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Treatment for Fetal Atrioventricular Block in Pregnant Individuals with Anti-SSA and Anti-SSB Antibodies

The Patient-Centered Outcomes Research Institute (PCORI) is partnering with the Agency for Healthcare Research and Quality (AHRQ) to develop a systematic evidence review on the treatment for fetal atrioventricular block in pregnant individuals with anti-SSA and anti-SSB Antibodies. This topic was nominated to PCORI by the Society for Maternal-Fetal Medicine (SMFM). SMFM plans to use the findings of the review to develop clinical guidance; the review will also offer an up-to-date overview of the state of the science and identify evidence gaps for future research.

Fetal atrioventricular block (AVB) is a fetal cardiac condition that occurs during gestation in an otherwise normally developing heart. Fetal AVB can occur because of an immune- or non-immune-mediated process. Autoimmune-mediated fetal AVB is almost always associated with the transplacental transport of maternal autoantibodies, especially anti-Ro/SSA and anti-La/SSB, to a fetus whose heart has no underlying anatomical malformation to explain the condition. The maternal autoantibodies likely damage the conduction tissues and myocardium of the fetal heart leading to blocking of signal conduction at the atrioventricular node.[1-4] The fetal conduction disturbance can be transient or permanent, with conduction that is delayed (first degree AVB), intermittent (second degree AVB), or absent (third degree or complete AVB). [1-3] First-degree fetal AVB can rapidly progress to second- or third-degree AVB. [1,2]

Fetal AVB is a rare condition. Maternal autoantibodies associated with fetal AVB are typically found in persons giving birth who have connective tissue disease including those diagnosed with Sjögren's syndrome (SS) or systemic lupus erythematosus (SLE) as well as among those with asymptomatic positive autoantibodies but undiagnosed conditions.[1-3] It is estimated that only 2–3% of the offspring of women who are seropositive for anti-Ro/SSA or anti-La/SSB antibodies will develop fetal AVB or abnormalities of the myocardium. However, if a previous child has been affected, the recurrence risk in subsequent pregnancies increases to 17–20%. [1-6] Complete AVB (CAVB) is very rare, occurring in approximately 1 in 20,000-25,000 live births in the U.S; [1-4] CAVB is irreversible and is associated with an 18% perinatal mortality rate.[2-3] Pacemaker implantation is required in more than 65% of surviving newborns.[1-4] CAVB can also manifest in other ways, such as endocardial fibroelastosis, valvular insufficiency, and/or frank cardiomyopathies with significantly reduced cardiac function. [3]

At present, there is a lack of consensus on the best strategies to prevent and manage fetal AVB among pregnant individuals with anti-Ro/SSA or anti-La/SSB antibodies. Recent clinical practice guidelines on the topic are limited, are generally focused on a broader population, and often lack strong guidance around the management of immune-mediated fetal AVB. In 2020, the American College of Rheumatology (ACR) published a clinical practice guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. [6] This guideline conditionally recommends that pregnant women with anti-SSA/SSB antibodies with abnormal fetal echocardiograms showing 1st and 2nd degree

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fetal heart block be treated with steroids (very low SoE) and recommends against steroid treatment in the case of 3rd degree or complete heart block (very low SoE). In 2023, the Society for Maternal-Fetal Medicine (SMFM) published an expert consensus document, Consult Series #64: Systemic Lupus Erythematosus in Pregnancy,[5] with recommendations related to the diagnosis and treatment of fetal AVB. In contrast to the ACR guideline, this consensus document recommends against screening for or treating heart block with steroids, citing that both remain unproven.

Evidence for this review will most likely be derived from observational studies due to the lack of randomized clinical trials on the condition. Several observational studies assessing the prevention of progression and treatment of fetal AVB have been published since the 2020 ACR clinical practice guideline but no recent comprehensive systematic review has synthesized this new evidence. Findings from a systematic review of the evidence could inform clinical guidance, provide an up-to-date overview of the state of the science and identify evidence gaps for future research.

Draft Key Questions

KQ1. What are the benefits and harms of treatment with hydroxychloroquine (HCQ), compared to no treatment, to prevent fetal AVB in pregnant individuals with anti-SSA/SSB antibodies?

KQ2. What are the benefits and harms of steroid treatment, with or without HCQ, to prevent the progression of fetal AVB in pregnant individuals with anti-SSA/SSB antibodies whose fetuses have first- or second-degree heart block?

KQ3. What are the benefits and harms of the addition of intravenous immunoglobulin (IVIG) to steroid treatment, as compared to steroid treatment alone, to prevent the progression of fetal AVB in pregnant individuals with anti-SSA/SSB antibodies whose fetuses have first- or second-degree heart block?

KQ4. What are the benefits and harms of the addition of beta-mimetics to steroid treatment, as compared to steroid treatment alone, to prevent the progression of fetal AVB in pregnant individuals with anti-SSA/SSB antibodies whose fetuses have first- or second-degree heart block?

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PICOTS

Table 1: PICOTS for KQ1: Does treatment with hydroxychloroquine (HCQ), compared to no treatment, prevent fetal AVB in pregnant individuals with anti-SSA/SSB antibodies?

Inclusion Criteria	Exclusion Criteria
Population:	
KQ1. Pregnant people with anti-SSA or anti-SSB antibodies and their fetuses	
Intervention:	
KQ1. Treatment with hydroxychloroquine (HCQ).	
Comparator	
KQ1. No treatment	
Outcomes	
KQ1. Incidence of fetal AVB; fetal harms such as congenital malformations, vision problems, preterm birth, low birthweight; maternal harms such as acute toxicity, retinopathy, heart rhythm changes, aplastic anemia, hypoglycemia, rash	
Timing	
KQ1. All times	
Setting	
KQ1. All health care settings.	
Study Design	
KQ1. RCT; CT and observational studies	

anti-SSA= anti–Sjögren's-syndrome-related antigen A; anti-SSB= anti–Sjögren's-syndrome-related antigen B; AVB=Atrioventricular Block; CHB=Congenital Heart Block; HCQ=hydroxychloroquine; IVIG=Intravenous immunoglobulin; RCT=randomized controlled trial.
*Steroid treatment includes fluorinated steroids; fluorinated corticosteroids; fluorinated glucocorticoids; glucocorticoids; corticosteroids; adrenocorticosteroids (e.g., dexamethasone); betamethasone.

Table 2: PICOTS for KQ2: Does steroid treatment compared to no treatment, with or without HCQ, prevent the progression of fetal AVB in pregnant individuals with anti-SSA/SSB antibodies whose fetuses have first- or second-degree heart block?

Inclusion Criteria	Exclusion Criteria
Population:	
KQ2. Pregnant people with anti-SSA or anti-SSB antibodies and their fetuses who have first- or second-degree heart block.	
Intervention:	
KQ2. Steroid treatment* with or without HCQ	
Comparator	
KQ2. No treatment, treatment with HCQ alone	
Outcomes	
KQ2. Progression of fetal AVB; fetal harms such as malformations (specifically oral clefting), intrauterine growth restriction, low birthweight, preterm birth, oligohydramnios, constriction of the fetal ductus arteriosus; maternal harms such as hypertension, fluid retention, infection, avascular necrosis, moon facies, gestational diabetes, preeclampsia, premature rupture of membranes, psychosis	

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Timing
KQ2. All times
Setting
KQ2. All health care settings
Study Design
KQ2. RCT; CT and observational studies

anti-SSA= anti–Sjögren's-syndrome-related antigen A; anti-SSB= anti–Sjögren's-syndrome-related antigen B; AVB=Atrioventricular Block; CHB=Congenital Heart Block; HCQ=hydroxychloroquine; IVIG=Intravenous immunoglobulin; RCT=randomized controlled trial.
*Steroid treatment includes fluorinated steroids; fluorinated corticosteroids; fluorinated glucocorticoids; glucocorticoids; corticosteroids; adrenocorticosteroids (e.g., dexamethasone); betamethasone.

Table 3: PICOTS for KQ3: Does the addition of intravenous immunoglobulin (IVIG) to steroid treatment, as compared to steroid treatment alone, prevent the progression of fetal AVB in pregnant individuals with anti-SSA/SSB antibodies whose fetuses have first- or second-degree heart block?

Inclusion Criteria	Exclusion Criteria
Population:	
KQ3. Pregnant people with anti-SSA or anti-SSB antibodies and their fetuses who have first- or second-degree heart block.	
Intervention:	
KQ3. IVIG and steroid treatment*	
Comparator	
KQ3. Steroid treatment alone	
Outcomes	
KQ3. Progression of fetal AVB; fetal harms such as congenital malformations, preterm birth, low birthweight; maternal harms such as renal impairment, thrombosis, arrhythmia, aseptic meningitis, hemolytic anemia, and transfusion-related acute lung injury.	
Timing	
KQ3 All times	
Setting	
KQ3. All health care settings	
Study Design	
KQ3. RCT; CT and observational studies	

anti-SSA= anti–Sjögren's-syndrome-related antigen A; anti-SSB= anti–Sjögren's-syndrome-related antigen B; AVB=Atrioventricular Block; CHB=Congenital Heart Block; HCQ=hydroxychloroquine; IVIG=Intravenous immunoglobulin; RCT=randomized controlled trial.
*Steroid treatment includes fluorinated steroids; fluorinated corticosteroids; fluorinated glucocorticoids; glucocorticoids; corticosteroids; adrenocorticosteroids (e.g., dexamethasone); betamethasone.

Table 4: PICOTS for KQ4: Does the addition of beta-mimetics to steroid treatment, as compared to steroid treatment alone or steroid treatment with HCQ, improve fetal outcomes in pregnant individuals with anti-SSA/SSB antibodies whose fetuses have advanced heart block?

Inclusion Criteria	Exclusion Criteria
Population:	
KQ4. Pregnant people with anti-SSA or anti-SSB antibodies and their fetuses who have advanced heart block.	

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Intervention:
KQ4. Beta-mimetics and steroid treatment*
Comparator
KQ4. Steroid treatment alone/steroid treatment with HCQ
Outcomes
KQ4. Progression of fetal AVB, tachycardia, stillbirth, hydrops, pregnancy prolongation; maternal harms such as tachycardia, arrhythmias, tremor, anxiety, agitation, pulmonary edema, hyperglycemia, acute toxicity.
Timing
KQ4. All times
Setting
KQ4. All health care settings
Study Design
KQ4. RCT; CT and observational studies

anti-SSA= anti–Sjögren's-syndrome-related antigen A; anti-SSB= anti–Sjögren's-syndrome-related antigen B; AVB=Atrioventricular Block; CHB=Congenital Heart Block; HCQ=hydroxychloroquine; IVIG=Intravenous immunoglobulin; RCT=randomized controlled trial.
*Steroid treatment includes fluorinated steroids; fluorinated corticosteroids; fluorinated glucocorticoids; glucocorticoids; corticosteroids; adrenocorticosteroids (e.g., dexamethasone); betamethasone.

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