First Report of the Italian Registry on Immune-Mediated Congenital Heart Block (Lu.Ne Registry)

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Objective: Neonatal Lupus (NL) is a rare syndrome caused by placental transfer of maternal anti-SSA/Ro and anti-La/SSB autoantibodies to the fetus. The rarity of this condition requires the establishment of multidisciplinary registries in order to improve our knowledge.

Method: Inclusion criteria in this retrospective study were the maternal confirmed positivity for anti-SSA/Ro and/or anti-SSB/La antibodies, and the presence of II or III degree congenital heart block (CHB) in utero or neonatal period (up to 27 days after birth).

Result: Eighty-nine cases of CHB were observed in 85 women with 88 pregnancies that occurred between 1969 and 2017. CHB was mostly detected in utero (84 cases, 94.2%), while five cases were observed in the neonatal period. A permanent pacemaker was implanted in 51 of 73 children born alive (69.8), whereas global mortality rate was 25.8% (23 cases): 16 in utero, five perinatal, and two during childhood. By univariate analysis, factors associated with fetal death were pleural effusion ($p = 0.005$, OR $> 100$; CI 95% 2.88–$>$100 and hydrops ($p = 0.003$, OR $= 14.09$; CI 95% 2.01–122). Fluorinated
INTRODUCCIÓN

La lupus neonatal (LN) es un trastorno raro causado principalmente por el paso transplacentario de autoanticuerpos anti-SSA/Ro y/o anti-SSB/La (1, 2), usualmente durante el segundo trimestre de la gestación (3, 4); estas anticuerpos pueden llegar al corazón fetal, induciendo inflamación (macrófago infiltración y células ganglionares), calcificación y fibrosis, que llevan a un bloqueo señal conducido a la auriculo-ventricular. Los más comunes manifestaciones son cutáneas o cardíacas, mientras que los daños hepáticos o citopenia son menos frecuentes. LN puede suceder en los hijos de mujeres con una enfermedad de trato tegido (CTD), generalmente síndrome de Sjögren (SS) o lupus eritematoso sistémico (SLE), pero la mayoría de los casos se han reportado en mujeres asintomáticas.

La participación cardíaca es usualmente irreversible y representa la complicación más temida. Se caracteriza por avanzado bloqueo cardíaco de segundo o tercer grado en un corazón de forma estructuralmente normal.

Anti-SSA/Ro autoanticuerpos se encuentran en más del 85-90% de madres de hijos con CHB (1), y estudios prospectivos de enfermedades en anti-SSA/Ro positivas estiman que el riesgo de CHB es 1-2% (5, 6). La tasa de recurrencia en embarazos consecutivos es aproximadamente 12-19% (1, 7, 8).

Se han realizado varios grupos para abordar la mortalidad y morbilidad asociados con CHB en diferentes países (9-13). La mortalidad varía desde el 16 al 29%, mientras que la supervivencia de los niños que reciben un marcapasos varía de 50 a 79%, con frecuencia dentro del primer año de vida. Las enfermedades son heterogéneas, incluyendo casos no asociados con enfermedades maternas (9-14) (Tabla 1). El Registro Italiano de Lupus Neonatal (Lu.Ne) fue creado para recoger datos también en Italia, con el apoyo de la Sociedad Italiana de Reumatología. El objetivo fue determinar la mortalidad y morbilidad asociados con CHB en un cohorte de mujeres italianas con una confirmación positiva para anti-SSA/Ro y/o anti-SSB/La autoanticuerpos.

PATIENTES Y MÉTODOS

Estudio Cohorte

El registro de Lu.Ne fue creado en 2016, financiado parcialmente por la Sociedad Italiana de Reumatología, aprobado por el Comité de Investigación de la Coordinación de Centro en Brescia. Los criterios de inclusión fueron la confirmación del positivo para autoanticuerpos anti-SSA/Ro y/o anti-SSB/La y la presencia de II o III grado de CHB in utero o dentro del periodo neonatal (0-27 días después del nacimiento) (15) documentado por electrocardiografía y/o ecocardiografía fetal. Los casos de estudio fueron seleccionados entre los que ingresaron al registro hasta mayo de 2018. Los registros médicos de madres embarazadas en 11 centros italianos fueron estudiados retrospectivamente. En casos de variabilidad de CHB grado, el más serio grado de CHB ya había ocurrido fue considerado para el análisis estadístico. Este estudio fue realizado de acuerdo con los principios de la Declaración de Helsinki con el consentimiento informado de todos los participantes y aprobado por el Comité Ético de la Coordinating Center (approval number 2,417) and the participating centers.

Recopilación de datos y definiciones

Los datos se recogieron a través de un formato de cuestionario electrónico en una plataforma REDCap. Los datos se obtuvieron de archivos médicos que incluyen: edad gestacional en el momento de la ocurrencia de CHB, morbilidad y mortalidad asociados con CHB en diferentes países (9-13). La mortalidad varía desde el 16 al 29%, mientras que la supervivencia de los niños que necesitan un marcapasos varía de 50 a 79%, con frecuencia dentro del primer año de vida. Las enfermedades son heterogéneas, incluyendo casos no asociados con enfermedades maternas (9-14) (Tabla 1). El Registro Italiano de Lupus Neonatal (Lu.Ne) fue creado para recoger datos también en Italia, con el apoyo de la Sociedad Italiana de Reumatología. El objetivo fue determinar la mortalidad y morbilidad asociados con CHB en un cohorte de mujeres con una confirmación positiva para anti-SSA/Ro y/o anti-SSB/La autoanticuerpos.

Estos centros no trataron ningún caso. CHB fue incompleto en 24 fetos, y de ellos cinco casos de II grado de block reverte a un grado de block más bajo después de tratamiento. La recurrencia en embarazos posteriores fue de 17.6% (3 de 17). Un tratamiento profiláctico fue introducido en 10 de estos 16 casos (58.8%) después de tratamiento. La supervivencia de los niños mejoró. Algunos centros trataron todos los casos con esteroides y otros trataron los casos grado CHB grado más bajo con tratamiento. Recurrencia del CHB grado fue de 1-2% (16-29%), aunque el porcentaje de niños que requieren la implantación de un marcapasos varió de 50 a 79%, frecuentemente después de tratamiento.

Conclusion: This is the first report from the Italian Registry of neonatal lupus/CHB. The live birth rate was nearly 80%, with nearly two thirds of the children requiring the implantation of a pacemaker. The management of fetuses diagnosed with CHB was heterogeneous across Italian Centers. The registry at present is mainly rheumatological, but the involvement of pediatric cardiologists and gynecologists is planned.

Keywords: pregnancy, congenital heart block, neonatal lupus, outcome, risk factors, therapy
TABLE 1 | Outcome of infants with CHB in the present study and in five large international series of cases (9–13).

|                         | Lopes et al. (9) | Eliasson et al. (10) | Izmiry et al. (11) | Levesque et al. (12) | Van der Berg et al. (13) | Present study |
|-------------------------|-----------------|----------------------|-------------------|----------------------|--------------------------|--------------|
| N. of fetuses           | 57 with normal cardiac anatomy | 175 | 325 | 202 in utero +12 in the neonatal period | 56 | 84 in utero +5 in the neonatal period |
| Total mortality         | 13 (23%)        | 27 (15%)             | 57 (17.5%)        | 49 (23%)             | 9 (16%)                  | 23 (25.8%)   |
| Mortality in utero      | 6 (10%)         | 16 (9%)              | 18 (6%)           | 27 (13%)             | 8 (14.2%)                | 16 (17.9%)   |
| Perinatal mortality     | 7 (14%)         | 10 (6.2%)            | 39 (12.7%)        | 8 (4%)               | 1 (2.3)                  | 5 (5.6%)     |
| PM cumulative prevalence| 29 (56.7%)      | 102 (64%)            | 70% (the cumulative probability) | 148 (79%) | 30 (70%)                  | 51 (69.8%)   |
| Late onset cardiomyopathy| 3 (5.6%)       | 8 (5.8%)             | Four cases of heart transplantation | 35 (18%) | 6 (14%)                  | 2 (2.2%)     |
| Treated with FS         | 6 (10%)         | 67 (38%)             | 152 (47.8%)       | 79 (39%)             | 14 (27%)                 | 60 (71.4%)   |
| Effects of FS           | None            | None on mortality; possibly reversal on II CHB | Possibly reversal on II CHB | None | None | None on mortality; possibly reversal on II CHB |
| Reversal of II degree CHB after FS | None | In 3/7 fetuses treated vs. 0/8 untreated | In 4/13 fetuses treated vs. 1/8 untreated | In 1/13 treated vs. 1/11 untreated | In 2/14 treated vs. 1/42 | Five cases, all treated; see footnote* |
| Variables associated with death | Atrial rate <120 bpm, ventricular rate <55 bpm, hydrops, | Detection <20 gW, ventricular rate <50 bpm, hydrops, impaired left ventricular function | Earlier gestational age, lower ventricular rate, hydrops, EFE | Hydrops, prematurity (<37 weeks gestation) | Not analyzed | Hydrops, pleural effusion |
| Survival rate at 10 years for a child born alive | NA | NA | 86% | 88% | NA | 90% |
| Maternal anti-SSA/Ro antibodies | 72% | 80% of 162 pregnancies with documented antibody status | 100% | 99.5 % | 89% | 100% |

* 1 case regressed from II degree to variable CHB (alternating between I and II degree), 2 from II to I degree and 2 regression from II degree to no CHB. Three out of the five fetuses were treated with a combined protocol composed by fluorinated steroids plus plasmapheresis plus IVIg, one received dexametasone plus plasmapheresis and one only dexametasone. NA, not available; CHB, congenital heart block; EFE, endocardial fibroelastosis; DCM, dilated cardiomyopathy; FS, fluorinated steroids; bpm, beats per minute.

children, we collected information on pacemaker implantation (PM), postnatal DCM, death, and other complications.

Fetal complications were defined according to common definitions (10–13). Atrioventricular block (AVB)-II was defined as the intermittent mechanical dissociation of atrial and ventricular activation diagnosed by M-mode echocardiography and AVB-III as the complete mechanical dissociation of atrial and ventricular activation diagnosed by M-mode (10, 13). AVB-III was assessed only in the recent years, using pulsed Doppler echocardiography in the left ventricular outflow tract to record simultaneously mitral valve inflow and aortic outflow (mitral-aorta), from which the time delay from atrial systole to ventricular systole could be inferred. AVB-I was diagnosed when this fetal mechanical Doppler PR interval was found to be >150 ms (16).

DCM was defined as increased size of the left ventricle or multiple chambers in the absence of chamber wall hypertrophy with associated decreased contractility on echocardiogram (11, 12); endocardial fibroelastosis as the presence of abnormal areas of echogenicity on the endocardial surface of the cardiac chambers and/or valve leaflets on echocardiogram or endocardial fibrosis on biopsy or autopsy. Hydrops fetalis was defined as an abnormal accumulation of fluid in at least two fetal compartments (11, 12).

In each center, autoantibodies tests were performed in a referral laboratory certified for diagnosis.

Statistical Evaluation

Categorical variables were reported as proportion and/or percentage, while continuous variables as mean (±SD) values. Fisher’s exact test or Chi-square test for categorical variables and Student’s t-test or Wilcoxon–Mann–Whitney test for continuous variables were applied as appropriate. Multivariate analysis was not performed due to limited number of cases collected. $P <$
0.05 were considered significant and Odds Ratio (OR) with 95% Confidence Interval (95% CI) was indicated.

RESULTS

Patients

By May 2018, the registry included 89 cases of CHB from 85 patients who had 88 pregnancies. The 85 women were Caucasian (n = 79, 92.9%), African (n = 3, 3.5%), Asian (n = 2, 2.3%), and Afro-Caribbean (n = 1, 1.2%) (Table 2). An organ-specific autoimmune disease was diagnosed in 12 women: autoimmune thyroiditis (n = 8, 9.4%), celiac disease (n = 3, 3.5%), multiple sclerosis (n = 1, 1.2%).

Sixty patients reported previous pregnancies, without previous documented cases of CHB, except for one case of cutaneous NL. When their first child with CHB was diagnosed, 46 mothers (54.1%) fulfilled the classification criteria for CTDs: undifferentiated connective-tissue disease (UCTD) (n = 24, 28.2%), SS (n = 18, 21.2%), SLE (n = 4, 4.7%), whereas the others were considered as anti-SSA/Ro carriers. Few cases of acquired cardiovascular risk factors were collected: two patients were smokers, one suffered from hypertension and obesity, and one had diabetes mellitus.

Four cases of multiple pregnancies were collected: three were spontaneous dichorionic biamniotic twins, with one affected, and one unaffected fetus for each pair. The other multiple pregnancy was a triplet gestation after in vitro fertilization: two out of the three fetuses were affected by CHB (one III and one II degree) and one unaffected. The triplet pregnancy has already been described (17).

Including the triplet pregnancy, three gestations that occurred after assisted reproductive technology procedures were collected. All mothers were anti-SSA/Ro positive by inclusion criteria, and SSB/La antibodies were present in 58.8%. AntiRo52 status was available in 58.8% of the mothers, and all were positive.

The mean age at conception was 31.5 years (SD 5.3, range 22–42), 84 cases (94.4%) were diagnosed in utero at a median term of 21 gestational weeks (gw) (SD 4, range 17–38) and five (5.6%) were diagnosed in the neonatal period (15). CHB was initially incomplete in 24 fetuses (five with alternating II-III degree, two with alternating I-II degree, and 17 II degree). Considering the highest degree of CHB shown by the fetus/child, 71 (66 in utero and 5 neonatal) (79.8%) third-degree (complete) CHB, 18 (20.2%) second-degree CHB were included (Table 2).

Fetal/Neonatal Outcomes

Among the 89 cases, 73 (82%) children were born alive at a mean gestational week (gw) of 35.3 (SD 3.0, range 28–41), 7 elective terminations of pregnancy (TOP) were performed at a mean term of 22 gw, and nine intra-uterine fetal deaths occurred at a mean term of 26 gw (Table 3). All the cases of TOP were CHB grade III. Table 4 reports the univariate statistical comparison of clinical and demographic features among survivors at birth and the deceased. By univariate analysis, factors associated with fetal death were pleural effusion (p = 0.005, OR > 100; CI 95% 2.88–100) and hydrops (p = 0.003, OR = 14.09; CI 95% 2.01–122).

The five cases diagnosed in the perinatal period or within the neonatal period (0–27 days after birth) occurred in the 1970–1980s: all these five newborns had III degree CHB; four of them received a pacemaker at a mean age of 7.2 years (range 2–18).

Treatment

Prior to CHB identification, only a limited number of patients were receiving treatments (Table 5), in all cases for maternal disease: nine were treated with low dose aspirin (LDA), eight with not-fluorinated steroids, seven with hydroxychloroquine (HCQ), and one with immunosuppressive therapy (Table 5).

TABLE 2 | Demographic information.

| Maternal demography          | N = 85 (%) |
|------------------------------|------------|
| ETHNICITY                    |            |
| Caucasian                    | 79 (92.9)  |
| African                      | 3 (3.5)    |
| Asian                        | 2 (2.3)    |
| Afro-Caribbean               | 1 (1.2)    |
| MATERNAL DIAGNOSIS AT CHB DETECTION |          |
| Undifferentiated Connective Tissue Disease | 24 (28.2) |
| Sjögren’s Syndrome           | 18 (21.2)  |
| Systemic Lupus Erythematosus | 4 (4.7)    |
| Carriers of anti-SSA/Ro      | 24 (28.2)  |
| Carriers of anti-SSA/Ro + anti-SSB/La | 15 (17.6) |
| ASSOCIATED ORGAN-SPECIFIC AUTOIMMUNE DISEASE |          |
| Autoimmune thyroiditis       | 8 (9.4)    |
| Celiac disease               | 3 (3.5)    |
| Multiple sclerosis           | 1 (1.2)    |
| None/Unknown                 | 73 (85.6)  |
| AUTOANTIBODIES PROFILE       |            |
| Anti-SSA/Ro                  | 85 (100)   |
| Anti-SSB/La                   | 50 (58.8)  |
| CHB, congenital heart block. |            |

TABLE 3 | Outcomes of 89 cases of CHB.

| Pregnancy outcome               | N = 89 (%) |
|---------------------------------|------------|
| Live birth                      | 73 (82)    |
| Intrauterine fetal death        | 9 (10.1)   |
| Termination of pregnancy        | 7 (7.8)    |
| CHB DETECTION                   |            |
| In utero                        | 84 (94.2)  |
| CHB GRADE                       |            |
| II degree                       | 18 (20.2)  |
| III degree                      | 71 (79.8)  |
| OVERALL MORTALITY               |            |
| In utero                        | 16 (18)    |
| Neonatal                        | 5 (5.6)    |
| Childhood                       | 2 (2.2)    |
After CHB detection, fluorinated steroids (FS) were administered in 60 (71.4%) pregnancies, with a mean total duration of treatment of 9.5 weeks (range 4–18 weeks). Twenty steroid-treated fetuses (33%) received intravenous immunoglobulin (IVIg) and 17 (28.3%) received cycles with plasma exchange as well. Sixteen newborns received IVIg at birth.

Effects of treatments in the 60 treated pregnancies were analyzed and in the majority of the cases no variation in the progression of CHB was observed (46 cases, 76.7%) (Table 5).

CHB was initially incomplete in 24 fetuses, all of them were treated at least with FS; five cases of regression from grade II CHB was observed. In detail: one change occurred from II degree to variable CHB (alternating between I and II degree), two from II to I degree and two regression from II degree to no CHB. Three out of the five fetuses were treated with a combined protocol composed by fluorinated steroids plus plasmapheresis plus IVIg. One received dexamethasone plus plasmapheresis, and one only dexamethasone.

Fourteen cases of newborns small for gestational age, five cases of intrauterine growth retardation, four cases of oligohydramnios, one case of maternal hypertension were recorded in the 60 mothers treated with FS; these complications may be related to the treatment with FS, particularly oligohydramnios and hypertension.

Postnatal Outcomes

Among the 73 live births, five newborns died within 10 days after birth (Table 6). These five children were born prematurely and in four cases death occurred even if a pacemaker was placed at birth.

Out of the remaining 68 children, two died later, one due to late onset DCM at the age of 21 months after a PM placed at birth, and 1 at the age of 6 years for a sudden death, probably due to a thrombotic event, however autopsy was not performed. Another child underwent cardiac transplantation at the age of 17 months for late onset DCM in 2003, and at present he is doing well.

Overall DCM was recorded in six cases at birth, while two cases of late onset DCM were observed (2.2%) (see Table 1). All the children with DCM were permanently paced, and two of them died (25%). Overall a PM was placed in 51 of the 73 children born alive (69.8%): 19 (37.2%) at birth, 10 (19.6%) within the first month of life, 11 (21.5%) within the first year of life, and 11 later (21.5%).

### TABLE 4 | Comparison of clinical and demographic features among children born alive and fetuses died in utero.

|                        | Live birth n = 68 (%) | Deceased n = 16 (%) | p-value |
|------------------------|-----------------------|--------------------|---------|
| **IN UTERO DETECTED PATIENTS (84 CASES)** |                       |                    |         |
| Maternal diagnosis of CTD | 37 (54.4)            | 7 (43.7)           | 0.44    |
| Non-Caucasian ethnicity  | 4 (5.4)               | 2 (12.5)           | 0.31    |
| Maternal age at conception (SD) | 31 (6.03)          | 32 (4.16)          | 0.76    |
| Type of conception      |                      |                    |         |
| Spontaneous             | 64 (94.1)            | 16 (100.0)         | 0.73    |
| Assisted reproduction techniques | 4 (5.9)            | 0                 |         |
| Timing of pregnancy     |                      |                    |         |
| Planned                 | 21 (30.9)            | 6 (37.5)           | 0.767   |
| Unplanned/unknown       | 47 (69.1)            | 10 (62.5)          |         |
| Gestational age at detection (gw) (SD) | 22.8 (4.7)       | 20.7 (1.0)         | 0.27    |
| Ventricular rate at nadir ≤50 bpm (n = 73) | 21 (36.2)       | 6 (40)             | 0.78    |
| Mean ventricular rate at nadir bpm (SD) (n = 73), CHB grade (n = 84) | 44.7 (27.9) | 43.5 (30.8) | 0.41    |
| II degree               | 16 (23.5)            | 2 (12.5)           | 0.3     |
| III degree              | 52 (76.5)            | 14 (87.5)          |         |
| Impaired left ventricular function (n = 71) | 5 (8.9)         | 3 (18.7)           | 0.35    |
| Dilated cardiomyopathy (n = 74) | 10 (1.6)       | 3 (27.3)           | 0.39    |
| Hydrops (n = 82)        | 2 (3.0)              | 5 (31.2)           | 0.003*  |
| Pleural effusion (n = 81) | 0                    | 3 (18.7)           | 0.005** |
| Pericardial effusion (n = 81) | 8 (12.3)        | 5 (31.2)           | 0.12    |
| Endocardial fibroelastosis (n = 81) | 1 (1.5)        | 2 (13.3)           | 0.09    |
| Intrauterine growth restriction (n = 75) | 12 (19.3)       | 3 (23.1)           | 0.71    |
| Oligohydramnios (n = 84) | 5 (7.8%)             | 0                   | 0.58    |

CTD, connective tissue disease; gw, gestational week; bpm, beats per minute; **OR, 14.09; CI 95% 2.01–122; *OR > 100; CI 95% 2.88–100.

### TABLE 5 | Therapy before and after CHB detection.

|                        | Live birth n = 73 (%) | Deceased n = 16 (%) | p-value |
|------------------------|-----------------------|--------------------|---------|
| **THERAPY BEFORE CHB DETECTION** |                       |                    |         |
| LDA                    | 6 (8.2)               | 3 (16.6)           | 0.36    |
| Non-fluorinated steroids | 6 (8.2)             | 2 (12.5)           | 0.67    |
| Hydroxychloroquine     | 7 (9.6)               | 0                  | 0.33    |
| DMARDs                 | 0 (0)                 | 1 (6.2)            | 0.19    |
| **MATERNAL THERAPY AFTER FETAL CHB DETECTION (n = 84)** |                       |                    |         |
| Any treatment          | 50 (73.5)             | 10 (62.5)          | 0.46    |
| Fluorinated steroids   | 50 (73.5)             | 10 (62.5)          | 0.46    |
| Intravenous            | 18 (26.4)             | 2 (12.5)           | 0.41    |
| Immunoglobulin         |                       |                    |         |
| Plasma exchange        | 16 (23.5)             | 1 (6.2)            | 0.28    |
| Other (beta-mimetics)  | 6 (8.9)               | 1 (6.2)            | 0.81    |
| **CHB VARIATION DURING/AFTER THERAPY (n = 60)** |                       |                    |         |
| Regression             | 5 (10)                | 0                  | 0.74    |
| Progression            | 3 (6)                 | 1 (10)             |         |
| Unchanged              | 38 (76)               | 8 (80)             |         |
| Unknown                | 4 (8)                 | 1 (10)             |         |

LDA, low dose aspirin; DMARDs, immunosuppressive therapy.
within the first year of life, more than 50% of the surviving children were paced (40 children, 54.8%).

Recurrence

After the index pregnancy, 14 women had 17 subsequent pregnancies (reviewed in Table 7): three were complicated by a CHB therefore the recurrence rate in our cohort was 17.6%. Nine patients received treatments during 10 pregnancies (58.8%): hydroxychloroquine in 1, IVIg alone in 1, non-fluorinated steroids (for maternal indication) alone in 3, non-fluorinated steroids and IVIg in 3, IVIg and HCQ in 1, and IVIg with plasmapheresis and fluorinated steroids in 1. Non fluorinated steroids and HCQ were administered before pregnancy, fluorinated steroids were introduced at conception in two cases, and IVIG and plasmapheresis were started from week 12 (see Table 7 for details).

Adverse events possibly related with a prolonged use of steroids (maternal hypertension, intra-uterine growth restriction, oligohydramnios) occurred in three. The recurrence rate was not statistically different in mothers who received steroids compared to those who did not (28.6 vs. 11.1%, respectively, p = 0.55), but the numbers are low. All the three recurrences of CHB occurred after an index pregnancy complicated with fetal or neonatal death due to a complete CHB.

Maternal Follow-Up

At the time of index pregnancy, 39 patients were considered as asymptomatic autoantibodies carriers. Two years after the latest pregnancy, 11 patients of them developed signs/symptoms that fulfilled the criteria for connective tissue disease: six cases of UCTD and five of SS. In six patients, a chronic treatment was required: oral steroids in four, HCQ in three, and methotrexate in one.

DISCUSSION

This paper describes the first data from the Italian Registry of neonatal cardiac lupus syndrome, including 89 retrospective cases of CHB associated with anti-SSA/Ro and/or anti-SSB/La antibodies. This registry was created in order to collect the cases diagnosed and treated in different Centers, some of them with a longstanding interest in this rare condition. Although some of the cases included in this registry have been already published (17–20), this remains the first effort to analyze all the data as a collaborative national study.

The results that were obtained are in many aspects in line with the published large retrospective studies (Table 1) (9–13). The number of cases of complete and incomplete CHB (79.8 vs. 20.2%) and the cumulative probability of pacemaker implantation, almost 70%, were very similar to already published data (1, 9–13) (see Table 1).

The risk of fetal mortality in the present cohort was 18% and the overall mortality was 25.8%, slightly higher in our cohort than reported in other publications (see Table 1). On statistical analysis, several risks factors that were associated or had a trend toward an increased risk for mortality were confirmed. The presence of hydrops and fetal serositis are well established risk factors for adverse outcome, confirmed in several previous papers (1, 11, 12). No other risk factors were identified in our cases, in particular fetal mortality was not associated with a maternal diagnosis of SLE or SS at the time of pregnancy or a specific ethnicity as previously reported (11).

Some confusion existed in the past on the definition of “congenital” heart block, with some cases detected after birth; for this reason a multidisciplinary group proposed to define congenital heart block as an atrioventricular block diagnosed in utero, at birth or within the neonatal period (15) and in the present report five cases were diagnosed after birth.

In our registry data on subsequent pregnancies after a case of CHB were also collected; recurrence rate of CHB was 17.6%, strikingly similar to what found (17.4%) (7) in the American Research Registry for Neonatal Lupus; in our registry all the three fetuses with recurrent CHB were born alive.

Till date, the management of CHB remains very controversial and there are no generalized recommendations on how to treat CHB or if a prophylactic treatment is required during pregnancy. Various treatment approaches have been reported, including steroids, plasmapheresis, IVIg, several immunosuppressive agents, and hydroxychloroquine (21). Fluorinated steroids (FS) could cross the placenta because they are only partially inactivated by 11β-hydroxysteroid dehydrogenase complex expressed in syncytial trophoblast cells and have satisfactory bioavailability to the fetus (22), and are the drugs with the largest clinical experience. Side effects of high dose

### TABLE 6 | Pregnancy outcome and postnatal follow-up in pregnancies ended with a live birth.

| Pregnancy outcome | Live birth n = 73 (%) |
|-------------------|----------------------|
| Medium gestational week of delivery (SD) (n = 70) | 35.3 (3.0) |
| Delivery (n = 73) | cesarean section 58 (82.3) | vaginal 12 (17.1) | unknown 3 (6) |
| Preterm deliveries <37 weeks | 53 (72.6) |
| Preterm deliveries <34 weeks | 26 (35.6) |
| Sex (n = 71) | female 44 (62) | male 27 (38) |
| Medium weight at birth (grams) (SD) (n = 69) | 3405.5 (553.5) |
| Medium length (cm) (SD) (n = 40) | 40.5 (5.8) |
| APGAR (1-10) (n = 55) | 8.5 (1) |
| DCM at birth (n = 72) | 5 (7.0) |

**POSTNATAL OUTCOME**

| At birth/Neonatal PM implantation | 29 (39.7) |
| Neonatal death | 5 (6.8) |
| Infant/childhood PM implantation | 22 (30.1) |
| Infant/childhood death | 2 (3.1) |
| Overall PM pacing | 51 (69.8) |
| Overall mortality | 23 (31.5) |

DCM, dilated cardiomyopathy; PM, pacemaker.
TABLE 7 | Subsequent pregnancies after an index pregnancy complicated with CHB: treatment and pregnancy outcomes.

| Index pregnancy outcome | Maternal diagnosis | Year of pregnancy | Fetal ECHO | Treatment | Pregnancy outcome | Pregnancy complications |
|-------------------------|-------------------|------------------|------------|-----------|------------------|------------------------|
| Pt 1 CHB III degree, born alive | SS | 2006 | yes | Prednisolone 28 mg/w IV Ig 400mg/kg every 3 w between 12 and 24th gw | Born alive, without CHB | no |
| Pt 2 CHB III degree, neonatal detection, infant death | SS | 1978 | yes | no | Neonatal CHB III degree | no |
| Pt 3 CHB III degree, born alive | Carrier anti-SSA/Ro | 2014 | yes | no | Born alive, without CHB | no |
| Pt 4 CHB III degree, infant death | UCTD | 2003 | yes | no | Born alive, without CHB | no |
| Pt 5 CHB II degree, born alive | SS | 2007 | yes | IV Ig 400 mg/kg every 3 w between 12 and 24th gw HCQ 200 mg/daily | Born alive, without CHB | no |
| Pt 6 CHB III degree, TOP | UCTD | 2006 | yes | Prednisone 35 mg/w; IV Ig 400 mg/kg every 3 w between 12 and 24th gw 2008 | yes | Prednisone 25 mg/w; IV Ig 400 mg/kg every 3 w between 12 and 24 th gw | Born alive, without CHB | Maternal hypertension |
| Pt 7 CHB III degree, TOP | SS | 2002 | yes | Prednisone 35 mg/w; | Born alive, without CHB | no |
| Pt 8 CHB III degree, intra-uterine fetal death | Carrier SSA/Ro +SSB/La | 2012 | yes | Betametasone 28 mg/w; IV Ig 1 g/kg every 2 w for 13w, Plasmapheresis for 14 w | CHB II degree | Olygohydramnios |
| Pt 9 CHB III degree, born alive | UCTD | 1999 | yes | Betametasone 10 mg/w | Born alive, without CHB | IUGR, maternal hypertension |
| Pt 10 CHB III degree, intra-uterine fetal death | Carrier SSA/Ro +SSB/La | 2001 | yes | Dexametasone 28 mg/w | CHB III degree | PM at birth |
| Pt 11 CHB III degree, TOP | UCTD | 2007 | yes | IV Ig 400 mg/kg every 3 w between 12 and 24th gw | Born alive, without CHB | no |
| Pt 12 CHB III degree, born alive | Carrier SSA/Ro +SSB/La | 2015 | yes | no | Born alive, without CHB | no |
| Pt 13 CHB III degree, intra-uterine fetal death | UCTD | 2014 | yes | HCQ | Born alive, without CHB | Olygohydramnios |

We did not include in the table one case that ended with an early termination of pregnancy required by parents at 11 gw. ECHO, echocardiography; HCQ, hydroxychloroquine; TOP, termination of pregnancy; PM, pacemaker; UCTD, undifferentiated connective tissue disease; SS, Sjögren Syndrome; IUGR, intra-uterine growth restriction; IV Ig, intravenous immunoglobulin; HCQ, hydroxychloroquine.

FS during pregnancy may be important: increased blood pressure, osteopenia, osteonecrosis, susceptibility to infections, gestational diabetes, premature rupture of the membranes and olygohydramnios. In the present study 60 women were treated with FS: olygohydramnios occurred in 6.6% of cases, intrauterine growth retardation in 8.3% and hypertension in 1.7%.

Retrospective data over a wide time span ranging from the 1970s through 2017 were collected in the present study, therefore the treatment strategies were very heterogeneous. Steroids resulted as the most used drugs, reaching the highest rate compared with other registries (see Table 1) and this result confirms that there is no consensus regarding treatment with steroids. Moreover, in many occasions, it depends on the historical approach followed in the single center (23): some centers treated no patients, irrespective of the fetal status, whereas in others hospitals FS were used almost in all cases. The most consistent data on the possible efficacy in CHB were
published by Jaeggi et al. (24) in 2004. The authors reported a higher one-year survival rate and less complications or features associated with NL in 21 treated complete CHB compared with 11 patients who did not receive FS. This study, however, displays some limitations. Firstly, the authors compared fetuses from two different eras: the historical cohort from 1990 to 1996 did not receive steroids, whereas all fetuses between 1997 and 2003 were treated. A second important limitation was the higher rate of risk factors for a poor prognosis present in the untreated cohort. Subsequent works did not confirm these findings (10–12, 25). In fact, we also did not find any significant differences on fetal mortality between the groups treated and not with FS, which is consistent with the large international series.

In particular Izmirlly et al. (25) compared 71 fetuses with isolated CHB who received FS within 1 week of detection with 85 who received no treatment and evaluated the development of EFE, dilated CMP, hydrops, mortality, and PM implantation. These authors observed that FS did not significantly prevent development of disease beyond the atrio-ventricular node [adjusted Hazard Risk (HR) = 0.90; p = 0.77], nor reduce mortality (HR = 1.63; p = 0.47), or forestall/prevent PM implantation (HR = 0.87; p = 0.53), so they concluded that no evidence supports fluorinated steroids to prevent disease progression or death in isolated CHB.

Another possible indication for the use of FS is for the prevention of the evolution from incomplete to complete CHB. Whereas, complete CHB is considered irreversible, regression from incomplete block after treatment has been described (10, 11, 26–28). In our cohort an improvement was observed in five cases, all treated with FS and three treated with a combination therapy recently published (29). In brief, in that paper (29) the authors wanted to summarize the possible effects of each single procedure: they demonstrated that plasmapheresis could remove anti/SSA-Ro autoantibodies (30), FS could reduce local inflammation and IVIg could limit the effects of autoantibodies. They used this approach in 12 patients with second or third degree CHB. No variation occurred in the six cases with complete CHB, whereas an improvement occurred in 50% of second degree CHB. The authors reported no side effects in the fetuses or in the mothers, proposing this combination therapy as a therapeutic option in second degree CHB. Unfortunately, since such improvement has been observed also in the absence of any treatment (12) or only with FS, it is not possible to draw any definite conclusion. The recent paper by Cuneo et al. (28) underlines as timing may be very relevant for a possible therapeutic windows.

Several hypotheses have been proposed showing the potential usefulness of IVIG to prevent cardiac tissue damage: firstly increasing the elimination of maternal autoantibodies through IVIG saturation, secondly decreasing placental transport of autoantibodies through FcyRn leading to the modulation of inhibitory signaling on macrophages, with consequent reduction of the inflammatory response and fibrosis. This explain the patients treated during pregnancies and the 16 newborns treated immediately after birth (31–33).

There are no specific guidelines for the prevention of recurrence of CHB in subsequent pregnancies and this explains the extreme heterogeneity of treatment that was observed in this cohort, ranging from only clinical and echocardiography monitoring to combined therapies during pregnancy. Non-fluorinated steroids do not cross the placenta and would not be useful at all. Intravenous immunoglobulin has been proposed in the prevention of recurrence in small case series and in two prospective studies that were performed in Europe and in United States (34, 35) with a similar protocol (400 mg/kg every 3 weeks from 12 to 24 gw). Four of our cases were included in the European trial. Both the studies were terminated early because of an unchanged prevalence of recurrence and it was concluded that IVIg at the proposed dose was ineffective at reducing the recurrence rate of cardiac NL.

In the last years, the use of HCQ was shown to be a possible approach to the secondary prevention of the recurrence of CHB. Retrospective analysis from an international cohort (36) reported a higher recurrence rate in pregnancies not treated with HCQ compared with those treated with HCQ. In our study only a limited number of pregnancies were exposed to HCQ not allowing any possible further analysis. However, since the use of HCQ is compatible with pregnancy (37) and is generally a well-tolerated drug, it may be proposed in patients with known antibody positivity.

Our study has several limitations. Data were collected retrospectively and in some pregnancies not all of the data were available, which limits the power of our statistical analysis. It is well established that the distinction between II and III degree AV block in utero may be difficult, problematic and time consuming and, when revised centrally, some diagnoses of II degree might be reclassified as III degree and vice versa (13). For this paper it was not possible to reassess the diagnosis centrally therefore some complete CHB could be misdiagnosed as incomplete (13). CHB cases whose mothers were anti-SSA/Ro negative were not included (17). This first report of the registry is mainly driven by rheumatological centers, and some geographical Italian regions are not represented; only the centers whose ethical committees approved the study enrolled cases for this initial analysis. This peculiarity might also explain why in our registry the majority of the mothers already had a diagnosis of CTD at the time of the index pregnancy, an evidence that differs from other experiences. The syndrome of course requires a multidisciplinary approach, not only for the clinical management of each case but also for the systematic collection of the data and their analysis. Pediatric cardiologists and gynecologists play a fundamental role in the management of this condition, and it is planned to involve them in further collections and analyses of data.

In conclusion, this is the first preliminary report of the data from the Italian Registry of neonatal cardiac lupus syndrome, that was established in 2016. Italian centers showed an heterogenous pattern of management of CHB fetuses, with
some centers treating all cases with FS and some centers treating no cases. The establishment of this registry might help to share the data, to make more homogenous the management of this rare condition and to stimulate further multidisciplinary studies.

AUTHOR CONTRIBUTIONS

AB, AT, MF, and LA: designed the study. MF, SC, VC, and LA: created the registry on RedCap platform. MF, TB, AB, SF, FC, RC, SD, ED, EE, FF, MG, MGo, AH, AL, LM, AMi, PM, AM, MMO, MMu, MeP, MaP, RP, VR, AR, CT, MT, LT, and SZ: evaluated the patients. MF, TB, ABo, SF, FC, ED, MG, AH, AMi, MeP, MaP, VR, CT, BB, and MT: recruited the patients. MF, LA, AB, and AT: wrote the manuscript. All the co-authors reviewed the manuscript.

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