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AOGS SYSTEMATIC REVIEW

Maternal steroid therapy for fetuses with second-degree immune-mediated congenital atrioventricular block: a systematic review and meta-analysis

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Key words
Atrioventricular block, fetal heart, fetal echocardiography, steroids, ultrasound, heart block, autoimmune

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Conflict of interest
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Abstract

Introduction. The aim of this study was to explore the effect of maternal fluorinated steroid therapy on fetuses affected by second-degree immune-mediated congenital atrioventricular block. *Material and methods.* Studies reporting the outcome of fetuses with second-degree immune-mediated congenital atrioventricular block diagnosed on prenatal ultrasound and treated with fluorinated steroids compared with those not treated were included. The primary outcome was the overall progression of congenital atrioventricular block to either continuous or intermittent third-degree congenital atrioventricular block at birth. Meta-analyses of proportions using random effect model and meta-analyses using individual data random-effect logistic regression were used. *Results.* Five studies (71 fetuses) were included. The progression rate to congenital atrioventricular block at birth in fetuses treated with steroids was 52% (95% confidence interval 23–79) and in fetuses not receiving steroid therapy 73% (95% confidence interval 39–94). The overall rate of regression to either first-degree, intermittent first-/second-degree or sinus rhythm in fetuses treated with steroids was 25% (95% confidence interval 12–41) compared with 23% (95% confidence interval 8–44) in those not treated. Stable (constant) second-degree congenital atrioventricular block at birth was present in 11% (95% confidence interval 2–27) of cases in the treated group and in none of the newborns in the untreated group, whereas complete regression to sinus rhythm occurred in 21% (95% confidence interval 6–42) of fetuses receiving steroids vs. 9% (95% confidence interval 0–41) of those untreated. *Conclusions.* There is still limited evidence as to the benefit of administered fluorinated steroids in terms of affecting outcome of fetuses with second-degree immune-mediated congenital atrioventricular block.

Abbreviations: AV, atrio-ventricular; AVB, congenital atrioventricular block; CI, confidence interval; NOS, Newcastle-Ottawa Scale.

Introduction

Congenital atrioventricular block (AVB) encompasses a wide spectrum of conditions characterized by the interruption of the conduction of electrical impulses from the atria to the ventricles (1,2). First-degree AVB is characterized by a prolonged atrioventricular (AV) interval, whereas in second-degree ABV, some beats are conducted and others are blocked. In third-degree AVB, there is complete interruption of AV conduction so that atria and ventricles beat independently (1,2). AVB can occur in fetuses with congenital heart disease; however, when isolated it is commonly associated with maternal autoantibodies, especially SSA/Ro and SSB/La (3,4). Although the pathophysiology of immune-mediated AVB has not been fully elucidated, transplacental passage of maternal IgG antibodies with subsequent inflammation and fibrous replacement of the conduction system is the most likely explanation (4).

Early gestational age at diagnosis, low ventricular rate and the presence of fetal hydrops have been reported to be the major determinants of perinatal outcome in fetuses affected by immune-mediated AVB (1,2). Despite this, optimal management once AVB has been detected in utero has yet to be established (5).

Whereas third-degree AVB is usually irreversible once established, several reports suggest that fluorinated steroids such as betamethasone and dexamethasone may prevent in utero progression of immune-mediated second-degree AVB and may improve the short- and long-term outcome in these children (6,7). However, there is still a paucity of data on the actual role of antenatal steroids in the management of fetuses affected by second-degree AVB. Series published to date differ in conclusions and have small sample sizes (8–12).

The primary aim of this systematic review is to ascertain whether maternal steroid therapy can prevent the progression of second-degree immune-mediated AVB in utero. Secondary aims are to explore the association between steroid therapy and regression of AVB, pacemaker implantation after birth, and fetal and neonatal mortality.

Material and methods

This review was performed according to a protocol designed a priori and recommended for systematic review (13). MEDLINE, Embase and ClinicalTrials.gov databases were searched electronically on 30 July 2017 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words and word variants for "fetal heart block," "autoimmune disease," "echocardiography," "corticosteroids" and "outcome." Reference lists of relevant articles and reviews were hand-searched for additional reports. Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration no.: CRD42016045713) following the PRISMA guidelines for protocols (PRISMA-P) (14).

Only studies reporting the outcome of fetuses affected by second-degree immune-mediated AVB who were treated with fluorinated steroids compared with those who were not treated were considered eligible for inclusion (13). Cases with non-immune AVB, those for whom maternal antibody status could not be ascertained and those associated with major congenital heart disease were excluded. Therapy with steroids included the use of any type of fluorinated corticosteroid.

Two authors (A.C., F.D.A.) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus with a third reviewer (V.B.); full text copies of those articles were obtained and the first two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed and consensus was reached or the dispute was resolved by discussion with a third author. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. The authors of those articles in which information was not reported but the methodology was such that this information would have been recorded initially, were contacted.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS). According to NOS, each study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups and the ascertainment outcome of interest. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, the ascertainment of the outcome of

Key Message

There is still limited evidence as to the benefit of administered fluorinated steroids in terms of affecting outcome of fetuses with second-degree immune-mediated congenital atrioventricular block.

interest includes the evaluation of the type of the assessment of the outcome of interest and the length and adequacy of follow up. According to NOS, a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability (15).

The primary outcome was the overall progression of AVB to either intermittent (second/third) or continuous III degree AVB at birth (overall progression).

The secondary outcomes were:

- Regression to either first-degree, intermittent first-/second-degree AVB or sinus rhythm (overall regression)
- Regression to first-degree AVB
- Regression to intermittent first-/second-degree AVB
- Regression to sinus rhythm
- Persistence of second-degree AVB
- Fetal death
- Neonatal death
- Pacemaker insertion

First-degree immune-mediated AVB was diagnosed at M-mode or pulsed wave Doppler ultrasound when the AV conduction time was prolonged. Prenatal diagnosis of second-degree AVB was done in the presence of a progressive lengthening of AV conduction, until an isolated impulse was blocked (Mobitz I) or, in the case of a sudden block of an isolated impulse, without prior lengthening of the AV conduction time (Mobitz II). Finally, third-degree AVB was diagnosed when there was no AV conduction (2), with the atria and ventricles beating independently (1,2).

Second-degree immune-mediated AVB was defined as continuous when the postnatal electrocardiographic tracing showed the presence of permanent and constant second-degree AVB, and intermittent when there was an alternation between second- and third-degree AVB (1,2).

We aimed to ascertain the occurrence of each of the explored outcomes either at the first electrocardiographic assessment after birth or at follow up, which we defined as the last assessment according to the duration of each study (preferably at 1 year).

To quantify the incidence of the outcome explored, meta-analyses of proportions using random effect model were used to combine data. Funnel plots displaying the outcome rate from individual studies vs. their precision (1/standard error) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than 10; in this case, the power of the tests is too low to distinguish chance from real asymmetry (16–19). Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance (19).

Furthermore, we evaluated separately the risk of overall regression, overall progression, fetal and neonatal death, and postnatal pacemaker implantation in fetuses that were treated compared with those not treated prenatally with steroids. We included observational cohort studies in which: (i) comparisons reported zero events in one groups; (ii) comparisons reported zero events in both groups; (iii) exposed and unexposed group sizes were unbalanced. In such a case, many of the most commonly used meta-analytical methods – including those using risk difference (which can be used to handle total zero event studies) – may produce biased estimates when events are rare (20–22). When many studies are also substantially imbalanced, the best performing methods are the Mantel–Haenszel odds ratio without zero-cell continuity corrections, logistic regression and an exact method. Mantel–Haenszel odds ratios cannot be computed in studies reporting zero events in both groups, the exclusion of which may, however, cause a relevant loss of information and the potential inflation of the magnitude of the pooled exposure effect. Therefore, to keep all studies in the analyses, we performed all meta-analyses using individual data random-effect logistic regression, with single study as the cluster unit (20–22). The pooled datasets with individual data were reconstructed using published 2×2 tables. When one of the overall pooled arms showed no events, we used exact logistic regression (20–22). Finally, a Wald test was performed to explore the power of the test for each given sample size.

All analyses were performed using StatsDirect Ltd. STATSDIRECT statistical software (England: StatsDirect Ltd. 2013) and STATA version 13.1 (2013; StataCorp, College Station, TX, USA).

Results

Of the 426 articles identified, 46 were assessed with respect to their eligibility for inclusion (Table S1) and five were included in the systematic review (Table 1, Figure 1). All pregnancies included were positive for SSA/Ro and SSB/La antibodies. Maternal therapy other than fluorinated steroids was not described in detail in the majority of the included studies (Table 1). The route of steroid administration was enteral in all included studies.

No randomized controlled trial on steroid therapy in fetuses affected compared with those not affected by second-degree immune-mediated AVB was found in the medical databases explored, thus only non-randomized studies were included. These five studies included 71 fetuses with a prenatal diagnosis of second-degree immune-mediated AVB.

Table 1. General characteristics of the included studies.

Author	Year	Country	Study design	Time interval	Cases, *n*	Steroid type	Dose	Follow-up	Post natal assestment
Doti (8)	2016	Spain	Retrospective	1997–2014	5	DEX	NS	NS	12-lead ECG
Levesque (9)	2015	France	Retrospective	2000–2014	24	DEX	NS	12.7 years	EKG and/or echocardiography
Izmirly (10)	2011	USA	Retrospective	From 2010	21	DEX	NS	NS	NS
Eliasson (11)	2011	Europe/ Brazil	Retrospective	2000–2006	7	DEX, BET	DEX, 4 mg/day (2–12) BET 4 mg/day (3–5)	3.2 years	NS
Friedman (12)	2009	United States	Prospective	2000–2006	6	DEX	4 mg/day	2 years	EKG and echocardiography at birth and at 1 year

BET, betamethasone; DEX, dexamethasone; EKG, electrocardiography, GA, gestational age; NS, not stated.

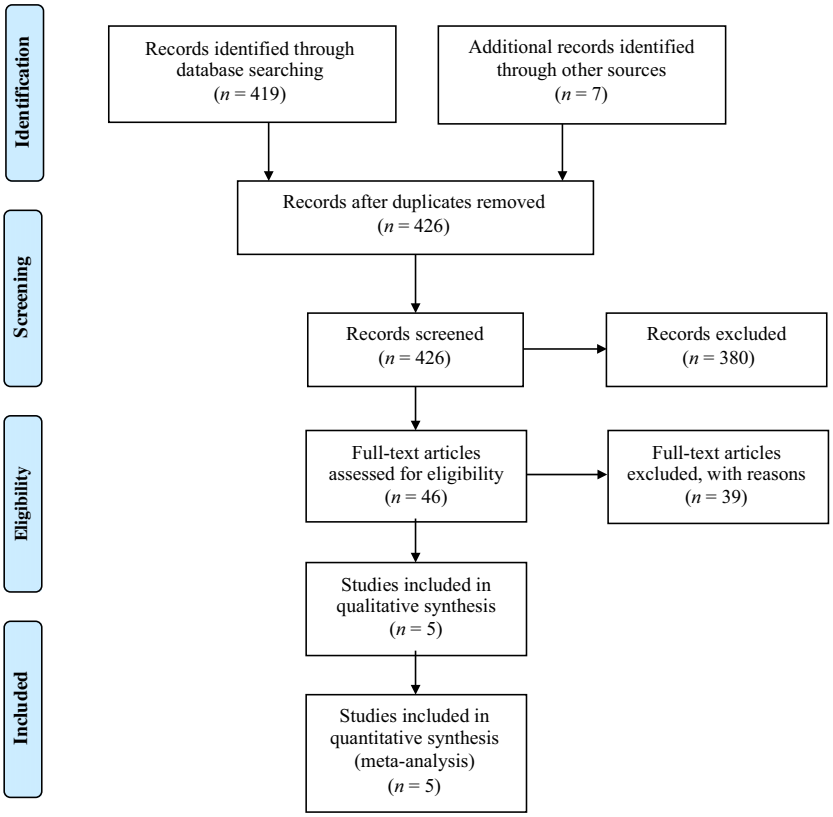

Figure 1. Systematic review flowchart. [Color figure can be viewed at wileyonlinelibrary.com].

The included studies differed in their inclusion criteria and not all the included cases had a clear prospective diagnosis of second-degree immune-mediated AVB during pregnancy, as some of the cases presented as bradycardia in women with unknown immune status. The study by Doti et al. (8) included cases followed up longitudinally during pregnancy, but the other studies did not specify whether the diagnosis of second-degree immune-mediated AVB was carried out prospectively or retrospectively (i.e. fetuses presenting with bradycardia in women with unknown immune status). Although the studies by Friedman et al. (12) and Izmirly et al. (10) included cases from the same population, they were both included in the present systematic review because they examined different outcome measures. Dexamethasone was the fluorinated steroid used in the vast majority of included

studies at a preferred dose of 4–8 mg/day, although the dose protocol and the gestational age at administration of the drug were not reported in all the studies. The interval between diagnosis and treatment was reported only in the study by Doti et al. (8), in which dexamethasone was started the same day as the diagnosis. Type and timing of postnatal assessment was reported in only a few of the included studies (Table 1). Unfortunately, heterogeneity and lack of information on time at follow up did not allow a comprehensive data synthesis to be performed regarding the occurrence of the explored outcome at follow up; thus we reported only the prevalence of each observed outcome at birth.

Quality assessment of the included studies performed using NOS for cohort studies is shown in Table 2. Most of the included studies showed an overall good rate with regard to the selection and comparability of the study groups. The main weaknesses of these studies were their retrospective designs, small sample size and the large heterogeneity in drug protocols, gestational ages at therapy and the duration of follow up.

Progression

Four studies (42 cases) explored the likelihood of overall progression of the block, defined as a progression towards either intermittent second/third or third-degree (complete) AVB (7,8,10,11). The progression rate in fetuses treated with steroids was 52% (95% CI 23–79), whereas the rate in fetuses not receiving steroid therapy was 73% (95% CI 39–94) at birth (Table 3, Figure 2). The large majority of fetuses progressed to persistent third-degree AVB, whereas only a small proportion of them progressed to intermittent forms of AVB.

Regression

The overall rate of regression at birth from prenatal to first-degree, intermittent first-/second-degree or sinus rhythm in fetuses treated with steroids was 25% [95% confidence interval (CI) 12–41] compared with 23% (95% CI 8–44) in those not treated (Table 3). Regression to first-degree AVB at birth occurred in 5% (95% CI 0-15) of cases in the steroid group and 18% (95% CI 2–52) in untreated fetuses. Stable (persistent) second-degree AVB at birth occurred in 11% (95% CI 2–27) of the treated group and in none of the newborns in the untreated group, mainly because of the higher proportion of untreated fetuses progressing to third-degree AVB (Table 2). Complete regression to sinus rhythm occurred at birth in 21% (95% CI 6–42) of fetuses receiving steroids vs. 9% (95% CI 0–41) of those untreated.

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcome
Doti (8)	2016	★	★★	★★
Levesque (9)	2015	★	★	★★
Izmirly (10)	2011	★★	★	★
Eliasson (11)	2011	★★	★	★★
Friedman (12)	2009	★★	★★	★★

Fetal and neonatal death, and permanent pacemaker implantation

Fetal death occurred in none of the cases in the treated group; no information on the occurrence or either fetal or neonatal death could be extrapolated from the untreated group (Table 3).

Five studies including 58 fetuses explored the rate of postnatal pacemaker insertion. A permanent pacemaker was implanted postnatally in 25% (95% CI 9–46) of cases treated with steroids and in 50% (95% CI 16–84) of those receiving no treatment; it was mainly related to a higher rate of progression to third-degree AVB observed in the untreated group.

Assessment of the risk of each of the outcomes in the present systematic review was problematic as only a small proportion of the included studies reported a direct comparison between fetuses treated and those not treated with steroids (Table S2). The very small number of included cases led to a lack of statistical power which precluded a comprehensive assessment of the strength of association between antenatal steroid therapy and each of the outcomes observed. In our review, antenatal steroid therapy was not associated with a statistically significant reduced risk of regression, and it was not possible to compute the odds ratios for the progression of AVB, survival and pacemaker insertion. In view of these limitations, the figures for the odds ratios reported in this systematic review should be interpreted with caution and may not reflect the actual strength of association between antenatal steroid therapy and the outcomes observed.

Discussion

The findings from this systematic review show that there is still limited evidence on the role of fluorinated steroids in affecting the natural history of second-degree immune-mediated AVB in utero. Progression to continuous or intermittent second/third-degree AVB occurred in 52% of fetuses treated with maternal steroids and in 73% of those

Table 3. Pooled proportions for the different outcomes observed in this systematic review.

Outcome	Fetuses treated				Fetuses not treated			
	Studies	Fetuses	I^2	Pooled % (95% CI)	Studies	Fetuses	I^2	Pooled % (95% CI)
Overall progression	4[7,8,10,11]	17/31	65.3	51.53 (23.2–79.3)	1[8]	8/11	–	72.73 (39.0–94.0)
Progression to second-/third-degree AVB	4[7,8,10,11]	1/31	0	6.07 (0.6–16.6)	1[8]	0/11	–	0 (0–28.5)
Progression to third-degree AVB	4[7,8,10,11]	16/31	57	49.36 (23.9–75.0)	1[8]	8/11	–	72.73 (39.0–94.0)
Overall regression	4[7–10]	9/38	15.7	25.09 (12.0–41.1)	2[8,9]	4/19	0	23.32 (7.9–43.8)
Regression to first-degree AVB	4[7–9,11]	1/31	0	4.80 (0.3–14.6)	1[8]	2/11	–	18.18 (2.3–51.8)
Partial regression (intermittent first-/second-degree AVB)	4[7–9,11]	0/31	0	0 (0–11.1)	1[8]	0/11	–	0 (0–28.5)
Regression to sinus rhythm	4[7–9,11]	6/31	42.2	20.55 (5.7–41.6)	1[8]	1/11	–	9.10 (0.2–41.3)
Stable rhythm	4[7–10]	4/38	40	11.00 (1.8–26.7)	2[8,9]	0/19	0	0 (0–13.5)
Fetal death	2[7,10,11]	0/16	0	0 (0–17.8)	–	–	–	–
Neonatal death	2[7,10,11]	0/16	0	0 (0–17.8)	–	–	–	–
Pacemaker insertion	2[7,9]	4/18	0	24.80 (8.5–46.1)	1	8/4	4	50.00 (15.7–84.3)

AVB, congenital atrioventricular block.

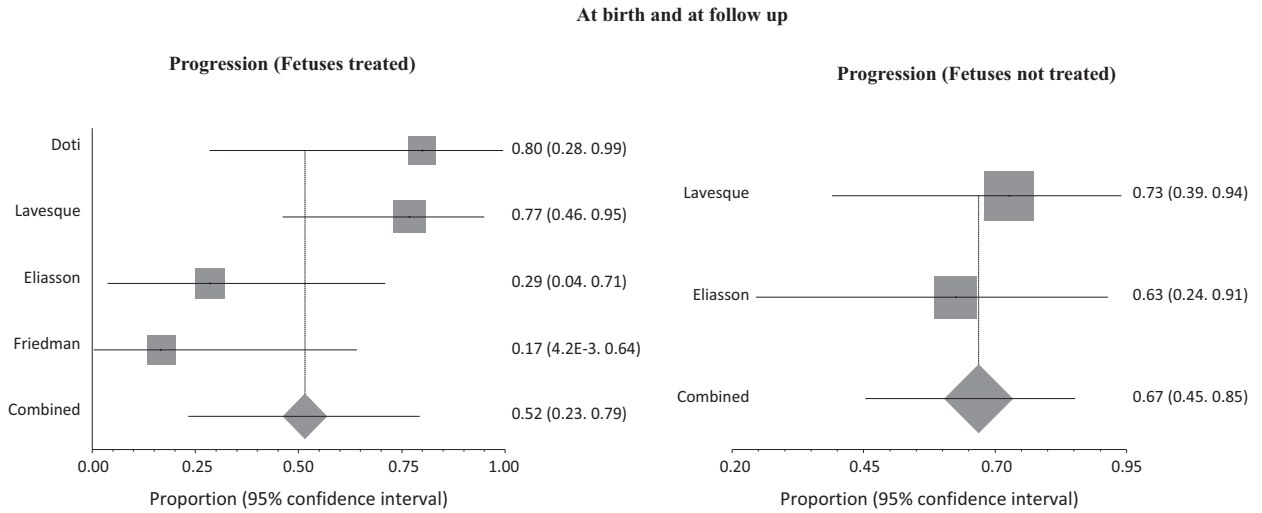

Figure 2. Pooled proportions for the rate of progression of second-degree congenital atrioventricular block at birth and at follow up in fetuses treated and in those not treated with steroids.

not treated. Persistent second-degree AVB was present at birth in 11% of treated fetuses and in none of the untreated. Postnatal pacing was required in 25% of treated vs. 50% of untreated fetuses. In view of the very small number of included cases and the subsequent lack of statistical power, it was not possible to quantify objectively the strength of association between fluorinated steroid therapy and any of the observed outcomes.

This is the first meta-analysis assessing the role of antenatal steroid administration in fetuses affected by second-degree immune-mediated AVB. The strengths of this study are its robust methodology for identifying all possible studies for inclusion, assessing data quality and synthesizing all suitable data. Another strength of this review is the inclusion of cases treated only with corticosteroids in order to reduce the bias associated with the presence of other co-treatments.

The very small number of included studies, their retrospective non-randomized design, different periods of follow up, lack of information on postnatal confirmation of the arrhythmia, dissimilarity in the populations (due to varied inclusion criteria) and a lack of fixed criteria for when to treat represented the major limitations of this meta-analysis. Assessment of the potential publication bias was also problematic both because of the outcome nature (rates with the left side limited to the value zero), which limits the reliability of funnel plots, and because of the scarce number of individual studies, which strongly limits the reliability of formal tests. Many of the included studies were non-controlled. The level of evidence for this

type of study is very low. Furthermore, we could not stratify the analysis according to gestational age at diagnosis and treatment, type of AV conduction block (Mobitz I vs. II), antibody levels, time at follow up and the drug protocol adopted, as this information was reported only in a small number of included cases. The interval between prenatal diagnosis and treatment is another relevant issue, as it is plausible that steroid therapy may be more effective if started immediately after diagnosis. In addition, the large majority of the included studies did not differentiate between immune and non-immune AVB; this is fundamental, because steroid therapy is likely to be beneficial only in immune-mediated AVB.

The occurrence of co-treatments is another relevant issue. Cases receiving multiple forms of treatment for fetal AVB were excluded from the present systematic review. However, it is entirely possible that some fetuses identified by us as having been treated only with steroids may have received additional co-treatments not specified in the original report, thus potentially biasing the results.

Despite these limitations, the present review represents the most comprehensive published estimate of the effect of maternal steroid therapy on second-degree immune-mediated AVB.

Prenatal diagnosis of fetal arrhythmias is challenging and requires an indirect assessment of the heart rhythm using M-mode or pulsed-wave Doppler ultrasound (1,2). Furthermore, differential diagnosis of fetal arrhythmias is not always feasible in utero and second-degree AVB may be sometimes difficult to differentiate from atrial bigeminism with blocked premature atrial contractions (PACs) and from both third-degree AVB and isorhythmic dissociation (1,2).

Antenatal steroid treatment of fetuses with a second-degree AVB has been suggested to improve myocardial performance and to prevent progression to third-degree AVB, which is associated with a high burden of perinatal mortality and morbidity, permanent pacemaker implantation and late onset cardiomyopathy. The rationale for steroid administration in this setting relates to its potential anti-inflammatory and immunosuppressive effects and the possibility that it may inhibit the development of conduction system disease and even reverse cardiac failure.

In the present systematic review, estimation of the pooled odds ratios for the different outcomes explored was limited by the small number of included studies, preventing us from reaching an adequate statistical power. Despite this, it is the collective authors' opinion that the use of corticosteroids once second-degree AVB is diagnosed should not be discouraged until more robust evidence is available.

Large prospective and adequately powered randomized trials are needed to elucidate the role of maternal fluorinated steroid therapy in modifying the natural history of second-degree immune-mediated AVB in utero.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Excluded studies and reason for the exclusion.

Table S2. Pooled odd ratios (OR) showing the likelihood for regression and persistent second-degree AVB in fetuses treated vs. fetuses not treated with corticosteroids at birth.