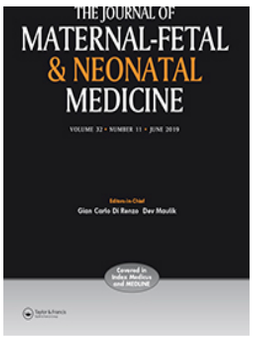

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REVIEW ARTICLE

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

Andrea Ciardulli[a], Francesco D'Antonio[b], Elena Rita Magro-Malosso[c], Gabriele Saccone[d], Lamberto Manzoli[e], Mackenzy Radolec[f] and Vincenzo Berghella[f]

[a]Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Rome, Italy; [b]Department of Clinical Medicine, Faculty of Health Sciences, UiT – the Arctic University of Norway and Department of Obstetrics and Gynecology, University Hospital of Northern Norway, Tromsø, Norway; [c]Department of Health Science, Division of Pediatrics, Obstetrics and Gynecology Careggi Hospital University of Florence, Florence, Italy; [d]Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples "Federico II", Naples, Italy; [e]Department of Medicine Sciences, University of Ferrara, Ferrara, Italy; [f]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA

ABSTRACT

Introduction: To explore the effect of maternal fluorinated steroid therapy on fetuses affected by immune-mediated complete atrio-ventricular block (CAVB) *in utero*.

Material and methods: Pubmed, Embase, Cinahl, and ClinicalTrials.gov databases were searched. Only studies reporting the outcome of fetuses with immune CAVB diagnosed on prenatal ultrasound without any cardiac malformations and treated with fluorinated steroids compared to those not treated were included. The primary outcome observed was the regression of CAVB; secondary outcomes were need for pacemaker insertion, overall mortality, defined as the occurrence of either intrauterine (IUD) or neonatal (NND) death, IUD, NND, termination of pregnancy (TOP). Furthermore, we assessed the occurrence of all these outcomes in hydropic fetuses compared to those without hydrops at diagnosis. Meta-analyses of proportions using random effect model and meta-analyses using individual data random-effect logistic regression were used to combine data.

Results: Eight studies (162 fetuses) were included. The rate of regression was 3.0% (95%CI 0.2–9.1) in fetuses treated and 4.3% (95%CI 0.4–11.8) in those not treated, with no difference between the two groups (odds ratio (OR): 0.9, 95%CI 0.1–15.1). Pacemaker at birth was required in 71.5% (95%CI 56.0–84.7) of fetuses-treated and 57.8% (95%CI 40.3–74.3) of those not treated (OR: 9, 95%CI 0.4–3.4). There was no difference in the overall mortality rate (OR: 0.5, 95%CI 0.9–2.7) between the two groups; in hydropic fetuses, mortality occurred in 76.2% (95%CI 48.0–95.5) of the treated and in 23.8% (95%CI 1.2–62.3) of the untreated group, while in those without hydrops the corresponding figures were 8.9% (95%CI 2.0–20.3) and 12% (95%CI 8.7–42.2), respectively. Improvement or resolution of hydrops during pregnancy occurred in 76.2% (95%CI 48.0–95.5) of cases treated and in 23.3% (95%CI 1.2–62.3) of those nontreated with fluorinated steroids.

Conclusions: The findings from this systematic review do not suggest a potential positive contribution of antenatal steroid therapy in improving the outcome of fetuses with immune CAVB.

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KEYWORDS
Fetal heart; fetal echocardiography; steroids; ultrasound; heart block; autoimmune

Introduction

Atrioventricular block (AVB) encompasses a wide spectrum of conditions characterized by a delay or interruption in the transmission of an impulse from the atria to the ventricles due to an anatomical or functional impairment in the conduction system [1]. AVB can be a situation where there is no AV conduction at all, and the atria and ventricles beat independently [1].

Complete AVB (CAVB) is the most severe type of AVB and is associated with high rate of perinatal mortality and morbidity. Slow ventricular rhythm, hydrops, and early gestational age at birth represent the main determinants of perinatal outcome in fetuses affected by CAVB [1–4].

CAVB is usually irreversible; however, some have suggested that administration of fluorinated steroids may improve the outcome of these fetuses [5].

CONTACT Vincenzo Berghella vincenzo.berghella@jefferson.edu Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Thomas Jefferson University, 833 Chestnut, Philadelphia, PA, USA

Supplemental data for this article can be accessed here.

Furthermore, the actual occurrence of hydrops, mortality, and pacing in fetuses affected by CAVB block has not been fully elucidated yet. The aim of this systematic review was to ascertain the role of maternal steroids therapy in affecting the outcome of fetuses diagnosed with immune CAVB.

Materials and methods

This review was performed according to a protocol designed *a priori* and recommended for systematic reviews [6]. Medline, Embase, and ClinicalTrials.gov databases were searched electronically on 24 June 2016 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "complete" or "third degree" 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) [7].

Only fetuses with immune-mediated CAVB block and morphologically normal heart diagnosed on prenatal ultrasound and treated with fluorinated steroids compared to those not treated were included. Therapy with steroids included any type of fluorinated corticosteroids used.

Only full text articles were considered eligible for the inclusion; case reports and conference abstracts were excluded to avoid publication bias. Furthermore, only studies published in the last two decades (1997–2017) were considered suitable for the inclusion, as we considered that advances in prenatal imaging techniques, and improvements in the diagnosis and management of CAVB make these less relevant. Cases with nonimmune AVB, those for which maternal antibody status could not be ascertained and those associated with major CHD were excluded. Finally, studies not providing a clear classification of the anomaly were not considered suitable for the inclusion in the current review.

Two authors (AC, FD) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus with a third reviewer (VB); full text copies of those articles were obtained and the same 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. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors 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 nonexposed 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 interest includes the evaluation of the type of the assessment of the outcome of interest, 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 [8].

The primary outcome observed was the regression of the CAVB to either first- or second-degree AVB in fetuses-treated compared to those not treated with fluorinated steroids during pregnancy.

The secondary outcomes were:

- Need for pacemaker
- Overall mortality, defined as the occurrence of either intrauterine (IUD) or neonatal (NND) death.
- IUD
- NND
- Termination of pregnancy (TOP)

We also aimed to stratify the analysis assessing all the explored outcomes according to the fetal status at diagnosis (hydrops versus no hydrops) and we evaluated whether steroid therapy was associated with an improvement of hydrops. Furthermore, we planned to ascertain the occurrence of all the explored outcomes at either the first electrocardiographic (ECG) assessment after the birth and at follow-up, defined as the last assessment according to the duration of each study [1].

For the quantification of 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 versus 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 [9–12]. 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 [12].

Furthermore, we evaluated separately the risk of pacemaker insertion, regression, mortality in fetuses-treated compared to those not treated with steroids prenatally. We included observational cohort studies in which: (a) comparisons reported zero events in one groups; (b) comparisons reported zero events in both groups; and (c) exposed and unexposed group sizes were unbalanced. In such a case, many of the most commonly used meta-analytical methods – including those using risk differences (which could be used to handle total zero event studies) – can produce biased estimates when events are rare [10–12]. 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 the 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 into the analyses, we performed all meta-analyses using individual data random-effect logistic regression, with single study as the cluster unit [10]. 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 [10]. Finally, the Wald test was performed in order 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 (Stata Corp, College Station, TX, 2013).

Results

Three hundred and seventy articles were identified, 20 were assessed with respect to their eligibility for inclusion (Supplementary Table 1) and 8 studies included in the systematic review (Table 1, Figure 1). All pregnancies included were positive for SSA/Ro and/or

Table 1. General characteristics of the included studies.

Author	Year	Country	Study design	GA at diagnosis (w)	GA at treatment (w)	Steroid type	Dose	Postnatal assessment	Cotreatments	Cases (*n*)
Doti	2016	Spain	Retrospective	24.4 (18–28)	Same day of diagnosis	DEX	NS	12 h lead ECG	None	10
Tunks	2013	United States	Retrospective	19–22	NS	DEX	4 mg/d	NS	None	4
Fesslova	2009	Italy	Retrospective	25 (19–32)	Within 2 weeks	DEX	4 mg/d	EKG (at short time initially, then 2–3 times a year, according to the individual situation)	None	25
Friedman	2009	United States	Prospective	NS	NS	DEX	4 mg/d	EKG (at birth and after 1 year of age)	Terbutaline (one woman)	31
Berg	2005	USA/Germany	Retrospective	25.6 ± 4.5	Within 1 week	DEX	4 mg/d	NS	None	16
Jeggi	2004	USA/Canada	Prospective	25 ± 4.3	Same day of diagnosis	DEX	4–8 mg/d	NS	None	23
Saleeb	1999	United States	Retrospective	NS	A mean of 1.6 weeks elapsed from the diagnosis	DEX, BET	DEX, 3/4–9 mg/d for 3–20 wks BET 12–24 mg/w for >6 wks	NS	Prednisone (three women), terbutaline, plasmapheresis	39
Shinohara	1999	Japan	Retrospective	in treated group at 20 or 21 weeks	After 16 weeks	BET	NS	NS	NS	14

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

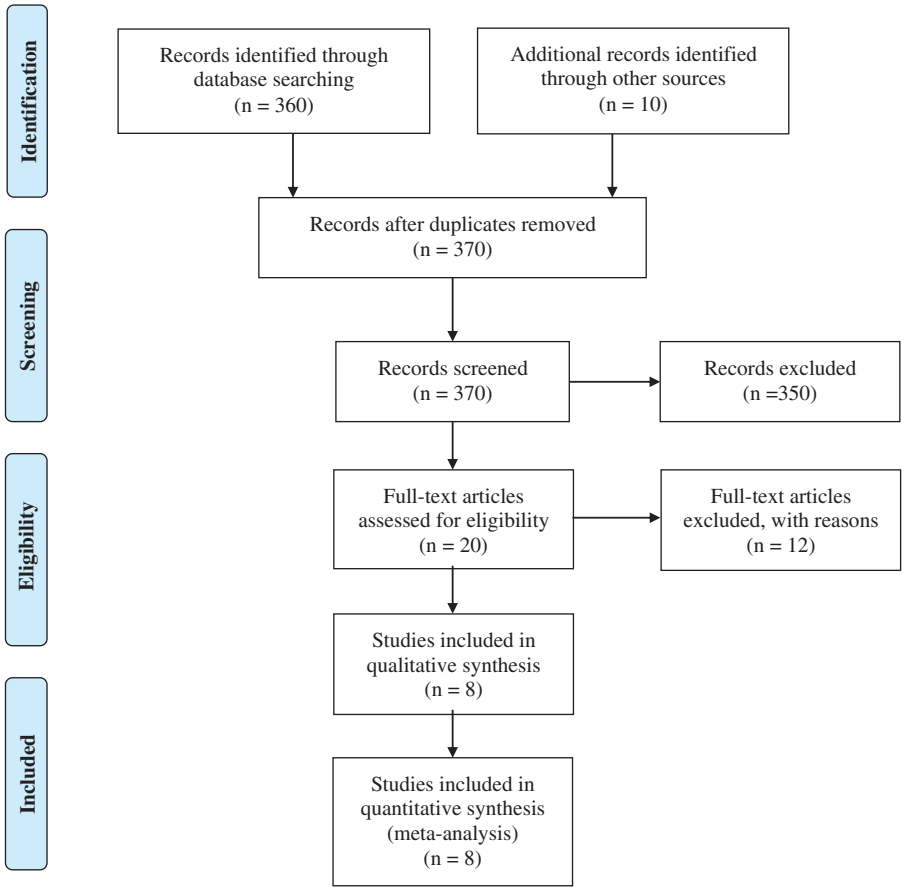

Figure 1. Systematic review flowchart.

SSB/La antibodies; maternal therapy other than fluorinated steroids was not described in detail in the majority of the included studies.

No randomized controlled trial on steroid therapy versus no such therapy or placebo in fetuses affected by CAVB was found in the medical databases explored, thus only nonrandomized studies were included in the present systematic review. These 8 studies included 162 fetuses with a prenatal diagnosis of immune CAVB (85 treated and 67 not treated).

Dexamethasone was the fluorinated steroids used in the vast majority of 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 included in the review. Type and timing of postnatal assessment was reported only by few of the included studies (Table 1); finally, the type of pacing (permanent versus temporary) adopted in each study was not specified.

Quality assessment of the included studies performed using Newcastle–Ottawa scale (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 design, small sample size, and a large heterogeneity in drug protocol, gestational age at therapy, and time at follow-up.

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 and a maximum of two stars can be given for comparability.

Author	Year	Selection	Comparability	Outcome
Doti	2016	★	★★	★★
Tunks	2013	★	★	★★
Fesslova	2009	★★	★	★
Friedman	2009	★★	★	★★
Berg	2005	★★	★	★★
Jaeggy	2004	★★	★	★★
Saleeb	1999	★★	★	★
Shinohara	1999	★★	★	★

Assessment of the risk for each of the outcomes explored in the present systematic review was problematic. Only a small proportion of the included studies reported a direct comparison between fetuses-treated versus those not treated with steroids, thus not representing the entire population of fetuses included in this systematic review (Table 3, Table 4).

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

	Fetuses treated				Fetuses not treated			
Outcome	Studies	Fetuses	I^2	Pooled % (95%CI)	Studies	Fetuses	I^2	Pooled % (95%CI)
Overall regression	6	1/49	0	3.04 (0.2–9.1)	5	1/45	0	4.31 (0.4–11.8)
Need for pacemaker	6	29/40	8.8	71.49 (56.0–84.7)	5	22/37	18.1	57.77 (40.3–74.3)
Mortality (overall)	7	7/64	0	12.66 (5.9–21.6)	6	8/60	52.5	11.97 (2.9–25.9)
IUD	7	6/64	0	11.51 (5.1–20.1)	6	6/60	32	10.07 (2.9–20.8)
NND	6	1/61	0	3.71 (0.5–9.7)	5	2/49	0	5.29 (0.9–13.0)
TOP	7	1/64	0	2.71 (0.2–7.9)	6	10/60	74.7	14.95 (2.2–36.1)

CI: confidence interval; IUD: intrauterine death; NND: neonatal death; TOP: termination of pregnancy.

Table 4. Pooled odd ratios for the need for pacemaker insertion, regression of the block and mortality in fetuses treated compared to those not treated with fluorinated steroids.

Outcome	Studies	Fetuses	I^2 (%)	Pooled OR (95%CI)
Overall regression	4	1/49 versus 1/45	–	0.92 (0.1–15.1)
Need for pacemaker	5	26/36 versus 22/37	0	1.09 (0.4–3.4)
Overall mortality	6	7/64 versus 8/60	13.4	0.49 (0.9–2.7)

CI: confidence interval; OR: odds ratio.

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 the present systematic review. Therefore, we opted to report the occurrence of outcomes explored in this systematic review as pooled proportions and then as OR (Tables 3 and 4).

Synthesis of results

Regression

Six studies including 49 cases treated and 45 nontreated with fluorinated steroids explored the likelihood of regression to either first or second degree of CAVB. The rate of regression was 3.0% (95%CI 0.2–9.1) in fetuses-treated and 4.3% (95%CI 0.4–11.8) in those not treated, with no significant difference between the two groups (OR: 0.9, 95%CI 0.1–15.1) (Table 4; Figure 2).

Pacing

Six studies including 40 fetuses-treated and 37 not treated with fluorinated steroids reported the need for pacemaker insertion at birth for immune CAVB. In the group of fetuses-treated with fluorinated steroids therapy the need for pacemaker was 71.5% (95%CI 56.0–84.7) and 57.8% (95%CI 40.3–74.3) in those not treated, with no statistical difference between the two groups (OR: 1.09, 95%CI 0.4–3.4) (Table 3 and 4; Figure 3).

Mortality

The occurrence of either IUD or NND (overall mortality) was 12.7% (95%CI 5.9–21.6) in fetuses-treated and 12.0% (95%CI 2.9–25.9) in those nontreated with fluorinated steroids during pregnancy, with no statistical difference between the two groups (OR: 0.5, 95%CI 0.9–2.7) (Table 3 and Table 4).

IUD occurred in 11.5% (95%CI 5.1–20.1) of fetuses-treated and in 10.1% (95%CI 2.9–20.8) of those nontreated; while the corresponding figures for NND were 3.7% (0.5–9.7) and 5.3% (0.9–13.0), respectively.

Finally, termination of pregnancy was requested in 2.7% (95%CI 0.2–7.9) of women treated with fluorinated steroid and 15.0% (95%CI 2.2–36.4) of women in the untreated group.

Fetal status at presentation (hydropic versus nonhydropic fetuses)

Subanalysis according to fetal status at presentation was affected by the very small number of included studies (Supplementary Table 2). In fetuses presenting with hydrops, pacemaker at birth was needed in all cases (treated and nontreated) included in the present systematic review [100% (95%CI 43.9–100)], while in those without hydrops the corresponding figures for treated and nontreated cases were 63.5% (95%CI 45.0–79.8) and 66.2% (95%CI 47.5–82.4), respectively. There was no case of regression of the AVB in hydropic fetuses while in nonhydropic fetuses the regression occurred in 6.4% (95%CI 0–23.8) in the treated group and 10.6% (95%CI 0.6–30.4).

In fetuses with hydrops, mortality occurred in 76.2% (95%CI 48.0–95.5) in the treated and 23.8% (95%CI 1.2–62.3) in the untreated group, while the corresponding figures in those without hydrops were 8.9% (95%CI 2.0–+20.3) and 12% (95%CI 8.7–42.2), respectively.

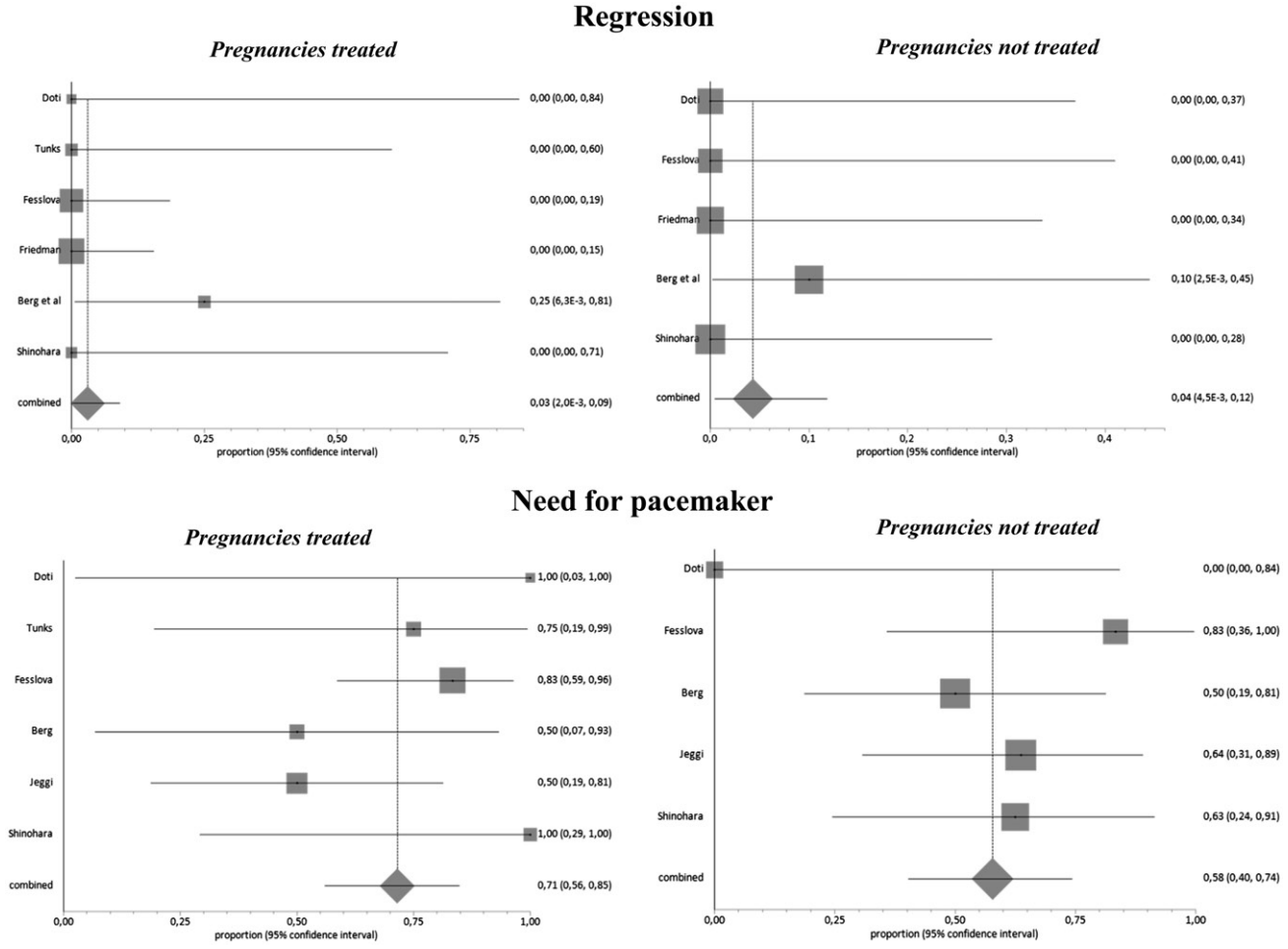

Figure 2. Pooled proportions showing the rate of regression and need for pacemaker in fetuses-treated and in those not treated with steroid.

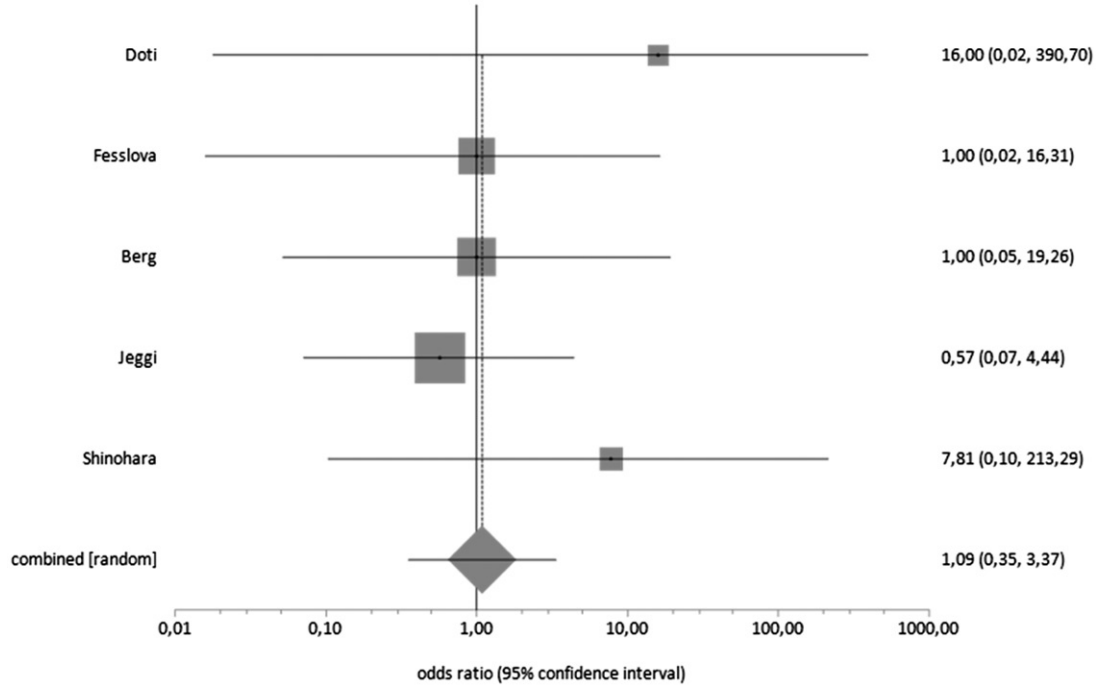

Figure 3. Odds ratio for the need of pacemaker in fetuses-treated compared to those not treated with steroids.

Improvement or resolution of hydrops during pregnancy occurred in 76.2% (95%CI 48.0–95.5) of cases treated and in 23.3% (95%CI 1.2–62.3) of those nontreated with fluorinated steroids (Supplementary Table 2).

Discussion

The findings from this systematic review show that in fetuses affected by immune CAVB the chance of regression is negligible and it is not affected by steroid therapy. The large majority of fetuses with immune CAVB require pacemaker insertion at birth, with no difference between cases treated and nontreated with fluorinated steroids. Mortality occurs in about 12% of fetuses affected by CAVB and it is not influenced by steroids. Finally, fetuses presenting with hydrops are at generally higher risk of adverse outcome compared to those not affected.

This is the first meta-analysis assessing the role of antenatal fluorinated steroids administration in fetuses affected by immune-mediated CAVB. The strengths of this study are its robust methodology for identifying all possible studies for inclusion, assessing data quality, and synthesizing all suitable data.

The small number of cases in the included studies, their retrospective nonrandomized design, different periods of follow-up, lack of information of postnatal confirmation of the arrhythmia, dissimilarity of the populations (due to various inclusion criteria), and the lack of fixed criteria for when to treat represent the major limitations of this meta-analysis. The 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 noncontrolled. The level of evidence for these types of studies is very low.

The very small number of included cases and the lack of statistical power for all the outcomes explored in the present systematic review did not allow in estimating the actual strength of association between antenatal steroid treatment and each of the observed outcomes. Small sample size of previously published studies, lack of stratification according to fetal status at diagnosis, degree of fetal bradycardia, presence of additional cotreatments either before or after birth, differences in drug protocols, gestational age at administration, interval between diagnosis and treatment and length of treatment, and follow-up preclude to draw any strong objective evidence to guide management.

A major limitation of the present systematic review was the lack of stratification according to the degree of fetal bradycardia. Sustained fetal bradycardia is associated with a high risk of hydrops, thus limiting the potential effect of steroids treatment. Lack of stratification of the analysis according to the interval between diagnosis and treatment is another major limitation of the present systematic review. Immune AVB is characterized by a progressive impairment of cardiac function and it is entirely possible that cases in which treatment is started immediately after diagnosis may experience a better outcome compared to those in which treatment is delayed. In fact, when fetal immune heart block is detected at earlier stages, i.e. second-degree AVB, maternal steroid therapy has been associated with some benefit in regression or resolution of the AVB, and lower need for pacemaker after birth [13]. Furthermore, although we have stratified the analysis according to the presence of hydrops, the very small number of included cases and the even smaller number of events did not allow us to perform any meaningful data synthesis to assess the risk of the different outcomes in these fetuses compared with those without hydrops. The presence of other cotreatments was another relevant issue. Often studies dealing with CAVB include fetuses receiving multiple treatments, such as sympathomimetics, azathioprine, hydroxychloroquine, and immunoglobulin. Although cases receiving only multiple treatments were excluded, it might be entirely possible that cases including other treatments might have not been mentioned in some of the included studies, thus potentially biasing the figures reported. In view of these limitations, the figures reported in this systematic review should be interpreted with caution and might not reflect the actual strength of association between antenatal steroid therapy and each of the outcomes observed. Finally, this review was limited by the study design. Meta-analyses of observational studies are subject of bias [14–17].

Despite this, the present review represents the best published estimate of the effect of maternal steroid therapy for immune CAVB, which can be used to guide clinical counseling and management. This is important as counseling for parents based on small studies that are subject to publication bias may be inadequate.

Advances in prenatal echocardiography have led to an increase in the diagnosis of AVB. CAVB is the most severe type of AVB and is associated with high rate of perinatal mortality and morbidity. Prenatal diagnosis

of CAVB *in utero* relies on the precise assessment of the heart rhythm and the relationship between atrial and ventricular depolarization and it is usually accomplished by M-Mode or pulsed wave Doppler echocardiography. CAVB is characterized by a slow ventricular rhythm (usually <60 bpm) in association with AV dissociation and the atria and ventricles beat independently [1].

Risk factors for adverse outcome in fetuses affected by CAVB are fetal hydrops, endocardial fibroelastosis, premature delivery, and ventricular rate <55 bpm.

In the present systematic review, we found that about 30% of fetuses with a prenatal diagnosis of CAVB present with hydrops. Fetuses affected by hydrops are known to be at higher risk of perinatal mortality and morbidity compared to those not affected; furthermore, the presence of hydrops can affect transplacental passage of steroids, thus limiting their bioavailability. In the present systematic review, there was no difference in most of the observed outcomes between hydropic fetuses treated and not treated with fluorinated steroids. However, mortality occurred in 16.7% (95%CI 3.0–56.4) of cases presenting with and in 6.9% (95%CI 0.4–20.2) of those without hydrops, irrespective of steroids administration. These findings concur with those from postnatal studies, which report high rates of mortality in hydropic fetuses. Unfortunately, in view of the very small number of included cases, we could not elucidate whether steroid treatment improved survival rates in those cases presenting with hydrops.

In the present systematic review, we found that improvement or resolution of hydrops during pregnancy occurred in 76.2% (95% CI 48.0–95.5) of cases treated and in 23.8% (95%CI 1.2–62.2) of those non-treated with fluorinated steroids (Supplementary Table 2). These figures should be interpreted with caution; the pathophysiology of hydrops in fetuses affected by immune CAVB is related to a maladaptation of fetal heart to sustained bradycardia which leads to ventricular dilatation, hypertrophy, and subsequent reduction of the shortening fraction. Fluorinated steroids do not have any relevant direct effect on ventricular rate; therefore, it might be entirely possible that the high rate of resolution of the hydrops was related to the smaller number of cases of fetuses not treated included in this review or to the presence of additional treatments. Beta-mimetics have been anecdotally reported to increase ventricular rate and improve the outcome of fetuses affected by CAVB [1], although the presence of other cotreatments in these cases makes it difficult to ascertain their actual role in the management of this condition.

In conclusion, the findings from this systematic review do not suggest a potential positive contribution of antenatal steroid therapy in improving the outcome of fetuses with immune CAVB. However, in view of all mentioned limitations, it was not possible to completely rule out any potential beneficial effect of steroids therapy on the outcome of fetuses affected by immune CAVB and further evidence is needed before discouraging steroid administration in this anomaly. Prenatal counseling of fetuses affected by immune CAVB should stress the high risk of occurrence of hydrops and mortality in these fetuses, underling the very low chance of regression and the need of pacemaker insertion immediately after birth in the majority of affected cases.

Large prospective and adequately powered randomized trials, sharing a common protocol of antenatal management, are urgently needed in order to elucidate the role of maternal fluorinated steroid therapy in modifying the natural history of CAVB *in utero*.

What's already known about this topic? Complete AVB (CAVB) is irreversible, however, some have suggested that administration of fluorinated steroids may improve the outcome of these fetuses.

What does this study add? The findings from this systematic review do not suggest a potential positive contribution of antenatal steroid therapy in improving the outcome of fetuses with immune CAVB.

Disclosure statement

The authors declare no conflict of interest.

ORCID

Francesco D'Antonio https://orcid.org/0000-0002-5178-3354
Gabriele Saccone http://orcid.org/0000-0003-0078-2113
Vincenzo Berghella http://orcid.org/0000-0003-2854-0239

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