Původní sdělení | Original research article

Development, effectiveness, and current possibilities in prenatal detection of congenital heart defects

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ARTICLE INFO

Article history:
Submitted: 15. 8. 2019
Revised: 8. 12. 2019
Accepted: 20. 12. 2019
Available online: 27. 1. 2020

Klíčová slova:
Fetální echokardiografie
Intrauterinní úmrtí
Screening
Ukončení gravidity
Vrozená srdeční vada

SOUHRN

Cíl: Studium vývoje a efektivity prenatální diagnostiky vrozených srdečních vad (VSV). Sledování celkového výskytu VSV a úrovně fetální detekce jednotlivých typů vad.
Metodika: Retrospektivní studie, která zpracovala údaje o ultrazvukových vyšetřeních fetálního srdce provedených gynekology, genetiky a dětskými kardiology a postnatálních vyšetřeních dětí s VSV dětskými kardiology v letech 2011 až 2018. Přítomnost dětského kardiologa u všech autopsií plodů po ukončení gravidity z důvodu fetálně detekované VSV. Došetření genetických a extrakardiálních patologií u plodů a novorozenců s významnou VSV.
Výsledky: Během sledovaného osmiletého období bylo v populaci 90 880 živě narozených diagnostikováno 351 (3,9/1 000) významných VSV. V 72 % (252/351) se VSV vyskytly jako izolované patologie. Prenatálně bylo detekováno 66 % (230/351) VSV. Efektivita screeningu významných VSV postupně stoupala, z 57 % v roce 2008 na 80 % v roce 2018. Nejvyšší fetální detekci měly vady alterující morfologii komor (80–100 %). Ve skupině prenatálně detekovaných VSV se 47 % (109/230) rodičů rozhodlo pro ukončení gravidity, 5 % (10/230) fetů intrauterinně zemřelo a 48 % (111/230) rodin pokračovalo v graviditě.
Závěr: VSV se vyskytují většinou jako izolovaná anomálie. Významné VSV jsou dobře detekovatelné prenatálně, jejich fetální detekce má vysokou efektivitu a trvale se zlepšuje. Nejvyšší detekce je u VSV diagnostikovatelných ze základní čtyřdutinové projekce.
Participace dětské kardiologie na fetálním screeningu VSV zvyšuje jeho efektivitu a při finální diagnostice se jeví nezbytná.

Keywords:
Congenital heart defect
Fetal echocardiography
Intrauterine death
Screening
Termination of pregnancy

ABSTRACT

Aim: To study the development and effectiveness of prenatal diagnostics for congenital heart defects (CHDs). To monitor the overall incidence of CHDs and the level of detection for individual types of fetal defects.
Methods: This retrospective cohort study retrieved data on ultrasound examinations of the fetal heart (fetal echocardiography), conducted by a gynecologist or pediatric cardiologist, and postnatal standardized examinations, conducted by a pediatric cardiologist, between 2011 and 2018. A pediatric cardiologist was present at all fetal autopsies and provided precise descriptions of the heart defect. All fetuses and newborns with severe pathologies were included to identify associated genetic and extracardiac pathologies.
Results: During the 8-year monitoring period, a total of 351 cases of severe heart defects were diagnosed in a population of 90,880 live births (3.9/1 000). CHDs manifested as an isolated anomaly in 72% of cases (252/351). In total, 66% of CHDs (230/351) were detected prenatally and 34% (121/351) of CHDs remained undetected until after birth. Screening effectiveness gradually improved over time; among the severe CHDs, 57% and 80% were detected prenatally in 2011 and 2018, respectively. Among all CHDs, the highest prenatal detection rates (80–100%) were observed for pathologies that affected ventricular morphology. In the group of prenatally diagnosed CHDs, 47% (109/230) of families decided to terminate the pregnancy, 5% (10/230) of fetuses died intrauterine, and 48% (111/230) of families continued the pregnancy.
Conclusion: CHDs mostly occurred as an isolated anomaly. The most severe CHDs were detected prenatally. We found that prenatal detection of CHDs was highly effective and gradually improved over time. The highest detection rate was for defects in the four-chamber projection. The participation of a pediatric cardiologist in fetal screening appeared to be necessary for determining the final diagnostics and for counseling the affected family.

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DOI: 10.33678/cor.2019.090

Please cite this article as: Pavlíček J, Piegzová A, Klásková E, et al. Development, effectiveness, and current possibilities in prenatal detection of congenital heart defects. Cor Vasa 2020;62:21–28.

Introduction

Congenital heart defects (CHDs) are the most frequently observed morphological defects in the population.[1] It is generally accepted that heart defects occur in 1% of the population, with a range of 2 to 12 CHDs per 1 000 live births.[2] Among the total number of CHDs, one third manifests with a critical symptomatology (i.e., hypoxemia-cyanosis and heart failure). Advances in pediatric cardiology and pediatric heart surgery have made it possible to manage even the most complex anomalies, with good outcomes and low morbidity and mortality. In addition, prenatal cardiology has developed extensively. Currently, most CHDs are detected prenatally, due to the improved diagnostics for fetal heart defects and fetal arrhythmias, the definition of feto-placental circulation, the development of screening programs and ultrasound techniques, and the increasing experience of physicians.[3] In the fetus, the first contractions of the primitive heart tube are visible in the third week of gestation; and heart development is complete in the eighth week. During the first trimester, between the 11th and 14th week of gestation, it is possible to assess the heart rate of the fetus, together with the basic heart structures. In the second trimester (18 to 22 weeks), it is possible to perform a detailed examination of heart morphology and function. Early diagnostics for CHDs allow physicians to provide the family with detailed information regarding the significance of a fetal defect. Further examinations of genetic and extracardiac pathologies are also required. The prenatal diagnosis of a CHD requires monitoring the gestation and planning for the birth to take place at a specialized center.

The knowledge of a CHD prior to birth might reduce the risks of morbidity and mortality, in certain types of critical and serious heart defects.[4] Despite the current recommendation that fetal heart assessments should be performed in a standardized way,[5] the success rate in detecting CHDs vary greatly among individual countries, with varying effectiveness. The present study aimed to assess the development of prenatal screening for CHDs in a region with a stable birth rate and to assess its current quality and future possibilities.

Methods

The present 8-year retrospective study analyzed data from 90,880 live births that occurred in 2011–2018 to determine the incidence of CHDs. The study was conducted in the Moravian-Silesian region, in the northern part of Moravia, in the Czech Republic, with approximately 1,200,000 inhabitants. This region had a stable birth rate of around 11,500 births per year. The population represented the catchment area of the University Hospital Ostrava, a tertiary referral center for pediatric and prenatal cardiology. Data were retrieved from hospital databases on fetuses, newborns, and toddlers with severe heart defects.

All pregnant women from the monitored area underwent fetal echocardiography, performed by a gynecologist or pediatric cardiologist. When a CHD was diagnosed, the fetus was thoroughly examined for the presence of extracardiac and genetic anomalies. When the pregnancy was terminated, an autopsy was always performed in the presence of a pediatric cardiologist. Continued pregnancies were followed, and infants with heart defects were delivered at a specialized center.

For the purpose of assessing prenatal diagnostics and the significance of the perinatal period, we included only critical and severe CHDs in this study. The category of severe defects included severe illnesses in the newborn period or early infancy, which typically required postnatal heart surgery or a catheterization procedure during the first year of age. The definitions of the studied CHDs and their abbreviations are shown in Table 1.

Complex cardiac abnormalities were classified according to the dominant heart lesion. In all complex heart lesions, an atrioventricular septal defect was the primary diagnostic lesion. A double outlet right ventricle was diagnosed when the aorta or pulmonary trunk overrode the ventricular septal defect at over fifty percent. A single ventricle was classified as a univentricular atrioventricular connection with a double inlet or common atrioventricular valve. When an atrioventricular connection was absent, the diagnosis was either tricuspid or mitral atresia. Hypoplastic left heart syndrome was defined as a heart with a small left ventricle and flow reversal in the aortic arch. Coarctation of the aorta with a ventricular septal defect was classified as coarctation of the aorta.[6,7]

The collected data were stored and processed with Microsoft Excel software. Excel software was also used for descriptive statistics and basic charts. Basic assessments are expressed as the number and percentage. The Chi-square test was used for other comparisons. The level of

Table 1 – Classifications of studied CHDs and their abbreviations

IAA	Interruption of the aortic arch
AS	Aortic stenosis*
AVSD	Atrioventricular septal defect
CAT	Common arterial trunk
COA	Coarctation of aorta
CTGA	Corrected transposition of the great arteries
DORV	Double outlet right ventricle
EBST	Ebstein's anomaly
ECT	Ectopia cordis
HLH	Hypoplastic left heart syndrome
PAIVS	Pulmonary atresia with intact ventricular septum
PAVSD	Pulmonary atresia with ventricular septal defect
PS	Pulmonary stenosis*
SV	Single ventricle
TA	Tricuspid atresia
TAPVR	Total anomalous pulmonary venous return
TGA	Transposition of the great arteries
TOF	Tetralogy of Fallot
VSD	Ventricular septal defect (large)*

CHD – congenital heart defect; * a form of CHD that required surgery or a catheterization procedure during the first year of age.

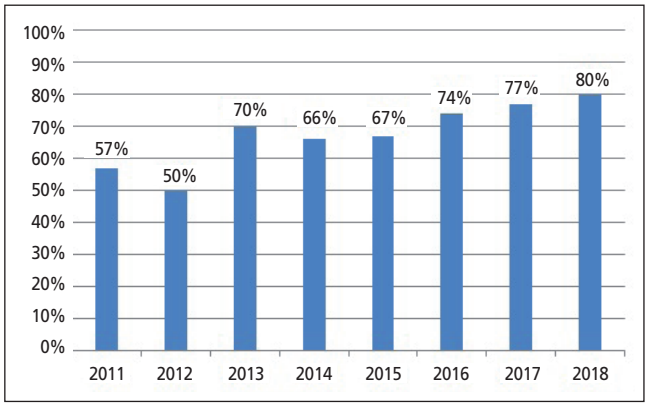

Fig. 1 – The percentages of prenatally detected heart defects in 2011–2018

significance, α, for type I errors (p-value) was set at 0.05 for tests. All analyses were performed with IBM SPSS software, v. 24.

Results

Basic evaluation

A total of 351 severe heart defects were diagnosed in the population of 90,880 live births (i.e., 3.9 cases/1000) between 2011 and 2018. Screening effectiveness gradually improved over time; in 2011, 57% of CHDs were detected, and in 2018, up to 80% were detected (Fig. 1). In the prenatal period, 230 CHDs (66%) were diagnosed between the 12th and 28th weeks of pregnancy (median: 20 weeks), but only 6% (14/230) of CHDs were detected in the first trimester. Among the 351 CHDs, 34% (121/351) were not detected until after birth (Fig. 2). The highest rate of prenatal detection (over 80%) was found for CHDs that substantially altered the shape and morphology of the heart. The basic, four-chamber scan could typically detect morphological heart disorders, such as: hypoplastic left heart syndrome, pulmonary and tricuspid atresias, and single ventricle. Low detection rates (50–80%) were observed for valve defects and defects in the outflow tracts and large arteries. The lowest detection rates were observed for aortic coarctations and ventricular septal defects (Table 2).

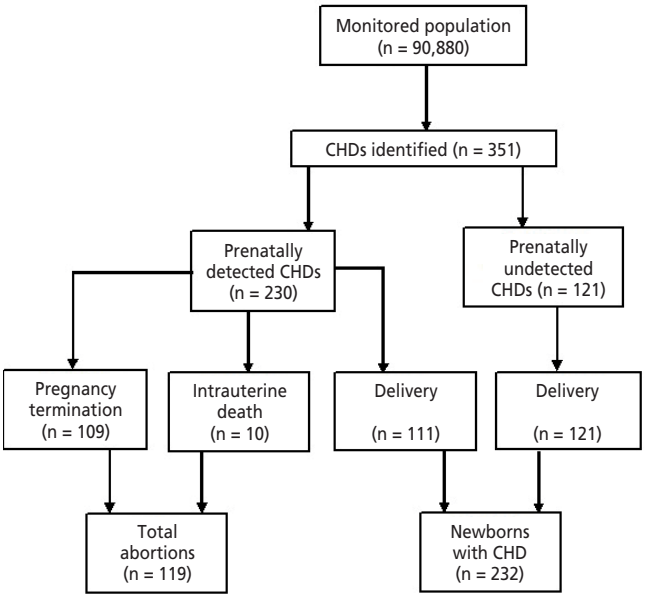

Fig. 2 – Flow chart of the monitored population

Table 2 – The incidence and proportion of CHDs, according to the prenatal detection rate

CHD	N	Prenatally detected (%)	Prenatally undetected (%)
PAVSD	**8**	8 **(100)**	0 (0)
PAIVS	**4**	4 **(100)**	0 (0)
CTGA	**2**	2 **(100)**	0 (0)
ECT	**1**	1 **(100)**	0 (0)
HLH	**31**	29 **(94)**	2 (6)
SV	**7**	6 **(86)**	1 (14)
TA	**7**	6 **(86)**	1 (14)
AVSD	**48**	37 **(77)**	11 (23)
DORV	**24**	18 **(75)**	6 (25)
TOF	**33**	24 **(73)**	9 (27)
AS	**25**	18 **(72)**	7 (28)
PS	**24**	17 **(71)**	7 (29)
IAA	**3**	2 **(67)**	1 (33)
CAT	**8**	5 **(63)**	3 (37)
EBST	**5**	3 **(60)**	2 (40)
TGA	**31**	17 **(55)**	14 (45)
CoA	**27**	13 **(48)**	14 (52)
VSD	**60**	20 **(33)**	40 (67)
TAPVR	**8**	0 (0)	3 (100)
Total	**351**	**230 (66)**	**121 (34)**

Abbreviations are defined in Table 1.

Course of pregnancy, when CHDs were detected prenatally

In the group of prenatally diagnosed CHDs, 47% (109/230) of families decided to terminate the pregnancy, 5% (10/230) of fetuses died intrauterine, and 48% (111/230) of families continued the pregnancy. The high rate of termination (70–100%) in cases with prenatally detected CHDs was associated with defects that often lead to significant changes in heart morphology, including tricuspid and pulmonary atresias and hypoplastic left heart syndrome, but also in cases of aortic arch interruption. A low rate of termination (below 20%) was found in cases with ventricular septal defects, pulmonary stenosis, and aortic coarctation. Termination was chosen more frequently in the group faced with defects that caused permanent single ventricle circulation, compared to the group that had the option of a surgical intervention that could correct the defect and preserve both ventricles. In our sample, pregnancies were terminated in 43% (47/109) of fetuses

Table 3 – Prenatally detected CHDs that ended in pregnancy termination or intrauterine death, according to genetic and morphological pathologies

CHD	Termination (%)				Intrauterine death (%)				Total abortions
	n	CHD I	CHD + G	CHD + M	n	CHD I	CHD + G	CHD + M	
AVSD	**24**	3 (13)	14 (58)	7 (29)	**2**	1 (50)	1 (50)	0 (0)	**26**
HLH	**22**	16 (74)	3 (13)	3 (13)	**1**	1 (100)	0 (0)	0 (0)	**23**
TOF	**12**	2 (17)	9 (75)	1 (8)	**1**	1 (100)	0 (0)	0 (0)	**13**
DORV	**10**	5 (50)	3 (30)	2 (20)	**0**	0 (0)	0 (0)	0 (0)	**10**
AS	**6**	5 (83)	1 (17)	0 (0)	**1**	1 (100)	0 (0)	0 (0)	**7**
PAVSD	**6**	4 (68)	1 (16)	1 (16)	**1**	1 (100)	0 (0)	0 (0)	**7**
TA	**5**	4 (80)	1 (20)	0 (0)	**0**	0 (0)	0 (0)	0 (0)	**5**
PAIVS	**4**	1 (25)	0 (0)	3 (75)	**0**	0 (0)	0 (0)	0 (0)	**4**
TGA	**4**	3 (75)	0 (0)	1 (25)	**0**	0 (0)	0 (0)	0 (0)	**4**
VSD	**2**	0 (0)	2 (100)	0 (0)	**2**	0 (0)	2 (100)	0 (0)	**4**
CAT	**3**	1 (33)	2 (67)	0 (10)	**0**	0 (0)	0 (0)	0 (0)	**3**
SV	**3**	1 (33)	1 (33)	1 (34)	**0**	0 (0)	0 (0)	0 (0)	**3**
COA	**2**	0 (0)	2 (100)	0 (0)	**0**	0 (0)	0 (0)	0 (0)	**2**
EBST	**1**	1 (100)	0 (0)	0 (0)	**1**	1 (100)	0 (0)	0 (0)	**2**
IAA	**2**	1 (50)	1 (50)	0 (0)	**0**	0 (0)	0 (0)	0 (0)	**2**
PS	**1**	0 (0)	1 (100)	0 (0)	**1**	0 (0)	0 (0)	1 (100)	**2**
CTGA	**1**	0 (0)	0 (0)	1 (100)	**0**	0 (0)	0 (0)	0 (0)	**1**
ECT	**1**	0 (0)	0 (0)	1 (100)	**0**	0 (0)	0 (0)	0 (0)	1
Total	**109**	**47 (43)**	**41 (38)**	**21 (19)**	**10**	**6 (60)**	**3 (30)**	**1 (10)**	**119**

Abbreviations for CHDs are defined in Table 1. G – concomitant genetic disorder; I – isolated; M – extracardiac malformation with a normal karyotype.

with isolated CHDs, 38% (41/109) of fetuses with confirmed genetic pathologies associated with the CHD, and 19% (21/109) of fetuses with a morphological anomaly and normal karyotype. Isolated CHDs prevailed among the 10 fetuses that died intrauterine (aortic stenosis, atrioventricular septal defect, Ebstein's anomaly, hypoplastic left heart syndrome, pulmonary atresia with ventricular septal defect, and tetralogy of Fallot). The distribution of anomalies associated with CHDs and their relationship to pregnancy termination and intrauterine death are shown in Table 3.

Among the group of prenatally detected defects, 48% (111/230) of families continued the pregnancies and delivered the infant. In this group, 83% (92/111) had isolated CHDs and the other 17% (19/111) had CHDs associated with extracardiac diseases (Table 4).

Prenatally undetected CHDs

In the study region, 34% (121/351) of CHDs were undetected, and the babies were born with a previously unrecognized heart defect. In this group, 88% had isolated CHDs (107/121) and 12% (14/121) had CHDs associated with genetic (8%, 9/121) or morphological (4%, 5/121) pathology. In absolute numbers, the most common prenatally undetected defects were: a ventricular septal defect, great artery transposition, and aortic coarctation (Table 4).

The influence of extracardiac anomalies on CHD screening

Among the CHDs observed in fetuses and infants, 72% (252/351) manifested as isolated anomalies. In 28% (99/351) of cases, a concomitant genetic or extracardiac morphological pathology was found. A concomitant genetic disorder was diagnosed in 18% (63/351) of cases. Among these, 80% comprised trisomy 21, 18, and 13 and the 22q11 deletion (DiGeorge syndrome). In this sample, we observed no genetic pathology associated with Ebstein's anomaly, pulmonary atresia with an intact ventricular septum, transposition of the great arteries, total anomalous pulmonary return, corrected transposition of the great arteries, or rare ectopia cordis. An extracardiac pathology with a normal karyotype was present in 10% (36/351) of cases. Among these, the most common pathologies were gastrointestinal and urogenital tract malformations and limb deformities.

Among the chromosomal aberrations and extracardiac anomalies with a normal karyotype, 86% (54/63) and 86% (31/36), respectively, were diagnosed prenatally, and 14% (9/63) and 14% (5/36), respectively, were diagnosed postnatally. CHDs associated with a genetic pathology were detected more frequently prenatally (23%, 54/230) than postnatally (7%, 9/121; $p<0.05$). CHDs associated with an extracardiac pathology were also detected prenatally (13%, 31/230) significantly more often than postnatally (4%, 5/121; $p<0.05$).

Table 4 – Newborns with prenatally detected or undetected CHDs, according to genetic and morphological pathologies

CHD	Prenatally detected (%)				Prenatally undetected (%)				Newborns
	n	CHD I	CHD + G	CHD + M	n	CHD I	CHD + G	CHD + M	
VSD	**16**	13 (81)	2 (13)	1 (6)	**40**	34 (86)	3 (7)	3 (7)	56
TGA	**13**	12 (92)	0 (0)	1 (8)	**14**	14 (100)	0 (0)	0 (0)	27
CoA	**11**	8 (73)	0 (0)	3 (27)	**14**	14 (100)	0 (0)	0 (0)	25
AVSD	**11**	8 (73)	2 (18)	1 (9)	**11**	7 (64)	4 (36)	0 (0)	22
PS	**15**	14 (93)	1 (7)	0 (0)	**7**	6 (86)	1 (14)	0 (0)	22
TOF	**11**	8 (73)	2 (18)	1 (9)	**9**	9 (100)	0 (0)	0 (0)	20
AS	**11**	11 (100)	0 (0)	0 (0)	**7**	6 (86)	1 (14)	0 (0)	18
DORV	**8**	8 (100)	0 (0)	0 (0)	**6**	5 (83)	0 (0)	1 (17)	14
HLH	**6**	5 (83)	0 (0)	1 (17)	**2**	2 (100)	0 (0)	0 (0)	8
EBST	**1**	1 (100)	0 (0)	0 (0)	**2**	2 (100)	0 (0)	0 (0)	3
CAT	**2**	2 (100)	0 (0)	0 (0)	**3**	3 (100)	0 (0)	0 (0)	5
SV	**3**	2 (67)	0 (0)	1 (33)	**1**	0 (0)	0 (0)	1 (100)	4
TAPVR	**0**	0 (0)	0 (0)	0 (0)	**3**	3 (100)	0 (0)	0 (0)	3
TA	**1**	1 (100)	0 (0)	0 (0)	**1**	1 (100)	0 (0)	0 (0)	2
IAA	**0**	0 (0)	0 (0)	0 (0)	**1**	1 (100)	0 (0)	0 (0)	1
CTGA	**1**	1 (100)	0 (0)	0 (0)	**0**	0 (0)	0 (0)	0 (0)	1
PAVSD	**1**	0 (0)	1 (100)	0 (0)	**0**	0 (0)	0 (0)	0 (0)	1
PAIVS	**0**	0 (0)	0 (0)	0 (0)	**0**	0 (0)	0 (0)	0 (0)	0
ECT	**0**	0 (0)	0 (0)	0 (0)	**0**	0 (0)	0 (0)	0 (0)	0
Total	**111**	**92 (83)**	**10 (9)**	**9 (8)**	**121**	**107 (88)**	**9 (8)**	**5 (4)**	**232**

Abbreviations for CHDs are defined in Table 1. G – concomitant genetic disorder; I – isolated; M – extracardiac malformation with a normal karyotype.

Discussion

Heart defects are the most frequently observed morphological anomalies in the human population.[8] They represent up to 40% of all congenital malformations.[9] The incidence varies between 4 and 50 cases per 1000 live births, but these numbers can reach 75/1000 live births, when all insignificant CHDs are considered. Most CHDs are detectable prenatally. Fetal echocardiography is typically performed during prenatal screening for CHDs by a gynecologist, pediatric cardiologist, or geneticist. Fetal echocardiography is a very precise method for detecting cardiac malformations; it produces excellent results, when performed by an experienced physician.[10,11] The main findings of this study were as follows: (*i*) prenatal CHD screening has become increasingly effective over the past 8 years, and the number of diagnosed heart defects has increased; (*ii*) most CHDs were detected in the second trimester; the four-chamber projection provided the highest detection rate; (*iii*) CHDs were isolated in most cases; (*iv*) in the group of prenatally detected CHDs, almost half of the families decided to terminate the pregnancy; (*v*) the participation of a pediatric cardiologist in fetal screening for CHDs appeared to bring long-term benefit, and it was necessary for final counseling.

In summary studies, the overall incidence of severe CHDs was estimated to be between 2.5 and 3/1000 live births.[12] In our study, the incidence of severe CHDs was 3.9/1000 fetuses and newborns, which was consistent with findings from other studies.[13] The incidence of CHDs in the Czech Republic remains to be calculated, according to Professor Šamánek.[14] They reported an incidence of 6.4 CHDs per 1000 live births, which was nearly twice the incidence of cardiac pathologies observed in our patient sample. Although the success rate of CHD diagnostics has generally improved throughout the world, the rates have varied among individual countries.[15,16] The Czech Republic has a high rate of prenatal CHD detection, compared to other countries in Europe. The rate of prenatal CHD detection in the entire Czech Republic increased from 0.6% in 1986 to 36.5% in 2009;[17] then, the rate varied between 70% and 83% in 2002 and 2009.[18] Currently, for some types of defects (single ventricle, hypoplastic left heart syndrome), the detection rate is 100%.[19] In the catchment area of the present study, screening began in 1991; however, the data were not thoroughly analyzed until 1998, when 10% of significant CHDs were detected prenatally; a 50% success rate was achieved in 2005, and most recently, the estimated rate was 80%.

Fetal CHD screening can be performed in the first and second trimesters. First-trimester CHD screening is feasible with a high-quality transabdominal probe, vaginal probe, or a combination of both.[20] The number of CHDs detected in the first trimester has recently increased.[21] The main

role of the gynecologist in the first trimester is to assess the heart rate and morphology, with the four-chamber view. To examine the whole heart, the fetus must be in a favorable position and the examining physician must have extensive experience. In many cases, another control examination is performed in the following weeks, and a definite diagnosis is determined later. Although first--trimester CHD screening is possible, it can lead to a large number of terminated pregnancies, and significantly impairs the outcome of pregnancy.[7] In up to 70% of cases, an early fetal diagnosis of a significant CHD results in pregnancy termination. In the present study, more than 90% of fetal diagnoses were determined in the second trimester. The authors preferred this period, ideally between 18th and 22nd weeks, because it offered the best opportunity to assess heart morphology and function, and it allowed sufficient time to perform further examinations of the fetus and provide definitive counseling.[22] An earlier diagnosis might be offered in high-risk pregnancies (due to risk factors in the fetus, the mother, or the gestation).[20,23,24] In the present study, early CHD diagnostics were offered in the 16th week, and a subsequent control examination was performed in the 20th week.

The spectrum of CHDs that can be diagnosed prenatally is significantly different from the spectrum that can be diagnosed postnatally. Prenatally detected CHDs are dominated by serious, complex fetal anomalies, and more chromosomal anomalies are diagnosed compared to postnatally detected CHDs. During prenatal CHD screening, the most frequent diagnoses were pathologies recognizable from the basic four-chamber projection.[25]

The prenatal identification of hypoplasia of the left or right ventricle was successful in 80–100% of cases during the last three years of this study, identical to other centers.[6] The size and shape of ventricles could be examined well. However, evaluations of the atrioventricular valves partly failed in our study population; diagnosis of an atrioventricular septum defect was successful in only two thirds of fetuses. The probability of missing a defect in the atrioventricular septum is related to the probability of missing certain trisomies, because these defects are typically associated. An isolated ventricular septal defect occurred most frequently; however, its prenatal diagnosis occurred least frequently. Ventricular septal defects are predominantly located in the muscular part of the septum; consequently, they do not typically manifest hemodynamically in the fetus. A fetal diagnosis typically requires the use of Doppler techniques.[25] Generally speaking, defects detectable with the basic four-chamber projection prevailed during prenatal CHD screening.[26] Nevertheless, the success rate of this approach was limited, because only certain defects could be detected.[27] Indeed, significant defects in the outflow tracts of large vessels were associated with a lower detection rate.[28] These diagnoses require the projection of outflow tracts and large vessels, ideally with color Doppler flow mapping.[29–33] Some diagnoses might be specified further with the use of 4D ultrasound techniques.[34]

In the present study, CHD was identified as an isolated anomaly in two-thirds of the cases. Currently, about 20% of CHDs are estimated to be associated with a precise genetic cause, consistent with our finding of 18%.[35] The most frequent genetic abnormality was the atrioventricular septal defect, and the dominant cause was Down syndrome.[36] On the other hand, in some CHDs (Ebstein's anomaly, pulmonary atresia, transposition of the great arteries), the rates of genetic abnormalities were typically low. However, these patients were not typically karyotyped; therefore, some genetic pathologies might have been overlooked.[37] Most extracardiac pathologies were identified prenatally. This effectiveness was facilitated by the development of combined ultrasound and genetic diagnostics. The field of medical genetics has developed extensively. Although we continue to use karyotyping and fluorescence *in situ* hybridization most often, other techniques are available, including comparative genomic hybridization arrays and molecular genetics. Whole genome sequences have not yet been applied to fetal medicine in clinical practice. Potential genetic causes and causal mutations continue to be studied, but in pediatric cardiology, despite improvements in detection and interpretation, complications of phenotype heterogeneity and incomplete penetration can impede interpretations.[38–40]

In the present study, 47% of families decided to terminate the pregnancy upon receiving a prenatal CHD diagnosis. The Czech Republic has one of the highest pregnancy termination rates in the world. Among the various national registries, the number of pregnancy terminations related to a CHD diagnosis varies between 0 and 50%. It is known that parental decision-making is influenced by the severity of the CHD, parental age, and associated anomalies.[41] In the area studied here, most terminated pregnancies were associated with isolated CHDs, but decisions to terminate were significantly more frequent when the CHD caused single-ventricle circulation and required repeated postnatal surgical interventions. Prenatal screening and parental decisions have significantly reduced the incidence of these defects in the population. Intrauterine death due to a heart defect is possible, but in this group, it accounted for only 5% of prenatally observed CHDs, and it mostly occurred in the second trimester.

The aim of prenatal diagnostics is not termination, but a more detailed examination of pathological pregnancies, to facilitate correct, careful counseling. Moreover, detailed findings facilitate plans to ensure that the delivery and postnatal interventions are performed in an adequate workplace. Current studies have provided different results on the beneficial effects of fetal diagnostics on morbidity and mortality in newborns and children.[4,42–44] The authors of this work consider the prenatal care system to be very effective in the Czech Republic. It is essential to have complete information on pathological pregnancies to provide the affected family with proper counseling and fetal transport "*in utero*" for delivery to an adequate workplace. All fetuses with diagnosed CHDs should undergo very thorough ultrasound examinations by a fetal medicine specialist to exclude extracardiac anomalies; moreover, a genetic consultation should be offered to the family. In the catchment area of the present study, the final consultation on a heart defect is always performed by a pediatric cardiologist.

The main strengths of the present study were the long--term follow-up, which allowed us to monitor the deve-

lopment of prenatal diagnostics for CHDs in the observed region, and the large cohort, which provided accurate determinations of the effectiveness of prenatal CHD assessments. A potential limitation of the study was the fact that we restricted the cohort to include severe heart defects only; nevertheless, the authors considered this cohort sufficient for the purpose and sense of a prenatal care investigation.

In conclusion, we showed that prenatal CHD detection was highly effective, and it has improved over time. However, despite the continuously increasing effectiveness, the highest detection rate was achieved with the basic four-chamber projection. In contrast, the diagnostics of defects in the outflow tracts, the great arteries, and the aortic arch were less effective. The participation of pediatric cardiologist during the fetal screening improved the effectiveness of CHD monitoring, and appeared to be crucial for the final diagnosis.

Funding
This work was supported by Ministry of Health, Czech Republic – conceptual development of research organization (FNOl, 0098892). Additional support came from the Faculty Hospital in Hradec Kralove (a long-term organization development plan).

Authors' contributions
Dr. Pavlíček conceptualized and designed the study and was responsible for manuscript writing, Drs Pavlíček and Klásková were investigators for fetal echocardiography and collected fetal data, Drs Piegzová and Špaček were investigators in obstetrics, collected data, mainly during fetal screening and extra-cardiac fetal findings, Drs Kaprálová and Palátová were consultants for post-natal heart diseases and collected postnatal data, Dr. Gruszka critically reviewed the manuscript from the overall pediatric viewpoint and was responsible for final approval. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Ethics approval and consent to participate
All pregnant women and parents of affected fetuses and children provided informed consent to participate in examinations during the prenatal and postnatal period. Consent from the families was not required for pathological examination of the fetus. According to legislation in the Czech Republic, a pathological-anatomical autopsy of the fetus is required in all cases where an artificial termination was performed due to an indication of a genetic or congenital developmental defect in the fetus.

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