ORIGINAL RESEARCH

Outcome of Antibody-Mediated Fetal Heart Disease With Standardized Anti-Inflammatory Transplacental Treatment

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BACKGROUND: Transplacental fetal treatment of immune-mediated fetal heart disease, including third-degree atrioventricular block (AVB III) and endocardial fibroelastosis, is controversial.

METHODS AND RESULTS: To study the impact of routine transplacental fetal treatment, we reviewed 130 consecutive cases, including 108 with AVB III and 22 with other diagnoses (first-degree/second-degree atrioventricular block [n=10]; isolated endocardial fibroelastosis [n=9]; atrial bradycardia [n=3]). Dexamethasone was started at a median of 22.4 gestational weeks. Additional treatment for AVB III included the use of a β-agonist (n=47) and intravenous immune globulin (n=34). Fetal, neonatal, and 1-year survival rates with AVB III were 95%, 93%, and 89%, respectively. Variables present at diagnosis that were associated with perinatal death included an atrial rate <90 beats per minute (odds ratio [OR], 258.4; 95% CI, 11.5–5798.9; \(P<0.001\)), endocardial fibroelastosis (OR, 28.9; 95% CI, 1.6–521.7; \(P<0.001\)), fetal hydrops (OR, 25.5; 95% CI, 4.4–145.3; \(P<0.001\)), ventricular dysfunction (OR, 7.6; 95% CI, 1.5–39.4; \(P=0.03\)), and a ventricular rate <45 beats per minute (OR, 12.9; 95% CI, 1.75–95.8; \(P=0.034\)). At a median follow-up of 5.9 years, 85 of 100 neonatal survivors were paced, and 1 required a heart transplant for dilated cardiomyopathy. Cotreatment with intravenous immune globulin was used in 16 of 22 fetuses with diagnoses other than AVB III. Neonatal and 1-year survival rates of this cohort were 100% and 95%, respectively. At a median age of 3.1 years, 5 of 21 children were paced, and all had normal ventricular function.

CONCLUSIONS: Our findings reveal a low risk of perinatal mortality and postnatal cardiomyopathy in fetuses that received transplacental dexamethasone±other treatment from the time of a new diagnosis of immune-mediated heart disease.

Key Words: cardiomyopathy □ fetal □ heart block □ outcome □ steroids □ treatment

Neonatal lupus erythematosus (NLE) refers to a spectrum of maternal antibody-mediated fetal and early childhood disorders. The most important disease manifestations of NLE are cardiac and associated with the fetal exposure to high-titer maternal anti-Ro antibodies. The current understanding of the disease origin is that these antibodies increasingly enter the fetal circulation during midgestation, where they may bind to fetal proteins and trigger a cascade of inflammatory responses in the susceptible fetus. Subsequent fibrosis of injured cardiac tissues may then manifest as atrioventricular block (AVB), sinus node disease (SND), endocardial fibroelastosis (EFE), and dilated cardiomyopathy (DCM). Complete or third-degree AVB (AVB III), the main cardiac manifestation, characteristically develops between 18 and 24 gestational weeks. Incomplete first-degree AVB or second-degree AVB (AVB II) heart block are rare fetal observations that may rapidly progress to AVB III. Other disorders, such as EFE and SND, may present with and without AVB. AVB III carries a significant risk of mortality as the fetus needs to adapt to the sudden...
onset of sustained bradycardia and perhaps concomitant injury of the myocardium. Findings previously associated with perinatal mortality have included an earlier gestational age at diagnosis, a ventricular rate ≤50 beats per minute (bpm), hydrops, EFE, ventricular dysfunction, and prematurity.8,9 Moreover, 5% to 30% of live births with AVB III will develop DCM in early childhood with high odds of the need of heart failure treatment, cardiac transplantation, and/or premature death.6,10,11

Although there is widespread agreement that cardiac NLE represents a spectrum of potentially lifethreatening conditions, there is no consensus on the optimal prenatal management, including indications on the use of anti-inflammatory medication. Although some centers systematically offer transplacental fetal treatment (TFTX) with steroids to control the cardiac inflammation and reduce the risk of further tissue damage,12 others have used TFTX inconsistently, infrequently, or not at all.9,12–16

The present retrospective multicenter study examined the impact of routine TFTX with steroids on the different cardiac NLE manifestations. In addition, we compared the outcome of fetuses diagnosed with advanced AVB in this study with the results of predominantly untreated patient series in the literature.

METHODS

The study was approved by the Institutional Research Ethics Boards at all participating centers. The requirement of patient consent for study enrollment was waived. The data that support the findings of this study are available from the corresponding author on reasonable request.

Patients

Included were all fetal cases diagnosed with cardiac NLE until July 1, 2019, that received TFTX according to the following protocol. Our recommendations included:

1. Initiation of maternal dexamethasone administration at a dose of 4 to 8 mg/d on the diagnosis of cardiac NLE, including various degrees of AVB, EFE/carditis, and sinus bradycardia, and the gradual reduction or, on occasion, complete weaning off of the steroid dosage during the third trimester.
2. Addition of β-stimulation with maternal salbutamol (30–40 mg/d) or terbutaline (5–30 mg/d) for ventricular bradycardia below 50 to 55 bpm and/or ventricular dysfunction.12,17
3. Addition of maternal intravenous immune globulin (1 g/kg or 70 g/dose; between one dose to every 2–3 weeks to birth; 2 g/kg given to the infant at birth) for extensive EFE or incomplete AVB.18,19 If these findings persisted to birth, prednisone (1 mg/kg per dose twice daily) was continued by some sites for up to 8 weeks after birth.

Mothers received a stress dose of steroids during labor and then were slowly weaned off the medication to avoid adrenal insufficiency. American College of Cardiology/American Heart Association class I indications were used as criteria for postnatal pacing.20

Excluded from the study were patients who: (1) elected pregnancy termination without TFTX (n=7); (2) declined prenatal steroid treatment (n=3; 2/3 live born); (3) did receive steroids but only later in gestation (n=6; 6/6 live born); or (4) were not offered steroids (n=5;
late-gestational AVB III [n=4]; maternal renal failure [n=1]; 5/5 live born). Also not included were anti-Ro/La antibody-negative pregnancies with fetal AVB, as steroids are not advised in this situation.$^{21}$

Methods

Detailed fetal echocardiograms to evaluate the cardiac anatomy, rhythm, function, and hemodynamics were obtained in all cases. AVB I was defined as 1:1 atrioventricular conduction with atrioventricular prolongation >6 z-score of the normal mean for gestational age, which is unlikely to resolve spontaneously.$^{22}$ AVB II was diagnosed when normal atrial impulses failed to consistently conduct to the ventricles. AVB III was defined by the complete absence of atrioventricular conduction. AVB II to AVB III was diagnosed when there were episodes of AVB II and AVB III. The diagnosis of hydrops was based on the presence of effusion in at least 2 of the fetal body compartments. EFE was identified as areas of abnormal echogenicity of endocardial surfaces of the cardiac chambers and/or valvar leaflets. The diagnosis of DCM was based on the postnatal development of left ventricular (LV) dysfunction (LV ejection fraction <50%) and LV dilation.$^{8}$

Institutional data were collected by the site investigator and entered in a Research Electronic Data Capture platform for data analysis.$^{23}$ Data collected on the mother included age, maternal antibodies, health condition and treatment, and previous children with NLE. Collected pediatric data included gestational age at NLE diagnosis and birth, birth weights, gestational age adjusted birth weight percentiles,$^{24}$ spectrum, severity, and evolution of cardiac findings, treatment, and outcome to December 31, 2019. To determine the impact of routine TFTX on outcome, our findings were compared with the results of predominantly untreated cohorts with a prenatal diagnosis of antibody-mediated AVB II and AVB III that have been published in the medical literature since 2007.$^{9,13-16}$

Statistical Analysis

Clinical characteristics were described using summary statistics, overall and by diagnostic groups (ie, the type of AVB or, if absent, of other findings). Continuous variables were characterized using mean and SD or median and interquartile range (IQR), as appropriate. In addition, we assessed baseline fetal findings in growth-restricted versus normally grown newborns and evaluated the differences using 2-sample t-tests for continuous variables and Fisher exact tests for dichotomous and polytomous variables. Next, fetal/neonatal death and live births were reported among the fetal cases with AVB III. The associations of the baseline fetal findings with fetal/neonatal death were assessed using logistic regression and are reported in terms of odds ratios and 95% CIs. Kaplan-Meier survival estimates were used to plot freedom from fetal and postnatal death and permanent pacing curves of live births with AVB III. Finally, we contrasted our results in fetal cases with AVB II or AVB III with those previously published ones. In this exercise, we reported the median and range of continuous variables as in the previous publications. For dichotomous and polytomous variables reported, we evaluated between-study differences using Fisher exact tests. All analyses assume a significance level of 5%.

RESULTS

Baseline Characteristics

Table 1 summarizes the clinical characteristics, treatment, and outcomes of all 130 study cases by NLE diagnosis. A total of 108 fetuses (83%) were diagnosed with AVB III, 2 (1.5%) with AVB II to AVB III, 4 (3%) with AVB II, 4 (3%) with AVB I, 3 (2.3%) with atrial bradycardia, and 9 (7%) with EFE without AVB. Institutional patient numbers, including the year of start of routine steroid use at a site, were as follows: The Hospital for Sick Children, Toronto, ON, Canada (n=72; since 1997); Centre Hospitalier Universitaire Sainte-Justine, Montréal, QB, Canada (n=17; since 2001); Stollery Children’s Hospital, Edmonton, AB, Canada (n=12; since 2009); Children’s Hospital Colorado, Denver, CO (n=8; since 2013); Children’s Hospital of Eastern Ontario, Ottawa, ON, Canada (n=8; since 2010); UCSF Benioff Children’s Hospital, San Francisco, CA (n=8; since 1998); and Rush University Medical Center, Chicago, IL (n=5; since 2008). Twenty-one patients with AVB III/EFE had been reported in earlier studies.$^{12,18}$ All mothers were anti-Ro antibody positive, 59% (n=77) were anti-La antibody positive, 8% (n=11) had a previous child with immune-mediated AVB, and 11% (n=15) were receiving hydroxychloroquine before 10 gestational weeks.

Transplacental Treatment

Gestational age at diagnosis and the start of steroids of the different NLE subtypes were comparable (Table 1). In all cases, dexamethasone was started within 1 week of the cardiac anomaly diagnosis at a daily dose of 8 mg (59%), 6 mg (1.5%), 4 mg (39%), or 2 mg (0.7%), respectively. The dosage was maintained in 32 (mainly at 4 mg/d), was reduced in 87 (mainly to 2 mg/d), and was stopped before delivery in 11. Overall, patients started on 8 mg/d of dexamethasone received treatment earlier in gestation (median, 22 [IQR, 20.7–24.1] versus 24 [IQR, 21.3–26.9] weeks; $P=0.01$) and for a longer duration (median, 14 [IQR, 11.6–16.6] versus 10.2 [IQR, 7.9–14] weeks; $P=0.0002$) when compared with the lower starting doses.

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### Table 1. Clinical Characteristics, Treatment, and Outcomes of 130 Fetuses With Cardiac NLE and According to the Primary Diagnosis

| Variable                        | All       | AVB III  | AVB II or AVB II to AVB III | AVB I      | Isolated EFE | SND  |
|---------------------------------|-----------|----------|----------------------------|------------|--------------|------|
| **Maternal demographics**       |           |          |                            |            |              |      |
| Affected pregnancies            | 130       | 108 (83) | 6 (5)                      | 4 (3)      | 9 (7)        | 3 (2) |
| Singleton                       | 123 (95)  | 102      | 6                          | 4          | 8            | 3    |
| Twin                            | 7 (5)     | 6        |                            |            |              |      |
| Maternal age, y                 | 30.7±5.1  | 30.6±5.4 | 29.7±4.4                   | 33.5±3.1   | 31.4±3.5     | 30±2.6 |
| **Race or ethnicity**           |           |          |                            |            |              |      |
| White                           | 75 (58)   | 65       | 4                          | 3          | 2            | 1    |
| Asian                           | 28 (18)   | 23       | 1                          | 1          | 2            | 1    |
| Middle Eastern                  | 15 (12)   | 10       |                            |            |              |      |
| Other race or ethnicity         | 12 (9)    | 10       | 1                          |            |              |      |
| Anti-Ro antibodies              | 130 (100) | 108      | 6                          | 4          | 9            | 3    |
| Anti-La antibodies              | 77 (59)   | 61       | 3                          | 4          | 3            | 3    |
| Collagen disease                | 61 (47)   | 48 (44)  | 4 (67)                     | 2 (50)     | 5 (56)       | 2 (67) |
| Systemic lupus erythematosus    | 30 (23)   | 21       | 3                          | 2          |              |      |
| Sjogren syndrome                | 22 (17)   | 19       | 1                          |            | 1            |      |
| Other/unspecified               | 9 (7)     | 8        |                            |            |              |      |
| Previous cardiac NLE            | 10 (8)    | 6        | 1                          | 2          | 1            | 0    |
| **Fetal baseline findings**     |           |          |                            |            |              |      |
| Age at diagnosis, wk            | 22.1 (20.5–25) | 22.2 (20.7–25.7) | 21.0 (19.9–22.8) | 22.7 (20.7–24.3) | 22.1 (20.8–23.3) | 21.1 (20.6–25.6) |
| Atrial rate, bpm                | …         | 140 (131–145) | 135 (130–145) | 147 (144–151) | 147 (140–160) | 84 (42–67) |
| Ventricular rate, bpm           | …         | 60 (53–66)  | 122 (80–130) | 147 (144–151) | 147 (140–160) | 84 (76–87) |
| Fetal hydrops                   | 10 (8)    | 9 (8)    | 0 (0)                      | 0 (0)      | 0 (0)        | 1 (33) |
| Effusion(s)                     | 38 (29)   | 36 (33)  | 1 (17)                     | 0 (0)      | 0 (0)        | 1 (33) |
| Endocardial fibroelastosis      | 57 (44)   | 42 (39)  | 3 (50)                     | 1 (25)     | 9 (100)      | 3 (100) |
| **Prenatal treatment**          |           |          |                            |            |              |      |
| Dexamethasone                   | 130 (100) | 108 (100)| 6 (100)                    | 4 (100)    | 9 (100)      | 3 (100) |
| 8 mg/d (start)                  | 75 (58)   | 60       | 4                          | 3          | 6            | 2    |
| 6 mg/d (start)                  | 3 (2)     | 2        |                            |            |              | 1    |
| 4 mg/d (start)                  | 51 (39)   | 45       | 2                          | 1          | 3            |      |
| 2 mg/d (start)                  | 1 (1)     | 1        |                            |            |              |      |
| Duration, wk                    | 13 (9–15.6) | 12.3 (9–15) | 15.5 (13.5–16.8) | 15.5 (12.3–16.9) | 16 (12.9–17) | 13 (10.1–15) |
| Total dose, mg                  | 312 (223–398) | 301 (206–389) | 397 (370–455) | 390 (361–423) | 244 (224–330) | 412 (338–424) |
| **β-Mimetic therapy**           | 47 (36)   | 47 (44)  | 0 (0)                      | 0 (0)      | 0 (0)        | 0 (0) |
| Duration, wk                    | 6 (3.3–10.7) | 6 (3.3–10.7) | 3 (3.5–6) | 8 (8) | 4 (4–6) | 2 (2–3) |
| Immune globulins                | 55 (47)   | 34 (31)  | 3 (50)                     | 2 (50)     | 8 (89)       | 3 (100) |
| Maternal injections             | 3 (1–5)   | 3 (1–5)  | 5 (3.5–6)                  | 8 (8)      | 4 (4–6)      | 2 (2–3) |
| Born alive                      | 125 (96)  | 103 (95) | 6 (100)                    | 4 (100)    | 9 (100)      | 3 (100) |
| Age at delivery, wk             | 36.9 (35.1–37.7) | 38.7 (35–37.3) | 37.5 (36.7–38.6) | 38.1 (37.5–38.7) | 37.0 (36.7–38.3) | 38 (35.5–38.1) |
| Birth weight, kg                | 2.4 (2–2.8) | 2.4 (2–2.8) | 2.6 (2.4–3.1) | 2.6 (2.3–2.9) | 2.3 (2–2.7) | 2.7 (2.2–3) |
| Birth weight, percentile        | 15 (4.5–37) | 16 (5–37) | 11.5 (7.8–28.8) | 3 (2.5–12) | 7 (1.8–20.5) | 35 (24.5–40.5) |
| Birth weight <10th percentile   | 39 (31)   | 29 (28)  | 2 (33)                     | 3 (75)     | 5 (56)       | 0 (0) |
| AVB III at birth                | 101 (81)  | 99 (96)  | 1 (17)                     | 0 (0)      | 0 (0)        | 0 (0) |

(Continued)
Sympathomimetics were added in 36% and intravenous immune globulin (IVIG) in 47% of cases and were generally well tolerated, with minimal adverse effects. Maternal effects were severe enough to lower the initial dexamethasone dose in 2 (1.5%) women for mood disturbances, including one episode of psychosis. No other serious maternal adverse events were documented.

Intrauterine growth restriction (birth weight <10th percentile) was documented in 39 (31%) of 125 live births. When compared with a total of 86 normally grown newborns, intrauterine growth restriction was associated with earlier NLE diagnosis (median [IQR], 22 [20–24] versus 23 [21–26] weeks; \( P=0.042 \)), as well as a longer duration (median [IQR], 14.8 [11.5–16.6] versus 12.3 [9–14.9] weeks; \( P=0.014 \)) and a higher amount of prenatal exposure to dexamethasone (361±109 mg versus 294±126 mg; \( P=0.0055 \)). No significant correlations were found between fetal growth restriction and AVB III (29/103 versus other diagnosis: 10/21; \( P=0.12 \)), maternal autoimmune disease (23/39 versus 35/86; \( P=0.081 \)), and the development of oligohydramnios (8/39 versus 10/86; \( P=0.27 \)). Growth-restricted and normally grown newborns did also not differ in gestational age at delivery (median [IQR], 36.9 [36–37.1] versus 36.9 [35–38] weeks; \( P=0.35 \)) and 1-year survival rates (92.3% versus 94.2%; log-rank \( P=0.73 \)).

Of 113 children with follow-up at our centers beyond the first year of life (median [IQR], 6.3 [2.3–12] years), 5 of 93 (5%) with AVB III and 0 of 20 (0%) without AVB III were diagnosed with mild (n=3; learning difficulties), moderate (n=1; global delay/seizures after cardiac arrest secondary to mitral valve chordal rupture), or severe (n=1; genetic disorder) neurodevelopmental delay.

### Outcomes by NLE Diagnosis

**AVB III**

Of initially 108 fetal cases, 1 underwent termination of pregnancy at 23 gestational weeks for maternal eclampsia, 4 died in utero between 23.4 and 29 weeks, and 3 died in the neonatal period. Baseline echocardiographic findings significantly associated with perinatal death by univariate analysis included slower atrial and ventricular rates, ventricular dysfunction, EFE, and fetal hydrops (Table 2). Of the 7 actively managed fetal/neonatal nonsurvivors, 6 initially presented either with an atrial rate <90 bpm (death: 4/4) or a ventricular rate <45 bpm (death: 2/5), with no improvement with treatment. The remaining case, referred at 33 gestational weeks, responded to TFTX with resolution of hydrops, but the finding of hypoxic encephalopathy led to withdrawal of neonatal care. On the other hand, hydrops/effusions and increased cardiac echo brightness resolved with transplacental treatment in 24 of 36 (43%) and 10 of 41 (19%) between the first and last fetal echocardiograms, whereas moderate or severe atrioventricular valve regurgitation had improved in 8 of 10 (80%) with this finding. In 5 fetuses, dexamethasone±IVIG transiently restored 1:1 atrioventricular conduction.

The Figure shows Kaplan-Meier estimates of postnatal survival and freedom from permanent pacing of our cohort with a baseline diagnosis of AVB III. Epicardial ventricular pacing (n=82) was used for all children with a body weight <10 kg and transvenous pacing (n=6) for most of the new pacemaker implants >2 years of age. Six deaths occurred after the neonatal period, mainly from noncardiac causes (renal failure, persistent pulmonary hypertension; sepsis; brain malformation secondary to genetic disorder; and undetermined) and, in one child, from cardiac strangulation by a pacing wire. At a median follow-up of 5.9 (IQR, 2–12) years, 85 of 100 neonatal survivors were paced and 97 of 100 had normal LV function at the last echocardiogram. Of the 3 remaining cases, 2 displayed mild LV dysfunction (ejection fraction, 40%–49%) without the need of anticongestive treatment, whereas one developed severe dysfunction in infancy and required a heart transplant. Finally, spontaneous rupture of

### Table 1. Continued

| Variable | All | AVB III | AVB II or AVB II to AVB III | AVB I | Isolated EFE | SND |
|----------|-----|---------|-----------------------------|-------|-------------|-----|
| Postnatal outcome | | | | | | |
| Follow-up, y | 4.5 (1.8–11.5) | 5.5 (2–12) | 1.9 (1.8–3.1) | 9.4 (8–10) | 3.4 (1.4–7.6) | 1.5 (0.8–4.2) |
| Survival | | | | | | |
| Neonatal | 122 (94) | 100 (93) | 6 (100) | 4 (100) | 9 (100) | 3 (100) |
| To study end | 117 (90) | 94 (87) | 6 (100) | 4 (100) | 9 (100) | 2 (66) |
| Permanent pacemaker | | | | | | |
| Neonatal | 58/125 (58) | 57/103 (55) | 1/6 (17) | 0/4 (0) | 0/9 (0) | 0/3 (0) |
| At study end | 93/125 (74) | 88/103 (85) | 3/6 (50) | 1/4 (25) | 0/9 (0) | 1/3 (33) |
| Dilated cardiomyopathy | 3/122 (2) | 3/99 (3) | 0/6 (0) | 0/4 (0) | 0/9 (0) | 0/2 (0) |

Values are mean±SD, median (interquartile range), or number (percentage). Age indicates gestational age; AVB I, first-degree atrioventricular block; AVB II, second-degree atrioventricular block; AVB III, third-degree atrioventricular block; bpm, beats per minute; EFE, endocardial fibroelastosis; NLE, neonatal lupus erythematosus; and SND, sinus node disease.
fibrotic tricuspid or mitral valvar chordae affected 2 infants with AVB III/EFE at 6 and 4 months and required surgical repair of the tricuspid valve or replacement of the mitral valve, respectively.

**Incomplete AVB**

All 10 cases diagnosed with incomplete AVB survived with normal cardiac function (Table 1). Of 6 cases with AVB II or AVB II to AVB III, 4 displayed transient improvement in fetal atrioventricular conduction with TFTX. At the last postnatal follow-up, however, 4 of them had progressed to AVB III (3 paced). Of 4 fetuses with AVB I, 1 had normal atrioventricular conduction at the last visit, 2 had AVB I, and 1 was paced for AVB II to AVB III.

**Atrial Bradycardia or Standstill**

Atrial bradycardia of 84 and 90 bpm without AVB was observed in 2 fetuses, compatible with isolated SND. Atrial rates did not improve with TFTX. The first patient was delivered with intruterine growth restriction and oligohydramnios at 33 weeks. The child appeared well at hospital discharge but died unexpectedly at home at 2 months of life. The second patient required a dual-chamber antitachycardia pacemaker system at 3.5 years of life after developing atrial flutter and has remained asymptomatic since. A third fetus presented without atrial contractions (atrial standstill) and a ventricular rate of 67 bpm. Postnatal ECGs and a transesophageal atrial pacing study revealed a junctional rhythm at a rate >70 bpm and no atrial activity/capture. At 1.5 years of life, this patient was well and unpaced.

**Isolated Endocardial Fibroelastosis**

Nine fetuses had EFE in the absence of AVB/SND, affecting the ventricular (n=4) and atrial (n=2) walls, papillary muscles (n=7), and/or perivalvar tissues (n=6). Spontaneous rupture of a tricuspid valvar cord occurred in one child at the time of delivery, but this did not require surgical repair. All cases with isolated EFE remain alive, with normal cardiac function and normal 1:1 atrioventricular conduction.

**Comparison of Findings to Previous Studies**

Table 3 summarizes the findings of 5 contemporary publications of fetuses with advanced AVB. As these reports do not allow distinguishing between the management and outcome of AVB II and AVB III, our data

| Table 2. AVB III: Findings Associated With Fetal and Neonatal Mortality |
|----------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Variable                              | Death (n=7) | Alive (n=100) | P Value | OR (95% CI) |
| Maternal findings                     | Maternal age, y | Maternal age, y |
|                                      | 7 35±6.1 | 100 30.3±5.2 | 0.024 |
| Fetal findings                        | Gestational age at diagnosis, wk | Gestational age at diagnosis, wk |
|                                      | 20 (19.4–23.4) | 100 22.6 (21–25.7) | 0.16 |
|                                      | 17–20 wk | 2 (29) | 9 (9) |
|                                      | 20–24 wk | 3 (43) | 50 (50) |
|                                      | 24–28 wk | 1 (14) | 28 (28) |
|                                      | 28–32 wk | 11 (11) |
|                                      | 32 wk | 1 (14) |
|                                      | Atrial rate at diagnosis, bpm | Atrial rate at diagnosis, bpm |
|                                      | 84 (80–132) | 100 140 (133–145) | 0.015 |
|                                      | <90 bpm | 4 (57) | 0 (0) | 258.4 (11.5–5798.9) |
|                                      | Ventricular rate at diagnosis, bpm | Ventricular rate at diagnosis, bpm |
|                                      | 51 (46–56) | 100 60 (54–67) | 0.016 |
|                                      | <45 bpm | 2 (29) | 3 (3) | 12.9 (1.75–95.83) |
|                                      | 45–49 bpm | 0 (0) | 6 (6) |
|                                      | ≥50 bpm | 5 (71) | 91 (91) |
|                                      | Atrial rate <90 bpm or ventricular rate <45 bpm | Atrial rate <90 bpm or ventricular rate <45 bpm |
|                                      | 6 (86) | 100 3 (3) | <0.0001 | 194.0 (17.4–2158.4) |
|                                      | Atrial rate ≥90 bpm and ventricular rate ≥45 bpm | Atrial rate ≥90 bpm and ventricular rate ≥45 bpm |
|                                      | 1 (14) | 100 97 (97) | <0.0001 | 0.005 (0.0005–0.057) |
|                                      | Endocardial fibroelastosis | Endocardial fibroelastosis |
|                                      | 7 (100) | 100 34 (34) | 0.0009 | 28.9 (1.6–521.71) |
|                                      | Hydrops | 7 (57) | 100 5 (5) | 0.0008 | 25.5 (4.4–145.3) |
|                                      | Impaired ventricular function | Impaired ventricular function |
|                                      | 7 (42) | 100 9 (9) | 0.03 | 7.6 (1.5–39.4) |
|                                      | Gestational age at birth, wk | Gestational age at birth, wk |
|                                      | 3 34.6 (31.8–34.8) | 100 36.7 (35–37.3) | 0.027 |

Values are mean±SD, median (interquartile range), or number (percentage). AVB III indicates third-degree atrioventricular block; bpm, beats per minute; and OR, odds ratio.
are also shown as the combined findings of these conditions (n=114). When compared with others, our experience comprises a larger proportion of fetuses with AVB III and fewer cases with AVB II. Steroids, IVIG, and betamimetics were used more often, and fetal and neonatal mortality was significantly lower. Other parameters, including gestational age at AVB diagnosis and, if reported, at birth, were largely comparable among most studies. In the only other study by Levesque et al that also provided long-term outcome data of fetal immune-mediated AVB, DCM was diagnosed in 32 of 174 (18%) children (Table 3) when compared with 3 (3%) of 106 neonatal survivors in our experience (P<0.0001).

**DISCUSSION**

This retrospective multicenter study reports the results of routine TFTX of antibody-mediated fetal heart disease. In a smaller retrospective study of 2 Canadian centers that was published in 2004, Jaeggi et al first reported a significantly better outcome of immune-mediated fetal AVB simultaneous with the introduction of prenatal treatment guidelines in 1997 that included the routine use of steroids. Trucco et al subsequently reported marked improvement in survival and cardiac function with the combined use of steroids and IVIG for fetuses with immune-mediated EFE when compared with historical controls. The authors attributed the favorable results to the anti-inflammatory treatment effects that rendered the diseased fetus less likely to acquire more extensive cardiac tissue injury.

**Pathological Features of Cardiac NLE**

Postmortem findings seen in patients with seropositive AVB support that cardiac involvement often extends beyond the electrical conduction system. As such, immunoglobulin G deposition has been demonstrated throughout the fetal myocardium with immunofluorescent techniques. Autopsy findings of fetuses that had been diagnosed weeks earlier with AVB III also reveal pancarditis, EFE, fibrosis of the sinus node and papillary muscles, and atrioventricular valvar damage among the spectrum of disease. Finally, histological features obtained from cardiac specimens of children with DCM displayed myocyte hypertrophy, interstitial fibrosis, and myocyte degeneration, suggesting that late-onset LV dysfunction represents a sequela of intrauterine autoimmune carditis that might be preventable with early transplacental anti-inflammatory treatment. More important, the true extent of this pathological condition, including EFE, is not consistently identified by echocardiography.

**Prenatal Diagnoses of Cardiac NLE and Determinants of Outcomes**

Despite the diagnostic limitations of ultrasound, 40% of fetuses with advanced AVB in this study displayed areas of abnormal cardiac echogenicity, 10% had ventricular dysfunction, and 30% had a pericardial effusion already present at the time of fetal diagnosis. A more widespread disease pattern was apparent in the 7 patients with AVB III who died in utero or as neonates: all presented with at least 2 risk factors of mortality, including EFE, ventricular dysfunction, hydrops, and, most important, the lowest atrial or ventricular rates of
all fetuses. An atrial rate of <90 bpm or a ventricular rate <45 bpm was associated with a perinatal mortality of 100% and 40%, respectively, despite the use of TFTX, whereas 99% (97/98) of AVB III cases with faster baseline rates and 100% of cases with incomplete AVB survived, as shown in Table 2.

Cardiac manifestations without concomitant AVB III were only infrequent observations (17%). Consistent with previous experiences,7,17,28,29 treatment of AVB II or AVB II to AVB III with steroids±IVIG did transiently improve or stabilize the fetal atrioventricular conduction, but this did not prevent the development of AVB III in 4 of 6 cases. TFTX had no effects on the atrial bradycardia of fetuses with isolated SND, although, unlike those with AVB III, SND alone was not associated with perinatal death. None of our cases with isolated EFE died or developed AVB, SND, or DCM.

**Study Comparisons**

A primary study aim was to compare our findings with those of other published experiences. Routine administration of steroids to mitigate any cardiac inflammation differs fundamentally from management strategies that consider the main NLE manifestation, AVB III, a condition confined to the electrical conduction tissue with a favorable natural history. Consistent with this perception, the American Heart Association has recommended observation without the use of prenatal

| Variable | Current | Lopes13 | Eliasson9 | Levesque14 | Van den Berg15 | Fredi16 |
|----------|---------|---------|-----------|------------|--------------|---------|
| Study years | 1997–2018 | 1988–2006 | 2000–2007 | 1976–2014 | 2003–2013 | 1969–2017 |
| Fetal cases (AVB II or AVB III) | 114 | 57 | 175 | 202 | 56 | 84 |
| Included | 114 | 57 | 175 | 198 | 51 | 77 |
| Excluded (primary TOP) | ... | ... | ... | 4 | 5 | 7 |
| Anti-Ro antibodies | | | | | | |
| Positive | 114 (100) | 41 (72)* | 129 (74)* | 197 (99) | 48 (86)* | 84 (100) |
| Negative or unknown | 0 | 16 | 46 | 1 | 8 | 0 |

**Table 3.** Comparison of Prenatal Findings and Clinical Outcomes in Fetal AVB II and AVB III Between the Current Cohort With Routine TFTX and Previously Published Cohorts With Variable TFTX

| Variable | Current | Lopes13 | Eliasson9 | Levesque14 | Van den Berg15 | Fredi16 |
|----------|---------|---------|-----------|------------|--------------|---------|
| Study years | 1997–2018 | 1988–2006 | 2000–2007 | 1976–2014 | 2003–2013 | 1969–2017 |
| Fetal cases (AVB II or AVB III) | 114 | 57 | 175 | 202 | 56 | 84 |
| Included | 114 | 57 | 175 | 198 | 51 | 77 |
| Excluded (primary TOP) | ... | ... | ... | 4 | 5 | 7 |
| Anti-Ro antibodies | | | | | | |
| Positive | 114 (100) | 41 (72)* | 129 (74)* | 197 (99) | 48 (86)* | 84 (100) |
| Negative or unknown | 0 | 16 | 46 | 1 | 8 | 0 |

Prenatal findings

| Variable | Current | Lopes13 | Eliasson9 | Levesque14 | Van den Berg15 | Fredi16 |
|----------|---------|---------|-----------|------------|--------------|---------|
| Age at diagnosis, wk | 22.1 (17–33) | 29 (18–40) | 24.3±4.3 | 23 (16–39) | 23±4.5 | 21 (17–38) |
| Fetal hydrops | 9/114 (8) | 11/57 (19)* | 16/175 (9) | 22/175 (13) | 5/50 (10) | 7/84 (8) |
| AVB III | 108/114 (95) | 35/57 (61)* | 146/175 (83)* | 167/202 (83)* | 35/56 (63)* | 66/84 (79)* |
| Ventricular rate | 61.3±12.2 | 58.6±13.6 | 59.8±11.4 | N/A | 61±14 | N/A |
| Ventricular rate ≤50 bpm (nadir) | 38/114 (33) | N/A | 36/173 (21)* | 44/198 (22)* | N/A | 27/73 (37%)
| AVB II | 6/114 (5) | 22/57 (39) | 29/175 (17) | 35/202 (17) | 21/56 (37) | 18/84 (21) |

Prenatal treatment

| Variable | Current | Lopes13 | Eliasson9 | Levesque14 | Van den Berg15 | Fredi16 |
|----------|---------|---------|-----------|------------|--------------|---------|
| Yes | 114 (100) | 11/57 (19)* | 67/175 (38)* | 77/198 (39)* | 21/51 (41)* | 60/84 (71)* |
| Fluorinated steroids | 114 (100) | 6 (11)* | 67 (38)* | 77 (39)* | 14 (27)* | 60 (71)* |
| Duration, wk | 12.8 (0.3–18) | N/A | 10 (1–21) | 8 (1.3–18) | N/A | 9.5 (4–18) |
| β-Mimetics | 47 (41) | 7 (12)* | 41 (23)* | N/A | 17 (33) | 7 (8)* |
| Duration, wk | 6 (0.3–15.1) | N/A | 8 (2–18) | N/A | N/A | N/A |
| IVIG | 46 (40) | 0 (0)* | 0 (0)* | 4 (2)* | 0 (0)* | 20 (24)* |

Outcome

| Variable | Current | Lopes13 | Eliasson9 | Levesque14 | Van den Berg15 | Fredi16 |
|----------|---------|---------|-----------|------------|--------------|---------|
| Fetal survival | 109/114 (96) | 51/57 (89) | 159/175 (91) | 175/198 (88)* | 43/51 (84)* | 68/77 (88) |
| Gestational age at birth, wk | 36.7 (26.6–39.1) | N/A | N/A | 37 (28–41) | 38±2 | 35.3±3 |
| Neonatal survival | 106/114 (93) | 44/57 (77)* | 138/164 (84)* | 167/198 (84)* | N/A | 63/77 (82)* |
| Postnatal follow-up, y | 4.9 (0–18) | N/A | N/A | 7 (0–36) | N/A | N/A |
| Alive | 100/114 (88) | 155/198 (78) | | | | |
| Dilated cardiomyopathy | 3/106 (3) | 32/174 (18)* | | | | |

Values are number (percentage), mean±SD, or median (range). AVB II indicates second-degree atrioventricular block; AVB III, third-degree atrioventricular block; bpm, beats per minute; IVIG, intravenous immune globulins; N/A, information not available; TFTX, transplacental fetal treatment; and TOP, termination of pregnancy.
*P<0.001.
†P<0.05.
‡P<0.01.
steroids as the most useful and effective procedure for patients with AVB III (class I/A level of evidence). Prenatal dexamethasone may still be considered to improve survival or reduce the incidence of DCM or to prevent progression from incomplete to complete AVB (class II/B). Indeed, the prenatal administration of dexamethasone is a contentious topic. As such, several studies comparing perinatal outcomes of sporadically treated and untreated fetal cohorts with advanced AVB have failed to detect any significant treatment benefits with fluorinated corticosteroids, but raised concerns of possible adverse effects on the child and costreated mother. Yet, as summarized in Table 3, the conclusions of these studies were based on significantly smaller numbers (6–77 cases) and proportions (19%–71%) of steroid-treated fetuses when compared with our current multicenter experience. Furthermore, fetuses of seronegative mothers and/or with late-gestational AVB diagnoses were also included in previous outcome analyses. When compared with immune-mediated AVB, idiopathic/genetic forms of heart block are more often incomplete and transient, do not improve with steroids, have a better prognosis, and therefore represent different diseases. Likewise, a late-gestational diagnosis of AVB III carries only a small risk of perinatal death and is unlikely to benefit from steroid treatment.

Outcome Data

In contrast to past investigations, our collective experience consisted of routinely treated fetuses with immune-mediated AVB that predominantly were diagnosed before 24 gestational weeks. Even so, we found rates of fetal (96%) and neonatal (93%) survival in our experience to be significantly higher when compared with the fetal (84%–91%) and neonatal (77%–84%) survival rates of inconsistently treated patient cohorts that have been reported by others to date (Table 3). Moreover, we encountered a lower prevalence of postnatal DCM when compared with mostly untreated patient cohorts with a similar length of postnatal follow-up. Only a single child with AVB III developed severe postnatal cardiac dysfunction requiring treatment in our cohort. In the study of Levesque et al., DCM was detected at a mean age of 5.5 months in 35 (19%) of 186 children with a prenatal (32/174) or neonatal (3/12) diagnosis of immune-mediated AVB, of which 14 (40%) died. Similarly, DCM affected 16 of 56 (29%) children with AVB at a mean follow-up of 4.6 years, of which 38% died in a study by Villain et al.

Our study findings therefore support that routine transplacental treatment of cardiac NLE, including the use of steroids±IVIG±a β-adrenergic agent, reduces the risk of perinatal death and the postnatal development of DCM. Perinatal survival can be expected with TFTX unless poor prognostic factors are already manifest at the time of initial AVB III diagnosis. Once TFTX was started, we did not observe new disease manifestations resulting in early death and, in fact, often observed improvement in cardiac functional parameters and hydrops. This is an important difference from our earlier observation with untreated immune-mediated AVB III, where a significant proportion of patients displayed or developed findings linked with an adverse outcome only weeks after the initial diagnosis.

Safety Data

A main argument against the use of transplacental steroids has been the potential of serious adverse effects of the mother and her child. On the basis of the published scientific evidence, however, treatment-related serious adverse events either are rare or have not been documented. Comparable to the studies of Eliasson and van den Berg, we experienced one mother with an episode of psychosis after initiation of high-dose dexamethasone that required a dose reduction. It is therefore important to closely monitor the fetal-maternal health to immediately adjust the TFTX if required. Fetal growth restriction affected 30% of our cardiac NLE cases, which is comparable to the reported rates of growth restriction of predominantly steroid-treated fetuses with AVB II to AVB III by Fredi et al and Skog et al. In an earlier study by Skog et al., significantly smaller weights, lengths, and head circumferences at birth were also reported in prenatally untreated newborns with AVB III, although the degree of growth restriction seemed to be more pronounced in treated pregnancies. In this study, the median birth weight percentiles were not significantly different between AVB III and other cardiac diagnoses, suggesting that prolonged prenatal exposure to steroids at least contributed to the impairment in fetal growth, although this did not affect patient age at delivery and postnatal survival. We would therefore argue that the benefit of improved survival probably outweighs the risks of TFTX-related complications. Finally, in 2 earlier studies, AVB III±TFTX with dexamethasone was not associated with neurocognitive impairment in younger children. In agreement with these observations, most children in the current study displayed no evidence of neurodevelopmental delays, and formal neurological assessments were therefore not warranted. In the rare cases displaying global delay, this outcome was attributed to either a postnatal hypoxic-ischemic event or a genetic brain disorder.

Study Limitations

A limitation of this study is the retrospective study design and the extended enrollment period. Patient data were not systematically reviewed unless there were
inconsistencies among reported findings or data were missing. The number of cases with adverse outcomes was too small to evaluate the effects of IVIG in this study. Some variations also existed (eg, in the starting dose of steroids among centers), although most followed the same TFXT. This includes that most patients diagnosed before 24 weeks of gestation were started on 8 mg/d of dexamethasone, including 4 of 5 cases that died in the perinatal period. On the other hand, we found no difference in perinatal outcomes of fetuses with a cardiac NLE diagnosis after 24 weeks if 4 mg/d rather than 8 mg/d of dexamethasone was used. Cardiac manifestations without concomitant AVB III were infrequent observations (17%), and the role of TFXT in such pregnancies will need confirmation in future studies.

CONCLUSIONS

Our findings indicate that TFXT, including the routine use of steroids, not only improved survival of fetuses with cardiac NLE but also reduced the postnatal prevalence of DCM when compared with the previously published experiences of others. Given that the cumulative rate of postnatal pacing in our cohort was comparable to patient series without routine TFXT, it is reasonable to assume that postnatal DCM is not related to ventricular pacing per se but rather relates to the severity of the inflammatory insult on the fetal myocardium. TFXT was largely well tolerated in our experience, with a rare incidence of adverse events.

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