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Fetal total atrioventricular block in transgender man with systemic lupus erythematosus – literature review and establishment of a protocol with management and treatment with terbutaline

Totální fetální atrioventrikulární blokáda u transgender muže se systémovým lupus erythematodes – přehled literatury a stanovení léčebného protokolu při léčbě terbutalinem

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Summary: This case report describes a case of total atrioventricular block (TAVB) with positive anti-Ro/SSA antibodies ina transgender man who began follow-up at 31 weeks and 3 days of gestation. Despite many disagreements regarding treatment, corticosteroids were recommended for this patient. The fetal ventricular rate at the second weekly visit was 50 bpm and terbulin was started to increase heart rate. Hospitalization and intravenous terbutaline for 3 days was chosen to better control maternal symptoms and monitor fetal vital signs, as well as daily monitoring of the ventricular rate. There was an increase in baseline ventricular rate of approximately 15%. After discharge from the hospital, weekly control fetal echocardiography was performed in addition to the indices proposed by Huhta for echocardiographic assessment of fetal cardiac function. Fetal ventricular rate in ambulatory controls did not fall below 55 bpm. Cesarean section was indicated at 35 weeks and 4 days of gestation due to premature rupture of ovular membranes. A male newborn was delivered weighing 2,250 grams with Apgar scores of 8 and 9 at the 1st and 5th minute, respectively. After 88 days of life, the infant was weighing 4,580 grams and a definitive bicameral epicardial pacemaker was implanted without complications. Even if there is a transient increase in fetal ventricular rate with the use of terbutaline, a pacemaker is indicated. Delivery should be at term to allow the fetus to achieve adequate weight and pulmonary maturity for definitive pacemaker implantation.

Key words: fetal atrioventricular block – maternal systemic lupus erythematosus – corticosteroids – β-sympathomimetics – management

Souhrn: Tato kazuistika popisuje případ totální atrioventrikulární blokády (TAVB) s pozitivními anti-Ro/SSA protilátkami u transgender muže, který byl sledován ve 31. týdnu a 3. dni gestace. Navzdory mnoha neshodám ohledně tohoto pacienta byly doporučeny kortikosteroidy. Komorová frekvence plodu při druhé týdenní návštěvě byla 50 tepů/min a ke zvýšení srdeční frekvence bylo zahájeno podávání terbulinu. Pro lepší kontrolu mateřských symptomů a sledování vitálních funkcí plodu bylo přikročeno k hospitalizaci a nitrožilnímu podání terbutalinu po dobu 3 dnů a rovněž ke každodennímu monitorování komorové frekvence. Došlo ke zvýšení výchozí komorové frekvence přibližně o 15 %. Po propuštění z nemocnice byla navíc k indexům navrženým Huhtou pro echokardiografické hodnocení srdeční funkce plodu prováděna týdenní kontrolní echokardiografie plodu. Fetální komorová frekvence u ambulantních kontrol neklesla na < 55 tepů/min. Císařský řez byl indikován ve 35. týdnu a 4. dni gestace z důvodu předčasné ruptury ovulárních membrán. Byl porozen novorozenec mužského pohlaví o hmotnosti 2 250 g s Apgar skóre 8 v 1. minutě a 9 v 5. minutě. Po 88 dnech života kojenec vážil 4 580 g a bez komplikací mu byl implantován trvalý dvoukomorový epikardiální kardiostimulátor. Kardiostimulátor je indikován i v případě, že při použití terbutalinu dojde k přechodnému zvýšení komorové frekvence plodu. Porod by měl proběhnout v termínu, aby plod mohl dosáhnout adekvátní hmotnosti a plicní zralosti pro implantaci trvalého kardiostimulátoru.

Klíčová slova: fetální atrioventrikulární blok – mateřský systémový lupus erythematodes – kortikosteroidy – β-sympatomimetika – léčba

Introduction

Total atrioventricular block (TAVB) is caused by an electrical disturbance leading to electromechanical dissociation, with interruption of electrical impulses from the atria to the ventricles. Fetal congenital TAVB is an autoimmune disease, acquired passively by the transplacental passage of anti-Ro/SSA antibodies into susceptible fetuses. This type of block occurs more commonly in structurally normal hearts [1], with an incidence of 2% to 6% in pregnant women with systemic lupus erythematosus, and can have different outcomes, depending on how these pregnancies are monitored and managed [2,3]. It is known that around 50% of pregnant women with anti-Ro (SSA) have no symptoms at the time of delivery or at the time of diagnosis [1].

Studies are controversial regarding the use of corticosteroids and β-sympathomimetics in cases of fetal congenital TAVB [4]. With this case report, we sought to carry out a literature review and apply a protocol to help guide treatment in a satisfactory manner, as well as measures for monitoring pregnancy using the cardiovascular profile (Huhta score) and assessment of ventricular function by shortening the fraction (ΔD%).

Case report

A 24-year-old transexual male in a stable relationship with a cisgender female. Onset of symptoms with polyarthritis of small and large joints at age 11. Erythema on the face (malar rash) and upper limbs/neck, which worsened by exposure to sunlight. He was diagnosed with systemic lupus erythematosus at the age of 12. He had positive anti-Ro/SSA and anti-La/SSB tests and used prednisone from age 12 to 20. Started hydroxychloroquine at the age of 20 and he is still taking it. Took over-the-counter hormone therapy for 1 year and stopped 5 years ago. During prenatal care, gestational age at 20 weeks and 1 day, the 2nd trimester scan showed fetal arrhythmia compatible with extrasystole. At 26 weeks and 4 days, fetal echocardiogram was compatible with congenital TAVB. At 31 weeks and 3 days, he was referred to our service and the fetal echocardiogram showed: persistence of the left superior vena cava and TAVB with a ventricular rate of 50 bpm and a Huhta score of 10/10. Following our protocol established after reviewing the literature, the patient was admitted to the hospital and received intravenous terbutaline using a continuous infusion pump at a dose of 2.5 mcg/min with a gradual increase to a maximum dose of 5 mcg/min on the 3rd day of infusion. On the 2nd day of infusion, the patient complained of precordial pain, which was discontinued pending evaluation and resumed after troponin dosage and electrocardiogram showed no evidence of ischemia. On the 3rd day, with the maximum dose initiated, the fetal ventricular rate reached 66 bpm, and according to our protocol, the infusion was stopped and fetal heart rate was monitored at 24 hours. He was discharged from the hospital with a ventricular rate of 56 bpm and a Huhta score of 10/10. Based on the advice of the rheumatology team, prednisone 15 mg/d was started after hospital discharge.

One day after discharge from the hospital, he returned to the outpatient clinic with a fetal ventricular rate of 55 bpm, ΔD33%, and a Huhta score of 10/10. Patient was scheduled for weekly monitoring, with cardiovascular risk assessed by the Huhta score, ventricular function assessed by ΔD%, and fetal weight estimated to be as close to 2,800 grams at delivery. In subsequent weeks, fetal ventricular rate reached 51 bpm, with ΔD% within normal limits, but the Huhta score dropped to 9/10 (loss of 1 point due to an inverted A wave in the ductus venosus on Doppler) and in the last week before the delivery date to 7/10 (umbilical artery with positive diastole, umbilical vein with pulsation, and ductus venosus on Doppler with an inverted A wave) with an estimated fetal weight of 2,128 grams (Fig. 1).

At 35 weeks and 4 days of gestation, he was admitted to obstetric emergency because of vaginal loss of a large amount of clear fluid, which progressed to moderate intensity contractions and blood pressure of 140 × 100 mmHg, with no other symptoms. Cesarean section was scheduled due to premature rupture of ovular membranes and fetal TAVB, which made it impossible to monitor fetal well-being during labor.

A male newborn was delivered weighing 2,250 g, with Apgar scores of 8 and 9 at the 1st and 5th minute, respectively. Postnatal electrocardiogram confirmed the diagnosis of congenital TAVB with a fetal ventricular rate of 56 bpm showing a fossa ovalis-type atrial septal defect measuring 3 mm, and mild dilation of the right and left ventricles with preserved systolic function. Newborn progressed with the need for supplemental inhaled O_2 due to the drop in saturation, and it was decided to start intravenous dobutamine 5 mcg/kg/hours, which he received for about 24 hours. After evaluation by cardiac surgery and clinical cardiology, definitive pacemaker placement was indicated and it was decided to wait until the newborn was an active 3,000 grams if there were signs of heart failure or 4,000 grams if it was asymptomatic. Newborn progressed with hemodynamic stability, with a ventricular rate between 45 and 52 bpm. At 40 days of life, newborn developed a significant systolic murmur, progressive dyspnea, and signs of discomfort. A new echocardiogram showed moderate valvular stenosis, thickened pulmonary valve, mild right ventricular hypertrophy, and minimal tricuspid and mitral regurgitation. Percutaneous pulmonary valvuloplasty was performed with significant improvement (Fig. 2).

Definitive pacemaker implantation was performed at 88 days of age when the infant weighed 4,580 grams. The procedure was performed under general anesthesia with a median sternotomy

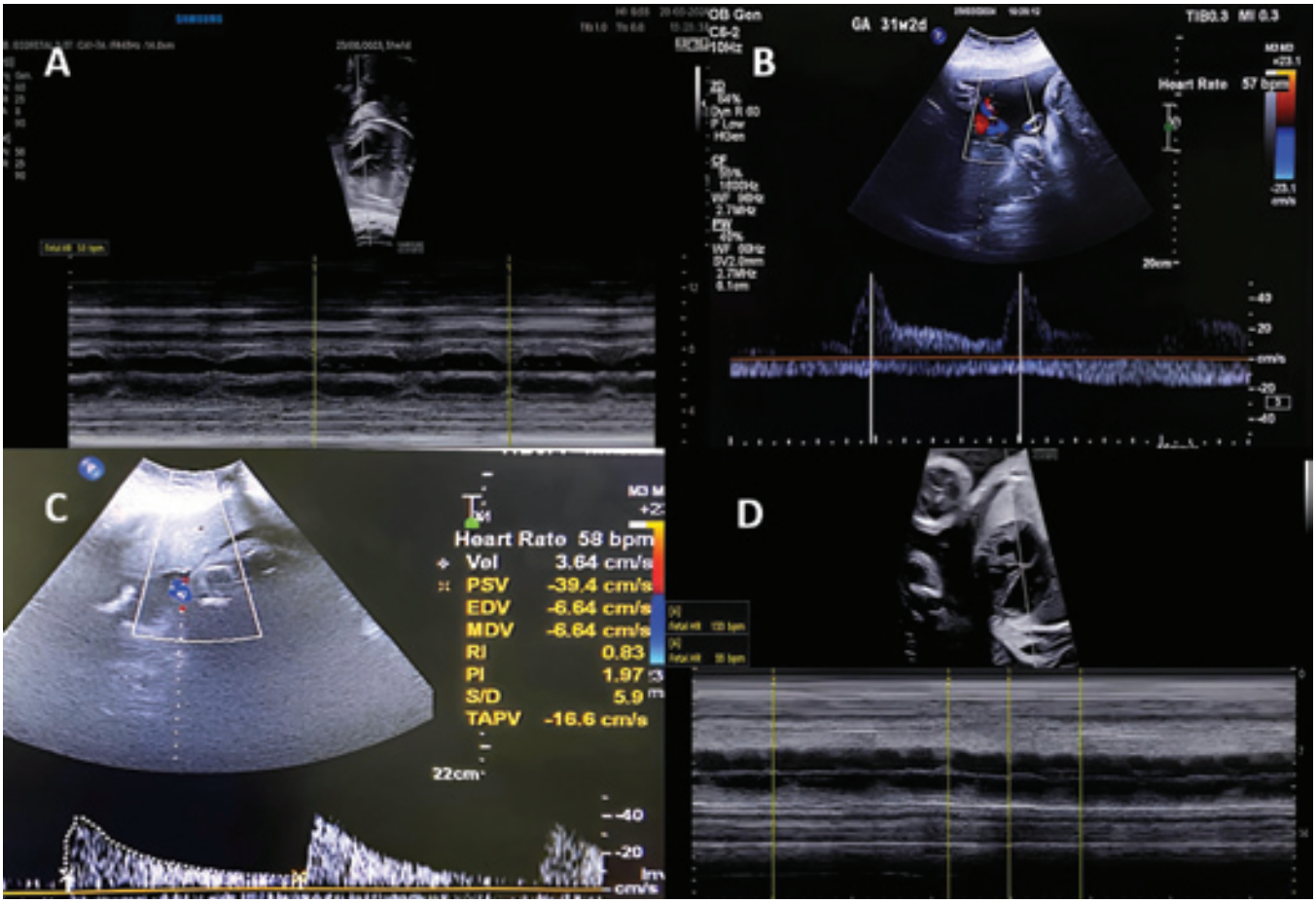

Fig. 1. Fetal heart rate assessment using spectral Doppler of umbilical artery and M-mode showing right atrial and left ventricular contraction. A) M-mode of ventricular contraction with heart rate of 50 bpm obtained at the first echocardiography. B) Spectral Doppler of the umbilical artery with a heart rate of 57 bpm on the first day of hospitalization with terbutaline. C) Spectral Doppler of the umbilical artery with heart rate of 58 bpm on the 2nd day of hospitalization receiving terbutaline. D) M-mode of atrial and ventricular contraction with atrial rate of 133 bpm and ventricular rate of 55 bpm obtained 1 week after discharge from the outpatient clinic.

Obr. 1. Hodnocení fetální srdeční frekvence pomocí spektrálního Dopplera umbilikální arterie a M-módu zobrazující kontrakci pravé síně a levé komory. A) M-mód komorové kontrakce se srdeční frekvencí 50 tepů/min získaný při první echokardiografii. B) Spektrální doppler a. umbilikical s tepovou frekvencí 57 tepů/min v první den hospitalizace s terbutalinem. C) Spektrální dopplerismus pupeční tepny se srdeční frekvencí 58 tepů/min 2. den hospitalizace při podávání terbutalinu. D) M-mód síňové a komorové kontrakce se síňovou frekvencí 133 tepů/min a komorovou frekvencí 55 tepů/min získaný 1 týden po propuštění z ambulance.

and pericardial incision for pacemaker implantation. The postoperative heart rate was 100 bpm (pacemaker programming) (Fig. 3). The infant was discharged at 103 days of age, weighing 4,645 grams and in good general condition.

Discussion

Atrioventricular blocks (AVB) are electrical conduction disturbances that occur between atrial depolarization and ventricular depolarization. Bradycardia and electromechanical dissociation cause the fetal heart to accommodate a larger systolic volume to maintain adequate cardiac output. AVB can be classified as 1st degree – cardiac impulse is conducted from the atrium to the ventricle with a prolongation of the atrioventricular conduction time, characterized by a PR interval > 150 ms, 2nd degree or incomplete – progressive increase in the PR interval until no atrial electrical impulse is conducted to the ventricle, and 3rd degree or complete (TAVB) – interruption of electrical impulses from the atria to the ventricles due to an anatomical or functional defect in the conduction system, with uncoordinated contraction between the atria and the ventricles [5,6]. The incidence of AVB is 1 in 15,000–20,000 live births, with 50% to 55% is associated with structural congenital heart disease, 60% of which is associated with left atrial isomerism, and 40% is associated with

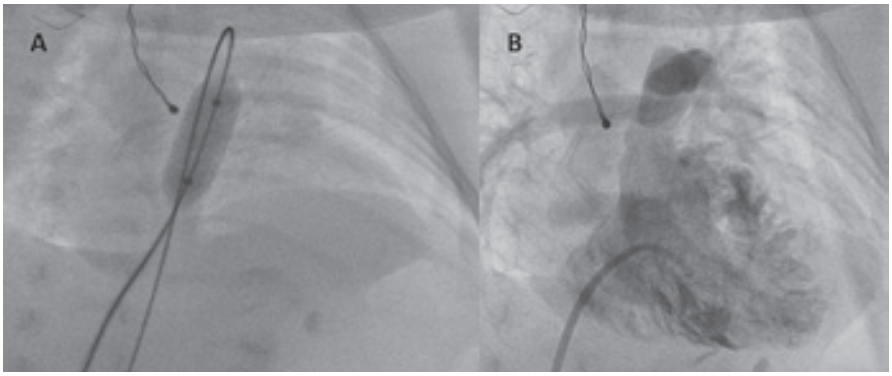

Fig. 2. Angiography of the right heart. A) Balloon catheter dilatation of the pulmonary valve. B) Right ventriculography in the elongated anterior oblique view, showing adequate flow through the pulmonary valve.
Obr. 2. Angiografie pravé strany srdce. A) Balónková dilatace pulmonální chlopně. B) Pravá ventrikulografie v prodlouženém předním šikmém pohledu ukazující adekvátní průtok plicní chlopní.

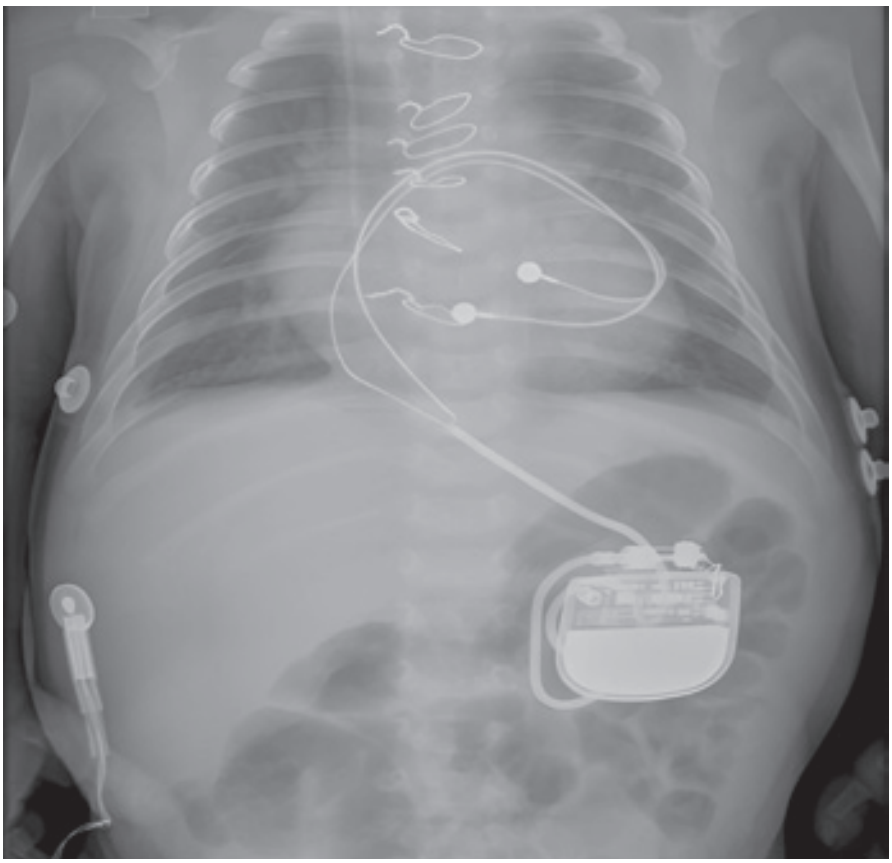

Fig. 3. Radiograph of thorax/abdomen in antero-posterior incidence showing an epimyocardial atrioventricular pacemaker implant. Pacemaker is located in the left hypochondrium.
Obr. 3. Rentgenový snímek hrudníku/břicha v anteroposteriorní incidenci ukazující epimyokardiální atrioventrikulární kardiostimulátor. Kardiostimulátor se nachází v levém hypochondriu.

positive maternal SSA/Ro or SSB/La antibodies [1,6]. A pregnant woman with systemic lupus erythematosus and anti-Ro/SSA antibodies can have congenital AVB in 2% to 6%, with a recurrence rate in subsequent pregnancies of 18% and a mortality rate of approximately 30% [2].

Although the pathophysiology of immune-mediated AVB is not fully understood, in susceptible fetuses, autoantibodies bind to ribonucleotide proteins (antibodies) expressed in cardiomyocytes of the fetal myocardium, specifically 52 kD Ro/SSA (Ro52), 60 kD Ro/SSA (Ro60), and 48 kD La/SSB (La48). These antibodies enter the fetal circulation in the middle of the 2nd trimester and trigger an immunological process leading to inflammation of the fetal conduction tissues and myocardium, with progressive and irreversible fibrosis being the most likely explanation [1]. Immune-mediated congenital AVB usually presents with a fetal heart without associated structural heart defects, but functional abnormalities may coexist, including cardiomegaly, ventricular hypertrophy, impaired ventricular function, and atrioventricular valve regurgitation, which may contribute to pericardial effusion, and in severe cases, fetal heart failure and hydrops fetalis [1]. In addition, one study described the presence of ventricular fibroelastosis [2].

Because of the unique aspects of the intrauterine environment, fetal heart failure has peculiar characteristics. Some situations may improve spontaneously or respond to treatment in utero or after delivery; others respond poorly or are refractory to therapy and may progress to heart failure with hydrops, multiple organ failure, and fetal death [7]. Indices for echocardiographic assessment of fetal cardiac function is a proposed system for grading and monitoring the severity of fetal heart failure using five echocardiographic parameters:

1. fetal effusions/hydrops;
2. venous Doppler;
3. cardiac size;
4. cardiac function;
5. arterial Doppler.

Assessment and quantification of heart failure are fundamental steps in

counseling and decision making for these at-risk pregnancies, both intrauterine and neonatal [7]. There are various parameters used to assess cardiac function, some of which are easily reproducible and some of which are not, depending on the pathology. One of the parameters used in our case report that is easy to apply was the shortening fraction (ΔD%) with normal values > 28% and cardiovascular profile (Hutha score):
1. 8–9 = mild;
2. 6–7 = moderate;
3. ≤ 5 = severe heart failure.
Scores < 7 require intervention [8].

Various treatments have been tried for fetal congenital AVB, but no consistent studies have been achieved. Ciardulli et al. [9] proposed a review to evaluate maternal corticosteroid therapy in preventing progression of immune-mediated 2nd degree congenital AVB. Progression from 2nd degree to continuous or intermittent 3rd degree congenital AVB occurred in 52% of treated fetuses and in 73% of untreated fetuses. The results had limited evidence on the role of corticosteroids in the natural history and it was suggested that this treatment improves myocardial performance and prevents progression to TAVB. The opinion of the authors was that once 2nd degree immune-mediated AVB is diagnosed, the use of corticosteroids should not be discouraged. The aim is to interfere with the inflammatory process in the fetal conducting tissues and to accelerate lung maturation if there is a risk of preterm birth [9]. In cases with positive anti-Ro/SSA and/or anti-La/SSB antibodies and without an installed congenital AVB, it is recommended to monitor the PR interval weekly, especially between 18 and 26 weeks of gestation. If PR interval is < 150 ms, monitor this interval every 4 weeks until delivery. If PR interval is > 150 ms or its progressive increase, consider using dexamethasone and monitor the interval every 2 weeks [10].

Carrilho et al. [5] demonstrated that there is evidence against the use of corticosteroids in cases of established congenital AVB due to adverse effects on the pregnant woman and the presence of irreversible fibrosis in cardiac conduction tissues of the fetus. A multicenter study in 175 patients demonstrated that in fetuses with ventricular rate < 50 bpm or in the presence of hydrops and/or cardiomegaly, there was no benefit to the use of corticosteroids [11]. Yoshida et al. [12] concluded that maternal treatment with corticosteroids in early pregnancy has been used, but it does not appear to be effective in fetuses with established congenital AVB.

Cases of congenital AVB with fetal ventricular rate > 55 bpm have a good prognosis. Fetal ventricular rate < 55 bpm is associated with cardiac decompensation and low cardiac output. Fetuses with ventricular rate < 50 bpm may develop signs of heart failure and hydrops. Immature fetuses with very early hydrops and ventricular rate < 50 bpm have a poorer prognosis and the only possible intervention is premature delivery and implantation of a temporary pacemaker. The use of salbutamol, terbutaline, or isoprenaline is indicated when the ventricular rate is < 55 bpm and/or in the presence of fetal heart failure and hydrops. These drugs are usually well tolerated, but extrasystoles and maternal sinus tachycardia may occur. There is an increase in fetal heart rate of approximately 10–15% of the baseline rate, and although small, may prolong pregnancy to term or near term. There are no studies showing that the use of these medications can alter the survival of these fetuses. Follow-up and management of these cases is not well established. The indication for timing of delivery should be assessed according to the degree of manifestations [10,12].

Studies also differ regarding sympathomimetic treatment. In one study, oral terbutaline was chosen as the β-sympathomimetic drug because of its good transplacental passage [4]. In another study, terbutaline, which stimulates adrenergic receptors in the heart, increased heart rate, but this increase was transient and not very effective in reducing mortality [13]. Yoshida et al. [12] showed a case of β-sympathomimetic administration in successfully treated isolated congenital AVB. They started intravenous terbutaline in the hope of increasing the fetal heart rate and improving cardiac function, and this drug proved to be effective in preventing heart failure, especially in those fetuses not affected by hydrops or structural heart disease. The only contraindication to β-sympathomimetic therapy with high doses of salbutamol is placental insufficiency [14].

So 46 of the 57 cases of isolated congenital AVT (32 with positive and 14 with negative Ro/SSA and La/SSB antibodies) had no treatment with dexamethasone or β-sympathomimetics. The 32 untreated seropositive fetuses had survival rates of 93% and 90% at 1 year. In 5 fetuses, β-sympathomimetics were started without steroids and then continued intravenously or orally because of ventricular rate of 55 bpm and hydrops, with no survivors. One fetus in 5 received oral terbutaline (2.5 to 5.0 mg over 4 hours). These treatments caused a transient increase in fetal ventricular rate (5 to 20 bpm), with a return to baseline after a short period of time despite the medication (1 to 5 days). Untreated patients did not have such an unfavorable outcome, with live birth and 1-year survival rates similar to those in the treated group. The better outcome is explained by the improvement in intensive care facilities and not by the introduction of dexamethasone into the treatment [15].

Follow-up protocols for isolated congenital AVB show that fetal ventricular rate > 55 bpm with normal cardiac function start with dexamethasone alone. The use of dexamethasone therapy is based on the assumption that the cause is inflammatory carditis. If ventricular rate is < 55 bpm, β-sympathomimetics

are added to dexamethasone. Follow-up is weekly or bi-weekly. Delivery should be scheduled at a tertiary center and caesarean section or vaginal delivery is indicated up to 37 weeks of gestation if the course is satisfactory. In the event of progression of fetal hydrops, cesarean section and pacemaker placement is indicated immediately after delivery [16].

Some authors recommend the use of intravenous immunoglobulin in cases where the fetus has systolic cardiac dysfunction and/or signs of endocardial fibroelastosis and/or myocarditis, but its efficacy has not been proven. Other authors recommend immunoglobulin at a dose of 1 g/kg, Max. 70 gram dose, every 3–4 weeks in the presence of endocardial fibroelastosis or incomplete AVB [6]. Hydroxychloroquine is not a reversal agent for antibody-mediated atrioventricular block; however, it may reduce the recurrence rate in future pregnancies by > 50 % [6].

In those hydropic and immature fetuses with a very low ventricular rate, intrauterine pacemaker implantation can be considered, which still has technical limitations and is still under experimental study [10].

Conclusion

Treatment with intravenous terbutaline with the pregnant woman hospitalized and fetal ventricular rate is < 50 bpm offers greater safety in terms of controlling any side effects and better control of the heart rate and vitality of the fetus. Furthermore, even if it is transient, the increase in heart rate for the fetus is very important, with a gain of sometimes another week of gestation and consequently an increase in fetal weight, and finally definitive implantation of the pacemaker is not recommended in very low birth weight premature newborns.

References

1. Hunter LE, Simpson JM. Atrioventricular block during fetal life. J Saudi Heart Assoc 2015; 27(3): 164–178. doi: 10.1016/j.jsha.2014.07.001.

2. Batra AS, Silka MJ, Borquez A et al. Pharmacological management of cardiac arrhythmias in the fetal and neonatal periods: a scientific statement from the American Heart Association: endorsed by the Pediatric & Congenital Electrophysiology Society (PACES). Circulation 2024; 149(10): e937–e952. doi: 10.1161/CIR.0000000000001206.

3. Brucato A, Cimaz R, Caporali R et al. Pregnancy outcomes in patients with autoimmune diseases and anti-Ro/SSA antibodies. Clin Rev Allergy Immunol 2011; 40(1): 27–41. doi: 10.1007/s12016-009-8190-6.

4. Cuneo BF, Lee M, Roberson D et al. A management strategy for fetal immune-mediated atrioventricular block. J Matern Fetal Neonatal Med 2010; 23(12): 1400–1405. doi: 10.3109/14767051003728237.

5. Carrilho MC, Bravo-Valenzuela NJ, Araujo Júnior E. Congenital complete atrioventricular heart block in a pregnant woman with Sjögren syndrome: prenatal care follow-up and the challenge of intrauterine treatment. Rev Bras Ginecol Obstet 2020; 42(4): 228–232. doi: 10.1055/s-0040-1709738.

6. Kashou AH, Goyal A, Nguyen T et al. Atrioventricular block. Treasure Island (FL): StatPearls Publishing 2024.

7. Huhta JC. Fetal congestive heart failure. Semin Fetal Neonatal Med 2005; 10(6): 542–552. doi: 10.1016/j.siny.2005.08.005.

8. Azeka E, Jatene MB, Jatene IB et al. I Guidelines of heart failure and heart transplantation in the fetus, in children and adults with congenital cardiopathy, the Brazilian Society of Cardiology. Arq Bras Cardiol 2014; 103(6 Suppl 2): 1–126. doi: 10.5935/abc.2014S005.

9. Ciardulli A, D'Antonio F, Magro-Malosso ER et al. Maternal steroid therapy for fetuses with immune-mediated complete atrioventricular block: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2019; 32(11): 1884–1892. doi: 10.1080/14767058.2017.1419182.

10. Pedra SR, Zielinsky P, Binotto CN et al. Brazilian Fetal Cardiology Guidelines – 2019. Arq Bras Cardiol 2019; 112(5): 600–648. doi: 10.5935/abc.20190075.

11. Eliasson H, Sonesson SE, Sharland G et al. Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. Circulation 2011; 124(18): 1919–1926. doi: 10.1161/CIRCULATIONAHA.111.041970.

12. Yoshida H, Iwamoto M, Sakakibara H et al. Treatment of fetal congenital complete heart block with maternal administration of beta-sympathomimetics (terbutaline): a case report. Gynecol Obstet Invest 2001; 52(2): 142–144. doi: 10.1159/000052960.

13. Zimmer LP, Silva AP, Andrade A et al. Intrauterine and perinatal management of complete atrioventricular block in the fetus. Arq Bras Cardiol 1996; 67(1): 11–15.

14. Groves AM, Allan LD, Rosenthal E. Therapeutic trial of sympathomimetics in three cases of complete heart block in the fetus. Circulation 1995; 92(12): 3394–3396. doi: 10.1161/01.cir.92.12.3394.

15. Lopes LM, Tavares GM, Damiano AP et al. Perinatal outcome of fetal atrioventricular block: one-hundred-sixteen cases from a single institution. Circulation 2008; 118(12): 1268–1275. doi: 10.1161/CIRCULATIONAHA.107.735118.

16. Jaeggi ET, Fouron JC, Silverman ED et al. Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. Circulation 2004; 110(12): 1542–1548. doi: 10.1161/01.CIR.0000142046.58632.3A.

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