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A review of congenital heart block

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Abstract

Congenital heart block is a rare disorder. It has an incidence of about 1 in 22,000 live births. It may be associated with high mortality and morbidity. This should generate a high index of suspicion for early diagnosis and aggressive therapy when appropriate. The congenital heart block associated with neonatal lupus is considered a form of passively acquired autoimmune disease in which maternal autoantibodies to the intracellular ribonucleoproteins Ro (SS-A) and La (SS-B), cross the placenta and injure the previously normal fetal heart. Women with serum titers of anti-Ro antibody carry a 3% risk of having a child with neonatal lupus syndrome. Recurrence rates are about 18%. We believe that serial echocardiograms should be acquired so that early diagnosis is made and aggressive therapy administered, if signs of conduction system disease such as PR interval prolongation by Doppler are found, so as to optimize the outcome. Establishment of guidelines for therapy have been set empirically, should signs of congenital heart block develop. Those patients whose congenital heart block is associated with structural heart disease have a higher morbidity and mortality, which is determined more by the underlying structural congenital heart disease than it is by the need for a pacemaker per se.

MeSH: congenital heart block, neonatal lupus

Introduction

The definition of congenital heart block for the purposes of this review will be the presence of conduction system disease of any form, which is diagnosed on or before 28 days of life. The incidence of congenital heart block has been estimated from several studies to be about 1 in 22,000 live births.¹ Although this is clearly an uncommon disorder, it may be associated with high mortality and morbidity and therefore requires a high index of suspicion for early diagnosis and aggressive

therapy when appropriate. Aggressive therapy can be defined as offering the prenatal use of dexamethasone or the other maternal drugs, fetal pacing, or early delivery. There are no data on the “appropriateness” of aggressive therapy, but our recent paper² implies it may improve hydrops in the sickest fetuses.

This paper will be divided into two major sections. Initially, we will discuss congenital heart block with and without structural heart disease. Secondly, we will spend some time discussing the unique subtype of congenital heart block, that which occurs in the absence of major structural anomalies and which is associated with maternal autoimmune antibodies.

Congenital heart block is frequently associated with underlying structural congenital heart disease. The commonest forms of congenital heart disease associated with heart block include left atrial isomerism, often with an accompanying atrioventricular septal defect, as well as levo transposition of the great arteries. When diagnosed in the postnatal period, approximately one-third of cases of congenital conduction system disease have associated structural disease. In utero, diagnosis of congenital heart block is associated with structural heart disease in approximately one half of the cases.¹ There is a higher association of congenital heart block occurring with congestive heart failure in utero, and thus a poorer prognosis.

Clinical Course

The outlook for patients with congenital heart block depends largely on the presence or absence of underlying structural heart disease, as well as the rate of ventricular activation and the presence or absence of congestive heart failure. If the heart block is diagnosed as a bradycardia during the fetal period, there is a very high rate of fetal and neonatal loss. Prenatal risk factors for mortality prenatally depend on the presence of structural heart disease and a heart rate less than a critical value, frequently quoted as 55 bpm. The presence of hydrops fetalis or other signs of physiologic disturbance in cardiac function, are very poor prognostic signs. In severe cases, there has been as high as an 85% mortality rate in the neonatal period.

According to the Jaeggi paper³, mortality in complete atrioventricular block in the fetus was 43% (13 out of 15 total deaths were fetal); in the neonatal stage was 6%; and in children there were none. In fetal hydrops there was a 100% mortality. With endocardial fibroelastosis (EFE), there was also a 100% mortality. If the fetal heart rate (FHR) was less than 55bpm, the majority died (9 out of 15).

According to the Kertesz paper¹, in various series of fetal congenital complete atrioventricular block, 30 to 53% of cases have associated congenital heart disease. Of these, only 14% survived the neonatal period compared to 85% survival of the autoimmune isolated congenital complete atrioventricular block.

If the congenital heart block is first diagnosed in the newborn period, presumably the higher risk fetuses have not survived, and therefore the prognosis is somewhat better. Once again, the presence or absence of underlying structural heart disease often determines the outcome. The survival rate in newborns with congenital heart block and no structural heart disease is about 85%. Many, if not eventually all, of these patients require pacemaker implantation. If the congenital heart block first presents beyond the newborn period, the outlook for survival is improved. These patients are unlikely to have severe structural heart disease, and the survival rate is much higher than 85%. Such children, however, still almost always require pacemaker implantation as well as treatment for any underlying structural heart disease. Finally, some patients are first diagnosed with their presumably “congenital” conduction system disease in later childhood or adulthood. Such patients are unlikely to have structural heart disease and they tend to have a good prognosis after pacemaker implantation. However, it must be remembered that they might present with severe life threatening events as their first manifestation of bradycardia, and

they seem to have a late risk of developing left ventricular dilation and mitral insufficiency, presumably from longstanding bradycardia or immunological damage to the heart.

Risk Factors for Poor Outcome and the Need for Pacemaker Therapy:

Several studies have attempted to elucidate the risk factors for the requirement of pacemaker implantation in patients with congenital heart block.¹ It is fairly well accepted that a mean resting heart rate below a determined number for the age group could be an indication to place a pacemaker. This is frequently quoted as a 55 bpm in the newborn period and gradually decreases with advancing age. Here we give some examples of electrocardiograms displaying varying degrees of heart block (Figures 1-4). It is also well accepted that any symptomatic bradycardia requires pacemaker implantation, and it should be recognized that this may be either a sudden presentation or simply limited exercise capability. In addition, the presence of significant structural congenital heart disease is felt to be an indication to pace a patient with congenital heart block. Significant pauses on 24-hr. ambulatory electrographic monitoring may also be an indication for putting in a pacemaker. Some studies have suggested that a prolonged QTC interval or a wide QRS escape rhythm with complex ventricular ectopy may warrant the use of pacemaker therapy. It is sometimes difficult to determine if the child is having symptomatic bradycardia, because children will limit their exertion based on their symptomatology. Therefore, Holter monitoring or exercise stress testing may be helpful in this regard. Echocardiograms may be helpful also to determine progressive loss of systolic function of the ventricle with increasing heart size and the development of mitral regurgitation.

Figure 1 Electrocardiogram showing first degree atrioventricular block (PR= 160 msec, heartrate= 170 bpm) in a newborn.

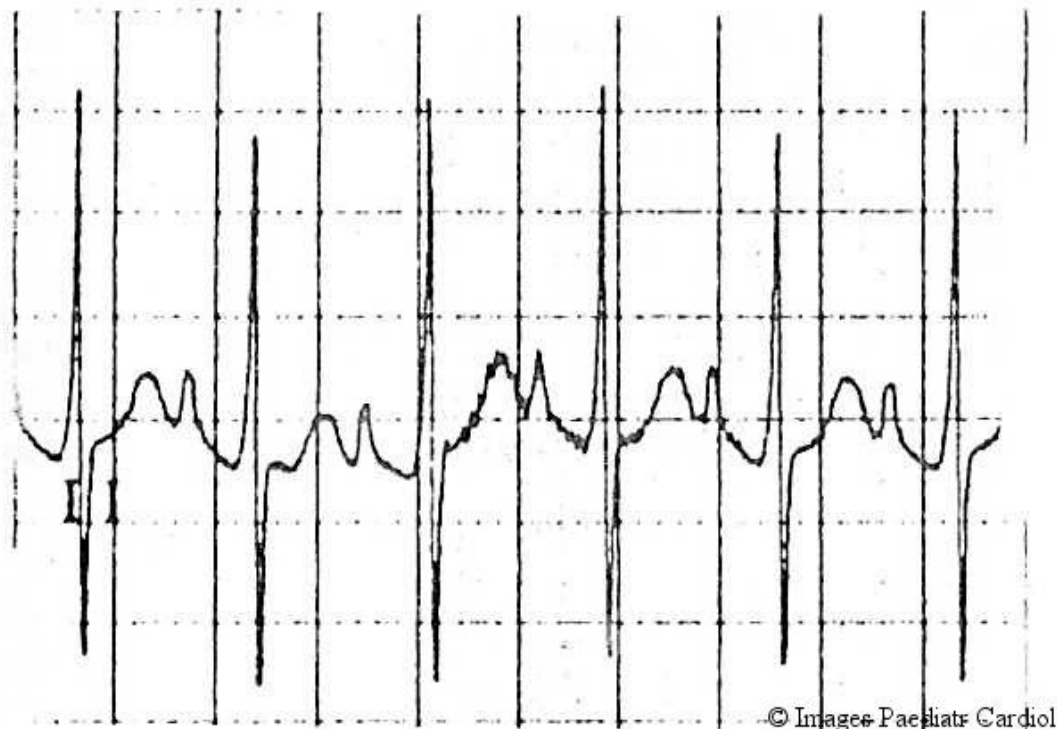


Figure 2 Electrocardiogram showing second degree atrioventricular block (Mobitz Type II) with progressive PR prolongation leading to dropped beats.

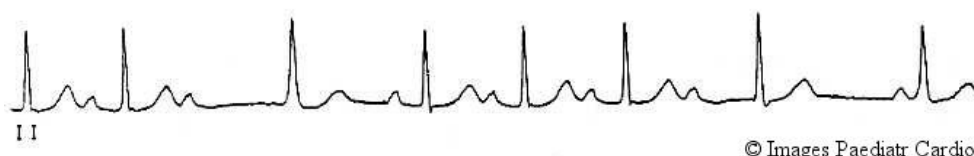


Figure 3 Electrocardiogram showing third degree heart block with atrioventricular dissociation and slow ventricular rate (atrial rate is 150, ventricular rate is 85 bpm).

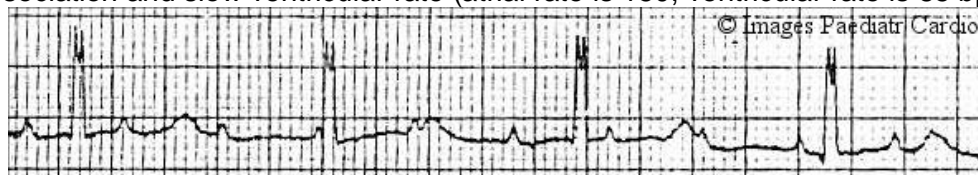
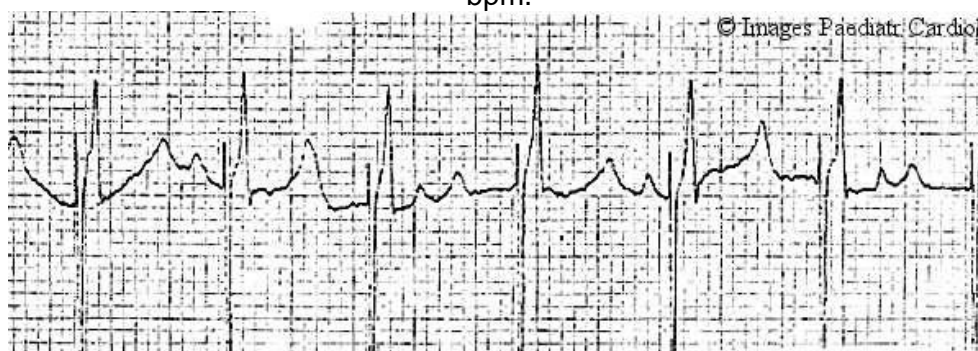


Figure 4 Electrocardiogram showing third degree heart block (atrioventricular dissociation with atrial rate of 170 bpm) and ventricular pacemaker capturing at 125 bpm.



Congenital Heart Block in Neonatal Lupus

The congenital heart block associated with neonatal lupus is considered a form of passively acquired autoimmune disease in which maternal autoantibodies to the intracellular ribonucleoproteins Ro (SS-A) and La (SS-B), cross the placenta and injure the previously normal fetal heart. Other manifestations of neonatal lupus may include the presence of skin rashes, liver abnormalities determined biochemically and abnormalities in the cellular elements of the blood including various cytopenias.² While the non-cardiac manifestations of neonatal lupus are generally transient and resolve at approximately the time that the maternal antibodies are cleared from the infant's circulation at several months of age, the conduction system disease is essentially irreversible.

Neonatal lupus is usually diagnosed in the presence of a slow heart rate discovered in a fetus or newborn in the absence of associated structural cardiac abnormalities. Maternal serum testing subsequently reveals antibodies to Ro and/or La, usually evaluated by ELISA testing. While the mother may have systemic lupus or other autoimmune diseases such as Sjogren's Syndrome, approximately half of the women at the time of diagnosis are asymptomatic. *In utero*, the peak onset of the diagnosis of bradycardia is between 18 and 24 weeks of gestation, corresponding to the window of opportunity about six weeks after effective placental transport of maternal IgG antibodies begin. While the precise mechanism is unknown it is presumed that anti-Ro/La antibodies directly or indirectly cause the cardiac damage. The degree of

heart block may vary from first degree to third degree block, but most cases diagnosed *in utero* present with a least second degree or more advanced block. There is a high mortality rate, particularly in fetuses diagnosed *in utero* with hydrops, and it is approximately 20%. Of all cases that have been recognized with congenital heart block, current data show that approximately two-thirds of these patients will have a pacemaker placed before reaching adulthood (see Table 1).

Table 1 Autoimmune Congenital Heart Block Statistics²

Incidence in +Ro/La pregnancies	3%
Recurrences after first index case	18%
Mortality	20%
Need for pacemaker	>60%
Late onset cardiomyopathy	10%

In those cases of autoimmune conduction system disease due to neonatal lupus, the bradycardia alone is not always the full extent of disease. Recently, there has been the recognition of a relatively high incidence of the development of late cardiomyopathy leading to heart failure, death or transplantation despite successful pacemaker implantation (Table 1).^{3,4} As referenced in the Moak paper⁴, late cardiomyopathy is associated with immune-related congenital heart block in 5-11% of cases. Clinical deterioration of cardiac function was seen up to 9.3 years. In our experience, our oldest patient was 4 years old. Other organ systems may be involved in the newborn as well, including the characteristic neonatal rash which appears generally as annular lesions, mostly on the face, particularly around the eyes and is photosensitive (Figure 5). In addition, on serum testing, some of the newborns with maternal autoantibodies will have various low levels of red blood cell counts, white blood cell counts, and platelets. There may also be abnormalities of liver enzyme levels and jaundice.

The occurrence rate of neonatal lupus has been estimated at approximately 2 to 3% in all pregnancies born to women with anti-Ro or anti-La antibodies. The recurrence rate in a mother with antibodies who has a previous child who was affected, is approximately 18%.⁵

Pathophysiology

The mechanism of causation of neonatal lupus is not completely understood but evidence points to the fetus beginning life with a normal cardiac structure and conduction system. At approximately 12 weeks of gestation, maternal IgG antibodies against Ro and La intracellular ribonuclear proteins are actively transported across the placenta and are thought to bind specific cells of the fetal conduction system. This may result in a cycle of inflammation, later scarring and fibrosis. There is also an element of maturation of the fetal immune system involved in the development of fetal immune disease. The mechanism of late cardiomyopathy after birth is unknown.

Fetal Diagnosis

The majority of cases of congenital heart block, diagnosed *in utero* are detected by either auscultation or routine obstetrical ultrasound in low risk pregnancies. The

diagnosis is confirmed by the performance of maternal fetal monitoring (MFM) and a fetal echocardiogram with Doppler techniques (Figures 6-10). In the past, only second or third degree block would be clinically manifest as a bradycardia. The purpose of the fetal echocardiogram is to determine the level of block and also to rule out major associated structural lesions of the heart, such as left atrial isomerism with or without atrioventricular septal defects, and ventricular inversion, which are structural diseases associated with the presence of heart block without antibodies. The fetal echocardiogram is also able to detect any associated myocarditis by looking for the presence of decreased contractility on fetal echocardiogram as well as any secondary changes of cardiac enlargement, tricuspid regurgitation, pericardial effusion, or the development of hydrops fetalis (Figure 11).

Figure 5 Top shows 2D-directed M-mode echocardiogram of a newborn with a normal shortening fraction as the ventricle contracts in systole. The interventricular septum and the left ventricular posterior wall thicken toward each other during systole. Bottom shows 2D-directed M-mode echocardiogram of a newborn showing a very poorly contractile, dilated ventricle. The ventricular walls are barely thickening during systole.

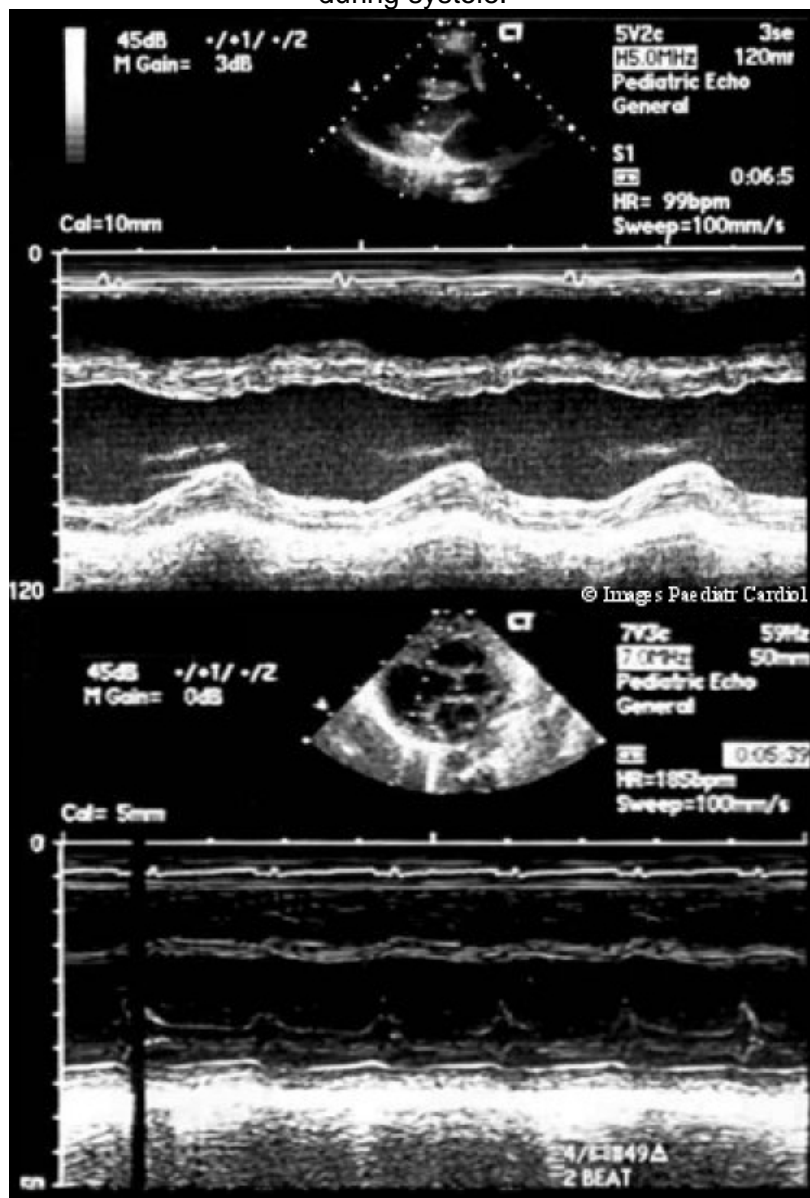


Figure 6 Skin rash of neonatal lupus.



Figure 7 Electronic fetal monitoring tracing in labor with fetal 3rd degree CHB. Upper tracing is fetal ventricular heart rate. Lower tracing is uterine contractions. Note slow fetal heart rate (FHR) of 80-115 bpm.

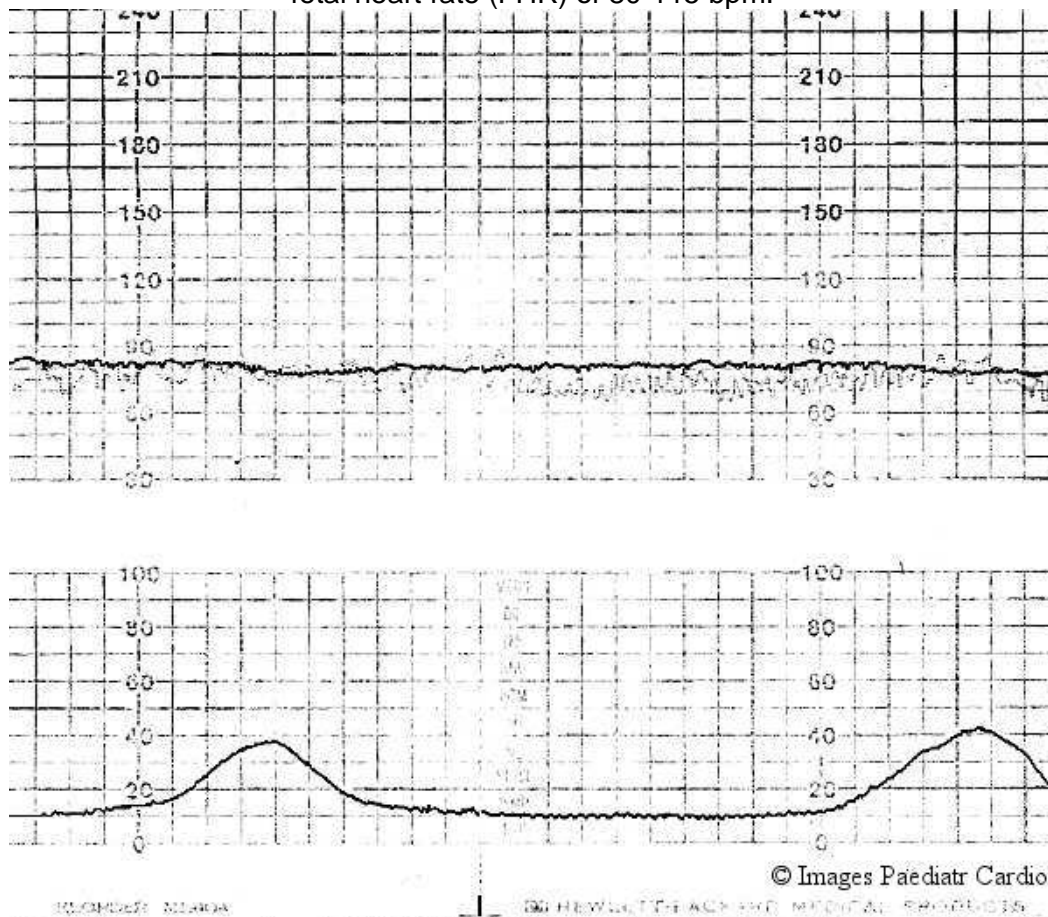


Figure 8 Top shows normal fetal Doppler PR. Placement of Doppler sample volume in LVOT. Bottom shows fetal LVOT Doppler with measurement of mechanical PR interval, from onset of mitral "a" wave (nadir of flow between the "e" wave and the "a" wave, when "e" and "a" are not distinctly separated) to the onset of aortic flow. (Normal PR interval should be between 90 to 150 msec.) X axis= time in seconds; Y axis= velocity in meters/second.



Figure 9 Fetal Doppler PR interval shows 1st degree heart block with the addition of profound sinus bradycardia (fetal heart rate of 60 bpm). Long pause between the onset of the atrial contraction and onset of ejection time (PR interval). PR interval = 404 msec.

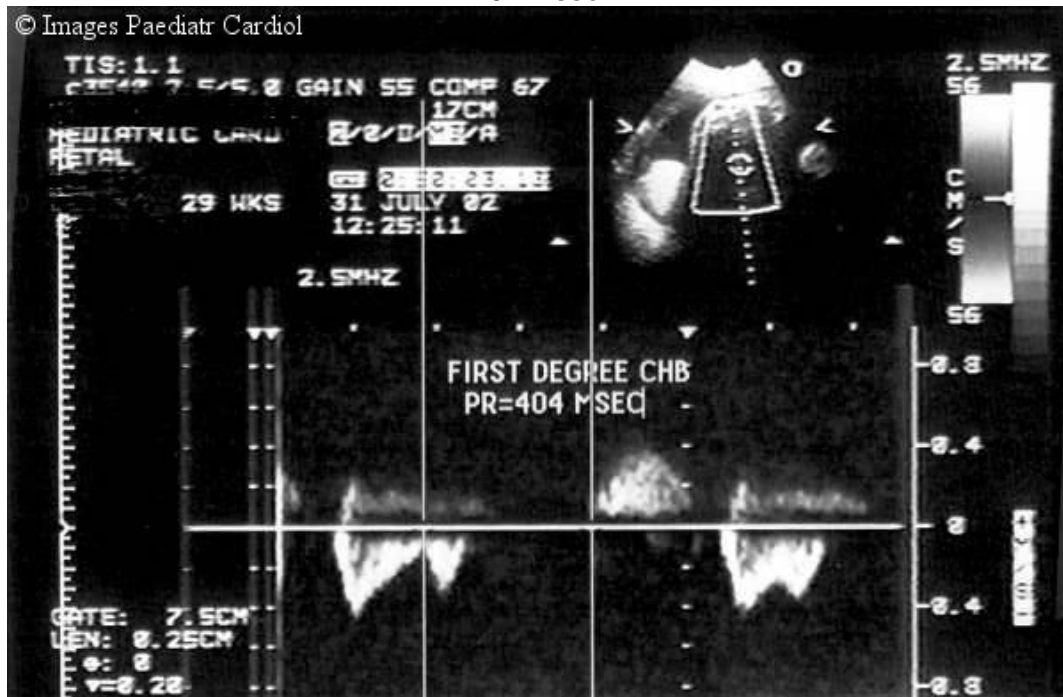


Figure 10 Fetal Doppler PR interval shows Wenckebach Mobitz Type I, a type of 2nd degree heart block. Initial beat shows a short PR interval of 63 msec (top left). The PR intervals become progressively longer (top right and bottom left), with a non-conducted PR interval (bottom right)

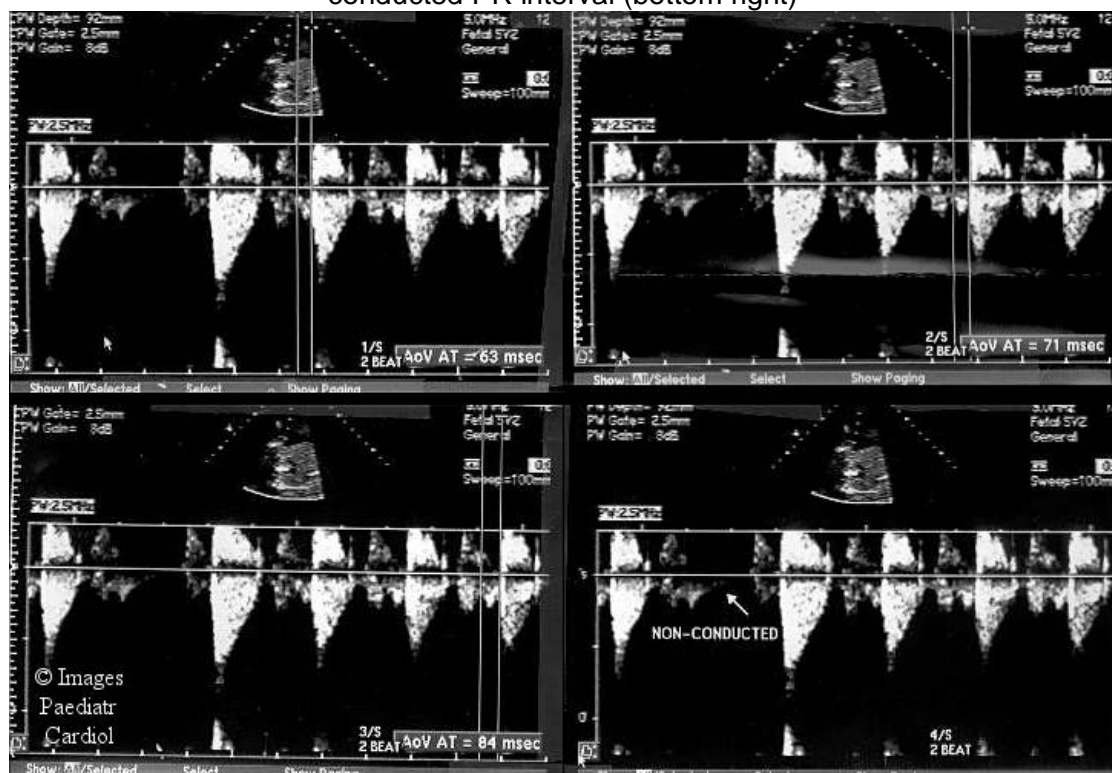
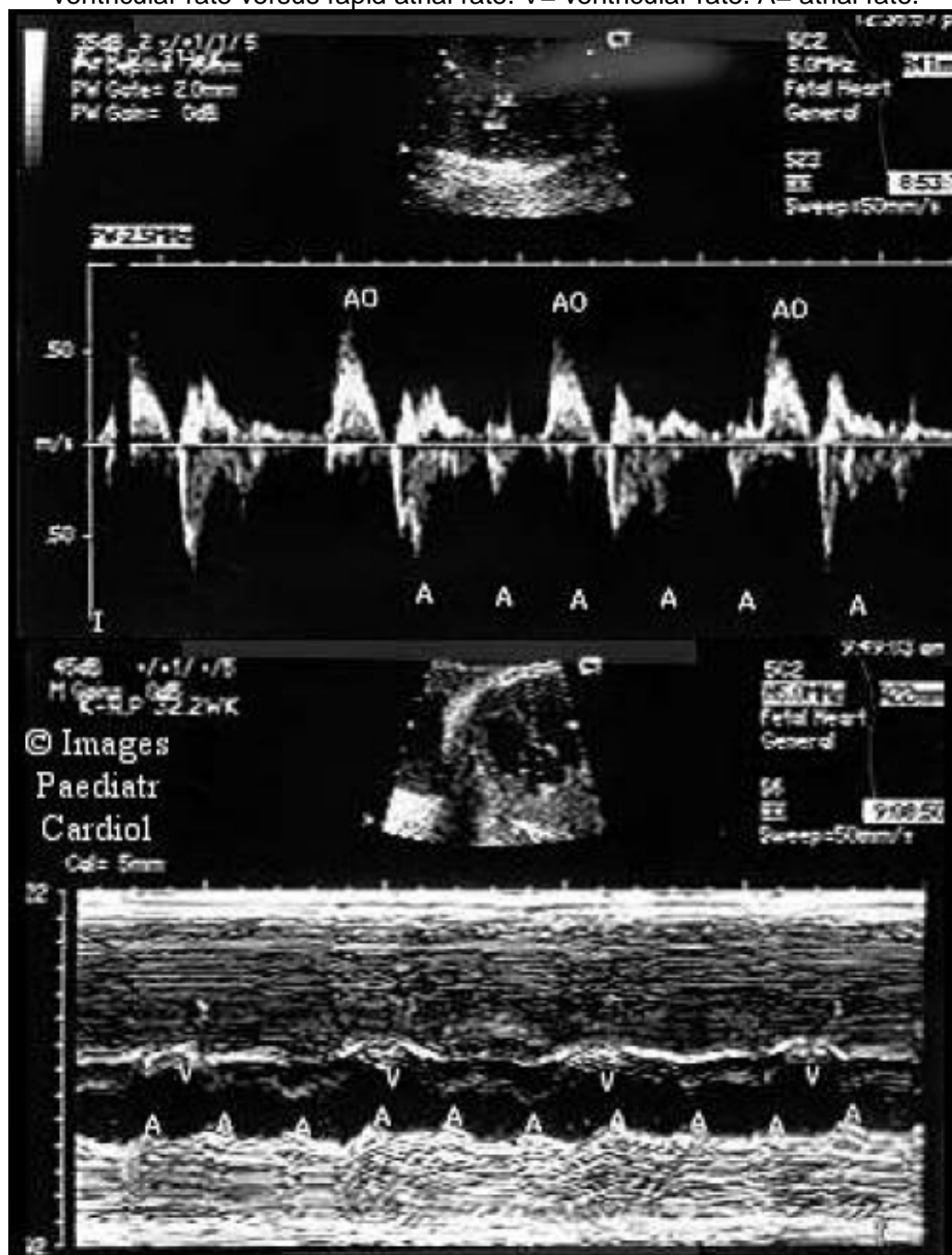


Figure 11 Top shows fetal Doppler PR interval with 3rd degree heart block. Spectral Doppler labeled AO indicates a slow ventricular rate seen above the baseline. Spectral Doppler labeled A symbolizes a rapid atrial rate moving about 3 times as fast as ventricular rate seen below the baseline. Atria and ventricles are dissociated. Bottom shows M-mode of ventricle and atrium in 3rd degree heart block with slow ventricular rate versus rapid atrial rate. V= ventricular rate. A= atrial rate.



Therapeutic Approach to Congenital Heart Disease Diagnosed *in utero*

With increasing prenatal care and use of ultrasound technology in pregnancy, increasing numbers of cases of autoimmune congenital block are being diagnosed between 18 and 24 weeks of gestation. This raises the expectation for better prognostication and possibly for definite therapy. Unfortunately, although these

babies are at high risk for morbidity and mortality, guidelines are not well established nor based on definite scientific evidence.

Based on the assumption that treatment for identified heart block *in utero* may be effective if it can reduce a generalized inflammatory insult and lower the titer of maternal autoantibodies, several prenatal therapeutic protocols have been utilized. These include the use of adrenocorticosteroids, which are not metabolized by the placenta, principally dexamethasone. Some researchers have also attempted plasmapheresis and the use of maternal alpha adrenergic agents.²

Our therapeutic approach to a fetal diagnosis of congenital heart block is as follows.² If the heart block is already third degree and has been present for more than three weeks, we feel that an attempt at reversing this complete heart block is futile, and therefore we provide serial echocardiographic and obstetrical follow-up but no therapy is initiated. If, however, the third degree heart block has been recently diagnosed, we offer the patient a therapeutic course of dexamethasone 4 mg. orally once a day for a period of six weeks. If there has been no change in fetal status, we taper the course and discontinue it. On the other hand, if the fetus' conduction system disease has improved to second degree block or better, then we continue dexamethasone until delivery and subsequently taper in the mother.

If the fetus presents with alternating second and third degree block, we again offer dexamethasone at 4 mg orally daily for a six-week period of time. If the conduction system disease progresses to third degree block then we taper the drug and stop it. But if there has been improvement to second degree or better, we continue the steroids until delivery and taper thereafter.

If the fetus is discovered to have only second degree or a simply prolonged mechanical PR interval (first degree block),⁶ then we offer the mother dexamethasone 4 mg. orally daily until delivery and taper her dose after that. On the other hand, if this early block progresses to permanent third degree block, we will taper the steroid if third degree block has been present for six weeks or longer.

Occasionally, the fetal congenital heart block is associated with early signs of myocarditis and fetal hydrops. In such a case, we again offer dexamethasone at 4 mg orally daily until improvement of the hydrops fetalis *per se*, and then taper. Some studies have suggested⁷ that in severely hydropic fetuses there may be some benefit to daily dexamethasone at 4 mg. Other varied therapies in such cases of hydrops have included plasmapheresis, maternal terbutaline, digoxin, diuretics or direct fetal pacing. There has been no long-term survival from these desperate measures, and therefore if the lungs are mature at this point, we would advise early delivery.

The proposed maternal use of dexamethasone, is of course, not without risks. These include the glucocorticoid associated risks of increased infection, loss of bone density, diabetes, hypertension and cataracts. The fetal risks of maternal steroids include oligohydramnios, intrauterine growth retardation and adrenal suppression. There is also some suggestion of a risk to the developing fetal brain when exposed to steroids.

Some questions have arisen as to the appropriate use of prophylactic therapy in the pregnancy with a high-risk mother, such as those women with very high titers of the antibodies or a previous child with neonatal lupus. We feel that there is no support for the initiation of immune modulating treatment as a pre-emptive strike prior to the development of fetal conduction system disease.

It is clearly advantageous to provide close fetal follow-up for monitoring the patient at risk for congenital heart block in the presence of maternal autoantibodies. We recommend that all women with anti-Ro antibodies be evaluated by serial fetal echocardiograms. Particularly high-risk groups appear to be those women with very high titers of anti-Ro and anti-La antibodies, as well as those with previously affected pregnancies. We have recently developed a new technique in fetal echocardiography that allows us the possibility to detect the first possible changes of fetal conduction system disease, that is, the presence of first degree heart block in the fetus. In this

case, the overall fetal heart rate will still be normal, but our new non-invasive Doppler technique can measure the “mechanical PR interval” in the absence of an electrocardiogram from the left ventricular outflow tracing. This will allow the earlier diagnosis and the possibility of very early treatment, which may be able to reverse the disease.^{6,8} For this reason, we strongly suggest weekly fetal echocardiograms with Doppler for pregnancies at risk.

The therapeutic approach to the newborn after birth has somewhat more options. Supportive treatment for low output or congestive heart failure can clearly be offered as well as pacemakers for babies with significant bradycardia, such as those with a heart rate less than 55 bpm. Although we recognize that the newborn serum contains maternal antibody titers, we have no real data on immune modification of the newborn after birth. Similarly, we cannot comment on the fact that anti-Ro and anti-La antibodies have been detected in maternal breast milk.

We do know that neonates at risk for developing lupus rashes should be protected from sun exposure, but otherwise treatment is fairly conservative with the use of topical corticosteroids. The liver enzyme abnormalities and blood count irregularities are usually self-limited and require no specific treatment.

The risk of a baby born with neonatal lupus syndromes developing active lupus in the future, is small and probably related to the genetic inheritance of the risk of developing rheumatic diseases rather than the maternal antibodies themselves.

Figure 12 Hydrops fetalis. Transverse section of fetal thorax displaying 4 chamber view of heart surrounded by pleural and pericardial effusions. Lungs are collapsed.



Summary

Women with serum titers of anti-Ro antibody carry a 3% risk of having a child with neonatal lupus syndrome. If she has a prior experience with affected fetuses, her risk rises to about 18%.⁵ Therefore, we believe that all women at risk with antibodies present, should be closely followed during the pregnancy with serial echocardiograms, specifically looking for the earliest signs of conduction system disease such as PR interval prolongation by Doppler. Although prophylactic therapy

is not indicated at the present time, if manifestations of congenital heart block develop, we have established empiric treatment guidelines. Neonatal lupus congenital heart block has a fairly high morbidity and mortality but we believe that the outcome can be improved with early diagnosis and aggressive therapy.

Those patients whose congenital heart block is associated with structural heart disease have a higher morbidity and mortality, which is determined more by the underlying structural congenital heart disease than it is by the need for a pacemaker per se.

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