Cardiol Young 2009; 19: 282–290

ISSN 1047-9511
doi:10.1017/S1047951109004053
First published online 22 April 2009

Original Article

The impact of treatment of the fetus by maternal therapy on the fetal and postnatal outcomes for fetuses diagnosed with isolated complete atrioventricular block

Vlasta Fesslova,[1] Gabriele Vignati,[2] Antonio Brucato,[3] Marina De Sanctis,[4] Gianfranco Butera,[1] Maria Pia Pisoni,[5] Enrico Chiappa,[6] Barbara Acaia,[7] Pier Luigi Meroni[8]

[1]Centre of Fetal Cardiology, Policlinico San Donato IRCCS, Milano; Departments of [2]Pediatric Cardiology, [3]Rheumatology, [5]Obstetrics and Gynecology, Ospedale Niguarda, Milano; [4]Department of Pediatrics, Policlinico San Matteo, Pavia; [6]Department of Pediatric Cardiology, Azienda Ospedaliera-Universitaria Meyer, Firenze; [7]Department of Obstetrics, Gynecology and Neonatology, Fondazione Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena, Milano; [8]Allergy and Immunology Unit, University of Milan, Istituto Auxologico Italiano, Milano, Italy

Abstract *Objectives:* to analyse retrospectively the data of fetuses diagnosed with isolated complete atrioventricular block and efficacy of treatment of the fetus by maternal therapy. *Materials:* Between 1992 and 2004, we diagnosed complete atrioventricular block in 26 singleton and 2 twins fetuses of 27 pregnant women known to have anti Ro/La antibodies, 11 with autoimmune disease, one patient analysed in 2 pregnancies. At presentation, 20 of the fetuses were compensated and non-hydropic, while 8 had hydrops. Twenty patients were treated with dexamethasone, 2 with associated salbutamol and one mother with isoproterenol. *Results:* Age at presentation was not different between the hydropic and non-hydropic fetuses. The fetuses with hydrops, however, had a lower mean heart rate at presentation, 48.5 ± 9.25 with a range from 32 to 60, compared to 59.95 ± 7.9 beats per minute, with a range from 50 to 80, in the non-hydropic fetuses (p less than 0.002). Equally, after birth the mean heart rate in hydropic fetuses was 42.6 ± 5.1, with a range from 38 to50, as opposed to 56.05 ± 11.8 beats per minute, with a range from 29 to 110, in the non-hydropic fetuses (p less than 0.015), The hydropic fetuses were delivered at 31.7 ± 3.8 weeks' gestation, with a range from 29 to 38 weeks (p less than 0.003) compared to 35.5 weeks' gestation ±2.04, with a range from 31 to 38, in the non-hydropic fetuses. Mortality was 37.5% in the hydropic fetuses, versus 5% of those without hydrops (p less than 0.02). Pacemakers were implanted in 22 of 26 infants born alive, at a median of 45 days, with a range from 1 day to 5 years, in those without hydrops during fetal life, and 3 days, with a range from 1 day to 8 months in those afflicted by hydrops, of whom 2 died despite the implant of the pacemaker. The presence and degree of hydrops had a significantly negative predictive value. No significant differences were observed between the treated and non treated cases, albeit that administration of steroids ameliorated rapidly the hydrops in 3 of 5 cases. *Conclusions:* The outcome in our cases was mainly dependent on the presence and degree of fetal cardiac failure. Treatment of the fetus by maternal administration of steroids did not result in any regression of the conduction disorder, but had a favourable effect on fetal hydrops.

Keywords: congenital atrioventricular block; fetal echocardiography; neonatal lupus; anti-Ro antibodies; steroids

Correspondence to: Dr Vlasta Fesslova, Centre of Fetal Cardiology, Policlinico San Donato, Via Morandi 30, San Donato Milanese, Milano 20097, Italy. Tel: 0039 02 52774 511/393; Fax: 0039 02 52774 459; E-mail: cardiologiafetale@grupposandonato.it

Accepted for publication 17 February 2009

Isolated congenital complete atrioventricular block occurs mostly in presence of maternal connective tissues disease, or anti SSA/Ro or anti SSB/La antibodies, with otherwise structurally normal hearts.[1,2] Such congenital complete atrioventricular block is known to develop in 1 to 2% of all pregnancies in mothers that carry anti-Ro/La antibodies.[3] The passive transplacental passage of the maternal autoantibodies occurs since the middle of the second trimester, and is thought to be responsible for inflammation and fibrosis of the conduction system, with documented evidence of binding of the antibodies to the myocytes of the conduction tissues.[3]

Signs of myocarditis and endocarditis, as well as endocardial fibroelastosis and dilated cardiomyopathy, have been reported both in necropsy specimens and in clinical studies.[4–8] The antibodies may also involve other organs, inducing the clinical and the laboratory manifestations of the neonatal lupus syndrome.[1,2,9] The fetuses with complete atrioventricular block with a low heart rate, less than 50 to 55 beats per minute, can rapidly develop hydrops, often leading to intrauterine or postnatal death.[10,11]

In the last decade, it has been suggested that treatment of the fetus by maternal administration of steroids might produce regression of the conduction disorder, or improve the fetal compensation.[12–17]. As an alternative, others have used sympaticomimetics to increase the fetal heart rate.[15] The benefits of the treatment in the fetal life with respect to outcomes are still under evaluation. With this in mind, we have analysed retrospectively a series of fetuses diagnosed with isolated congenital complete atrioventricular block, examining their characteristics, their course during fetal life and after birth, and the differences in outcome with respect to the heart rate and cardiac compensation with or without maternal-fetal treatment.

Patients and methods

Between 1992 and 2004, congenital complete atrioventricular block was diagnosed echocardiographically in three centres in 28 fetuses of 27 pregnant women. The mothers were aged from 23 to 35 years, with a median of 28 years, one mother being followed during 2 pregnancies. All were found to carry anti-Ro/La antibodies. The age of the fetuses at presentation ranged from 19 to 32 weeks gestation, with a median of 25 weeks. Of the mothers, 11 had known autoimmune disease, lupus erythematosus in 10, none on specific treatment, and one had autoimmune thyroiditis. There was 1 case of a bichorionic, biamniotic twin pregnancy, and 1 trichorionic, triamniotic, triple pregnancy, after in-vitro fertilization. The mother carrying the twins had previously borne a fetus with complete atrioventricular block who died at 25 weeks' gestation. We followed this mother during both her pregnancies.

The mothers were usually referred subsequent to the discovery of fetal bradycardia. The mother with the twin pregnancy had been followed regularly since the onset of pregnancy due to the previous history, while the mother with triplets had been referred at 21 weeks gestation for signs of myocarditis in the 2 female fetuses, with a subsequent appearance of complete atrioventricular block in one of them, at 24 weeks, with a rapid progression to hydrops. At presentation, 8 fetuses already showed signs of fetal hydrops, mild in 3, moderate in 3, and severe in 2, while the other 20 fetuses were compensated, with no evidence of hydrops.

Methodology

Echocardiography was performed using Acuson 128 XP/10, Acuson Sequoia 512, Imagegate, Siemens, Erlangen, Germany and Vingmed System Five, General Electrics machines, using transducers 5 or 3.5 megaherz according to the gestational age. A complete ultrasonic scan was performed in all cases.

The fetal heart was analysed by means of M-mode or Colour Doppler M-mode, evaluating the sequences of atrial and ventricular contractions. Complete atrioventricular block was diagnosed when atrial contractions were independent and dissociated from ventricular contractions. We used the cut in the parasternal long axis view showing both the aorta and the left atrial wall so as properly to assess the contractions of the atrial wall. Doppler and Colour Doppler were used to detect any abnormal regurgitant flows across the atrioventricular valves. Since 2000, we have also evaluated the sequences of flow in the superior caval vein, the ascending aorta, and the venous duct. The general state and behaviour of the fetus was analysed by means of Doppler interrogation to provide the pulsatility index of the umbilical artery and median cerebral artery, eventual fluctuation pattern of the flow in the umbilical vein, and by observing fetal movements. We diagnosed fetal hydrops when serous effusions were observed in at least 2 compartments.

Protocol of management

We checked both the clinical state and laboratory findings in all the mothers. All had initially been hospitalized, permitting evaluation of routine laboratory examinations.

Having documented anti-Ro/La antibodies, we started treatment of the fetus by dosing the mother

in 21 cases, in 16 with non-hydropic fetuses, and in 5 with hydrops. In 20 cases, we used dexamethasone at 4 mg per day, combined in 2 mothers with salbutamol. In 1 mother seen early in our experience, we used isoprotenerol, the fetus in this case having a very low heart rate, 32 beats per minute, at presentation. In most cases, treatment was started within 2 weeks of presentation, albeit that in 3 of the fetuses without hydrops, and 2 with hydrops, we started treatment after a delay of 4 to 7 weeks, having noted a decrease in the heart rate. Treatment was usually continued until the end of the pregnancy, lasting from for 1 to 14 weeks, with a median of 4 weeks. The dose of dexamethasone was progressively reduced towards the planned time for delivery.

We did not attempt treatment in 7 mothers, 4 of the ones seen earlier in our experience who were carrying non-hydropic fetuses, with heart rates of 50, 54, 80, and 73 beats per minute respectively, and in 3 hydropic fetuses. In the latter group, 1 fetus had a very low heart rate and severe anasarca, and was considered to be preterminal, while the other 2 had only minor degrees of cardiac failure, and showed stable heart rates. We followed all mothers at short time intervals, usually once or twice a week, until the ends of their pregnancies. In all instances, management was made by a multidisciplinary team of a gynaecologist, a paediatric cardiologist, and a neonatologist.

After birth, we have followed the infants for a median of 7 years, with a range from 3 to 14 years. The postnatal follow-up included clinical and echocardiographic evaluation at short time intervals initially, then 2 to 3 times a year, according to the individual situation. When they were around 2 years of age, we also had the neurodevelopmental state assessed by a specialist in our group who used the developmental scale developed by Griffiths. We summarise our data in Table 1.

Statistical analysis

Data is expressed as a frequency or percentage for nominal variables, as a median with range for categorical variables, and as a mean ± standard deviation for continuous variables.

We analysed as dependent variables whether the fetuses were alive or had subsequently died, the need for insertion of a pacemaker, and if required, the timing of its implantation. As independent variables we included gestational ages and heart rate of the fetuses at presentation, their age at delivery, the neonatal heart rate, whether the mothers had been treated, and the presence or absence of fetal hydrops. Fetal hydrops, if present, was graded as mild, moderate, or severe. We grouped heart rates for fetuses and neonates as less than 50 beats per minute, from 50 to 60 beats per minute, or more than 60 beats per minute. Implantations of pacemakers were grouped for insertions at 1 to 30 days, 1 to 2 months, 2 to 12 months, or longer than 12 months. We performed univariate analysis using the chi-squared test, Fisher's exact test, the unpaired Student's t test, the Wilcoxon rank sum test, the paired t test, and the Mann-Whitney U test. Multivariate analysis was performed by using multiple logistic regression analysis. The diagnostic of the regression model was made obtaining the standardized residuals and plotting them by use of the Wilks-Shapiro/rankit plot test. Independent variables were included in the multivariate model if in the univariate analysis p was less than 0.2. Odds ratios with 95% confidence intervals were calculated for independent variables included in the multivariate model. All tests were two-sided. A probability value of p less than 0.05 was considered as significant.

Results

Characteristics

In Table 2, we present the main data of the hydropic as opposed to non-hydropic fetuses. Age at presentation of the fetuses in the 2 groups was not significantly different, but both fetal and neonatal heart rates were lower in those with hydrops (p less than 0.002 and 0.005 respectively). The heart rate reduced throughout pregnancy in fetuses of both groups (p less than 0.05 in those without hydrops, and p less than 0.08 in those with hydrops).

Outcomes

Non-hydropic fetuses. All 4 fetuses without hydrops that were not treated survived. In 3 of them (cases 12, 15 and 16), pacemakers were implanted at 12, 16, and 60 months, while the fourth child remains stable at 3 years.

Of the 17 fetuses without hydrops that received treatment, 1 (case 34) died at 34 weeks gestation having presented at 24 weeks gestation with a heart rate of 60 beats per minute. There had been a sudden drop in the heart rate at 34 weeks, followed by death. Of the remaining fetuses, 15 were delivered at a median gestational age of 34 weeks, with a range from 31 to 37 weeks, with 4 requiring inotropic treatment after birth, and all 15 having pacemakers implanted at a median age of 45 days, 6 requiring implantation at 1 to 30 days, the remaining fetuses having the devices implanted later, at 1.5 to 60 months.

Hydropic fetuses. Of the mothers with hydropic fetuses, 3 received no treatment. Amongst these, one mother lost a fetus with anasarca at 25 weeks gestation, after presentation at 24 weeks (case 22).

https://doi.org/10.1017/S1047951109004053 Published online by Cambridge University Press

Table 1. Data of the series.

Case	Dg. w.g.	Conn. antib.	FHR	Heart failure	Therapy. w.g.	Outcome preg./w.g.	Neon. HR	Neon. HF	Inotr.	PM-age	Neon.Outcome		Note
											Alive	Died	
Non-hydropic group:													
1	19w	Y, ro	60	no	Y-d-23w	CS 35w	60	no-	no	no	Y	no	
2	20w	Y, ro	70	no	Y-d,s-24w	CS 32w	46	no	no	Y-1m	Y	no	
3	20w	no,ro	62	no	Y-d-22w	CS 36w	60	no	no	no	Y	no	
4	21w	Y, ro	56	no	Y-d-23w	CS 31w	49	no	no	Y-8d	Y	no	
5	21w	no,ro	65	no	Y-d-24w	CS 35w	70	no	no	no	Y	no	
6	23w	no,ro	50	no	Y-d-24w	CS 37w	45	no	no	Y-1d	Y	no	
7	24w	no,ro	55	no	Y-d-24w	CS 38w	58	no	no	Y-6m	Y	no	
8	24w	Y,ro	60	no	Y-d-24w	**IUD 34w**							
9	25w	Y,ro	50	no	Y-d-32w	CS 34w	45	no	no	Y-2m	Y	no	
10	27w	Y,ro	60	no	Y-d-27w	CS 38w	56	no	no	Y-1m	Y	no	
11	28w	no,ro	58	no	Y-d-28w	CS 34w	55	no	no	Y-8m	Y	no	
12	29w	Y,ro	50	no	no	CS 38w	50	no	Y	Y-60m	Y	no	
13	23w	no,ro	80	no	no	CS 37w	75	no	no	no	Y	no	
14	30w	no,ro	54	no	no	CS 37w	65	no	no	Y-16m	Y	no	
15	20w	no,ro	73	no	no	CS 38 w	70	no	no	Y-12m	Y	no	
16	24w	no,ro	60	no	Y-d-24-25w	CS 34w	50	no	no	Y-20d	Y	no	
17	27w	Y,ro,la	53	no	Y-d-27w(5w)	CS 34w	52	no	no	Y-1m	Y	no	
18	21w	Y,ro,la	65	no	Y-d-22w	SD 37w	70-110	no	no	Y-30m	Y	no	
19	24w	no,ro,la	63	no	Y-d-24w	CS 35w	55	no	Y	Y-1.5m	Y	no	
20	20w	no,ro,la	55	no	Y-d-20w	CS 34w	55	no	Y	Y-1m	Y	no	Twin preg*
Total 20					16	1 IUD				15 PM 12/16 treated, 3/4 not treated	19 alive	0	
Hydropic group:													
21	25w	no,ro	48	Y+ 29w	no	CS 32w	50	no	no	Y-15d	Y	no	
22	24w	no,ro,la	40	Y+++	no	**IUD 25w**							
23	24w	no,ro,la	52	Y++	Y-d-25w	CS 32w	40	no	Y	Y-40d	Y	no	Triplet preg
24	20w	no,ro	45	Y++	Y-d,s-24w	CS 29w	38	Y	no	Y-1d	no	**Y-1d**	
25	22w	no,ro	56	Y++27w	Y-d-22w	CS 27w	40	Y+++	no	Y-1d	Y	no	
26	25w	no,ro	60	Y+ 34w	Y-d-34w	CS 39w	50	no	no	Y-8m	Y	no	
27	28w	Y,ro	32	Y+++	Y-isopr	CS 29w	40	Y+++	Y	Y-1d	no	**Y-2d**	
28	32w	Y,ro	55	Y+ 35w	no	CS 35w	40	Y+	Y	Y-3d	Y	no	
Total 8				5	1 IUD					7 PM 5/5 treated 2/2 not treated	5 alive	2 postn.death	

Dg – diagnosis, Conn – connectivitis, antib. – antibodies, FHR – fetal heart rate, Neon HR – neonatal heart rate, Neon HF – neonatal heart failure, w.g., w. – weeks' gestation, Y – yes, preg – pregnancy, d – dexamethasone, s – salbutamol, isopr – isoproterenol, neon – neonatal, postnat – postnatal, d – days, m – months, PM – pacemaker, CS – cesarean section, SD – sponntaneous delivery, IUD – intrauterine death.

*2nd pregnancy after a previous one ended in intrauterine death – case 23.

Table 2. Main data of non-hydropic and hydropic fetuses at statistical analysis.

Group	Age at presentation w.g. (mean ± SD, range, median)	FHR beats/min (mean ± SD, range, median)	NHR beats/min. (mean ± SD, range, median)	Age at delivery w.g. (mean ± SD, range, median)	Pacemaker Implant N. Median age (range)	Total mortality
Non-Hydropic 21 cases	23.5 ± 7.3 (19–30) median 23	59.95 ± 7.9 (50–80) median 60	56.0 ± 11.8 (29–110) median 55	35.5 ± 2.04 (31–38) median 36	15 cases – median 45 d (1 d–5 yrs)	1/20 5% 1 IUD
Hydropic 8 cases	25.4 ± 3.66 (20–32) median 25	48.5 ± 9.25 (32–60) median 50	42.6 ± 5.1 (38–50) median 40	31.7 ± 3.8 (29–38) median 32	7 cases- median 3 d (1 d–8 m)	3/8 37.5% 1 IUD, 2ND
p	NS	p = 0.002	p = 0.005	p = 0.003	NS p = 0.17	p = 0.02

FHR – fetal heart rate, NHR – neonatal heart rate, w – weeks' gestation, d – days, m – months, SD – standard deviation, IUD – intrauterine death, ND – neonatal death, d – days, m – months, yrs – years, NS – not significant at Student t-test.

The fetal heart rate in this case progressively reduced from 45 to 25 beats per minute. The other 2 fetuses survived (cases 21 and 28), and had pacemakers implanted at 15 and 3 days.

We treated the other 5 mothers, 2 of these were carrying fetuses in which fetal hydrops progressed to severe anasarca and died both after birth, despite implantation of pacemakers on the day of birth (cases 24 and 27).

The other 3 fetuses were delivered at 27, 32, and 38 weeks gestation, respectively, and survived following implantation of pacemakers at 1 day, 40 days, and 8 months.

Age at delivery

The non-hydropic fetuses were delivered at later gestational ages, of 35.5 +− 2.04 weeks as opposed to 31.7 +− 3.8 weeks for the hydropic fetuses (p less than 0.003 – Table 2). Emergency caesarean section was required in 6 cases because of an abrupt decrease of the heart rate in 5 instances, and because of premature rupture of the membranes in the triplet pregnancy. The remaining mothers underwent planned delivery according to the situation, all but one by caesarean section.

Effect of maternal treatment

In no case did we observe any regression of the conduction disorder after treatment. There was, however, a rapid improvement in hydrops in 3 of the 5 hydropic fetuses after treatment, with no noted deterioration of cardiac compensation observed in 15 of the 16 treated non-hydropic fetuses, albeit that 3 of these suffered an abrupt decrease of the heart rate and underwent emergency caesarean sections as reported above. In Table 3, we summarise the results for treated as opposed to untreated cases. We failed to detect any statistically significant differences.

Adverse effects of dexamethasone treatment

We did observe adverse effects of dexamethasone in 2 fetuses, noting a reduction of amniotic fluid leading to progressive cessation of therapy. No other adverse effects were observed, either in fetuses or mothers. Fetal growth was within the normal limits, between the 10th and 50th centile for the gestational age, with a median of the 25th centile. The weights at birth ranged from 1600 to 3100 grams, with a median of 2400 grams.

Pacemaker implantation

We implanted devices in 22 of the 26 fetuses born alive (84.6%). Of these, 15 had not suffered hydrops and 12 had the devices implanted at a median age of 45 days, with a range from 1 day to 5 years. In the

https://doi.org/10.1017/S1047951109004053 Published online by Cambridge University Press

Table 3. Data of treated compared to untreated cases.

Group/Number cases	Age at present. W.g. Median (range)	FHR Beats per minute Median (range)	Age at delivery w.g. Median (range)	NHR Beats per minute Median (range)	Pacemaker Implant Number cases – median age (range)	Mortality Number cases – %
Non-hydropic group	29	54	37–38	65	3/4 cases – ***late***	0/4
4 cases not treated	(20–30)	(50–73)		(50–75)	median age 16 m (range 12–60)	
16 cases treated	24	60	15 cases	55	15 cases	1/16–6.25%
	(19–29)	(50–80)	34 (31–37)	(45–100)	median age 45 d (1 d–60 m)	(1 IUD-34 w.g.)
Hydropic group	25	48	CS 32, 35 IUD	40, 50	2/2 cases live-born	0/2 with a longer follow up,
2 cases followed-up, not treated and 1 IUD one week after dg.	(24,25,32)	(40,48,55)	25, dg 24		3–15 d	1 IUD 25 w.g.
5 cases treated	24	52	3 delivered at 27, 32, 37	40	5 cases	2/5–40%
	(20–28)	(32–60)		(38–50)	1 d, 1 d, 2 d, 40 d, 8 m	ND – 1, 2 d, post PM implant
Total not treated 6 cases (1 IUD shortly after present. not considered)					5/6 live-born = 83.3%	0/6–0%
Total treated 21 cases					20/21 (95.2%)	3/21–14.3%

Note: no statistically significant differences were found at multivariate analysis between the variables in the treated as opposed to untreated mothers.
w.g. – weeks' gestation, present – presentation, FHR – fetal heart rate, NHR – neonatal heart rate, IUD – intrauterine death, ND – neonatal death, d – day, m – month, PM – pacemaker.

cases not treated in fetal life, devices were implanted at a later median age of 16 months, with a range from 12 to 60 months. In the 7 liveborn infants who had suffered hydrops, 5 of which having been treated, devices were implanted at a median age of 3 days, with a range from 1 day to 8 months (Tables 2 and 3). Epicardial pacemakers were implanted using subxyphoid access, positioning the device in the upper abdomen, and using VVI pacing at a heart rate of 90 beats per minute. At multiple logistic regression analysis, no predictive variables were found.

Mortality

Four of the 28 fetuses died (14.3%), 2 during fetal life and 2 after birth. Of the 21 fetuses treated, 3 died (14.3%), but none of the fetuses not treated died, if we exclude the fetus with severe anasarca who died shortly after fetal presentation (Table 3). Mortality was lower in cases without hydrops, 1 from 20 (5%) than for those with hydrops, of whom 3 of 8 died (37.5% – p less than 0.02).

In all cases, death was due to cardiac failure. At multiple logistic regression analysis, the only predictive variable for outcome was the presence and degree of hydrops (ß coefficient equal to 2.2; p less than 0.018; OR: 9,2(95% CI: 1.5 to 58).

Postnatal and longterm outcomes

Of our initial cohort, 24 infants (82.7%) are alive at a median follow-up of 7 years, with a range from 5 to 14 years. None have developed dilated cardiomyopathy, nor showed any abnormal neurological development as estimated using Griffith's neurodevelopmental scale. The cases born prematurely suffered from disorders of prematurity, albeit without any significant consequences. One of our twin infants presented after birth moderate pulmonary stenosis, with a transvalvar gradient of 50 mmHg, that subsequently improved without the need for an invasive procedure. The patient is now well at 6 years.

The second female of the triplet pregnancy showed, after birth, the first and episodical second degree atrioventricular block. She is currently stable at the age of 7 years. In her case, a slightly prolonged P-R interval, of 0.14 msec, was seen 2 weeks before the caesarean section at 32 weeks gestation when using the Doppler evaluation of the pattern of flow in the superior caval vein compared to the ascending aorta.

Discussion

The natural history of isolated immune-mediated congenital complete atrioventricular block depends mainly upon the degree of fetal bradycardia, the fetal heart being limited in its ability to produce a valid cardiac output in the setting of very low heart rates. A high morbidity and mortality has been reported for such fetuses, depending usually on the hydropic state.[2,10,16,17] This data, however, mostly reflects cases studied in the previous era, when no maternal-fetal treatment was available.

The reasoning for treatment of the mother with steroids so as to influence the fetus is to act against the immune-mediated inflammatory process produced by the passive passage of antibodies, with the dual aims of, first, potentially producing regression in the degree of the conduction disorder, and second, to act against all other sites of the inflammatory process that characterize the neonatal lupus syndrome. Prophylatic use of such transplacental treatment for prevention of congenital heart block is not justified in women with anti-Ro/La antibodies, since there are no known predictive markers for its development, and the incidence of atrioventricular block is low in this population.[2,18–20]

Also, some manifestations of the interactions of the maternal antibodies in the fetus, such as myocarditis and endocardial fibroelastosis, can develop only during the pregnancy, or after the delivery. Myocarditis preceded the development of the conduction disorder to different degrees in our triplet pregnancy, with complete atrioventricular block seen in one fetus and first and second degree block in the second, but with the third fetus showing only mild signs of neonatal lupus after birth.[5] Equally, in our twin pregnancy, only one fetus was affected by complete atrioventricular block, albeit this being a recurrence, with a previous sibling suffering the same disorder, but with the second twin being completely free of symptoms of neonatal lupus syndrome. Our data confirms, therefore, the known discordance in the clinical manifestations of neonatal lupus in multiple pregnancies, mainly in bi- or tri-chorionic ones.[21,22] Females appear to be at higher risk for neonatal lupus and complete atrioventricular block, as was also the case in our triplet pregnancy.[5,23]

Several previous retrospective studies have suggested that the use of glucocorticoids might temper immune-mediated fetal cardiac damage, and indirectly improve cardiac contractility in suspected fetal myocarditis and, rarely, lessen the degree of atrioventricular block or even produce its regression.[16,24,25] Jaeggi and colleagues[14] stated that the routine use of dexamethasone given to mothers at the time of diagnosis of fetal heart block, in combination with ß-sympathomimetic therapy for persistent fetal bradycardia of less than 55 beats per minute, significantly improved survival compared with untreated fetuses that had a lower postnatal survival due to a higher frequency of immune-mediated complications and

endocardiacal fibroelastosis. In contrast, Saleeb and colleagues[26] reported no regression of complete atrioventricular block, but observed in some cases a resolution of incomplete atrioventricular block, and a resolution of effusions and fetal hydrops, albeit without any benefit in outcome in comparison with untreated fetuses. Equally, Breur and colleagues,[27] in a review of 19 studies on 93 fetuses with atrioventricular block, failed to find any cases having regression of complete block, but did document regression of incomplete block in a few cases.

In our study, the treatment was not randomized, but rather depended on the era of the diagnosis of complete atrioventricular block, and on the severity of the fetal compensation. Since the mid 1990s, we have adopted a policy to treat the patients by dexamethasone shortly after the documentation of anti-Ro/La antibodies, both in cases with and without cardiac failure.

The majority of our cases, 20 in all, were treated, with additional use of a beta- sympathomimetic in 2 fetuses having a low heart rate. In one of our first cases, having a very markedly reduced heart rate of 32 beats per minute, we used immediate treatment with isoproterenol, albeit without benefit, as documented for other severely compromised cases.[14,15]

Treatment with steroids did not reverse the degree of the block in our fetuses. The main effect of treatment was to produce a rapid improvement in the degree of fetal hydrops in 3 of 5 cases. Thus, we have failed to show any statistically significant benefit of treatment on the eventual outcome of our fetuses suffering complete atrioventricular block, possibly due to the small number of cases not treated. We found no statistically significant differences in mortality, age at delivery, or in the need for implantation of permanent pacemakers, between the fetuses whose mothers had or had not been treated. There are limitations in the comparisons to be made between our treated and untreated fetuses, nonetheless, not least because treatment was generally not started until after the 22nd week of gestation, when the conduction disorder was already well established

We found it necessary to insert permanent pacemakers in most of our children, their ventricular rates being less than 50 to 55 beats per minute. We timed the insertion of the device on the basis of the heart rate, but also of the weight of the infants. In a few very premature babies, we preferred to offer initial postnatal support with inotropes, proceeding to implantation of the pacemaker when the neonate weighed around 1900 to 2000 grams. In all, we have inserted pacemakers in 22 of the 26 infants born alive, this being necessary at an earlier age in the hydropic compared to the non-hydropic fetuses. Despite this, 2 of our hydropic fetuses subsequently died soon after birth. It was possible to delay insertion of the pacemakers in the untreated non-hydropic cases because of their better fetal and postnatal heart rates.

It is evident from our results that the main negative prognostic factors in our series were the presence and degree of cardiac failure, and a lower heart rate at presentation, confirming previous data.[14,27,28] We found statistically significant differences between the fetuses with and without cardiac failure at presentation, those with hydrops having a lower mean heart rate at presentation and after birth, being delivered at a younger gestational age, and carrying higher mortality. In all those dying, death was due to the cardiac failure. The presence and degree of fetal hydrops, furthermore, were found to be the only predictive variable for outcome at multiple logistic regression analysis. Hydropic infants needed permanent pacemakers implanted sooner after birth.

Side effects of the maternal steroid therapy have already been reported,[14,27] mainly oligohydramnios, which occurred to mild degree in 2 of our cases, but reversed promptly after reduction and eventual cessation of the therapy. We encountered no instances of fetal retardation of growth, nor did we observe any neurodevelopmental side effects having carried out specific neurodevelpmental assessment around the age of 2 years.[29,30]

Equally, we did not find any instances of the postnatal late dilated cardiomyopathy reported by some authors.[8,31] This may be due to progressive myocardial damage, absence of improvement after the pacemaker implant, or the type of pacing, with VVI pacing favouring ventricular desynchronization and possibly predisposing to myocardial damage. In our population, only the hydropic fetuses showed signs of endocardial fibroelastosis, with a higher echogenicity of the ventricular walls and impaired contractility. This was especially the case in 2 of the triplets, who presented with myocarditis, albeit that both improved after implantation of the pacemaker and provision of a better cardiac output.

In conclusion, the outcome of our fetuses was mainly dependent on the presence and degree of hydrops at presentation. Our data does not show any significant differences between fetuses treated or not treated by steroids, recognising that only a small number of our cases were not treated. Treatment did not produce regression of the conduction disorder, but did have a favourable effect on the fetal hydrops. Randomized, and larger scale, prospective studies are needed in order to fully define the efficacy of the treatment with steroids in fetuses with complete atrioventricular block.

References

1. Taylor PV, Scott JS, Gerlis LM, Esscher E, Scott O. Maternal antibodies against fetal cardiac antigens in congenital complete heart block. New Engl J Med 1986; 315: 667–672.
2. Buyon JP, Hiebert R, Copel J, et al. Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a national lupus registry. J Am Coll Cardiol 1998; 31: 1658–1666.
3. Ho YS, Esscher E, Anderson RH, et al. Anatomy of congenital complete heart block and relation to maternal anti-Ro antibodies. Am J Cardiol 1986; 58: 291–294.
4. Lang B, Wilhelm C, Gildein P, Vaith P, Schillinger H, Peter HH. Fetal complete heart block with myocarditis and maternal SS-A-/AA-B/ antibodies. Schweiz Med Wochenschr 1990; 120: 1741–1744.
5. Fesslova V, Mannarino S, Salice P, et al. Neonatal lupus: fetal myocarditis progressing to atrioventricular block in triplets. Lupus 2003; 12: 775–778.
6. Nield LY, Silverman ED, Taylor GP, et al. Maternal anti-Ro and anti-La antibody- associated endocardial fibrolelastosis. Circulation 2002; 105: 843–848.
7. Nield LE, Silverman ED, Smallhorn JF, et al. Endocardial fibroelastosis associated with maternal anti-Ro and anti-La antibodies in the absence of atrioventricular block. J Am Coll Cardiol 2002; 40: 796–802.
8. Moak JP, Barron KS, Hougen TJ, et al. Congenital heart block: development of late-onset cardiomyopathy, a previously underappreciated sequela. J Am Coll Cardiol 2001; 37: 238–242.
9. Cimaz R, Catelli L, Luzzana C, Panzeri P, Meroni PL. Neonatal lupus syndromes. IMAJ 2000; 2: 228–231.
10. Schmidt KG, Ulmer HE, Silverman NH, Kleinman CS, Copel JA. Perinatal outcome of fetal complete atrioventricular block: a multicenter experience. J Am Coll Cardiol 1991; 17: 1360–1366.
11. Groves AMM, Allan LD, Rosenthal E. Outcome of isolated congenital complete heart block diagnosed in utero. Heart 1996; 75: 190–194.
12. Bierman FZ, Baxi L, Jaffe I. Fetal hydrops and congenital complete heart block: Response to maternal steroid therapy. J Pediatr 1988; 112: 646–648.
13. Rosenthal D, Druzin M, Chin C, Dubin A. A new therapeutic approach to the fetus with congenital complete heart block: preemptive, targeted therapy with dexamethasone. Obstet Gynecol 1998; 92: 689–691.
14. Jaeggi ET, Fouron JC, Silverman ED, Ryan G, Smallhorn J, Hornberger LK. Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. Circulation 2004; 110: 1542–1548.
15. Groves AM, Allan LD, Rosenthal E. Therapeutic trial of sympathomimetics in three cases of complete heart block in the fetus. Circulation 1995; 92: 3394–3396.
16. Jaeggi ET, Hamilton RM, Silverman ED, et al. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block: a single institution's experience of 30 years. J Am Coll Cardiol 2002; 39: 130–137.
17. Vignati G, Brucato A, Pisoni MP, et al. Clinical course of pre- and post-natal isolated congenital atrioventricular block diagnosed in utero. G Ital Cardiol 1999; 29: 1478–1487.
18. Gladman G, Silverman ED, Yuk-Law, et al. Fetal echocardiographic screening of pregnancies of mothers with anti-Ro and/or anti-La antibodies. Am J Perinatol 2002; 19: 73–80.
19. Brucato A, Franceschini F, Gasparini M, et al. Isolated congenital complete heart block. Longterm outcome of mothers, maternal antibody specificity and immunogenetic background. J Rheumatol 1995; 22: 533–540.
20. Costedoat-Chalumeau N, Georgin-Lavialle S, Amoura Z, Piette JC. Anti-SSA/Ro and anti-SSB/La antibody-mediated congenital heart block. Lupus 2005; 14: 660–664.
21. Watson RM, Scheel JN, Petri M, et al. Neonatal lupus erythematosus. Report of serological and immunogenetic studies in twin discordant for congenital heart block. Brit J Dermatology 1994; 130: 342–348.
22. Cooley HM, Keech CL, Melny BJ, Menaheim S, Morahan G, Kay TWH. Monozygotic twins discordant for complete congenital heart block. Arthritis Rheum 1997; 40: 381–384.
23. Miyagawa S, Dohi K, Yoshioka A, Shirai T. Female predominance of immune response to SSA/Ro antigens and risk of neonatal lupus erythematosus. Br J Dermatol 1990; 123: 223–227.
24. Buyon JP, Swersky S, Fox H, Bierman F, Winchester R. Intrauterine therapy for presumptive fetal myocarditis with acquired heart block due to systemic lupus erythematosus: experience in a mother with a predominance of SSB (La) antibodies. Arthritis Rheum 1987; 30: 44–49.
25. Copel JA, Buyon JP, Kleinman CS. Successful in utero therapy of fetal heart block. Am J Obstet Gynecol 1995; 173: 1384–1390.
26. Saleeb S, Copel J, Friedman D, et al. Comparison of treatment with fluorinated glucocorticoids to the natural history of autoantibody-associated congenital heart block: retrospective review of the research registry for neonatal lupus. Arthritis Rheum 1999; 42: 2335–2345.
27. Breur JM, Visser GHA, Kruize AA, Steoutenbeek O, Meijboom. Treatment of fetal heart block with maternal steroid therapy: case report and review of the literature. Ultrasound Obstet Gynecol 2004; 24: 467–472.
28. Brucato A, Gasparini M, Vignati G, et al. Isolated congenital complete heart block. Longterm outcome of children and immunogenetic study. J Rheumatol 1995; 22: 541–543.
29. Brucato A, Li Destri M, Astori MG, et al. Normal neuropsychological development of children with congenital complete heart block exposed or not exposed in utero to dexamethasone. Lupus 2004; 13: 762 (abs).
30. Tincani A, Rebaioli CB, Frassi M, et al. Pregnancy and autoimmunity: maternal treatment and maternal disease influence on pregnancy outcome. Autoimmun Rev 2005; 4: 423–428.
31. Udink ten Cate FE, Breur JM, Cohen MI, et al. Dilated cardiomyopathy in isolated congenital complete atrioventricular block: early and long-term risk in children. J Am Coll Cardiol 2001; 37: 1129–1134.