettina Cuneo MD |
| ***Participating Centers*** | ***Site PI*** |
| 2. Hospital for Sick Kids, Toronto Ontario CA | Edgar Jaeggi MD |
| 3. Stollery Children’s Hospital, Edmonton, Alberta CA | Lisa K. Hornberger MD |
| 4. St. Justine Hospital, Montreal, Quebec CA | Marie-Josee Raboisson MD |
| 5. Mattel Children’s Hospital, UCSF San Francisco CA | Anita Moon-Grady MD |
| 6. Children’s Hospital, Philadelphia, PA | Anita Szwast MD |
| 7. Children National Hospital, Washington DC | Anita Krishnan MD |
| 8. New York-Presbyterian/Morgan Stanley Children's Hospital and New York-Presbyterian/Columbia, NY. | Stephanie Levasseur MD |
| 9. All Children’s Hospital, Tampa FL | Grace Freire MD |
| 10. The Karolinska Institute, Stockholm, Sweden | Sven-Erik Sonesson MD |
| 11. Sanford Health System, Fargo ND | Peter van Eerden, MD |
| 12. Children’s Hospital Seattle | Bhawna Arya MD |
| 13. Eastern Virginia Medical School | Elena Sinkova, MD |
| 14. University of Minnesota |  |

Research protocol**:**

*Initial Visit: (16-18 6/7 weeks) (see* ***FIGURE 2)***

The subject is recruited if the inclusion criteria are met (Figure 2). If the subject agrees to participate, the site PI or his/her designate explains the study and obtains consent. Maternal anti-SSA antibody titers will be obtained at the first visit and sent to ARUP laboratories (Salt Lake City, Utah) (see specific aim #2). The site PI or his/her delegate will teach the mother how to use the hand-held Doppler monitor to obtain the fetal heart rhythm (FHR) and the fetal heart rate. The mother will be taught (1) how to listen to the FHR for 1 minute 2x/day (**FIGURE 3**); (2) write the FHR and fetal heart rate results in a log book that will be reviewed at every subsequent visit; and (3) to differentiate a normal regular FHR from an abnormal irregular FHR. The site PI will show her how to access examples of regular and irregular FHRs on the research website (heartsoundsathome.com). Also during the initial visit, the mother will demonstrate her ability to obtain FHR/rate and differentiate a regular from an irregular rhythm to the site PI. The site PI/his delegate gives the mother the phone number to call if: (1). She hears an irregular FHR or a fetal heart rate < 100 bpm at any time during home monitoring (**FIGURE 4**),(2) If she is having difficulty obtaining the FHR/rate after 3 attempts. As there is no data on the false positive and false negative Doppler FHR readings, any irregular rhythm will be evaluated by a diagnostic Fetal Echo under the direction of the site PI in < 12 hours after the mother’s call.

Figure 2: Initial Visit Figure 3: Monitoring Heart Sounds at Home

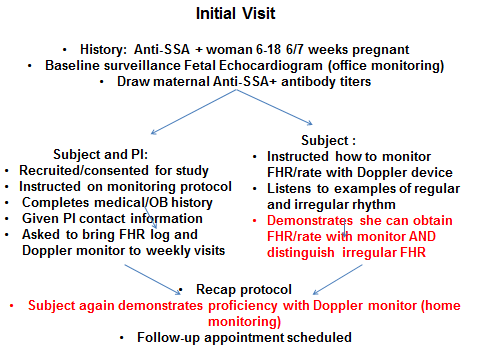
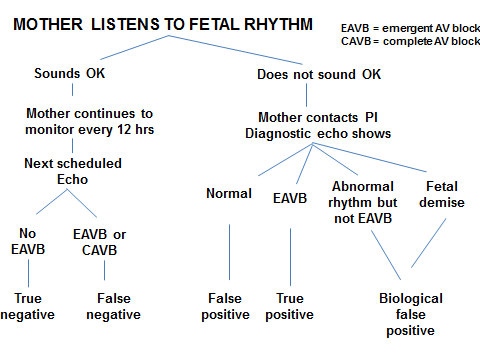
 C:\Users\bettina\Desktop\Submitted and reviewed manucripts\Submitted\Prelim results HSAH\heart sound pic.tif

Figure 4: Action plan for mother after monitoring fetal rhythm



In addition to instructions on home Doppler monitoring and demonstrating her proficiency with the Doppler monitor, we will record the mother’s medical and obstetrical histories and her current medications.

When subjects are recruited at participating sites, the site PI will send an email to the core PI to inform her that a study subject has been recruited. Data collected at the participating sites will be scanned into REDcap by the participating site and sent within 48 hours to the core PI.

*Follow-up Visits: Weekly until 26 weeks*

At all weekly visits, the mother will be asked to demonstrate to the site PI or his delegate her proficiency with the Doppler monitor. In addition, at each weekly visit, the results of the last week of monitoring will be reviewed (see **TABLE 3**) and the mother will undergo a standard surveillance Fetal Echo (office monitoring). At the final visit (26 0/7 - 26 6/7 weeks), the Doppler monitor and the logbook documenting the FHR data will be returned to the site PI. The mother will continue to be followed by her OB practitioner according to OB standard of care guidelines. The mother is instructed to call the site PI after the baby is born. The site PI will then speak to the nursery personnel or pediatrician and ask that an ECG be performed and faxed to DW Benson, MD, Ph.D. the single ECG reader for interpretation (see personnel justification). The purpose of the ECG is to determine if eCAVB has developed between the end of the monitoring period and delivery of the infant.

Table 3: Schedule of Visits

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Visit | Echo  (Office monitoring) | Teach/review FHR monitoring  (Home monitoring) | Sampling Mom’s anti-SSA antibody titers | Review Mom’s Medical /OB History | Infant’s ECG |
| Initial Visit  16-18 0/7th wks | X | X | X | X |  |
| Weekly visits | X | X |  |  |  |
| Final Visit  25-25 6/7 wks | X | X |  |  |  |
| Birth of infant |  |  |  |  | X |

*Beyond the Monitoring Period:*

If at any time during the period between the end of the monitoring period and birth of the baby an irregular FHR is detected by the OB provider, the site PI will be informed and the mother referred to the site PI for an evaluation of the rhythm. After the birth of the infant, a 12 lead ECG will be performed and sent to a single reviewer for interpretation.

The primary endpoints will be: 1). Conclusion of the monitoring period without eCAVB. 2). Development of eCAVB within the monitoring period. 3). Development of eCAVB after the monitoring period (diagnosed by postnatal ECG). The study protocol is summarized in **FIG 4.**

Figure 4: Summary of study protocol

