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Use of antenatal fluorinated corticosteroids in management of congenital heart block: Systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate outcomes of fluorinated corticosteroids, with or without other medications, for treatment of congenital heart block in-utero.
Study design: A search was conducted through MEDLINE, EMBASE, WEB OF SCIENCE and SCOPUS from inception to October 2017. Only comparative studies are considered eligible. Outcomes include fetal death, downgrade of heart block, neonatal death, need for neonatal pacing, fetal and maternal complications. Random effects model was used.
Results: Out of 923 articles, 12 studies were eligible. Compared to no treatment, there was no significant difference in incidence of fetal death (OR 1.10, 95%CI 0.65–1.84), neonatal death (OR 0.98, 95%CI 0.41–2.33), or need for pacing (OR 1.46, 95%CI 0.78–2.74). Heart block downgrade was significantly higher in treatment group (9.48%vs.1.76%, OR 3.27, 95%CI 1.23–8.71).
Conclusion: antenatal fluorinated corticosteroids do not improve fetal/neonatal morbidity or mortality of congenital heart block and are associated with higher incidence of fetal and maternal complications.

Contents

Introduction

Congenital heart block (CHB) is a rare fatal condition that may eventually lead to fetal demise, neonatal death, or permanent pacemaker implantation [1]. Incidence of CHB is approximately 1 in 20,000–30,000 live births [2]. CHB may occur in a structurally normal heart (isolated CHB) as a complication of maternal autoimmune disease or in fetuses with congenital heart defects (complex CHB) [3].

The incidence of CHB is 2% among women with Ro-positive antibodies without previously affected offspring, 15–20% among women with Ro-positive antibodies and with previously affected offspring, and 5% among women with mixed connective tissue and/or Sjögren Syndrome [4–6]. Among fetuses

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exposed to anti-Ro antibodies, 17.5% may be complicated by fetal demise, and 70% would eventually need permanent pacemaker implantation in the 10 years of life [7]. Permanent pacemaker implantation has been considered the only intervention that improves survival rate among neonates with CHB [8,9].

Prenatal diagnosis of CHB can be achieved early in the second trimester, either incidentally during intermittent auscultation or during anatomical survey ultrasound, and can be confirmed by fetal echocardiogram with Doppler techniques to determine level of heart block and verify any underlying major structural heart lesions. Therefore, several studies investigated a possible role of immediate post-diagnosis fetal therapy to improve fetal and neonatal outcomes of CHB. Treatment options include fluorinated and non-fluorinated corticosteroids, immunoglobulins or combined treatment. The aim of treatment is to reverse or downgrade CHB and to prevent intrauterine progression of the disease which can be manifested as hydrops fetalis, pericardial effusion, cardiomegaly, which impacts overall survival rate and lines of treatment [10].

In this study, the aim is to summarize the effect of fetal treatment of CHB with fluorinated corticosteroids, with or without other medications, on fetal and neonatal survival rates and the need for permanent pacemaker implantation. We also aimed to evaluate potential maternal and fetal complications associated with prenatal treatment.

Materials and methods

Literature search

The authors conducted a literature search for studies that assessed maternal, fetal and neonatal outcomes among pregnant women whose fetuses were diagnosed with congenital heart block during pregnancy. Studies that compared the use of fluorinated corticosteroids with or without other medications in comparison to no treatment during pregnancy. The search covered MEDLINE, EMBASE (with online Ovid interface), WEB OF SCIENCE and SCOPUS and was done in collaboration with an expert librarian. Studies conducted from the date of database inception to October 2017 were included. We used the following search terms: "Treatment" OR "management" AND "fetal" OR "congenital" OR "in utero" AND "heart block" OR "aterioventricular block". Search was set to filter out conference papers and review articles. In addition, manual search on additional references was achieved by reviewing references of articles retrieved by initial search. The detailed search strategy is appended (Appendix I). The risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) [11]

Eligibility criteria and study selection

After conduction of literature search, 2 reviewers performed independent screening of titles and abstracts to exclude irrelevant studies. After exclusion of irrelevant studies, we reviewed the full text of the remaining studies for final selection of eligible articles. Minor discrepancies in data were adjudicated by consensus among reviewers. Comparative studies that address obstetric and neonatal outcomes among pregnant women who and who did not receive fluorinated corticosteroids (with or without other medications) to manage congenital heart block. Case reports, case series, and single arm studies were not included. However, neither language nor sample size was considered for exclusion.

Fetal death, downgrade of heart block, development of hydrops, average intrauterine fetal heart rate, neonatal death, and the need for neonatal pacing present our primary outcomes. Secondary outcomes were fetal and maternal complications that could be potentially related to treatment e.g. oligohydramnios, intrauterine growth restriction (IUGR). These outcomes were analyzed separately. However, average intrauterine fetal heart was not included in final analysis because documentation was missing in the majority of selected studies.

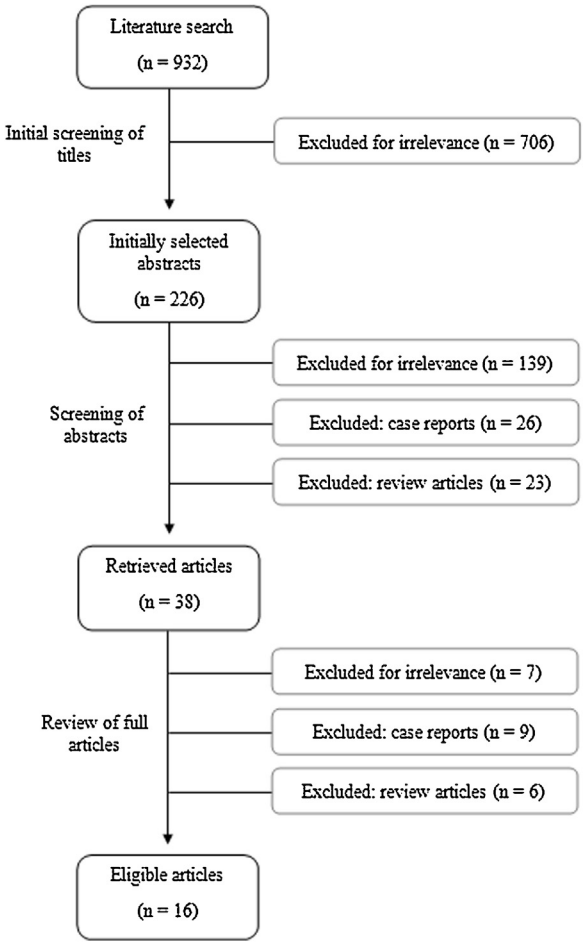

Fig. 1. Study selection flow chart.

Data abstraction

A standardized form was designed for abstraction of data from selected studies. The form consists of study authors, study origin, type of study, time frame during which the study was conducted, sample size, gestational age at diagnosis, maternal and fetal risk factors, selection criteria of study population, study arms, type of medications used,duration of intervention and studied outcomes. The form also included primary and secondary outcomes as listed above.

Data analysis

Binary outcomes were expressed as odds ratios (OR) and 95% confidence interval (CI). Due to anticipated heterogeneity, pooling of results was performed using random-effect model [12].

Heterogeneity was evaluated using I squared statistic. I squared value over 50% is consistent with substantial heterogeneity [13]. Review Manager (RevMan) Version 5.3 was used to conduct statistical analysis for this review (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) [14].

Table 1
Demographics of population of included studies.

Authors	Study origin	Study type	Time frame	Sample size	Gestational age at diagnosis	Maternal/fetal risk factors
Buyon et al. (1995)	New York, USA	Retrospective study	1985-1993	72	16 to 40 weeks of gestation. In 4 (5.6%) pregnancies, diagnosis time was not reported	• Fetal risk factors: • Stenotic dysplastic pulmonary valve was diagnosed in only 1 fetus. No other fetal anomalies were diagnosed in this study
Shinohara et al. (1999)	Osaka, Japan	Retrospective study	1979-1996	15	20-21 weeks of gestation	• Maternal risk factors: • Systemic lupus erythematosus • Primary Sjogren's syndrome • Idiopathic thrombocytopenic purpura • Undifferentiated connective tissue disease • Raynaud's phenomenon
Saleeb et al. (1999)	New York, USA	Retrospective study	1983-1998	50	21.6 weeks and 24.2 weeks of gestation for the treated and untreated groups, respectively	• Maternal risk factors: • Systemic lupus erythematosus (8 patients in the treated group, 4 in the untreated group) • Sjegren's syndrome (5 patients in the treated group versus 5 in the untreated group) • Unspecific autoimmune syndrome (4 patients in the treated group versus 8 in the untreated group) • Fetal risk factors: • Tricuspid regurgitation (7 treated fetuses, 2 untreated fetuses) • Mitral regurgitation (5 of treated fetuses, 1 of untreated fetus)
Jaeggi et al. (2004)	Ontario, Canada	Retrospective study	1990-2003	37	27 ± 6.5 weeks of gestation (1990–1996), 24.7 ± 3.7 5 weeks (1997-2003)	• Maternal risk factors: • Anti-Ro/La autoantibodies (92%) • Congenital long-QT syndrome (1 case) • Fetal risk factors: • Endocardial fibroelastosis was detected in 9 fetuses (24.3%)
Lopes et al. (2008)	São Paulo, Brazil	Retrospective study	1988-2006	57	29 (18–40) weeks of gestation	• Maternal risk factors: • Anti-Ro antibodies were detected in sera of 41/116 (35.3%) women.
Fesslova et al. (2009)	Milan, Italy	Retrospective study	1992-2004	28	25 (19 to 32) weeks of gestation	• Maternal risk factors: • Anti Ro/La antibodies were detected in sera of all women. • Autoimmune diseases were diagnosed in 11/27 women. • Multiple pregnancies (2 cases)
Jaeggi et al. (2010)	Ontario, Canada	Prospective study	2000-2008	34	22.5 weeks (19-39 weeks)	None reported
Trucco et al. (2011)	Ontario, Canada	Retrospective study	1998-2009	20	23 weeks (range 18 to 38 weeks)	• Maternal risk factors: • Anti-Ro antibody was detected in the sera of 19 women. • Anti-La antibody was detected in the sera of 8 women. Clinical autoimmune disease was diagnosed in 7 women.
Eliasson et al. (2011)	27 centers in Europe and 1 in Brazil	Retrospective study	2000-2007	175	24.3 ± 4.3 weeks for all cases, 23.4 ± 2.9 weeks for steroid treated, and 24.9 ± 4.9 weeks for the untreated group	• Maternal risk factors: • Collagen disease was present in 77/167 (46%) women: sjögren syndrome in 18 women, systemic lupus erythematosus in 11 women, and unspecified disease in 48 women. • Anti-Ro/SSA positive sera in 129/162 (80%) women • Anti-La/SSB positive sera in 85/144 (59%) women
Izmirly et al. (2011)	New York, USA	Retrospective study	1963-2010	21	24.8 weeks (for deceased cases) and 26.9 weeks (for survived cases)	None reported
Miyoshi et al. (2012)	Suita, Japan	Questionnaire study	2002-2008	77	24 ± 3.2 weeks for intervention group and 28 ± 5.7 weeks for non-intervention group	• Maternal risk factors (For cases with isolated complete heart block): • Anti-SSA antibodies positive cases were diagnosed in 29 (76.3%) of 38 treated cases versus 11 (47.8%) of the 23 untreated cases.
Perin et al. (2014)	Granada, Spain	Retrospective multicenter study	2008-2010	19	23.5 week of gestation	• Maternal risk factors: • Auto-antibodies were detected in the sera of 12/19 patients. • Fetal risk factors: • Congenital heart defects were detected in 3/19 women.

Table 1 (*Continued*)

Authors	Study origin	Study type	Time frame	Sample size	Gestational age at diagnosis	Maternal/fetal risk factors
Levesque et al. (2015)	Paris, France	Retrospective study	1976-2014	202	Median gestational age at time of diagnosis was 23 weeks of gestation	• Maternal risk factors: • Anti-SSA antibodies were detected in the sera of 194 (99.5%) women • Anti-SSB antibodies were detected in the sera of 117 (60%) women • Fifty one mothers (26.2%) were known to have an autoimmune disease • Fetal risk factors: • Valvular disease was diagnosed in 6 (10.9%) fetuses • Congenital cardiac Malformations were detected in 33 (16%) fetuses
Kuleva et al. (2015)	Paris, France	Retrospective study	2002-2012	39	22 – 23 weeks of gestation on average	• Fetal risk factors: • Left isomerism, single ventricle, congenitally corrected transposition of great vessels, atrioventricular septal defect and complex cardiac malformation were detected in 1/39 (5.9%), 4/39 (23.5%), 4/39 (23.5%), 1/39 (5.9%), 7/39 (41.2%), respectively.
Izmirly et al. (2016)	New York, USA	Retrospective study	1972-2013	156	22.1 ± 2.8 weeks for intervention group and 22.8 ± 3.1 weeks for the non-intervention group	• Maternal risk factors: • In the intervention group: 39 (54.9%) women were diagnosed with asymptomatic or undifferentiated autoimmune syndrome, 18 (25.4%) with Sjogren's syndrome, 7 (9.9%) with systemic lupus erythematosus and 7 (9.9%) with both systemic lupus erythematosus and Sjogren's syndrome • In the no-intervention group: 50 (58.8%) women were diagnosed with asymptomatic or undifferentiated autoimmune syndrome, 18 (21.2%) with Sjogren's syndrome, 12 (14.1%) with systemic lupus erythematosus and 5 (5.9%) with both systemic lupus erythematosus and Sjogren's syndrome
Van den Berg et al. (2016)	Utrecht, The Netherlands	Retrospective study	2003-2013	56	Mean gestational age was 23.4 ± 5 weeks of gestation	• Maternal risk factors: • Autoantibodies, Anti-Ro/SSA, Anti-La/SSB, lupus anticoagulant antibodies were detected in 13, 13, 10, and 0 women of intervention group versus 36, 35, 25, and 1 woman of non-intervention group, respectively. • Auto-immune disease, systemic lupus erythematosus, Sjogren's syndrome, other were diagnosed in 10, 4, 3, and 3 women in the intervention group versus 14, 4, 8, and 2 women in the non-intervention group respectively.

Results

Database search yielded 923 articles. Preliminary screening of titles allowed exclusion of 706 articles for irrelevance. Reviewing abstracts of the remaining 217 articles, 87 were excluded for irrelevance, 26 were case reports, 23 were review articles. Full texts of the remaining 38 articles were retrieved. Of those 38 articles, 16 articles meet our inclusion criteria (Fig. 1). Summary of study demographics and study design is illustrated in Tables 1 and 2 [7,15–29]. Appendix II summarized risk of bias of included studies.

Comparing fetuses diagnosed with CHB who were treated with fluorinated steroids with or without other treatment options to fetuses who were not exposed to any treatment, 12 studies reported the rate of fetal death. The rate of fetal death among exposed group was 9.5% (33/347) compared to 9.16% (36/393) in the non-exposed group, the difference was not statistically significant (OR 1.10, 95% CI 0.65–1.84), I square value is 0%. Downgrading of CHB was reported in 8 studies. The incidence of downgrading was reported in 9.5% (22/232) versus 1.8% (5/283) in treated and non-treated groups, respectively. The difference was statistically significant (OR 3.27, 95% CI 1.23–8.71) with I square value of 0%. There was no significant difference in the incidence of neonatal death between both group as reported in 11 studies (9.1% [25/276] in the treated group versus 11.3% [34 / 300] in the untreated group, OR 0.98, 95% CI 0.41–2.33). I square value is 38%. Also, twelve studies assessed the need for pacing among treated and untreated fetuses, which was reported in 54.35% of the treated group (181/333) versus 46.56% (183/393) of the untreated group (OR 1.46, 95% CI 0.78–2.74). Data on this outcome yielded substantial heterogeneity (I square value is 62%) (Fig. 2).

Subgroup analysis of studies was conducted for studies that compared steroids only to no treatment. In 4 studies, fetal death was 9.2% (12/130) in the treated group and 8.8% (15/171) in the untreated group (OR 1.18, 95% CI 0.51 – 2.73, I square value is 0%). CHB downgrading was documented in 4 studies. The incidence was 9.7% (13/134) and 2.6% (5/195) among treated and untreated groups, respectively (OR 2.96, 95% CI 0.74 – 11.86, I square value is 19%). Five studies compared the rate of pacing among treated and untreated groups (53.1% [76 / 143], 60.3% [108 / 179], respectively, OR 0.65, 95% CI = 0.40–1.05, I square value is 0% (Fig. 3).

The incidence of oligohydramnios was documented in 7 studies. Among all treated fetuses, the incidence of oligohydramnios was significantly higher in the treated group (16.6% [27/164]) than untreated group (1.2% [2/173]) (OR 6.47, 95% CI 2.37–17.62). Similarly, 4 studies showed that the incidence of IUGR is 19% (20/105) in the treated group compared to 6.8% (8/117) in the untreated group, which is statistically significance (OR 3.61, 95% CI 1.43–9.13),

Table 2
Study design of included studies.

Authors	Eligibility criteria	Comparison groups	Type of intervention	Duration of intervention	Study outcomes
Buyon et al. (1995)	Women with positive anti-SSA/Ro and/or SSB/La antibodies whose fetuses were diagnosed with congenital heart block	45 pregnancies received no treatment, 8 pregnancies received prednisone only, and 19 pregnancies received fluorinated steroids	• Fluorinated steroids therapy: 16 women received dexamethasone 4-10 mg/Day and 3 received betamethasone. • Prednisone therapy: 30 to 100 mg/day.	From the time of diagnosis to the time of delivery.	• The feasibility and effectiveness of prenatal therapy of congenital heart block. • The effectiveness of prenatal therapy on pacemaker implantation need and prognosis of body effusions in fetuses with congenital heart block.
Shinohara et al. (1999)	Positive maternal serum for anti-Ro/SSA antibodies.	11 fetuses received no treatment and 4 fetuses received corticosteroid therapy.	15–20 mg of prednisolone per day or betamethasone	After 16 weeks' gestation (as a prophylaxis) till delivery	• Prevention and treatment of cardiac or cutaneous manifestations of neonatal lupus • The efficacy of corticosteroid on reducing mortality rate, pacemaker implantation and fetal body effusions.
Saleeb et al. (1999)	Positive maternal serum for antibodies for 52/60-kd SSA/Ro, and/or 48-kd SSB/La RNPs during or within 1 year of pregnancy, and isolated heart block diagnosed in-utero before 5 weeks of birth	22 fetuses received no treatment in-utero compared to 28 fetuses that were exposed to fluorinated steroids.	Trans-placental treatment with fluorinated steroids (dexamethasone 4–9 mg/day or betamethasone 12–24 mg/week)	Treatment started within three weeks of diagnosis of heart block and for 3–19 weeks (for dexamethasone) or > 6 weeks (for betamethasone)	• Efficacy of fluorinated steroids on the natural history of congenital heart block diagnosed in utero and need for pacemaker implantation. • Efficacy of fluorinated steroids on body fluid accumulation. • Fate of anatomical heart problems.
Jaeggi et al. (2004)	Isolated congenital atrioventricular block diagnosed by M-mode or Doppler echocardiography.	• Fetuses with heart rate < 55 beats/min (18 cases): • 7 cases received no treatment and 11 received dexamethasone • Fetuses with heart rate > 55 beats/min (16 cases): 6 cases received no treatment, 3 received dexamethasone or □-sympathomimetic and 7 received dexamethasone and □-sympathomimetic	• Dexamethasone only (4–8 mg/day): 13 cases • Dexamethasone and Ritodrine (30–60 mg/day): 5 cases • Dexamethasone and Terbutaline (10 mg/d): 2 cases • Dexamethasone and Salbutamol (30–40 mg/day): 1 case • Salbutamol only (10 mg/day): 1 case.	For the time of diagnosis till delivery	• The efficacy of in-utero dexamethasone with and without □-sympathomimetics on outcomes of congenital heart block.
Lopes et al. (2008)	Isolated fetal heart block diagnosed via standard echocardiography by a fetal cardiologist	46 fetuses received no treatment compared to 11 fetuses who received trans-placental therapy.	Trans-placental therapy for 11 (19.5%) fetuses (dexamethasone (4 or 8 mg/d for 2 weeks, followed by 4 mg/d maintained for the duration of the pregnancy) (3.5%), Steroid and sympathomimetic for 4(7%) and sympathomimetic only for 6(9%).	From the time of diagnosis for the duration of the pregnancy.	• Factors affecting prognosis of isolated congenital heart block. • Efficacy of trans-placental treatment on prognosis of isolated heart block.
Fesslova et al. (2009)	Diagnosis of isolated heart block via echocardiography by a cardiologist.	7 fetuses with isolated heart block unexposed to any treatment compared to 21 fetuses treated with dexamethasone and/or sympathomimetics in-utero	Dexamethasone alone (18 cases) at 4 mg per day, combined with salbutamol (2 cases) or isoproterenol (1 case)	Treatment was started within 2 weeks of presentation until time of delivery	• Efficacy of treatment on prognosis of isolated fetal heart block. • The need for pacemaker implantation. • Gestational age at delivery • Adverse effects of dexamethasone therapy. • Mortality rate • Postnatal and long term outcome
Jaeggi et al. (2010)	Positive maternal anti-Ro and-La antibodies by ELISA.	Six fetuses were not exposed to any treatment in utero compared to 28 fetuses treated with dexamethasone and intravenous immunoglobulins.	Maternal dexamethasone (4 or 8 mg/day for 2 weeks, followed by 4 mg/day) then (2 mg/day) and intravenous immunoglobulins 70 gram every 2 to 3 weeks.	Starting from the time of diagnosis till the third trimester	• Relationship between cardiac complications of systemic lupus and levels of maternal anti-Ro and anti-La autoantibody. • Efficacy of prenatal treatment on congenital heart block.

Table 2 (*Continued*)

Authors	Eligibility criteria	Comparison groups	Type of intervention	Duration of intervention	Study outcomes
Trucco et al. (2011)	• Positive maternal anti-Ro and/or anti-La antibodies. • Fetuses with maternal autoantibody-related cardiomyopathy, endocardial fibro-elastosis by echocardiography and/or reduced cardiac function. • Fetal complex structural heart disease.	three fetuses were not exposed to any treatment in utero compared to 17 fetuses treated with dexamethasone only or plus intravenous immunoglobulins and/or beta-sympathomimetic.	Dexamethasone only (4-8 mg/day) for 4 (%20) mothers. Dexamethasone (4-8 mg/day) plus intravenous immunoglobulins (1 g/dose) for 4 (20%) mothers. Dexamethasone (4-8 mg/day) plus beta-sympathomimetic for 4 (20%) mothers. Dexamethasone (3-16 mg/day), beta-sympathomimetic plus intravenous immunoglobulins (1 g/dose) for 5 (25%) mothers.	From diagnosis till delivery and during neonatal period	• Efficacy of prenatal therapy on prognosis of maternal autoantibodies mediated fetal heart diseases. • Tolerance of mothers with trance-placental medications.
Eliasson et al. (2011)	• Diagnosis of fetal second- or third-degree atrioventricular block via standard fetal Echocardiography by a fetal cardiologist. • Exclusion criteria included unavailable birth outcome data, reversion from AVB II or III, and cardiac structural malformations.	108 untreated fetuses compared to 67 fetuses (38%) treated fetuses with trans-placental steroids	• Fifty two women received dexamethasone beginning with 4 mg/day (range, 2–12 mg/day) • Fifteen women received betamethasone at 4 mg/day (range, 3–5 mg/day) • Two were given prednisolone in combination with fluorinated steroids.	Treatment started from a median of 10 weeks (1–21 weeks) till delivery.	• Risk factors associated with death of fetus with heart block. • Efficacy of fluorinated corticosteroids on outcome of heart block. • Gestational age and birth weight at delivery. • Complications of treatment.
Izmirly et al. (2011)	• Positive maternal serum for anti SSA/Ro and/or SSB/La. • Confirmation of second to third degree heart block by electrocardiogram or echocardiogram, history of pacemaker, or statement in the medical record; and/or presence of cardiac injury or cardiomyopathy. • Exclusion criteria are isolated first heart block and isolated sinus bradycardia	8 fetuses with second degree heart block were not treated in utero versus 13 fetuses treated with fluorinated steroid	In utero treatment with dexamethasone	From diagnosis till delivery	• The prognosis of cardiac neonatal lupus and associated risk factors. • Efficacy of dexamethasone on prognosis of second degree congenital heart block and the need for pacemaker
Miyoshi et al. (2012)	Diagnosis of fetal atrioventricular block with structurally normal hearts	31 fetuses (23 with complete heart block and 8 with second degree hear block (untreated) compared to 46 fetuses (38 with complete heart block and 8 second degree) that did not receive treatment in utero	Trans-placental Beta-sympathomimetic and/or a steroid (dose was not specified)	From the time of detection till delivery	• Effects and risks of trans-placental treatment of isolated congenital heart block. • Comparison between third and second degree heart block regarding to response to trans-placental medications.
Roy et al. (2014)	• Positive anti-SSA/Ro or anti-SSB/La antibodies. • Isolated congenital heart block was detected by fetal echocardiography. • Exclusion criteria included structural cardiac anomalies, positive maternal serum for IgM anti-toxoplasma, herpes or rubella virus and cytomegalovirus	No comparison groups in terms of treatment	Intrauterine treatment with dexamethasone 4 mg/day	Treatment started at 25 weeks till delivery	• Efficacy of fluorinated steroids on prognosis of isolated congenital heart block. • Impact of fluorinated steroids on pacemaker implantation.
Perin et al. (2014)	Diagnosis of fetal bradycardia	Nine cases who did not receive any medication compared to 10 cases treated with steroids and beta-stimulants.	Trans-placental dexamethasone (administered in doses of 4 mg every 24 hours; a loading dose of 6-8 mg/day was administered in 3 cases). Two cases were treated with beta-stimulants.	Treatment continued for an average of 5 weeks (ranged from 2 to 12 weeks)	• Prognosis and efficacy of treatment of fetal heart block. • Pacemaker implantation need and complications of treatment.
Levesque et al. (2015)	Inclusion: • Positive maternal anti-SSA and/or anti-SSB antibodies • Confirmation of second- or third-degree fetal heart	One hundred twenty three fetuses who were not exposed to trans-placental corticosteroids compared to 79 fetuses	Intrauterine treatment with fluorinated steroids with median initial dose of 2 mg-10 mg/d that was progressively tapered	A median of 56 days (10 to 126 days).	• Fetal prognosis of congenital heart block. • Efficacy of fluorinated steroids on the prognosis of fetal heart block.

Table 2 (*Continued*)

Authors	Eligibility criteria	Comparison groups	Type of intervention	Duration of intervention	Study outcomes
	block by fetal electrocardiography. • Diagnosis of CHB in utero or in the neonatal period. Exclusion: • Isolated first-degree fetal heart block or isolated endocardial fibro-elastosis.	exposed to fluorinated steroids			• The need for pacemaker implantation postnataly
Kuleva et al. (2015)	• Confirmation of diagnosis of fetal heart block by a pediatric cardiologist. • Available follow up data.	Twenty two fetuses not exposed to fluorinated steroids compared to 17 fetuses treated with fluorinated steroids in utero	Maternal administration of dexamethasone (4 mg/day) or betamethasone (4–8 mg/day.	Treatment started around the mid-gestation till delivery.	• The course and outcome of fetuses with congenital atrioventricular block and the efficacy of in-utero treatment. • The need for permanent PM placement
Izmirly et al. (2016)	Inclusion: • Second or third degree heart block in utero documented by echocardiogram • No evidence of extranodal disease Exclusion: • Extra-nodal disease • Diagnosis of advanced heart block after 30 weeks of gestation. • Isolated 1 st degree heart block or sinus bradycardia • Usage of fluorinated steroids before detection of heart block or more than 1 week after diagnosis of heart block • Inadequate records.	Seventy one fetuses were treated with fluorinated steroids compared to 85 fetuses not exposed to fluorinated steroids	Dexamethasone was given with an average daily dose of 2.8 ± 1.8 mg daily (range: 2–8 mg/day)	Treatment started within the first week of diagnosis of isolated block detection till delivery	• Efficacy of fluorinated steroids on prognosis of fetal congenital heart block or development of extra-nodal disease. • The need for permanent PM placement
Van den Berg et al. (2016)	Inclusion: • Isolated congenital second or third degree heart block. Exclusion • complex congenital heart disease, long QT syndrome or • chromosomal abnormalities	Forty two fetuses did not receive any medication compared to 14 fetuses treated with dexamethasone in-utero	Intrauterine dexamethasone treatment with median initial dose of 2-16 mg/day.	From time of diagnosis till delivery.	• The effects of prenatal treatment with corticosteroids on the outcome of congenital heart block in the Netherlands • Adverse effects of corticosteroids

I square value is 0%. Similarly, the incidence of maternal complications was higher among the treated than untreated group as reported in 6 studies (4.4% [8/183], 0% [0/229], OR 4.28, 95% CI 1.16–15.86). I square value is 0% (Fig. 4).

Discussion

Several therapeutic options have been investigated to achieve early prenatal management of congenital heart diseases including CHB with the aim of reducing significant morbidity and mortality in utero [30]. In this systemic meta-analysis, we investigated the potential role of fluorinated steroids, alone or in combination with other medical options, to improve intrauterine or postnatal outcomes of CHB. According to our results, the use of fluorinated steroids, either alone or in combination with sympathomimetic drugs, did not reduce the rate of fetal death, neonatal death, or the rate of neonatal pacing compared to no intervention. Medical treatment showed superiority to no intervention in the incidence of CHB downgrading. This advantage is not evident with the use of fluorinated steroids alone. However, this effect does not seem to be clinically significant. On the other sides, as medical intervention was administered from the time of diagnosis to the time of delivery in most studies, our results also showed increased risk of oligohydramnios, IUGR and maternal complications among women receiving medical treatment for CHB compared to no intervention.

Understanding the etiology and mechanism of CHB may clarify the theoretical basis of prenatal medical treatment. CHB secondary to fetal cardiac structural anomalies typically yields poor prognosis known for a congenital heart disease [31]. Poor prognosis is not fully understood. However, it is likely related to the underlying disease which contributes to complexity of care [31]. In these cases, in-utero administration of beta-receptor agonists may increase fetal heart rate to above 55 beats / minute. Beta-adrenergic agonists act on both atrial and ventricular rates with varying response due to defect in the A-V node or other anomalies of the conduction system of the heart [32]. They seem to act locally with no neural affection during the stimulation process of primary (i.e., atrial) and secondary (i.e., ventricular) pacemakers or even theoretical suggestion that there is a nodal pacemaker responsible for heart rate acceleration under effect of beta receptor agonists [32]. However, long-term outcomes including survival did not improve. Moreover, fetal Tachycardia

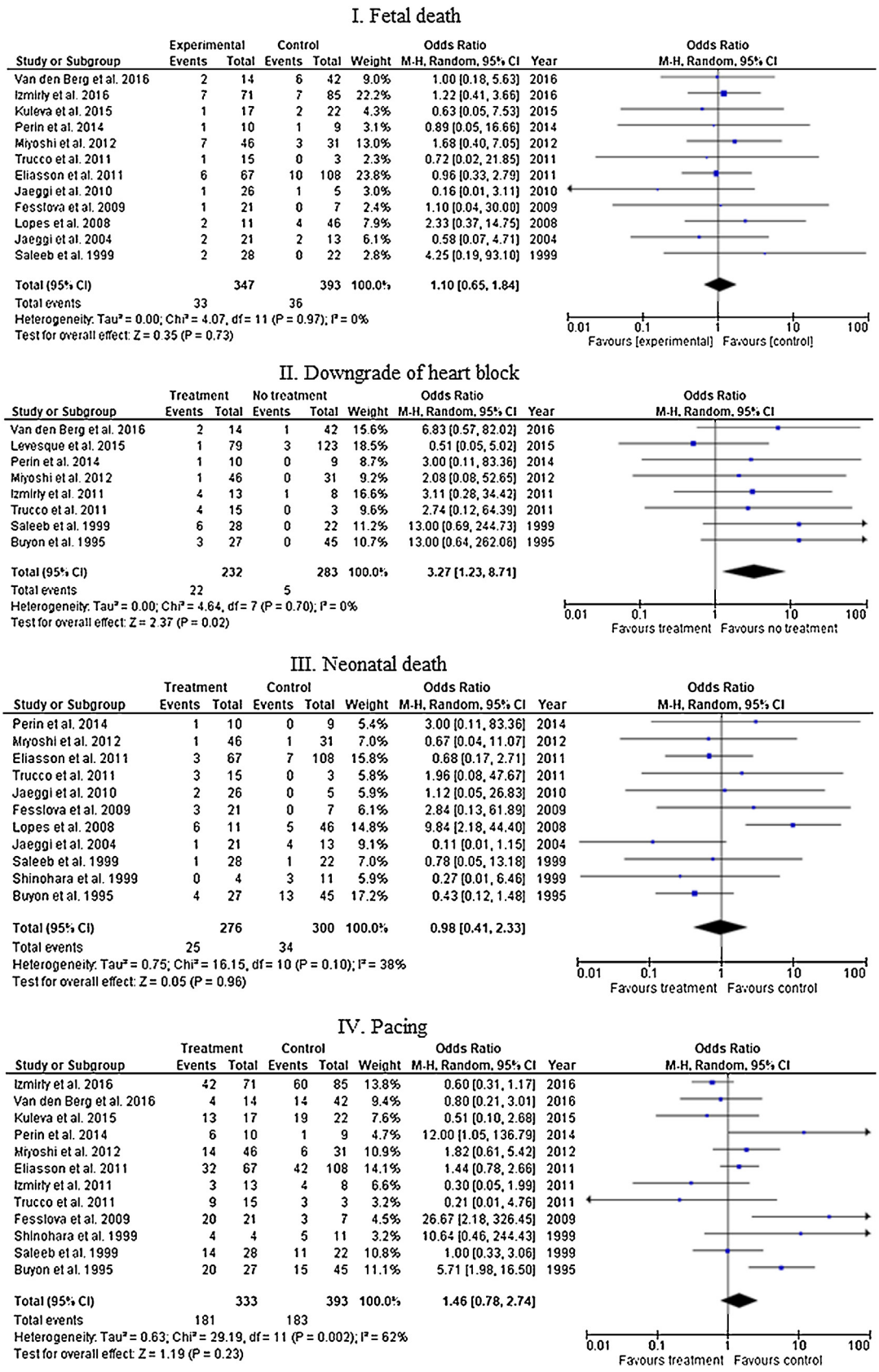

Fig. 2. Fetal and neonatal outcomes of treatment versus no-treatment among fetuses with congenital heart block.

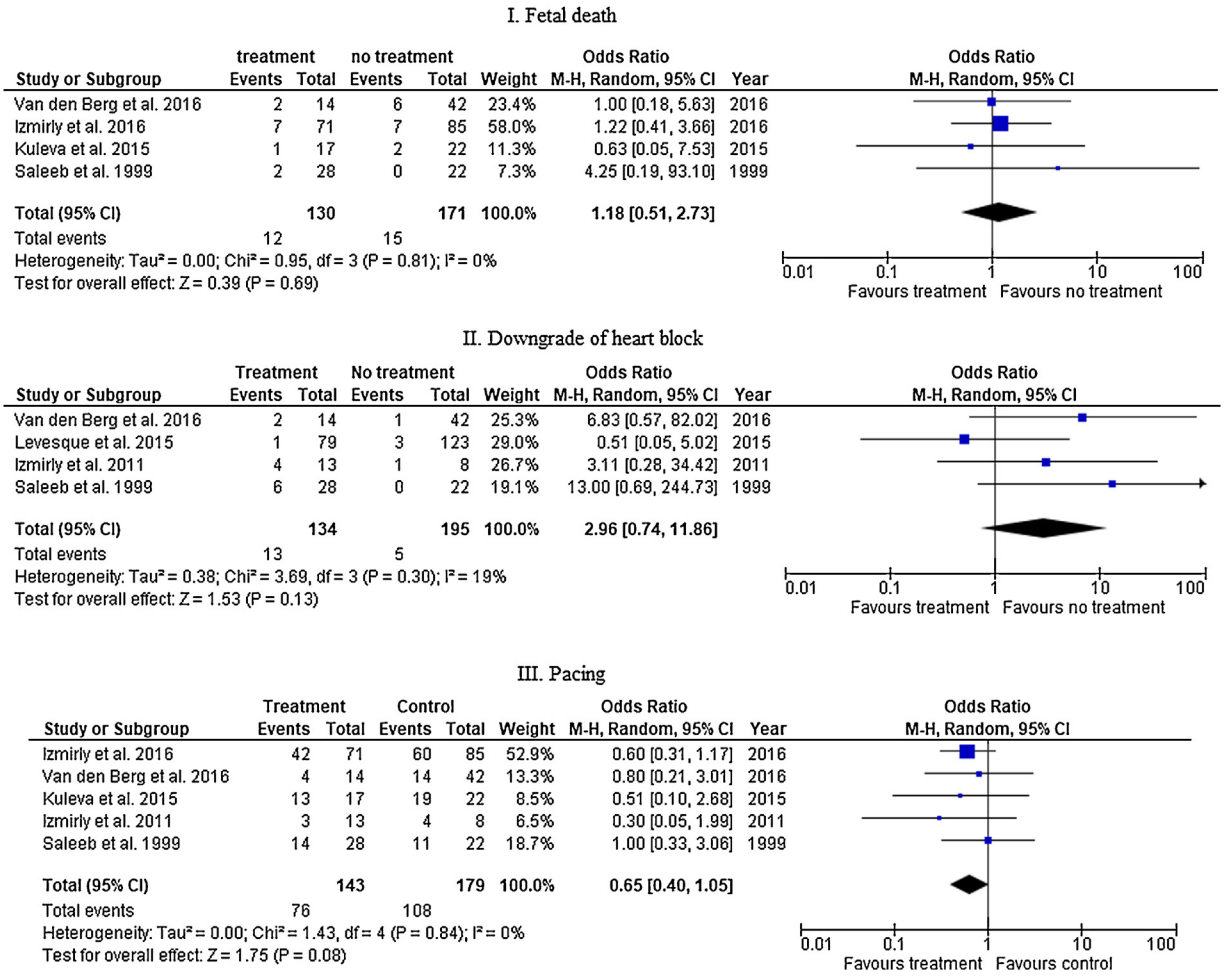

Fig. 3. Fetal and neonatal outcomes of fluorinated steroids only versus no-treatment among fetuses with congenital heart block.

with arrhythmia and maternal tachycardia were reported as complications [30–32]. On the other side, CHB secondary to maternal immunological disorders is likely related to immune response in form of inflammation and fibrosis, which subsequently damages conduction fibers and myocardium. Therefore, a proposed treatment approach would be to control immune response before permanent tissue damage occurs [33]. Nevertheless, plasmapheresis as well as intravenous injection of immunoglobulin (to decrease serum levels of anti- Ro and La antibodies) did not produce long term satisfactory results [34–36]. The familiar antimalarial agent Hydroxychloroquine (HCQ) plays a big modulating role in the action of toll-like receptor ligation and signaling which in turn affects the inflammatory process and fibrosis in cardiac tissue [37,38]. The effect of HCQ in decreasing the incidence of fetal heart block makes it a good alternative for traditional lines of treatment. However, HCQ use is still limited. This is mostly attributed to the lack of confirming prospective studies and its probable hearing and visual adverse effects [39]. Combination of plasmapheresis and immunosuppressive medications, including cyclophosphamide and azathioprine, was also investigated in pregnant women with Sjögren's syndrome with good results. However, evidence was limited to case reports [40] [41].

An alternative option is fluorinated steroid preparations, which have been investigated because of their anti-inflammatory proprieties, availability, easy administration and low cost [30,34,42]. It has been known that auto-antibodies have role in pathogenesis of congenital atrioventricular block through mediating several inflammatory processes of conductive system of fetal heart and reduction of L-type calcium channels [43–46]. Pharmacologically placental 11ß-hydroxysteroid dehydrogenase complex inactivates maternal active prednisolone but minimally affects fluorinated steroids so dexamethasone and betamethasone are available to fetus in active form. [47]. On the other hand, non-fluorinated steroids are present in fetal circulation in inactive form because of immaturity of fetal hepatic function. [34]. Maternal administration of dexamethasone is effective in modulating immunological reactions and subsequent inflammation and fibrosis [27,48,49]. Initial studies have shown potential benefits when used alone or in combination with other medications [17,50–52], which ranges from regression of the disease to first degree or sinus rhythm [15,53,54] to resolution of pleural and/or pericardial effusion complicating CHB [15]. Steroid treatment was initiated around the twentieth week of gestation when universal sonographic examination is usually performed as the onset of disease process is thought to start as early as the sixteenth week of gestation [55,56]. Data on the role of fluorinated steroids to prevent the development of CHB among high risk population is still limited [34].

In this meta-analysis, fluorinated steroids were not superior to no-treatment except in the incidence of downgrading of CHB after initiation of treatment. However, some reviews have reported that transplacental steroid rarely reverse complete CHB, the fact that may explain the lack of improvement of outcomes despite steroid

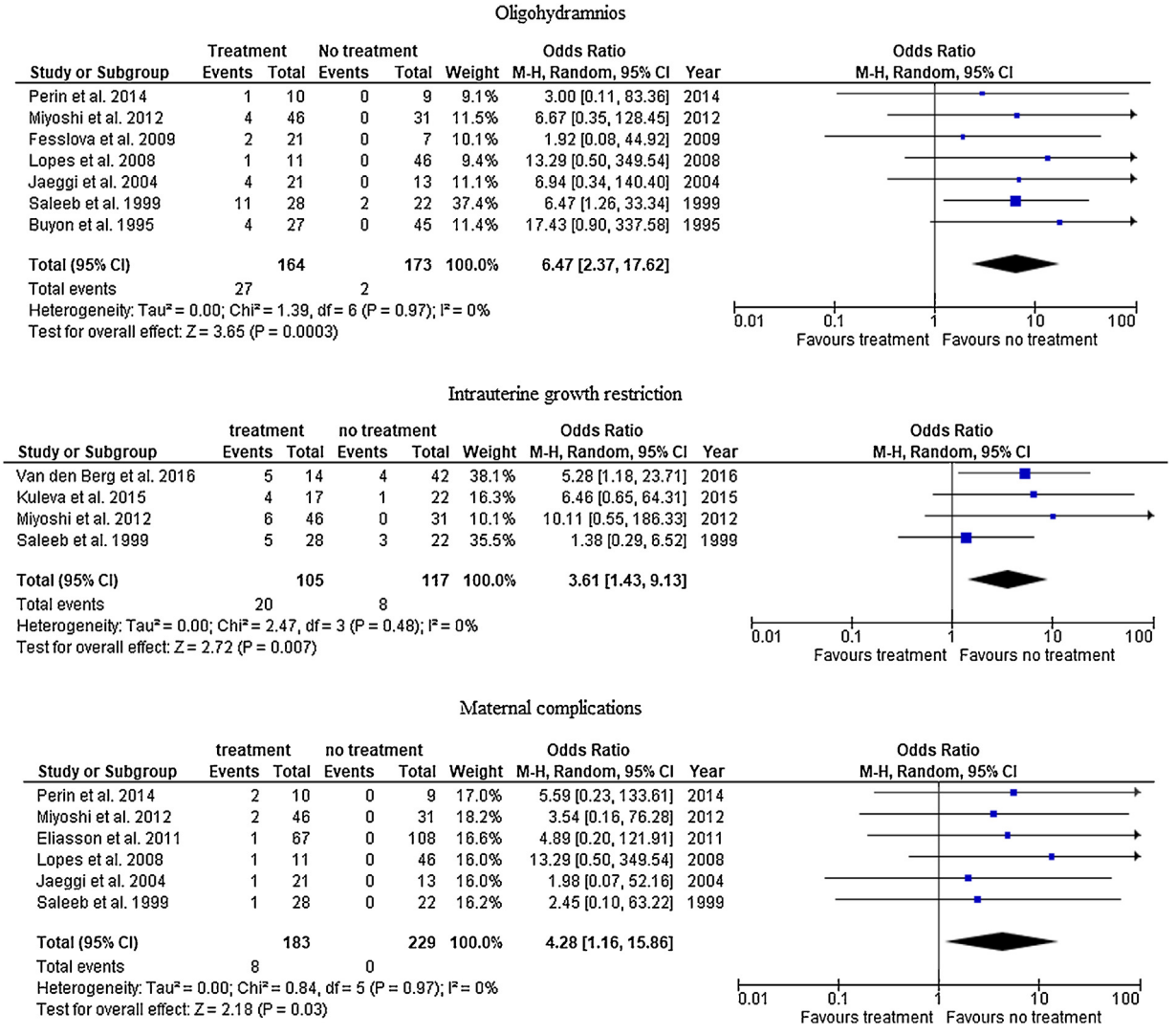

Fig. 4. Complications of treatment.

downgrading effect [57,58]. In addition, our results raise serious concern on the risk of oligohydramnios and IUGR, particularly as regimens described in these studies include high dose and/or prolonged use of corticosteroid. Brucato et al. [59] reported neurodevelopmental adverse effect of fluorinated steroids, which may be less prominent with betamethasone than dexamethasone. Several studies also reported the association between prenatal steroid administration and maternal adverse effects as gestational diabetes and hypertension, which is also consistent with our findings [16,22–24,49,50,54,60]

The results of this review emerge from a total of more than 1000 cases, which presents an advantage of this study. The review investigated possible direct and indirect benefits of fluorinated steroids as well as their potential disadvantages. However, limitations include inconsistency in treatment regimens, retrospective nature of many studies and deficiency of some critical data including development of plural effusion and ascites with and without treatment.

In conclusion, fluorinated steroids do not provide significant benefit in fetuses with CHB. With the exception of CHB downgrading, it does not improve fetal or neonatal survival. On the other hand, prolonged regimens are associated with increased risk of fetal and maternal complications. Therefore, their use for this indication is not recommended.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eurox.2019.100072.

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