Received: 11 July 2018 | Revised: 19 September 2018 | Accepted: 20 October 2018

DOI: 10.1111/chd.12713

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Prenatal heart block screening in mothers with SSA/SSB autoantibodies: Targeted screening protocol is a cost-effective strategy

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Abstract

Objective: Maternal anti-Ro/SSA and anti-La/SSB antibodies can lead to fetal complete heart block (CHB). Current guidelines recommend weekly echocardiographic screening between 16 and 28 weeks gestation. Given the cost of screening and the rarity of conduction abnormalities in fetuses of mothers with low anti-Ro levels (<50 U/mL), we sought to identify a strategy that optimizes resource utilization.

Design: Decision analysis cost-utility modeling was performed for three screening paradigms: "standard screening" (SS) in which mid-gestation mothers are screened weekly, "limited screening" (LS) in which fetal echocardiograms are avoided unless the fetus develops bradycardia, and "targeted screening by maternal antibody level" (TS) in which only high anti-Ro values warrant weekly screening. A systematic review of existing literature and institutional cost data were used to define model inputs.

Results: The average cost of LS, TS, and SS was $8566, $11 038, and $23 279, respectively. SS was cost-ineffective with an incremental cost-effectiveness ratio (ICER) of $322 756 while TS was cost-effective with an ICER of $43 445.

Conclusion: While the efficacy of fetal intervention for first or second degree AV block remains unclear, this analysis supports utilizing antibody levels to stratify this population for optimized surveillance for CHB. SS is cost-ineffective and results in resource overutilization.

KEYWORDS

complete heart block, cost-utility, neonatal systemic lupus erythematosus

1 | INTRODUCTION

Autoantibodies against Ro/SSA and La/SSB are found in patients with lupus and Sjogren's syndrome in addition to many other autoimmune conditions.[1-3] The prevalence of these antibodies is ~2.5% of all childbearing women.[4] Pregnant women with positive anti-Ro/SSA and anti-La/SSB autoantibodies are at risk for fetal complete heart block (CHB) and neonatal lupus.[5,6] The risk is about 2% of pregnancies with positive autoantibodies.[7,8]

Anecdotally antenatal treatment with steroids has been given to fetuses with CHB, because of the perception that the inflammatory effects resulting from antibody exposure may be preventable if detected and treated.[6] Some cases with CHB are also preceded by first or second degree heart block.[9-11] Treatment with steroids was also suggested to prevent the progression of first or second degree heart block to CHB although the effect is controversial.[8-10] Fetal echocardiogram can detect first or second degree AV block by measuring mechanical PR interval.[12,13] Due to the ability of fetal echocardiogram to detect first and second degree block and the plausible

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effect of treatment, it has been recommended that SSA/SSB-positive women be referred for fetal echocardiography surveillance. The current standard screening (SS) protocol is weekly to bi-weekly fetal echocardiograms beginning in the early second trimester (16-18 weeks) until 28 weeks of gestation.[9] Many studies questioned the utility of the current practice as CHB largely develops without a "warning period" and screening may not lower the incidence of CHB as there is no proven effective treatment to prevent CHB.[8] SS leads to high cost and resource utilization in the fetal echocardiography laboratory. Alternative screening protocols have been suggested, including targeted screening for high risk population or limited screening (LS) approaches, acknowledging the limited data supporting the efficacy of fetal treatment.[14]

Some of the factors that increase the risk of development of CHB include positive family history of CHB in previous pregnancies and high antibody levels. The risk increases to 15%-20% for those with a positive family history in a previous pregnancy with CHB.[8] Another high-risk group is patients with high antibody levels. In a recent study that risk stratified pregnancies according to the anti-Ro/SSA levels, no cases of conduction abnormalities were detected in pregnancies with an antibody level below 50 U/mL. On the other hand 8/127 (6%) of fetuses with levels above 50 U/mL developed conduction abnormalities and 3% had CHB.[4,14] While it is unlikely the possibility of fetal conduction abnormalities in those pregnancies with an antibody level below 50 U/mL is zero, the rarity of events in this group has resulted in a change of the screening strategies of some centers to targeted screening that includes weekly SS only in pregnancies with high antibody levels.[4,14]

In this study, we sought to identify the strategy that optimizes resource utilization in screening for CHB to deliver high value prenatal care using decision analysis modeling techniques. The study compared the utility and cost-effectiveness of SS paradigm to an approach in which only those fetuses with high maternal antibody levels are closely monitored with weekly echocardiograms: "targeted screening by maternal antibody level" (TS). Finally, these two approaches were compared against a LS paradigm in which only one fetal echocardiogram is performed and routine obstetrical care is recommended if there is no evidence of conduction abnormalities.

2 | MATERIAL AND METHODS

A decision analytic model (Figure 1) was developed which simulated three treatment paradigms, whereby a pediatric cardiology provider may approach a pregnant woman with known positive autoantibodies using TreeAge Pro (Williamstown, Massachusetts). The SS paradigm modeled the current approach at our institution which adheres to American Heart Association recommendations for weekly PR

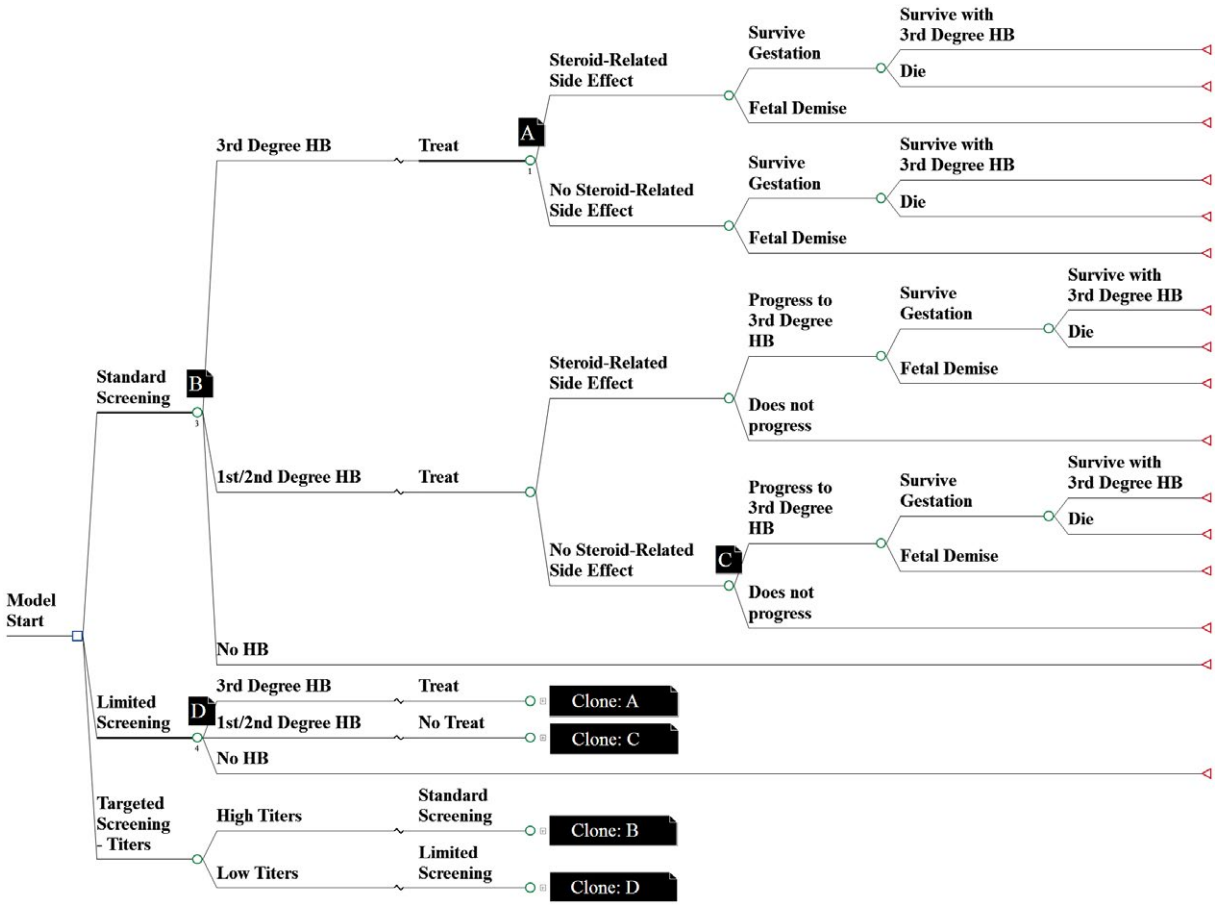

FIGURE 1 Cost-utility model. Abbreviation: HB, heart block

interval screening between 16 and 28 weeks gestational age.[5] Under SS, if first or second degree heart block (other heart block, OHB) is detected, a steroid treatment of the mother is initiated in an attempt to prevent progression to CHB. The LS paradigm serves as the cost-baseline approach: if the initial fetal echocardiogram illustrates no structural abnormalities or findings concerning for immune-mediated disease such as dysfunction, effusion or valvular regurgitation, then no further PR interval screening is undertaken. The final paradigm, TS, models an approach in which only women with anti-Ro or anti-La levels >50 U/mL are subject to prenatal weekly PR screening, whereas those with anti-Ro and anti-La levels <50 U/mL, undergo only one initial fetal echocardiogram and if reassuring, routine obstetrical heart rate assessments. In all paradigms, if CHB develops as detected by routine obstetrical heart rate monitoring, patient was referred to fetal cardiology for evaluation and treatment with steroids.

Sensitivity analyses and Monte-Carlo analyses were used to evaluate the influence of variation in model inputs and assumptions on base case results across ranges outlined in Table 1. Paradigm costs were varied by ±25% around the base case assumption. The range for all other variables was chosen as the range of what was thought to be clinically reasonable values. For the Monte-Carlo analysis, costs were assumed to follow a Gaussian distribution around the mean while probabilities were expected to follow a Beta distribution between 0 and 1; measures of variance were estimated from the range outlined in Table 1.

2.1 | Cost assumptions

As is standard for cost-utility analyses, costs were defined as payer costs thereby operating from societal perspective facilitating extrapolation to other centers. While this study is not intended as a description of our institutions surveillance results, in order to calculate cost assumptions for the model, an internal cost database that includes women surveilled with SS methodology from 2010 to 2016 was compiled and incorporated into the SS and TS at nodes labeled "B" and "Clone B" in Figure 1. These costs include all professional fees, facility fees, and fetal echocardiograms billed by fetal cardiology providers. Subsequent to the first complete fetal echocardiogram, serial studies were billed as follow-up studies with Doppler and umbilical flow assessments. The costs of the antibody assay were added to the cost estimates of the SS and TS models. The costs for the LS paradigm was calculated for a single fetal echocardiogram and fetal cardiologist clinic visit and incorporated in Figure 1 at node "D" and "Clone D." Costs pertaining to obstetrical fetal heart rate screening were not included in the model as this would likely be equal in all models and thus not impact the cost-effectiveness calculation since checking fetal heart rate is part of routine obstetrical evaluation. To identify the cost of postnatal CHB care, the fetuses who developed conduction abnormalities in utero and were admitted postnatally were identified. Neonates who underwent major procedures unrelated to CHB, such as a patent ductus arteriosus closure, were excluded to minimize unrepresentative costs. The net present value of a lifetime with pacemaker therapy was calculated as 2017 $USD using a 3% discounting rate from existing literature and assuming pacemaker battery replacement every 5-10 years.[15]

2.2 | Probability assumptions

Model inputs were derived from the existing literature (Table 1). To allow for sensitivity analyses affecting all paradigms in tandem, all probabilities pertaining to OHB or CHB were a factor of a single incidence variable, "Fetal Heart Block (any degree)." Using the limited available data on the incidence of OHB, it was assumed that OHB would be twice as common as CHB in all models.[9] The assumptions were challenged with sensitivity analyses. We assumed the probability of fetal conduction abnormalities in those with antibody levels <50 U/mL to be rare, but non-zero. Because the efficacy of steroid therapy to prevent progression of AV block is controversial, a sensitivity analysis was performed to characterize the probability of treatment benefit. It was assumed in the LS and TS paradigms that after an initial reassuring fetal cardiology assessment, CHB would be identified through routine obstetrical screening by the discovery of bradycardia and receives treatment.

2.3 | Utility assumptions

For metrics of efficacy, quality-adjusted life years (QALY) from the infant's perspective were used. Utility values were extracted from the literature and where an appropriate utility value could not be found, an assumption was made for the baseline analysis and subsequently challenged with sensitivity analyses (Table 1). The incremental cost-effectiveness ratio (ICER) was used to define cost-effectiveness with a willingness-to-pay (WTP) threshold of $50 000, acknowledging this is considered the lower boundary defining cost-effectiveness.[16] There was an assumed steroid-related neonatal reduced utility given the associated risk of prematurity and growth restriction.[8]

2.4 | Time assumptions

Life-expectancy was in accordance with updated Center for Disease Control estimates.[16] The length of time suffering the steroid-related sequelae described above was assumed to be 0.5 years. The length of neonatal hospitalization was averaged from our internal patient data.

3 | RESULTS

Our internal database identified 77 pregnancies who had been followed using SS surveillance methodology. For these 77 pregnancies, an average of 7.6 fetal echocardiograms were performed for the length of gestation with a total average prenatal cost of $18 880 per pregnancy. Of these, 11 fetuses presented with CHB in utero amongst whom postnatal cost data was averaged. Of these 11 patients, 4 (36%) presented in extremis, 8 (73%) had a pacemaker

TABLE 1 Model inputs.[18-21]

Variable	Baseline		Sensitivity analyses			
Costs	**USD $**	**Citation**	**Min**	**Max**	**One-way sensitivity analysis thresholds: standard screening dominant**	**One-way sensitivity analysis thresholds: limited screening dominant**
Prenatal steroid treatment	$10	Primary data	$8	$13	None	None
Prenatal limited screening[a]	$2,490	Primary data	$1,868	$3,113	None	None
Prenatal standard screening[a]	$18 880	Primary data	$14,160	$23,600	None	>$20,745
Anti-Ro/SSA, anti-La/SSB antibody assay	$140	Primary data	$105	$175	None	None
Postnatal hospitalization[a]	$157 190	Primary data	$117,893	$196,488	None	None
Pacemaker lifetime maintenance[a]	$177 600	Feingold[15]	$133,200	$222,000	None	None
Utilities	**Utility**	**Citation**	**Min**	**Max**		
Unimpaired life	1					
Death	0					
Hospitalization[b]	0.75	Mahle[19]	0.5	0.99	None	None
Steroid-related Side effect[b]	0.95	*Assumption*	0.5	0.99	None	None
Life with pacemaker[b]	0.88	Sears[20]	0.5	0.99	None	>0.92
Time	**Years**	**Citation**	**Min**	**Max**		
Life expectancy	78.8	CDC	50	100	None	<68.8
Steroid-related side effect	0.5	*Assumption*	0.01	1	None	None
Postnatal hospitalization length of stay	0.036	Primary data	0.01	1	None	None
Probabilities	**Probability**	**Citation**	**Min**	**Max**		
Fetal heart block (any degree)	0.03	Friedman[10]	0	0.25	>0.156	<0.027
Fetal 1° or 2° heart block	0.02	Friedman[10]				
Fetal 3° heart block	0.01	Brucato[21]				
High titers; fetal 3° heart block	0.03	Kan[4]				
High titers; fetal 1° or 2° heart block	0.06	*Assumption*				
Low titers; fetal 3° heart block	0.005	Jaeggi[14]; Kan[4]				
Low titers; fetal 1° or 2° heart block	0.01	*Assumption*				
Prevalence of high titers	0.20	*Endogenous variable*				
Treated fetal 1° or 2°, progressing[b]	0.25	Friedman[10]; Jaeggi[14]	0.1	1	None	>0.275
Untreated fetal 1° or 2°, progressing[b]	0.5	Friedman[10]; Levesque[8]	0.1	1	None	<0.451
Fetal 3° heart block, fetal demise[b]	0.1	Levesque[8]; Eliasson[22]	0.01	0.5	None	<0.058
Steroid-related side effect[b]	0.3	*Assumption*	0.01	0.5	None	None
Postnatal 3° heart block, 1 year survival[b]	0.95	Jaeggi[14]; Eliasson[22]	0.5	1	None	>0.989

[a]Incorporated into Monte Carlo with assumed Normal distribution.
[b]Incorporated into Monte Carlo with assumed beta distribution.

placed during the initial hospitalization, and 3 (27%) patients with CHB had a fast escape rhythm and did not require pacemaker implantation during the newborn admission. The average length of stay was 13.2 days, costing $157 190 per patient. In our sample, payer mix was 49% Medicaid, 36% private insurance, and 15% self-pay.

The base case analysis revealed that LS established the cost baseline for ICER calculation, with a forecast average total cost of $8566, and least effective with a QALY of 78.41 (Table 2, Figure 2). SS was most expensive with a forecast average total cost of $23 279, but also maximized efficacy with a forecast QALY of 78.50. Targeted screening was an intermediary by both metrics with a forecast average cost of $11 038 and 78.47 QALYs. These values are summated in an ICER below WTP for TS of $43 445/QALY and above WTP for SS of $322 756/QALY.

A Tornado Analysis was performed across the variable range outlined in Table 1 to isolate those variables most impactful on the model. In descending order of magnitude of influence, variables influential to the model conclusions were the prevalence of conduction abnormalities, the utility of life after pacemaker placement, the likelihood of fetal demise after onset of CHB, the likelihood of neonatal death prior to pacemaker placement, the likelihood of progression of untreated OHB to CHB, efficacy of steroids at preventing progression of untreated OHB to CHB, and lastly the cost of the SS approach. The results of one-way sensitivity analyses across all variables are outlined in Table 1. The only situation in which SS met the WTP threshold was the condition in which the incidence of any degree of fetal heart block exceeded 15.6% in this population. LS was the advised paradigm—neither alternative was cost-effective—if the prenatal cost of SS exceeded $20 745, if the utility experienced by a patient with a pacemaker exceeded 0.92 for the duration of their life, if the incidence of any degree of fetal conduction block was less than 2.7%, if the likelihood of progressing from untreated OHB to CHB in fetal life was less than 45.1% or of progressing despite treatment is greater than 27.5%, if the likelihood of fetal demise once CHB ensues is less than 5.8% or if the survival for infants born with CHB exceeds 98.9%. No variation in assumed cost of postnatal care—as would be the case if the rate of pacemaker placement differed from the 73% in our sample—across the sensitivity analysis range resulted in a change in analysis conclusion.

Two-way sensitivity analyses were performed upon several variable pairs highlighted in the tornado analysis. Focusing on the probabilities pertaining to progression of OHB to CHB, Figure 3 illustrates a two-way sensitivity analysis in which the probability of progression from OHB to CHB of an untreated fetus is varied against the degree to which steroid therapy reduces that risk of progression across the assumption ranges outlined in Table 1. The figure graphically conveys that if the likelihood of progressing from untreated OHB to CHB in fetal life is less than 45.1% or if progressing despite treatment is greater than 27.5% (relative risk reduction of treatment less than 0.45), then LS will be the advised model. Similarly, Figure 4 is a two-way sensitivity analysis wherein the prevalence of conduction abnormalities in this population was varied against the efficacy of steroid treatment. The analysis shows that at the baseline assumed steroid efficacy of a 0.5 relative risk reduction, if the incidence of any degree of fetal conduction block was less than 2.7% the LS will be the advised model. The SS becomes cost effective if conduction abnormalities are more common than 15.6%. Additionally, a Monte Carlo was performed utilizing a hypothetical 10 000 patient cohort (Figure 5). From this was extrapolated a cost-acceptability curve which illustrated that at a WTP of $50 000, TS was the cost-effective paradigm in 40% of the simulations with LS the advised paradigm in the reciprocal 59% (Figure 6). In only 1% of simulations was SS found to be cost-effective.

4 | DISCUSSION

Maternal autoantibodies for anti-Ro/SSA and anti-LA/SSB are the most common cause of congenital CHB.[11] The current screening protocol used by many centers in North America (SS) results in high-cost and high-resource utilization while emerging data suggests targeted screening for pregnancies with high autoantibody levels.[4,5] This study used our institutional experience and modeled the different screening strategies for fetal conduction abnormalities. The findings revealed that the current SS approach is not cost-effective and that the new emerging strategy of TS using the antibody level of maternal antibodies is a cost-effective alternative strategy in this population.

The SS includes weekly or bi-weekly visits with fetal echocardiograms. This approach has the highest QALY in our study as it was thought to detect and treat conduction abnormalities across the study population whereas the TS approach allowed rare conduction abnormalities to progress to CHB without treatment in the <50 U/mL group.[9] However, in the PRIDE study that included 98 pregnancies, 3 fetuses developed CHB and none had preceding conduction abnormalities.[9] Significant assumption changes would be required in order to conclude SS would be cost-effective; for conditions in which the clinician feels the prevalence of conduction abnormalities are more common than 15.6%, as may be the case in which a prior sibling of that fetus had experienced CHB prenatally, our analysis would support a SS approach (Figure 4).[4] Furthermore, the model did not take into consideration the effects of SS on the mothers including inconvenience, anxiety, and the indirect costs of work days missed because of the frequent visits which makes this strategy even less appealing and less practical as a universal approach.

The antibody levels are now clinically and commercially available.[4] Kan et al, reviewed their experience with risk stratification using maternal antibody levels. Their screening strategy was similar to the TS proposed in our study. Their study proved the safety of the TS strategy as no cases of complete or incomplete heart block developed in pregnancies with antibody levels less than 50 U/mL over a 5 year period among the 189 screened fetuses.[4] Their study showed a prevalence of high titers of about 20% which resulted in about 80% decrease in utilization of fetal echocardiograms.[4]

TABLE 2 Cost-utility analysis results

Cost-effectiveness analysis results					
Paradigm	**Cost**	**Effectiveness (QALY)**	**Incremental cost**	**Incremental effectiveness**	**ICER**
Limited screening	$ 8,566	78.41			
Targeted screening	$ 11,038	78.47	$ 2,472	0.06	$ 43,445
Standard screening	$ 23,279	78.50	$ 12,242	0.04	$ 322,756

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

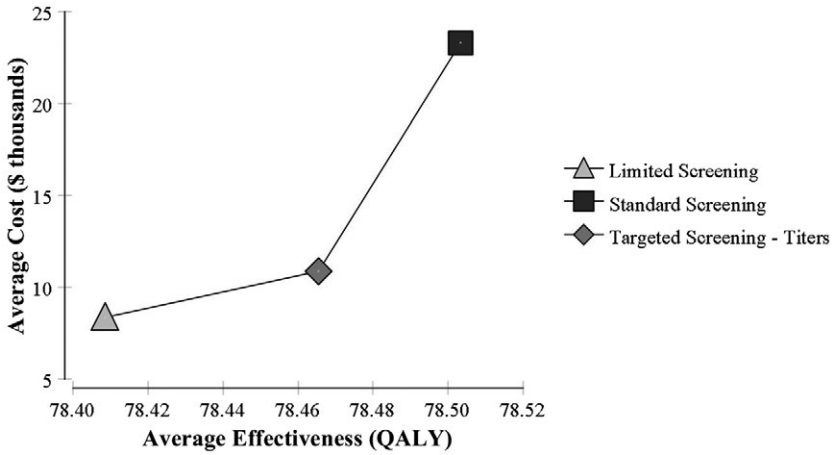

FIGURE 2 Cost-utility baseline results. Abbreviation: QALY, quality-adjusted life years

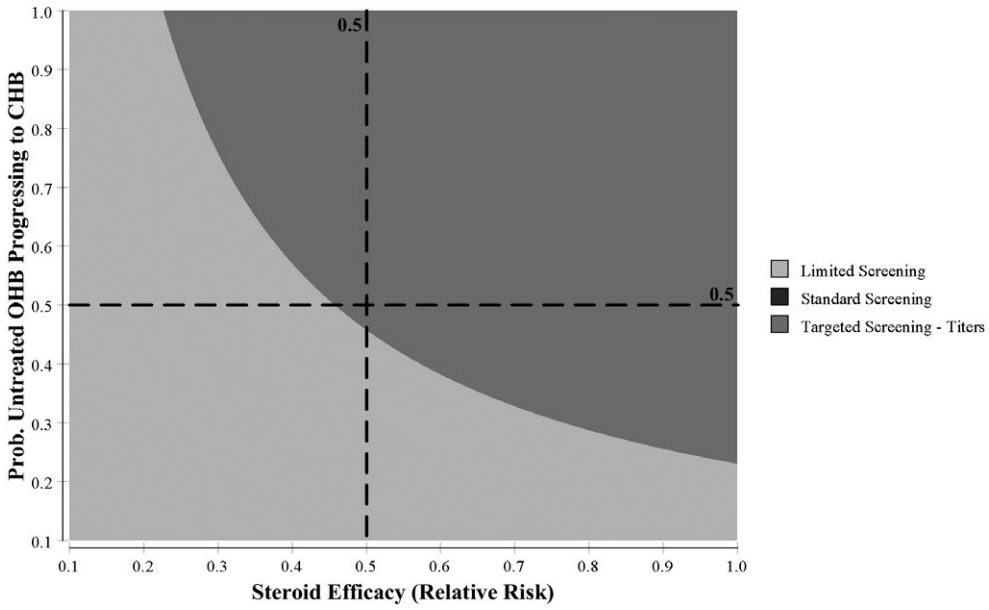

FIGURE 3 Two-way sensitivity analysis varying the probability of progression of untreated first or second degree heart block to third degree heart block and the efficacy of treating first or second degree heart block at preventing progression to third degree. Baseline assumptions (---). Abbreviations: CHB, complete heart block; OHB, other heart block

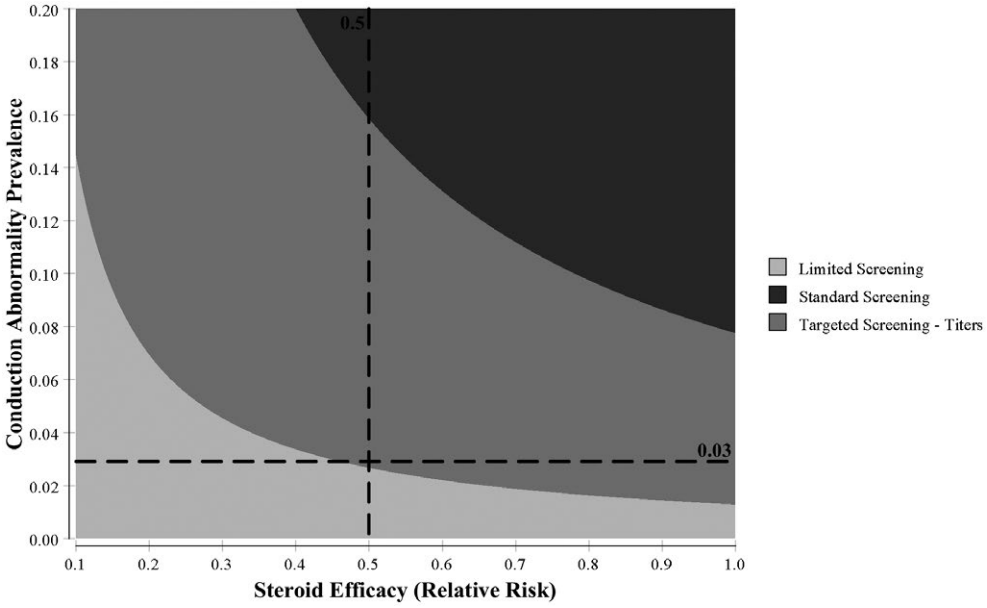

FIGURE 4 Two-way sensitivity analysis varying the probability of a conduction abnormality (any degree) in utero and the efficacy of treating first or second degree heart block at preventing progression to third degree. Baseline assumptions (---)

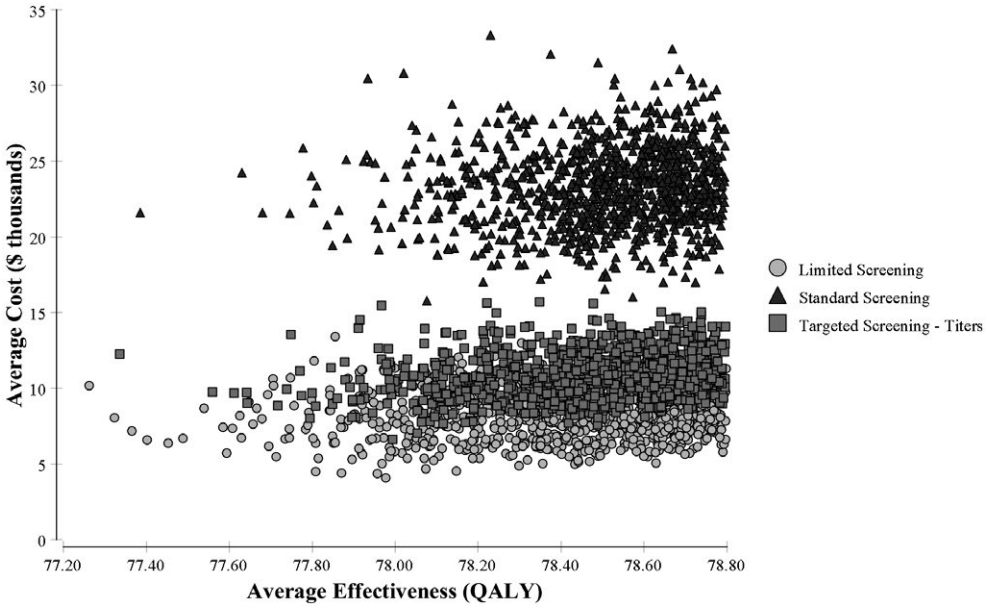

FIGURE 5 Monte Carlo. Abbreviation: QALY, quality-adjusted life years

The sensitivity analyses illustrate boundary conditions for the model conclusions. As indicated in Figures 3 and 4, the base case assumptions are near boundary conditions for three of the more controversial variables: "untreated first or second degree, progressing," "treated first or second degree, progressing," and "fetal heart block (any degree)." Therefore, variations in reader assumptions regarding these values can affect the conclusion of this analysis. However, if any variations in these assumptions change the conclusion, as Figures 3 and 4 indicate, this would advocate for LS over either alternative.

The variable that seems to have the most effect on the model is the efficacy of the steroid treatment. While some studies advocate for treatment with steroids for OHB, recent studies challenge the efficacy of steroids.[4] In our analysis, we assumed that steroids prevent the progression of OHB to CHB in 50% of the cases which would otherwise have progressed, with 25% progression in untreated cases based on the results of the PRIDE study.[9,10] If steroid efficacy is much less than 50% that will advocate for LS strategy. As the actual efficacy of steroids is yet to be determined, TS may be a

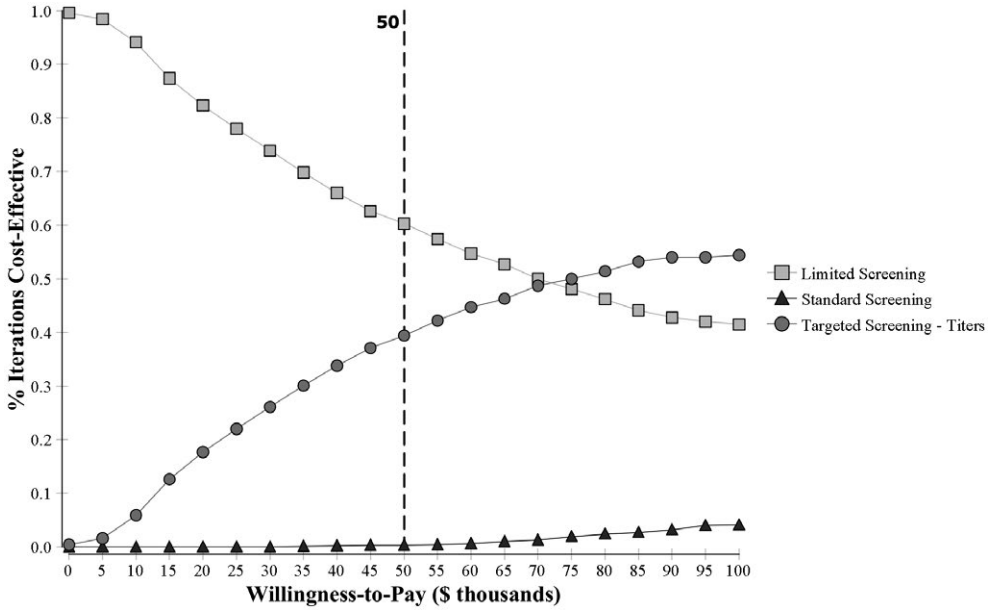

FIGURE 6 Cost-effective acceptability curve

reasonable alternative to the SS strategy that optimizes resource utilization compared to the current SS. Finally, our sensitivity analyses have shown our model conclusion to be insensitive to LS prenatal costs; if an obstetrics group were to increase their fetal heart rate surveillance frequency in response to a TS or LS approach by the pediatric cardiologist or add an ambulatory fetal heart rate surveillance program,[17] our recommendations remain the same as it will take a very significant increase in the prenatal cost of LS or TS to make SS justified.

Given that mortality and the lifelong need for a pacemaker is extremely uncommon in these models, the QALY difference between surveillance approaches is small. The Monte Carlo analysis in Figure 5 illustrates that the range of QALYs experienced by these infants is concentrated and maximized in the SS approach while the variation in QALYs experienced is widest in LS, including a few simulations with QALYs below 77.5. However, our analysis would indicate that the avoidance of these low QALY outcomes by pursuit of SS is not cost-effective. Figure 5 illustrates that TS achieves near-as concentrated a QALY distribution as SS, yet for less cost in all but a few cases.

5 | LIMITATIONS

Our center receives referrals of fetuses in known heart block for consideration of future pacemaker placement, so our data cannot be used for derivation of incidence values. All of the cost and hospitalization data is from our institution only, thus cost analysis did not include the cost of stay at an outside hospital or the cost of transfer to our institution. Also, some newborns had complications unrelated to CHB and thus excluded from the analysis not to exaggerate the cost of neonatal admission in cases of CHB. Furthermore, this model assumes that bradycardia will be detected by the obstetricians and will trigger referral back to cardiology. Finally, the effect of steroid treatment to prevent the progression to CHB is not well known and thus, was addressed using sensitivity analysis.

6 | CONCLUSION

While the efficacy of fetal intervention for first or second degree AV block remains unclear, given the morbidity implications of CHB, the current recommendations advocate for fetal surveillance efforts. Our analysis proves that the current commonly used SS strategy is not cost-effective except in situations in which the prevalence of disease is elevated, as would be the case for a woman with a prior affected fetus. However, a targeted screening strategy using maternal antibody levels is a cost-effective alternative strategy.

CONFLICT OF INTERESTS

The authors have no conflicts of interest relevant to this article to disclose.

AUTHOR CONTRIBUTIONS

Patrick D. Evers conceptualized and designed the study, assisted in data acquisition, performed the data analysis, drafted portions of the initial manuscript and approved the final manuscript as submitted. Tarek Alsaied conceptualized and designed the study, assisted in data acquisition, drafted portions of the initial manuscript and approved the final manuscript as submitted. Jeffrey B. Anderson and

James F. Cnota interpreted the data analysis, drafted portions of the initial manuscript and approved the final manuscript as submitted. Allison A. Divanovic conceptualized and designed the study, interpreted the data analysis, drafted portions of the initial manuscript and approved the final manuscript as submitted.

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How to cite this article: Evers PD, Alsaied T, Anderson JB, Cnota JF, Divanovic AA. Prenatal heart block screening in mothers with SSA/SSB autoantibodies: Targeted screening protocol is a cost-effective strategy. *Congenital Heart Disease*. 2019;14:221–229. https://doi.org/10.1111/chd.12713