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# Congenital Heart Block Not Associated with Anti-Ro/La Antibodies: Comparison with Anti-Ro/La-positive Cases

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# Abstract

Objective—To study anti-Ro/La-negative congenital heart block (CHB).

**Methods**—Forty-five fetuses with CHB were evaluated by analysis of anti-Ro/La antibodies using sensitive laboratory methods.

**Results**—There were 9 cases of anti-Ro/La-negative CHB; 3 died (33.3%). Only 3 (33.3%) were complete *in utero* and 5 (55.5%) were unstable. No specific etiology was diagnosed. Six infants (66.6%) were given pacemakers. There were 36 cases of anti-Ro/La-positive CHB. All except 2 infants (94.4%) had complete atrioventricular block *in utero*. Ten died (27.8%), one (2.7%) developed severe dilated cardiomyopathy, and 26 (72.2%) were given pacemakers.

**Conclusion**—Nine of the 45 consecutive CHB cases (20%) were anti-Ro/La-negative with no known cause. They were less stable and complete than the anti-Ro/La positive cases.

# **Key Indexing Terms**

HEART BLOCK; ANTINUCLEAR ANTIBODIES; AUTOIMMUNE DISEASES

Most cases of congenital heart block (CHB) detected *in utero* and unrelated to structural cardiac abnormalities are associated with anti-Ro/La antibodies, although the percentages of positive cases vary  $1^{-5}$ . Descriptions of the prevalence and outcome of anti-Ro/La-negative atrioventricular (AV) block also tend to differ<sup>2–1</sup>0. According to some investigators, mortality and morbidity are similar to those in anti-Ro/La-positive AV block<sup>3,4,7,8</sup>, while others report spontaneously reversible CHB and a more favorable course<sup>6,9,10</sup>.

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# MATERIALS AND METHODS

Forty-five consecutive fetuses with AV block were observed from 1990 to 2007 in 5 tertiary referral centers in Northern Italy (2 rheumatological, 2 cardiological, and one obstetric clinic). The inclusion criteria were congenital AV block detected *in utero* or at birth by fetal echocardiography and electrocardiogram. The exclusion criteria were structural cardiac abnormalities, congenital long QT syndrome<sup>11</sup>, mothers who had taken drugs during pregnancy that could induce fetal bradycardia, mothers who had had infectious diseases during pregnancy, or who had tested positive to hepatitis B/C viruses or human immunodeficiency virus, or to IgM anticytomegalovirus, Herpes or rubella virus and toxoplasma at the beginning of pregnancy.

Maternal sera were collected when CHB was detected and at delivery and tested for autoantibodies to Ro/SSA and La/SSB ribonucleoproteins using ELISA. Sera were tested a second time at the Padua University Hospital rheumatology laboratory employing a customdesigned counter-immunoelectrophoresis (CIE) method<sup>12</sup>; the fine specificities for 52-kDa and 60-kDa anti-Ro/SSA and 48-kDa anti-La/SSB were determined using a commercial ELISA (Diamedix, Delta Biologicals, Rome, Italy) and a line-blot assay (Inno-Lia, Innogenetics, Ghent, Belgium). Maternal sera negative to anti-Ro/SSA and anti-La/SSB antibodies were tested for confirmation by immunoblotting analysis using human salivary gland cell lysates, by ELISA using recombinant Ro52 protein, and by immunoprecipitation analysis with Ro60 and La *in vitro* translated proteins<sup>13</sup>, all at the laboratory of the University of Florida Department of Oral Biology. Maternal sera were also tested at the Padua laboratory for a battery of autoantibodies, including antinuclear (ANA), anti-dsDNA, anti-extractable nuclear antigens (ENA), anticardiolipin, and anti- $\beta_2$ -glycoprotein I antibodies.

Statistical analysis was done using SPSS software, version 14.0.

# RESULTS

Forty-five fetuses with CHB were examined. Thirty-six were born to anti-Ro/La-positive mothers (80%) and 9 to anti-Ro/La-negative mothers (20%). Negative maternal sera lacked reactivity to both Ro/SSA and La/SSB according to ELISA, CIE, and line-blot assays. These results were confirmed by the University of Florida Department of Oral Biology.

#### Anti-Ro/La-negative CHB infants (Table 1)

Five (55.5%) of the 9 infants were female. Three developed complete AV block *in utero* (Patients 1, 2, 3) and one also presented congenital sensorineural deafness. Two others had a stable second-degree AV block (Patients 4 and 5). Two fetuses had a second-degree AV block, one progressing to complete block soon after birth and the other at 3 months (Patients 6 and 7). The block alternated with normal sinus rhythm in the other 2 infants (Patients 8 and 9) and reverted to a stable normal sinus rhythm in Patient 9. Five blocks were unstable, changing their degree (nos 3,6,7,8,9).

Six blocks (66.6%) were detected *in utero* Three (33.3%) were diagnosed at birth (Table 1 and 2) when cesarean delivery was needed because of fetal bradycardia. Six were given pacemakers. Two presented signs of heart failure *in utero* and 3 died (33.3%) shortly after birth. The 6 survivors had a mean age of  $5.5 \pm 3.5$  years at the end of followup. Echocardiography showed no signs of cardiomyopathy or myocarditis.

#### Anti-Ro/La-negative mothers

Eight mothers were asymptomatic and one had photosensitivity and Raynaud's phenomenon. All were negative for ANA, anti-dsDNA, anti-ENA, and antiphospholipid antibody. Eight had further pregnancies, with no recurrences. One had a family history of AV block (11.1%).

#### Anti-Ro/La-positive CHB infants (Table 3)

Twenty-five (69.4%) cases were female. None of the 34 presenting with complete AV block *in utero* reverted to a lesser degree (Table 2 and 3), but the 2 infants with incomplete block did. One of the fetuses with a second-degree AV block reverted to a normal sinus rhythm after therapy with high-dose dexamethasone and was born with a first-degree block that remained stable throughout the followup. The other fetus, with a second-degree AV block, reverted to an alternating pattern between second-degree block and normal sinus rhythm during treatment with dexamethasone 4 mg daily and weekly plasmapheresis; at age 27 months she developed a complete AV block.

AV block was always diagnosed *in utero* on the basis of fetal bradycardia (mean gestational age 23.03 weeks). There were 2 cases of sudden death *in utero* and 4 were aborted, 3 with severe heart failure. Three died immediately after birth due to heart failure and a fourth, who was given a pacemaker shortly after birth, died suddenly at age 21 months. Twenty-six neonates (72.2%) were given a pacemaker (Table 2 and 3); 4 of them died. Twenty-six infants were alive at the end of the followup, with mean age  $6.6 \pm 4.5$  years. Echocardiography showed myocarditis *in utero* in 2 cases (5.5%). One male received a heart transplant at age 17 months because of severe dilated cardiomyopathy.

#### Anti-Ro/La-positive mothers

Eleven mothers were asymptomatic; 12 had Sjögren's syndrome, 11 undifferentiated connective tissue disease, and 2 systemic lupus erythematosus. Thirteen (36.1%) were anti-La/SSB-positive. Only 4 had been diagnosed with connective tissue disease before the index pregnancy. Twelve had further pregnancies and there were no recurrences. There was a family history in one case  $(2.7\%)^{14}$ .

# DISCUSSION

Cardiologists have been skeptical in the past about the existence of immune-mediated CHB, and some rheumatologists may still be doubtful about the existence of CHB not associated with anti-Ro/La antibodies. The exact percentages of anti-Ro/La antibody positivity in mothers of fetuses with CHB detected in utero and not associated with structural cardiac abnormalities are not known. Immunological studies using the most sensitive laboratory methods give positive results close to 100%, but these mothers were selected mainly from rheumatology centers<sup>2</sup>. Cardiological studies report lower percentages of anti-Ro/La-positive cases but do not always provide details about the laboratory methods<sup>3,6–10</sup>. Schmidt, et  $al^3$  and Maeno, et  $al^7$  reported 35% of anti-Ro/La negativity but did not indicate the laboratory tests. Using Ouchterlony double-diffusion and quantitative radio-ligand assays, Villain, et al<sup>5</sup> reported that 55/111 cases (49.5%) of complete AV block detected before age 15 years were anti-Ro/Lanegative. They also reported that 6/56 blocks (10.7%) detected in utero were anti-Ro/Lanegative, and another 25 had to be excluded because their antibody status was not known<sup>5</sup>. Lopes, et  $al^{15}$  reported that 41/57 (71.9%) mothers of fetuses with isolated AV block "were seropositive for antinuclear antibodies, most often anti-Ro antibodies," but did not indicate the test method. In agreement with our findings that report showed that spontaneous regression of AV block was possible in cases of anti-Ro/SSA-negative block and that mortality was similar in anti-Ro/SSA-positive and negative blocks, so these blocks too call for close followup.

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Referral and ascertainment bias might have skewed our results. However, we used state of the art laboratory methods and took the extra step of investigating further the initially negative reactivity for anti-Ro/SSA and La/SSB. In fact there were concerns that the negative reactivity was the result of low sensitivity of some assays or of failure to detect conformational epitopes (e.g., Ro60), which are readily detectable with immunoprecipitation of radiolabeled recombinant Ro60. By including these extra steps, we are confident about the negative reactivity reported here.

It has been suggested that cases of complete *in utero* AV block are often anti-Ro/La-positive, while incomplete blocks are generally negative<sup>5,6,8–10</sup>. Our study is the first to specifically compare anti-Ro/La-negative CHB with positive cases (Table 2) using sensitive laboratory methods. Twenty percent of our consecutive CHB cases were negative, but only 8.1% were negative when the analysis was limited to AV blocks that became complete *in utero*.

As no definite etiology (such as tumors, myocarditis, drugs) was found in the cases of anti-Ro/La-negative CHB, these must be considered "idiopathic." It is possible that there was some viral involvement, but it goes beyond the aims of our study to assess the role of viruses in the pathogenesis of CHB, whether anti-Ro/La-positive or negative. That one anti-Ro/La-negative female infant presented congenital sensorineural deafness is an interesting finding that warrants further study, since it has been correlated with congenital long QT syndrome<sup>11</sup>.

The early diagnosis of Ro/La-positive CHB cannot be explained by the fact that the mothers were attending rheumatology centers, as 32 of the 36 mothers were unknown to us before the blocks were detected.

The mortality rate was similar in the anti-Ro/La-negative and positive groups (33.3% and 27.8%, respectively), in agreement with Lopes, *et al*<sup>15</sup>, but the causes were different. No anti-Ro/La-negative fetuses developed cardiomyopathy. The cardiological courses of the cases of negative blocks were partially different for later gestational age and because they presented less often as complete, but often had a changing or progressive course.

While these findings have all the limitations of an observational study, there can be no doubt about the antibody negativity of the 9 cases we found. Although no single variable clearly distinguished Ro/La-positive from negative cases of CHB, the latter were often incomplete, were detected later during pregnancy, and were less stable.

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	Outcome (2007)	Died (at 5 mo from respiratory distress complicated by sepsis)	Alive (congenital sensorineural deafness)	Died (suddenly at 2 mo despite pacing)	Alive	Alive	Alive	Alive	Died (at 15 days from respiratory distress, pulmonary hypertension, and cardiac failure)	Alive (NSR at 2 yrs of age) age)
	Features of Block	Stable 3rd degree r coi	Stable 3rd degree Dexamethasone 84 mg in sen utero pending autoantibody finding	2nd degree, progressed to Die 3rd degree in utero and then stable. Betamethasone 102 mg in utero pending autoantibody finding	Stable 2nd degree	Stable 2nd degree	2nd degree at birth; 3rd degree at 3 days	Extrasystoles at 29 and 30 wks; 2nd degree AV block at birth, 3rd degree at 3 mo	2nd degree alternating with Di 3rd degree in utero. In Betamethasone 24 mg to pulr enhance fetal lung a maturity. 3rd degree at birth, reverted to NSR 30 min after birth but worsened to 2nd degree block the next day	28 wks fetus in NSR; at 29 Al. wks complete AV block was repeatedly found in 2 referral centers, over 3 days; betamethasone 12 mg was given to induce lung maturity; NSR the day after; 2 days later 3rd degree AV block recurred, and betamethasone was restarted, pending autoantibody finding; after 2 days NSR again, stable till delivery, at 34 wks;
	Age at Permanent Pacing	1 day	1 day	20 days	1 yr	No pacing	20 days	4 mo	No pacing	No pacing
	Fetal Heart Failure	Ascites, LV dilatation	No	Hydrops, LV dilatation	No	No	No	No	°N	°Z
	Apgar Score	78	89	8-8 8-8	8 - 10	6-7	7–8	9-10	5-7	6-6
others.	HR at Birth	27	58	40	100	70	75	96	60	110
legative m	GA at Delivery	30	36	37	41	34	34	41	35	¥
Features of fetuses/infants born to anti Ro/La-negative mothers.	Lower Fetal HR	35	30	45	80	80	80	96	40	80
born to an	GA CHB	22	32	19	At birth	29	At birth	At birth	29	29
es/infants	Year of Birth	2005	1996	2005	1999	2001	2005	2001	1996	2005
of fetus	Sex	Μ	Ц	Ц	ц	M	ц	Μ	Ц	W
Features (	Patient	Т	7	ω	4	5	9	٢	×	6

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Table 1

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GA CHB: gestational age at detection of CHB weeks; HR: heart rate; AV: atrioventricular; LV: left ventricle; NSR: normal sinus rhythm.

#### Table 2

Comparison of anti-Ro/La-positive (n = 36) and anti-Ro/La-negative (n = 9) CHB.

	<b>Ro/La-positive</b>	<b>Ro/La-negative</b>	Method	p*
Total deaths (%)	10 (27.78)	3 (33.33)	Fisher	0.384**
Male/female	11/25	4/5	Fisher	0.454
Mean gestational age at detection, wks	$23.03\pm3.90$	$30.56\pm7.30$	U test	0.005
Mean lowest fetal HR (bpm)	$57.17 \pm 11.92$	$62.89 \pm 24.93$	U test	0.628
Mean gestational age at delivery, wks	$34.67\pm3.41$	$35.67\pm3.53$	t test	0.400
Mean weight at birth, g	$2168.67 \pm 606.61$	$2567.78 \pm 659.05$	t test	0.098
Mean length at birth, cm	$38.16\pm8.15$	$44.44 \pm 5.98$	U test	0.073
Mean Apgar 1 min	$7.63 \pm 2.24$	7.44 + 1.24	U test	0.241
Mean Apgar 5 min	$8.71 \pm 1.52$	$8.78 \pm 1.00$	U test	0.433
Mean HR at birth (bpm)	$59.20\pm21.13$	$70.67 \pm 27.82$	U test	0.165
Incomplete AV block at end of followup (%)	1 (2.78)	4 (44.44)	Fisher	0.004
AV block complete in utero (%)	34 (94.44)	3 (33.33)	Fisher	0.000
AV block detected at birth (%)	0	3 (33.33)	Fisher	0.006
Pacemaker (%)	26 (72.22)	6 (66.67)	Fisher	0.704
Mean age at pacemaker insertion, days	$454.12 \pm 1056.89$	$87.83 \pm 142.93$	U test	0.497
Asymptomatic mothers (%)	11 (30.55)	8 (88.89)	Fisher	0.002

\*Significant at p < 0.05.

To calculate this p value the 4 terminations are considered as missing values. AV: atrioventricular; Fisher's exact test.

F 200 19 60 31 147 9-9 No 32 and degree block in turn. 1st Altre (1st degree stath)   F 202 2 64 9 No 459 Altre Altre (1st degree stath)   M 198 37 100 43 5 9 No 314 Altre (1st degree stath)   M 198 37 100 35 45 9 No 314 Altre (1st degree stath)   F 2016 21 64 3 7 7 314 Altre   F 2016 21 64 8 No 314 Altre   F 2016 21 64 8 No 314 Altre   F 2016 21 64 8 9 9 9 9 9 400 400 400   F 2010 21 21 8 9 9 9 9 9 40 <th>Patient Sex</th> <th>r Year of Birth</th> <th>GA CHB</th> <th>Lower Fetal HR</th> <th>GA at Delivery</th> <th>HR at Birth</th> <th>Apgar Score</th> <th>Fetal Heart Failure</th> <th>Age at Permanent Pacing</th> <th>Features of Block</th> <th>Outcome (2007)</th>	Patient Sex	r Year of Birth	GA CHB	Lower Fetal HR	GA at Delivery	HR at Birth	Apgar Score	Fetal Heart Failure	Age at Permanent Pacing	Features of Block	Outcome (2007)
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2001 18 70 35 80 9-9 No 1yr 3d   2000 24 62 38 70 8-9 No 10 yrs 3d   1992 29 50 37 60 70 8-9 No 3d   2001 23 60 27 65 NO 10ys 3d   2004 23 60 27 8 No 1day 3d   2004 20 56 7-8 No 1day 3d   2004 20 57 7-8 No 1day 3d   2005 28 48 70 8-9 No 3d   2002 28 32 0-2 Yes(inutero) 7 days 3d   1990 28 32 0-2 Yes(inutero) 2 days 3d   1990 28 32 0-2 Yes(inutero) 2 days 3d   1991 24	ц	1997	20	42	29	50	ND	Yes (in utero)	1 day	3rd	Died
2000 24 62 38 70 8-9 No 3m0 3m1   1992 29 50 37 50 9-9 No 10yrs 3m1   2001 23 50 37 50 9-9 No 10yrs 3m1   2001 23 60 37 55 7-8 No 1day 3m1   2004 23 60 37 55 7-8 No 1day 3m1   2004 20 55 7-8 No 1day 3m1   2004 20 55 7-8 No 2days 3m1   2004 20 55 7-8 Yes (in utero) 7 days 3m1   1998 22 55 57 7-9 Yes (in utero) 3m2   2004 24 45 No 1 day 3m1   2004 24 58 No 1 day 3m1   2005	Ц	2001	18	70	35	80	6-6	No	1 yr	3rd	Alive
192 $29$ $50$ $37$ $50$ $9-9$ $No$ $10ys$ $3d$ $2001$ $23$ $50$ $37$ $65$ $ND$ $No$ $2 days$ $3d$ $2004$ $23$ $60$ $27$ $55$ $7-8$ $No$ $2 days$ $3d$ $2004$ $23$ $60$ $27$ $55$ $7-8$ $No$ $2 days$ $3d$ $2000$ $20$ $56$ $32$ $60$ $8-9$ $No$ $2 days$ $3d$ $2000$ $20$ $55$ $32$ $9-9$ $No$ $2 days$ $3d$ $2002$ $28$ $32$ $29$ $9-9$ $No$ $2 days$ $3d$ $1990$ $28$ $32$ $29$ $9-9$ $No$ $2 days$ $3d$ $1090$ $28$ $32$ $29$ $9-9$ $No$ $1 day$ $3d$ $2001$ $22$ $55$ $32$ $9-9$ $No$ $1 day$ $3d$ $2001$ $24$ $56$ $36$ $No$ $1 day$ $3d$ $2001$ $22$ $55$ $32$ $9-10$ $No$ $1 day$ $3d$ $2001$ $24$ $52$ $32$ $9-10$ $No$ $2 mo$ $3d$ $2001$ $24$ $56$ $32$ $9-10$ $No$ $2 mo$ $3d$ $2001$ $24$ $52329-10No3d20012452329-10No2 mo3d20012452329-10No2 mo$	Ц	2000	24	62	38	70	89	No	3 mo	3rd	Alive
2001 23 50 37 65 ND No 2 days 31   2004 23 60 27 55 7-8 No 1 day 31   2004 23 60 27 55 7-8 No 1 day 31   2000 20 50 32 9-9 No 2 days 31   2000 20 55 32 9-9 No 2 days 31   2002 28 48 34 40 5-8 Yes (in utero) 7 days 31   2002 28 32 29 7 7 days 31   2003 28 32 9-9 No 1 day 31   2004 29 7 7 days 1 day 31   2005 29 9-9 No 1 day 31   2001 24 45 5-8 No 31   2001 24 5	Ц	1992	29	50	37	50	6-6	No	10 yrs	3rd	Alive
2004 23 60 27 55 7-8 No 1 day 3rd   2000 20 50 38 60 8-9 No 2 days 3rd   2000 20 55 32 50 9-9 No 2 days 3rd   2000 20 55 32 50 9-9 No 2 mo 3rd   2002 28 48 34 40 5-8 Yes (in uero) 7 days 3rd   1990 28 32 29 32 0-2 Yes (in uero) 3rd 3rd   1998 22 55 36 8-9 No 1 day 3rd   2004 24 40 No Yes (in uero) 1 day 3rd   2001 21 62 9-10 No 2 mo 3rd   2002 24 45 5-8 No 1 day 3rd   2001 24 5-8 No	Μ	2001	23	50	37	65	ND	No	2 days	3rd	Alive (heart transplant)
2000 20 50 38 60 8-9 No 2 days 31d   2000 20 55 32 50 9-9 No 2 mo 31d   2002 28 48 34 40 5-8 Yes (in utero) 7 days 31d   1990 28 32 29 32 0-2 Yes (in utero) 7 days 31d   1990 28 32 29 40 ND Yes (in utero) 7 days 31d   1998 22 55 32 0-2 Yes (in utero) 1 day 31d   2006 22 55 36 No 1 day 31d   2001 22 62 9-10 No 1 day 31d   2001 24 45 5-8 No 1 day 31d   2001 24 5 5-9 Yes (in utero) 31d 31d   2001 24 5 5-8 No	Ц	2004	23	60	27	55	7-8	No	1 day	3rd	Alive
2000 20 55 32 50 9-9 No 2 mo 3 mo   2002 28 48 34 40 5-8 Yes (in utero) 7 days 3 mo   1990 28 32 29 32 0-2 Yes (in utero) 2 days 3 mo   1990 28 32 29 32 0-2 Yes (in utero) 2 days 3 mo   1998 22 55 35 0-2 Yes (in utero) 2 days 3 mo   2006 22 55 8-9 No 1 day 3 mo   2001 22 62 9-10 No 2 mo 3 mo   2002 24 45 5-8 No 3 mo 3 mo   2001 24 55 3-9 Yes (in utero) 3 mo 3 mo   201 24 45 5-8 No 1 mo 3 mo   201 24 55 3-9 Yes (in utero)	Μ	2000	20	50	38	60	89	No	2 days	3rd	Alive
2002 28 48 34 40 5-8 Yes (in utero) 7 days 3rd   1990 28 32 29 32 0-2 Yes (in utero) 2 days 3rd   1998 22 55 29 40 ND Yes (in utero) 1 day 3rd   2006 22 55 35 50 8-9 No 1 day 3rd   2001 22 55 36 9-10 No 2 mo 3rd   2001 22 62 9-10 No 2 mo 3rd   2001 24 45 763 No 1 mo 3rd   2001 24 55 76 763 1 mo 3rd   2001 23 66 35 47 NO 1 mo 3rd   2001 23 66 35 NO 1 mo 3rd   2001 23 67 NO 1 mo 3rd 3rd <td>Μ</td> <td>2000</td> <td>20</td> <td>55</td> <td>32</td> <td>50</td> <td>6-6</td> <td>No</td> <td>2 mo</td> <td>3rd</td> <td>Alive</td>	Μ	2000	20	55	32	50	6-6	No	2 mo	3rd	Alive
190 28 32 29 32 0-2 Yes (in utero) 2 days 3rd   198 22 55 29 40 ND Yes (in utero) 1 day 3rd   2006 22 55 35 50 8-9 No 1 day 3rd   2001 22 62 36 62 9-10 No 1 day 3rd   2001 22 62 36 62 9-10 No 3rd 3rd   2001 24 45 5-8 No 1 mo 3rd   2001 24 52 33 50 3-9 Yes (in utero) 3rd   2001 23 53 3-9 Yes (in utero) 1 mo 3rd   2001 23 55 3-9 Yes (in utero) 1 mo 3rd   2001 23 55 3-9 Yes (in utero) 3rd 3rd   2007 26 35 9-9 <t< td=""><td>Μ</td><td>2002</td><td>28</td><td>48</td><td>34</td><td>40</td><td>5-8</td><td>Yes (in utero)</td><td>7 days</td><td>3rd</td><td>Alive</td></t<>	Μ	2002	28	48	34	40	5-8	Yes (in utero)	7 days	3rd	Alive
1938 22 55 29 40 ND Yes (in utero) 1 day 3rd   2006 22 55 35 50 8-9 No 1 day 3rd   2001 22 62 3-6 0 9-10 No 2 mo 3rd   2002 24 45 3-4 45 5-8 No 1 mo 3rd   2001 24 55 3-9 Yes (in utero) 1 mo 3rd   2001 23 55 3-9 Yes (in utero) 1 mo 3rd   2001 23 55 3-9 Yes (in utero) 1 mo 3rd   2001 23 55 3-9 Yes (in utero) 1 mo 3rd   2001 23 55 92 NO No 2 days 3rd   2007 20 57 90 No 1 yrs 3rd   2007 20 57 NO No 1 yrs 3rd<	Ц	1990	28	32	29	32	$0^{-2}$	Yes (in utero)	2 days	3rd	Died
2006 22 55 35 50 8-9 No 1 day 3rd   2001 22 62 36 62 9-10 No 2 mo 3rd   2001 24 45 34 45 5-8 No 1 mo 3rd   2001 24 52 33 50 3-9 Yes (in utero) 1 mo 3rd   2001 23 53 50 3-9 Yes (in utero) 1 mo 3rd   2001 23 55 37 No 23 days 3rd   2001 23 55 32 92 No 1 yrs 3rd   2007 20 57 36 00 9-9 No 3rd	Μ	1998	22	55	29	40	ND	Yes (in utero)	1 day	3rd	Died
2001 22 62 36 62 9-10 No 2 mo 3 rd   2002 24 45 34 45 5-8 No 1 mo 3 rd   2001 24 52 33 50 3-9 Yes (in utero) 1 mo 3 rd   2001 23 66 35 47 ND No 23 days 3 rd   1992 32 55 32 92 NO 11 yrs 3 rd   2007 20 57 36 60 9-9 No 10 yrs 3 rd	Μ	2006	22	55	35	50	89	No	1 day	3rd	Alive
2002 24 45 34 45 5-8 No 1 mo 3rd   2001 24 52 33 50 3-9 Yes (in utero) 1 mo 3rd   2001 23 66 35 47 ND No 23 days 3rd   1992 32 55 32 92 NO 11 yrs 3rd   2007 20 57 36 60 9-9 No No 3rd	Ц	2001	22	62	36	62	9–10	No	2 mo	3rd	Alive
2001 24 52 33 50 3-9 Yes (in utero) 1 mo 3rd   2001 23 66 35 47 ND No 23 days 3rd   1992 32 55 32 92 ND No 11 yrs 3rd   2007 20 57 36 60 9-9 No No 3rd	Μ	2002	24	45	34	45	5-8	No	1 mo	3rd	Alive
2001 23 66 35 47 ND No 23 days 3rd   1992 32 55 32 92 ND No 11 yrs 3rd   2007 20 57 36 60 9-9 No No 3rd	Ц	2001	24	52	33	50	3–9	Yes (in utero)	1 mo	3rd	Alive
1992 32 32 92 NO 11 yrs 3rd   2007 20 57 36 60 9–9 No No 3rd	Ц	2001	23	99	35	47	ND	No	23 days	3rd	Died
2007 20 57 36 60 9–9 No No 3rd	Ц	1992	32	55	32	92	ND	No	11 yrs	3rd	Alive
	Μ	2007	20	57	36	60	6-6	No	No	3rd	Alive

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Table 3

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uent	Sex	Year of Birth	GA CHB	Lower Fetal HR	GA at Delivery	HK at Birth	Apgar Score	Fetal Heart Failure	Age at Permanent Pacing	Features of Block	Outcome (2007)
28	ц	2007	23	55	34	55	6-6	No	22 days	3rd	Alive
29	ц	2007	26	55	35	55	ND	No	No	3rd	Alive
30	ц	2007	24	45	37	50	89	No	No	3rd	Alive
31	ц	2006	22	60				No	No	3rd	Died in utero
32	ц	1993	22	50				No	No	3rd	Died in utero
33	ц	2001	19	65				Yes (in utero)	No	3rd	Aborted
34	ц	1996	20	45				Yes (in utero)	No	3rd	Aborted
35	ц	1999	20	60				Yes (in utero)	No	3rd	Aborted
36	ц	2007	20	99				No	No	3rd	Aborted