Diagnosis, management and outcome of congenital atrio-ventricular block

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Introduction

Atrio-ventricular block (AVB) refers to a disturbance of electrical impulse conduction within the AV node, the His bundle, or the bundle branches. Three grades of severity are distinguishable after birth by means of surface electrocardiograms:

- 1st degree AVB is defined as a prolongation of the AV conduction time beyond the normal limits for age (<170ms in newborns), but all impulses are conducted.
- 2nd degree AVB refers to a failure to conduct some, but not all atrial impulses to the ventricles. Two forms occur: Type I (Wenckebach) 2nd degree AVB denotes progressive lengthening of the AV conduction time, until an isolated impulse is blocked. Type II (Mobitz II) block is characterized by occasional or repetitive sudden AV block without prior lengthening of the AV conduction time. Mobitz II block is often a precursor of the development of complete heart block.
- In 3rd degree or complete AV block (CAVB), there is a complete interruption of the antegrade electrical communication between atria and ventricles. The atria and ventricles therefore beat independently.

First degree and type I 2nd degree AVB may occur in healthy children and require no treatment. By contrast, Mobitz II and 3rd degree AVB are far more serious conduction anomalies, which may cause bradycardia- and pause-related symptoms including congestive heart failure, syncope and sudden death.

Fetal diagnosis of AV conduction anomalies

Trans-maternal fetal electrocardiograms are based on an average QRS complex and do not allow detailed analysis of individual cardiac cycles. However, evaluation of the chronology of fetal atrial and ventricular contractions may be achieved by M-mode or Doppler ultrasonography. With it, atrial and ventricular depolarizations are identified indirectly by their mechanical (M-mode) or hemodynamic (Doppler) consequences. Especially helpful is the simultaneous recording of Doppler flow signals in the superior vena cava (retrograde a-wave flow during atrial systole) and the ascending aorta (antegrade ejection flow wave during ventricular systole), as this approach allows reliable measurement of fetal atrio-ventricular time intervals (Figure 1). Values measured experimentally with this Doppler technique are closely related to the PR and RP intervals of surface electrocardiograms and may be valid to rule out first and second degree AVB in fetuses. Ultimately, this approach may be helpful in the surveillance of fetuses at risk of progressive AV conduction block. Nevertheless, 1st degree and Wenckebach 2nd degree AV block have not yet been recognized in the neonatal period.

On the other hand, the majority of congenital heart block is presently identified in utero prior to 30 weeks of gestation as 3rd degree AV block. In complete heart block, the atria are contracting at a much faster rate than the independently beating ventricles (Figure 2). The fetal heart needs to accommodate the evolving AV block and slow heart rate by increasing its stroke volume, resulting in cardiomegaly and biventricular hypertrophy. As a consequence of the increased stroke volume, aortic and pulmonary arterial Doppler flow velocities are frequently raised to peak flows between 1 and 2 m/s. Ventricular systolic function is predominantly preserved, but can be abnormally reduced in the fetus with cardiac decompenstation, myocarditis and endocardial fibroelastosis. If the heart is not able to sufficiently compensate for the reduced heart rate, which occurs particularly at lower ventricular rates, reduced myocardial function and the presence of structural heart disease, congestive heart failure may develop. Trivial pericardial effusion is common and not necessarily a sign of impending heart failure. By contrast, fetal hydrops -defined as fluid accumulation in more than one body cavity or anasarca- should be considered as an advanced stage of cardiac failure with a high risk of poor outcome.

Incidence and etiology of complete heart block

Congenital CAVB is an uncommon arrhythmia: it accounts for about 20% of all major arrhythmias detected in utero and is seen in about 1 in 14,000 to 20,000 live births.

Complete heart block and congenital heart disease

In about half of the fetuses, heart block is associated with complex structural heart disease, most commonly left atrial isomerism and congenitally corrected transposition. Heart block associated with cardiac anomaly is explained by an anatomical disruption of the AV conducting pathways. The outcome of fetuses with both CAVB and major structural heart...
disease is particularly poor: only about 15% survive the fetal and neonatal period.3

Isolated heart block

Neonatal lupus erythematous (NLE) accounts for at least 90% of cases of CAVB without structural heart disease identified prior to 1 month of age.4 NLE is associated with the transplacental passage of maternal anti-Ro/SS-A or anti-La/SS-B autoantibodies.5,9 These IgG antibodies enter the fetal circulation beginning in the mid-second trimester and may subsequently elicit immune-mediated tissue injury, which may cause permanent destruction of the AV conduction system, autoimmune-myo-carditis and dilated cardiomyopathy.10 Isolated CAVB usually develops between 16 and 24 weeks of gestation, coincident with the increased transplacental transfer of maternal autoantibodies. Less common are non-cardiac NLE abnormalities affecting the skin (dermatitis), liver (hepatitis) and blood cells (thrombocytopenia). Unlike complete heart block, the non-cardiac manifestations are temporary and if present, resolve within the first 6 months after birth coincident with the disappearance of maternal antibodies from the infant’s circulation.

Although isolated CAVB has been recognized as a distinct clinical entity for 100 years, the understanding that the AV conduction defect is linked to mothers with connective tissue disease has been established only in the last 25 years.10,11,12 Meanwhile, it has become clear that most women with autoimmune antibodies are asymptomatic and only about 10% of mothers do have diagnosed connective tissue disease at the time of their offspring’s presentation with heart block.10,12 Current data suggest that anti-Ro/SS-A or anti-La/SS-B antibodies may be prevalent in about 1% of pregnant women.13 Whether the magnitude of anti-Ro/anti-La antibody titers is a risk factor for the development of fetal heart block remains controversial. Nevertheless, the presence of maternal lupus erythematous or Sjögren syndrome carries an increased risk for fetal heart block of up to 5%.10,14 The probability of having a second child with autoimmune-mediated heart block is even higher and varies from 8% to 18%.10,14,15 As many unexplained fetal deaths in apparently healthy women may be the result of autoimmune CAVB the true incidence of heart block might be underestimated.

Outcome

Series of patients have demonstrated significant morbidity and mortality associated with congenital complete AV block. Most survivors will require permanent pacemaker therapy prior to adulthood.16,17,18 Isolated CAVB detected in utero represents a more severe spectrum of the disease than that encountered postnatally. Most cases with fetal hydrops, poor ventricular function and endocardial fibroelastosis either die in utero or immediately after birth. Accordingly, the risk factors for poor outcome that we identified in a retrospective study at the Hospital for Sick Children in Toronto on 102 cases of isolated CAVB;4 this included fetal diagnosis (fetal series: 24% fetal and 19% neonatal mortality; postnatal series: 6% mortality), fetal hydrops (100% mortality), ventricular endocardial fibroelastosis (100% mortality) and premature delivery at < 32 weeks gestation (66% mortality). Additional risk factors found in other studies included the presence of structural heart disease,7 fetal ventricular rates < 55 bpm11 and a rapid drop in the fetal heart rate.11 Conversely, isolated CAVB with ventricular rates above 80 bpm has a relatively low mortality of 6%.11

Fetal management

The availability of ultrasound technologies for identifying and monitoring fetal arrhythmias has prompted the search for effective therapies. Unfortunately, it is difficult to predict the course of pregnancies complicated by fetal heart block and it becomes even more challenging to determine which fetuses might profit from treatment. Moreover, guidelines for management of the fetus with heart block or at risk of developing heart block have not been established, and the lack of prospective randomized data warrants a careful risk-benefit analysis. The rationale of the various and predominantly pharmacological treatment regimes is to eliminate harmful maternal auto-antibodies, to prevent or to mitigate an inflammatory fetal cardiac insult and to augment the fetal cardiac output. The benefits and problems of the most commonly used therapeutic approaches in CAVB management will be briefly discussed.

Immunosuppressive therapy

Maternal steroid treatment aims to reduce the level of auto-antibodies and to suppress the immune response in the fetus. Prednisone and prednisolone, which possess significant glucocorticoid and mineralocorticoid activity, undergo significant transformation to inactive metabolites when crossing the placenta. By contrast, the fluorinated steroids betamethasone and dexamethasone have mainly glucocorticoid activity with little effect on salt and water handling. Fluorinated compounds are only minimally metabolized by the placenta. It follows that the fetal exposure is reduced to a minimum if prednisone or prednisolone is given for maternal disorders, whereas betamethasone or dexamethasone becomes useful when anti-inflammatory treatment of the fetus is desired. Fluorinated steroid administration for incomplete AV block may offer a chance of reversal, as supported by a small number of fetal cases presenting with 2nd degree AVB. Unfortunately, most fetuses are diagnosed with established complete heart block, which represents an irreversible stage of AV conduction tissue damage, regardless of the chosen therapy. Despite persistence of heart block, resolution of fetal hydrops on
maternal dexamethasone treatment has been noted by different authors. Because concurrent myocarditis may be suspected in these selected cases, in utero treatment of the inflammation with steroids may indirectly improve cardiac contractility, leading to the observed resolution of serous fluid accumulations. Rarely hydrops has also resolved spontaneously, perhaps when the underlying myocarditis and the cardiac function is recovering or when the effusions are due to transient serositis.8

Although maternal tolerance of steroids is in general excellent, a variety of possible adverse effects should be considered. This includes the increased risk of infectious diseases and oligohydramnios, both serious and potentially life-threatening complications, which warrant careful surveillance of the pregnancy course.21

Modulation of the fetal heart rate and function

Fetal cardiac output depends largely on heart rate: it appears that a ventricular rate < 55 bpm in the structurally normal heart is associated with congestive heart failure and death.14-15 Different strategies to improve the fetal heart rate and cardiac output have been attempted more or less successfully. Direct fetal ventricular pacing, undertaken so far in two hydropic fetuses with poor outcome,27-28 is technically possible but challenging (e.g. electrode dislodging): at present, it can not be recommended as a viable treatment modality. Similarly, premature delivery for immediate pacing of the fetus in heart failure has not been a satisfactory approach in our and others’ experiences, as it places the infant at additional risk from the complications of prematurity.42,52 Still, in some delivered hydropic cases there have been good results with early temporary, followed by permanent epicardial pacing.32,33

Maternally administered β-adrenergic agents, such as salbutamol, ritodrine and terbutaline, are used as treatment of 3rd choice of premature labor. As these drugs may raise the fetal cardiac output by an increase in heart rate and myocardial contractility, β-agonists have also been tried in complete heart block (Table I): the ventricular rates may increase by up to 15 bpm, but not uncommonly the fetal heart rate does not respond at all.12,18 In 8 pregnancies with fetal CAVB we reviewed in a multicenter study,28 only 4 cases responded to β-adrenergic stimulation with a sustained increase in fetal heart rate of maximally 8-19 bpm. Unlike others, we did not observe resolution of cavity effusions and a hydropic fetus died after 2 weeks on medication despite a persistent heart rate increase from 38 to 55 bpm. Nevertheless, in our series of isolated CAVB with heart rates < 55 bpm (n=13), there was a significant difference in terms of survival of treated (6/7 cases) versus untreated (1/6 cases; p<0.05) fetuses, which may suggest an additional favorable inotropic effect of the β-agonists. Again, the use of β-adrenergic agents should be balanced against the risks of potentially severe adverse maternal effects, such as pulmonary edema, myocardial ischemia, arrhythmia and rarely death.

Occasionally, hydropic fetuses have been successfully treated with transcplacental or directly given digoxin and furosemide, without or in combination with dexamethasone or ritodrine.44-45 However, transcplacental digoxin transport is poor in the setting of hydrops, and direct administration of digoxin to the fetus is inevitably associated with the risk of infection and preterm labour. This explains the marginal role of digoxin in the management of fetal heart block.

Current approach

Theoretically all mothers at risk for delivering a child with autoimmune-mediated heart block may be considered for preventive treatment. However, considering the low fetal risk of CAVB (0.5%-1% for asymptomatic anti-Ro positive mothers; 8%-18% after an affected sibling) it becomes difficult to justify such an unrestricted approach to predominantly unaffected fetuses. Accordingly, the experience with prophylaxis is mainly anecdotal and a benefit has not been shown. Preventive therapy has been undertaken in a small number of pregnancies by maternal plasma exchange, as well as maternal immunoglobulin, steroid, or azathioprine administration beginning prior to 16 weeks of gestation.23,40,41 Treatment aims primarily at reducing maternal autoantibody titers, but may result in a state of severe antibody depletion which renders both the mother and her offspring at an increased risk of infectious diseases.

We prefer the following strategy: fetuses with a known risk of CAVB undergo weekly complete echocardiographic studies beginning at 17 to 18 weeks of gestation. The examination includes assessment of the AV conduction time and myocardial function. If there is no cardiac abnormality until 24 gestational weeks, the fetus is re-studied once or twice prior to delivery. If there is suspicion of AV conduction delay and/or beginning cardiacis, maternal dexamethasone is immediately initiated (4-9mg/day) and the patient monitored serially throughout gestation and at least the first 6 months after birth.

Where a diagnosis of isolated complete AVB has been made, the atrial and ventricular rates, ventricular function, cardiothoracic ratio and Doppler indices are recorded. The fetus is then re-studied at weekly-biweekly intervals depending on the progress. Until recently, we would have initiated pre-emptive dexamethasone therapy if the fetus in heart block showed early signs of cardiac dysfunction, suspicious of myocardial inflammation.45 However, our most recent data on autoimmune CAVB indicates less morbidity and an improved fetal and neonatal survival (15/17, 89%), when dexamethasone (4-9 mg/d) is initiated for the rest of the pregnancy prior to any deterioration, preferably with a β-sympathomimetic if the heart rate declines below 55 bpm. When there is
oligohydramnios, maternal dexamethasone is tapered off, while persistence of reduced amniotic fluid may prompt an earlier delivery.

Perinatal and postnatal management. Fetal diagnosis of CAVB allows redirecting confinement to tertiary centers with expertise in neonatal critical care, influencing time and mode of delivery, and initiating appropriate perinatal treatment wherever indicated. Premature delivery by cesarean section followed by an aggressive postnatal management is initiated when fetal loss is imminent. In a hemodynamically stable situation, we favor a C-section delivery at about 36 to 37 gestational weeks, as there are no good means of continuously monitoring the fetal vital parameters during labor. On the other hand, vaginal delivery is considered safe if the fetal well-being is surveyed by ultrasound and repeated scalp blood samplings. On delivery, most neonates will require immediate medical care, consisting primarily of respiratory and cardiac support, including the use of isoproterenol and/or pacing to increase the heart rate. Steroids to suppress cardiac and extra-cardiac NLE abnormalities may be essential, especially during the first months of life. In our experience, most prenatally diagnosed cases will undergo permanent epicardial pacemaker implantation in early infancy, mainly because of congestive heart failure and/or mean ventricular rates of <55 bpm. Pacing may reduce mortality; however, it is not without significant morbidity which includes pacemaker malfunctions and the need for repeat interventions for generator, lead and battery replacements already during childhood.

Summary

Prenatally diagnosed complete atrio-ventricular (AV) block is associated with a high mortality, particularly in combination with structural heart disease, hydrops, myocarditis, cardiomyopathy, ventricular rates < 55 beats/minute, and premature delivery. In isolated heart block, mainly associated with maternal anti-RO/anti-La antibodies, transcatheter administration of steroids aims to prevent or temper the immune-mediated inflammation and destruction of the fetal AV conduction system and myocardial tissue. Sympathomimetics are useful at low ventricular rates and reduced myocardial function. Sequential Doppler recording of the fetal AV conduction time during mid-gestation may help in the surveillance of the fetus at risk of developing heart block and allow the initiation of a targeted immunosuppressive treatment prior to irreversible damage.

<table>
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<tr>
<th>Authors</th>
<th>GA at T</th>
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*GA = GA at time of treatment.

Table 1. Efficacy of In Utero Treatment of Complete AV block with B-Sympathomimetics.

180 Frontiers in Fetal Health
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34. Harris JP, Alexson CG, Manning JA, Thompson HO. Medical therapy for the hydropic fetus.

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