Isolated Atrioventricular Block in the Fetus
A Retrospective, Multinational, Multicenter Study of 175 Patients

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Background—Isolated complete atrioventricular block in the fetus is a rare but potentially lethal condition in which the effect of steroid treatment on outcome is unclear. The objective of this work was to study risk factors associated with death and the influence of steroid treatment on outcome.

Methods and Results—We studied 175 fetuses diagnosed with second- or third-degree atrioventricular block (2000–2007) retrospectively in a multinational, multicenter setting. In 80% of 162 pregnancies with documented antibody status, atrioventricular block was associated with maternal anti-Ro/SSA antibodies. Sixty-seven cases (38%) were treated with fluorinated corticosteroids for a median of 10 weeks (1–21 weeks). Ninety-one percent were alive at birth, and survival in the neonatal period was 93%, similar in steroid-treated and untreated fetuses, regardless of degree of block and/or presence of anti-Ro/SSA. Variables associated with death were gestational age <20 weeks, ventricular rate ≤50 bpm, fetal hydrops, and impaired left ventricular function at diagnosis. The presence of ≥1 of these variables was associated with a 10-fold increase in mortality before birth and a 6-fold increase in the neonatal period independently of treatment. Except for a lower gestational age at diagnosis in treated than untreated (23.4 ± 2.9 versus 24.9 ± 4.9 weeks; P = 0.02), risk factors were distributed equally between treatment groups. Two-thirds of survivors had a pacemaker by 1 year of age; 8 children developed cardiomyopathy.

Conclusions—Risk factors associated with a poor outcome were gestation <20 weeks, ventricular rate ≤50 bpm, hydrops, and impaired left ventricular function. No significant effect of treatment with fluorinated corticosteroids was seen. (Circulation. 2011;124:00-00.)

Key Words: atrioventricular block ■ fetal heart ■ lupus erythematosus, systemic ■ therapeutics

Congenital complete atrioventricular block (AVB III) without associated cardiac malformation is a rare disease with an incidence in newborn babies of 1 in 15 000 to 1 in 20 000.1 Some studies have suggested that maternal administration of high-dose steroids that cross the placenta can inhibit the progression or even reverse second-degree AVB (AVB II) to sinus rhythm.2–5 Treatment with fluorinated steroids and betamimetics has been proposed to improve outcome in AVB III,6 but repeated doses of steroids have potentially serious side effects in the fetus, including alteration of brain development.7–10 Thus, fetal cardiologists lack consensus on treatment11; many are not supportive of universal steroid treatment for fetal AVB III but may use steroids if the fetus presents with or develops hydrops because there is some evidence that steroids promote the resolution of hydrops. Maternal betamimetic therapy for fetuses with ventricular rates <55 bpm has also been given, with minimal benefit in most reports.6,12–14

Editorial see p ●●●
Clinical Perspective on p ●●●

After a previous unsuccessful attempt to start a prospective therapeutic study in 1995, the Fetal Working Group of the European Association for Pediatric Cardiology recognized that the rarity of isolated AVB III contributed to the difficulties in providing an evidence base for the management of heart block diagnosed in the fetus. This retrospective, multinational, multicenter observational study was therefore initiated to provide a review of current practice and outcomes. All members of the Fetal Working Group of the European Association of Pediatric Cardiology acknowledged that they have not contributed to this study in any way.

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With the exception of Dr Granath, all of the authors are members of the Fetal Working Group of the European Association of Pediatric Cardiology. Dr Granath is affiliated with the Clinical Epidemiology Unit, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden. In addition, for a full list of contributors to the Fetal Working Group of the European Association of Pediatric Cardiology, please see the acknowledgments.

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Association of Pediatric Cardiology were invited to contribute data to a communal database of fetuses diagnosed with isolated AVB II and III between 2000 and 2007. The objectives of this study were to identify risk factors predictive of a poor outcome, to describe current practice regarding steroid treatment of isolated AVB II and III in the contributing centers, and to compare the outcome in fetuses treated with fluorinated glucocorticoids with untreated fetuses in respect to morbidity and mortality.

Methods

Patient Selection

Data on 189 fetuses were submitted from 28 centers, 27 in Europe and 1 in Brazil. The contributing institutions are listed in the Acknowledgments, and the number of cases per center is shown in Figure 1. Fourteen fetuses were excluded after data evaluation; no birth outcome data were available in 10, and another 4 fetuses were thought to have reverted from AVB II or III. However, in 2 of these 4 fetuses, review was not possible because of lack of documentation, and in the other 2 fetuses, initial diagnosis of AVB could not be retrospectively confirmed. The resulting final study population consisted of 175 fetuses (174 pregnancies) of 172 women diagnosed with isolated AVB II or III (2000–2007) and a minimum follow-up, were assessed for neonatal mortality. Both of these outcomes were analyzed by exact logistic regression including only steroid treatment and an adjusted model conditioned on gestational age at diagnosis (categorized as <20, 20 to 24, 25 to 29, ≥30 weeks). These analyses were also performed on the subgroups of patients defined by a positive anti-Ro/SSA and/or anti-Ro/SSB test and a positive test further restricted to AVB II–III/III. Results of the logistic regressions are presented as odds ratios with exact 95% confidence limits. We describe the effect of betamimetics on heart rate, including only patients with data on ventricular rate before and within 2 weeks after treatment was initiated. Follow-up of the cohort beyond the neonatal period is incomplete with missing information on the time points when the patients were lost to follow-up. Therefore, data on long-term outcomes and characteristics are purely descriptive. All analyses were performed with SAS 9.2 software (SAS Institute, Inc, Cary, NC) or Statistica 10.0 (Stat Soft, Tulsa, OK).

Results

Baseline Characteristics

Table 1 details the clinical characteristics. To summarize the available data, approximately half of the women were diagnosed with collagen disease, and 80% were anti-Ro/SSA positive and 59% anti-La/SSB positive. Two tested negative for anti-Ro/SSA but positive for anti-La/SSB. Fifteen fetuses (9%) were diagnosed with AVB II, 14 (8%) with AVB II to III, and 146 (83%) with AVB III. The average ventricular rate of the whole cohort was 60 bpm, and 21% had a ventricular rate ≤50 bpm; 9% were hydropic.

Transplacental Treatment

Sixty-seven fetuses (38%) were treated with transplacental steroids starting at 23.5 gestational weeks (range, 19–31 weeks; Table 1). Fifty-two received dexamethasone beginning with 4 mg/d (range, 2–12 mg/d) and 15 betamethasone at 4 mg/d (range, 3–5 mg/d). In 2 pregnancies, fluorinated steroids were given in combination with prednisolone. The
The duration of treatment was 10 weeks (range, 1–21 weeks), and in most cases, the dose remained unchanged. Side effects were reported in 11 pregnancies (6%), mainly oligohydramnios, growth restriction, and constriction of the arterial duct. One mother developed diabetes mellitus, adrenal insufficiency, and psychosis.

Forty-one fetuses (23%) were treated with betamimetics, usually salbutamol, from 25 gestational weeks (range, 19–33 weeks) for 8 weeks (range, 2–18 weeks). Betamimetics were more frequently combined with steroid administration than given alone (23 of 67 versus 18 of 108; \(P < 0.01\)).

Ventricular rate increased from 50.1 ± 3.8 to 55.1 ± 3.7 bpm (\(P < 0.001\)) in 15 patients with data before and after initiation of treatment.

Two mothers from the same center received prophylactic treatment with plasmapheresis twice a week for 9 and 14 weeks. Their fetuses had AVB III at the time of diagnosis, were treated with steroids (1 with dexamethasone, 1 with prednisolone followed by dexamethasone), were born in AVB III, and were alive at 0.9 and 2.2 years. A third woman with a previous history of fetal AVB III was given 1 g/kg immunoglobulin intravenously at 14 and 18 weeks of gestation to minimize the risk of having a second child with AVB. The fetus was diagnosed with AVB II at 19 weeks that reverted after 1 week of treatment with betamethasone and remained in sinus rhythm at 0.9 years of age.

### Baseline Characteristics and Neonatal Survival

Sixteen of the 175 fetuses with AVB II or AVB III died in utero (Figure 2). This included 1 pregnancy terminated at 23 weeks of gestation because the fetus was not responding to treatment with steroids and betamimetics. Of 159 live-born babies, 10 died during the first month (neonatal deaths), 138 were reported alive at 1 month, and 11 were lost to follow-up.

Baseline characteristics for the groups based on intrauterine and neonatal survival outcome are presented in Tables 2 and 3. Fetuses with a poor outcome were diagnosed 3 to 4 weeks earlier than survivors. Hydrops and impaired left

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**Table 1. Clinical Characteristics at the Time of Diagnosis and Transplacental Treatment of 175 Fetuses of 172 Women With Second- or Third-Degree Atrioventricular Block**

<table>
<thead>
<tr>
<th></th>
<th>All Cases (n=175)</th>
<th>Steroid Treated (n=67)</th>
<th>Untreated (n=108)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td>30.3±5.9</td>
<td>31.0±5.7</td>
<td>29.9±6.0</td>
<td>0.18</td>
</tr>
<tr>
<td>Parity</td>
<td>1.0±1.0</td>
<td>1.1±1.0</td>
<td>0.9±1.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Collagen disease, n (%)</td>
<td>77/167 (46)</td>
<td>33/63 (52)</td>
<td>44/104 (42)</td>
<td>0.26</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>18</td>
<td>11</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>11</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>48</td>
<td>17</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Previous history of AVB, n (%)</td>
<td>9/172 (5)</td>
<td>7/66 (11)</td>
<td>2/106 (2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anti-Ro/SSA positive</td>
<td>129/162 (80)</td>
<td>55/64 (86)</td>
<td>74/98 (76)</td>
<td>0.25</td>
</tr>
<tr>
<td>Anti-La/SSB positive</td>
<td>85/144 (59)</td>
<td>38/61 (62)</td>
<td>47/83 (57)</td>
<td>0.61</td>
</tr>
<tr>
<td>GA at diagnosis, wk</td>
<td>24.3±4.3</td>
<td>23.4±2.9</td>
<td>24.9±4.9</td>
<td>0.02</td>
</tr>
<tr>
<td>AVB II, II–III, III, n (%)</td>
<td>15, 14, 146 (9, 8, 83)</td>
<td>7, 6, 54 (10, 9, 81)</td>
<td>8, 8, 92 (7, 7, 86)</td>
<td>0.48, 0.71, 0.43</td>
</tr>
<tr>
<td>Ventricular rate, bpm</td>
<td>59.8±11.4</td>
<td>61.3±11.3</td>
<td>58.9±11.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Ventricular rate ≥50 bpm, n (%)</td>
<td>36/173 (21)</td>
<td>13/66 (20)</td>
<td>23/107 (21)</td>
<td>0.77</td>
</tr>
<tr>
<td>Isolated ascites, pericardial or pleural effusion, n (%)</td>
<td>32/154 (21)</td>
<td>11/62 (18)</td>
<td>21/92 (23)</td>
<td>0.45</td>
</tr>
<tr>
<td>Hydrops, n (%)</td>
<td>16/175 (9)</td>
<td>5/67 (7)</td>
<td>11/108 (10)</td>
<td>0.54</td>
</tr>
<tr>
<td>Impaired LV function, n (%)</td>
<td>17/141 (12)</td>
<td>7/55 (13)</td>
<td>10/86 (12)</td>
<td>0.84</td>
</tr>
<tr>
<td>Steroid treatment, n (%)</td>
<td>67/175 (38)</td>
<td>52</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamimetics</td>
<td>41/175 (23)</td>
<td>23/67 (34)</td>
<td>18/108 (17)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

SLE indicates systemic lupus erythematosus; AVB, atrioventricular block; GA, gestational age; and LV, left ventricular. Cases are divided into groups based on transplacental steroid treatment. Values are mean±SD when appropriate Comparisons are untreated versus steroid-treated fetuses.

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**Figure 2.** Outcome of all 175 fetuses with second- or third-degree atrioventricular block at diagnosis. IUD indicates intrauterine death.
ventricular function were observed more frequently in fetuses not surviving to 1 month of age, whereas a ventricular rate \( \leq 50 \text{ bpm} \) was associated only with intrauterine mortality. The effects of gestational age, ventricular rate, and the presence of hydrops at diagnosis on survival outcome are also more directly illustrated in Figure 3. Intrauterine mortality rate was >4 times higher in fetuses diagnosed with AVB before 20 weeks of gestation compared with those diagnosed after 23 weeks. Fetuses with a ventricular rate \( \leq 50 \) bpm had 5 times higher intrauterine mortality than those with a ventricular rate \( >55 \) bpm. The presence of hydrops and impaired left ventricular function increased both intrauterine mortality and neonatal mortality by a factor of 6 and 4, respectively. Considering a gestational age <20 weeks, ventricular rate \( \leq 50 \text{ bpm} \), and the presence of hydrops and impaired left ventricular function as risk factors, intrauterine mortality was 11 times higher in fetuses with at least 1 risk factor, and neonatal mortality was 6 times higher when at least 1 risk factor was present at time of diagnosis (Table 3).

Steroid Treatment and Survival to 1 Month of Age
Transplacental treatment with steroids and betamimetics was given in the same proportion to survivors and nonsurvivors (Table 2). The logistic regression model (Table 4) could not demonstrate any effect of transplacental steroid treatment on intrauterine or neonatal survival. In steroid-treated fetuses, intrauterine survival was 91%, the same as in those not treated; neonatal survival among the 148 children alive at birth was 95% in the steroid-treated group and 92% in the untreated group. Adjusting for effects of gestational age at diagnosis had only a minor influence on the model without demonstrating any treatment effect (Table 4). Table 1 shows that the steroid-treated and untreated cohorts had similar ventricular rates, frequency of hydrops, rates of impaired left ventricular function, and rates of incomplete AVB and only a

| Table 2. Clinical Characteristics at the Time of Diagnosis and Transplacental Treatment Among Survivors at Birth Versus Intrauterine Death and Survivors at 1 Month Versus Neonatal Death |
|---------------------------------------------------------------|---------------|----------------|----------------|---------------|----------------|
| Survivors at Birth (n=159) Intrauterine Death (n=16) | P | Survivors at 1 mo (n=138) Neonatal Death (n=10) | P |
| Maternal age, y | 30.6±6.0 | 27.4±3.3 | 0.02 | 31.0±6.0 | 29.7±6.4 | 0.54 |
| Anti-Ro/SSA positive, n (%) | 117/148 (79) | 12/14 (86) | 0.84 | 102/127 (80) | 4/10 (40) | 0.28 |
| Anti-La/SSB positive, n (%) | 74/131 (56) | 11/13 (85) | 0.38 | 63/113 (56) | 5/9 (56) | 1.0 |
| GA at diagnosis, wk | 24.6±4.3 | 21.6±3.3 | 0.01 | 24.8±4.2 | 20.6±3.3 | 0.004 |
| Ventricular rate, bpm | 60.8±10.9 | 49.9±11.8 | 0.0002 | 61.0±10.8 | 59.6±14.6 | 0.70 |
| Treatment, n (%) | | | | | |
| Steroids | 61/159 (38) | 6/16 (38) | 1.00 | 53/138 (38) | 3/10 (30) | 0.74 |
| Betamimetics | 35/159 (22) | 6/16 (38) | 0.21 | 27/138 (20) | 3/10 (30) | 0.42 |

GA indicates gestational age. Values are mean±SD when appropriate.

| Table 3. Intrauterine Mortality Related to Clinical Observations Made at the Time of Diagnosis in 175 Fetuses With Known Outcome at Birth and Neonatal Mortality in 148 Newborns With Known Outcome at 1 Month of Age |
|-----------------|----------------|
| GA at diagnosis, wk | Intrauterine Death (n=16), % (n) | P | Neonatal Death (n=10), % (n) | P |
| <20 | 38 (5/13) | 0.001 | 13 (1/8) | 0.10 |
| 20–23 | 10 (7/73) | 0.0019 | 11 (2/61) | 0.50 |
| >23 | 8 (4/86) | 0.001 | 3 (2/76) | 0.02 |
| Ventricular rate, bpm | ≤50 | 25 (9/36) | 0.02 | 13 (3/24) | 0.50 |
| | 51–55 | 6 (2/31) | 7 (2/28) | 0.04 |
| | >55 | 5 (5/106) | 5 (5/95) | 0.04 |
| Hydrops | Yes | 38 (6/16) | 0.001 | 30 (3/10) | 0.02 |
| | No | 6 (10/159) | 5 (5/138) | 0.04 |
| Impaired LV function | Yes | 24 (4/17) | 0.0001 | 23 (3/13) | 0.009 |
| | No | 6 (8/124) | 5 (5/111) | 0.02 |
| Any risk factor | ≥1 | 22 (12/55) | 0.001 | 18 (7/40) | 0.009 |
| | No | 2 (2/101) | 3 (3/92) | 0.04 |

GA indicates gestational age; LV, left ventricular. Risk factor denotes presence of hydrops, impaired LV function, ventricular rate \( \leq 50 \text{ bpm} \), and/or a GA \(<20 \text{ wk} \).
small difference in gestational age at diagnosis. Pregnancies with a previous history of fetal AVB were more often treated, but no relationship between the size of the center and the proportion of steroid-treated cases could be demonstrated (Figure 1). Limiting the analysis to antibody-exposed fetuses in whom steroid treatment theoretically might have the best effect, survival was similar without any positive treatment effect (Table 4). If the presence of at least 1 risk factor was included, it was still not possible to detect any significant effect of steroid treatment on survival at birth or at 1 month of age (Figure 4).

### Steroid Treatment and Atrioventricular Conduction

Fifteen fetuses (9%) had AVB II diagnosed at a gestation of 22 weeks (range, 19–29 weeks; Figure 5). Exposure to maternal anti-Ro/SSA and/or anti-La/SSB antibodies was established in 10 cases, seven of whom were treated with steroids, and in 3 fetuses, treated from 19, 22, and 23 weeks of gestation, the rhythm converted to 1:1 conduction within 1 to 2 weeks after the start of treatment. All 3 fetuses were in sinus rhythm at birth, but only 1 was known to remain so at a year of age; the second had reverted to AVB I to II at 5 years of age, and no information was available for the third. The remaining 12 fetuses remained in AVB II (n=110052), progressed to AVB III (n=101), or were lost to follow-up after birth (n=2).

Fourteen fetuses were reported to have AVB II–III, 12 of whom progressed to AVB III by birth. Of the remaining 2 fetuses, 1 was diagnosed at 20 weeks and showed reversion to 1:1 atrioventricular conduction after initiation of steroid treatment but had AVB III by 4 years of age. This fetus was exposed to maternal antibodies. The other fetus was diagnosed at 21 weeks to an antibody-negative woman and was in sinus rhythm at birth and at 2.7 years.

### Table 4. Transplacental Steroid Treatment and Outcome of All 175 Included Fetuses (at Birth) and the 148 Live-Born Neonates With Known Outcome at 1 Month of Age

<table>
<thead>
<tr>
<th>Categories</th>
<th>All Patients, % (n)</th>
<th>Steroid Treated, % (n)</th>
<th>Untreated, % (n)</th>
<th>Crude OR</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival at birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All fetuses (n=175)</td>
<td>91 (159/175)</td>
<td>91 (61/67)</td>
<td>91 (98/108)</td>
<td>0.96 (0.27–3.10)</td>
<td>0.79 (0.21–2.67)</td>
</tr>
<tr>
<td>Anti-Ro/SSA and/or La/SSB positive (n=131)</td>
<td>91 (119/131)</td>
<td>91 (51/56)</td>
<td>91 (68/75)</td>
<td>0.95 (0.22–3.72)</td>
<td>0.85 (0.20–3.41)</td>
</tr>
<tr>
<td>Anti-Ro/SSA and/or La/SSB positive and AVB III (n=121)</td>
<td>90 (109/121)</td>
<td>90 (44/49)</td>
<td>90 (65/72)</td>
<td>1.05 (0.25–4.15)</td>
<td>0.97 (0.22–3.96)</td>
</tr>
<tr>
<td>Survival at 1 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All neonates (n=148)</td>
<td>93 (138/148)</td>
<td>95 (53/56)</td>
<td>92 (85/92)</td>
<td>0.69 (0.11–3.18)</td>
<td>0.58 (0.23–1.79)</td>
</tr>
<tr>
<td>Anti-Ro/SSA and/or La/SSB positive (n=108)</td>
<td>95 (103/108)</td>
<td>96 (44/46)</td>
<td>95 (59/62)</td>
<td>0.89 (0.07–8.16)</td>
<td>1.00 (0.08–10.2)</td>
</tr>
<tr>
<td>Anti-Ro/SSA and/or La/SSB positive and AVB III (n=101)</td>
<td>95 (96/101)</td>
<td>95 (39/41)</td>
<td>95 (57/60)</td>
<td>0.97 (0.08–8.92)</td>
<td>1.04 (0.08–10.7)</td>
</tr>
</tbody>
</table>

Crude OR indicates unadjusted odds ratio; Adjusted OR, odds ratio adjusted for gestational age (categorized as <20, 20–24, 25–29, and ≥30 wk) at diagnosis. OR is presented with 95% confidence limits.

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**Figure 4.** Intrauterine (A; n=107) and neonatal (B; n=90) mortality in fetuses with known presence or absence of risk factors at diagnosis, second- and third-degree atrioventricular block, and fetal exposure to maternal anti-Ro/SSA and/or anti-La/SSB antibodies. Mortality is shown by treatment group. High risk denotes the presence of at least 1 risk factor: gestational age <20 weeks, ventricular rate ≤50 bpm, presence of hydrops, or impaired left ventricular function. Low risk denotes those without any risk factors. Numbers on top of bars are numbers of cases. Comparisons are between treated and untreated patients.
Postnatal Outcome

Of 175 fetuses originally enrolled in the study, 26 died before birth or during the neonatal period and 11 were lost to follow-up (Figure 2). The remaining 138 infants were followed up for an average of 3.2 years (range, 1 month–8.1 years; Table 5). Two infants died before and another 2 died after 1 year of age. Twenty-four had not reached the age of 1 year within the time limit of the study, and 6 were lost to follow-up (Figure 2). One child’s death was due to a pacemaker complication. Eight patients developed cardiomyopathy, which resulted in the death of 1 infant. All but 1 mother were antibody positive (6/8 Ro positive; one LA positive), and in 3, the diagnosis of cardiomyopathy was made before birth. Fetuses receiving translacental steroids were delivered somewhat earlier (gestational age, 36.6 ± 2.4 weeks; *P* = 0.04) with no significant difference in birth weight (2.7 ± 0.6 versus 2.9 ± 0.6 kg; *P* = 0.08).

In this study, 31 pregnancies were reported to be antibody negative. If these pregnancies are considered to be truly antibody negative, then fetal mortality and neonatal mortality did not differ significantly between antibody-positive and -negative pregnancies (17 of 120 [14%] versus 7 of 31 [23%]; *P* = 0.27) in those with known outcome at 1 month of age.

Pacing

A permanent pacemaker was implanted in 102 children. Sixty of the children (43%) alive at 1 month were paced, and 69% were paced by 1 year (Table 5). An epicardial approach was used in the majority (81%) at a median age of 10 days (range, 1 day–7.9 years), and a transvenous approach was used in 19% (median, 2 months; range, 1 day–2.2 years). Fifty-nine had a dual-chamber pacemaker as the initial pacing mode with 1 death at 8 days of age from septicemia after pacemaker implantation and 1 in childhood from cardiac strangulation by the pacing wire.

Discussion

In this retrospective multicenter study, we describe the current treatment practices and outcomes in the largest reported data set of fetuses diagnosed with isolated AVB II and III. Our results confirm that there is no consensus regarding treatment with steroids. At some centers, no patients were treated, whatever the fetal status, whereas at others, almost all were treated. There was no correlation between the number of cases submitted from a center and the proportion treated.

In contrast to what might have been expected, the sicker fetuses were not more likely to be offered therapy. Because the groups were comparable at the time of diagnosis, except for a lower gestational age at diagnosis in the treated group, we could compare outcomes between the treated and untreated cohorts. We detected no significant differences in fetal or neonatal mortality, even when adjusting for earlier gestation at diagnosis in the treated group. Our results contrast with those of Jaeggi and colleagues, who described a lower mortality rate in fetuses treated with steroids compared with their untreated historical control subjects. The most striking difference was a mortality rate close to 50% in the control subjects, whereas the 1-month survival during the later treatment period was similar to the results of the present study. An examination of the Jaeggi et al data demonstrates that risk factors shown in our study to be associated with a poor early outcome were present in half of the 16 historical control subjects compared with one third of the 21 cases reported from the later period. Our survival experience in untreated cases is more comparable to that published in a more recent study, the largest single-center study so far in which 51 of 57 (89%) of fetuses with isolated AVB II or III not receiving steroid treatment had a 1-month survival of 80%. However, in contrast to our study, mortality was high in the steroid-treated fetuses, with only 3 of 6 surviving to 1 month of age.

Table 5. Outcome of 148 Children With Atrioventricular Block and Known Outcome at 1 Month of Age

<table>
<thead>
<tr>
<th>Follow up time of survivors at 1 mo of age (n=138), y</th>
<th>All Cases</th>
<th>Steroid Treated</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at pacing (d)</td>
<td>10 d (1 d–7.9 y)</td>
<td>7 d (1 d–5.2 y)</td>
<td>10 d (1 d–7.9 y)</td>
</tr>
<tr>
<td>Pacemaker (at 1 mo of age), n (%)</td>
<td>60/138 (43)</td>
<td>25/53 (47)</td>
<td>35/85 (41)</td>
</tr>
<tr>
<td>Pacemaker (at 1 y of age), n (%)</td>
<td>74/107 (69)</td>
<td>32/42 (76)</td>
<td>42/65 (65)</td>
</tr>
<tr>
<td>Cardiomyopathy, n (%)</td>
<td>8/120 (7)</td>
<td>4/52 (8)</td>
<td>4/68 (6)</td>
</tr>
<tr>
<td>Infant death (≥1 y), n (%)</td>
<td>2/109 (2)</td>
<td>0/42</td>
<td>2/67 (3)</td>
</tr>
<tr>
<td>Childhood death (&gt;1 y), n</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are given as median with range when appropriate. Cases are divided into groups based on transplacental steroid treatment.
We found a clear correlation between gestational age at diagnosis and the risk of intrauterine or neonatal death, with a better outcome in those diagnosed after 23 weeks, when 92% were alive at birth. Patients in the Jaeggi et al study were approximately the same gestational age at diagnosis as in ours, without any significant difference in nonsurvivors compared with those who survived (median, 26.5 versus 25 weeks). Fetuses in the Lopes et al study were diagnosed at a median gestation of 29 weeks. Caution must be exercised, however, because the time interval between onset of disease and age at diagnosis may depend on the frequency and timing of midwife surveillance and ultrasound screening programs, which may differ between countries.

In agreement with others, we report reversion of incomplete heart block in 5 steroid-treated fetuses with AVB II (3 of 5) or AVB II to III (2 of 5), but only two of these children (with known outcome) remained in sinus rhythm at a follow-up of 1 and 2.7 years. Permanent reversal of fetal AVB II in anti-Ro/SSA– and/or anti-La/SSB–positive mothers is a rare finding, and to the best of our knowledge, no cases of spontaneous resolution of verified AVB II in fetuses of antibody-positive mothers have been reported, whereas cases of reversal after steroid treatment have been described before. This indicates a possible effect of early steroid treatment in some of our cases.

Fetal hydrops is associated with a high risk of intrauterine death unless a treatable cause is identified and left ventricular function are also bad prognostic signs, but the impact of having at least one of these risk factors, including early gestational age at time of diagnosis, has, to the best of our knowledge, not been studied before.

In our study, intrauterine mortality and neonatal mortality were 22% and 18% in the groups with risk factors compared with 2% and 3% in those without risk factors. We think these findings support risk stratification of cases and enable more appropriate counseling and management.

Morbidity outcome in terms of requirement for pacing or prevalence of cardiomyopathy could not be evaluated adequately owing to a substantial variation in follow-up time and loss to follow-up. However, the incidence of cardiomyopathy may be underestimated in those with shorter periods of follow-up. Villain and colleagues compared outcomes in children with AVB III and found that 28% of the antibody-positive children developed cardiomyopathy compared with none in the antibody-negative group; the mean age at follow-up was 4.6 years (range, 0.6 to 23 years). Only a few centers in our study reported side effects of steroids in the fetus; 5 of 11 reported cases came from 1 center, which suggests universal underreporting and is perhaps more common when fetal cardiology is practiced independently from a fetal medicine unit. Even fewer maternal side effects were described: in one case, managed in a fetal medicine center, serious side effects were recognized, including diabetes mellitus, adrenal insufficiency, and psychosis.

Study Limitations

The limitations of retrospective studies are well known, especially those with a multicenter design, in which it is more difficult to verify or check data. Consequently, our results cannot rule out the possibility that some patients or groups of patients may benefit from steroid treatment. Moreover, AVB II to III was difficult to verify from the limited traces available. This can frequently be very difficult to distinguish from sustained complete AV block with a seemingly constant time relationship between atrial and ventricular activation, therefore resembling AVB II. Fetuses were considered to have no risk factors only if confirmation was provided for all 4 variables; thus, we have potentially underreported the absolute numbers of the cohort without risk factors, which accounts for the missing data in Table 3 and Figure 4.

Conclusions

The results of our study do not support a therapeutic strategy of universal treatment with steroids for fetuses of anti-Ro/SSA– or anti-La/SSB–positive women with AVB III. However, it is important to emphasize that because of the retrospective design, we cannot rule out a possibly beneficial, or even harmful, effect of steroids. Our results in the subgroup with AVB II indicate that in this situation, steroids might be beneficial in decreasing the risk of progression to AVB III.

Because our data do not point to a clearly beneficial or harmful effect of steroids on the fetus with isolated AVB II or III, a randomized trial would, in our opinion, be ethical. However, because the observed mortality in this report was 16%, 253 patients would be required in each arm (treated versus untreated) to detect a 50% reduction in mortality from steroid treatment at a 5% significance level with 80% power. An alternative study would be to include only fetuses with AVB II in a randomized study with the hypothesis that steroids decrease the risk of progression to AVB III, but recognition of such cases is even rarer. The difficulty in recruiting large numbers of fetuses with such a rare condition is likely to make such studies impossible to conduct.

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Disclosures
None.

References

Isolated congenital complete atrioventricular block in the fetus is a rare but potentially lethal condition, most frequently associated with transplacental passage of maternal anti-Ro/SSA autoantibodies. With the assumption that this triggers an inflammatory reaction and subsequent fibrosis in the atrioventricular node, transplacental steroid treatment has been used with the aim to mitigate cardiac damage, but the effect of steroid treatment on outcome is still unclear. In this retrospective multicenter study of 175 fetuses with second- or third-degree atrioventricular block, 38% were treated with fluorinated steroids. Ninety-one percent were alive at birth, and survival in the neonatal period was 93%, without any difference between steroid-treated and untreated patients. A gestational age <20 weeks, a ventricular rate ≤50 bpm, the presence of fetal hydrops, and impaired left ventricular function at diagnosis were associated with an increased risk of death. The presence of ≥1 of these risk factors was associated with a 10-fold increase in mortality before birth and a 6-fold increase in the neonatal period independently of treatment. Except for a slightly lower gestational age at diagnosis in treated than untreated patients, risk factors were equally distributed between groups. Reversion of incomplete atrioventricular block was seen in 5 steroid-treated patients, but only 2 of them remained in sinus rhythm at 1 and 2.7 years of age. Our results do not support universal treatment with steroids for antibody-exposed fetuses with complete atrioventricular block, but because of the retrospective design, we cannot rule out a possibly beneficial, or even harmful, effect of steroids.
Isolated Atrioventricular Block in the Fetus: A Retrospective, Multinational, Multicenter Study of 175 Patients

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