Does First-Trimester Screening Modify the Natural History of Congenital Heart Disease?

Analysis of Outcome of Regional Cardiac Screening at 2 Different Time Periods

BACKGROUND: The study analyzed the impact of first-trimester screening on the spectrum of congenital heart defects (CHDs) later in pregnancy and on the outcome of fetuses and children born alive with a CHD.

METHODS: The spectrum of CHDs, associated comorbidities, and outcome of fetuses, either diagnosed with a CHD in the first trimester (Group I, 127 fetuses) or only in the second-trimester screening (Group II, 344 fetuses), were analyzed retrospectively between 2007 and 2013. Second-trimester fetuses diagnosed with a CHD between 2007 and 2013 were also compared with Group III (532 fetuses diagnosed with a CHD in the second trimester from 1996 to 2001, the period before first-trimester screening was introduced).

RESULTS: The spectrum of CHDs diagnosed in the first and second trimesters in the same time period differed significantly, with a greater number of comorbidities ($P<0.0001$), CHDs with univentricular outcome ($P<0.0001$), intrauterine deaths ($P=0.01$), and terminations of pregnancy ($P<0.0001$) in Group I compared with Group II. In Group III, significantly more cases of CHDs with univentricular outcome ($P<0.0001$), intrauterine demise ($P=0.036$), and early termination ($P<0.0001$) were identified compared with fetuses diagnosed with CHDs in the second trimester between 2007 and 2013. The spectrum of CHDs seen in the second-trimester groups differed after first-trimester screening was implemented.

CONCLUSIONS: First-trimester screening had a significant impact on the spectrum of CHDs and the outcomes of pregnancies with CHDs diagnosed in the second trimester. Early detection of severe forms of CHDs and significant comorbidities resulted in an increased pregnancy termination rate in the first trimester.

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Clinical Perspective

What Is New?

- The implementation of first-trimester ultrasound screening programs has fundamentally changed prenatal care by moving the detection of major abnormalities, including cardiac abnormalities, to early stages of gestation.
- First-trimester screening changes the spectrum of congenital heart defects (CHDs) later in pregnancy.
- First-trimester screening has a major impact on the outcome of pregnancies with CHDs because early detection of more severe forms of cardiac abnormalities and a higher number of comorbidities lead to an increase in early termination of first-trimester pregnancies.

What Are the Clinical Implications?

- Moving prenatal cardiac ultrasound screening to early stages of pregnancy would, in some countries, reduce the numbers of children born with severe cardiac abnormalities and with associated comorbidities.
- To provide detailed echocardiographic evaluation and appropriate counseling, fetuses suspected of having CHDs in the first trimester should be referred to a fetal cardiology specialist.
- Because of diagnostic uncertainty in some first-trimester fetuses with CHDs and possible development of CHDs later in pregnancy, second-trimester screening should continue to be part of an integral screening program scheme in pregnancy.

First-trimester screening only recently started to play a pivotal role in the management of pregnancies. Through the combination of maternal age, serum biochemistry, ultrasound anomaly scan, and additional ultrasonographic markers, this screening can identify most fetal aneuploidies and structural abnormalities in the fetus.[1,2] In addition, most congenital heart defects can be detected in the first trimester using a combination of increased nuchal translucency, reverse A wave after atrial contraction in ductus venosus, and tricuspid regurgitation on Doppler assessment. Increased nuchal translucency in euploid fetuses is associated with increased incidence of congenital heart defects (CHDs).[3] This finding is supported by Chelemen, [4] who claims that using increased nuchal translucency and reverse A wave in ductus venosus can detect CHD in the first trimester with a success rate of ≈40%. According to Huggon, [5] an increased number of chromosomal abnormalities and CHDs appear in fetuses diagnosed with tricuspid regurgitation during first-trimester screening.

Samanek[6,7] argues that the postnatal incidence of CHDs is roughly 1% (4.2–12.2 per 1000 live born infants); however, the prenatal incidence is much higher. The highest incidence is in the earliest weeks of gestation, gradually decreasing (in later weeks) with increasing weeks of gestation.[8] True prenatal incidence is unknown because of frequent intrauterine demise in the early postconceptual stages, particularly in fetuses with severe CHDs and associated comorbidities.

In this study, we aimed to compare the spectrum of CHDs, associated comorbidities, and the outcome of fetuses diagnosed with CHD in the first and second trimesters and to assess the impact of first-trimester screening on the spectrum of CHDs and the outcomes of fetuses with CHDs and associated comorbidity diagnosed in the second trimester before and after implementation of the first-trimester screening in the South Moravian region of the Czech Republic.

METHODS

In Southern Moravia, a region of the Czech Republic, 2 ultrasound screening scans are performed and financially supported by the government: 1 in the first trimester (from 11 to 13+6 weeks of gestation) and 1 in the second trimester (from 18 to 22 weeks of gestation) of pregnancy. The first-trimester ultrasound screening program was introduced in the Southern Moravian region in 2002 and formally implemented in most fetal medicine centers in the other regions of the Czech Republic by 2003.[9] Both scans are performed by trained primary obstetricians (obstetrics and gynecology is recognized as a primary, first-line specialization in the Czech Republic) or by fetal medicine specialists if a primary obstetrician is unavailable to perform the scan. Specialist fetal echocardiography is performed by fetal cardiologists.

Study Group

From January 2007 to December 2013, 87 901 fetuses (99% of all registered fetuses) from the Southern Moravian region underwent prenatal cardiac screening scans (92% in the first and second trimesters and 8% in the second trimester only). A total of 6145 fetuses (7.0% of all 87 901 screened fetuses) were referred for specialist fetal echocardiography to the Fetal Medicine Center in Brno (the principal referring center for Southern Moravia; population 1.2 million) because of the presence of a risk factor for CHDs or heart anomaly suspected on the first- or second-trimester scan. Out of 6145 referred fetuses, 296 were referred for detailed fetal echocardiography in the first trimester. Of those 296 fetuses, 127 were subsequently confirmed with cardiac abnormalities. This group of fetuses is referred to as Group I (Figure 1). The remaining 5849 fetuses were referred for fetal echocardiography only in the second trimester. CHD was diagnosed in 344 of the 5849 fetuses referred for fetal echocardiography in the second trimester. These 344 fetuses constitute Group II. Group II was formed by 2 subgroups. Group IIa consisted of 112 fetuses screened in the first trimester but whose CHD was missed. They were later screened again and subsequently referred for fetal echocardiography and diagnosed with CHD in the second trimester. Group IIb consisted of 232 fetuses of women who declined or missed the first-trimester scan and were screened

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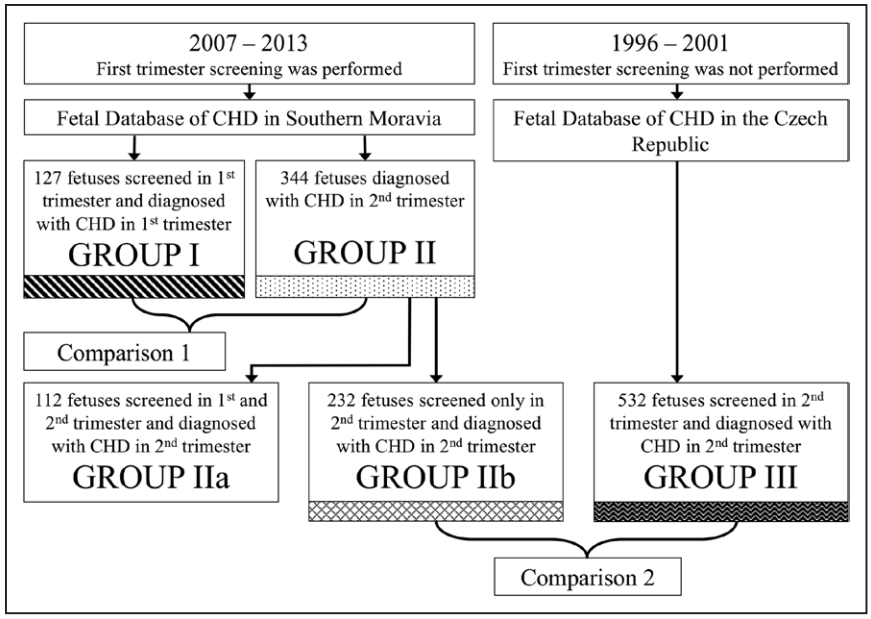

Figure 1. Study group.
CHD indicates congenital heart defect.

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in the second trimester and subsequently referred for fetal echocardiography and diagnosed with CHD. Group III comprised 532 fetuses with CHD diagnosed prenatally in the Czech Republic in the second trimester from 1996 to 2001 before the first-trimester screening was introduced and after the implementation of outflow tracts evaluation to screening protocol (same screening protocols for Groups II and III). These data were obtained from the National Fetal Database of Congenital Heart Defects in the Czech Republic.[10] Group III consisted of fetuses from the Southern Moravian region as well as the entire Czech Republic because a major region reorganization in 2001 changed the Southern Moravian population from 2.06 to 1.17 million inhabitants. Therefore, it was not possible to create a comparable study group of fetuses strictly from Southern Moravia from 1996 to 2001. The National Fetal Database of CHD in the Czech Republic was chosen as a data source to include more fetuses into the study group. This decision was fully justified because the Czech Republic population is rather homogenous both ethnically and socioeconomically.

The indications for specialist fetal echocardiography in the first trimester were abnormal fetal cardiac screening examination, presence of noncardiac or chromosomal abnormality, family history of CHD, increased nuchal translucency thickness, abnormal waveform in ductus venosus, and tricuspid regurgitation. In the second trimester, the indications were the same, plus maternal metabolic disease, maternal infection, maternal autoimmune disease, maternal exposure to teratogens, hydrops or arrhythmia in the fetus, conception through assisted reproductive technology, monochorionic twins, and abnormalities of umbilical cord, placental, or intraabdominal venous anatomy.[11–13]

Study Protocol

These defined groups of fetuses were compared with regard to the spectrum of CHDs, associated comorbidities, type of circulation in CHD, and outcome of fetuses. Fetuses diagnosed with a CHD in the first trimester (Group I) were compared with fetuses diagnosed with a CHD in the second trimester in the same period from 2007 to 2013 (Group II). Because Group II consists of two subgroups (Groups IIa and IIb), we compared the responses of the spectrum of CHDs, associated comorbidities, and outcome of fetuses between Groups IIa and IIb. Because our data, for almost all of the responses, do not indicate differences between Groups IIa and IIb, we used the combination of these 2 groups (which is the whole of Group II) for comparison with Group I.

To assess the impact of first-trimester screening on the second trimester, we compared fetuses screened and diagnosed with CHDs in the second trimester before 2001 (Group III), when first-trimester screening in our country was not routinely performed, with fetuses screened and diagnosed with CHDs only in the second trimester after 2007 (Group IIb), when first-trimester screening in our unit became available (Figure 1) because this group of fetuses is the only one that would be not confounded with other factors.

Classification of Cardiac Abnormalities

Complex cardiac abnormalities were classified according to the dominant heart lesion. For example, coarctation of the aorta with ventricular septal defect was classified as coarctation of the aorta. Atrioventricular septal defect, when it coexisted with double outlet right ventricle, was classified as atrioventricular septal defect. A single ventricle was classified as univentricular atrioventricular connection with double inlet or common atrioventricular valve. When an atrioventricular connection was absent, the diagnosis of tricuspid or mitral atresia was established. Hypoplastic left heart syndrome was defined as a heart with atrioventricular and ventriculoarterial concordance, small left ventricle, and reversed flow in the aortic arch. Cases with vascular rings (typically right aortic arch with aberrant left subclavian artery or double aortic arch) were included. Cases with isolated mirror imagery right aortic arch, left superior vena cava, and left aortic arch with aberrant right subclavian artery were not included.

CHDs with univentricular circulation, "functionally univentricular heart" unified different anatomic malformations, where

1 of the 2 ventricles was unable to sustain the pulmonary or systemic circulation because of diminutive size or deficiency in function.[14] In these cases, the ventricles were not amenable to biventricular repair.

Assessment of Fetal Heart (First- and Second-Trimester Cardiac Scan) and Genetic Evaluation

In the Czech Republic, from 1996, fetal cardiac screening in the second trimester was performed by analyzing a 4-chamber view and outflow tracts relationship. From 2002, the first-trimester cardiac screening included a 4-chamber view as well as both arterial outflow tract views.

Similar fetal echocardiography protocols were used in the second-trimester scan (both periods 1996–2001 and 2007–2013) and in the first-trimester scan (2007–2013): examination of the visceroatrial situs, cardiac axis, 4-chamber view, systemic venous connections, pulmonary venous return, evaluation of both arterial outflow tracts, 3 vessels and trachea view, and sagittal views of the aortic and ductal arches. Pulmonary veins were not consistently identified in every first-trimester scan.

The ultrasound machines used in the earlier and later eras differed in quality. In both periods, detailed fetal 2-dimensional, M-mode, color Doppler, and spectral Doppler echocardiograms were performed for detailed fetal cardiac assessment. In the earlier years, electronic phased array (convex and linear) probes operating on 3-7 MHz were used. In later years, multifrequency probes and matrix 2-dimensional/3-dimensional probes (4–8 MHz) were often used to assess cardiac structures in detail. Three-dimensional imaging (including Spatio-Temporal Image Correlation) was not routinely used to establish definitive cardiac diagnosis. In contrast, a high-definition power Doppler imaging was used routinely in all cases after 2007.

In all second-trimester and in the majority of first-trimester fetuses, the ultrasound examination was performed by transabdominal approach. Transvaginal approach was used in 7 of 127 (5.5%) first-trimester fetuses because of suboptimal quality of the transabdominal echocardiogram.

The diagnoses were verified through serial ultrasound examinations, a second examiner, midtrimester scans, postnatal echocardiography, or postmortems. Genetic consultation and karyotype were performed prenatally in all 127 fetuses diagnosed with CHDs in the first trimester. Out of the 876 fetuses diagnosed with CHDs in the second trimester (344 in Group II and 532 in Group III), in 656 fetuses (227 of 344 fetuses in Group II and 429 of 532 fetuses in Group III), genetic consultation and karyotype were performed prenatally. In the remaining 220 fetuses (117 of 344 fetuses in Group II and 103 of 532 fetuses in Group III), genetic evaluation (ie, clinical examination, genetic consultation, and, in some indicated cases, genetic testing) was performed postnatally. Prenatal cytogenetic and molecular genetic analyzes were performed on fetal cells obtained by chorionic villus sampling or amniocentesis.

Significant developments have occurred in prenatal genetic testing. From 1996 to 2001, karyotypes were done by cytogenetic analysis. In fetuses with suspected DiGeorge syndrome, the karyotype was completed by fluorescent in situ hybridization. From 2007 to 2013, quantitative fluorescence-polymerase chain reaction was performed as a first-line examination to exclude the most frequent chromosomal aneuploidies: trisomy 13, 18, and 21 and X chromosome monosomy. In cases of normal quantitative fluorescence-polymerase chain reaction, the karyotype was done by cytogenetic analysis or comparative genomic hybridization array. In fetuses with suspected DiGeorge syndrome, the karyotype was completed by fluorescent in situ hybridization, multiplex ligation-dependent probe, or comparative genomic hybridization array, if not done previously. In selected cases with a family history of CHDs where all mentioned techniques showed a normal result, targeted next-generation sequencing was performed.

Ethical Considerations

This study was discussed with the Institutional Review Board, but specific ethical approval was not necessary because the evaluation of fetuses was part of the management of pregnancies with CHDs in fetuses. Data analysis was assessed retrospectively.

Statistical Analysis

In the statistical analysis, dichotomous and multicategory response variables (congenital heart defect abnormalities, comorbidities, and outcomes) were investigated. All dichotomous response variables were analyzed by applying linear logistic regression model with logit transformation of probability of the event of interest with respect to group indicators, with reference-level parametrization. All response variables that allow for multiple categories in the response were analyzed using a multicategory logistic regression model with a generalized logit link with logarithms of ratios of probabilities of the category of interest and the reference category. In Tables 1–4, we present estimates of probabilities of outcome categories together with corresponding 95% confidence intervals (CIs) and *P*-values for group comparisons resulting from likelihood ratio tests. For multiple comparisons, we applied Tukey-Kramer adjustment to protect the probability of type I error. The analysis was carried out in SAS, Statistical Software System, Version 9.4.

RESULTS

Spectrum of Cardiac Abnormalities

From 2007 to 2013, 127 fetuses were diagnosed with CHDs in the first trimester (Group I) and 344 in the second trimester (112 fetuses with missed CHDs in the first trimester [Group IIa] and 232 fetuses with CHDs in pregnancies not attending first-trimester screening [Group IIb]). Within this period, in the first trimester (Group I), the most common diagnosed lesions were hypoplastic left heart syndrome in 27 cases (21.3%), atrioventricular septal defect in 26 cases (20.5%), pulmonary atresia in 10 cases (7.9%), and coarctation of the aorta (great vessels disproportion) in 9 cases (7.1%). In the second trimester, from 2007 to 2013 (Group II), the most common diagnosed lesions were atrioventricular septal defect in 45 cases (13.1%), transposition of great arteries in 31 cases (9.0%), coarctation of aorta in 30 cases (8.7%), and hypoplastic left heart syndrome and

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Table 1. Spectrum of Congenital Heart Defects Diagnosed in First and Second Trimesters from 2007 to 2013 (Groups I and II)

Cardiac Abnormality	First Trimester (2007–2013) Group I			Second Trimester (2007–2013) Group II			Group I Versus Group II *P* value
	N=127	Frequency (%)	95% CI	N=344	Frequency (%)	95% CI	
Hypoplastic left heart	27	21.3	15.0–29.2	28	8.1	5.7–11.5	<0.001
Atrioventricular septal defect	26	20.5	14.3–28.4	45	13.1	9.9–17.1	0.053
Pulmonary atresia	10	7.9	4.3–14.0	7	2.0	1.0–4.2	0.005
Coarctation of the aorta	9	7.1	3.7–13.1	30	8.7	6.2–12.2	0.563
Tricuspid atresia	8	6.3	3.2–12.1	7	2.0	1.0–4.2	0.028
Tetralogy of Fallot	8	6.3	3.2–12.1	26	7.6	5.2–10.9	0.635
Ventricular septal defect	8	6.3	3.2–12.1	25	7.3	5.0–10.5	0.712
Aortic stenosis	5	3.9	1.6–9.1	27	7.8	5.4–11.2	0.115
Vascular rings	5	3.9	1.6–9.1	28	8.1	5.7–11.5	0.094
Double inlet ventricle	3	2.4	0.8–7.1	7	2.0	1.0–4.2	0.829
Double outlet ventricle	3	2.4	0.8–7.1	24	7.0	4.7–10.2	0.038
Persistent truncus arteriosus	2	1.6	0.4–6.1	8	2.3	1.2–4.6	0.605
Ebstein anomaly	2	1.6	0.4–6.1	3	0.9	0.3–2.7	0.526
Transposition of the great arteries	1	0.8	0.1–5.4	31	9.0	6.4–12.5	<0.001
Pulmonary stenosis	0	0.0	0–1	17	4.9	3.1–7.8	0.001
Others	10	7.9	4.3–14.0	31	9.0	6.4–12.5	0.695

CI indicates confidence interval.

vascular ring each in 28 cases (8.1%) fetuses. The frequency of hypoplastic left heart syndrome ($P<0.001$), pulmonary atresia ($P=0.005$), and tricuspid atresia ($P=0.028$) was significantly higher in the first trimester, whereas the detection of double outlet right ventricle ($P=0.038$), transposition of great arteries ($P<0.001$), and pulmonary stenosis ($P=0.001$) was higher in the second trimester during the same period. Furthermore, in the second trimester, more fetuses were diagnosed with aortic stenosis and vascular ring (Table 1).

In Group IIb, of 232 fetuses diagnosed with CHDs in the second trimester from 2007 to 2013, the most common lesions were atrioventricular septal defect in 36 cases (15.5%), hypoplastic left heart syndrome and coarctation of aorta each in 21 cases (9.1%), and transposition of great arteries in 20 cases (8.6%). In the second trimester, from 1996 to 2001 (Group III), 532 fetuses were diagnosed with CHDs. During this period, when first-trimester screening was not routinely performed, the most frequent cardiac abnormalities were atrioventricular septal defect in 101 cases (19.0%), hypoplastic left heart syndrome in 91 cases (17.1%), and double outlet right ventricle in 55 cases (10.3%). Before 2001, significantly more fetuses were diagnosed with hypoplastic left heart syndrome ($P=0.003$) and pulmonary atresia ($P=0.006$) compared with after 2007. In contrast, the detection of coarctation of aorta ($P=0.004$), Tetralogy of Fallot ($P=0.034$), vascular ring ($P<0.0001$), and pulmonary stenosis ($P=0.008$) was significantly higher in the second trimester in Group IIb after 2007 (Table 2).

Associated Comorbidity and Outcome of Fetuses

Out of 127 fetuses detected with CHDs in the first trimester (Group I), any comorbidity (chromosomal or structural noncardiac anomalies) was found in 85 fetuses (66.9%, 95% CI, 58.3–74.5), whereas isolated cardiac abnormality was confirmed in 42 fetuses (33.1%). Chromosomal anomalies were found in 63 fetuses (49.6%, 95% CI, 41.0–58.2) and structural noncardiac anomalies in 58 fetuses (45.7%, 95% CI, 37.2–54.4). CHDs with univentricular circulation were identified in 54 fetuses (42.5%, 95% CI, 34.2–51.3) (Figure 2). Only 12 (9.5%, 95% CI, 5.4–15.9) of 127 fetuses diagnosed in the first trimester were born alive, and the diagnosis of CHD was confirmed postnatally in all. Seven fetuses (5.5%, 95% CI, 1.5–9.5) died in utero, and pregnancy was terminated in another 108 fetuses (85.0%, 95% CI, 78.8–91.2) (Figure 3).

In all terminated fetuses, the diagnosis was confirmed by a second examiner within 1 to 3 weeks after the first cardiac scan before termination of pregnancy. In the Czech Republic, postmortem is mandatory by law. Thus, of the 115 fetuses that were not born (7 intrauterine deaths + 108 terminations of pregnancy), in 47 (41.0%), the main diagnosis was confirmed by postmortem (from

Table 2. Spectrum of Congenital Heart Defects Diagnosed in Second Trimester From 2007 to 2013 (Group IIb) and in Second Trimester from 1996 to 2001 (Group III)

Cardiac Abnormality	Second Trimester (2007–2013) Group IIb			Second Trimester (1996–2001) Group III			Group IIb Versus Group III *P* value
	N=232	Frequency (%)	95% CI	N=532	Frequency (%)	95% CI	
Hypoplastic left heart	21	9.1	6.0–13.5	91	17.1	14.1–20.5	0.003
Atrioventricular septal defect	36	15.5	11.4–20.8	101	19.0	15.9–22.5	0.246
Pulmonary atresia	5	2.2	0.9–5.1	35	6.6	4.8–9.0	0.006
Coarctation of the aorta	21	9.1	6.0–13.5	20	3.8	2.4–5.8	0.004
Tricuspid atresia	5	2.2	0.9–5.1	19	3.6	2.3–5.5	0.285
Tetralogy of Fallot	18	7.8	4.9–12.0	21	3.9	2.6–6.0	0.034
Ventricular septal defect	18	7.8	4.9–12.0	46	8.6	6.5–11.4	0.682
Aortic stenosis	15	6.5	3.9–10.4	24	4.5	3.0–6.6	0.269
Vascular rings	15	6.5	3.9–10.4	0	<0.001	<0.001–1	<0.0001
Double inlet ventricle	6	2.6	1.2–5.6	30	5.6	4.0–8.0	0.053
Double outlet ventricle	19	8.2	5.3–12.5	55	10.3	8.0–13.2	0.349
Persistent truncus arteriosus	6	2.6	1.2–5.6	20	3.8	2.4–5.8	0.399
Ebstein anomaly	2	0.9	0.2–3.4	5	0.9	0.4–2.2	0.917
Transposition of the great arteries	20	8.6	5.6–13.0	33	6.2	4.4–8.6	0.235
Pulmonary stenosis	9	3.9	2.0–7.3	5	0.9	0.4–2.2	0.008
Others	16	6.9	4.3–11.0	27	5.1	3.5–7.3	0.324

CI indicates confidence interval.

13 to 23 weeks of gestation, median 16+3). In 46 fetuses (40.0%) who died or were terminated in the earlier weeks of pregnancy (from 12 to 14 weeks of gestation, median 12+5), the diagnosis was impossible to confirm postmortem because of fragmentation of the fetus. In the remaining 22 fetuses (19.0%), postmortem information was unavailable.

Similarly, of 344 fetuses (Group II) diagnosed with CHDs in the second trimester from 2007 to 2013, any comorbidity was found in 112 fetuses (32.6%, 95% CI, 27.8–37.7), and isolated cardiac abnormality was detected in 232 fetuses (67.4%). Chromosomal anomalies were found in 57 cases (16.6%, 95% CI, 13.0–20.9), structural noncardiac anomalies were found in 84 cases (24.4%, 95% CI, 20.2–29.2), and CHDs with univentricular circulation in 50 cases (14.5%, 95% CI, 11.2–18.7) (Figure 2). Four fetuses (1.2%, 95% CI, 0.03–2.3) from Group II died in utero, pregnancy was terminated in 112 cases (32.5%, 95% CI, 27.6–37.5), and 228 fetuses (66.3%, 95% CI, 61.1–71.8) were born alive (Figure 3).

In all fetuses terminated in second trimester, the diagnosis was confirmed by a second examiner before

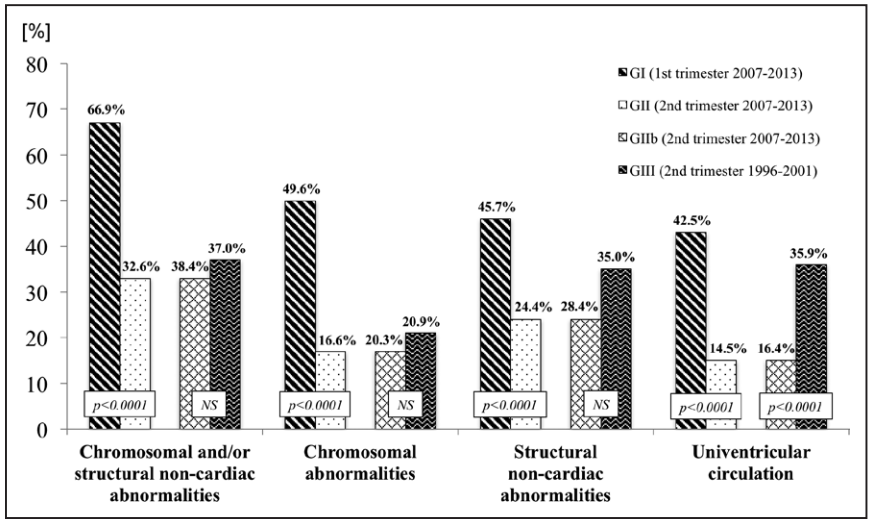

Figure 2. Associated comorbidity and type of circulation in first and second trimesters from 2007 to 2013 and in second trimester from 1996 to 2001.
NS indicates not significant.

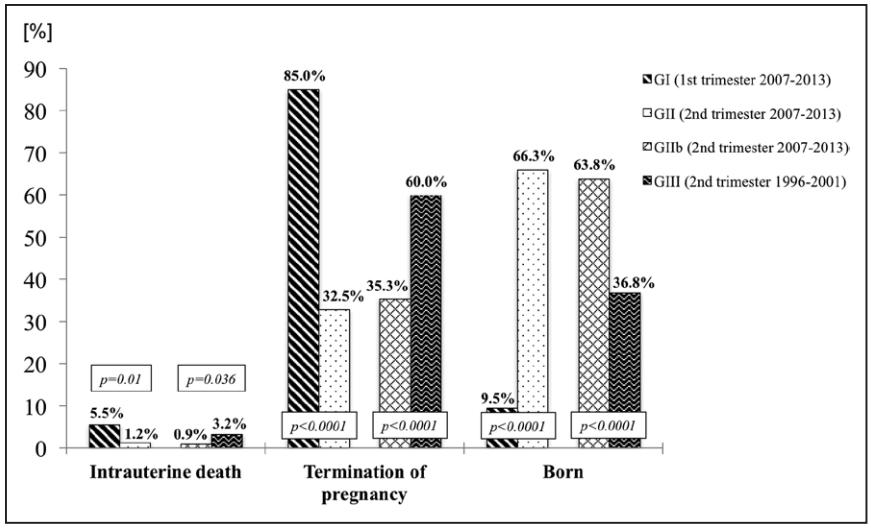

Figure 3. Outcome of fetuses with congenital heart defect diagnosed in the first and second trimesters from 2007 to 2013 and in the second trimester from 1996 to 2001.

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termination of pregnancy. Out of 116 fetuses that were not born (4 intrauterine deaths + 112 terminations of pregnancy), the diagnosis was confirmed by postmortem in 114 cases (98.3%). Only 2 families declined postmortem. In 228 fetuses born alive, the CHD diagnosis was confirmed postnatally.

Our data indicate that significantly more comorbidities ($P<0.0001$), chromosomal abnormalities ($P<0.0001$), structural noncardiac abnormalities ($P<0.0001$), CHD with univentricular outcome ($P<0.0001$), intrauterine deaths ($P=0.01$), and terminations of pregnancy ($P<0.0001$) were identified in the group of CHD cases diagnosed within the first trimester (Group I) compared with the second trimester (Group II) from 2007 to 2013 (Figures 2 and 3).

Out of 232 fetuses from Group IIb (subgroup of Group II), comorbidity was found in 89 fetuses (38.4%, 95% CI, 32.3–44.8), whereas isolated cardiac abnormality was confirmed in 143 fetuses (61.6%). Chromosomal anomalies were found in 47 fetuses (20.3%, 95% CI, 15.6–25.9) and structural noncardiac anomalies in 66 fetuses (28.4%, 95% CI, 23.0–34.6). CHDs with univentricular circulation were identified in 38 fetuses (16.4%, 95% CI, 12.2–21.7) (Figure 2). Two fetuses (0.9%, 95% CI, 0.0–2.1) from Group IIb died in utero, pregnancy was terminated in 82 cases (35.3%, 95% CI, 29.2–41.5), and 148 fetuses were born (63.8%, 95% CI, 57.4–69.7) (Figure 3).

In 532 fetal CHD cases diagnosed in the second trimester from 1996 to 2001 (Group III), any comorbidity was detected in 197 cases (37.0%, 95% CI, 33.0–41.2) and isolated cardiac abnormality in 335 cases (63.0%). Chromosomal anomalies were detected in 111 cases (20.9%, 95% CI, 17.6–24.5), structural noncardiac anomalies in 186 cases (35.0%, 95% CI, 31.0–39.1), and CHDs with univentricular circulation in 191 cases (35.9%, 95% CI, 32.0–40.1) (Figure 2). Intrauterine death occurred in 17 fetuses (3.2%, 95% CI, 1.7–4.7), pregnancy was terminated in 319 cases (60.0%, 95% CI, 55.8–64.1), and 196 fetuses were born (36.8%, 95% CI, 32.8–41.0) (Figure 3).

Lastly, we observed a significantly higher frequency of CHD cases with univentricular outcomes ($P<0.0001$), intrauterine deaths ($P=0.036$), and terminations of pregnancy ($P<0.0001$) in Group III compared with Group IIb (Figures 2 and 3).

Significantly more fetuses were detected with trisomy 21 ($P=0.0008$), trisomy 18 ($P=0.023$), trisomy 13 ($P<0.0001$), and X chromosome monosomy ($P<0.0001$) in the first trimester compared with the second trimester from 2007 to 2013 (Table 3). A higher detection of the other chromosomal abnormalities ($P=0.030$) was found in the second trimester in Group IIb from 2007 to 2013 compared with the second trimester from 1996 to 2001 in Group III (Table 4).

DISCUSSION

It has been confirmed by epidemiological and postmortem studies that the spectrum and frequency of the individual lesions found prenatally differ from those found postnatally.[15–17] In this study, we confirmed that the spectrum of congenital heart abnormalities diagnosed in the first and second trimesters differed significantly as well with more comorbidities, conditions with univentricular outcomes, intrauterine deaths, and pregnancy terminations in the first trimester. Furthermore, we confirmed for the first time on a large group of fetuses in 2 time periods that first-trimester screening implementation as part of prenatal care changes the spectrum of congenital heart defects in later pregnancy and has a major impact on the postnatal outcome of children with CHDs.

Second-trimester cardiac screening programs were implemented and financially supported by governments in many developed countries back in 1980 to 1990.

Table 3. Chromosomal Abnormalities Diagnosed in First and Second Trimesters From 2007 to 2013 (Groups I and II)

Chromosomal Abnormalities	First Trimester (2007–2013) Group I			Second Trimester (2007–2013) Group II			Group I Versus Group II *P* value
	N	Frequency (%)	95% CI	N	Frequency (%)	95% CI	
Trisomy 21	18	14.2	(8.1–20.2)	16	4.7	(2.4–6.9)	0.0008
Trisomy 18	13	10.2	(5.0–15.5)	15	4.4	(2.2–6.5)	0.023
Trisomy 13	11	8.7	(3.8–13.6)	4	1.2	(0.02–2.3)	<0.0001
Monosomy X	13	10.2	(5.0–15.5)	5	1.5	(0.2–2.7)	<0.0001
Deletion 22q11	0	0.0	(0.0-0.0)	6	1.7	(0.4–3.1)	0.051
Others	8	6.3	(2.1–10.5)	11	3.2	(1.3–5.1)	0.150
Total	63	49.6	(41.0–58.2)	57	16.6	(13.0–20.9)	<0.0001

CI indicates confidence interval.

Several national and international recommendations and guidelines[11–13] have helped to develop organizational, structural, and educational programs to offer standard quality of care to all patients in each country. These programs have been successfully supported by health organizers in almost all countries within the European Union. The implementation of first-trimester ultrasound screening programs at the beginning of the new millennium fundamentally changed prenatal care by moving the detection of major abnormalities to the early stages of gestation.[1] A recent review of published data in 13 centers indicated that first-trimester detection rates of major CHDs varied between 2.3% and 54.5% in euploid fetuses and between 36.8% and 82.1% in euploid and aneuploid fetuses.[18]

We documented that in the early weeks of gestation, the incidence of cardiac abnormalities was higher and more often associated with chromosomal abnormalities. In our study, 49.6% of heart abnormalities detected in the first trimester were associated with chromosomal abnormalities. A similar study, also performed in the first trimester, revealed chromosomal abnormalities in 72.9% of cases.[19] Other published studies documented that the frequency of chromosomal abnormalities in fetuses varied between 16% and 47% depending on the gestational age.[20,21] The differences in outcomes of 2 screening programs in the 2 different time periods of our study are influenced by the tremendous progress in the detection of chromosomal abnormalities as several new techniques (quantitative fluorescent polymerase chain reaction, array comparative genomic hybridization, and noninvasive prenatal testing) have emerged, offering more detailed and rapid genetic qualitative evaluation. In our study, associated cumulative (first- and second-trimester) frequencies of chromosomal aberrations were 49.6% (first trimester) and 16.6% (second trimester) compared with only 20.9% aneuploidies detected during second-trimester screening between 1996 and 2001.

Although major structural abnormalities can be identified at 11 to 13 weeks of gestation, the accuracy of diagnosis in the first trimester depends on multiple factors, such as the expertise of the sonographer, time allocated for fetal examination, quality of the equipment, and presence of an easily detectable marker for CHD (increased NT, abnormal flow in the ductus venosus, and tricuspid regurgitation).[3–5,18,22]

Table 4. Chromosomal Abnormalities Diagnosed in Second Trimester From 2007 to 2013 (Group IIb) and in Second Trimester From 1996 to 2001 (Group III)

Chromosomal Abnormalities	Second Trimester (2007–2013) Group IIb			Second Trimester (1996–2001) Group III			Group IIb Versus Group III *P* value
	N	Frequency (%)	95% CI*	N	Frequency (%)	95% CI	
Trisomy 21	13	5.6	(2.6–8.6)	47	8.8	(6.4–11.2)	0.116
Trisomy 18	14	6.0	(3.0–9.1)	34	6.4	(4.3–8.5)	0.844
Trisomy 13	2	0.9	(0.0–2.1)	5	0.9	(0.1–1.8)	0.911
Monosomy X	4	1.7	(0.0–3.4)	12	2.3	(1.0–3.5)	0.636
Deletion 22q11	4	1.7	(0.0–3.4)	5	0.9	(0.1–1.8)	0.376
Others	10	4.3	(1.7–6.9)	8	1.5	(0.5–2.5)	0.030
Total	47	20.3	(15.6–25.9)	111	20.9	(17.6–24.5)	0.849

CI indicates confidence interval.

Better quality ultrasound machines with more advanced technology were used in the latter period of our study (2007–2013) compared with the former period (1996–2001). We believe that the new advanced technology, such as high-definition imaging and high-definition power Doppler ultrasound in particular, may contribute to better detection of CHDs associated with vascular abnormalities such as vascular rings, aortopulmonary collaterals, coronary fistulae, and pulmonary vein abnormalities. The progress in cardiovascular imaging is documented by a higher number of detected vascular rings and anomalies of aortic arches and neck arteries in the latter period (2007–2013).

Also, the differences in detection of major structural cardiac abnormalities are related to the quality of training provided, the skills of individual colleagues, and improved technology over this period. Therefore, it is crucial to improve the technological aspects of ultrasound scanning as well as provide high-level training in first-trimester ultrasound screening for fetal sonographers and obstetricians. Introducing new training standards significantly helped improve detection rates of vascular abnormalities and great artery lesions.[23] The 3-vessels and trachea view has been implemented recently in fetal anomaly scans in the United Kingdom, and similar trends are seen in other countries as well.

Persico[24] suggested that the vast majority of major CHDs (≤84%) can be detected during the first-trimester fetal ultrasound scan performed by experienced fetal sonographers and obstetricians. Moving prenatal cardiac ultrasound screening to the early stages of pregnancy would, in some countries, reduce the numbers of children born with severe cardiac abnormalities and with associated comorbidities. However, such first-trimester screening will possibly miss some heart conditions (eg, ventricular septal defects, total anomalous pulmonary venous connection, aortic and pulmonary stenosis).

Similarly, early termination might be considered in CHD cases that could have rather good postnatal outcomes (eg, typically in aortic coarctation, wrongly diagnosed as hypoplastic left heart syndrome). In addition, in the first trimester, it is not always possible to detect cardiac abnormalities in enough detail to provide the family with correct information about the natural progress of disease, the postnatal patient's management, and treatment options. Typical abnormalities falling under the category of likely incomplete diagnosis in the first trimester are common arterial trunk, pulmonary atresia with ventricular septal defect, and the majority of complex CHDs. Furthermore, some heart lesions are detectable or develop at later stages of pregnancy (eg, heart tumors [typically rhabdomyoma], aortic coarctation, and cardiomyopathy), whereas some heart abnormalities can progress throughout the pregnancy. It has been known that disproportion in the 4-chamber view may be caused by a variety of cardiac abnormalities (typically aortic coarctation and arch hypoplasia)[25] and noncardiac abnormalities, including abnormal blood flow distribution (persistent left superior vena cava draining coronary sinus),[26] as well as the presence of chromosomal abnormalities.[27] The progression of aortic stenosis toward hypoplastic left heart syndrome is well known.[28,29] In many of these cases, family counseling is extremely difficult because physicians are expected to predict as much as possible from little diagnostic information. Detection of heart abnormalities, which can develop into such a vast variety of conditions, causes uncertainty and significant stress for families.[30,31]

In 2011, noninvasive prenatal testing of some chromosomal aneuploidies and submicroscopic chromosomal aberrations using cell-free DNA analysis was introduced into clinical practice.[32] In some countries, this approach could potentially result in the diagnosis of fetuses with trisomies or other chromosomal abnormalities and subsequently increase the termination rate of pregnancies with chromosomal abnormalities without ultrasound screening. However, based on the recommendations of professional societies, noninvasive prenatal testing is not a diagnostic test, and confirmatory invasive testing (amniocentesis preferably) is required in case of any abnormal result.[33] However, direct-to-consumer noninvasive prenatal testing examinations (mostly those that are targeted on chromosomes 13, 18, and 21 only) without previous discussion with a health professional (gynecologist, obstetrician, geneticist, etc.) could lead to missed diagnoses of heart defects that are caused by submicroscopic aberrations (ie, DiGeorge syndrome) or germline mutations or have a nongenetic background.

We are in agreement with Persico's[24] recommendation for all fetuses with CHD detected in the first trimester to be referred for specialized fetal echocardiography to better evaluate the cardiac abnormality, confirm the correct diagnosis, and provide appropriate family counseling. We believe that the second-trimester cardiac screening program should be maintained to confirm normal cardiovascular structures or reassess fetuses with cardiac abnormalities detected in the first trimester; for all these reasons, we would not change the existing practice. Also, Nicolaides's[1] inverted pyramid model of prenatal investigations, which moves prenatal care into the first trimester, keeps second-trimester screening in the prenatal care process for all the pregnancies to re-evaluate fetal anatomy and growth. This approach is also recommended by the International Society of Ultrasound in Obstetrics and Gynecology consensus statement that a pregnant woman with family history of CHD, increased NT, or abnormal fetal cardiac screening evaluation in the fetus should be offered a fetal echocardiography scan at or before 14 weeks of gestation with a follow-up scan at 20 to 22 weeks.[13] First-trimester counseling should be carried out with the parents made aware that a more detailed diagnosis and more accurate prediction of fetal

outcome should be achievable in the later stages of the pregnancy. Nevertheless, we still perceive first-trimester screening to be perilous because it could lead to more frequent terminations of pregnancies in euploid fetuses with CHDs that otherwise might have had favorable outcomes.

In addition, pre- and postnatal diagnostic protocols and follow-up data collection (including postmortem data) are necessary to assess the impact of prenatal diagnoses on postnatal outcomes and learn from the natural and unnatural histories of CHDs.

CONCLUSIONS

Our results from the Southern Moravian region confirmed the significant impact of first-trimester screening on the spectrum of CHDs later in pregnancy and on the outcomes of pregnancies with a CHD, in that more severe forms of cardiac abnormalities and higher comorbidities resulted in an increase in early termination of first-trimester pregnancies. In the second trimester, less severe forms of cardiac abnormalities were diagnosed. These fetuses had better postnatal outcomes because of more frequent biventricular circulation and fewer associated comorbidities. However, first-trimester screening was unable to detect some serious heart conditions with duct-dependent circulation, which have good long-term postnatal outcomes if treated appropriately. In addition, the early diagnostic ultrasound appearance does not allow the accurate prediction of later clinical outcomes. We believe that the second-trimester screening program has its place in an integral, multimodality screening program scheme in pregnancy. National healthcare providers should continue supporting these programs, including educational programs for specialized sonographers and doctors. The concept of the implementation of fetal medicine centers with specialized sonographers or doctors collaborating with first-line healthcare providers and tertiary experts in fetal/pediatric cardiology appears to be optimal for the Czech Republic as well as other countries.

LIMITATIONS

We are aware of a rather small screening population sample in our study. However, the prenatal cardiac screening program has been well organized, with 98% of pregnant women in the entire Czech Republic participating in prenatal screening. Not all children born alive in our geographical area had complete cross-section imaging confirming normal cardiac structures, and not all terminated fetuses, or those who died before reaching term, had a postmortem examination to confirm prenatal diagnosis. However, all children who died postnatally did have a postmortem examination (mandatory in children <18 years of age), and all those who presented with a heart murmur or any clinical symptoms suggestive of a heart condition did have comprehensive cardiology review, including detailed echocardiography.

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DISCLOSURES

None.

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FOOTNOTES

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Does First-Trimester Screening Modify the Natural History of Congenital Heart Disease?: Analysis of Outcome of Regional Cardiac Screening at 2 Different Time Periods

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