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RESPONSE TO LETTER TO THE EDITOR

To Be or Not to Be: Surviving Immune-Mediated Fetal Heart Disease

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In Response: we read with great interest the Letter to the Editor authored by Buyon et al[1] in response to our recent publication by Mawad et al in the *Journal of the American Heart Association*.[2] We are grateful for the opportunity to respond and present our viewpoint.

Patients in our multicenter study were not all treated with "steroids and/or IVIG" as suggested by Buyon and colleagues, but all did receive treatment with dexamethasone from the time of new fetal diagnosis of antibody-mediated heart disease, including atrioventricular block (AVB), endocardial fibroelastosis, and/or sinus node disease. The usual starting dose of dexamethasone was 8 mg/d, because most patients were diagnosed before 24 gestational weeks. Indications for the addition of intravenous immunoglobulin and a beta-mimetic agent to the dexamethasone treatment are also detailed in the Methods section.

From a methodical standpoint, a major advantage of the routine use of prenatal steroids included the avoidance of selection bias in patient management and confounded study results. The clinical rationale for a universal treatment approach included the following: (1) our earlier poor experience with untreated complete AVB and/or endocardial fibroelastosis[3,4]; (2) histological evidence that cardiac involvement often extends beyond the conduction system and is not accurately detected by fetal echocardiography[5,6]; and (3) the up to 30% risk of dilated cardiomyopathy after birth, with high odds of heart failure, cardiac transplantation, and/or premature death.[5,7,8] In line with this concept, we fully agree with the statement of Buyon and colleagues[1] that it does remain highly disconcerting that histological studies support the presence of endocardial fibroelastosis even when undetected by ultrasound surveillance. A decision to not treat versus to treat AVB is based on limited evidence on the true extent and severity of concomitant extranodal disease.

When compared with contemporary studies of high-degree AVB[2] that included relevant proportions of untreated fetuses, our approach resulted in significantly improved perinatal survival, with a neonatal survival advantage between 9% and 16%. Of patients with other disease manifestations including isolated endocardial fibroelastosis, incomplete AVB, and isolated sinus node disease, all but one survived. Importantly, steroid treatment was generally well tolerated without evidence of neurodevelopmental impairment of prenatally treated children.

As mentioned in the Methods section, we did not include studies in our comparative outcome analyses that were published before 2007. Nonetheless, Hoxha et al[9] in their meta-analysis of 9 studies that had been published from 1999 to 2016 also found a significant protective role of fluorinated steroids for survival of immune-mediated complete AVB to birth. Likewise, in the multicenter NAFTNet retrospective report from 2022,[10] which included 98 steroid-treated pregnancies (including 35 patients from the Mawad study) as well as 29 untreated pregnancies, prenatal treatment of antibody-mediated fetal conduction system disease with dexamethasone significantly decreased neonatal morbidity and overall mortality without increasing overall pregnancy complications.

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We stand by our observations that support treatment but agree that risk stratification is imperfect and requires further refinement. The optimal approach would be to recognize pregnancies at risk, monitor for the development of conduction system and myocardial disease, and treat incomplete block before it progresses to complete AVB and/or myocardial disease early in its course. There are currently 2 prospective studies recruiting patients from qualified centers. The first risk stratifies pregnancies by anti-Ro/SSA antibody titer and investigates the efficacy of steroid and intravenous immunoglobulin treatment on fetal immune-mediated incomplete heart block to restore normal rhythm or prevent progression to complete heart block (STOP BLOQ [Surveillance and Treatment to Prevent Fetal Atrioventricular Block Likely to Occur Quickly]; ClinicalTrials.gov: NCT04474223). The second compares morbidity and mortality of treated and untreated fetuses with a complete heart block until 2 years after birth (SLOW HEART REGISTRY of Fetal Immune-mediated High Degree Heart Block: ClinicalTrials.gov: NCT04559425).

Considering Hamlet's original quote, the "to be or not to be" for a significant proportion of children with immune-mediated fetal heart disease may indeed hinge on prenatal anti-inflammatory treatment effects that mitigate myocardial damage and avoid progressive pre- and postnatal cardiomyopathy and its consequences.

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Disclosures

None.

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