



Review

Description of 214 cases of autoimmune congenital heart block: Results of the French neonatal lupus syndrome☆



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Abbreviations: CHB, congenital heart block; DCM, dilated cardiomyopathy; EFE, endocardial fibroelastosis; CTD, connective tissue disease; WG, weeks' gestation; TOP, terminations of pregnancy; HR, hazard ratio; CI, confidence interval.

☆ There is no relationship with the industry.

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ABSTRACT

Background: Cardiac neonatal lupus syndrome is due to anti-SSA or SSB antibodies and mainly includes congenital heart block (CHB) and dilated cardiomyopathy (DCM). Its optimal management is still debated. We report a large series of autoimmune high degree CHB.

Methods: Inclusion criteria in this retrospective study were fetuses or neonates with high-degree CHB associated with maternal anti-SSA/SSB antibodies.

Results: 214 CHB were included: 202 detected *in utero* at a median term of 23 weeks' gestation (WG) [range 16 to 39 WG] and 12 neonatal cases diagnosed at a median age of 0 days [range birth to 8 days]. The 214 cases of CHB included 202 (94.4%) third-degree CHB, 8 (3.7%) second-degree CHB, and 4 (1.9%) intermittent CHB.

In multivariate analysis, the factors associated with fetoneonatal deaths (15.7%) were hydrops ($p < 0.001$; hazard ratio [HR] 12.4 [95% confidence interval (95%CI) 4.7–32.7]) and prematurity ($p = 0.002$; HR 17.1 [95%CI 2.8–103.1]). During a median follow-up of 7 years [birth to 36 years], 148 of 187 children born alive (79.1%) had a pacemaker, 35 (18.8%, one missing data) had DCM, and 22 (11.8%) died. In multivariate analysis, factors associated with child death were *in utero* DCM ($p = 0.0157$; HR 6.37 [95%CI: 1.25–32.44]), postnatal DCM ($p < 0.0001$; HR 227.58 [95%CI: 24.33–2128.46]) and pacemaker implantation ($p = 0.0035$; HR 0.11 [95%CI: 0.02–0.51]). The use of fluorinated steroids was neither associated with survival nor with regression of 2nd degree CHB.

Conclusion: In this second largest series of CHB, we confirm some of the previous results. We were unable to find data supporting the routine use of *in utero* fluorinated steroids.

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1. Introduction

Neonatal lupus syndrome caused by passive transplacental passage of maternal anti-SSA and/or anti-SSB antibodies is a rare disorder mainly represented by cardiac neonatal lupus and skin rash. Cardiac manifestations include congenital heart block (CHB), endocardial fibroelastosis (EFE) and dilated cardiomyopathy (DCM) [1–9]. CHB is defined by atrio-ventricular block occurring in utero or in the neonatal period (<28 days of life) [9]. Its prevalence is less than 1% in anti-SSA-positive women [9,10] and the recurrence rate is estimated at 19% [11]. Its treatment is currently very controversial. Fluorinated steroids, that do cross the placenta, have been used for some decades, including in France but their efficacy has been recently challenged by 2 different groups [12,13].

International efforts have attempted to improve the understanding and management of this condition, with major contributions from different groups [8,12,14–19]. However, registries are needed to improve our knowledge and the management of CHB. Buyon first established the US registry of neonatal lupus and recently reported 312 cases of second- and third-degree CHB [13]. A European and Brazilian study,

which did not include French cases, reported 175 CHB cases, but only 131 with anti-SSA or anti-SSB antibodies [12]. To our knowledge, no data on other large registries are available.

Here, we give a descriptive analysis of 214 cases of high-degree CHB associated with maternal anti-SSA and/or -SSB antibodies that are included in the neonatal lupus French registry.

2. Patients and methods

2.1. Patients

This registry, established in 2000 with Institutional Review Board approval, includes fetuses or children with neonatal lupus born to mothers with anti-SSA and/or anti-SSB antibodies. Inclusion criteria were (1) enrolment in the registry by September 2014, (2) maternal anti-SSA and/or anti-SSB antibodies, (3) confirmation of second- or third-degree CHB documented by electrocardiography and/or fetal echocardiography, and (4) diagnosis of CHB *in utero* or in the neonatal period. In cases of CHB progression or CHB regression, we considered

for inclusion the most severe degree of CHB present during the evolution. We excluded cases of isolated first-degree CHB or isolated EFE.

2.2. Methods

Data collection was as thorough as possible by the receipt of information from the physicians involved in each case and from the parents. Maternal age at birth, race/ethnicity and presence of a connective tissue disease (CTD) were assessed.

In utero information on pregnancies was collected, including the time of occurrence of CHB, the lowest prenatal ventricular heart rate, the presence of EFE, pericardial effusion, hydrops fetalis, DCM, valvulopathy or other anomalies (including ventricular and atrial-septal defects, intra-auricular communication), as well as treatment for CHB (dose and duration). The cardiac echography were performed by cardiologists specialized in fetal heart ultrasound. We used the same standard definition for hydrops fetalis (abnormal accumulation of fluid in 2 or more fetal compartments), presence of EFE (abnormal areas of echogenicity on the endocardial surface of the cardiac chambers and/or valve leaflets), valvular disease (moderate to severe valves stenosis and/or regurgitation excluding the tricuspid regurgitation because of its functional relationship with the underlying cardiac disease), and DCM (increased size of the left ventricle or multiple chambers in the absence of chamber wall hypertrophy with associated decreased contractility) as those used by Izmirly et al. [13]. Cardiomegaly was defined by increased cardiac chamber diameter without decreased contractility.

For children, we collected information on pacemaker implantation, postnatal DCM and death. The presence of postnatal DCM was defined by left ventricular systolic dysfunction with left ventricle ejection fraction <45% and overt left heart failure requiring treatment or by death related to end-stage heart failure.

2.3. Statistical analysis

Survival distribution for mortality was estimated by the Kaplan–Meier method with approximate weeks since conception used as the time scale for deaths that occurred *in utero* or in the first week of life (neonates born alive were censored at the time of birth) and years after a live birth in the live analysis (neonates born alive were censored at the time of last follow-up). Survival distribution for CHB cases with DCM was estimated by the Kaplan–Meier method with years after the live birth used as a time scale. CHB cases with no DCM diagnosis were censored at the time of last follow-up, and only live births were included in this analysis. To account for the within-cluster correlation due to multiple offspring from the same mother, shared frailty models were used to identify potential risk factors of survival (i.e., death or DCM) and to estimate corresponding hazard ratios (HRs) with 95% confidence intervals (95% CIs). In such models, cluster effects were incorporated as independent and identically distributed random variables. Multivariate models were fit by a backward selection approach based on an initial model that included all covariates significant at the 0.20 level on bivariate analyses.

The distribution of time to pacemaker implantation was estimated by the Fine and Gray model, considering death as a competing risk event.

$P < 0.05$ was considered statistically significant. Statistical analysis involved use of SAS 9.4 (SAS Inst. Inc., Cary, NC).

3. Results

3.1. Patient demographics

By September 2014, the registry included 254 cases of cardiac neonatal lupus: 214 cases of second- or third-degree CHB, 19 cases of EFE, 13 heart blocks diagnosed after the neonatal period and 8 other miscellaneous manifestations. To have homogeneous data and

according to our inclusion and exclusion criteria, we analyzed data of the 214 advanced CHB cases.

These 214 fetuses or children were born to 195 mothers between 1976 and 2014 (142 pregnancies between 2000 and 2014); 194 mothers (99.5%) were positive for anti-SSA antibodies and 117 (60%) were positive for anti-SSB antibodies. In total, 115 mothers (59%) were of European origin (i.e. white/Caucasian population of Europe), 45 (23.1%) were from North Africa, 21 (10.8%) were of Afro-Caribbean origin and 13 (6.7%) were of another origin (one missing data). When their first child with CHB was diagnosed, only 51 mothers (26.2%) fulfilled the classification criteria for an autoimmune disease: Systemic Lupus Erythematosus ($n = 23$), Sjogren syndrome ($n = 14$), undifferentiated connective-tissue disease ($n = 7$), or other autoimmune disease ($n = 7$).

Two hundred and two cases (94.4%) were diagnosed *in utero* at a median term of 23 weeks' gestation (WG) [range 16 to 39 WG] and 12 (5.6%) were diagnosed in the neonatal period at a median age of 0 days [birth to 8 days] (Fig. 1).

CHB was initially incomplete in 35 fetuses (11 with intermittent CHB and 24 second-degree CHB), and some of them progressed to complete CHB. If we considered the highest degree of CHB shown by the fetus/child during evolution, the 214 cases of CHB included 202 (94.4%) third-degree CHB (i.e. complete CHB), 8 (3.7%) second-degree CHB, and 4 (1.9%) intermittent CHB.

3.2. Outcomes of fetal CHB

To analyze the fetal prognosis and the efficacy of *in utero* treatment, we excluded the 12 cases diagnosed in the neonatal period, leaving the 202 CHB diagnosed *in utero*.

Among the 202 cases were 175 (86.6%) children born alive at a median term of 37 WG [28 to 41 WG], 13 intra-uterine fetal deaths that occurred at a median term of 32 WG [24–38 WG], and 14 elective terminations of pregnancy (TOP) performed at a median term of 25.5 WG [22–36 WG] (Table 1). All fetuses with TOP had a complete CHB, and their mean fetal heart rate was lower than in the other 188 cases ($49 \pm 10/\text{min}$ vs $57 \pm 11/\text{min}$). Four TOPs were requested by the parent(s), and then excluded from survival analysis and the 10 others were performed on fetuses with at least one poor prognosis factor (including hydrops in 6).

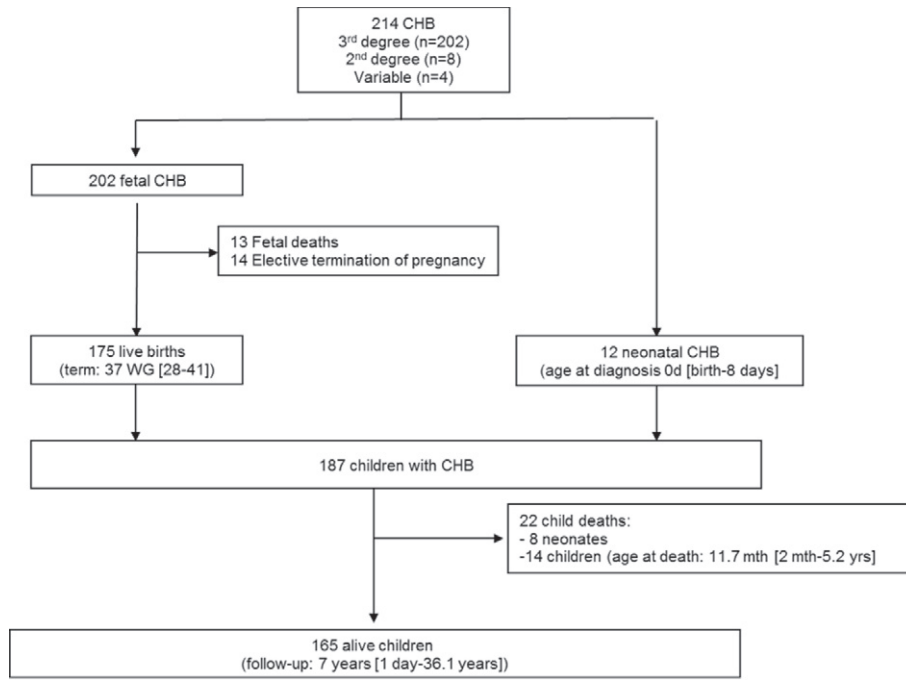
On univariate analysis, factors associated with no live-birth (after excluding the 4 above mentioned TOPs) were nulliparity, EFE, cardiomegaly, *in utero* DCM, pericardial effusion, and hydrops. On multivariate analysis, only the presence of hydrops remained significant ($p < 0.001$; HR 31.8 [95%CI: 11.3–89.5]).

Among the 175 fetuses with CHB born alive, 8 died in the first days of life. They often had been extracted because of their poor condition, and died quickly of heart failure. From a mechanistic point of view, we considered that these deaths were similar to the fetal deaths. Thus the fetoneonatal mortality was 17.3% (35/202) and 15.7% after excluding the 4 TOPs requested by parent(s).

On univariate analysis, factors associated with not being alive at 1 week after birth (after excluding the 4 TOPs) were nulliparity, EFE, cardiomegaly, *in utero* DCM pericardial effusion, hydrops, prematurity (<37 WG) and birth before 2000 (Table 2). On multivariate analysis, two factors remained significant: hydrops ($p < 0.001$; HR 12.4 [95%CI: 4.7–32.7]) and prematurity ($p = 0.002$; HR 17.1 [95%CI: 2.8–103.1]).

3.3. Treatment of fetal CHB

Of the 202 fetuses diagnosed *in utero*, only four received intravenous immunoglobulins and only one was treated with plasma exchanges, precluding any analysis of efficacy of these treatments. By contrast, 79 (39.1%) received fluorinated steroids, with initial doses ranging from 2 to 10 mg/day (4 mg/d for 56 fetuses). The doses were usually



Legends: Data are median [range]. CHB: congenital heart block; WG: weeks' gestation.

Fig. 1. Flow chart of the 214 cases of congenital heart block. **Legends:** Data are median [range]. CHB: congenital heart block; WG: weeks' gestation.

progressively tapered, with a median total duration of treatment of 56 days [10 to 126 days].

We analyzed the effects of steroids on the 24 second-degree CHB, including 13 treated and 11 untreated with fluorinated steroids. Among the 13 treated fetuses, 9 progressed to third degree, 2 had stable second-degree CHB, 1 changed from second-degree to variable CHB (alternating between first and third degree), and 1 regressed from second-degree to no CHB at last follow-up. By comparison, among the 11 untreated fetuses, 8 progressed to third degree, 2 regressed from second to first-degree, and 1 regressed to no CHB in 1. When CHB reached third degree at one point, no regression was observed, whatever the treatment, except for one untreated case. This fetus had second-degree CHB at 27 WG that worsened to third degree *in utero* and was confirmed on electrocardiography at birth. Later, the CHB progressively reversed to first degree without any treatment during pregnancy or childhood. The child still had first-degree CHB at 11 years of age.

Table 1
Mortality of the 214 cases of congenital heart block (CHB) and causes of death.

| | |
|---|---------------|
| Prenatal death (among 202 fetuses) | 27 (13.4%) |
| Fetal death, no. | 13 |
| Elective termination of pregnancy (TOP), no. | 14 |
| Requested by parent(s), no. | 4 |
| Postnatal deaths during a median follow-up period of 7 years [birth to 36 years] (among 185 children) | 22 (11.9%) |
| Neonatal period, no. | 8 |
| Age at death (days), no. | 1.5 [0–6] |
| Causes of death | |
| - Postnatal dilated cardiomyopathy (DCM), no. | 8 |
| Later in life, no. | 14 |
| Age at death (months), median [range] | 11.7 [2–62] |
| Causes of death | |
| - Postnatal dilated cardiomyopathy (DCM), no. | 9 |
| - Infection, no. | 3 |
| - Both, no. | 2 |
| Overall mortality (among 214 cases of CHB), no. (%) | 49 (22.9%) |

3.4. Description of CHB diagnosed in the neonatal period

Twelve of all cases of CHB (5.6%) were diagnosed in the neonatal period at a median age of 0 day [birth to 8 days]: 10 were diagnosed at birth, 1 at 1 day and 1 at 8 days of age. Seven cases had third-degree CHB at discovery. The others had incomplete CHB, which probably explained why they were missed *in utero*: 1 had first-degree CHB that progressed to second-degree CHB, 2 had variable CHB, and 2 had second-degree CHB.

Among these 12 children and after a follow-up of 12.7 years [2 months to 36 years], 10 had received a pacemaker, 3 had developed DCM (2 at 1.6 years, and 1 at 19.6 years of age), and 2 had died (at 2 months from an infection and at 1.7 years from DCM).

3.5. Outcome of children with CHB

The subsequent analyses refer to the 187 surviving children with CHB (175 fetuses with CHB who were born alive plus 12 children with CHB diagnosed in the neonatal period).

3.5.1. Pacemaker implantation

In total, 148 children (79.1%) had a pacemaker implanted at a median age of 1.8 months [birth to 17.3 years]. The cumulative probability of pacemaker implantation at 1, 5 and 10 years was 46.8%, 66.7% and 75.3%, respectively.

Sixteen children with a pacemaker died, 4 in the 3 days after pacemaker implantation. Three of the 4 were neonates with severe DCM, and death occurred despite pacemaker implantation. By contrast, in one otherwise healthy child with a pacemaker at 1 year, severe DCM was diagnosed immediately after the pacemaker implantation, which led to his death in 3 days. The 12 other children died at a median of 9 months [46 days to 4 years] after pacemaker implantation. Among these 12 children, 10 had DCM, diagnosed before the pacemaker

Table 2
Maternal and fetal risk factors of fetoneonatal mortality (n = 198, excluding the 4 cases of elective terminations of pregnancy requested by parent[s]).

| | Deceased (n = 31) | Living (n = 167) | HR overall | p |
|--|----------------------|---------------------|---------------------|---------|
| <i>Maternal risk factors</i> | | | | |
| Non-European origin (n = 197) | 16 (53.3) | 70 (41.9) | 1.28 [0.61–2.70] | 0.50 |
| Maternal age (n = 196), median [range] | 30 [27.8–34.6] | 30.2 [26.3–33.8] | 1.04 [0.97–1.12] | 0.30 |
| Parity > 0 (n = 195) | 14 (45.2) | 114 (69.5) | 0.39 [0.19–0.82] | 0.0112 |
| Anti-SSB antibodies (n = 195) | 21 (70.0) | 100 (60.6) | 1.55 [0.70–3.43] | 0.28 |
| Maternal diagnosis of CTD (n = 198) | 10 (32.3) | 41 (24.6) | 1.66 [0.77–3.6] | 0.20 |
| Hydroxychloroquine ^a (n = 197) | 6 (19.4) | 18 (10.8) | 1.76 [0.71–4.36] | 0.22 |
| Non-fluorinated steroids ^a (n = 185) | 6 (23.1) | 30 (18.9) | 0.92 [0.34–2.48] | 0.87 |
| Fluorinated steroids ^a (n = 198) | 14 (45.2) | 63 (37.7) | 1.52 [0.73–3.16] | 0.26 |
| <i>Fetal echocardiographic risk factors</i> | | | | |
| Gestational age at detection (n = 198), median [range] | 22.5 [22.0–26.0] | 23.0 [22.0–25.0] | 0.97 [0.89–1.07] | 0.54 |
| Ventricular rate at nadir < 50 (n = 183) | 11 (42.3) | 32 (20.4) | 2.25 [0.99–5.12] | 0.0511 |
| Endocardial fibroelastosis (n = 178) | 11 (42.3) | 30 (19.7) | 3.08 [1.38–6.88] | 0.0062 |
| Cardiomegaly (n = 170) | 15 (65.2) | 31 (21.1) | 4.19 [1.70–10.31] | 0.0019 |
| <i>In utero</i> DCM (n = 171) | 9 (39.1) | 3 (2.0) | 15.19 [5.78–39.91] | <0.0001 |
| Pericardial effusion (n = 176) | 23 (82.1) | 44 (29.7) | 15.04 [4.50–50.23] | <0.0001 |
| Hydrops (n = 175) | 16 (59.3) | 6 (4.1) | 31.80 [12.27–82.38] | <0.0001 |
| Valvular disease (n = 176) | 0 (0) | 6 (3.9) | NA | 0.99 |
| Malformation (n = 176) | 1 (4.2) | 32 (21.1) | NA | 0.99 |
| Complete CHB (n = 198) | 31 (100) | 159 (95.2) | NA | 0.99 |
| <i>Neonatal risk factors</i> | | | | |
| Past history of CHB in siblings (n = 198) | 0 (0) | 17 (10.2) | NA | 0.99 |
| Female sex (n = 189 ^b) | 13 (59.1) | 93 (55.7) | 1.19 [0.48–2.92] | 0.70 |
| Year of birth < 2000 (n = 198) | 7 (22.6) | 57 (34.1) | 0.35 [0.13–0.93] | 0.0358 |
| Prematurity (n = 198) | 27 (87.1) | 61 (36.5) | 47.9 [8.52–269.43] | <0.0001 |

This is a bivariate analysis of the factors associated with not being alive at 1 week after birth (after excluding elective terminations of pregnancy).

Legends: Data are no. (%) unless indicated. HR, hazard ratio; CTD, connective tissue disease; CHB: congenital heart block; DCM: dilated cardiomyopathy, Q1: quartile 1; Q3: quartile 3; NA: not applicable.

In total, 33 fetuses or children had at least one cardiac malformation, some combining 2 malformations: atrial septal defect (n = 17), ventricular septal defect (n = 6), patent ductus arteriosus (n = 11), pulmonary stenosis (n = 1), and/or foramen ovale (n = 1).

^a Hydroxychloroquine and non-fluorinated steroids were given for maternal disease whereas fluorinated steroids were given for the CHB.

^b Sex was unknown for some deceased fetuses.

implantation for 2 children, and after a median of 5.9 months [3.5–40.6] after pacemaker implantation for 8 children.

3.5.2. Postnatal DCM

After a median follow-up of 7 years [birth to 36 years], DCM was present or developed in 35 of 186 children (18.8%, 1 missing data). Postnatal DCM was diagnosed at a median age of 5.5 months [birth to 22.8 years]. Among these 35 children, 9 had a pacemaker implantation and 14 died (40%).

3.5.3. Mortality

After a median follow-up of 7 years [birth to 36 years], 22/187 surviving neonates (11.8%) had died: 8 in the first week of life due to severe neonatal DCM and 14 at a median age of 11.7 months [2 months to 5.2 years] (Table 1). Among the 14 children, 9 deaths were directly attributed to DCM, 3 to infection and 2 to both (Table 1).

On univariate analysis, factors associated with death during childhood were maternal treatment with fluorinated steroids and hydroxychloroquine, *in utero* cardiomegaly and DCM, hydrops, and postnatal DCM. On multivariate analysis, factors associated with death were *in utero* DCM (p = 0.0157; HR 6.37 [95%CI: 1.25–32.44]), postnatal DCM (p < 0.0001; HR 227.58 [95%CI: 24.33–2128.46]) and pacemaker implantation (p = 0.0035; HR 0.11 [95%CI: 0.02–0.51]). The use of fluorinated steroids was not associated with survival.

4. Discussion

We report for the first time, data from the French national registry of neonatal lupus syndrome, with 214 cases of high-degree CHB associated with anti-SSA and/or anti-SSB antibodies. By comparison, the two other large studies from the US registry [13] and from a European/Brazilian

registry [12] recently included 278 and 131 of such cases, respectively. Maternal disease data were relatively similar between the three registries, most of the mothers having no CTD. The respective number of cases of complete and incomplete CHB was also very similar as was the cumulative probability of pacemaker implantation [12,13].

The risk of fetoneonatal death was 17.3% (15.7% after excluding 4 TOPs requested by parents). On multivariate analysis, factors associated with fetoneonatal death were hydrops and prematurity. These results are in keeping with previous reports [12,13,20].

Postnatal DCM was present or developed in 35/187 children (18.8%) in our cohort. This rate was 7% in the European/Brazilian study with a shorter follow-up [12] (not available in the US registry [13]). DCM was strongly associated with death since 40% of these 35 children died.

As regularly emphasized [21–23], the management of CHB remains questionable and controversial, especially regarding the use of fluorinated steroids. In our series, 39.1% of cases received fluorinated steroids versus 38% and 47.8%, respectively, in the European/Brazilian and US registries. We first analyzed the effect of fluorinated steroids on CHB degree and we did not observe any association with use of fluorinated steroids: 1 of 13 second-degree CHB cases exposed to fluorinated steroids *in utero* reverted to normal sinus rhythm as compared with 3 of 11 second-degree CHB cases not exposed who reverted to first-degree heart block (n = 2) or normal sinus rhythm (n = 1). Also, an additional case of third degree reverted to first degree without any treatment during pregnancy or childhood. Saleeb et al. first reported a positive effect of fluorinated steroids in this setting with data from the US registry [24]. In the recent update of the US registry, 4 of 13 second-degree CHB cases exposed *in utero* to dexamethasone reverted to first-degree CHB or normal sinus rhythm as compared with 1 of 8 cases not exposed. The analysis of this point in the European/Brazilian registry is difficult given that antibody status was not available for the cases of

incomplete CHB. Then, if we regroup the analyzable cases (ours and from the US registry), for 5 of 26 (19.2%) treated fetuses, CHB reverted to first-degree CHB or normal sinus rhythm as compared with 4 of 19 (21.1%) untreated fetuses.

We then analyzed the effect of fluorinated steroids on the fetoneonatal mortality, and we did not observe any beneficial effects of steroids. This is in keeping with other large studies [12,13]. By contrast, Jaeggi et al. [17] found a 1-year survival rate of 90% in cases treated with fluorinated steroids ($n = 21$) as compared with 46% in those not treated ($n = 13$, $p < 0.02$). However, as emphasized by others [12,21], the authors used historical controls, which had poorer prognosis risk factors and an unusually high rate of death, compared to that of untreated cases of other series [12,13,19], including ours.

Finally, the efficacy of fluorinated steroids to reduce hydrops has been reported by some [24] but not confirmed by others [14,17,20]. We observed such efficacy in our cases, but it did not translate to improved mortality.

This absence of demonstrated efficacy of fluorinated steroids should be balanced against their potential side effects. Adverse events may include adrenal insufficiency, poor clinical tolerance, excessive weight gain in mothers as well as adrenal insufficiency, oligoamnios, fetal death or *in utero* growth restriction mimicking untreated Cushing syndrome in fetuses or neonates [12,17,19,24,25]. Thus, given our result and the literature on the subject, we believe that this treatment should probably not be routinely recommended and should be studied in clinical trials.

Our study contains some limitations, all of which are inherent to study of rare diseases. The data in this study were largely collected in a retrospective manner, and for a few pregnancies, not all of the data were available. Doses and duration of fluorinated steroids were not standardized and we cannot exclude that higher or different doses might have been more effective. Similarly, since only 4 of our cases received a maternal treatment of intravenous immunoglobulins, we cannot exclude its efficacy, or the efficacy of a combined strategy associating plasma exchanges, intravenous immunoglobulins and fluorinated steroids. Since only one neonate was treated with steroids and none received intravenous immunoglobulins, the same remark applied to these types of management. The most important limitation is the size of our series, which limits the power of the analyses. Some prognosis factors may have been missed, and we cannot exclude a moderate effect of fluorinated steroids. An effect on long term prognosis cannot be excluded either. Finally, as previously emphasized [21], comparisons with other registries are especially difficult because of different inclusion criteria, especially regarding the status of maternal antibodies, many studies having included positive as well as negative cases.

5. Conclusion

We confirmed some of the previous results from other large registries. Unfortunately, our data do not support the routine use of *in utero* fluorinated steroids for the treatment of cardiac neonatal lupus syndrome.

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Disclosures

None.

Take-home messages

- Feto-neonatal mortality of CHB was 15.7%.
- Factors associated with feto-neonatal deaths were hydrops and prematurity.
- During a median follow-up period of 7 years [birth to 36 years] of 148

- children born alive, 79% had a pacemaker, 19% had DCM, and 12% died.
- Factors associated with child death were *in utero* DCM, postnatal DCM and pacemaker implantation.
- We found no evidence that the use of fluorinated steroids was associated with improved survival or with regression of 2nd degree CHB.

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Autoantibodies to membrane-associated Estrogen Receptor α seem to have a pathogenetic role in systemic sclerosis

Immunomodulatory effects of estrogens have a clinical impact on immune-mediated rheumatic diseases, including systemic sclerosis (SSc). Molecular effects of estrogens are mediated by both intracellular estrogen receptors (ER), i.e. ER α and ER β , and membrane-associated ER α . In particular, autoantibodies against membrane-associated ER α seem to act as estrogen agonists, able of interfering with T lymphocyte homeostasis. In order to assess the clinical relevance of autoantibodies to ER α in patients with SSc, **Giovannetti et al. (PloS One 2013;8:e74332)** investigated the prevalence and clinical associations of these antibodies in 71 consecutive patients with SSc. Moreover, the relationship of anti-ER α antibodies with peripheral blood T cell immunophenotype was explored. Serum IgG anti-ER α antibodies were quantitated by specific ELISA in SSc patients and healthy controls, and peripheral T lymphocyte subsets were analysed by flow cytometry, using combinations of conjugated monoclonal antibodies against markers of naïve, central and effector memory lymphocytes and regulatory T cells (Treg). Anti-ER α antibodies were detected in 42% patients with SSc, yet not in healthy controls. The antibodies were associated with SSc disease activity, anti-Scl70 antibody positivity and the diffuse form of the disease. Significant associations between anti-ER α antibodies and ex vivo T cell apoptosis, reduction of peripheral total Treg, and expansion of activated Treg subset, were found, suggesting that autoantibodies to membrane-associated ER α may be implicated in regulatory T cell abnormalities in SSc patients.

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