

# Which Intrauterine Treatment for Autoimmune Congenital Heart Block?

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**Abstract:** Autoimmune Congenital Heart Block (CHB) is considered an immune mediated manifestation, caused by the action of maternal autoantibodies anti-Ro/SSA and anti-La/SSB on fetal cardiac tissues. The incidence of CHB is 2% in anti-Ro/SSA positive women, 3% when both anti-Ro/SSA and anti-La/SSB are positive. In the subsequent pregnancies the risk of recurrence is 9 times higher.

The antenatal diagnosis of CHB is possible by the measurement of the “mechanical” PR interval with fetal echocardiography. When CHB is diagnosed, an intrauterine therapy is possible to increase the atrioventricular conduction speed and improve the fetal outcome.

Authors recommend maternal treatment with fluorinated steroids, as Dexamethasone or Betamethasone, which reduce the antibody-mediated inflammatory damage of nodal tissue. Other possibilities are the maternal administration of beta-sympathomimetics, in order to increase the fetal heart rate.

In the last years three cases of complete CHB in infants of women affected by autoimmune disease were treated in our centre. They were treated in utero with the maternal administration of Betamethasone 4 mg/day soon after the diagnosis until delivery. After delivery, all children needed cardiac pacemaker. The long-term outcome is good in all cases.

**Keywords:** Congenital heart block, intrauterine therapy, echocardiography.

## INTRODUCTION

Autoimmune congenital heart block (CHB) is grouped under the heading of Neonatal Lupus Syndrome (NLS) and is considered a model of passively acquired autoimmunity disease. It offers the exceptional opportunity to examine the effector arm of immunity and to define the pathogenicity of an autoantibody in mediating tissue injury [1].

After the first observation in 1983 that sera from nearly all mothers of children with isolated CHB contain specific autoantibodies [2], this disease attracts considerable attention. The study of CHB requires an “integrational” research [3], which attempts to fit clinical and basic observations together: only if the biology of the disease is understood and this knowledge is brought to the clinic, our clinical management could be improved.

This paper is divided into two sections. Initially, we discuss the epidemiology, the pathogenetic cascade, the clinical manifestation and the diagnostic modalities of CHB; secondly, we discuss the therapeutic approach proposed in literature and present our experience.

## DEFINITION

A correct definition of Heart Block (HB) implies a characterization of each term we use to define this disease. Each case could be characterized by major categories: the degree of conduction system disease at diagnosis (complete or incomplete), congenital or not congenital, associated with

structural anomalies or in absence of anatomical disease (isolated).

The HB may be divided into categories related to the current degree of functional disease that is complete versus incomplete. The latter category may be further divided into first-degree (Type I), second-degree (Type II) or intermittent third degree (Type II/III).

Recently, Brucato *et al.* [4] proposed this definition of HB as congenital: “an atrioventricular (AV) block is defined as congenital if it is diagnosed *in utero*, at birth, or within the neonatal period (0-27 days after birth)”. This is a significant advance on the original definition proposed by Yater in 1929: in his definition a slow heart rate, at a young age (neither defined), and with certain named infections excluded, was enough to make the discovery of HB classifiable as congenital. Subsequently, several advances in fetal echocardiography have been made: fetal echocardiography is now a diagnostic procedure of AV block antenatally; in addition, we could now record a postnatal ECG within the first few hours of birth. Then, Yater’s definition is no longer acceptable [5].

Furthermore, more than half of fetuses found to have CHB will have underlying structural congenital heart disease: the commonest forms of congenital heart disease associated with HB include left atrial isomerism, often with an accompanying atrioventricular septal defect, as well as levo transposition of the great arteries [6]. CHB is then defined “isolated” in the absence of structural heart disease that may be causally related to HB. This CHB with a structurally normal heart is frequently associated with maternal autoantibodies to Ro/SSA and La/SSB.

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It is important to distinguish these two forms of CHB because they differ not only in their pathogenesis and in their rate of recurrence, but also in the prognoses of children affected. In fact, infants with CHB associated with severe structural heart disease have a poorer prognosis than infants with isolated CHB [5] while the risk of recurrence is higher in mothers who have test positive for anti-Ro/SSA antibodies.

## EPIDEMIOLOGY

The autoimmune CHB is a rare condition: its incidence is about one in 22,000 live births [6, 7].

The occurrence rate of CHB has been estimated at approximately 2% in all infants born to women with anti-Ro/SSA antibodies [3, 7-10] and 3% in all infants born to women with anti-La/SSB [6, 11, 12]. The recurrence rate in a mother with antibodies, who has a previous child affected, is approximately 16-18% [9, 11, 13]: it is nearly nine times higher than the risk for CHB in a primigravida with the candidate antibodies.

About the sex ratio of CHB, the feminine predisposition for CHB is not clearly established. According to the studies, the proportion of girls among children having CHB is variable from 83% [14] to 50% [15] in a larger sample.

Autoantibody-associated CHB is not a benign condition and carries a substantial morbidity and mortality. The majority of surviving affected children requires permanent pacing before adulthood [6]: 33-53% [10, 15] require subepicardial pacemaker in the neonatal period; in the late ages, this percentile raised to 60% [6, 15]. The CHB mortality is variable from 12% to 43% in literature [11, 15-18].

## PATHOGENESIS

It is now widely accepted that the HB detected before or at birth, in the absence of structural abnormalities, is almost always accompanied by maternal autoantibodies to Ro/SSA and/or La/SSB ribonucleoproteins [2, 19], independent of whether the mother has Systemic Lupus Erythematosus (SLE), Sjögren's Syndrome (SS) or totally asymptomatic. The mechanism of CHB is not completely understood.

To explain the causal relationship of anti-Ro/SSA and anti-La/SSB antibodies with the development of CHB, three basic requirements should be satisfied. Firstly, the candidate antigens must be present in the target fetal tissues; secondly, the cognate maternal autoantibodies must be present in the fetal circulation; and third, these antigens must be accessible to the maternal antibodies [20]. Earlier studies have firmly demonstrated that soluble intracellular ribonucleoprotein La/SSB and Ro/SSA are present in the fetal cardiac tissues, including in the conduction system [20]. Moreover, Buyon *et al.* have proved the presence of anti-Ro/SSA and anti-La/SSB in fetal circulation, measuring them in cord blood [21].

The third requirement, the intracellular antigens' accessibility, has been more difficult to establish. Few years ago, several authors have proposed that anti-Ro/SSA and anti-La/SSB could cross-react with other surface antigens, immediately accessible for binding by maternal autoantibodies. Horsfall *et al.* proposed the cross-reaction of anti-La/SSB with laminin, one of the major components of cardiac myo-

cytes [22]; they also demonstrated that these cross-reactive anti-La antibodies are able to bind the surface of myocytes in sections of normal fetus, but not of adult cardiac tissue, consistent with the reports that laminin molecules undergo conformational changes during development. These autoantibodies show affinity for placental laminin too and react with the surface of trophoblast [23]. So, Horsfall *et al.* advanced the hypothesis that, in the majority of anti-La antibody positive individuals, a proportion of antibodies is able to cross-react with placental and fetal cardiac laminin. In addressing whether such cross-reactions have pathogenetic consequences, consideration must be given to the low frequency of CHB births among autoantibody positive women. During pregnancy these autoantibodies can be absorbed by the placenta which is rich in laminin. If the titre of antibodies exceeds the functional capacity of the placenta for absorption, they will be actively transported into the fetal circulation and could react with fetal cardiac laminin [23].

Another hypothesis evoked the cross-reactivity of anti-Ro/SSA and anti-La/SSB with calcium channel receptor. Alexander *et al.* reported that superfusion of newborn rabbit ventricular papillary muscles with IgG-enriched fractions from sera containing anti-Ro/SSA and anti-La/SSB antibodies, specifically reduces the plateau phase of the action potential consistent with an alteration of calcium influx [24]. Garcia *et al.* using isolated adult rabbit heart, showed that IgG fractions from women with anti-Ro/SSA and anti-La/SSB antibodies induce conduction abnormalities and reduce the peak slow inward calcium current [25]. Boutjdir *et al.* demonstrated that affinity-purified anti-Ro/SSA induce AV block in an isolated human fetal heart and inhibit inward calcium fluxes through L-type calcium channels in human fetal ventriculocytes. Moreover, the calcium channel's density is higher in the mother than in the fetus heart: so despite the exposition to the same levels of antibodies, the lower density of calcium channels that are present in the fetal heart causes the complete AV block [26], explaining the preferential fetal heart vulnerability.

To elucidate the accessibility of Ro/SSA and La/SSB antigens to their cognate extracellular antibodies, different hypotheses have been suggested. Baboonian *et al.* have demonstrated the sequential expression of La/SSB antigen from the periphery of the nucleus, to the cytoplasm and cell membrane in HEp-2 cells infected by Adenovirus: so, the cell transformation induced by the viral infection, causes the movement of La antigen from the nuclear matrix to the membrane [27]. Another explanation derived from the observation that elevated concentration of 17 $\beta$ -estradiol reached during the third trimester of pregnancy, enhances binding of anti-Ro/SSA and anti-La/SSB antibodies to cherratinocytes. Today, several authors proposed that apoptosis might result in translocation of intracellular antigens to the external leaflet of the membrane [28]. In fact, apoptosis occurs during cardiac development, whereas in the normal adult myocardium apoptosis has been observed only rarely: demonstrating because the maternal heart is unaffected despite identical circulating autoantibodies [29]. In this way it is also possible explain the preferential vulnerability of the AV node: in this region of high remodeling there is a higher rate of apoptosis. The timing of transplacental passage of maternal antibodies may coincide with the period of maximal remodeling and apoptosis in the AV node.

Several studies, *in vivo* and *in vitro* [29-31], have provided the demonstration that apoptosis results in surface translocation of Ro/SSA and La/SSB: this subcellular redistribution facilitates the binding of cognate maternal antibodies, with the subsequent formation of immune complexes.

The newly accessible Ro/SSA-La/SSB ribonucleoproteins, trafficked to the apoptotic surface, are not "inducing" an immune response (i.e. are not immunogenic) but rather become targets of cognate maternal antibodies already present in the fetal circulation (i.e. antigenic) [28]. Then, although apoptotic cells are already programmed to die and do not characteristically evoke an inflammatory response, "binding" of maternal antibodies to the surface of apoptotic cells could trigger an inflammatory response that results in damage to surrounding healthy tissue [12]. Physiologic apoptosis can be inadvertently converted from an inert process designed to remodel developing tissue into one in which inflammation is evoked [3]. Perhaps the triggering event is opsonization. Apoptotic cells have been regarded as immunosuppressive because internalization of apoptotic cells by phagocytes inhibits the release of proinflammatory cytokines [32], in contrast phagocytosis of opsonized apoptotic cells has been reported to be proinflammatory [33], with the release of proinflammatory cytokines as tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) and/or transforming growth factor  $\beta$  (TGF $\beta$ ) by macrophages. This observation has been proved by experimental studies in which macrophages cocultured with opsonized apoptotic cardiocytes produce TNF $\alpha$  [12] and TGF $\beta$  [34] at a higher rate comparing to the rate of the basal production. Macrophages potentially contribute to several aspects of the pathologic process mediated by maternal autoantibodies providing a critical link between inflammation and ultimate scarring, by secretion of proinflammatory and fibroblastic cytokines.

The signature lesion of CHB is the fibrosis of AV node. Perhaps CHB occurs as a consequence of unresolved scarring of AV node secondary to the transdifferentiation of cardiac fibroblasts to unchecked proliferating myofibroblasts. In this final pathologic cascade to inflammation and scarring, the role of TNF $\alpha$  and TGF $\beta$  seems to be very relevant. TGF $\beta$  activates gene transcription, thereby increasing synthesis and secretion of collagen and other matrix proteins [35].

So, the final outcome, the third-degree block is the consequence of a cascade started with translocation of the antigens to the cell surface. The attachment of maternal antibodies promotes the hypersecretion of both proinflammatory and profibrotic cytokines. These cytokines may contribute to myocardial dysfunction and eventuate in fibroblast transdifferentiation, and, ultimately, fibrotic replacement of the AV node [36].

Inherent in this hypothesis is the notion that most fetuses exposed even to maternal autoantibodies will not be affected at all [36]. Buyon *et al.* proposed a triple hit to elucidate the pathogenesis of this disease: one contributed by the mother; one contributed by the fetus and one contributed by the *in utero* environment [36].

The study of twins and triplets in anti-SSA/Ro-SSB/La antibody exposed pregnancies in which there is variability in the expression of cardiac disease lends credibility. Discordance of disease expression in monozygotic twins is particu-

larly intriguing since the placenta is shared and the fetal genetic characteristics are identical.

The maternal component is presumably the autoantibodies, which, binding their cognate antigens, initiates the first step to injury [28]. The necessity of anti-Ro/SSA-La/SSB antibodies is supported by their presence in more than 85% of mothers whose fetuses are identified with conduction abnormalities in a structurally normal heart [2]; however the low frequency of CHB in positive women is puzzling and suggests that the antibodies are necessary but not sufficient [37], and a fetal factor and/or the *in utero* environment are likely to amplify the effects of the antibody.

Another maternal factor was identified in the maternal myocardial cell [38, 39]: during pregnancy, maternal cells pass into the fetus where they may remain indefinitely in the child's blood and tissues, a state referred to as maternal microchimerism [39]; Stevens *et al.* have demonstrated in infants with NLS who died of CHB that the frequency of maternal cells in the tissues, especially the myocardium, was more than 20-fold higher than in the blood of controls or in cord blood in previous studies [38]. Maternal chimerism also correlate with NLS disease activity: so, maternal cells may be involved in the pathogenesis of NLS, because they act within tissues specific all as immune targets [39]; the persistence of maternal cells in the fetal heart could elicit a graft-versus host reaction or an allogenic response that may induce local inflammatory damage of the AV cardiac conduction tissue [40].

Several authors focused on the identification of fetal factors favoring the occurrence of CHB. Cytokines that lead from inflammation to fibrosis, such as TNF $\alpha$  and TGF $\beta$ , have been suggested to be involved in the pathogenesis of CHB. Polymorphisms of these cytokines were evaluated: Clancy *et al.* have demonstrated an increased frequency of the -308 allele of TNF $\alpha$ , which is associated with high cytokine production, in CHB children compared with controls. However, a clear association with disease could not be established because the unaffected children also had a higher prevalence of the -308A allele than the controls [41]; Cimaz *et al.* have confirmed in triplets and twins this lack of correlation between TNF $\alpha$  polymorphisms and CHB [40]. Several genetic and immunohistologic studies more convincingly suggest a link between TGF $\beta$  and the pathogenesis of disease [41]: Clancy *et al.* have found that the TGF $\beta$  polymorphism Leu10, which could lead to its exaggerated secretion, is more frequent in children with CHB than unaffected anti-Ro/SSA exposed children. Cimaz *et al.* have confirmed this finding in twins but not in the family of triplets.

Additional fetal factors have been reported: polymorphisms of the human Fc $\gamma$  receptor have also been proposed as representing a fetal factor that is potentially responsible for the development of CHB [42].

At least, the environmental factor was recently identified by Clancy in hypoxia [43]. *In vitro* exposure of cardiac fibroblasts to hypoxia resulted in transdifferentiation to myofibroblasts so hypoxia could potentiate a profibrotic phenotype of the fetal cardiac fibroblast: this finding was sustained by significantly elevated erythropoietin levels in cord blood from CHB affected, as compared with unaffected, anti-Ro/SSA exposed neonates [43].

In conclusion, these studies suggest not only that a mosaic of maternal, fetal, and possibly environmental factors might be involved in inducing CHB, but also the combination of such factors might be the way to induce the onset of CHB.

### CLINICAL MANIFESTATION

Detection of CHB in the fetuses generally occurs between 18 and 24 weeks gestation [7, 15, 20, 44, 45].

CHB may present in various stages of degree: since little year ago, complete CHB (CCHB) is the most frequently recognized. Nevertheless, Sonesson *et al.* following 24 women with anti-Ro/SSA antibodies between 18 and 24 weeks of gestation with weekly cardiac doppler echocardiography, have founded signs of first-degree AV block in 30% of these fetuses [46]. More recently PRIDE study found signs of first-degree AV block in only 3% of cases [47].

Moreover, in this study, three cases of third-degree block were identified, but none of which were preceded by a less advanced degree of block and no one were reversed by intrauterine therapy. So, they concluded that, if the prolongation of the PR interval represents tissue injury, it might be so rapid as to go unnoticed [47].

Several explanations could be proposed for these different results: firstly, the different population of the studies: in Sonesson's only high risk mothers were considered; these authors also used different definition of first-degree AV block.

However, the clinical significance of detection of less degree stages of CHB is in the possibility of administration of intrauterine therapy: the first-degree block unambiguously represents a warning sign, because early disease may be reversible. To date, CCHB is considered irreversible.

### ANTENATAL DIAGNOSE

For the surveillance and early detection of fetuses at risk of CHB, fetal echocardiograms have become the most useful low-invasive means. As Glickstein *et al.*'s demonstrated, with the fetal pulsed Doppler Echocardiography it's feasible to obtain the "mechanical" PR: they have demonstrated that it's technically feasible, it's independent of gestational age and it's has a great correlation with neonatal electrocardiographic PR interval [48]. This technique may be a valuable tool for identification of early and potentially reversible conduction abnormalities in fetuses at risk for more advanced and permanent forms of CHB [49].

Three different methods to calculate the AV interval were described in literature:

- MV-Ao: the AV interval was measured from the intersection of the mitral E- and A-waves to the onset of the ventricular ejection wave in the aortic outflow.
- MV: this time interval starts with the same event, but ends at the closure of the mitral wave [50].
- SVC-Ao: this time interval was measured from the beginning of the retrograde venous a-wave in the SVC to the beginning of the aortic ejection wave.

Using MV-Ao measurement, different values of too long PR interval were reported: Sonesson *et al.* set this at 135 ms

[46], the PRIDE group at 150 ms [47]. However, an isolated prolongation of the PR interval may be transient (spontaneously reversible), related to vagal tone, medication use, or reversible injury, or it may be permanent or progress to marked delay as a result of physical injury to the specialized electrical pathway, as a result of inflammatory or scarring. Perhaps the final outcome depends on the influence of fetal and environmental factors.

### INTRAUTERINE THERAPEUTIC APPROACH

The substantial morbidity and mortality associated with CHB and the readily available technology for identification of CHB *in utero* have prompted the search of effective therapies. Firm guidelines for the obstetric and rheumatologic management of the fetus identified with CHB are not established [32].

In this paragraph, we firstly describe three cases of CHB treated with maternal steroids administration and then report a review of the literature inherent the different options of CHB treatment.

In the last years, we treated three cases of CHB.

### Case Reports

1. Our patient was a primigravida who was diagnosed as having SLE eleven years before, according to the American College of Rheumatology revised criteria. In the preconceptional evaluation, the mother's autoantibodies were analyzed by ELISA and high titers of anti-SSA/Ro and anti-SSB/La were found. Anti-nuclear antibody (ANA), anti-double-stranded DNA (anti-ds DNA) and anti-thyroid antibodies were positive. Anti-cardiolipin immunoglobulin M (ACA IgM) and immunoglobulin G (ACA IgG), anti- $\beta$ 2Glycoprotein immunoglobulin M (anti- $\beta$ 2GP IgM) and immunoglobulin G (anti- $\beta$ 2GP IgG) were all negative. Lupus anticoagulant (LAC) screening was negative, too. Prior and during pregnancy she had been treated with prednisone, with varying dosage depending on disease activity.

The initial phase of the pregnancy was uncomplicated. Because of anti-SSA/Ro and anti-SSB/La autoantibodies positivity, regular echocardiographic evaluations were performed from 18 weeks of gestation onward. Completely normal heart rate and anatomy were recorded at 18 weeks and 20 weeks.

At 24 weeks, diagnosis of CCHB was made so we decided to start treatment with oral betamethasone 4 mg/day. No abnormalities were found in maternal and fetal velocimetry Doppler. Ultrasonographic evaluation showed no signs of fetal growth restriction or oligohydramnios; no pericardial and pleural effusions or ascites could be detected.

At 34 weeks of gestational age, an elective Cesarean section for CCHB was performed. The baby (a male) had Apgar scores of 8 and 8 at 1 and 5 minutes, respectively, and a birth weight of 2200 g (50<sup>o</sup>percentile). When he was seven years old, he needed permanent pacemaker.

Up to date, this 17-years old boy is fine and brilliant in sport activities.

2. The patient was primigravida with SLE diagnosed six years before according to the American College of Rheumatology revised criteria. In the last three years and during the first trimester of pregnancy, she didn't receive any medications according to the absence of disease activity. Immunological tests were performed at the beginning of pregnancy; anti-Ro/SSA, ANA, anti-ds DNA and anti-thyroid antibodies were positive. Anti-La/SSB, ACA IgM and ACA IgG, anti- $\beta$ 2GP IgM and IgG were all negative. LAC was found negative, too. In consideration of the anti-Ro/SSA positivity, regular echocardiographic evaluations were performed from 18 weeks of gestation onward. Normal cardiac anatomy and function were recorded.

At 20 weeks the uterine artery doppler velocimetry showed abnormal bilateral uterine resistance indexes. At 24 weeks an intrauterine growth restriction (IUGR), associated to abnormal umbilical pulsatility index, were detected. At the same gestational age, CCHB was diagnosed: the fetal ventricular heart frequency was 60-70 beats per minute (bpm). Oral maternal betamethasone 4 mg/day was initiated until delivery. Ultrasonographic evaluation showed no signs of pleural and pericardial effusion or ascites; no signs of oligohydramnios were found; in spite of this, IUGR persisted.

At 32 weeks, a diagnosis of gestational hypertension was made. At 36 weeks, we decided to perform an elective Cesarean section for a severe fetal growth restriction. The baby (a female) weighted 1940 (9<sup>o</sup> percentile) and had Apgar scores of 3 at 1 minute and 7 after the intra orotracheal intubation. When she was two years old, she needed of permanent pacemaker implantation.

At present, the parents describe her as intelligent girl and brilliant dancer.

3. This patient was a secundigravida with SS diagnosed six years before in accordance with the European Criteria. In her previous pregnancy, her daughter died in the first day of life for the consequences of CCHB. So, she was an higher risk patient, because of her precedent pregnancy complicated by CHB and concluded with the neonatal death. At preconceptional evaluation, she displayed dry eyes or dry mouth and presented high positivity of anti-Ro/SSA, anti-La/SSB and ANA. Anti-ds DNA, ACA IgM and ACA IgG, anti- $\beta$ 2GP IgM and anti- $\beta$ 2GP IgG were negative. LAC was found negative too.

From the beginning of pregnancy to 13 weeks the patient was treated with prednisone: the prednisone dose was 25 mg per day. From 13 weeks to 16 weeks, prednisone treatment was discontinued since the diagnosis of varicella-zoster virus infection. Steroid therapy was resumed at 16 weeks: the prednisone dose was 5 mg per day. From 18 weeks of gestation, once a week, echocardiographic evaluations were performed. At 20 weeks of gestation, CCHB was diagnosed so prednisone therapy was stopped and oral maternal betamethasone 4 mg/day was started. At 20 and 24 weeks of gestation, fetal doppler velocimetry

was assessed: high umbilical pulsatility index was detected. With serial ultrasonographic evaluation, a fetal growth reduction associated with oligohydramnios was detected.

Because of IUGR, oligoanhydramnios and elevated umbilical pulsatility index, at 31 weeks of delivery, an elective Cesarean section was performed. The baby (a female) had Apgar scores of 7 and 8 at 1 and 5 minutes respectively, and weighted 1210 g (10<sup>o</sup>percentile).

Fetal heart rate at birth was 77 bpm. Electrocardiogram recordings on the day of birth confirmed complete AV block. She needed permanent pacemaker on the third day of life. At 2 months of birth, she was fine.

## Review of the Literature

The intrauterine treatment of established disease consists of the use of anti-inflammatory and  $\beta$ -mimetic agents.

From the immunological perspective, elimination of candidate maternal autoantibodies and reduction of generalized inflammatory response are the logical approach to the treatment. The use of fluorinated steroids, as dexamethasone and betamethasone, is justified by the fact that they are only partially metabolized by fetal 11 $\beta$ -hydroxysteroid dehydrogenase with the remainder available to the fetus in an active form [51].

We review the literature with special emphasis on efficacy of maternal steroid therapy.

A Pubmed search was performed to obtain all the available data on maternal steroid therapy for the treatment of CHB. Search terms included: congenital atrioventricular block, congenital heart block, fetal therapy, maternal therapy, dexamethasone, betamethasone, steroids.

Table 1 shows the results of maternal steroid administration in complete and incomplete CHB in 124 fetuses of 25 studies and case reports.

The review of literature revealed 25 studies (including the present study) giving a total of 124 cases treated with maternal steroid administration of complete or incomplete CHB.

In all of 95 cases of third-degree heart block, it was proved irreversible despite the maternal therapy. In 8 cases with intermittent second-third degree heart block, it progressed to complete block in six fetuses (75%) and reverted to second stages of disease in two (25%). Of 17 patients with second degree heart block, two progressed to complete heart block (18%), seven stabilized at second degree (41%), eight reverted to lesser degree of heart block (47%): four fetuses reverted to sinus rhythm and four reverted to first degree block. Of the four fetuses with first degree block, only one stabilized at first degree (25%).

We would therefore emphasize that, in spite of the maternal steroid therapy, the regression's rate of CHB is progressively diminished with the onset of the severity of disease (see Fig. 1).

It is very intriguing to encounter the rate of HB degree's regression for the prognosis of affected fetuses.

**Table 1. Studies and Case Reports in which Only Maternal Steroid Administration was Used to Treat Fetal Heart Block (n=124)**

Reference	N°	Degree of block <sup>§</sup>	Medication at diagnosis*	Degree of block after medication <sup>§</sup>	Paced	Ascites/ Pleural/ pericardial effusion resolution
Bierman <i>et al.</i> (1988)	1	III	BETA	III	-	-
Petri <i>et al.</i> (1989)	1	III	DEXA	III	-	-
Chua <i>et al.</i> (1991)	1	III	DEXA	III	-	-
Carreira <i>et al.</i> (1993)	1	III	DEXA	III	-	-
Buyon <i>et al.</i> (1994)	1	III	DEXA	III	-	-
Buyon <i>et al.</i> (1995)	14	III	DEXA/BETA	III	-	Yes (n°8)
	3	II/III	DEXA	III (n°2)/ II (n°1)	-	
	2	II	DEXA	II (n°1)/ Sinus rhythm (n°1)	-	
Copel <i>et al.</i> (1995)	2	II/III	DEXA	III (n°1)/ II (n°1)	-	Yes
	1	II	DEXA	Sinus rhythm	-	-
Rosenthal <i>et al.</i> (1998)	1	III	DEXA	III	1	Yes
	1	I	DEXA	I	0	Yes
Saleeb <i>et al.</i> (1999)	21	III	DEXA/BETA	III	12	Yes (n°7)
	3	II/III	DEXA	III	2	Yes (n°3)
	4	II	DEXA	I (n°3)/ II (n°1)	0	Yes (n°1)
Vignati <i>et al.</i> (1999)	4	III	DEXA	III	-	-
Yamada <i>et al.</i> (1999)	1	III	DEXA	III	-	-
	1	II	DEXA	II	-	-
Shinoara <i>et al.</i> (1999)	4	III	BETA	III	-	-
Brackley <i>et al.</i> (2000)	1	III	DEXA	III	-	-
Theander <i>et al.</i> (2001)	1	II	DEXA	I	0	0
Wong <i>et al.</i> (2001)	1	III	DEXA	III	-	-
Brucato et al (2001)	2	III	DEXA	III	2	
Zemlin <i>et al.</i> (2002)	1	III	DEXA	III	-	-
Minassian and Jazayeri (2002)	1	III	DEXA	III	-	
Breuer <i>et al.</i> (2004)	1	II	DEXA	III	-	
Vesel <i>et al.</i> (2004)	1	I	DEXA	Sinus rhythm	0	0
Jaeggi <i>et al.</i> (2004)	12	III	DEXA	III**	5	-
Chun-Han <i>et al.</i> (2005)	1	III	DEXA	III	1	
Hagen <i>et al.</i> (2007)	1	II	DEXA	II	-	-
Friedman <i>et al.</i> (2009)	22	III	DEXA	III***		
	6	II	DEXA	III (n°1); II (n°3); Sinus rhythm (n°2)	1	
	2	I	DEXA	Sinus rhythm		
<b>Present Authors (2009)</b>	<b>3</b>	<b>III</b>	<b>BETA</b>	<b>III</b>	<b>3</b>	

-: No data provided.

\*DEXA as Dexamethasone; BETA as Betamethasone.

Dosage of medication: dexamethasone: 4-10 mg/day; betamethasone 4 mg/die or 12-24 mg/week.

\*\*One fetal death.

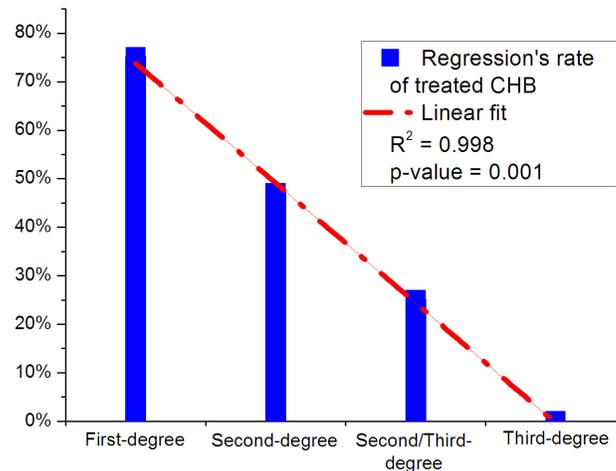
\*\*\*Four fetal deaths.

§I: first degree heart block.

II: second degree heart block.

II/III: intermittent second-third degree heart block.

III: third degree heart block.



**Fig. (1).** Regression's rate of treated CHB in relation to disease's degree. The dash line is the best fit of data.  $R^2 = 0.998$ ;  $p$ -value = 0.001.

We also considered the other possibilities of treatment of CHB: the use of  $\beta$ -mimetics. This treatment is devoted to increase fetal heart rate further than 55 bpm in order to maintain a better hemodynamic condition. Although  $\beta$ -mimetics could transiently increase fetal heart rate, they do not restore the coordination of AV conduction which is critical for the heart's adequate filling [3].

Table 2 shows the results of maternal  $\beta$ -mimetics administration in CHB of nine fetuses of seven studies.

In the literature we found seven studies on nine fetuses treated with different  $\beta$ -mimetics: in all of these babies there is no reversion to lesser degree of heart block; four of them needed the pacemaker implantation after the birth (44%); the overall one year survival was 89%, with one neonatal death due to an immune-mediated liver fibrosis [52].

## DISCUSSION

Confirming precedent studies, once fetal third-degree block is detected, it is irreversible regardless of treatment. In

**Table 2.** Studies and Case Reports in which Maternal  $\beta$ -Mimetics were Used to Treat Fetal Heart Block (n=9)

Reference	N°	Degree of Block <sup>§</sup>	Medication at diagnosis	Degree of block after medication <sup>§</sup>	Paced	Ascites/ Pleural/ pericardial effusion resolution	Alive
Groves <i>et al.</i> (1995)	1	III	Isoprenaline 10 mg ev in 1 L 5% SG; Salbutamol 80 mg in 1 L 4% SG then 16 mg oral	III	No	Yes	Yes
	1	III	Isoprenaline 10 mg ev in 1 L 5% SG; Salbutamol 80 mg in 1 L 4% SG	III	Yes	-	Yes
	1	III	Isoprenaline 10 mg ev in 1 L 5% SG; Salbutamol 80 mg in 1 L 4% SG	III	Yes	-	Yes
Chan <i>et al.</i> (1999)	1	III	Isoproterenolo ev; terbutaline oral	III	Yes	Yes	Yes
Yoshida <i>et al.</i> (2001)	1	III	Terbutaline	III	No	-	Yes
Matsushita <i>et al.</i> (2002)	1	III	Ritodrine ev	III	No	-	Yes
Novi <i>et al.</i> (2003)	1	III	B-mimetics <i>via</i> subcutaneous pump	III	-	Yes	Yes
Jaeggi <i>et al.</i> (2004)	1	III	Salbutamol 10 mg/die	III	Yes	-	No
Matsubara <i>et al.</i> (2008)	1	III	Ritodrine ev	III	-	Yes	Yes

-: No data provided.

<sup>§</sup>I: first degree heart block.

II: second degree heart block.

II/III: intermittent second-third degree heart block.

III: third degree heart block.

particular, we would emphasize that, in spite of the maternal steroid therapy, the regression's rate of CHB is progressively diminished with the onset of the severity of disease. However, this review confirmed the potential benefit of the gestational use of fluorinated steroids in reversing or stabilizing first- or second-degree CHB. So, Buyon *et al.* assumed that the critical times to intervene should have been: (i) when the PR interval is prolonged but atrial signals continue to reach the ventricles (type I or type II degree block) or (ii) when only signs of myocardial dysfunction are present [53].

The use of fluorinated steroids for an extended period of time must be balanced with the potential risks to the mother and her fetus. Maternal risks of Dexamethasone and Betamethasone are similar to any corticosteroid and include infection, osteoporosis, osteonecrosis, diabetes, hypertension, premature rupture of membranes, preterm labour and preeclampsia [51]. Fetal risks include oligohydramnios, a serious and potentially life-threatening complication for the fetus, and adrenal suppression [52, 55-58]. Moreover, another several obstetric complication observed in these pregnancies is the fetal growth restriction [55, 57, 59]. It's very difficult to establish the only factor causing the high incidence of fetal intrauterine growth restriction reported in this population in literature. We need to consider the different type of fluorinated steroid (dexamethasone vs betamethasone), the different time of intrauterine exposition, the different maternal and activity disease, the different maternal autoantibodies profile. As reported in our series of cases, the second and the third babies affected by CHB developed a severe fetal growth restriction: in the second case the onset of disease before starting steroid therapy and the abnormalities in utero-placental circulation may suggest the importance of the maternal disease in the genesis of fetal IUGR. IUGR can complicate lupus pregnancy causing low birth weight defined as <2500 g at delivery and small for gestational age newborns, defined as birth weight less than the 10<sup>th</sup> percentile for gestational age. These outcomes are reported in 10-30% of infants of SLE patients and are considered as the most frequent complication of pregnancy in patients with systemic autoimmune disease [60]. In the third case, fetal IUGR might be secondary to both the betamethasone treatment and the disturbance in utero-placental blood velocity.

However, in several animal studies, including mice, rats and rabbits, fetal growth restriction was observed with higher frequency in animals treated with steroid than in controls [59]. In a recent randomized controlled trial, it was demonstrated that infant exposed to multiple courses of antenatal corticosteroids weighted less, were shorter and had a smaller head circumference at birth than those exposed to placebo [61].

Several studies have also demonstrated that might be involved the human fetus neuropsychological development as well [62, 63]. In his multivariate analysis, Spinillo *et al.* showed that the risk of periventricular leukomalacia and 2-year infant neurodevelopmental abnormalities was increased with exposure to multiple doses of dexamethasone (OR=3,21 and 3,63 respectively) [64]. However, Brucato *et al.* reported no neurodevelopmental problems in anti-Ro/SSA and anti-La/SSB exposed children whose mothers had taken high-dose of dexamethasone for the treatment of CHB [65]. So, a

large prospective study is necessary to establish how fluorinated steroids can cause these complications.

Then, considering the low incidence of CHB and the potential side effects of the intrauterine exposure to fluorinated steroids, until today there is no convincing evidence for the use of steroids as preventive treatment in anti-Ro/SSA and anti-La/SSB antibodies positive women. With regard to prophylactic therapy of even highest-risk patient, initiation of fluorinated steroid therapy is not justified at the present time. In this setting the expected incidence is approximately 16%-18% [9, 11, 13]; then this kind of therapy may expose many patients (>80%) to treatment unnecessary. It's now recommended to evaluate all pregnant women with autoimmune disorders in first trimester with a complete immunological screening by ELISA. The absence of anti-Ro/SSA and anti-La/SSB antibodies excludes any risk; in case of anti-Ro/SSA positivity, it's possible to discriminate high and low risk patients with the immunoblot; the identification of high titer anti-Ro/SSA and anti-La/SSB antibodies, anti-48kD La/SSB and 52kD Ro/SSA on immunoblot and/or a previous child with NLS identify patients at high risk of CHB; it's recommended to monitor intensively high risk mothers performing serial fetal echocardiography assessed by an experienced pediatric cardiologist weekly from 18 to 24 weeks gestation. Low risk mothers (anti-Ro/SSA antibodies positive by ELISA but not by immunoblot) have to be screened with fetal echocardiography performed at 24 weeks [20].

In conclusion, the early diagnosis of CHB is mandatory during pregnancy, so we suggest the necessity of centers devoted to the management of women at risk. The data about CHB degree's rate of regression are substantial, implying the indication to occurrence of specific intrauterine treatment, as fluorinated steroids and  $\beta$ -mimetics. The appropriate care of pregnancies at risk for developing CHB requires a multidisciplinary approach among rheumatologist, obstetrician, pediatrician and cardiologist.

#### ABBREVIATION

CHB	= congenital heart block
NLS	= neonatal lupus syndrome
HB	= heart block
AV	= atrioventricular
SLE	= Systemic Lupus Erythematosus
SS	= Sjögren Syndrome
TNF $\alpha$	= tumor necrosis factor $\alpha$
TGF $\beta$	= transforming growth factor $\beta$
CCHB	= complete congenital heart block
ANA	= anti-nuclear antibody
Anti-ds DNA	= anti-double-stranded DNA
ACA IgM	= anti-cardiolipin immunoglobulin M
ACA IgG	= anti-cardiolipin immunoglobulin G
anti- $\beta$ 2GP IgM	= anti- $\beta$ 2Glycoprotein immunoglobulin M
anti- $\beta$ 2GP IgG	= anti- $\beta$ 2Glycoprotein immunoglobulin G

LAC = lupus anticoagulant  
IUGR = intrauterine growth restriction

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