Early Diagnosis and Treatment of Atrioventricular Block in the Fetus Exposed to Maternal Anti-SSA/Ro-SSB/La Antibodies
A Prospective, Observational, Fetal Kinetocardiogram–Based Study

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Background—A fetus exposed to maternal anti-SSA/Ro or anti-SSB/La antibodies (or both) may develop complete atrioventricular block (AVB), which results in high prenatal and postnatal morbidity and mortality. Until recently, only high-grade AVB could be diagnosed in utero. The tissue velocity–based fetal kinetocardiogram (FKCG) enables accurate measurement of AV conduction time and diagnosis of low-grade AVB. In the present multicenter observational study, we used FKCG to detect first-degree AVB in fetuses at risk.

Methods and Results—FKCG was performed in 70 fetuses of 56 mothers who were positive for anti-SSA/Ro and/or anti-SSB/La. Fetuses were monitored with weekly FKCG from 13 to 24 weeks’ gestation, followed by monthly assessments until delivery in unaffected fetuses and weekly assessments in affected fetuses. AV conduction in 70 at-risk and 109 normal fetuses was compared. FKCG was obtained readily in all fetuses; 6 showed first-degree AVB (AV conduction time \( z \) scores above normal mean) at 21 to 34 gestational weeks. Immediate maternal treatment with dexamethasone resulted in normalization of AV conduction in all affected fetuses within 3 to 14 days. AV conduction time in the remaining 64 untreated fetuses remained normal throughout gestation. The ECG PR interval immediately after birth was normal in all affected newborns. No child developed AVB or cardiomyopathy in the subsequent 1- to 6-year (median 4-year) follow-up.

Conclusions—The present findings suggest that an FKCG can detect first-degree AVB in the fetus exposed to maternal anti-SSA/Ro or anti-SSB/La antibodies (or both). Dexamethasone given on detection was associated with normalized AV conduction in fetuses with first-degree AVB. No fetus in the present study developed complete prenatal or postnatal AVB.

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Key Words: atrioventricular block ■ systemic lupus erythematosus ■ autoantibodies

Isolated congenital complete AV block (AVB) is a rare condition that occurs in approximately 1 of every 20 000 pregnancies.\(^1\) In >91% of affected neonates, complete AVB results from neonatal lupus erythematosus, a disease associated with transplacental passage of maternal anti-Ro/SSA and/or anti-La/SSB antibodies.\(^2\) The mothers of these neonates are commonly diagnosed with systemic lupus erythematosus (SLE), Sjögren syndrome (SS), or other rheumatic diseases, although many are asymptomatic. Complete fetal AVB, which usually develops during gestational weeks 16 to 24, conveys a significant fetal mortality rate (15% to 30%) and morbidity; two thirds of affected offspring will require permanent pacing.\(^3\)–\(^5\)

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Autoantibodies have been shown to play an important role in the pathogenesis of complete AVB, which may occur in 2% to 5% of neonates with neonatal lupus erythematosus.\(^2\)–\(^15\) After 1 child is affected, the risk of complete AVB in subsequent children increases to 18% to 25%; hence, maternal, fetal, and genetic factors may also contribute to the development of this condition.

Complete AVB in the fetus is almost always irreversible, although reduction from complete AVB to a lesser-degree block has been reported in rare cases.\(^16\) Several studies suggest that fluorinated steroids such as dexamethasone or betamethasone, which cross the placental barrier and are available to the fetus in active form, can prevent progression to third-degree AVB and alleviate cardiomyopathy;\(^17\)–\(^19\); however, indiscriminate prophylactic treatment of all anti-Ro/SSA– and anti-La/SSB–positive women during pregnancy has not been advocated, because >95% of these mothers and their unaffected fetuses would be unnecessarily exposed to the potentially deleterious effects of fluorinated corticosteroids.\(^20\)–\(^21\)

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It is thus important to detect low-grade AVB as soon as it occurs in fetuses exposed to anti-Ro/SSA and/or anti-La/SSB antibodies, before irreversible and deleterious effects to the AV node tissue have developed and before the fibrotic process has been completed. Early-stage diagnosis requires a reliable and reproducible method for measuring normal and prolonged AV conduction in utero. We elected to use fetal kinetocardiogram (FKCG), which has been shown to be accurate and reproducible in the measurement of AV conduction.

In January 1999, we initiated a prospective national, multicenter, observational study that recruited pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies. The goal of the present study was to assess the feasibility of detecting first-degree AVB in utero with FKCG.

Methods

Our institutional review board approved this offline diagnostic study, and participating women signed informed consent forms. All patients from the study and control groups were referred for clinically indicated fetal echocardiogram. FKCG is performed routinely as an integral part of fetal echocardiography in our unit. AV conduction (AVC) time is measured offline in all referred fetuses.

Patients

Study Group

Between January 1999 and December 2005, 70 fetuses of 56 anti-Ro/SSA– and/or anti-La/SSB–positive mothers were referred by family physicians, obstetricians, pediatricians, hematologists, and pediatric cardiologists from various medical centers in Israel to our tertiary care hospital for fetal echocardiography and FKCG. Consecutive women with positive serological findings for the presence of anti-Ro/SSA and/or anti-La/SSB antibodies on ELISA (BL Diagnostica, Mainz, Germany) evaluation were included in the study together with their fetuses.

Control Group

Scan-line raw data from 109 normal fetuses of similar gestational age were acquired from consecutive healthy pregnant women and stored for later offline analysis. In the case of twins, only 1 of the 2 fetuses was included among the controls. These women had been referred for clinically indicated fetal echocardiography.

Data Acquisition

Fetal Kinetocardiogram

Acquisition, scan-line raw data storage, and analysis of FKCG data were performed as described previously. Briefly, tissue velocity imaging (TVI) was performed with the GE Vivid FiVe or GE Vivid 7 ultrasound systems (General Electric Healthcare, Milwaukie Wis). TVI images were acquired with the 4-chamber view equivalent, with 3.5- to 5-MHz phased array (Vivid FiVe) or the M3S transducers (Vivid 7). The highest possible image frame rate was obtained by narrowing the angle of TVI interrogation and optimizing the field of view. Depending on the distance of the fetal heart from the transducer, the frame rate ranged from 72 to 220 Hz (mean 120 Hz). Three cine loops of TVI raw data, each of which contained 3 to 10 cardiac cycles (median 5 cycles), were stored as digital scan-line raw data for later offline analysis with EchoPac software (GE Healthcare).

Typical triphasic TVI curves were obtained by sampling the right ventricular free wall at the level of the AV valve annulus. They were composed of 2 diastolic waves produced by tissue motion away from the apex during the early diastolic rapid-filling phase (E), and during atrial contraction (A). The third wave (S) occurred in the opposite direction during systole and corresponded to ventricular contraction, with ventricular motion toward the apex. AVC time was measured from the onset of atrial contraction, which was defined as the point at which the TVI curve crossed the baseline, to the onset of ventricular activity, which in turn was defined as the point at which the curve returned to the baseline at the end of atrial contraction and the beginning of right ventricular isovolumic contraction. Right- and left-sided AVC times were measured and averaged over 3 to 5 consecutive cycles. For standardization purposes, we elected to use the right-sided AV conduction measurement, because it corresponds to the ECG-based PR interval that commences at the onset of right atrial activity. Temporal resolution of these TVI curves ranged from 12.3 to 16.9 ms (mean 14.2 ms) based on the formula 10 ms/(500/frame rate [Hz]) (manufacturer’s data).

Echocardiographic Protocol

Prenatal Assessment

Expectant mothers with a history of autoimmune disease such as SLE or SS or positive antinuclear antibodies were screened for anti-Ro/SSA and/or anti-SSB/La. Mothers with positive anti-Ro/SSA and/or anti-La/SSB antibodies were referred for their initial examination at 13 to 18 weeks of gestation (median 16 weeks). They were then asked to return for a weekly follow-up examination up to gestational week 24.

From week 25 until delivery, a monthly examination was performed in fetuses with no evidence of AVB. When first-degree AVB was diagnosed in a fetus, follow-up continued on a weekly basis until delivery.

Postnatal Assessment

Comprehensive postnatal examination of all newborns in the present study included a 12-lead ECG. Newborns with prenatal first-degree AVB underwent echocardiography within 12 hours of delivery (range 0.5 to 12 hours, median 3 hours). In these affected newborns, an umbilical cord blood sample was obtained to determine the anti-Ro/SSA and/or anti-La/SSB antibody level. Postnatal follow-up examination and echocardiography were scheduled at 1, 6, and 12 months and yearly thereafter. Blood tests to detect anti-Ro/SSA and/or anti-La/SSB antibodies were repeated 1 month after delivery to determine whether steroid therapy should be continued.

Treatment

The study was designed as a prospective observational study for the identification of first-degree AVB, defined as AVC time equal or superior to 2 $\text{z}$ scores above the mean calculated from the 109-fetus normal control group. On diagnosis of fetal first-degree AVB, dexamethasone (4 mg per day) was administered to the mother of the affected fetus until delivery, according to the clinical indication of treatment in prenatal AVB, 16,18,20,21,23,26. One patient had received prednisone (50 mg) for up to 34 weeks because of SLE exacerbation. Her treatment was switched to intramuscular betamethasone, followed by administration of dexamethasone (4 mg per day) initiated 72 hours later and continued to delivery. After delivery, 0.1 mg of prednisone per kilogram was given to newborns diagnosed prenatally with first-degree AVB, and this was continued for 6 weeks if the initial umbilical cord blood sample showed elevated anti-Ro/SSA and/or anti-La/SSB antibodies.

Statistical Analysis

Twins from the same mother were not considered statistically independent; therefore, we excluded twin B in 2 pairs of twins among the unaffected fetuses from the statistical analysis. The 95% prediction bands around the regression line were measured and plotted to detect prolonged AVC. Simultaneous right- versus left-sided AVC was compared in the control group with the Student’s paired $t$ test. Dependency of AVC on gestational age was studied with simple linear regression analysis and expressed as a Pearson correlation coefficient. The unpaired Student $t$ test was used to compare unaffected fetuses at risk with the normal population in the present study. $P<0.05$ was considered statistically significant. All data are reported as mean±SD unless otherwise specified.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.
**Results**

Adequate tissue velocity data were obtained in all 109 normal fetuses and 70 fetuses of anti-SSA/Ro-SSB/La-positive mothers. The first FKCG was performed from the 13th week to the 32nd week of gestation (median 17 weeks). TVI data acquisition time, including velocity-tracing display, ranged from 1 to 6 minutes (median 3 minutes). Offline measurement of AVC time required another 1 to 6 minutes (median 3 minutes).

**Control Group**

The average right-sided AVC time of 89 ± 8 ms exceeded the left-sided AVC time of 76 ± 9 ms (P < 0.0001). As reported previously, we elected to use the right-sided AVC time, which compared better with the electrical PR interval, for determination of AVB. Right-sided AVC time did not change significantly throughout gestation (Figure 1). The fetal heart rate in this control group ranged from 113 to 164 bpm (median 144 bpm). A nonsignificant tendency was found for AVC to shorten with increased fetal heart rate (r = 0.25).

**Study Group**

 Fifty-six mothers with anti-SSA/Ro-SSB/La antibodies were examined, including 42 mothers with a single pregnancy and 3 with twins. Eleven mothers delivered twice during the study period (Table 1). Twenty-seven (48%) of the mothers had anti-SSA only, whereas 29 (52%) had both anti-SSA and anti-SSB autoantibodies. Of 70 fetuses exposed to maternal anti-SSA/Ro-SSB/La antibodies, 64 (91.4%) had AVC times that were considered normal (mean 86 ± 9 vs 89 ± 8 ms in the normal control group, P = 0.28).

### Table 1. Diagnosis of Anti-SSA/Ro-SSB/La Mothers

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mothers, n</th>
<th>Fetuses, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>52</td>
<td>64</td>
</tr>
<tr>
<td>SS</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>MCTD</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>70</td>
</tr>
</tbody>
</table>

MCTD indicates mixed connective tissue disease.

### Table 2. AVC of the Fetus at Time of Initial Diagnosis of First-Degree AVB

<table>
<thead>
<tr>
<th>Diagnosis, GA, wk</th>
<th>HR, bpm</th>
<th>AVC, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Twin A) MCTD</td>
<td>32</td>
<td>126</td>
</tr>
<tr>
<td>2 (Twin B) MCTD</td>
<td>33</td>
<td>124</td>
</tr>
<tr>
<td>3 SLE (previous CAVB)</td>
<td>21</td>
<td>140</td>
</tr>
<tr>
<td>4 SS</td>
<td>25</td>
<td>150</td>
</tr>
<tr>
<td>5 SLE</td>
<td>26</td>
<td>110</td>
</tr>
<tr>
<td>6 SLE</td>
<td>34</td>
<td>140</td>
</tr>
</tbody>
</table>

GA indicates gestational age; HR, heart rate; MCTD, mixed connective tissue disease; and CAVB, complete AVB.

Six fetuses (8.6%) had first-degree AVB (Table 2; Figure 2), which was diagnosed during weeks 21 to 26 in 3 fetuses. Another fetus was diagnosed with first-degree AVB at 34 weeks of gestation; his mother had been treated with 50 mg of prednisone per day for severe SLE flare-up from the eighth week of gestation. Two additional fetuses, from a twin pregnancy in a mother with mixed connective tissue disease, had first-degree AVB that appeared almost simultaneously, at 32 weeks in the first fetus and at 33 weeks in the twin. The mother had received two 12-mg betamethasone intramuscular injections for fetal lung maturation at 24 weeks of gestation because of premature contractions. In these 6 fetuses, prolonged AVC reversed toward normal conduction within 4 to 14 days after initiation of fluorinated steroid treatment, with the mean AVC time of 130 ± 13 ms decreasing to 101 ± 12 ms after treatment (P < 0.0001 by paired t test; Figure 3). The P value includes the AVC time of 1 pair of dependent twins; the exclusion of the second twin did not change the P value of the paired t test (P < 0.0001).

All neonates in the study group, including fetuses diagnosed with first-degree AVB, were delivered after 37 weeks (range 37 to 40 weeks) at appropriate weight for gestational age. Postnatal examination, ECG, and echocardiography were normal in both the unaffected and 6 affected newborns treated with prenatal fluorinated steroids. At mean long-term follow-up of 4 years (range 1 to 6 years), these children are healthy, with normal development, as well as normal echocardiography and ECG.

### Discussion

Transplacental passage of maternal anti-SSA/Ro and/or SSB/La antibodies may cause AVC abnormalities as early as 18 weeks.
of gestation. Buyon et al.\textsuperscript{20} suggested that complete AVB may result from unresolved wound healing and scarring subsequent to transdifferentiation of cardiac fibroblasts into proliferating myofibroblasts, initiated by the specific maternal antibodies. The process that leads to AVB may rarely progress postnatally in exposed children for up to 2 months after delivery.\textsuperscript{27} Given the high reported recurrence in this population (18% to 25%), complete AVB could have been expected to occur in approximately 1 to 3 of the 70 newborns in the present study group. In fact, 6 (8.6%) of the 70 fetuses did develop AVB, which was detected by FKCG at the early, first-degree stage. The 6 fetuses with first-degree AVB showed significant improvement of AVC after dexamethasone treatment. None of them progressed to complete AVB.

Accurate measurement of AVC is mandatory for diagnosis of first-degree AVB. Assessment should begin at least by gestational week 16, before irreversible AV node fibrosis has occurred. First-degree AVB was diagnosed in the present series during gestational weeks 21 to 34, which is later than reported previously.\textsuperscript{20} In fact, in 3 of the 6 affected fetuses, first-degree AVB appeared during weeks 21 to 26, whereas in 3 others, it occurred much later, during weeks 32, 33, and 34. The mothers of these last 3 fetuses had been treated with high-dose steroids for lung maturation (patients 1 and 2 in Table 2) or severe flare-up of SLE (patient 6 in Table 2). We speculate that this high-dose steroid therapy might have postponed the occurrence of AVB in these 3 cases.

No accepted “gold standard” exists for normal fetal AVC time in the literature. Transient AVC prolongation in pregnancies complicated by maternal autoantibodies may occur,\textsuperscript{28} although this may be related to a low upper limit of normal AVC time as calculated by the blood-flow Doppler technique.\textsuperscript{29,30} We used the novel TVI-based FKCG technique to measure fetal AVC longitudinally from early second trimester (13 weeks) onward. TVI, when stored as scan-line raw data, offers the unique possibility of analyzing activity in any region of the heart and obtaining multiple tissue velocity curves within the same unique temporal domain. FKCG measures time intervals with high accuracy. The mean AVC time $\pm 2$ SD of $89 \pm 19$ ms in the 109-fetus normal control group in the present study was fairly narrow, did not change significantly throughout gestation, and was comparable to the manufacturer’s temporal resolution (14±3 ms). The 4-minute median acquisition time (range 1 to 6 minutes) was much shorter than the usual time spent in the acquisition of an M-mode echocardiogram of adequate quality, which could typically require 5 to 30 minutes. Thus, FKCG fulfilled the requirements for accuracy and clinical feasibility and is appropriate for diagnosis of first-degree AVB.

The present study shows that direct FKCG recording of atrial and ventricular mechanical activity is feasible at gestational ages of 14 to 40 weeks in all fetuses of positive anti-SSA/Ro and/or anti-SSB/La mothers, with no limitations. In the past, AVB has not been diagnosed accurately by the conventional M-mode technique unless it has progressed to its most serious degree, complete AVB. Assessment of the mechanical PR interval, with either the inflow/outflow Doppler technique\textsuperscript{31–33} or the superior vena cava–aorta approach,\textsuperscript{34} has been advocated for diagnosis of first-degree AVB in utero; however, a prolonged mechanical interval may be missed owing to overlap of inflow and outflow velocity spectra, which further increases with each increment of AVC time. In a recent article, mechanical PR interval has been shown to yield a low sensitivity (44%) and specificity (88%) for diagnosis of first-degree AVB in the fetus.\textsuperscript{29} Friedman et al.\textsuperscript{31} recently showed that left ventricular inflow/outflow Doppler methodology had such a large variability that it required 3 $z$ scores to increase the diagnostic specificity of first-degree AVB. In fact, with this definition of first-degree AVB, Doppler sensitivity dropped because of its failure to diagnose AV prolongation before the appearance of complete AVB.

Fetal ECG\textsuperscript{35–37} and magnetocardiogram\textsuperscript{38–41} have also been used to screen for AVB, although both techniques have limitations. Nii et al.\textsuperscript{42} reported that attainment of a fetal ECG is not feasible after 28 weeks of gestation because of the distribution of the vernix caseosa, and the fetal ECG p wave is poorly defined, which renders this methodology inadequate for accurate AVC measurement. In addition, ECG was feasible in only 61% of the cases.

Recently, a fetal ECG was shown to predict final abnormal fetal rhythm with a relatively high sensitivity (67%) and very high specificity (96%) in the 34 of 37 fetuses in which the AV interval could be measured.\textsuperscript{29} In contrast, the Doppler-based AV interval showed a low sensitivity (44%) and specificity (88%). An important limitation in that study was the lack of fetal ECG data from before 20 weeks of gestation because of poor tracings with wide variability. Also, in 2 (5%) of 37 fetal ECG recordings, the PR interval could not be measured.

Fetal heart time intervals, including PR interval, have been measured with some degree of accuracy with fetal magnetocardiography;\textsuperscript{43} however, we are not aware of the use of this technique for consistent diagnosis of first-degree AVB. Second-degree AVB can be diagnosed with this methodology.\textsuperscript{44} The major drawbacks for routine clinical use of the fetal magnetocardiogram are the need for a magnetically shielded room and the requirement of no fetal movement, which degrades the quality of the magnetic signal.

Although in the present study, the diagnosis of first-degree AVB was achieved in fetuses presenting with $z$ scores well beyond 2 SDs, we cannot state definitively the accuracy of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Right-sided AVC time in the 6 affected fetuses at initial diagnosis and after dexamethasone treatment, including mean and 1 SD, before and after treatment.}
\end{figure}
this diagnostic criterion because of the lack of a “gold standard” in the fetus. Nevertheless, there is no reason to presume that the accuracy of TVI-derived AVC time measurements, which have been validated in children and adults, should be intrinsically different in the fetus when a consistent methodology is used.

The accuracy of TVI-based measurement for AV interval has also been demonstrated recently by Nii et al. In fact, using the same TVI technique we had described previously, Nii et al measured an average normal AV interval of 94 ± 8 ms, which is almost identical to the AV interval we measured in the 109 normal fetuses in the present study (89 ± 8 ms). Obviously, one cannot rely on the presence of first-degree AVB after birth to evaluate the present findings, because the present study was interventional, and we treated fetuses that showed increased PR intervals in consecutive FKCGs in utero.

Fluorinated corticosteroids have been advocated and used in humans for fetal lung maturation for > 3 decades. Their use in the treatment of fetal AVB was first described more than 20 years ago, albeit with a partial response. Treatment of the mother and fetus with fluorinated steroids, mainly dexamethasone, may be associated with some deleterious effects on the developing central nervous system, lungs, retina, and adrenal glands24,44; however, it appears that these adverse side effects are primarily associated with premature or very-low-birth-weight newborns. Moreover, it appears that neurodevelopmental problems may be associated with postnatal dexamethasone therapy rather than antenatal exposure.25

In view of the debatable late effects from prenatal exposure to dexamethasone, our selective therapeutic approach, with treatment reserved for fetuses diagnosed with first-degree AVB, enables selection of a relevant high-risk group while sparing the vast majority of fetuses that are exposed to anti-Ro and/or anti-La antibodies but do not develop AVB. Given the lack of a prenatal “gold standard” and the few reports of transient AVC time prolongation,28,29 one may query the justification of treatment with fluorinated steroids; however, we believe, as do others,31 that the risk for escalation toward high-grade AVB in this high-risk population might outweigh this possibility.

The present study did not primarily address the question of efficacy of dexamethasone treatment for first-degree AVB. The rarity of anti-SSA/Ro– and/or SSB/La–positive mothers. The present data suggest that selective fluorinated steroid treatment may shorten a prolonged AVC time in fetuses exposed to maternal autoantibodies. Further studies are needed to support this observation.

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Disclosures

None.

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Fetal exposure to maternal anti-SSA/Ro or anti-SSB/La antibodies (or both) results in a 2% to 5% risk of complete AV heart block, or where to set the confidence limit: Arthritis Rheum. 2005;52:366–368.


CLINICAL PERSPECTIVE

Fetal exposure to maternal anti-SSA/Ro or anti-SSB/La antibodies (or both) results in a 2% to 5% risk of complete AV block, with up to 30% risk of intrauterine mortality; thus, detection of the first signs of AV conduction prolongation (first-degree AV block) is mandatory. We used a tissue velocity–based fetal keton cardiogram for accurate measurement of AV conduction time. We assessed AV conduction in 109 normal fetuses to define the range for normal fetal AV conduction and measured AV conduction from gestational weeks 13 to 40 in 70 fetuses exposed to maternal anti-SSA/Ro and/or SSB/La antibodies. Median acquisition and measurement time was 3 minutes. First-degree AV block, defined as >2 z-score prolongation of AV conduction, was found in 6 exposed fetuses (8.6%). Dexamethasone was administered to their mothers. Fetal AV conduction returned to normal within 4 to 14 days. All fetuses, including these 6, were normal after delivery. None had or developed AV block at 2 to 7 years of follow-up. We believe that tissue velocity imaging is a robust and accurate method for early diagnosis of first-degree AV block in fetuses. Although dexamethasone appeared to have a positive effect on the 6 affected fetuses, the effect of dexamethasone was not the purpose of the present study. Further prospective studies are needed to assess the role of dexamethasone in the treatment of fetal AV block.
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