Novel approaches in anti body mediated fetal atrioventricular block

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Scenario

- Pregnant woman SLE,Sogren referred to pediatric cardiologist for fetal echocardiography
- Pregnant woman referred for fetal bradycardia evaluation?

- Which disease?
- Ab body titer?
- Follow up duration?
- Treatment?

Autoimmune congenital heart block

- Autoimmune congenital heart block (ACHB) is an acquired autoimmune disease characterized by dysfunction of the cardiac conducting system, resulting in partial or complete atrioventricular block.
- It develops in fetuses of women with anti-Ro/SSA and anti-La/SSB autoantibodies who may have autoimmune diseases,such as Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE).

- The risk of developing a congenital fetal heart block varies between 0.2–2% in nulliparous women with positive anti-Ro antibodies, and increases to 15–20% in pregnancies with a previously affected fetus or neonate .

- Women who had two previously affected pregnancies have a risk of 50% of
- fetal CHB in subsequent pregnancies .
- In addition, autoimmune congenital atrioventricular block occurs in approximately 1/20,000 live births, most of which may develop into 3° atrioventricular block from 1° or 2° atrioventricular block

Role of Abs in prenatal diagnose

Anti-Ro/SSA Antibody: Pathogenetic Role and Possible Biomarker

- The molecular mechanisms by which anti-Ro/SSA antibody can cause heart injury are not yet fully understood. Two main hypotheses have been proposed.

- the first one is due to inflammatory-response,
- and the second to molecular mimicry.
- further studies have proven that anti-Ro antibodies can be detected in many other autoimmune diseases . On the other hand,anti-La antibodies are still regarded as being specific in the diagnosis of SLE and SS.

- Ro/SSA is a ribonucleoprotein constituted by two polypeptides,
- the 52 kDa and the 60 kDa: those peptides are targeted by the anti-52Ro and anti-60Ro autoantibodies

- Most of the evidence suggests the major role of anti-Ro52 in the initial damage of CHB .
- The type and the titer of the autoantibodies are also associated with tissue damage, because a significant link between anti-Ro/SSA levels and development of CHB is reported
- The central portion (amino acids 200–239) of Ro52, also known as p200, more than the full amino acid sequence of Ro-52,is recognized to be the fine specificity of anti-Ro associated to the highest risk of cardiac damage, considering its high prevalence in patients having affected child

- Because anti-p200, anti-Ro52, and anti-Ro60 antibodies, especially at high level, seem to identify pregnancies at higher risk for CHB, their finding can help the clinicians in identifying cases at major risk

- In our opinion, on the basis of the different results of the aforementioned studies regarding anti-p200, testing only for reactivity to p200 results not sufficient to recognize mothers with high risk of CHB.
- Moreover, anti-p200 antibodies are still not available in commercial kits, so routinely screening for these antibodies would not be easily achievable.

Intravenous immunoglobulin

- Intravenous immunoglobulin (IVIG) can reduce transplacental autoantibody passage and increase the release of anti-inflammatory factors.

- The results suggest that low-dose IVIG does not decrease the recurrence of ACHB in high-risk pregnancies. Whether IVIG at higher doses would be more effective needs further study.

Type I IFN: Pathogenetic Role and Possible Biomarker

- In addition, a correlation between IFN scores in mothers and their offspring has been identified, whereby evaluation of maternal IFN score could be used as novel biomarker for CHB risk

Who Should Be Tested for the Presence of Anti-Ro Antibodies?

- Patients with symptoms specific to Sjögren's syndrome: xerostomia, xerophthalmia, salivary gland enlargement .
- Women with Sjögren's syndrome or systemic lupus erythematosus who intend to become pregnant .
- Patients with symptoms suggesting the diagnosis of systemic lupus erythematosus, but with a negative indirect immunofluorescence test for antinuclear antibodies .
- Patients with rheumatoid arthritis or juvenile idiopathic arthritis .
- Women with a history of giving birth to a child with congenital heart block or neonatal lupus(tested before conception).
- Antinuclear antibody (ANA)-positive women who are planning to become pregnant
- Even asymptomatic mothers with slow fetal heart rate and echocardiographic findings of heart block should also be tested for the presence of these antibodies,as it is not unusual for neonatal lupus to be the first clue toward the detection of anti-Ro/SSA and anti-La/SSB antibodies

- For anti-Ro antibody titers higher than 50 UI/mL, the risk of developing CHB is 5%, with high risk of developing a complete atrioventricular (AV) block in the fetus .
- It is important to know that asymptomatic mothers with higher titers of anti-Ro antibodies (without symptoms or signs of SLE and/or SS) can give birth to children with neonatal lupus.

- Diagnosis with echocardiography & AB titer
- Management with HQ
- Treatment of fetus

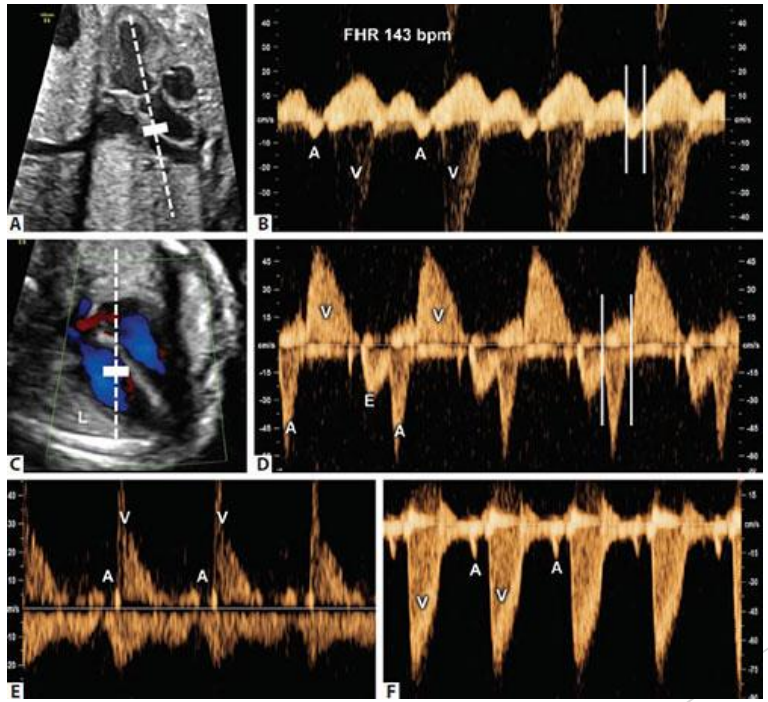
Prenatal Diagnosis: Fetal Echocardiograms (ECHOs) for PR Interval Measurement

- The management of anti-Ro/La-exposed pregnancies remains heterogeneous across different centers. Although the use of ECHO screening vs. heart rate monitoring is differently applied, fetal echocardiograms (ECHOs) for PR interval measurement is the most useful low-invasive means for surveillance of fetuses at risk of CHB

- The antenatal prediction of CHB is possible by the evaluation of the "mechanical" PR interval with serial fetal ECHOs, beginning at the 16th-18th gestational week, since CHB development usually occurs between 18 and 24 weeks of gestation

- Three methods to calculate the AV interval are described,as follows

- 1) MV-Ao: the AV interval was measured from the intersection of the mitral E and A waves to the onset of the ventricular ejection wave in the aortic (Ao) outflow.
- 2) MV: this time interval starts with the same event, but ends at the closure of the mitral wave (MV).
- 3) SVC-Ao: this time interval was measured from the beginning of the retrograde venous a-wave in the superior vena cava (SVC) to the beginning of the Ao ejection wave.”

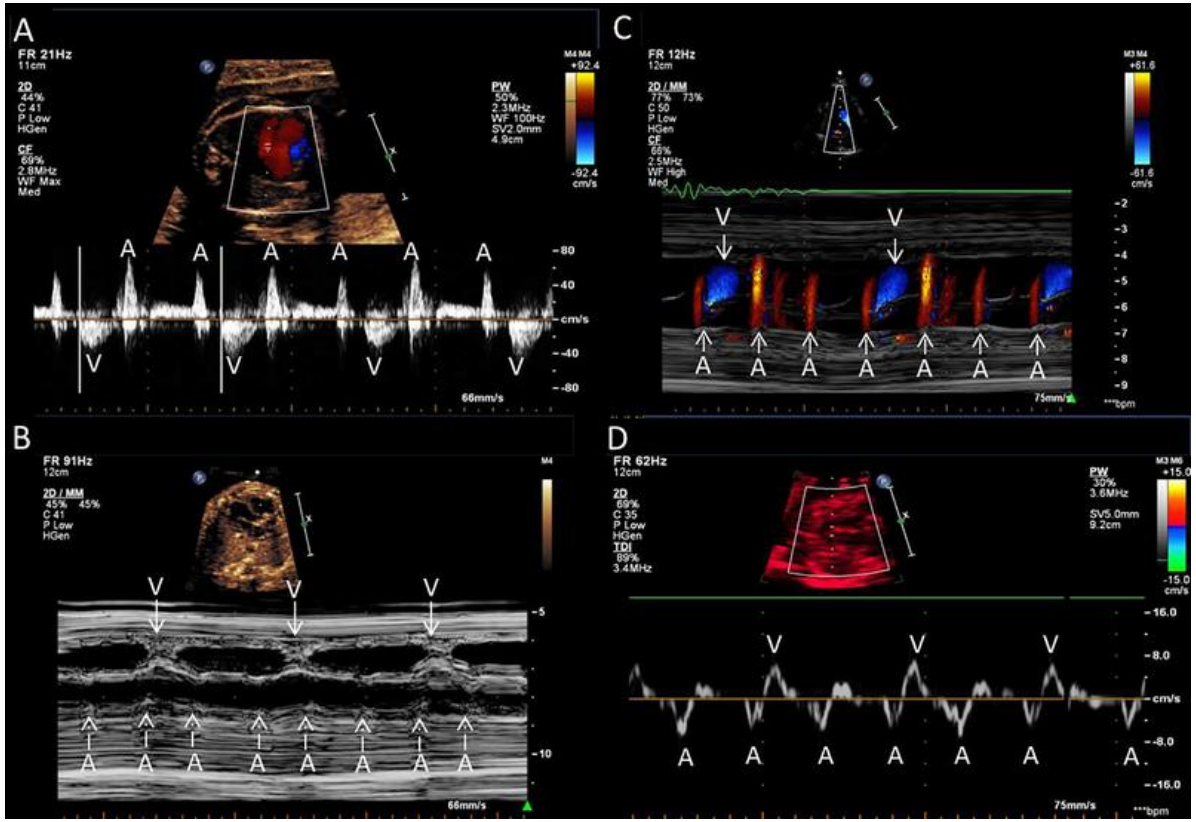


- Glickstein et al. by using MV-Ao technique firstly reported that the mechanical PR with the fetal pulsed Doppler ECHO was technically feasible. Moreover, this technique resulted independent of gestational age and showed a good relationship with electrical neonatal PR-interval. These results were subsequently validated by a prospective fetal ECHO study.

- In normal fetuses the mechanical PR interval was seen to range from 90 to 150 ms, independently of gestational age and heart rate

MV-Ao PR interval ≥150 ms is “highly suggestive”

and ≥160 ms “diagnostic” of fetal first-degree block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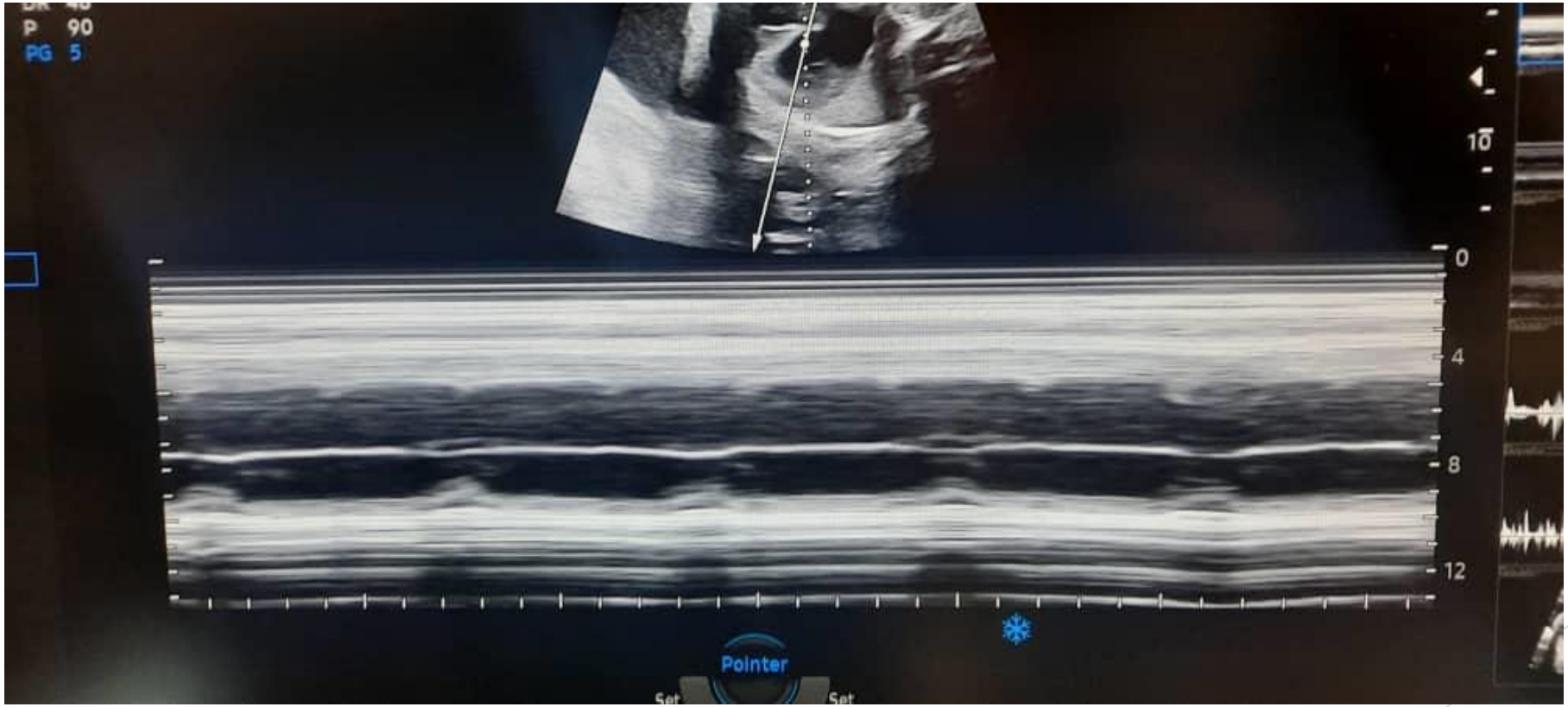
- A 32 weeks pregnant woman referred for evaluation of fetal bradycardia with Anti RO/SSA titer=80u/ml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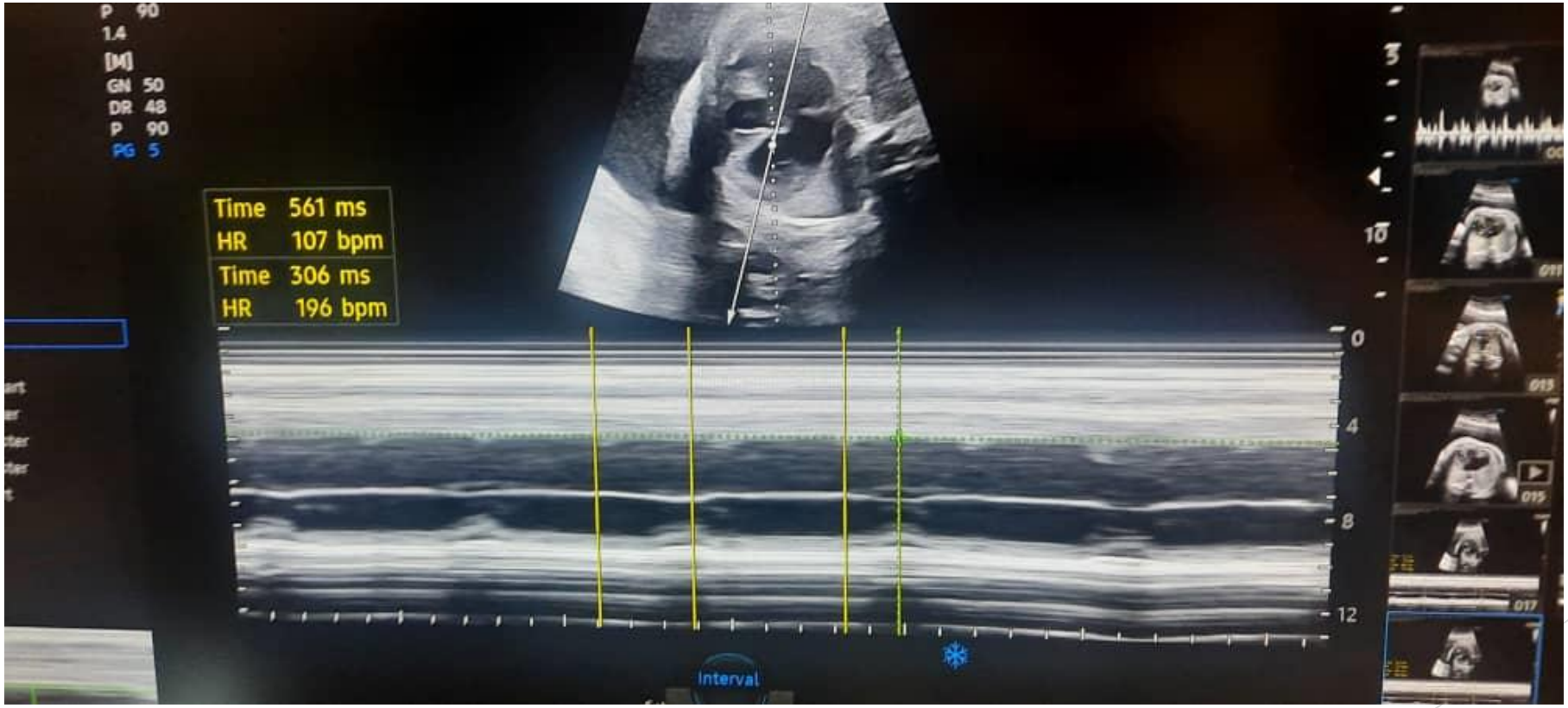
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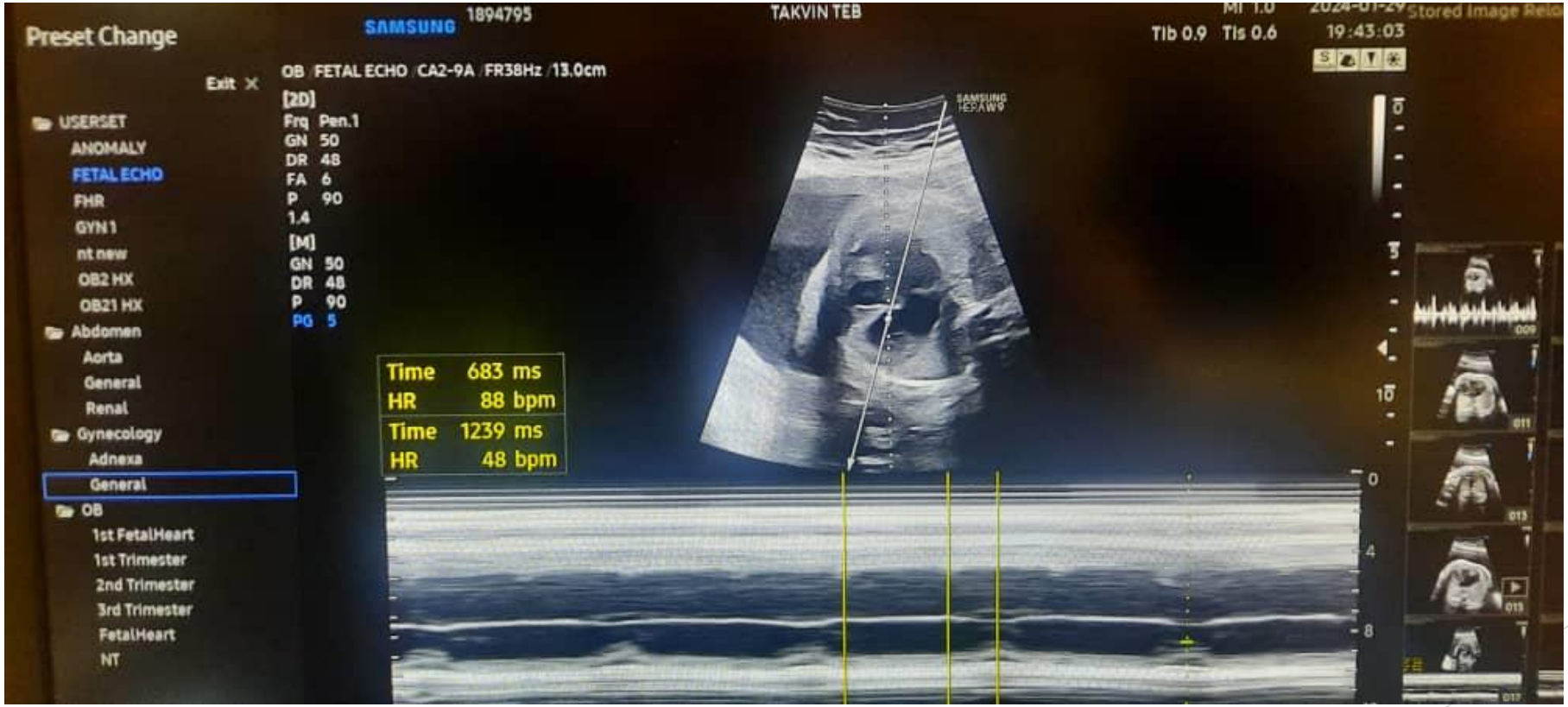
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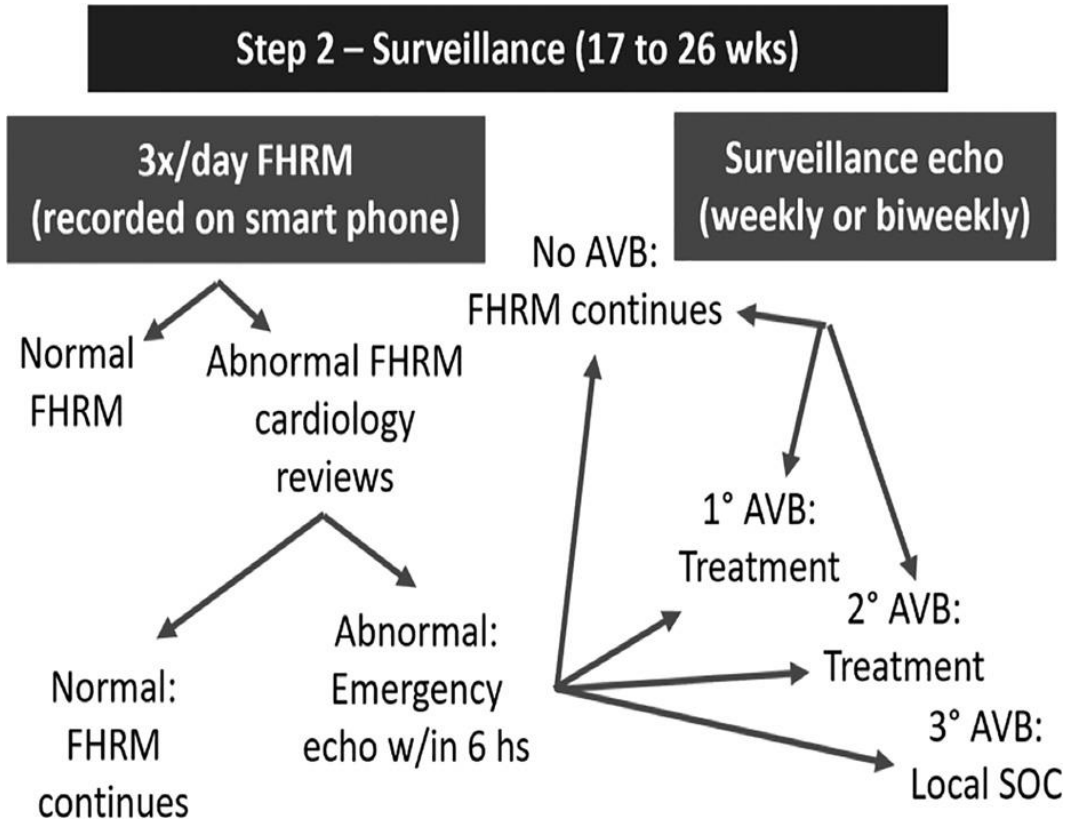
- For pregnant women who have previously delivered infants with ACHB or NLS, the 2020 American College of Rheumatology Reproductive Health Management
- Guidelines for Rheumatology and Musculoskeletal Diseases recommend
- weekly fetal echocardiography, beginning at weeks 16–18 and continuing through week 26.

- The recommendations conditionally recommend serial (less frequent than weekly; interval not determined) fetal echocardiography, beginning at weeks 16–18 and continuing through week 26 for pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies but no infant history of ACHB or NLS

Daily ambulatory fetal heart rate monitoring and fetal ultrasound echocardiography

- In fact, the transition from a normal rhythm to a third-degree atrioventricular block (AVB) occurs within 24 h, which highlights the importance of a closer surveillance of rhythm, eventually performed at home directly by the patients.
- It can prompt quicker access to dedicated care and improve outcomes at birth.
- In contrast, it is difficult for weekly monitoring to detect an early stage of ACHB before it progresses to third degree, and all data on therapies seem to emphasize that the earlier the stage at detection, the better the results of various therapies are.
- Daily ambulatory fetal heart rate monitoring (FHRM) allows for early detection of rhythm alterations and the administration of timely targeted treatments


Step 2 – Surveillance (17 to 26 wks)
3x/day FHRM (recorded on smart phone)
Surveillance echo (weekly or biweekly)
Normal FHRM
Abnormal FHRM cardiology reviews
Normal: FHRM continues
Abnormal: Emergency echo w/in 6 hs
No AVB: FHRM continues
1° AVB: Treatment
2° AVB: Treatment
3° AVB: Local SOC

Management of pregnant women with positive anti-Ro/SSA and/or anti-La/SSB antibodies during pregnancy

Hydroxychloroquine

The 2020 American College of Rheumatology Reproductive Health Management Guidelines for Rheumatoid and Musculoskeletal Diseases conditionally recommend hydroxychloroquine (HCQ) treatment for all pregnant women with positive anti-Ro/SSA and/or anti-La/SSB antibodies to minimizethe risk of ACHB.

Treatment for ACHB fetuses

- Fluorinated steroids

- Fluorinated steroids may prevent the fetus from progressing from incomplete atrioventricular block to complete atrioventricular block.
- Notably, for pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies and echocardiography showing fetal incomplete heart block, the 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases recommends oral dexamethasone of 4 mg per day .

- The personal recommendations by Dr Jill Buyon is to start dexamethasone 4 mg a day for 1 week, and when deterioration to third degree is detected, dexamethasone could be discontinued
- If the first-degree block reverses to normal rhythm or remains stable, it is difficult to establish if steroid treatment should be continued or not

- However, the adverse effects of fluorinated steroids should not be ignored. Mothers are prone to suffer from hypertension,hyperglycemia, and excessive weight gain, while fetuses have a high risk for growth restriction, adrenal insufficiency,and oligohydramnios

- dexamethasone prevents
- disease progression
- reduces mortality
- avoids pacemaker implantation and cardiomyopathy in cases of second-degree and third-degree AVB is controversial , but recent studies do not support its use.

Intravenous immunoglobulin

- In a case report, the fetus of a mother with positive anti-Ro/La antibodies was diagnosed with 2:1 AV block and intermittent complete heart block at 28 weeks' gestation.
- The mother promptly received therapy with IVIG (400 mg/kg per day) for 5 days. Improvement in sinus rhythm with intermittent AV block was recorded
- throughout the remainder of the pregnancy.

- In a 10-year retrospective study of NLS in China, five babies who had a prolonged PR interval on ECG at birth were treated with intravenous immunoglobulin (IVIG) at a dose of 1 g/kg for 2 days, all of whom reverted to a normal sinus rhythm, providing evidence for the effectiveness of IVIG

Terbutaline

- Use in cases of fetuses with heart rates <50 bpm or significantly reduced contractility, can increase HR by 5-10 bpm
- 2.5 - 5 mg every 46 hrs
- Tremor, palpitations
- sweating
- Should not use in fetal or
- maternal long QT consider
- evaluation with magnetocardiography

Plasmapheresis

- Plasmapheresis may be a potential effective therapeutic strategy for ACHB fetuses. The efficacy of plasmapheresis in removing anti-Ro/SSA and anti-La/SSB antibodies was evaluated in 10 consecutive pregnant women with ACHB fetuses, and the degree of ACHB at detection and at delivery was recorded.

Pacemaker implantation

- Invasive approaches to placement of pacing leads include open fetal surgery for patients with CCHB who were refractory to medical therapy
- Patients who are refractory to standard medical therapy for CCHB have few therapeutic options especially when fetal hydrops develops at a time when risks of delivery are high.
- In the first attempt at fetal pacing performed via open surgery for direct epicardial pacemaker implantation, a unipolar pacemaker was successfully implanted in a fetus with CCHB suffering from fetal hydrops and multi-organ failure via open fetal surgery.
- The fetal micropacemaker devices will be studied under a Humanitarian Use Designation (HUD) from the Food and Drug Administration, and the first human implant is expected soon.

Take home message

- 1.In fact, the new knowledge indicates that maternal IFN signature and maternal antibodies profile, such as the combination of anti-Ro52 and anti-Ro60 antibodies positivity, the positivity of anti-p200 antibodies, particularly at high levels, can identify women at higher risk for delivering child with CHB.
- 2.On the other hand, the prolongation of the PR interval by ECHOs represents is an indispensable tool for the diagnosis of fetal cardiac tissue injury and for maternal treatment timing.
- 3.Home monitoring of fetal heart rhythm (FHRM) is a feasible and reassuring method to surveil anti-Ro-exposed pregnancies and can be considered another novel monitoring biomarker for CHB.
- Finally, the usefulness of maternal prophylaxis with HCQ is a very important key message, and is actually recommended in all women at risk for recurrence of CHB.


Thank you