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Incidence of nonsyndromic congenital heart defects in the Republic of Srpska in the period 2015–2016

Učestalost nesindromskih urođenih srčanih mana u Republici Srpskoj u periodu od 2015. do 2016. godine

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Abstract

Background/Aim. Congenital heart defect (CHD) is the most common type of birth defect and one of the leading causes of infant mortality. It can be isolated or occur as a part of multiple different syndromes. The reported worldwide incidence of isolated CHD is between 70 and 120 *per* 10,000 live births. The aim of the study was to estimate the incidence of nonsyndromic CHD in the Republic of Srpska (RS), Bosnia and Herzegovina and compare it with other countries. **Methods.** The fetuses, live-born and stillborn infants with CHD during 2015 and 2016 in the RS, were analyzed using data from a cross-sectional study. **Results.** The total incidence of CHD was 163.95 *per* 10,000 total births, and the incidence of live-born with CHD was 136.64 *per* 10,000. The diagnosis was established prenatally in 8.09% of cases. The most common type of anomaly was ventricular septal defect (45.63%), followed by an atrial septal defect (31.40%), patent ductus arteriosus (7.44%), and pulmonary valve stenosis (5.18%). A significant difference in the incidence of CHD between regions and different maternal age groups was found. **Conclusion.** The incidence of CHD in the RS found in this study is higher than in other studies, with marked heterogeneity between different regions. This study provides baseline data for future monitoring of the risk factor changes and the implementation of primary preventive measures.

Key words:
bosnia and herzegovina; fetus; heart defects, congenital; incidence; infant, newborn.

Apstrakt

Uvod/Cilj. Urođena srčana mana (USM) je najčešći tip urođene mane i jedan od vodećih uzroka umiranja odojčadi. Može biti izolovana ili deo mnogobrojnih sindroma. Učestalost izolovane USM u svetu iznosi između 70 i 120 na 10 000 živorođene dece. Cilj rada bio je da se utvrdi učestalost nesindromskih USM u Republici Srpskoj (RS), Bosna i Hercegovina i da se uporedi sa drugim državama. **Metode.** Korišćenjem podataka iz studije preseka, analizirani su slučajevi fetusa, živorođene i mrtvorođene dece sa USM u 2015. i 2016. godini u RS. **Rezultati.** Ukupna učestalost USM iznosila je 163,95 na 10 000 porođaja, a učestalost novorođenčadi sa USM 136,64 na 10 000 živorođenih novorođenčadi. Dijagnoza je postavljana prenatalno u 8,09% slučajeva. Najčešći tip anomalije bio je ventrikularni septalni defekt (45,63%), zatim atrijalni septalni defekt (31,40%), otvoreni duktus arteriozus (7,44%) i stenoza plućne valvule (5,18%). Utvrđena je značajna razlika u učestalosti USM među regijama i između majki različitog životnog doba. **Zaključak**. Učestalost USM u RS utvrđena u ovoj studiji značajno je veća od učestalosti USM utvrđene u drugim studijama i značajno se razlikuje među regijama. Ova studija pruža osnovne podatke koji bi se mogli koristiti za praćenje USM i promenu faktora rizika, kao i sprovođenje primarnih preventivnih mera.

Ključne reči:
bosna i hercegovina; fetus; srce, kongenitalne mane; incidenca; novorođenče.

Introduction

Congenital heart defect (CHD) is a structural abnormality of the heart and great vessels that is present at birth [1]. It is the most common type of major birth defect and the leading cause of birth defect-associated infant death and illness [2]. The underlying causes of CHD remain poorly understood and are thought to be genetic and environmental. In the majority of cases, CHD is isolated, and in about one-third of cases occurs as a part of a syndrome [3].

The incidence of CHD at birth (sometimes referred to as birth prevalence) varies between studies. According to the

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latest reports, the worldwide incidence of CHD is between 70 and 120 *per* 10,000 births [4–7]. Owing to the improvement in diagnostics, the reported incidence of mild CHD is slightly increasing over time due to a higher detection rate [8]. On the other hand, the incidence of the most severe CHD, like hypoplastic left heart syndrome, is decreasing consistently with better prenatal diagnostics and consequent termination of pregnancy [9]. Prenatal diagnosis of CHD generally improves treatment success by allowing appropriate preparation for birth and fetal cardiac intervention.

Nowadays, primary prevention measures include rubella vaccination, good glycemic control, avoiding known teratogenic drugs, folic acid supplementation [10], avoiding contact with influenza and febrile illnesses, as well as exposition to organic solvents [11]. There is growing evidence of a link between maternal obesity [12] and limited evidence of a link between maternal smoking and advanced maternal age [13].

The aim of this study was to determine the incidence of nonsyndromic CHD in the Republic of Srpska (RS), which is a part of Bosnia and Herzegovina, and to compare our findings with other reports.

Methods

The study was cross-sectional and involved all the fetuses, live-born and stillborn children with CHD in the RS from 1 January 2015 to 31 December 2016.

The study was conducted according to the principles of the Declaration of Helsinki. There was no written informed consent obtained from the parents of the participants; however, they were verbally informed that their child's condition and other relevant information about the child and mother would be reported to the Clinic for Children's Diseases and that their personal information would not be available to the public. Bearing in mind that not all of the institutions involved in the study have an Ethics Committee, the study was approved by the Ministry of Health and Social Welfare of the RS from September 17, 2015.

Data were collected in the form of a questionnaire survey conducted by 52 physicians, 46 of whom were pediatricians and 6 were gynecologists working at university centers, general hospitals, or primary healthcare institutions from all six regions of the RS. Physicians reported the presence and the type of CHD, additional anomalies and chromosomal aberrations, time of diagnosis of the anomaly (prenatally or postnatally), child's birth date and gender, duration of pregnancy, and mother's age and place of living. These questionnaire surveys were sent by regular mail to the Clinic for Children's Diseases in the University Clinical Center of the RS, where they were collected and analyzed.

Diagnosis of CHD was established by a pediatric cardiologist using a color doppler echocardiogram. Infants and fetuses with chromosomal aberrations were excluded. In addition, a clinical geneticist manually reviewed the records of cases with multiple anomalies to exclude the ones in which CHD was suspected to be a part of a genetic syndrome. Since they were not considered structural abnormalities, normal physiological findings in premature or newborn infants younger than six weeks, such as patent ductus arteriosus, patent *foramen* ovale, or valve insufficiency unrelated to structural valve abnormality, were excluded from the analysis. Patent ductus arteriosus was only considered a CHD if it occurred in the term infants and was not maintained patent to ensure survival due to another cardiac condition.

Infants and fetuses with CHD were grouped in the following way: into 15 groups according to the type of defect (common arterial truncus, double outlet right ventricle, transposition of great vessels, single ventricle, ventricular septal defect, atrial septal defect, atrioventricular septal defect, tetralogy of Fallot, pulmonary valve stenosis, pulmonary valve atresia, hypoplastic left heart, coarctation of aorta, aortic atresia/interrupted aortic arch, total anomalous pulmonary venous return, and patent ductus arteriosus); into three groups according to the number of CHD (single, double, and triple); into six groups according to the region of the RS where the mother of the child was living (Banja Luka, Prijedor, Doboj, Bijeljina, Istočno Sarajevo, and Trebinje); into two groups according to the birth year (2015 and 2016); into three groups according to the gender of the child or fetus (male, female, and unknown); into two groups according to the maternal age (younger than 35 years and 35 years and older); into two groups according to the time of diagnosis (prenatally and postnatally).

The total incidence of CHD was defined as the total number of CHD among live-born and stillborn children plus the number of pregnancies terminated for severe fetal heart anomaly *per* 10,000 total births. Live birth incidence of CHD was defined as the number of live-born children with CHD *per* 10,000 live births.

The total number of births in the RS was as follows: 9,357 in 2015 and 9,452 in 2016 [14].

We compared the incidence of CHD between groups and data reported by other studies and discussed the possible causes for the differences found.

Statistical analysis

Statistical analyses were performed using the statistical package SPSS. The obtained data were expressed as counts and percentages. Differences among groups were evaluated using the chi-square (χ^2) test. A two-tailed $p \leq 0.05$ was considered to indicate statistical significance. The total numbers of live-born and stillborn infants have been taken from the official website of the RS Institute of Statistics [14].

Results

During the period of study, the total number of births in the RS was 18,841 (9,374 in 2015 and 9,467 in 2016), of which the number of live births was 18,809.

The total number of infants and fetuses with CHD was 263. Single CHD was found in 224 (85.17%), double CHD in 32 (12.17%), and triple CHD in 7 (2.66%) infants and fetuses. Therefore, the total number of CHD was 309 (160 in 2015 and 149 in 2016) (Table 1).

Six pregnancies (three each year) with a prenatal diagnosis of CHD were electively terminated, and 257 infants with CHD (141 in 2015 and 116 in 2016) were live-born (Table 2). Therefore, the total incidence of CHD in these two years was 163.95 *per* 10,000 total births, and the total incidence of live-born children with CHD was 136.64 *per* 10,000 live births. In 2015, the incidence of CHD was 170.63 *per* 10,000 total births, and the incidence of live-born children with CHD was 150.69 *per* 10,000 live births. In 2016, the incidence of CHD was 157.34 *per* 10,000 total births, and the incidence of live-born children with CHD was 122.73 *per* 10,000 live births.

There have been significant differences in the total incidence of CHD between regions. The highest was in Prijedor (340.26 *per* 10,000 live births), and the lowest was in Istočno Sarajevo (80.23 *per* 10,000 live births) (Table 3).

In our study, we found 15 different types of CHD. The most common were ventricular septal defects (45.63%), atrial septal defects (31.40%), patent ductus arteriosus (7.44%), and pulmonary valve stenosis (5.18%) (Table 4).

Table 1

Number of infants and fetuses with CHD and the total number of CHD

Period	Infants and fetuses with CHD (LB+TOPFA)				Total CHD
	single CHD n (%)	double CHD n (%)	triple CHD n (%)	Total n	n
2015	129 (89.58)	14 (9.72)	1 (0.69)	144	160
2016	95 (79.83)	18 (15.13)	6 (5.04)	119	149
Total	224 (85.17)	32 (12.17)	7 (2.66)	263	309

CHD – congenital heart defect; LB – live-born children; TOPFA – terminations of pregnancy for a fetal anomaly; n – number.

Table 2

Number of live-born infants with CHD and number of terminations of pregnancy for CHD

Period	LB n (%)	TOPFA n (%)	Total n
2015	141 (97.92)	3 (2.08)	144
2016	116 (97.48)	3 (2.52)	119
Total	257 (97.72)	6 (2.28)	263

For abbreviations, see Table 1.

Table 3

Number and incidence of CHD per region

Period	Banja Luka	Prijedor	Doboj	Bijeljina	Istočno Sarajevo	Trebinje	Total
2015	61 (38.13)	31 (19.38)	30 (18.75)	27 (16.88)	7 (4.38)	4 (2.5)	160
2016	63 (42.28)	30 (20.13)	10 (6.71)	34 (22.82)	8 (5.37)	4 (2.68)	149
Total	124 (40.13)	61 (19.74)	40 (12.94)	61 (19.74)	15 (4.85)	8 (2.59)	309
Total incidence*	164.34	340.26	128.96	152.13	80.23	142.85	163.95
p-value	0.911	< 0.05	0.051	0.569	< 0.05	0.271	

All values are expressed as numbers (percentages). CHD – congenital heart defect. * – per 10,000 total births.

Table 4

Number and incidence of different types of congenital heart defect (CHD)

Type of CHD	2015		2016		Total	
	n	Inc.	n	Inc.	n (%)	Inc.
Common arterial truncus	0	0	1	1.06	1 (0.32)	0.53
Double outlet right ventricle	1	1.07	1	1.06	2 (0.65)	1.06
Transposition of great vessels	4	4.27	2	2.11	6 (1.94)	3.18
Single ventricle	2	2.13	2	2.11	4 (1.29)	2.12
Ventricular septal defect	74	78.92	67	70.75	141 (45.63)	74.81
Atrial septal defect	48	51.19	49	51.74	97 (31.40)	51.47
Atrioventricular septal defect	2	2.13	0	0	2 (0.65)	1.06
Tetralogy of Fallot	4	4.27	1	1.06	5 (1.62)	2.65
Pulmonary valve stenosis	7	7.47	9	9.50	16 (5.18)	8.49
Pulmonary valve atresia	0	0	1	1.06	1 (0.32)	0.53
Hypoplastic left heart	2	2.13	0	0	2 (0.65)	1.06
Coarctation of aorta	6	6.40	1	1.06	7 (2.27)	3.71
Aortic atresia /interrupted aortic arch	1	1.07	0	0	1 (0.32)	0.53
Total anomalous pulmonary venous return	0	0	1	1.06	1 (0.32)	0.53
Patent ductus arteriosus	9	9.60	14	14.78	23 (7.44)	12.20
Total	160	170.63	149	157.34	309 (100)	163.95

n – number; Inc. – incidence per 10,000 total births.

Table 5

Time of establishing the diagnosis of congenital heart defect

Period	Prenatally	Postnatally
2015	11 (6.87)	149 (93.13)
2016	14 (9.40)	135 (90.60)
Total	25 (8.09)	284 (91.91)
p-value	0.417	

All values are expressed as numbers (percentages).

Table 6

Number of CHD in infants and fetuses depending on maternal age

Parameter	2015		2016		Total	
	< 35 y	≥ 35 y	< 35 y	≥ 35 y	< 35 y	≥ 35 y
Total births + TOPFA, n	7,981	1,396	8,041	1,429	16,022	2,825
CHD, n (%)	129 (1.62)	31 (2.22)	117 (1.46)	32 (2.24)	246 (1.54)	63 (2.23)
p-value	0.107747		< 0.00001*		0.007343*	

CHD – congenital heart defect; TOPFA – terminations of pregnancy for a fetal anomaly; y – years. * – statistically significant; n – number.

The diagnosis was made prenatally in 8.09% of cases. The higher proportion of prenatally diagnosed CHD found in 2016 (6.87%) compared to 2015 (9.40%) was not significantly different (Table 5).

We found no significant difference in gender distribution between infants and fetuses with CHD. There were 123 males, 134 females, and 6 infants and fetuses with unknown gender.

The incidence of CHD was significantly higher in infants and fetuses of mothers who were 35 years old or above (2.23%) compared to the infants and fetuses of younger mothers (1.54%) in 2016 and in a two-year period (Table 6).

Discussion

The incidence of CHD at birth is considered to vary significantly, depending on how a population is studied. According to Hoffman [4], the global incidence of CHD at birth is between 100 and 120 *per* 10,000 births. Other worldwide studies, such as those by Van der Linde et al. [5] and Liu et al. [9], reported CHD incidences of 91 and 94 *per* 10,000 births. The study from China reported an incidence of 110 *per* 10,000 live births [6]. In the latest European network of population-based registers for the epidemiological surveillance of congenital anomalies (EUROCAT) report, the average total incidence of nonsyndromic CHD in Europe is significantly lower compared to other reports, 70 *per* 10,000 live births [7]. In our study, the incidence of live-born children with CHD was 136.64 *per* 10,000, and the total incidence of CHD was 163.95 *per* 10,000 total births, which is higher than the incidence in other reports.

The difference in the incidence between our and other studies is mainly due to the higher reported incidence of mild types of CHD in our study. Compared to EUROCAT [7] and reports from Hoffman [4] and Van der Linde et al. [5], we found a much higher incidence of ventricular and atrial septal defects. The incidence of the ventricular septal defect in our study is 74.81 *per* 10,000, while in other studies, it is between 26.2 and 32.37 [4, 5]. In our study, the incidence of atrial septal defect is found to be 51.47 *per* 10,000, which is significantly higher than the incidence between 5.6 and 16.4 reported by others [4, 5]. On the other hand, the incidence of severe CHD (transposition of great vessels, tetralogy of Fallot, coarctation of the aorta, hypoplastic left heart, tricuspid atresia, etc.) in our study is similar to these reports. These findings lead us to the conclusion that the difference in total CHD incidence between our and other studies could be due to differences in research methods rather than representing the true difference in incidence. It is well known that the routine use of echocardiography increases the diagnosis of minor heart defects. Although we do not have data on the number of echocardiographic examinations performed during the study, it is assumed that, in some regions, this diagnostic method is widely used, often as screening in infants with or without mild symptoms of CHD, which significantly increased the detection rate of the ventricular septal defect and, therefore, the total incidence of CHD. On the other hand, the high incidence of atrial septal defect can be most likely explained by including a trivial type of this defect by some cardiologists.

We found significant differences in the incidence of CHD between different regions of the RS. That may be due to differences in the availability of echocardiography and reporting methods, but genetic causes, the impact of various environmental factors, and dissimilar implementation of preventive measures between regions cannot be ruled out. That could be a subject for future studies.

Prenatal detection of CHD results in less morbidity and mortality, but even in developed countries, the rate of prenatal detection for severe CHD ranges between 30% and 60% [15, 16]. Moreover, it is higher in countries with prenatal screening programs, like the Netherlands [17]. In our study, CHD was prenatally detected only in 8.09% of cases.

The incidence of CHD in our study was similar in males and females.

We found a higher incidence of CHD in infants and fetuses of mothers aged 35 years or above (2.23%) compared to younger mothers (1.54%). This result is consistent with the Reefhuis and Honein [13] report, in which advanced maternal age has been associated with an increased risk of non-chromosomal CHD. It is well known that advanced maternal age increases the incidence of chromosomal disorders and, therefore, the incidence of CHD related to these disorders. Since we studied only cases without chromosomal anomalies, a possible explanation for this finding could be other risk factors associated with advanced maternal age, such as poor glycemic control, higher body mass index, and the advanced age of their partners [18–21]. Furthermore, the higher incidence of premature birth in older women increases the incidence of ventricular septal defect at birth by detecting those defects that would close spontaneously until term [22].

Limitations of the study

The major limitation of our study was our inability to estimate the degree of overreporting and underreporting in data received from other hospitals; however, we believe that this limitation did not have a major effect on the results of the study. Second, the results of only two years cannot reflect the occurrence of CHD for every consecutive year. Finally, the data used for the study are relatively outdated. Nevertheless, although we have noticed that there were some changes in the meantime in the number of echocardiographic examinations, maternal age, and usage of folic acid during pregnancy, we believe that these changes could not have influenced the current incidence of CHD so much to make them significantly different from the results of this study.

Conclusion

The incidence of nonsyndromic CHD in the RS is higher than reported in other studies. A high detection rate of mild defects, differences in ascertainment methods, and the impact of environmental and genetic factors might be the reasons for this difference. The low percentage of prenatally detected CHD cases underscores the need to improve the prenatal detection rate of this anomaly through public health programs in order to enhance perinatal outcomes in children with CHD.

This study provides baseline data that could be used in future monitoring of the incidence of CHD in the RS to determine the risk factor changes and implementation of primary preventive measures.

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