MINIREVIEW

Fetal Cardiology in the Czech Republic: Current Management of Prenatally Diagnosed Congenital Heart Diseases and Arrhythmias

V. TOMEK[1], J. MAREK[1], H. JIČÍNSKÁ[2], J. ŠKOVRÁNEK[1]

[1]Center for Cardiovascular Research and Kardiocentrum, University Hospital Motol, Prague, [2]Department of Pediatric Cardiology, University Hospital Brno, Czech Republic

Summary

Reliable diagnosis of congenital heart defects and arrhythmias *in utero* has been possible since the introduction of fetal echocardiography. The nation-wide prenatal ultrasound screening program in the Czech Republic enabled detection of cardiac abnormities in 1/3 of patients born with any congenital heart disease and up to 83 % of those with critical forms. Prenatal frequency of individual heart anomalies significantly differed from the postnatal frequency. Fetal isolated complete atrioventricular block and supraventricular tachycardia may lead to heart failure and are important causes of fetal mortality. The regression of heart failure was achieved by a conversion to the sinus rhythm in the supraventricular tachycardia and by increase of ventricular rate in the complete atrioventricular block.

Corresponding author

V. Tomek, Kardiocentrum and Cardiovascular Research Centre, University Hospital Motol, V úvalu 84, 150 08 Prague 5, Czech Republic. Fax: +420 22443 2915. E-mail: viktor.tomek@fnmotol.cz

Introduction

Antenatal detection of congenital heart diseases by cross-sectional echocardiography has been possible for almost 20 years and has provided a new information on the early evolution of cardiac malformations. Since 1980, the centralized healthcare system in the Czech Republic enabled the creation of a comprehensive registry of all the pediatric patients born with congenital heart disease in the territory. In 1986, a nation-wide echocardiographic prenatal screening has been established (Šamánek *et al.* 1986). The screening is performed between 18 to 21 weeks of gestation (government guaranteed second level prenatal ultrasound scan program) by a local obstetrician/gynecologist in every pregnant woman resident in the Czech Republic. A routine ultrasound scan is based on two-dimensional imaging to obtain a good quality four-chamber view and to visualize the crossing of the great arteries as well as to assess the heart rhythm and frequency.

The normal cardiac rhythm in fetuses is characterized by a regular heart rate ranging between 100 and 180 beats per min., depending on gestational age and degree of fetal activity, with a normal 1:1 atrioventricular conduction at each cardiac cycle. Based on that definition, fetal heart arrhythmias are defined as any irregularity in the heart rate or abnormally slow or fast heart rate. Fetal arrhythmias have been diagnosed in at least 2 % of pregnancies during screening ultrasound examination, but only less than 10 % of all cases are of a clinical relevance. Major clinically relevant fetal arrhythmias detected were supraventricular tachycardias (SVT), atrial flutter and complete atrioventricular block (CAVB). All of them should be referred to a specialized prenatal centre.

Congenital Heart Diseases (CHD)

Pregnancies suspected as having congenital heart disease are referred to the centre for final evaluation performed exclusively by an experienced prenatal (pediatric) cardiologist. Echocardiographic examination is completed by subsequent specialized gynecologic ultrasound investigation either to exclude or to specify extracardiac abnormality. A genetic examination including karyotyping is offered and a complete counseling is carried out. All fetuses born alive with significant CHD are delivered at an obstetric clinic adjacent to the pediatric cardiologic centre and are admitted to its intensive care unit immediately after the delivery. Prenatal diagnosis is confirmed within the first hour of life and necessary therapeutic measures are carried out without delay. In case of termination prior to 24th week of gestation, prenatal death, or an early postnatal death, the post mortem examination is performed by a feto-pathologist experienced in cardiovascular system (Šamánek *et al.* 1985, 1986).

To assess the effectiveness and impact of fetal cardiac screening for each CHD, the number of antenatally diagnosed fetuses was compared to a hypothetical number estimated using the prevalence of the CHD in the Czech Republic between 1986 and 2007. The postnatal prevalence of individual heart lesions was calculated using the data of the nation-wide survey (Šamánek *et al.* 1999). Antenatal diagnosis was confirmed or modified by a post-mortem study in all the fetuses undergoing an early termination and in those who died *"in utero"* or postnatally whether treated or not. All live-born children with an abnormal antenatal scan were examined by experienced neonatologists and pediatric cardiologists.

Results

Prenatal echocardiographic examinations were performed in 10 027 fetuses between 13 to 41 weeks of gestation (median 23 weeks). In the entire cohort, a congenital heart disease was found in 1830 (18.3 %) fetuses (545 had additional extra cardiac anomalies).

Between 1986 and 2007, 2 380 909 children were live-born in the Czech Republic. Of these, 14 666 children have been estimated to be born with a congenital heart disease (6.16/1 000 livebirths). In total, 1 999 subjects estimated to be born with an atrial septal defect (prevalence 0.53/1 000 livebirths) and patent arterial duct (prevalence 0.31/1 000 livebirths) were excluded from the study protocol as the communications are physiological at this
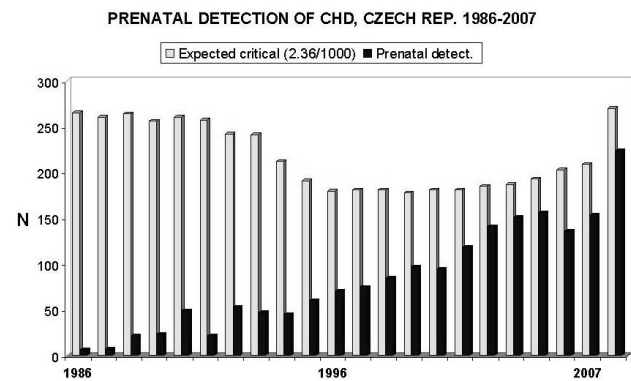
PRENATAL DETECTION OF CHD, CZECH REP. 1986-2007

Fig. 1. Prenatal detection of congenital heart diseases compared to the calculated numbers of children expected to be born with critical forms of cardiac abnormalities.

fetal stage. Out of the remaining 12 667 children assumed to be born with CHD, 4 779 children were expected to be born with a "critical" form of CHD (35.1 % of all CHD, 2.3/1 000 livebirths).

Between 1986 and 2007, 1 830 fetal CHD have been diagnosed prenatally in Czech Republic, giving the overall prenatal detection rate of 14.1 %. Detection rate increased from 0.6 % in 1986 to 30.7 % in 2007. Detection rate of critical heart diseases in the whole period was 38.3 %, and increased from 2.3 % in 1986 to 83 % in 2007 (Fig. 1).

Most frequent prenatally detected lesions were atrioventricular septal defect occurring in 15.2 %, hypoplastic left heart syndrome in 15 %, ventricular septal defect in 9.1 % and double outlet right ventricle in 8.7 % fetuses.

Prenatal detection rate of individual heart lesions was compared to their estimated postnatal frequencies calculated from our epidemiological data (Šamánek *et al.* 1989). Prenatal detection rate was high in the double outlet right ventricle (77.3 %), hypoplastic left heart (50.6 %), Ebstein anomaly (50 %), atrioventricular septal defect (42.9 %) and a single ventricle (42.5 %). Prenatal detection rate was low in pulmonary stenosis (3.2 %), in ventricular (2.4 %) and atrial (0.8 %) septal defects. We have found only one case of an isolated total anomalous pulmonary venous drainage.

Prenatal frequency of individual heart anomalies significantly differed from the postnatal one. Postnatally, the most frequent cardiac lesion, ventricular septal defect (41.6 % of all CHD), was detected in only 9.1 % of all prenatally examined heart lesions, aortic stenosis (postnatal frequency 7.8 %) was prenatally diagnosed in 4.9 %. The proportion of postnatal and prenatal frequency of

Table 1. Outcome of pregnancies with prenatally diagnosed congenital heart diseases (associated extra cardiac anomalies in 545 fetuses [30 %]).

Year	CHD (n)	Termination (%)	Intrauterine death (%)	Live-born alive (%)
<1990	106	64.1	28.9	29.6
1991	21	76.2	20.0	50.0
1992	52	57.7	18.2	33.3
1993	47	59.6	5.3	50.0
1994	45	40.0	3.7	38.5
1995	60	70.0	16.7	40.0
1996	70	65.8	16.7	65.0
1997	75	61.3	17.2	75.0
1998	85	60.0	8.8	87.0
1999	97	68.0	6.5	75.9
2000	94	56.4	4.9	76.9
2001	118	54.2	16.7	68.9
2002	141	52.4	7.5	80.6
2003	151	60.3	3.3	86.2
2004	155	52.0	1.4	91.0
2005	136	59.0	7.1	92.0
2006	153	51.0	1.3	92.0
2007	224	54.0	1.0	94.0
Total	1830	58.0	7.7	78.0

transposition of the great arteries was equal (5.4 %). In hypoplastic left heart, atrioventricular septal defect and double outlet right ventricle prenatal frequency was higher (15.1 %, 15 %, 8.7 %) as compared to postnatal frequency (3.9 %, 3.9 %, and 1.1 % respectively).

The early termination was performed in 1040 (56.9 %) cases. Sixty fetuses (7.6 %) died *in utero*, and 728 (92.4 % of continuing pregnancy) were born alive. Survival of the live-born babies gradually increased and reached 94 % in 2007 (Table 1). Decreasing rate of intrauterine deaths in recent years is caused probably by the early termination of complex heart diseases associated with extracardiac malformations and chromosomal aberrations that diagnosed more frequently due to improvement of integrated prenatal screening in the Czech Republic.

Fetal Arrhythmias

Supraventricular tachycardias (SVT)

Most of all prenatally diagnosed tachyarrhythmias are supraventricular. Fetal supraventricular tachycardia complicated by the myocardial dysfunction and hydrops fetalis caries a significant risk of morbidity and mortality (Simpson *et al.* 1998). Intrauterine conversion of SVT by antiarrhythmic drugs became standard approach to prevent development of the hydrops. The intrauterine treatment, however, may not always be successful either because of a low transplacental drug transfer (in both normal and edematous placenta), or because an inadequate response of the fetal myocardium (Naheed *et al.* 1996).

Re-entry tachycardias are the most common form, followed by the atrial flutter and the ectopic atrial tachycardia (van Engelen *et al.* 1994). Precise identification of the type of the arrhythmia using pulsed Doppler sampling of flow in the superior vena cava and the ascending aorta may contribute to good results of treatment (Fouron *et al.* 2003). The study goal is to distinguish between the tachycardia with a short ventriculoatrial time (usually atrioventricular re-entry) and the tachycardia with a long ventriculoatrial time (usually atrial ectopic tachycardia).

We use digoxin as the first choice drug in all the fetuses with SVT requiring a treatment. Sotalol (class III agent with a ß-blocker activity) is added in the fetuses in whom a conversion to sinus rhythm could not be achieved despite a therapeutic maternal digoxinemia of 2-3 ng/ml or in those considered having an ectopic SVT. In one severely hydropic fetus in the 23rd week of gestation, an intraumbilical infusion of adenosine and cordarone was used with success.

The severity of heart failure in each fetus can be scored using the Fetal Heart Failure Score (Falkensammer *et al.* 2001). This multifactorial score combines assessment of direct and indirect markers of cardiovascular function. Presence of hydrops, umbilical venous Doppler, heart size, myocardial function, and arterial Doppler are all scored at a scale from 0 to 2 points. The score of 10 indicates a normal cardiovascular profile.

The cardiothoracic index in fetus may be measured from a standard transverse section of the chest showing the four chamber view. The heart area is compared to the area of the thorax. Normally, the ratio is less than 0.35. Ventricular shortening fraction (SF) can be measured using M-mode and its normal value is 0.28 to 0.46.

Our results

Eighty six fetuses with SVT (reentry tachycardia

in 59, ectopic in 14 and atrial flutter in 13 cases) have been examined in our centre, 9 of them died (10 %).

The hemodynamic measurement was performed in 35 fetuses with a supraventricular tachycardia. Out of those, 27 fetuses responded to the therapy by the conversion to the sinus rhythm and 8 fetuses did not respond. In the non-responders, the ECHO parameters of the heart failure did not change significantly whereas in the responders all the parameters improved significantly: cardiothoracic index changed from 0.34 ± 0.06 to 0.30 ± 0.06 (p<0.001), shortening fraction improved from 0.28 ± 0.06 to 0.36 ± 0.07 (p=0.001) and Fetal Heart Failure Score improved from 6.6 ± 2.0 to 9.7 ± 0.4 (p<0.001). To predict the effectiveness of the prenatal treatment, the ECHO indices prior to the initiation of the treatment were compared between the responding and the non-responding fetuses. Only the shortening fraction was significantly lower in the non-responders (p<0.001) as compared to the responding fetuses.

Isolated complete atrioventricular block (CAVB)

Isolated congenital complete atrioventricular block is caused predominantly by maternal anti-Ro and anti-La autoantibodies in a susceptible fetus typically between 20 and 24 weeks of gestation (Buyon *et al.* 1998). Prenatal CAVB develops in 1 % to 2 % of anti-Ro/La antibody positive pregnancies (Gladman *et al.* 2002, Brucato *et al.* 2001). The antibodies enter the fetal circulation and subsequently may lead to an immune-mediated tissue injury resulting in progressive destruction of the AV node, myocardial inflammation, and in severe cases in endocardial fibroelastosis and dilated cardiomyopathy (Moak *et al.* 2001).

The anti-Ro/La antibodies are typically found in systemic lupus erythematosus and Sjögren's syndrome (Schmidt *et al.* 1991), but often the fetal CAVB may be the first sign of an auto-immune disease in a pregnant women having no clinical symptoms.

The compensatory cardiac mechanism in fetuses with complete atrioventricular block is increasing its stroke volume (Rudolph *et al.* 1976). If the heart fails to adapt, fetal hydrops develops subsequently with a high risk of fetal or neonatal death. The identified risk factors for adverse outcome are fetal hydrops, endocardial fibroelastosis, premature delivery and the fetal heart rate ≤55 bpm (Groves *et al.* 1996). Transplacental treatment may improve the outcome of prenatally diagnosed complete atrioventricular block without a structural heart disease.

To improve the pregnancy outcome, numerous preventive and therapeutic approaches have been used with a variable success. The treatment protocol published by Jaeggi *et al.* (2004) is used in our centre. According to this protocol, maternal peroral dexamethasone is initiated upon the diagnosis of the immune-mediated CAVB in the dose of 4 or 8 mg/d for initial 2 weeks, then followed by 4 mg/d up to the beginning of the third trimester when the dose is decreased to 2 mg/d. Beta-sympathomimetic maternal peroral therapy (salbutamol 3-4 x 10 mg) is added to increase the fetal cardiac output in fetuses with the average heart rate below 55 bpm. No serious adverse effects have been encountered so far. Oligohydramnios did occur in 20 % of cases after chronic steroid treatment and resulted in premature deliveries in some (Costedoat-Chalumeau *et al.* 2003).

Our results

Total of 24 fetuses with complete atrioventricular block with the mean ventricular rate of 58.6 ± 9.4 were diagnosed between the 19th and 32nd week of gestation (median 21 weeks). Anti-Ro and/or anti-La were detected in 18 mothers (75 %). Fetal heart failure was present in 15/20 (63 %) fetuses. Out of 22 ongoing pregnancies (two early terminations), all fetuses survived and 2 with intermittent complete atrioventricular block converted to sinus rhythm.

The same hemodynamic parameters as in the SVT protocol were analyzed in 12 fetuses with a diagnosis of the complete AV block to assess the effectiveness of the transplacental treatment. Echocardiographic signs of fetal heart failure were compared before and after the treatment (dexamethasone + salbutamol). Before to the treatment, 8 of 12 fetuses were hydropic (all of them had ventricular heart rate below 60 bpm). After the treatment, the shortening fraction increased from 0.34 ± 0.05 to 0.41 ± 0.06 (p=0.03). Cardiothoracic index decreased from 0.35 ± 0.09 to 0.31 ± 0.06 (p=0.01), and fetal heart failure score improved from 7.82 ± 1.72 to 9.27 ± 0.65 (p=0.01). Ventricular rate increased from 55.75 ± 7.36 to 63.25 ± 10.48 (p=0.02).

According to the obvious improvement in outcome and in agreement with the present state of knowledge (Jaeggi *et al.* 2005), we are convinced that there is no solid ground to deny the benefit of transplacental steroid treatment to the fetuses with the immune-mediated CAVB.

Ventricular tachycardia is rare prenatally,

contributing by less than 1 % to all the fetal arrhythmias. It may be present in association with a long QT syndrome. The fetal combination of sinus bradycardia, second degree atrioventricular block and transient ventricular tachycardia should raise a high suspicion of the long QT syndrome (Hofbeck *et al.* 1997). We have also suggested that an impaired ventricular relaxation documented by the short early deceleration time of the left ventricular filling can contribute to the final diagnosis of the long QT syndrome (Tomek *et al.* 2009).

Conclusions and perspectives

Reliable diagnosis of congenital heart defects and arrhythmias in utero has been possible since the introduction of fetal echocardiography. Prenatal echocardiography has the potential to improve postnatal survival in infants with critical heart defects, especially those with duct-dependent systemic or pulmonary circulations. If the diagnosis is known prenatally, the appropriate therapy avoiding the risk of circulatory collapse can be established immediately after the birth.

In the Czech Republic, a centralized health care system allowed for the creation of a nation-wide prenatal cardiac screening program (Šamánek *et al.* 1986). Referral for specialized fetal echocardiography is made on the basis of the risk factors for congenital heart defects or when obstetric screening raises a possibility of a fetal CHD or an arrhythmia. Data providing risk factors and proportion of individual heart anomalies and their postnatal outcome have been widely published (Allan *et al.* 1994, Cooper *et al.* 1995, Paladini *et al.* 2002). However, most infants with CHD are born to women without high-risk factors of heart anomalies (Simpson 2004). We know from our experience that more than 40 % of all the prenatally detected heart diseases did not carry any risk factor of CHD (Škovránek *et al.* 1997). The identification of fetuses with abnormal four-chamber views or with impossibility to visualize the crossing of the great arteries on screening examination improved detection of CHD prenatally. In recent years, the detection rate of cardiac abnormalities in the second trimester has also been influenced by the improved screening tests performed at the first trimester, such as the nuchal translucency measurement and biochemical screening tests (Makrydimas *et al.* 2005). Antenatal detection of complex heart diseases, along with a relatively high termination rate and the delivery of critical lesions in a specialized centre have had a positive impact on the surgical outcome in the Czech Republic in accordance with the reported significantly improved morbidity and mortality (Bonnet *et al.* 1999, Yates 2004).

True prenatal incidence of CHD remains unknown as it is impossible to examine all the fetuses that die during the early development either naturally or through terminations for extracardiac/chromosomal lesions. Several studies proved that the increase of the prevalence of cardiac anomalies with the decreasing fetal age contributes to relatively high numbers of miscarriages (Gerlis 1985, Hoffman 1995). Our study has shown that the spectrum of prenatally diagnosed CHD differs significantly from the postnatal spectrum with markedly higher proportion of associated additional abnormalities. Small ventricular septal defects, mild aortic and pulmonary stenoses and total anomalous pulmonary venous connection are not usually detected on fetal echocardiographic screening. On the other hand, hypoplastic left heart syndromes, atrioventricular septal defects and double outlet right ventricles are more frequent prenatally as compared to their postnatal frequency.

The option for prenatal treatment of congenital heart diseases is challenging and at the same time controversial. The experience with a fetal aortic and pulmonary balloon valvuloplasty has been reported. The indication for a prenatal catheterization is based on the hypothesis that timely and effective intervention for severe aortic stenosis *in utero* may prevent the development of postnatal hypoplastic left heart syndrome. The Boston group (Tworetzky *et al.* 2004) revealed that only in 9 of 24 fetuses considered for the fetal balloon valvuloplasty a technically successful dilation was achieved and only two of those did not developed hypoplasia of the left ventricle and were postnatally capable of the biventricular circulation. However, some centers have reported successful pulmonary valve dilations and subsequent biventricular management of fetuses with pulmonary atresia and intact ventricular septum, but the outcome remains unknown (Tulzer *et al.* 2002).

Fetal tachycardia is an important cause of fetal morbidity and mortality (Simpson *et al.* 1998). The efficacy of transplacental pharmacological treatment has been well established in supraventricular tachycardia. Precise identification of the type of arrhythmia should influence the strategy of the therapy (Fouron *et al.* 2003). Supraventricular tachycardia without an appropriate treatment usually leads to fetal heart failure with hydrops and fetal death. Prenatal treatment may convert

supraventricular tachycardia to the sinus rhythm in most of the patients and prenatal ECHO allows for a reliable monitoring of the fetal heart and placental circulatory function. The probability of a successful treatment has been significantly lower in fetuses with hydrops. Altered systolic function prior to the treatment was a significant predictor of failure of the prenatal pharmacological treatment in our study.

Fetal isolated complete atrioventricular block is usually a result of damage to the fetal atrioventricular conduction tissue due to the placental transfer of maternal auto-antibodies. Attempts to reverse an already established complete atrioventricular block by the transplacental steroid treatment have been unsuccessful with few exceptions (Jaeggi *et al.* 2004). In our setting, 2 fetuses with an intermittent complete atrioventricular block converted to the sinus rhythm during the maternal steroid therapy.

To prevent the development of an isolated CAVB would be the ideal strategy of the prenatal management. However, markers predicting which fetus will in the presence of maternal anti-Ro/La antibodies develop a complete AV block are not yet identified.

General prophylactic steroid treatment on the basis of the presence of the auto-antibodies alone has not been recommended (Jaeggi *et al.* 2004). Nevertheless, fetuses with an isolated complete atrioventricular block have a significant intra-uterine mortality (Groves *et al.* 1996) and in spite of the irreversibility of the complete heart block, treatment with fluorinated steroids has been associated with an improved survival, probably because of a lower rate of the immune-mediated complications such as endocardial fibroelastosis, myocarditis and hepatitis (Jaeggi *et al.* 2004) and we therefore recommend maternal dexamethasone treatment in all the isolated fetal CAVB.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

References

ALLAN LD, SHARLAND GK, MILBURN A, LOCKHART SM, GROVES AMM, ANDERSON RH, COOK AC, FAGG NLK: Prospective diagnosis of 1,006 consecutive cases of congenital heart disease in the fetus. *J Am Coll Cardiol* **23**: 1452-1458, 1994.

BONNET D, COLTRI A, BUTERA G, FERMONT L, LE BIDOIS J, KACHANER J, SIDI D: Detection of transposition of the great arteries in fetuses reduces neonatal morbidity and mortality. *Circulation* **99**: 916-918, 1999.

BRUCATO A, FRASSI M, FRANCESCHINI F, CIMAZ R, FADEN D, PISONI MP, MUSCARÁ M, VIGNATI G, STRAMBA-BADIALE M, CATELLI L: Risk of congenital complete heart block in newborns of mothers with anti-Ro/SSA antibodies detected by counterimmuno-electrophoresis: a prospective study of 100 women. *Arthritis Rheum* **44**: 1832-1835, 2001.

BUYON JR, HIEBERT R, COPEL J, CRAFT J, FRIEDMAN D, KATHOLI M, LEE LA, PROVOST TT, REICHLIN M, RIDER L, RUPEL A, SALEEB S, WESTON WL, SKOVRON ML: Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from the national lupus registry, *J Am Coll Cardiol* **31**: 1658-1666, 1998.

COOPER MJ, MARLENE AE, DYSON DC, ROGE CL, TARNOFF H: Fetal echocardiography: retrospective review of clinical experience and an evaluation of indications. *Obstet Gynecol* **86**: 577-582, 1995.

COSTEDOAT-CHALUMEAU N, AMOURA Z, LE THI HONG D, WECHSLER B, VAUTHIER D, GHILLANI P, PAPO T, FAIN O, MUSSET l, PIETTE JC: Questions about dexamethasone use for the prevention of anti-SSA related congenital heart block. *Ann Rheum Dis* **62**: 1010-1012, 2003.

FALKENSAMMER CB, HUHTA JC: Fetal congestive heart failure: correlation of Tei index and cardiovascular score. *J Perinat Med* **29**: 390-398, 2001.

FOURON JC, FOURNIER A, PROULX F, LAMARCHE J, BIGRAS JL, BOUTIN C, BRASSARD M, GAMACHE S: Management of fetal tachyarrhythmia based on superior vena cava/aorta Doppler flow recordings. *Heart* **89**: 1211-1216, 2003.

GERLIS LM: Cardiac malformations in spontaneous abortions. *Int J Cardiol* **7**: 29-43, 1985.

GLADMAN G, SILVERMAN ED, YUK-LAW, LUY L, BOUTIN C, LASKIN C, SMALLHORN JF: Fetal echocardiographic screening of pregnancies of mothers with anti-Ro and/or anti-La antibodies. *Am J Perinatol* **19**: 73-80, 2002.

GROVES AMM, ALLAN LD, ROSENTHAL E: Outcome of isolated congenital complete heart block diagnosed in utero. *Heart* **75**: 190-194, 1996.

HOFBECK M, ULMER H, BEINDER E, SIEBER E, SINGER H: Prenatal findings in patients with prolonged QT interval in the neonatal period. *Heart* **77**: 198-204, 1997.

HOFFMAN JI: Incidence of congenital heart disease. II. Prenatal Incidence. *Pediatr Cardiol* **16**: 155-165, 1995.

JAEGGI ET, NII M: Fetal brady- and tachyarrhythmias: new and accepted diagnostic and treatment methods. *Semin Fetal Neonatal Med* **10**: 504-515, 2005.

JAEGGI ET, FOURON JC, SILVERMAN ED, RYAN G, SMALLHORN J, HORNBERGER LK: Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. *Circulation* **110**: 1542-1548, 2004.

MAKRYDIMAS G, SOTIRIADIS A, HUGGON IC, SIMPSON J, SHARLAND G, CARVALHO JS, DAUBENEY PE, IOANNIDIS JP: Nuchal translucency and fetal cardiac defects: a pooled analysis of major fetal echocardiography centres. *Am J Obstet Gynecol* **192**: 89-95, 2005.

MOAK JP, BARRON KS, HOUGEN TJ, WILES HB, BALAJI S, SREERAM N, COHEN MH, NORDENBERG A, VAN HARE GF, FRIEDMAN RA, PEREZ M, CECHIN F: Congenital heart block: development of late-onset cardiomyopathy, a previously underappreciated sequela. *J Am Coll Cardiol* **37**: 238-242, 2001.

NAHEED ZJ, NAHEED JF, STRASBURGER BJ, DEAL DW, BENSON JR, GIDDING SS: Fetal tachycardia: mechanisms and predictors of hydrops fetalis. *J Am Coll Cardiol* **27**: 1736-1740, 1996.

PALADINI D, RUSSO M, TEODORO A, PACILEO G, CAPOZZI G, MARTINELLI P, NAPPI C, CALABRO R: Prenatal diagnosis of congenital heart disease in the Naples area during the years 1994-1999 - the experience of a joint fetal-pediatric cardiology unit. *Prenat Diagn* **22**: 545-552, 2002.

RUDOLPH AM, HEYMAN MA: Cardiac output in the fetal lamb: the effects of spontaneous and induced changes of heart rate on right and left ventricular output. *Am J Obstet Gynecol* **124**: 183-192, 1976.

SCHMIDT KG, ULMER HE, SILVERMAN NH, KLEINMAN CS, COPEL JA: Perinatal outcome of fetal complete atrioventricular block: a multicenter experience. *J Am Coll Cardiol* **17**: 1360-1366, 1991.

SIMPSON JM, SHARLAND GK: Fetal tachycardias: management and outcome of 127 consecutive cases. *Heart* **79**: 576-581, 1998.

SIMPSON LL: Indications for fetal echocardiography from a tertiary-care obstetric sonography. *J Clin Ultrasound* **32**: 123-128, 2004.

ŠAMÁNEK M, GOETZOVÁ J, BENEŠOVÁ D: Distribution of congenital heart malformations in an autopsied child population. *Int J Cardiol* **8**: 235-248, 1985.

ŠAMÁNEK M, BŘEŠŤÁK M, ŠKOVRÁNEK J: Prenatal cardiology. (in Czech) *Čs Pediat* **41**: 478-480, 1986.

ŠAMÁNEK M, GOETZOVÁ J, BENEŠOVÁ D: Causes of death in neonates born with a heart malformation. *Int J Cardiol* **11**: 63-74, 1986.

ŠAMÁNEK M, VOŘÍŠKOVÁ M: Infants with critical heart disease in a territory with centralized care. *Int J Cardiol* **16**: 75-91, 1987.

ŠAMÁNEK M, SLAVÍK Z, ZBOŘILOVÁ B, HROBOŇOVÁ V, VOŘÍŠKOVÁ M, ŠKOVRÁNEK J: Prevalence, treatment, and outcome of heart disease in live-born children: A prospective analysis of 91,823 live-born children. *Pediatr Cardiol* **10**: 205-211, 1989.

ŠAMÁNEK M, SLAVÍK Z, ZBOŘILOVÁ B, HROBOŇOVÁ V, VOŘÍŠKOVÁ M: Congenital heart disease among 815,569 children born between 1980 and 1990 and their 15-year survival: a prospective Bohemia survival study. *Pediatr Cardiol* **20**: 411-417, 1999.

ŠKOVRÁNEK J, MAREK J, POVÝŠILOVÁ V: Prenatal cardiology. (in Czech) *Čs Pediat* **52**: 332-338, 1997.

TOMEK V, ŠKOVRÁNEK J, GEBAUER RA: Prenatal diagnosis and management of fetal Long QT syndrome. *Pediatr Cardiol* **30**: 194-196, 2009.

TULZER G, ARZT W, FRANKLIN RC, LOUGHNA PV, MAIR R, GARDINER HM: Fetal pulmonary valvuloplasty for critical pulmonary stenosis or atresia with intact septum. *Lancet* **16**: 1567-1568, 2002.

TWORETZKY W, WILKINS-HAUG L, JENNINGS RW, VAN DER VELDE ME, MARSHALL AC, MARX GR, COLAN SD, BENSON CB, LOCK JE, PERRY SB: Balloon dilation of severe aortic stenosis in the fetus: potential for prevention of hypoplastic left heart syndrome. Candidate selection, technique, and results of successful intervention. *Circulation* **110**: 2125-2131, 2004.

VAN ENGELEN AD, WEIJTENS O, BRENNER JI, KLEINMAN CS, COPEL JA, STOUTENBEEK P, MEIJBOOM EJ: Management, outcome and follow-up of fetal tachycardia. *J Am Coll Cardiol* **24**: 1371-1375, 1994.

YATES RS: The influence of prenatal diagnosis on postnatal outcome in patients with structural congenital heart disease. *Prenat Diagn* **24**: 1143-1149, 2004.