Fluorinated steroids are not superior to any treatment to ameliorate the outcome of autoimmune mediated congenital heart block: a systematic review of the literature and meta-analysis

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Abstract

Objective

Fluorinated steroids are largely the therapeutic approach of autoimmune mediated congenital heart block (CHB). We performed a meta-analysis to assess the efficacy of fluorinated steroids for the treatment of CHB.

Methods

Studies evaluating the efficacy of fluorinated steroids versus no treatment in CHB patients were identified in electronic databases. Random-effects model was used to pool odds ratio (OR) (with 95% CI) of live births as the primary outcome. ORs of CHB progression, pacemaker implantation and extranodal disease were the secondary outcome. Subgroup analysis according to CHB grade and study type was performed.

Results

Data from nine studies involving 747 patients were analysed. The overall live birth rates were 86.8% and 86.7%, respectively, in the fluorinated steroids exposed foetuses and in the non-exposed ones. Fluorinated steroids did not ameliorate overall survival in CHB (OR 1.02; 95% CI: 0.65–1.61) with any significant statistical heterogeneity between studies (I^2 0%, p=0.45). No significant differences for the progression of CHB, the pacing and the presence of extranodal disease were observed. Subgroup analysis revealed a significant protective role of fluorinated steroids for survival in 3rd degree CHB and for pacing in monocentric studies, OR 4.07; 95% CI: 1.10–15.08 and OR 0.15; 95% CI: 0.02–0.99, respectively.

Conclusion

This meta-analysis shows that fluorinated steroids are not superior to any treatment in patients with CHB in terms of live birth, prevention of progression of incomplete CHB, pacemaker implantation and extranodal disease. Thus, considering their side effects, their use in CHB patients should be discouraged.

Key words

congenital heart block, fluorinated steroids, anti-SSA antibodies, cardiomyopathy

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Introduction

Autoimmune mediated congenital heart block (CHB) is a passively acquired autoimmune disease caused by the transplacental transfer of maternal anti-Ro/SSA and anti-La/SSB antibodies into the foetal circulation (1-3). CHB is typically characterised by the presence of immune complex deposits, inflammation, calcification and fibrosis at the atrio-ventricular node in a structurally normal heart (1). Likewise, antibodies may affect the myocardium and trigger endocardial fibroelastosis or dilated cardiomyopathy (4, 5). CHB can progress gradually from a first-degree to a second-degree atrio-ventricular block and then to the irreversible third-degree atrio-ventricular block within a week, (6, 7). III degree CHB is a potentially lethal condition associated with a high rate of morbidity and an overall mortality rate of 16% to 23% including in utero, neonatal and child deaths (8-10).

There are no standard guidelines for the management of CHB. Various treatments, some anecdotal, have been reported such as fluorinated steroids, therapeutic plasmapheresis, intravenous immunoglobulin, and beta-adrenergic mimetics (11). Fluorinated steroids, dexamethasone and betamethasone are the more largely therapeutic approach used, based on the rationale that they suppress the inflammatory processes in the atrio-ventricular node and the myocardium (11). However, available evidence is limited and discordant. By evaluating the effects of fluorinated steroids on CHB in the US registry, Saleeb *et al*. showed their efficacy in reversing second-degree CHB and in the treatment of pleural effusions, ascites, and hydrops fetalis (12). While, there were no significant differences on requirement for pacemaker implantation (12). Furthermore, in a monocentre study Jaeggi *et al*. strongly suggested the efficacy of prenatal use of dexamethasone alone or in association with β stimulations (in case of foetal bradycardia <55 bpm) on ameliorating survival rate in 21 cases of foetal complete CHB (13). The PRIDE study, moreover, showed a potential benefit of dexamethasone in reversing I or II degree CHB, in rare cases (14).

On the other hand, recent data from large series describe no significant effect on foetal survival or cardiac function of this treatment (8-10, 15). Thus, lack of evidence together with an increased risk of maternal and foetal toxicity associated with steroids use (16, 17) lead to a therapeutic dilemma regarding whether to use fluorinated steroids to treat CHB (18).

Therefore, we conducted a systematic review of the literature and meta-analysis to assess the efficacy of fluorinated steroids for the treatment of CHB.

Methods

We performed a review of the literature concerning clinical studies about fluorinated steroids therapy in CHB. The meta-analysis was performed in accordance with PRISMA guidelines; PRISMA checklist is provided in the online Supplementary Table I (19).

Literature search

Two main investigators (HA and ME) performed independently a detailed search in scientific databases Pubmed, Scopus, Cochrane Library and EMBASE for original articles. The period examined was February 1990-February 2018. The search strategy combined free text search, exploded medical subject headings (MESH/EMTREE) terms and all synonyms of the following MESH terms to identify relevant published articles: "fluorinated steroids", "fluorinated steroids therapy" and "steroids" in combination with "congenital heart block", "autoimmune congenital heart block", "congenital atrio ventricular block", "neonatal lupus syndrome, "cardiomyopathy" and "anti-SSA/Ro antibodies".

The computerised search was completed with a manual search of pertinent reference lists from the relevant articles retrieved. Articles written in languages other than English were excluded.

Study selection

Selection criteria were determined before data collection. Studies were considered eligible for meta-analysis if they met the following criteria: (i) 1st, 2nd and 3rd degree CHB diagnosed in the foetus/baby of a mother with anti-

SSA and/or anti-SSB antibodies, with no anatomical abnormalities of the foetal heart, and which was diagnosed in utero, at birth or within the neonatal period (0–27 days after birth) (20); (ii) either observational and interventional studies reporting on treatment of CHB with fluorinated steroids within the first week of detection. Reviews, editorials, case reports, case series, articles on prevention of CHB and/or other treatments such as plasma exchange, intravenous immunoglobulins and hydroxychloroquine, articles with poorly or non documented follow-up, were excluded. All discrepancies were resolved by consensus between the two main investigators.

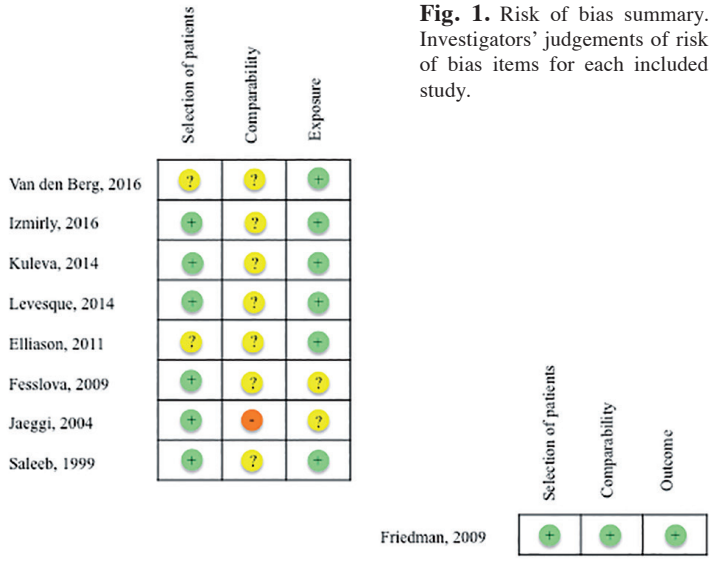

Fig. 1. Risk of bias summary. Investigators' judgements of risk of bias items for each included study.

Data extraction

According to PRISMA guidelines (19), after deleting duplicates and articles written in a language other than English, we excluded publications that were non-eligible based on title and abstract. The full text articles were reviewed and, based on inclusion/exclusion criteria; they were either excluded or included in analysis. The full text of the selected studies was retrieved and data were extracted in ad hoc data extraction form. In case of incomplete or unextractable data we contacted the authors.

The two main investigators simultaneously and independently extracted data. For each selected study, the information recorded included: study design, patients characteristics, the number of patients with 1st, 2nd or 3rd degree CHB, of live births, of progression of CHB, of extranodal diseases define as left ventricular dysfunction, dilated cardiomyopathy, endocardial fibroelastosis and foetal hydrops, and pacing among patients treated with steroids *versus* those not treated. For each study, a 2x2 table was constructed based on treatment with fluorinated steroids and no treatment with the occurrence of live birth, of progression of CHB, pacing and extranodal diseases.

Quality assessment

The Newcastle-Ottawa scale (21) for case-controls studies was used to evaluate risk of bias, for the retrospective studies evaluating the following items: i) selection of patients: low if patients were very representative of autoimmune CHB patients and the case definition and control description was adequate; ii) comparability: low if there was a comparability of cases and controls for the study outcome; for both retrospective and prospective studies; iii) exposure: low if there was an ascertainment of exposure for cases and controls. While the Newcastle-Ottawa scale (21) for cohort studies was used to evaluate risk of bias for the one prospective study by examined the following items: i) selection of patients: low if the exposure cohort was very representative of autoimmune CHB patients, and the non exposure cohort was selected from the same community of exposure one and there was an ascertainment of exposure for cases and controls and demonstration that the outcome of interest was not present at the start of the study; ii) comparability: low if there was a comparability of the cohort studies; iii) exposure: low if there was an independent blind assessment and there was and adequate long/complete follow-up for outcomes to occur. The risks of bias respectively for retrospective and prospective studies are reported in Figure 1.

Statistical analysis

Meta-analysis was performed after assessment of the homogeneity of designs, populations and outcomes. In the main analysis we considered the efficacy of fluorinated steroids to determine live birth in CHB. We used the odds ratio (OR) as the measure of association in this meta-analysis and we obtain pooled-risk estimates by using a random-effects model, according to the method of DerSimonian and Laird. Publication bias was examined using a funnel plot and Egger's regression test (22). Heterogeneity (Cochran's χ^2 and I^2 tests) was considered statistically significant at $p<0.10$ and $I^2>50\%$. Separate *a priori* subgroup analysis were planned for the progression of CHB from 1st/2nd degree to 3rd degree *versus* regression to a lower degree or stability of 1st/2nd degree CHB, for pacing *versus* non pacing, for the presence of extranodal disease *versus* no extranodal disease, for monocentric *versus* multicentric studies and for 2nd/3rd degree CHB *versus* 3rd degree CHB. The meta-analysis was performed with the use of the software Review Manager (RevMan) v. 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014

Results

Selection and characteristics of the studies

The reasons for the exclusion of several articles are shown in Figure 2. Nine articles were included in the meta-analysis (8-10, 12-15, 42, 43). The characteristics of these studies are reported in Table I. Eight retrospective (8-10, 12, 13, 15, 42, 43) and one prospective (14) cohort studies through a

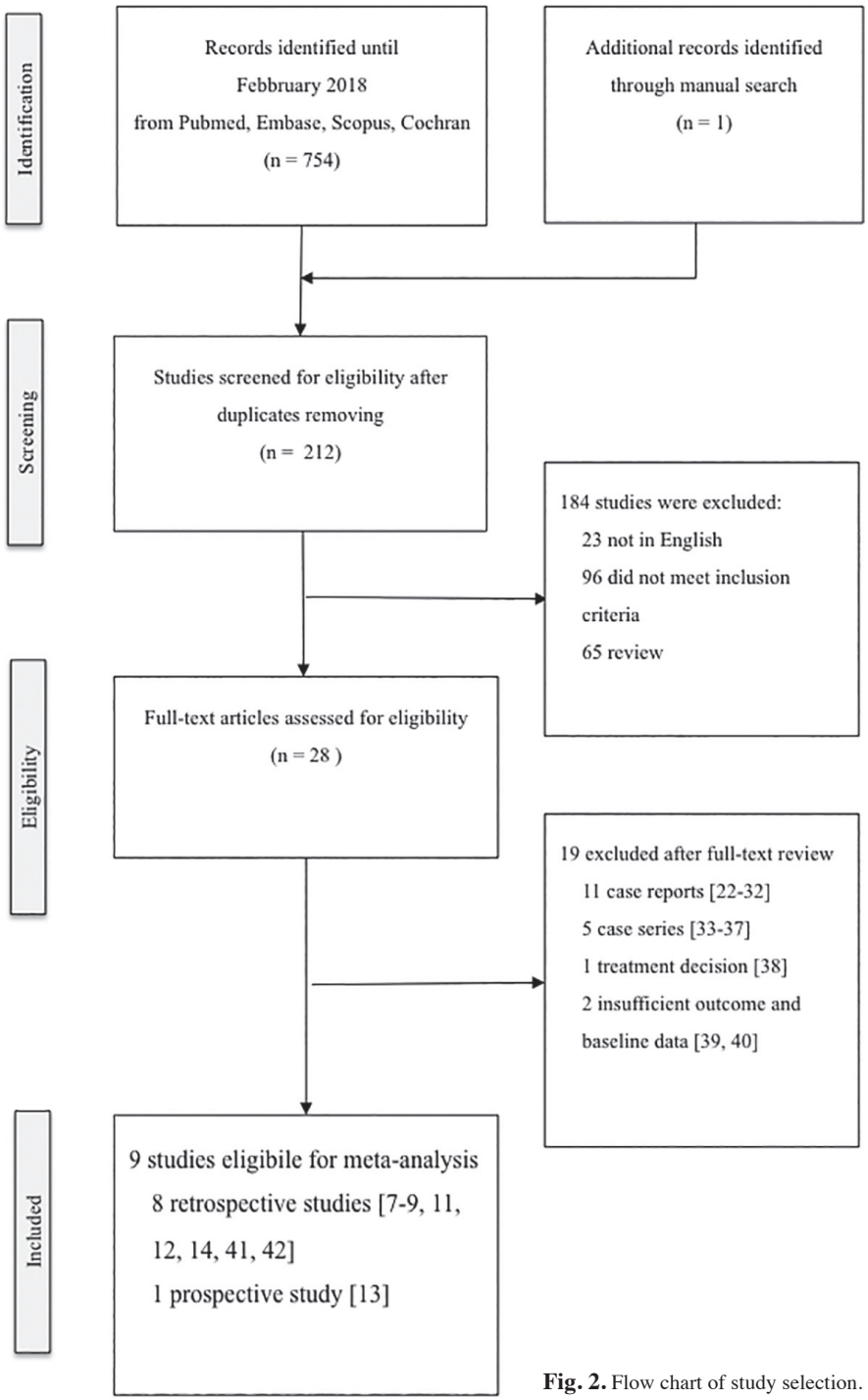

Fig. 2. Flow chart of study selection.

period running from 1990 to 2018 were included in the meta-analysis. Sample sized varied from 28 to 214 CHB cases for a total of 747 patients; due to voluntary termination of pregnancy 9 cases were excluded from the quantitative analysis. Four studies were multicentric (9, 10, 14, 42), three were registry (8, 12, 15), respectively two from the Research Registry for Neonatal Lupus established by the National Institute of Arthritis and Muscoloskeletal and Skin Diseases in 1994 (12, 15) and one from Neonatal Lupus French Registry established in 2000 (8), and two were monocentric (13, 43). Two studies included only 3rd degree CHB cases (13, 42). One out of seven studies which included 2nd degree CHB did not reported data regarding progression or regression/stability of it (15) thus it was not considered in subgroup analysis evaluating the efficacy of fluorinated steroids in the prevention of progression of CHB. The dosage of fluorinated steroids varied between 4 and 12 mg daily. Overall, dexamethasone was the most used steroid; in four studies was the only steroid used (10, 13, 14, 42), in other 2 studies was used respectively in 77.6% and 97% of the patients (9, 15) while, betamethasone was the mainly steroid used in 70.6% of the patients in only one study (42). Two studies did not report the data regarded the fluorinated steroids used (8, 12). Confounding factor, such as treatment with betamimetics was reported in seven studies (9, 10, 12, 13, 15, 42, 43).

Publication bias

As shown, in Figure 3, visual examination of the funnel plots for the main analyses and for the subgroup analyses did not show any asymmetry. Moreover, the Egger's test, for the main analysis (p=0.51) and for the subgroup analysis, respectively for the progression of CHB, pacing and extranodal disease (p=0.52, p=0.11 and p=0.29) did not revealed any statistical evidence for publication bias.

Efficacy of fluorinated steroids for the prevention of mortality

Among 738 CHB patients, 333 (45%) were treated with fluorinated steroids within one week from CHB detection. Overall, 289/333 (86.8%) fluorinated steroids exposed foetuses survived compared with 351/405 (86.7%) of non-exposed ones. As reported in Figure 4, fluorinated steroids did not ameliorate overall survival in autoimmune mediated CHB (OR 1.02; 95% CI: 0.65–1.61). However, when arranged the studies by CHB degree (Fig. 5), we observed that the risk of mortality, in the studies comprising only third degree CHB cases, was significantly higher if untreated (OR 4.07; 95% CI: 1.10–15.08). We did not find any significant statistical heterogeneity between studies ($I^2$0%, p=0.45), as also suggested by visual inspection of funnel plot (Fig. 3A).

Efficacy of fluorinated steroids for the prevention of progression of CHB

Overall, a total of 80/521 (15.3%) pa-

Table I. Studies addressing treatment of autoimmune congenital heart block with fluorinated steroids.

Author, Year	Study design	Number enrolled	Anti-SSA and/or anti-SSB positive patients, n (%)	Maternal autoimmune disease, n (%)	Patients treated with steroids, n (%)	Congenial heart block				Live births, n (%)
						Treated, n (%)	Untreated, n (%)	Treated, n (%)	Untreated, n (%)	
						II AVB		III AVB		
Saleeb 1999 [12]	Retro	50	50 (100)	not reported	28 (56)	7 (25)	4 (18.2)	21 (75.0)	18 (81.8)	45 (90)
Jaeggi, 2004 [13]	Retro	37	33 (89.2)	5 (15.2)	19 (57.6)	0	0	20 (100)	13 (100)	24 (72.7)
Fesslova, 2009 [42]	Retro	28	28 (100)	10 (35.7)	20 (71.4)	0	0	20 (100)	8 (100)	24 (85.7)
Friedman 2009 [14]	Pros	40	40 (100)	29 (72.5)	30 (75)	8 (26.7)	1 (10)	22 (73.3)	9 (90)	36 (90)
Elliasson, 2011 [9]	Retro	175	131 (74.9)	29 (22.1)§	56 (42.7)	7 (12.5)	8 (10.7)	49 (87.5)	67 (89.3)	114 (87)
Kuleva, 2014 [43]	Retro	62	39 (62.9)	24 (53.3)	17 (43.6)	2 (11.8)	2 (9.1)	15 (88.2)	20 (90.9)	36 (92.3)
Levesque, 2014 [8]	Retro	214	214^ (100)	51 (26.1)	79 (37.6)	13 (16.5)	11 (8.4)	66 (83.5)	117 (91.6)	179 (85.2)
Izmirly, 2016 [15]	Retro	156	156 (100)	69 (44.2)	71 (45.5)	9 (12.7)	4 (4.7)	62 (87.3)	81 (95.3)	139 (89.1)
Van den Berg, 2016 [10]	Retro	65	56* (86.2)	24 (43.6)	14 (27.5)	8 (57.1)	12 (32.4)	6 (42.9)	25 (67.6)	43 (84.3)

AVB: atrio-ventricular block; Retro,: retrospective cohort study; Pros: prospective cohort study.
*5 voluntary termination of pregnancy.
^4 voluntary termination of pregnancy.
§48 (36.6) the maternal disease was not reported.

tients with 2nd degree CHB were included in the subgroup analysis from six studies (8-10, 12, 14, 43). Forty-two/80 (52.5%) patients were treated with fluorinated steroids. Twenty-two/42 (52.4%) of fluorinated exposed II degree CHB foetuses *versus* 24/38 (63.1%) non-exposed ones progressed to 3rd degree CHB. Fluorinated steroids did not prevent the progression through the 3rd degree CHB (OR 0.71; 95% CI: 0.27–1.87) as shown in Figure 6A. We did not find any significant statistical heterogeneity between studies ($I^2$0%, p=0.76), as also suggested by visual inspection of funnel plot (Fig. 3B).

Efficacy of fluorinated steroids for the prevention of pacemaker implantation

A total of 637/649 (99.5%) babies were included in the subgroup analysis. Two hundred and eighty-two/637 (44.3%) patients were treated with fluorinated steroids. One hundred and ninety-eight/282 (70.2%) of fluorinated ex-

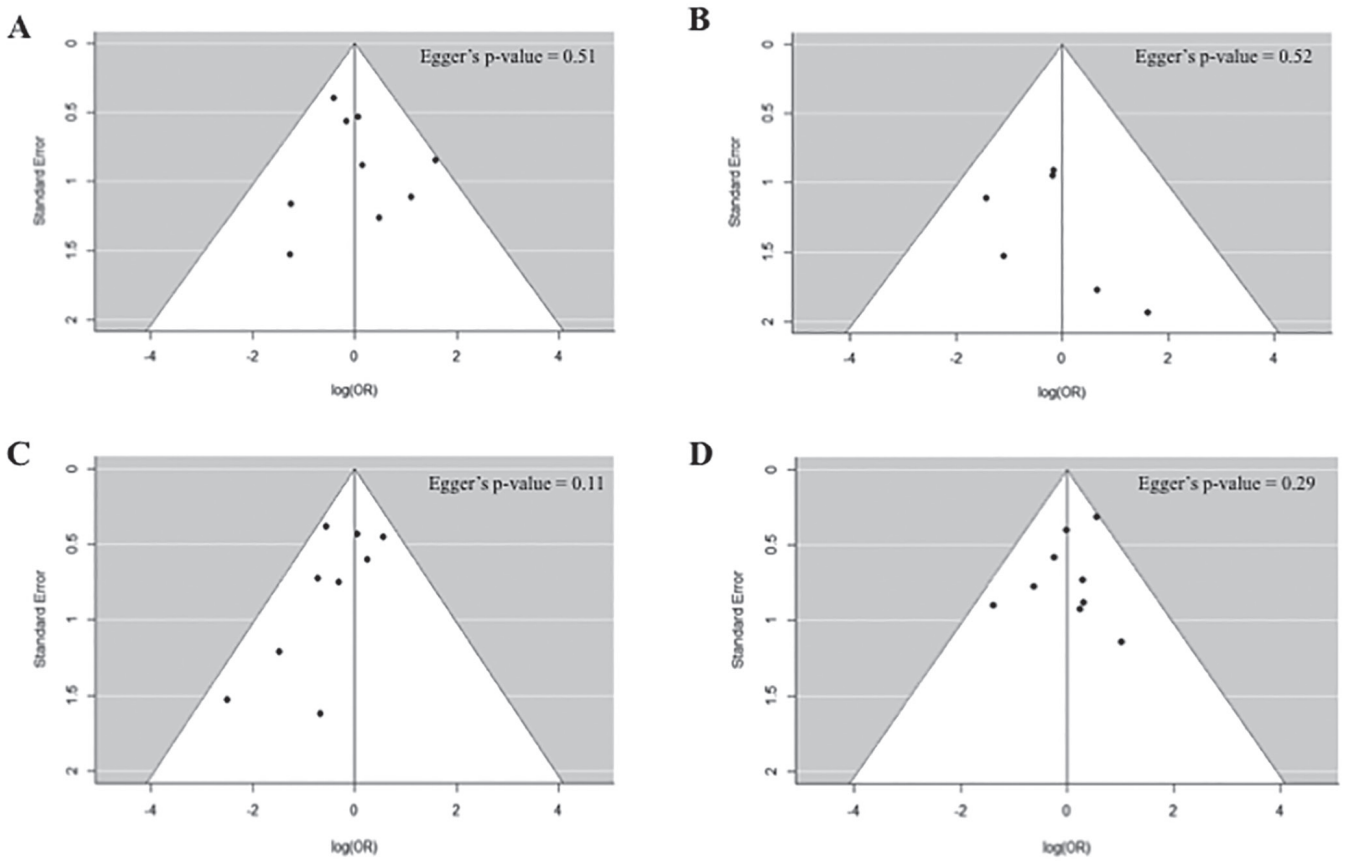

Fig. 3. Funnel plot for all included studies in **A**) main analysis, **B**) progression of incomplete congenital atrio-ventricular block, **C**) pacemaker implantation, **D**) extranodal disease.

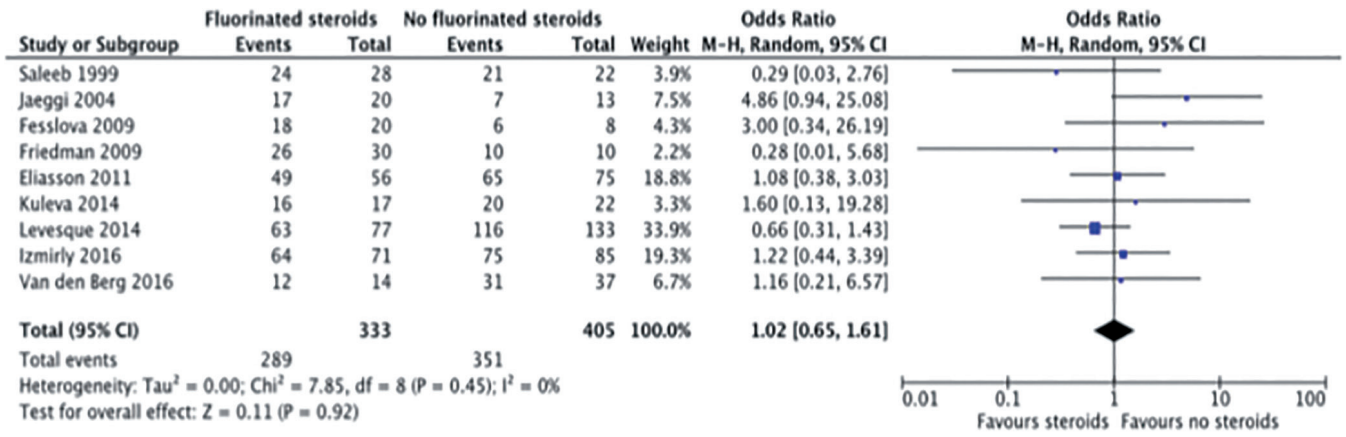

Fig. 4. Forest plot for the survival analysis.

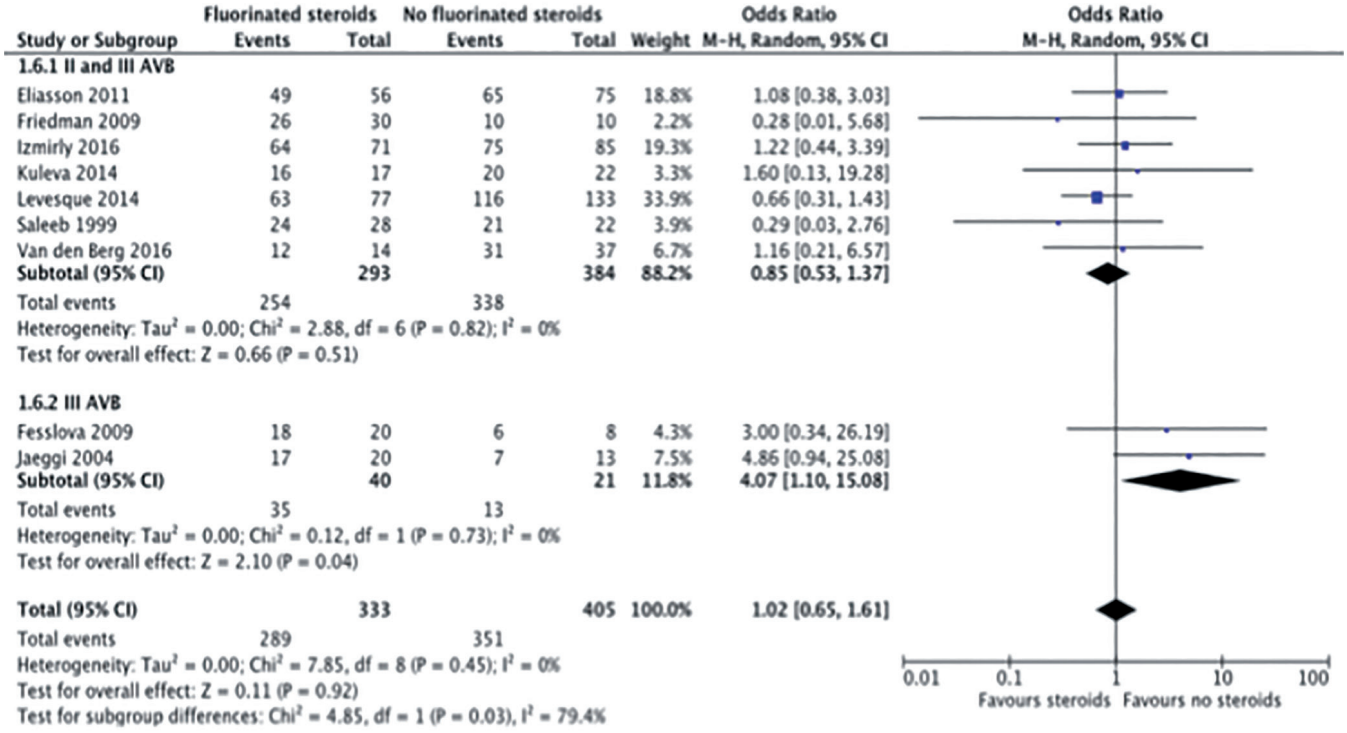

Fig. 5. Forest plot for survival analysis according to congenital heart block degree.

posed CHB foetuses *versus* 271/355 (76.3%) of non-exposed ones got pacemaker implantation within first year of life. Fluorinated steroids did not prevent the pacemaker implantation in autoimmune CHB (OR 0.83; 95% CI: 0.55–1.26) as showed in Figure 6B. When we arranged the subgroup analysis according to study design monocentric *versus* multicentre/registry (Fig. 7), a protective effect of fluorinated steroids for pacing have been observed, (OR 0.15; 95% CI: 0.02–0.99) in the monocentric ones .We did not find any significant statistical heterogeneity between studies (I^2 8%, p=0.37), as also suggested by visual inspection of funnel plot (Fig. 3C).

Efficacy of fluorinated steroids for the prevention of extranodal disease

A total of 721/738 (97.7%) of CHB patients from nine studies was included in the subgroup analysis. Three hundred and twenty-six/721 (45.2%) patients had been treated with fluorinated steroids. Seventy-nine/326 (24.2%) of fluorinated exposed CHB foetuses *versus* 83/395 (21.0%) of non-exposed one had or developed an extranodal disease. Fluorinated steroids did not prevent/recovered the extranodal disease in autoimmune CHB (OR 1.17; 95% CI: 0.81–1.7) as shown in Figure 6C. We did not find any significant statistical heterogeneity between studies (I^2 0%, p=0.53), as also suggested by visual inspection of funnel plot (Fig. 3D).

Discussion

Fluorinated steroids, which cross the placenta, and thus could suppress the inflammatory processes in the atrioventricular node and the myocardium (11, 44) have been used with the hope

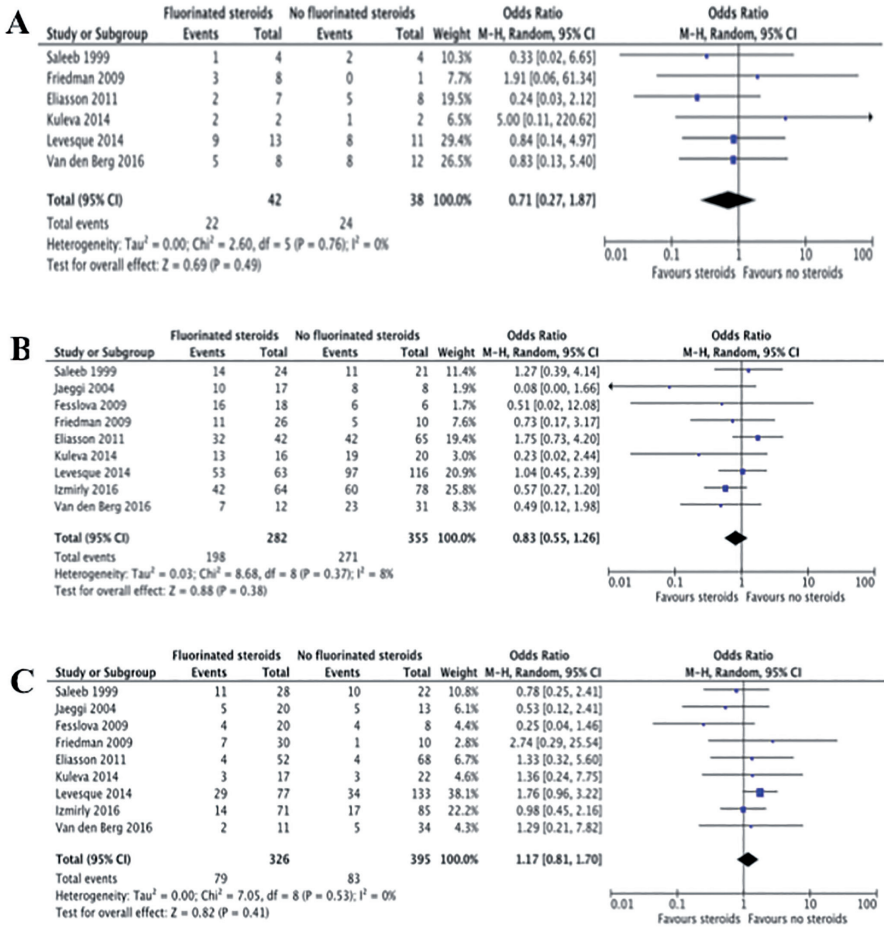

Fig. 6. Forest plot for the **A**) prevention of progression of incomplete congenital atrio-ventricular block, **B**) prevention of pacemaker implantation and **C**) prevention/treatment of extranodal disease

of surviving foetuses and children with CHB and to prevent the progression to the irreversible 3rd degree CHB and the myocardial injury leading to extranodal disease (11).

Current meta-analysis demonstrates that fluorinated steroids treatment of isolated CHB was not superior to any treatment in terms of live birth rates. Interestingly, when arranged by CHB degree, we observed that the risk of mortality, in the studies comprising only 3rd degree CHB cases, was significantly higher in the untreated patients, probably due to the higher rate of extranodal disease in those studies of untreated patients with respect to the fluorinated steroids exposed ones (13, 42). In fact, in both studies (13, 42), 100 % of untreated patients presented extranodal disease with respect to 58.8% (42) and 88.8% (12) in the fluorinated steroids treated ones. It could be argued that the study by Jaeggi *et al*. (13) compared two historical cohorts 1990–1996 and 1997–2003, with most of the treated ones being in the recent cohort, thus leading to bias. However, Fesslova *et al*. (42) reported a mortality rate of 37.5% in the hydropic foetuses *versus* 5% of those without hydrops, and the administration of fluorinated steroids has had a favourable effect on foetal hydrops. To note, it is reported by several studies (9, 40) that extranodal disease such as left ventricular dysfunction, dilated cardiomyopathy, endocardial fibroelastosis and foetal hydrops are markers of poor outcome. However, the subgroup analysis showed no significant protective effect of fluorinated steroids towards extranodal disease, even when 3rd degree CHB cases alone were considered, although a protective trend was observed in the treated ones (data not shown); thus, the result may be due to the low number of patients included.

Additionally, fluorinated steroids did not prevent the progression of incomplete CHB to the irreversible third degree atrio-ventricular block. To note, incomplete atrio-ventricular block was diagnosed in only 15.7% of the patients. Diagnosing incomplete atrio-ventricular block is challenging. In fact, recently Van den Berg *et al*. reported that they reclassified 10 out of 21 "complete" blocks as incomplete (10). Since, incomplete atrio-ventricular block could progress to the irreversible 3rd degree atrio-ventricular block within a week (7), this results might considered critically when a decision to treat or not have to be considered from the physician.

Moreover, in the current meta-analysis fluorinated steroids did not prevent pacemaker implantation. This could be related to the higher number of third degree CHB, with respect to incomplete CHB (89.2% *vs*. 10.8%) included in the studies analysed. Interestingly, when we arranged the subgroup analysis according to study design monocentric *versus* multicentre/registry a protective effect of fluorinated steroids for no-pacing have been observed, emphasising the differing approaches to the diagnosis and treatment timing and dosing. This data raise concerns, since pacemaker implantation was associated with post-natal cardiomyopathy in French registry (45).

Fluorinated steroids have been related with different adverse events such as the risk of developing gestational diabetes, hypertension, oligohydramnios, foetal growth restriction, low birth weight, early and late spontaneous abortion, premature rupture of the membrane and delayed neuro-motor development (9, 10, 12, 16, 17, 46). In this scenario of demonstrated side effects of fluorinated steroids in the absence of efficacy to ameliorate the CHB outcome their use should be caution.

A monocentre observational study reported the results of a combination therapy with therapeutic plasmapheresis, intravenous immunoglobulins and fluorinated steroids on 12 patients with 2nd and 3rd degree CHB (47), showing a regression of conduction disorders and a favourable effect on preventing pacemaker implantation. Furthermore, Trucco *et al*. (48), by using intravenous immunoglobulins and fluorinated ster-

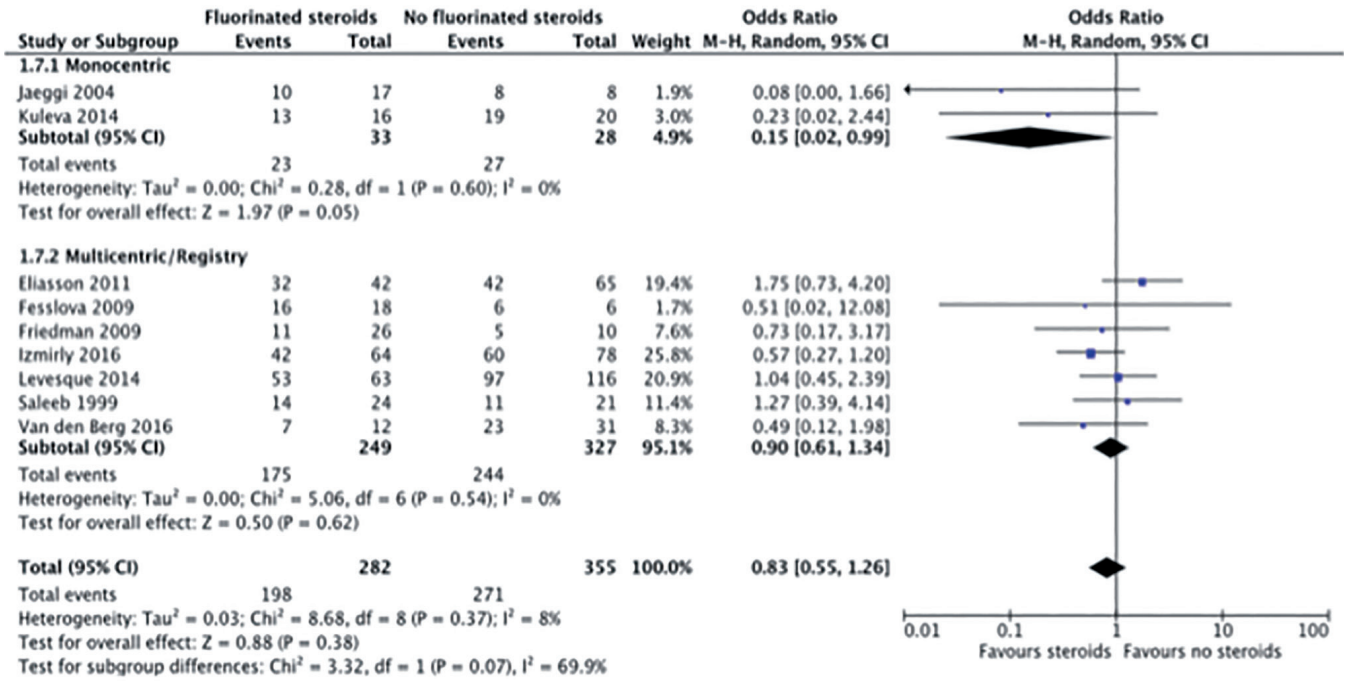

Fig. 7. Forest plot for pacemaker implantation according to study design.

oids in 20 patients with foetal cardiomyopathy reported a survival rate of 80% at a median follow-up of 2.9 years and none required cardiac transplantation. Both studies reported no side effects in the foetuses or in the mothers. Recently, in a multicentre trial (49) of 313 anti-Ro/SSA positive pregnant women prospectively followed by a home Doppler device monitoring heart rate and rhythm, was observed restoring of sinus rhythm in a II degree CHB treated with dexamethasone+intravenous immunoglobulins less than 12 hours from the detection of abnormal foetal heart rate, while the progression to III degree CHB in the other two cases who referred to the referral centre after 12-24 hours from the detection of abnormal foetal heart rate. Thus, emphasising the importance of early detection of atrio-ventricular block leading to early initiation of the treatment other than confirming the efficacy of the treatment dexamethasone+immunoglobulins.

There are several limitations to this study, which mainly depend intrinsically from meta-analysis and quality of the studies included. First, due to the relatively small number and the retrospective design in the majority of the studies involved in this meta-analysis, the result of this study is subjected to random error. Secondly, sample size of the studies may also affect the fidelity of the results; especially regarding the subgroup analysis of CHB progression. Thirdly, the multicentre nature of the majority of the studies led to different approach of the treatment of disease, opening the strong possibility of bias in term of treating more frequently with fluorinated steroids the sickest foetuses and the variation of dosage used, making the quality of most studies involved in this meta-analysis low.

In conclusion, to the best of our knowledge, this is the first meta-analysis that evaluates the efficacy of fluorinated steroids for the treatment of CHB. Taking into account all the studies included, fluorinated steroids are not superior to any treatment in patients with CHB in terms of live birth, prevention of progression of incomplete CHB, pacemaker implantation and extranodal disease. Thus, also considering the side effects, their use in CHB patients should be discouraged.

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