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ORIGINAL ARTICLE

Causes of fetal third-degree atrioventricular block and use of hydroxychloroquine in pregnant women with Ro/La antibodies

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Abstract

Introduction/objectives Complete congenital atrioventricular block (AVB) may be due to cardiac malformations or the presence of maternal antibodies (autoimmune AVB). Our objective was to estimate the prevalence of autoimmune AVB among all AVB in newborns treated at our hospital. Secondly, we estimated the prevalence of AVB among mothers with anti-Ro/La antibodies and examined the relationship of those fetal AVB with mother's use of hydroxychloroquine during pregnancy.

Methods Retrospective cohort in which we reviewed electronic medical records from years 2000 to 2014 of (a) all mothers with children born with third degree AVB and (b) all pregnant women with anti-Ro/La-positive antibodies.

Results Twenty-three AVBs were diagnosed. Ten (43.5%, 95% CI 23.2–65.5) were associated with maternal rheumatologic disease. The remaining 13 were associated with cardiac malformations. Sixty-two pregnancies in 47 mothers with Ro/La antibodies were identified; eight (12.9%, 95% CI 5.7–23.8) suffered AVB. Fourteen mothers consumed hydroxychloroquine during full pregnancy (one newborn (7.1%) suffered AVB) and 48 did not (7 newborns with AVB (14.6%); $p = 0.5$).

Conclusions All congenital AVB diagnosed at our hospital without cardiac malformations were associated with a maternal rheumatologic disease/antibodies. Therefore, if a AVB is diagnosed in a newborn without structural heart disease, the mother should be studied for an autoimmune disease. We found a high prevalence of AVB among mothers with anti-Ro/La antibodies. Although not statistically significant, AVBs in mothers with Ro/La antibodies were numerically more frequent in those not using hydroxychloroquine.

Key Points
- *Although structural heart malformations were the predominant cause of third-degree AVB, autoimmune AVB was still a significant cause.*
- *The distinction between structural or non-structural cause of AVB constitutes an essential issue since it determines the prognostic of these fetuses in terms of complications.*
- *Although not statistically significant, AVBs in mothers with Ro/La antibodies were more frequent in those not using hydroxychloroquine.*
- *If an AVB is diagnosed in a newborn without structural heart disease, the mother should be studied for an autoimmune disease.*

Keywords Anti-Ro/La antibodies · Atrioventricular block · Hydroxychloroquine

Introduction

Congenital third-degree atrioventricular block (AVB) is an uncommon complication with an incidence rate of 0.5-0.67/1000 liveborns. This complication is associated with autoimmune diseases such as systemic lupus erythematosus and Sjogren [1–3]. In fact, AVB is the most severe complication of neonatal lupus (complete AVB, hematologic, hepatic, and cutaneous manifestations) [4]. The risk of AVB is duplicated–triplicated up to 2% compared to the normal population when anti-Ro/La maternal antibodies are present. Incidence rises to 17–20% in mothers who have had a previous child with complete AVB [5]. This complication usually occurs between the18th and 24th weeks of gestational age [6].

The pathogenesis of congenital AVB in autoimmune diseases is not fully understood. The binding of the maternal Ro/La antibodies to fetus antigens is thought to be the first step of the subsequent injury [7]. The interaction with Ro/La proteins expressed in the apoptotic cardiac cells of the fetus leads to inflammation, fibrosis, and heart damage [3, 8].

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Substantial morbidity (70%) associated with pacemaker implantation and mortality (17.5% fetal/neonatal) are associated with AVB [9].

The use of hydroxychloroquine in pregnant women with anti-Ro/La antibodies who have had a previous child with third-degree AVB has been shown to decrease the risk of future AVB up to 64.5% [9]. However, there is lack of information regarding use of hydroxychloroquine in AVB in first pregnancies of mothers with anti-Ro/La antibodies.

Our objective was to evaluate all AVB causes in newborns treated at our hospital and the prevalence of mother's autoimmune disease and children with cardiac malformations. We then analyzed the prevalence of AVB among mothers with anti Ro/La antibodies and their relationship with mother's consumption of hydroxychloroquine during pregnancy [10].

Methods

We retrospectively reviewed electronic medical records of patients seen at the Hospital Italiano de Buenos Aires from years 2000 to 2014 according to the following criteria: (a) all mothers with newborns with third-degree AVB; (b) all pregnant women with anti-Ro/La-positive antibodies in the laboratory registries. Anti-Ro/SSA and anti-La/SSB antibodies were measured by enzyme-linked immunosorbent assay (Orgentec).

We included all third-degree AVBs in newborns to analyze their cause. We searched for the presence of anti-Ro/La maternal antibodies in all of these cases in order to determine the proportion of children who were exposed to anti-Ro/La maternal antibodies and those who were associated with cardiac malformations. Pacemaker implantation or death were registered.

On the other side, we included all pregnant women with anti-Ro/La-positive antibodies and registered results of all their pregnancies (outcomes and complications).

These mothers were divided in two groups according to whether they had received hydroxychloroquine (200–400 mg/day) during all their pregnancy or not in order to compare the AVB rate in each of them. For this purpose, we reviewed outpatient medical records, hospitalizations, and all cardiac ultrasounds performed during pregnancy follow-up.

Statistical analysis was performed with STATA program 14.1 (StataCorp, USA). All data was analyzed for each pregnancy (not patient). Continuous variables were computed as mean and standard deviation (SD) or median with interquartile range (IQR), depending on the distribution of the variable. Categorical variables were presented as number and percentage with their 95% confidence intervals (CIs). Chi-square or Fisher tests were used to compare categorical variables and *t* test or Wilcoxon rank-sum test to compare continuous ones. A p value < 0.05 was considered significant.

Results

Newborns with AVB

Between 2000 and 2014, 23 newborns were diagnosed with AVB at our hospital. Ten (43.5%, 95% CI 23.2–65.5) of them were associated with the presence of antibodies and/or a maternal rheumatologic disease (autoimmune AVB). The other 13 newborns had third-degree AVB associated with congenital structural heart disease. None of the latter had mothers with an autoimmune disease (including systemic lupus erythematosus or mixed connective tissue disease).

Three of the ten children with autoimmune AVB (30%) required placing of a pacemaker and 2 children (20%) died before a pacemaker could be implanted.

In contrast, all 13 newborns with AVB associated with congenital heart disease required a pacemaker implantation ($p < 0.001$ versus AVB without structural heart disease) (Table 1). Four children died due to cardiac disease. None of the 13 mothers were positive for anti-Ro/La antibodies (all of them were tested) and none of them had an autoimmune disease.

Mothers with anti-Ro/La antibodies

We identified 62 pregnancies in 47 mothers with anti-Ro/La antibodies. Eight pregnancies resulted in fetuses with complete autoimmune AVB and 54 did not (Table 2). Characteristics are shown in Table 3. Each pregnancy was considered separately. Pregnant women who had consumed hydroxychloroquine during pregnancy ($n = 14$) were compared to those who had not ($n = 48$). From the group of mothers who consumed hydroxychloroquine during all their pregnancy, nine consumed 400 mg/day of hydroxychloroquine whereas five consumed 200 mg/day. Three mothers had a first pregnancy without hydroxychloroquine and a subsequent pregnancy receiving hydroxychloroquine throughout. From the eight fetuses who developed a complete AVB, one newborn (7.1%) suffered AVB in the hydroxychloroquine group versus 7 newborns (14.6%) ($p = 0.5$) in the group without hydroxychloroquine. No mother had more than one pregnancy with AVB. AVB was detected at a median gestational age of 20 weeks (IQR 20–25 weeks), and they were all intrauterine (Table 1). From the ten newborns with autoimmune AVB, there were two newborns whose mothers were not followed at our institution, and therefore, we do not know whether they consumed hydroxychloroquine during their pregnancy.

The newborn with AVB in the hydroxychloroquine group prolonged PR and developed a second-degree atrioventricular block during the 19th week of pregnancy followed by a complete atrioventricular block on the 20th week. This fetus did not receive any treatment and did not require pacemaker implantation (Table 3). This was the mother's first pregnancy, and she had a subsequent one during which she also received hydroxychloroquine and delivered a healthy child.

Table 1 Children diagnosed with AVB

	AVB with structural heart disease ($n = 13$)	AVB without structural heart disease ($n = 10$)	*P* value
Mother with Ro antibodies/*n* tested (%)	0/13	8/8 (100)	0.0001
Mother with La antibodies/*n* tested (%)	0/13	7/8 (87.5)	< 0.0001
Neonatal death	0	1 (10)	0.2437
Pacemaker requirement, *n* (%)	13 (100%)	3 (30%)	< 0.001
Death, *n* (%)	4/10 (40%)	2/10 (20%)	0.34
Gestational age at the time of AVB (weeks), median (IQR)	–	20 (20–25)	
Postnatal AVB, *n* (%)	13 (100%)	0	< 0.0001
Pregnancy duration (weeks), median (IQR)	38 (37–38)	37 (35–37)	0.08

AVB atrioventricular block, I*QR* interquartile range

In the group without hydroxychloroquine, one fetus prolonged PR before complete AVB; all the rest ($n = 6$) were detected with a third-degree AVB despite adequate screening. Regarding treatment in the group of mothers who did not received hydroxychloroquine, four cases received dexamethasone as soon as the blockage was diagnosed, one intravenous immunoglobulin (IVIG), and two did not receive treatment. The fetus that prolonged PR before complete AVB was one of the four babies that received dexamethasone. None of the mothers were receiving prednisolone before the prolonged PR was detected. Three newborns required pacemaker insertion, and one of them died before a pacemaker could be implanted. (Tables 3 and 4) (Flowchart 1). None of the AVB newborns achieved reversal of their third-degree AVB. Three of the seven mothers who had not received hydroxychloroquine had further pregnancies and none of their subsequent children had AVB. Two of them received hydroxychloroquine during these new pregnancies.

Discussion

In our study, structural heart malformations were the predominant cause of third-degree AVB (56.5%). However, AVB due to the presence of anti-Ro/La maternal antibodies were still a significant cause (43.5%). From the latter, systemic lupus erythematosus was the most frequent maternal autoimmune disease (75%) followed by Sjogren (25%). Studies differ regarding the proportion of cardiac malformations leading to AVB and autoimmune-mediated AVB. In a recent study evaluating cardiovascular therapy in AVB reported that trasplacental passage of anti-Ro/La antibodies was the most common etiology of congenital AVB [11].

Table 2 Pregnancies in mothers with anti-Ro/La antibodies

	Pregnancies with AVB (8)	Pregnancies without AVB (54)	Total
Consumed hydroxychloroquine during pregnancy (14)	1	13	14
Did not consume hydroxychloroquine during pregnancy (48)	7	41	48
Total	8	54	62

The detection of AVB is important since it carries a high fetal mortality (9 to 25%) as well as a high mortality rate during early childhood (5 to 13%) [12]. The distinction between structural or non-structural cause of AVB constitutes an essential issue since it determines the prognostic of these fetuses in terms of complications [13]. This is in agreement with our study in which only 30% of the newborns required a pacemaker implantation in the autoimmune AVB whereas 100% of the babies were implanted pacemakers in the group with structural heart disease.

Mothers with anti-Ro/La antibodies are said to have a 2% risk of complete AVB [14]. In this study, we found a risk of 12.9% of third-degree AVB among all the pregnancies of mothers with anti-Ro-La antibodies. One of the reasons of this higher risk is that our hospital has an important high-risk pregnancy unit, and patients with early detection of AVB might have been sent for follow-up of their pregnancy at our institution.

Hydroxychloroquine is one of the most frequently prescribed medications during pregnancy in patients with autoimmune diseases, especially systemic lupus erythematosus, since it prevents flares, reduces renal diseases, and prolongs survival [15–17]. However, there are few studies regarding the use of hydroxychloroquine as a preventive agent for third-degree AVB [18–20] in Latin America. We know from de GLADEL cohort that ethnic component plays a role on the effectiveness of the drug on certain components of the disease [21] and race differences have been reported with some drugs in SLE [22]. According to GLADEL cohort, the mestizo ethnicity was an independent factor associated with the risk of developing earlier renal disease whereas the use of antimalarials had a protective effect and prolonged survival [17].

Table 3 Pregnancy characteristics of women with anti-Ro/La antibodies

	Treated with hydroxychloroquine during pregnancy ($n = 14$)	Without hydroxychloroquine during pregnancy ($n = 48$)	P value
Maternal age at the time of pregnancy (years), mean (SD)	34.1 (3.3)	34.6 (4.8)	0.7
Anti-Ro+, % (95% CI)	100	93.8 (86.6–100)	0.34
Anti-La+, % (95% CI)	42.9 (13.2–72.5)	50 (35.3–64.7)	0.64
Antiphospholipid antibodies, % (95% CI)			
Lupus anticoagulant	7.1 (0.18–33.9)	0	0.07
Anticardiolipins	21.4 (3.1–46)	4.2 (1.7–100)	*0.04*
Maternal rheumatologic disease, *n*			
Systemic lupus erythematosus	11	8	*< 0.001*
Sjogren syndrome	3	16	0.52
Mixed connective tissue disease	0	5	0.58
Rheumatoid arthritis	0	4	0.57
Scleroderma	0	2	1
Polychondritis	0	1	1
Unknown maternal diagnosis	0	12	0.052
Pregnancy outcomes, % (95% CI)			
Abortion	14.3 (1.8–42.8)	4.2 (0.51–14.2)	0.18
Fetal death	0	2.1 (0.05–11.1)	0.59
Live newborn	85.7 (64.7–106)	93.8 (86.6–100)	0.33
Fetal complications, % (95% CI)			
Intrauterine growth restriction	14.3 (1.8–42.8)	6.3 (1.3–17.2)	0.31
Preterm	0	0	
AVB	7.1 (1.8–33.9)	14.6 (6.1–27.8)	0.5
Neonatal complications	0	0	
Neonatal cutaneous lupus	0	0	
Maternal complications, % (95% CI)			
Pre-eclampsia	21.4 (4.7–50.8)	8.3 (0.2–16.4)	0.17
Eclampsia	0	0	
Gestational diabetes	0	0	
Gestational hypertension	7.1 (1.8–33.9)	4.2 (0.51–14.2)	0.54
Treatment during pregnancy, % (95% CI)			
Aspirin	28.6 (1.5–55.6)	4.2 (0.51–14.2)	*0.007*
Glucocorticoids	28.6 (1.5–55.6)	10.4 (1.5–19.4)	0.09
Azathioprine	14.3 (1.8–42.8)	0	*0.008*
Pregnancy duration (weeks), median (IQR)	36.5 (35–38)	38 (35–39)	0.12
Hospital follow-up (years), median (IQR)	9.1 (4.8–12.8)	9.1 (5–10.5)	0.47

SD standard deviation, *CI* confidence interval, *AVB* atrioventricular block, *IQR* interquartile range

Italic entries: statistically significant difference

The fact that there are few studies on the subject and that most of them are observational probably reflects the difficulties of performing studies on pregnant women and the ethical issues involved [23].

Several studies have addressed treatments following a complete AVB. Nevertheless, it is difficult to evaluate the efficacy of each separate treatment since fetuses frequently receive many drugs concomitantly. In an observational cohort, maternal dexamethasone seems to improve incomplete fetal AVB and myocardial dysfunction [24]. Therefore, there is some evidence that fluorinated steroids might be beneficial in incomplete AVB but adverse effects may be concerning. Beta-sympathomimetics may raise heart rate and improve the heart contractility [24–26]. Certain reports have shown that intravenous immunoglobulin (IVIG) may cause a reversal of third-degree AVB [27] and improved outcome of fetuses with cardiomyopathy or endocardial fibroelastosis [28]. Studies analyzing the role of IVIG in the prevention of AVB

Table 4 Newborn AVB of mothers with Ro/La antibodies

Newborn	Mother anti-Ro+	Mother anti-La+	Mother who received HCQ	Maternal diagnosis	Prolonged PR before complete AVB	Dexamethasone	IVIG	AAS	Gestational age at the time of AVB (weeks)	Pacemaker implantation	Death
1	1	1	1	SLE	1	0	0	0	20	0	0
2	1	1	0	SLE	0	1	0	0	28	0	0
3	1	1	0	SLE	0	0	0	1	20	1	0
4	1	1	0	Sjogren	0	0	1	0	20	0	1
5	1	1	0	SLE	0	1	0	0	16	1	0
6	1	1	0	SLE	1	1	0	1	25	1	0
7	1	1	0	Sjogren	0	1	0	0	22	0	0
8	1	0	0	SLE	0	0	0	0	ND	0	0

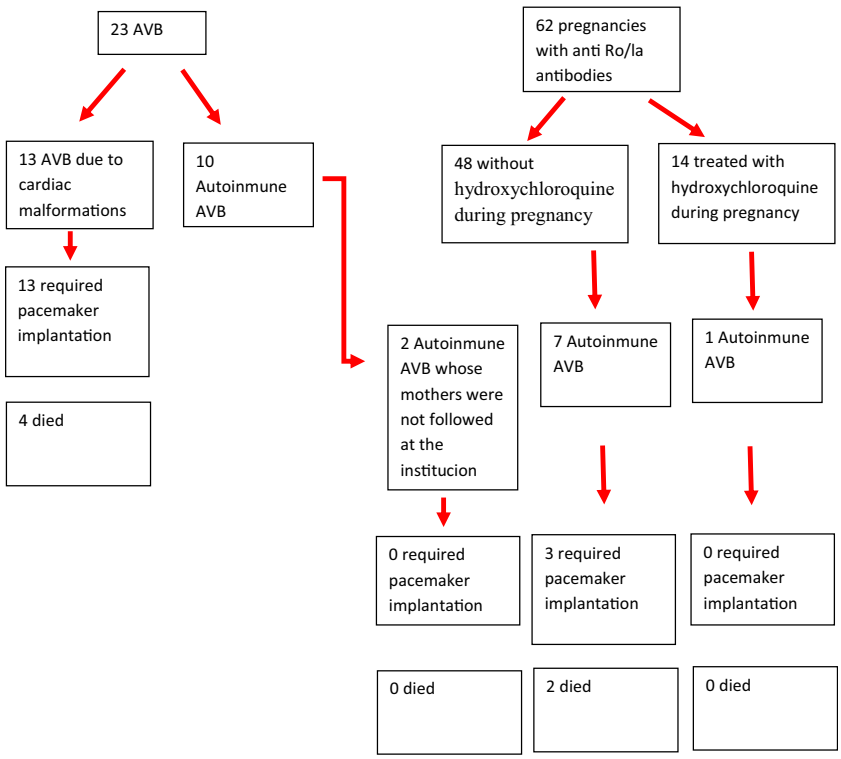
HCQ treatment with hydroxychloroquine during all pregnancy, *AVB* atrioventricular block, *IVIG* intravenous immunoglobulin, *AAS* aspirin, *SLE* systemic lupus erythematosus, *ND* no data

recurrence in cardiac neonatal lupus have been discouraging [29, 30].

Our study is consistent with previous ones showing that hydroxychloroquine tends to decrease the risk of third-degree AVB when anti-Ro/La maternal antibodies are present. A recent observational study compared the recurrence of complete AVB in mothers with anti-Ro/La antibodies who were exposed or unexposed to hydroxychloroquine from a cohort obtained from three databases (France, USA, and England). In the multivariate analysis, hydroxychloroquine was significantly associated with a diminished risk of cardiac neonatal lupus, odds ratio 0.23 (CI 95% 0.06–0.92); $p = 0.037$ [9]. The international survey organized by 9th International Conference of Reproduction, Pregnancy and Rheumatic Diseases reported that over two thirds of the practitioners recommend the use of hydroxychloroquine in pregnant asymptomatic women with anti/Ro/La antibodies [12].

One of the limitations of our study was that it was retrospective. Therefore, we had to rely on medical records and missed some data. For instance, of the ten newborns with autoimmune AVB, two were referred from another health center and we do not know whether the mothers consumed hydroxychloroquine during their pregnancy. Also, our results did not reach statistical significance, perhaps due to the small numbers.

Flowchart 1 Results



On the other hand, this study collected information of an infrequent but severe event over a long period of time. There are no studies done in Latin America, and ethnic component may play a role on the prevalence and complications of this arrhythmia.

It is important to stress that all congenital third-degree AVB diagnosed at our hospital without structural heart disease were associated with a maternal rheumatologic disease or the presence of maternal antibodies whereas those with structural damage were not and all required pacemakers. This data appears to suggest that if an AVB is diagnosed in a newborn, without structural heart disease, the mother should be studied for an autoimmune disease.

Compliance with ethical standards

Disclosures None.

Ethical approval This study was approved by the Clinical Research Ethics Committee of Hospital Italiano de Buenos Aires and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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