MINIREVIEW

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

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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 abnormalities 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.

Key words
Prenatal • Echocardiography • Congenital heart defect • Arrhythmias • Heart failure

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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 postnataally 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 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.

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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
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 carries 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

<table>
<thead>
<tr>
<th>Year</th>
<th>CHD (n)</th>
<th>Termination (%)</th>
<th>Intrauterine death (%)</th>
<th>Live-born alive (%)</th>
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<tbody>
<tr>
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<td>64.1</td>
<td>28.9</td>
<td>29.6</td>
</tr>
<tr>
<td>1991</td>
<td>21</td>
<td>76.2</td>
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<td>52</td>
<td>57.7</td>
<td>18.2</td>
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<td>47</td>
<td>59.6</td>
<td>5.3</td>
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<td>40.0</td>
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<tr>
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<td>60</td>
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<td>85</td>
<td>60.0</td>
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<td>97</td>
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<td>52.0</td>
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<tr>
<td>2006</td>
<td>153</td>
<td>51.0</td>
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<tr>
<td>2007</td>
<td>224</td>
<td>54.0</td>
<td>1.0</td>
<td>94.0</td>
</tr>
<tr>
<td>Total</td>
<td>1830</td>
<td>58.0</td>
<td>7.7</td>
<td>78.0</td>
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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 (Holbeck 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 (Škovráněk 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, ativoventricular 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 develop 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.

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