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LETTER TO THE EDITOR

To Be or Not to Be Treated: That Is the Question in Managing a Fetus With Cardiac Injury Exposed to Anti-SSA/Ro

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To the Editor:

We read with great anticipatory interest the recent article by Mawad et al, which represents a longstanding partnership between cardiology and rheumatology and delivers an important message regarding treatment of anti-SSA/Ro-associated fetal atrioventricular block and other cardiac manifestations: initiate transplacentally passaged anti-inflammatory medications to the mother.[1] The challenges faced by clinicians managing rare medical conditions are no better illustrated than in this disease that affects far too few fetuses to feasibly attempt traditional prospective randomized treatments. Thus, the best one can do is perform due diligence on well-phenotyped cohorts initiated and organized by dedicated physicians caring for these high-risk pregnancies. The bottom line delivered by the authors in this most recent retrospective study is that maternal treatment with dexamethasone at doses as high as 8 mg (equivalent to about 53 mg of prednisone) and/or pooled intravenous immunoglobulin should be instituted in all cases of anti-SSA/Ro cardiac manifestations inclusive of advanced block, substantial first-degree block, isolated endocardial fibroelastosis, and rare situations of sinus bradycardia. The title of the study states "Standardized" treatment but, based on the protocol provided, the dose of steroids and tapering schedule seem to be variable as well as the initiation and regimen of intravenous immunoglobulin.

Although the outcome and descriptive data from the 9 centers contributing to this retrospective study are informative, it is not clear whether in all the contributing centers, aside from Toronto, steroids were always the intended approach. Because it is implied, unfortunately that leaves no comparative data from the authors on cases not treated at the various centers. Instead, this data set of uniformly treated fetuses was measured against "historical" outcome data derived from a review of published cohorts. Based on a review of 5 studies that included fetuses exposed to maternal anti-SSA/Ro with advanced atrioventricular block predominantly untreated with transplacentally crossed medications such as fluorinated steroids and/or intravenous immunoglobulin, the authors concluded that treatment associates with a significantly lower rate of perinatal mortality and postnatal dilated cardiomyopathy. Because the cohorts cited included both treated and untreated fetuses, Mawad et al conclude that these collective cases show less benefit because overall fewer fetuses were treated. It would have been a much stronger message if these studies were evaluated for actual comparisons between fetuses treated or not and the indications for treatment likewise discussed, not trivial shortcomings. However, the data from these cited studies simply may not have been available. In addition, it is possible, even if there were an untreated comparison group, that patients who were sicker may have been treated, leading to results that were confounded by indication.[2]

Acknowledging that literature searches do not always identify every single pertinent study or there may be reasons for exclusion not fully elucidated, several large studies with data relevant to the management of

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fetuses identified to have anti-SSA/Ro-associated cardiac manifestations were not included in the study by Mawad et al. One was a recent meta-analysis covering 9 studies inclusive of 747 fetuses with varying degrees of conduction defects that supported the conclusion that fluorinated steroids do not influence overall birth rate, survival, progression of incomplete atrioventricular block, pacing, or presence of extranodal disease.[3] This publication swings the pendulum 180 degrees toward the discouragement of steroids. However, it is worth mentioning that a subgroup analysis did reveal that when only considering third-degree block (note that cases were included with or without extranodal disease), fluorinated steroids exhibited a significant protective effect on survival and pacing. The authors concluded that these specific findings likely reflected the fact that there was a higher rate of extranodal disease in those studies of untreated patients compared with the cases exposed to fluorinated steroids. This would imply that extranodal disease drives mortality, which has long been appreciated.[2,4] The second omitted article originated from the US Research Registry for Neonatal Lupus, the largest extant data set of families affected by at least 1 child with neonatal lupus. This US study focused solely on cases of advanced block in which there was no echocardiographic evidence of extranodal disease to address the question of whether treatment prevents further progression such as the development of extranodal disease.[5] With regard to third-degree block, it was reasoned that steroids would be less likely to be of benefit because the injury was complete. The initial steroid dose was equivalent to ≥4 mg/day dexamethasone in 97% of cases (range, 2–8 mg/day), with 82% receiving the equivalent of 4 mg dexamethasone. The average daily dose was 2.8±1.8 mg. Steroids were initiated an average of 1.8 days after the detection of block. The average cumulative dose of fluorinated steroids to which fetuses were exposed was the equivalent of 274±177 mg of dexamethasone. The answer was unambiguous: comparing 71 fetuses exposed to fluorinated glucocorticoids within 1 week of detection to 85 who were not treated, fluorinated glucocorticoids did not significantly prevent the development of disease beyond the AV node, reduce mortality, or forestall/prevent pacemaker implantation. Arguably, the dose of steroids seemed to fall below that recommended by Mawad et al. Finally, the US Registry did provide another comparative study to address postnatal morbidity. Although the incidence of postnatal cardiac dysfunction was higher (22.4% at 0–1 year, 15% at 1–17 years) than that reported by Mawad et al, there was not a significant association with dexamethasone exposure in utero and postnatal cardiac dysfunction in any age group.[6]

An important consideration in evaluating therapeutic approaches, which compounds further the rarity of anti-SSA/Ro-associated fetal cardiac disease, is clinical heterogeneity. Instead of exposing all pregnant women with affected fetuses to considerable doses of glucocorticoids for weeks to months, focusing on the higher risk fetus would seem a reasonable compromise, and this has been recommended by the European Alliance of Associations for Rheumatology (formerly known as the European League Against Rheumatism, or EULAR)-Sjögren's Syndrome Task Force Group.[7] The challenge here is to define high risk of poor outcome. Although echocardiographic studies support the negative effects of extranodal disease,[2,4] it remains highly disconcerting that histological studies support the presence of endocardial fibroelastosis even when undetected by clinical surveillance.[8] This may be part of the basis for the suggestion of aggressive treatment with steroids even for isolated advanced conduction diseases, although the study from the US Registry did not support the hypothesis that treatment with these medications prevents disease progression.[5]

In aggregate there really is no unambiguous conclusion to draw except to humbly embrace the limitations of the evidence presented. It would seem that guidelines for intervention with transplacental medications should target the fetus who is not likely to do well untreated. We should not let rarity compounded by heterogeneity force recommendations based on insufficient evidence. It is time to move beyond our silos and organize a uniform evaluation of collected data on the management approaches of affected fetuses derived from thorough chart extractions and registries. So it remains, to be or not to be treated… and we thought Prince Hamlet had it tough.

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Disclosures

None.

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