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ORIGINAL ARTICLE

Heart sounds at home: feasibility of an ambulatory fetal heart rhythm surveillance program for anti-SSA-positive pregnancies

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OBJECTIVE: Fetuses exposed to anti-SSA (Sjögren's) antibodies are at risk of developing irreversible complete atrioventricular block (CAVB), resulting in death or permanent cardiac pacing. Anti-inflammatory treatment during the transition period from normal heart rhythm (fetal heart rhythm (FHR)) to CAVB (emergent CAVB) can restore sinus rhythm, but detection of emergent CAVB is challenging, because it can develop in ⩽ 24 h. We tested the feasibility of a new technique that relies on home FHR monitoring by the mother, to surveil for emergent CAVB.

STUDY DESIGN: We recruited anti-SSA-positive mothers at 16 to 18 weeks gestation (baseline) from 8 centers and instructed them to monitor FHR two times a day until 26 weeks, using a Doppler device at home. FHR was also surveilled by weekly or every other week fetal echo. If FHR was irregular, the mother underwent additional fetal echo. We compared maternal stress/anxiety before and after monitoring. Postnatally, infants underwent a 12-lead electrocardiogram.

RESULTS: Among 133 recruited, 125 (94%) enrolled. Among those enrolled, 96% completed the study. Reasons for withdrawal ($n = 5$) were as follows: termination of pregnancy, monitoring too time consuming or moved away. During home monitoring, 9 (7.5%) mothers detected irregular FHR diagnosed by fetal echo as normal (false positive, $n = 2$) or benign atrial arrhythmia ($n = 7$). No CAVB was undetected or developed after monitoring. Questionnaire analysis indicated mothers felt comforted by the experience and would monitor again in future pregnancies.

CONCLUSION: These data suggest ambulatory FHR surveillance of anti-SSA-positive pregnancies is feasible, has a low false positive rate and is empowering to mothers.

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INTRODUCTION

Anti-SSA (Sjögren's) antibodies are found in 1 to 2% of women.[1] Approximately 2 to 4% of fetuses in anti-SSA-positive pregnancies (about 1000 per year in the United States) develop complete atrioventricular (AV) block (CAVB), histologically characterized by antibody-mediated inflammation and fibrosis of the AV node.[2,3] The period of highest risk for development of CAVB is ~ 18 to 25 weeks of gestation. Although of low penetrance, the disease burden of CAVB is considerable, as 31% of those affected die *in utero* and survivors usually require life-long cardiac pacing.[2–7] Once established, CAVB is irreversible.[2,3] However, results of small case series suggest that anti-inflammatory treatment during the transition period from normal fetal heart rhythm (FHR) to CAVB may arrest the progression to CAVB and even restore sinus rhythm[8–12] We refer to this transition period between sinus rhythm and CAVB as 'emergent' CAVB; it is the time when CAVB is developing but has not yet emerged. Emergent CAVB is characterized by an irregular rhythm, signifying type 1 or intermittent type 2, 2nd degree AV block.' As the transition from normal sinus rhythm to emergent CAVB and from emergent CAVB to CAVB can be quite rapid (⩽24 h), the recommended weekly or every other week echocardiogram surveillance rarely detects emergent CAVB.[13,14]

Continuous daily FHR monitoring at a medical facility might improve the chances of detecting emergent CAVB, but this is not feasible. We propose an alternative method—frequent fetal heart rate and FHR monitoring performed by mothers in the ambulatory setting. To determine whether such an approach is feasible and identify the steps required for successful implementation, we instituted a multicenter prospective observational study in which pregnant anti-SSA -positive women monitored fetal heart rate and FHR twice a day at home using a commercially available handheld Doppler device. We report results on the first 120 patients.

MATERIALS AND METHODS

Patient population and recruitment

This was a multi-center prospective observational study of anti-SSA-positive pregnant women (mothers) recruited from January 2014 to April 2016. Mothers were recruited from eight perinatal cardiology centers

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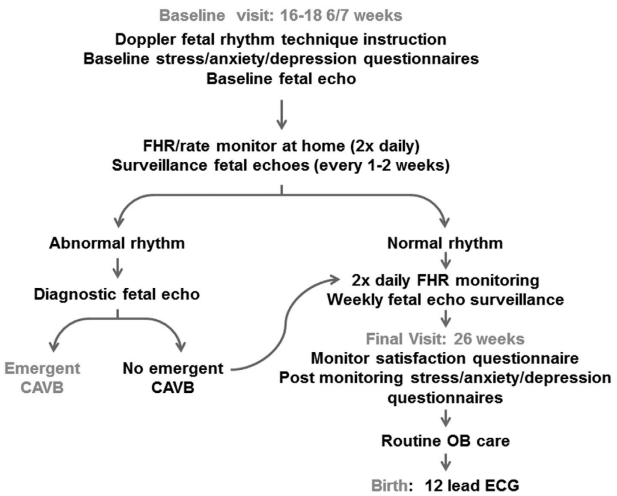

Figure 1. Heart sounds at home study protocol. Phrases in red indicate onset of study and endpoints.

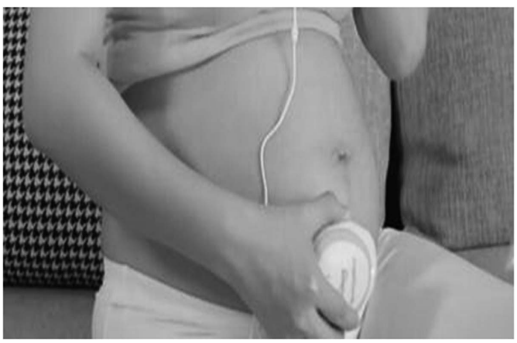

Figure 2. The Home Doppler FHR monitoring device.

(Children's Hospital Colorado, UCSF Benioff Children's Hospital, San Francisco, CA, USA; Children's Hospital of Philadelphia, Philadelphia PA, USA; Children's National Hospital, Washington DC, USA; Morgan Stanley Children's Hospital, New York, NY, USA; Stollery Children's Hospital, Edmonton, AB, Canada; Sick Kids Hospital, Toronto, ON, Canada; and the Karolinska Institute, Stockholm, Sweden). Typically, mothers had been referred by their obstetrical care providers or rheumatologists to the fetal cardiologist for fetal CAVB surveillance, but we also recruited potential research subjects through the study website, heartsoundsathome.com. The research study was approved by each of the local institutional review boards. Mothers were invited to participate if their gestational age was 16-186/7 weeks and they had a positive anti-SSA or anti-SSA and anti-SSB antibody screen. Mothers were not considered for recruitment if they were only anti-SSB positive, were >18: 6/7 weeks pregnant or if emergent CAVB, CAVB or a prolonged mechanical AV (atrio-ventricular) interval indicative of first degree AVB ($\geqslant$170 ms)[15] was present at initial fetal echocardiographic evaluation. All eligible women who declined to participate and all who initially enrolled but withdrew were queried for reasons for not participating or withdrawing from the study, which were recorded as part of data collection.

Research plan

The research plan is summarized in Figure 1.

Initial visit: (16 to 18 6/7 weeks)

We explained the study to participants and obtained informed consent. At the initial visit, the mother's medical and obstetrical histories and current medications were obtained. The mother was instructed on use of the hand-held Doppler device to obtain the fetal heart rate and FHR (Figure 2). Specifically, she was (1) taught to listen to the FHR and count the fetal heart rate for 1 min two times a day; (2) instructed to write the results in a log book to be reviewed at each provider visit; (3) informed how to differentiate a normal regular rhythm from an abnormal irregular rhythm either via verbal explanation or by examples of regular and irregular fetal heart recordings demonstrated on the heartsoundsathome.com website; and (4) apprised that a normal fetal heart rate was $>$ 120 and $<$ 180 beats per minute. Mothers were also instructed on a plan of action after listening to the fetal heart rate and FHR at home (Figure 3). In addition to instructing the mother on home Doppler monitoring and observing her proficiency with the Doppler device in assessing the fetal heart rate and FHR, we performed a fetal echocardiogram at baseline.

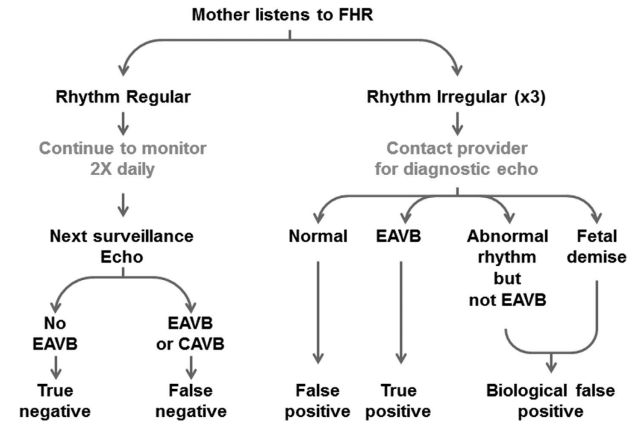

Figure 3. Decision tree for maternal home fetal FHR Doppler monitoring. The Home Doppler FHR monitoring device.

Fetal echocardiogram

We determined the fetal heart rate from measures of consecutive Doppler aortic or pulmonary valve waveforms during the echocardiogram. We also measured the AV interval, defined as the time between the onsets of atrial and ventricular contraction. Atrial contraction was measured either from the onset of the mitral a wave to onset of aortic outflow from simultaneous mitral and aortic outflow Doppler wave forms,[13] or from the onset of reverse flow during atrial systole in the superior vena cava to onset of aortic outflow from simultaneous superior vena cava/aortic outflow Doppler wave forms.[15] We averaged three to five measurements each of heart rate and AV interval to obtain the final results.

Assessment of satisfaction and maternal anxiety, depression and coping skills

In order to assess the impact of monitoring on the mother's well-being, we administered four questionnaires. The first questionnaire (monitor satisfaction questionnaire, MSQ) was designed to measure maternal satisfaction with the monitoring process and was completed only at the conclusion of the monitoring period (26 weeks). The three additional questionnaires, assessing maternal depression, anxiety and coping skills, were given both before (at baseline) and after (26 weeks) the monitoring period, and the pre- and post-monitoring results compared. The Beck Depression Index II (Beck Depression Inventory, BDI)[16] is a self-report rating inventory that measures characteristic attitudes and symptoms of depression. It has a high internal consistency (α-coefficient 0.81) in non-psychiatric populations and a high 1-week test–retest reliability (Pearson's $r = 0.93$).[16] The State-Trait Anxiety Inventory[17] is a commonly used measure of anxiety both by age (19–39 vs $>$39 years) and employment status (employed vs student). Internal consistency coefficients for the scale have ranged from 0.86 to 0.95; test–retest reliability coefficients have ranged from 0.65 to 0.75 over a 2-month interval.[17] The brief COPE inventory assesses a broad range of coping responses and includes responses expected to be dysfunctional, as well as those expected to be functional.[18]

Follow-up visits

The interval between follow-up visits varied from weekly to every other week until the final visit at 26 weeks gestation. At each subsequent visit, mothers reviewed results of the previous week(s) of monitoring with the investigator. The mother was again asked to demonstrate her proficiency with the Doppler device (Figure 3) and underwent a standard surveillance

fetal echocardiogram to assess FHR. At the final visit, the Doppler device and the logbook documenting the rhythm data were returned to the investigator and the subject filled out a monitoring satisfaction questionnaire.

Beyond the monitoring period

At the conclusion of the monitoring period, mothers continued standard prenatal care with their obstetricians until delivery. After the infant was born, a 12 lead electrocardiogram was performed and read by the local site investigator. The purpose of the electrocardiogram was to determine whether conduction system disease developed between the end of the monitoring period and birth of the infant.

All data collected during the study were de-identified and entered into a REDcap database approved by the local and core site Institutional Review Board. The primary endpoints were the conclusion of the monitoring period (26 weeks) or the development of first-degree, second-degree or CAVB during the monitoring period or fetal demise. The secondary endpoints were development of first-degree, second-degree or CAVB after of the monitoring period or completion of the infant's electrocardiogram.

RESULTS

Recruitment, enrollment and participation

Between January 2014 and April 2016, 8 sites recruited 133 study participants. Of those recruited, 125 (94%) enrolled. Reasons given for not enrolling were as follows: belief that monitoring would cause increased stress/anxiety, mothers were too busy or no reason was given. Among those who enrolled, 120 (96% of the enrolled cohort) completed the study. Reasons for withdrawal from the study were termination of pregnancy, monitoring too stressful or time consuming, or the subject moved away ($n = 5$).

Characteristics of the research cohort

The family, medical and obstetrical histories of the research cohort are summarized in Table 1. The mean age at enrollment was 17.8 ± 0.8 weeks of gestation. Thirty-three percent of mothers were primiparous. Antibody status was measured by different commercial laboratories and reported only as positive or negative. Among the cohort, 51% were positive for anti-SSA antibodies and 49% also had anti-SSB antibodies. Eleven mothers reported a previous fetus affected with anti-SSA-mediated cardiac disease, only 2/11 were receiving hydroxychloroquine during the current pregnancy. Overall, 42% of the mothers in the study were receiving hydroxychloroquine, but in only 26 was treatment initiated before 11 weeks of gestation or the recommended time for maximum efficacy.[19]

Results of home monitoring surveillance

The monitoring protocol (listening to fetal heart rate and FHR two times a day) was followed by 95% of the cohort. Problems the mothers experienced during monitoring were difficulty finding fetal heart tone, confusing fetal heart tones with their own heart tones and difficulty counting the fetal heart rate. These problems mostly occurred during the first week of monitoring and were corrected by further instruction and reinforcement of correct monitoring technique during the follow-up visits. Fewer than 25% of the women experienced problems with the monitoring.

Nine mothers detected abnormal fetal heart rates or irregular FHR during home surveillance (Table 2). Diagnostic fetal echo in two fetuses identified 1:1 conduction, normal AV intervals and normal fetal heart rates (false positives $< 2\%$). Four fetuses had intermittent atrial ectopy that resolved over a period of < 3 weeks. Two fetuses had extreme heart rate variability with 1:1 conduction and normal AV intervals, which persisted for 1 to 4 weeks and resolved spontaneously. An additional fetus had bradycardia due to blocked atrial bigeminy; this rhythm also resolved spontaneously. CAVB or emergent CAVB was not observed in any fetus.

Table 1. Characteristics of the research cohort

History	*% Positive*
Family Hx of CTD	20.5%
Personal Hx of CTD	74%
SLE	44%
RA	7.5%
Sjögren's syndrome	47%
Mixed	1.5%
Obstetrical history	
Primiparous	33%
Secundagravida	28%
>Secundagravida	39%
Previous pregnancy with fetal anti-SSA-mediated cardiac disease	9%
Current pregnancy treated with hydroxychloroquine	42%
Treatment initiated before 11 weeks	22%
Treatment before 11 weeks with a previous affected fetus	14%
Treatment with a previously affected child	2%

Abbreviations: CTD, connective tissue disease; Hx, history; mixed, mixed connective tissue disease; RA, rheumatoid arthritis; SSA, Sjögren syndrome; SLE, systemic lupus erythematosus.

Results of echo surveillance

Fetal echo surveillance began at 17.8 ± 0.8 weeks. Mothers were seen each week (five sites) or every other week (three sites) until the end of the monitoring period (26 weeks). All fetal heart rates were normal (> 120 and < 170 beats per minute) during the monitoring period. Two fetuses were identified to have prolongation of the AV interval (at 19.4 and 23 weeks) without a change in rhythm. Both babies had normal electrocardiograms at birth.

Results of MSQ

As indicated by results of the MSQ, the experience of monitoring FHR was 'comforting' and 'empowering' to mothers. The monitoring process was helpful and gave reassurance to 97% of the study cohort. The MSQ also assessed the mother's anxiety in performing the monitoring and being responsible for caring for her fetus. On a scale of 1 to 10, with 1 being most anxious and 10 being most calm, the average score was 8.3. In fact, no subject graded anxiety as < 3 and only 5% of the cohort had a response scale score of < 6.

Ease of use of the Doppler device was scored by the mothers at the conclusion of the monitoring period, with 1 being very difficult and 10 being very easy. A rating of 'easy' (response score of 7 to 8) or 'very easy' (response score of 9 or 10) was given by 97% of mothers. All mothers indicated they would monitor fetal heart rate and FHR with the home Doppler device if given the opportunity in future pregnancies.

In addition, we separately reviewed the MSQ scores in those mothers with abnormal monitoring results. All in this group monitored two times aday and found monitoring helpful and reassuring. The average score for calm versus anxious was 8 (10 being the most calm) and all indicated they would participate in the home fetal heart rate and FHR in subsequent pregnancies.

Results of maternal depression assessment

A score of < 13 on the BDI indicates minimal depression.[16] Before monitoring, BDI scores ranged from 0 to 9 (average 4.5 ± 3.3); after monitoring, scores improved (were lower) to a range of 0 to 8 (average of 3.2 ± 2.8). The BDI scores improved in 67% of subjects; in the remainder of subjects the BDI score increased, but all scores were < 13 at both time points. The new symptoms reported after

Table 2. Diagnosis of irregular heart rhythm detected by home Doppler monitoring

Subject	*Finding*	*GA onset (weeks)*	*Diagnostic echo results*	*GA resolution (weeks)*	*Newborn rhythm*
1	Irregular FHR	22.1	Extreme FHR variability	25.1	SR
2	Irregular FHR	20.2	PACs	22.4	SR
3	Irregular FHR	16.9	PACs	18.9	SR
4	Irregular FHR	23.3	PACs	23.3	SR
5	Irregular FHR	18.6	PACs	19.6	SR
6	Bradycardia	18.7	Blocked atrial bigeminy	21.7	SR
7	Irregular FHR	20.0	SR	-	SR
8	Irregular FHR	17	SR	-	SR
9	Irregular FHR	18	PACs	19	SR

Abbreviations: GA, gestational age; FHR, fetal heart rhythm; PACs, premature atrial contractions; SR, sinus rhythm.

Table 3. STAI scores before and after home Doppler monitoring

Variable	*Employed females*			*Women aged 19–39 years*		
	Standard	*Before monitor*	*After monitor*	*Standard*	*Before monitor*	*After monitor*
Mean	35.2	**48.7**	29.7	36.2	46.0	46.4
s.d.	10.6	6.1	2.0	11	4.2	4.2
Range	24.6–45.8	42.6–54.8	27.7–31.7	25.2–47.2	41.8–48.2	44.2–48.6

Abbreviation: STAI, State Trait Anxiety Inventory. Value in bold indicates mean STAI is outside the range of normal STAI.

monitoring were loss of energy, tiredness and fatigue, increased agitation, pessimism and loss of pleasure.

Results of maternal anxiety assessment

The overall results of the State Trait Anxiety Score[17] are shown in Table 3. The State Trait Anxiety Score showed that maternal stress was decreased or did not change during monitoring. Scores in the State Trait Anxiety Score indicated that the level of stress was moderately high before monitoring in the category of an employed female (48.7 ± 6.1; normal range 35.2 ± 10.6) and decreased to minimal stress after the monitoring period (29.7 ± 2.0). Scores for the cohort compared with scores for women age 19 to 39 (36.2 ± 11) indicated minimal levels of stress both before monitoring (46.0 ± 4.2) and after monitoring (46.4 ± 4.2).

Results of maternal coping assessment

The COPE inventory demonstrated that the cohort had good coping skills both before and after monitoring.[18] The mothers responded, 'I don't do this at all' to negative coping strategies such as self-medicating with drugs/alcohol, denying or refusing to believe a negative event has not happened, giving up trying to deal or cope with the negative situation and blaming themselves. The mothers responded 'I've been doing this a little bit' to 'I've been doing this a medium amount' to positive coping skills such as use of emotional support and instrumental support, active coping, acceptance and reframing.

Taken together, the results show that home fetal heart rate and FHR monitoring with a Doppler device was feasible. The protocol displayed high recruitment and retention. Further, there was a high rate of acceptance and satisfaction, and decreased stress among anti-SSA-positive mothers who participated. The false positive rate was low and no emergent CAVB or CAVB was missed.

Comment

Although the risk of fetal CAVB in anti-SSA-positive pregnancies is small, the consequences are significant: fetal or neonatal demise or life-long pacemaker dependency. Detecting and treating emergent CAVB have been reported to restore sinus rhythm,[8–11] but the outcomes of fetal AVB have not improved in the past 10 years.[20] We believe that the lack of a practical, reliable and accurate surveillance technique to frequently monitor fetal heart rate and FHR to detect the irregular rhythm of emergent CAVB has been a barrier to progress in the prevention of CAVB. The only two prior large studies of routine monitoring in these at-risk pregnancies by employing weekly echocardiographic surveillance failed to demonstrate a benefit to in-office monitoring. In the PRIDE study,[13] 95 women completed weekly evaluations. Three fetuses had CAVB; none had a preceding abnormal echocardiogram. In the study by Krishnan *et al.*,[14] 636 echoes on 140 fetuses of anti-SSA antibody-positive mothers did not detect emergent CAVB. This suggests that weekly monitoring is not sufficient for detection of emergent CAVB.

Inexpensive commercially available Doppler devices have been used by pregnant women in a non-clinical setting for many years, but to our knowledge this is the first time such a device has been used for specific medical indications. We employed this simple device for surveillance of anti-SSA-positive pregnancies and found it to be feasible, reliable, accurate, user friendly and highly satisfying to the mothers. Most importantly, the mothers correctly distinguished between normal and abnormal fetal rhythm and successfully contacted their providers with the abnormal results.

It was surprising that no fetus developed the irregular rhythm of emergent CAVB, as 12% of the cohort had a previously affected fetus, which increases the risk in subsequent pregnancies from 2 to 4, to 17 to 21%.[21] This may be because several of the mothers were on hydroxychloroquine, which has been shown to reduce recurrence of anti-SSA-mediated conduction system disease.[19] Alternatively, as inclusion in the study was based on positive anti-SSA antibody screens from multiple laboratories, serology may have included false positives or subjects with low maternal antibody levels, thus some fetuses may have been at very low risk for CAVB. Jaeggi *et al.*[22] has previously shown that fetal conduction system disease did not occur when maternal anti-SSA antibody levels were $< 50\ \mathrm{U\ ml^{-1}}$.

In summary, the preliminary results of this multicenter feasibility study of 120 subjects show that ambulatory fetal monitoring is

feasible, results in detection of arrhythmias and does not increase stress in participating women. Continued evaluation of this research protocol including additional subject recruitment, further understanding the ensuing and mitigating factors of maternal stress and taking advantage of improved monitoring techniques such as transmission of the fetal 'heart sounds' to the investigator, will help to define the optimal surveillance strategy for these high-risk fetuses.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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