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Epidemiology and structure of congenital anomalies of the newborns in the region of Novi Sad (Vojvodina, Serbia) in 1996 and 2006

Epidemiologija i struktura kongenitalnih anomalija novorođenčadi u regionu Novog Sada (Vojvodina, Srbija) u 1996. i 2006.

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Abstract

Background/Aim. According to the World Health Organization (WHO) definition, congenital anomalies are all disorders of the organs or tissues, regardless of whether they are visible at birth or manifest in life, and are registered in the International Classification of Diseases. The aim of this study was to compare the incidence and structure of prenatally detected and clinically manifested congenital anomalies in the newborns in the region of Novi Sad (Province of Vojvodina, Serbia) in the two distant years (1996 and 2006). **Methods.** This retrospective cohort study included all the children born at the Clinic for Gynecology and Obstetrics (Clinical Center of Vojvodina) in Novi Sad during 1996 and 2006. The incidence and the structure of congenital anomalies were analyzed. **Results.** During 1996 there were 6,099 births and major congenital anomalies were found in 215 infants, representing 3.5%. In 2006 there were 6,628 births and major congenital anomalies were noted in 201 newborns, which is 3%. During 1996 there were more children with anomalies of musculoskeletal system, urogenital tract, with anomalies of the central nervous system and chromosomal abnormalities. During the year 2006 there were more children with cardiovascular anomalies, followed by urogenital anomalies, with significant decline in musculoskeletal anomalies. The distribution of the newborns with major congenital anomalies, regarding perinatal outcome, showed the difference between the studied years. In 2006 the increasing number of children required further investigation and treatment. **Conclusions.** There is no national registry of congenital anomalies in Serbia so the aim of this study was to enlight this topic. In the span of ten years, covering the period of the NATO campaign in Novi Sad and Serbia, the frequency of major congenital anomalies in the newborns was not increased. The most frequent anomalies observed during both years implied the musculosketelal, cardiovascular, urogenital and central nervous system. In the year 2006 there was a significant eruption of cardiovascular anomalies and a significant decrease of musculoskeletal anomalies, chromosomal abnormalities and central nervous system anomalies, while the number of urogenital anomalies declined compared to the year 1996.

Key words:
infant, newborn; congenital abnormalities; epidemiology; risk factors; serbia.

Apstrakt

Uvod/Cilj. Prema Svetskoj zdravstvenoj organizaciji (SZO) kongenitalne anomalije su poremećaji organa ili tkiva, bilo da su vidljive na rođenju ili se manifestuju tokom života, i registrovane su u Međunarodnoj klasifikaciji bolesti. Cilj ove studije bio je da se uporede učestalost i struktura prenatalno utvrđenih i klinički ispoljenih kongenitalnih anomalija novorođenčadi na širem području Novog Sada (Vojvodina, Srbija) u dve udaljene godine (1996. i 2006). **Metode.** Ova retrospektivna studija obuhvatila je svu decu rođenu na Klinici za ginekologiju i akušerstvo u Novom Sadu (Klinički centar Vojvodine) tokom 1996. i 2006. Analizirani su učestalost i struktura kongenitalnih anomalija. **Rezultati.** Tokom 1996. bilo je 6 099 porođaja, a kongenitalne anomalije registrovane su kod 215 novorođenčadi što predstavlja 3,5% od ukupnog broja novorođenčadi. U 2006. bilo je 6 628 porođaja, a kongenitalne anomalije zabeležene su kod 201 novorođenčeta, što je 3% od ukupnog broja novorođenčadi. Tokom 1996. bilo je više dece sa anomalijama muskuloskeletnog sistema, urogenitalnog trakta, sa anomalijama centralnog nervnog sistema i sa hromozomskim abnormalnostima. Tokom 2006. godine, bilo

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je više dece sa anomalijama kardiovaskularnog sistema, slede anomalije urogenitalnog sistema, dok se broj anomalija muskuloskeletnog sistema značajno smanjio. Distribucija novorođenčadi sa velikim anomalijama, u odnosu na perinatalni ishod, pokazala je razliku između ispitivanih godina. U 2006. zabeležen je veći broj dece kod kojih je bila potrebna dalja dijagnostika i lečenje. **Zaključak.** U Srbji ne postoji nacionalni registar kongenitalnih anomalija i ova studija imala je za cilj da doprinese delimičnom sagledavanju ovog problema. U razmaku od deset godina koji pokriva i period NATO bombardovanja u Novom Sadu i Srbiji, učestalost značajnih kongenitalnih anomalija kod novorođenčadi nije povećana. Najčešći poremećaji uočeni tokom obe godine bile su malformacije lokomotornog, kardiovaskularnog, urogenitalnog i centralnog nervnog sistema. U 2006. godini došlo je do značajnog porasta broja kardiovaskularnih anomalija i značajnog sniženja broja anomalija lokomotornog sistema, hromozomskih abnormalnosti i anomalija centralnog nervnog sistema, dok je broj urogenitalnih anomalija bio niži u odnosu na 1996.

Ključne reči:
novorodjenče; anomalije; epidemiologija; faktori rizika; srbija.

Introduction

According to the World Health Organization (WHO) definition, congenital anomalies are all disorders of the organs or tissues, regardless of whether they are visible at birth or manifest in life, and are registered in the International Classification of Diseases. They can be morphological, structural or functional, hereditary or nonhereditary anomalies, as a result of teratogenic effects of external factors − drugs, infections or toxins in genetically healthy fetus [1–3]. In the occurrence of congenital anomalies, genetic disorders play a role in 20−25%, fetal infection in 3−5%, maternal disease in 2−4%, drugs in pregnancy in < 1%, while the unknown etiological factors reach even 65−75% [4–6].

Congenital anomalies are divided into major and minor. Major malformations are detected in 2-3% of the newborns before and immediately after birth, and express the same percentage up to fifth year of life (a total of 4−6%). One minor malformation was recorded in 15% of infants and the incidence of major malformations in this group was not higher than in infants without minor malformations [7, 8].

Successful control of acute infectious diseases and nutritional disorders (which are the leading causes of neonatal morbidity and mortality in developing countries) resulted in congenital anomalies becoming the most important cause of perinatal morbidity and mortality in developed countries, where the appropriate level of the epidemiological transition was achieved, *ie*, where the mortality rate in infants was decreased to below 15 deaths *per* 1,000 live births. Such was the case in Vojvodina (northern province of Serbia) where the infant mortality rate is 10.6‰. Further decline in infant mortality rates cannot be achieved by existing measures in primary health care of children (immunizations, rational antimicrobial therapy) [9, 10], but with developing of centers for prenatal diagnosis (expert ultrasound, early amniocentesis, cordocentesis, karyotype, biochemical analysis of amniotic fluid) [11, 12].

The aim of the study was to compare the number and structure of clinically manifested congenital anomalies of the newborns in Vojvodina, detected in prenatal period (by the methods mentioned above) or revealed upon physical examination and furher follow-up in the newborn period, in the two distant years (1996 and 2006). The study did not cover data concerning abortions due to fetal anomalies.

Methods

Vojvodina has a total population of about 2 million inhabitants and about 18,000 newborn babies a year. In this paper, the data of the Clinic for Gynecology and Obstetrics in Novi Sad with about 6,500 deliveries annually (Clinical Center of Vojvodina) were used. The study was approved by the Ethic Board and two separate years were analyzed − 1996 and 2006, considering that in 1999 there was the NATO campaign in Serbia, including Novi Sad and the surroundings.

The basic criterion for inclusion in this study was the existence of complete medical records on the number and structure of anomalies, newborn gender, anthropometric parameters, gestational maturity, Apgar score, congenital anomalies, fetal presentation, mode of delivery, parity, perinatal outcome, stillbirth and postnatal mortality.

The prenatal diagnostics was not done routinely (in the screening form) and was indicated only in pregnancies with high risk for congenital anomalies during 1996, while in 2006 it was more precise and complete. Also, the postnatal ultrasound diagnostics of newborns was not yet introduced at the Gynecology and Obstetrics Clinic in Novi Sad in 1996, while in 2006 it was performed upon clinical indications.

The results are presented in tables, and statistical significance was determined using the χ^2 test, *t*-test and Fisher test.

Results

At the Clinic for Gynecology and Obstetrics in Novi Sad (Clinical Center of Vojvodina) during 1996 there were 6,099 births and major congenital anomalies were found in 215 infants, representing 3.5%. In 2006, there were 6,628 births and major congenital anomalies were noted in 201 newborns, what was 3% of the total number of newborns. The gender structure of newborns with major congenital anomalies in 1996 and 2006 was about the same (Fisher test, $p > 0.05$). Comparing the mean values of body mass and length, newborns with major congenital anomalies in 1996 had a greater average body weight ($p < 0.01$) and length ($p < 0.01$). There was no difference in the average circumference of the head ($p > 0.05$) between the two groups of babies. Apgar scores in the first ($p < 0.01$) and the fifth minute ($p < 0.01$) significantly differed between the two groups. Children born in 1996 had higher average values of Apgar scores in the first and fifth minute of life. Anthropometric

parameters and final outcome among newborns with congenital anomalies are shown in Table 1. It is visible that in 2006 more newborns were transferred to the Institute for Children and Youth Health Care for further investigation (37.3% which was twice as more as in 1996) and followed-up till the end of the newborn period.

Analysis of the structure of major congenital anomalies showed that the total incidence of major congenital anomalies was almost the same, but there was a significant difference in its distribution.

The most frequent abnormalities observed during both years implied the musculosketelal, cardiovascular, urogenital and central nervous system. In the year 2006 there was a significant eruption of cardiovascular anomalies ($p < 0.01$) and a significant decrease of musculoskeletal anomalies, chromosomal and central nervous system anomalies. The number of urogenital anomalies in both years was at the second position (in 1996 involved 35.8% and declined in 2006 to 24.8%). During 1996 there were more children with anomalies of musculoskeletal system ($p < 0.01$), with anomalies of the central nervous system ($p < 0.01$) and chromosomal abnormalities ($p < 0.01$).

The detailed structure of major anomalies in the newborn infants in Novi Sad in 1996 and 2006 is shown in Table 2.

Most of the infants (70.4% in 1996 and 67.6% in 2006) with major anomalies diagnosed at birth, belonged to the normal zone of gestational age and body mass (*temporarius*/*eutrophicus*), with no differences observed between the two years (Fisher test, $p > 0.05$) (Table 3).

Among the group of the newborns with major congenital anomalies, 25 (11.6%) born in 1996 and 22 (10.9%) born

Table 1

Characteristics of the infants with major congenital anomalies in Novi Sad in 1996 and 2006

Infants characteristics	1996	2006
Total number of children, n (%)	215	201
males	96 (44.6)	108 (53.7)
females	119 (55.4)	93 (46.2)
Birth weight (g)*	3376.43	3065.08
Birth length (cm)*	49.60	48.70
Head circumference (cm)*	33.8	33.48
Apgar score 1 min.*	8.98	9.57
Apgar score 5 min.*	8.12	9.17
Perinatal outcome, n (%)		
discharged	181 (84.2)	126 (62.7)
transferred	34 (15.8)	75 (37.3)

***mean values.**

Table 2

Structure of major anomalies in the newborn infants in Novi Sad in 1996 and 2006

Major anomalies	1996		2006	
	n	%	n	%
Cardiovascular system	56	26.0	110	54.7
Urogenital system	77	35.8	50	24.8
Eye	0	0.0	1	0.5
Abdominal wall/organs	6	2.8	10	5.0
Central nervous system	25	11.6	7	3.5
Musculosceletal system	112	52.1	44	21.9
Chromosomopathia	14	6.5	7	3.5
Face	2	0.9	2	1.0
Respiratory system	0	0,0	1	0.5
Multiple (two or more) major anomalies	29	0.13	31	0.15

Table 3

Categorization of newborns with major congenital anomalies according to gestational age and body mass (growth) in 1996 and 2006

Body mass (growth)	*Pretemporarius*, n (%)		*Temporarius*, n (%)		*Posttemporarius*, n (%)	
	1996	2006	1996	2006	1996	2006
Hypotrophicus	1 (0.5)	6 (3.0)	17 (7.9)	7 (3.4)	0 (0.0)	0 (0.0)
Eutrophicus						
< 5 p	0 (0.0)	3 (1.5)	7 (3.2)	6 (3.0)	0 (0.0)	0 (0.0)
< 10 p	13 (6.0)	25 (12.4)	151 (70.4)	136 (67.6)	1 (0.5)	0 (0.0)
Hypertrophicus						
> 90 p	0 (0.0)	0 (0.0)	15 (6.9)	8 (4.0)	0 (0.0)	0 (0.0)
> 95 p	2 (0.9)	0 (0.0)	8 (3.7)	10 (4.9)	0 (0.0)	0 (0.0)
Total	16 (7.4)	34 (16.9)	198 (92.1)	167 (82.9)	1 (0.5)	0 (0.0)

p – growth percentile.

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in 2006 had intrauterine growth restriction (IUGR). Hypertrophic intrauterine growth had 25 (11.5%) of the neonates born in 1996 and 18 (8.9%) born in 2006. In 1996, hypertrophic intrauterine growth was present in 17 newborns with anomalies of musculoskeletal system, then in 6 newborns with anomalies of the cardiovascular system and in 1 newborn with anomaly of the anterior abdominal wall and abdominal organs and 1 with anomalies of the urogenital system. In 2006, hypertrophic intrauterine growth was noticed in 10 of the newborns with cardiovascular anomalies, in 4 of the newborns with anomalies of the musculosckeletal system, in 3 of the newborns with anomalies of the anterior abdominal wall and abdominal organs, and in 1 infant with anomalies of the urogenital system.

In 2006 an increase in the incidence of breech presentation was observed. Vaginal delivery was applied for 167 (77.67%) children in 1996, and for 118 (58.7%) in 2006. Delivery with intervention (*sectio Caesarea* and vacuum extraction) was performed in 48 (22.33%) births during 1996 and in 83 (41.3%) births in 2006 (Fisher test, $p < 0.05$). The distribution of the newborns with major congenital anomalies regarding perinatal outcome showed a significant difference between the studied years. In 2006, the increasing number of children required further investigation and treatment (Fisher test, $p < 0.05$). Related to the two observed years there were no significant differences between primiparas and multiparas concerning newborns with congenital abnormalities ($p > 0.05$) (Table 4).

The number of newborns with multiple major anomalies was nearly identical in both years. During 1996 multiple anomalies were recorded in 29 (0.13%), and in 2006 in 31 (0.15%) of the newborns.

The analysis of autopsy records (Institute of Histology and Pathology, Clinical Center of Vojvodina in Novi Sad, Serbia) revealed 150 registered stillbirths and neonatal deaths during 1996 (of which 23 children with congenital anomalies) and 75 children without anomalies, and 52 children that were not taken into analysis due to incomplete data. In 2006 there were 221 stillbirths and neonatal deaths, 54 of them with and 167 without congenital anomalies. Congenital anomalies were more frequently observed among stillborn children in the year 2006 ($p < 0.01$) (Table 5).

There was no significant difference in the gender structure of stillbirths and neonatal deaths between the two observed years ($p > 0.05$). The gestational age of stillborn children between the studied years was not significantly different. Structural analysis of the anomalies of the specific organ systems found in stillbirths and postnatal deaths of children up to 28 days of age in 1996 and 2006 year, showed the highest incidence of abdominal wall anomalies/organs, central nervous system or multiple anomalies (Table 6).

Table 4

Perinatal characteristics of the newborns with congenital anomalies in Novi Sad in 1996 and 2006

Perinatal characteristics	1996	2006
	n (%)	n (%)
Presentation		
occipital	205 (95.4)	188 (93.5)
breech	9 (4.1)	13 (6.5)
vertex	1 (0.5)	0 (0.0)
Completion of delivery		
vaginal-occipital presentation	156 (73.0)	116 (58.2)
vaginal–breech presentation	9 (4.2)	2 (1.0)
vaginal–vertex presentation	2 (0.9)	0 (0.0)
sectio cesarea– occipital presentation	41 (18.6)	72 (35.4)
sectio cesarea–breech presentation	0 (0.0)	10 (4.9)
vacuum extraction–occipital presentation	7 (3.3)	1 (0.5)
Partity of mother		
primiparous	104 (48.4)	118 (58.7)
multiparous	111 (51.6)	83 (41.3)

Table 5

Presence of anomalies in stillbirths and neonatal deaths in Novi Sad in 1996 and 2006

Presence of anomalies	Stillbirths, n (%)		Neonatal deaths, n (%)		Total, n (%)	
	1996	2006	1996	2006	1996	2006
Anomaly	16 (13.4)	47 (24.6)	7 (22.6)	7 (23.3)	23 (15.3)	54 (24.4)
No anomaly	65 (54.7)	144 (75.4)	10 (32.2)	23 (76.7)	75 (50.0)	167 (75.6)
Complete data lacking	38 (31.9)	0 (0)	14 (45.2)	0 (0)	52 (34.7)	0 (0)
Total	119 (100.0)	191 (100.0)	31 (100.0)	30 (100.0)	150 (100.0)	221 (100.0)

Table 6
Characteristics of stillbirths and neonatal deaths in Novi Sad in 1996 and 2006

Characteristics of stillbirhs and neonatal deaths	1996		2006	
	n	%	n	%
Total number of stillbirths and neonatal deaths	23	100.0	54	100.0
Gender structure				
male	11	47.8	25	46.3
female	12	52.2	27	50.0
ambigous	0	0.0	2	3.7
Anomalies				
urogenital system	2	8.7	3	6.4
chromosomopathia	0	0.0	8	17.0
central nervous system	5	21.7	6	12.8
face	2	8.7	3	6.4
cardiovascular system	1	4.3	5	10.6
abdominal wall/organs	6	26.1	11	23.4
musculosceletal system	2	8.7	7	14.8
multiple	5	21.7	11	23.4

Discussion

There is no national registry of congenital anomalies in Serbia and the aim of this study was to enlight this topic. The overall prevalence of congenital anomalies in the studied population of newborns in the area of Novi Sad (Vojvodina, Serbia) is congruent with the references showing that the incidence of anomalies in the population is about 5%, of which major anomalies participate with about 3% [7, 13, 14].

Comparing the two observed years, in 2006 there was a convincing change in the structure of the frequency of specified major anomalies of newborns. Anomalies of the urogenital system in 1996 were represented in 35.8% and in 2006 in 24.8% newborns. According to the WHO, anomalies of urogenital system are presented with 18% of the overall structure of anomalies. There was a convincing increase in cardiovascular anomalies, from 26% during 1996 to 54.7% in 2006, which is beyond the literature data on their incidence of 25%. A significant decrease in 2006 was recorded when it comes to musculoskeletal anomalies (21.9%), which dominated in 1996 with the percentage distribution of 52.1%, which exceeds the cited numbers of 22%. The decrease was registered and when it comes to chromosomal abnormalities, which in 1996 had the presence in 6.5%, while in 2006, in 3.5% of newborns. In summary, in 2006 there were more children with anomalies of the cardiovascular system, while in 1996 there were more children with anomalies of the musculoskeletal system, urogenital and central nervous system and chromosomal abnormalities. In 2006 it was found the occurrence of a major anomaly of the eye and respiratory systems, which are not registered in 1996, while major malformations of the face, jaw and palate did not exceede the most common literature values. The WHO data indicate that the most frequent anomalies are those of cardiovascular, musculoskeletal, genitourinary and of the central nervous system [9, 15, 16].

Low birth weight could be expected in newborns with structural anomalies, which in this study, except in one case, was not registered. There were a significantly higher body birth weight and length of newborns in 1996 than in 2006, but they did not deviate from the average values registered in 90% of newborns (birth weight 2500−4100 g, body length 46−54 cm, head circumference 33−36 cm) [17−19], except newborns with anomalies of the respiratory and musculoskeletal systems, where these average values were low.

Significant differences in the gender structure of the examined newborns with major congenital anomalies were not recorded between the observed years, nor within individual organ systems, which would indicate the absence of sexual dimorphism, except the locomotor system abnormalities that were two times more frequent in female infants in 1996 and three times more frequent, also in female newborns, in 2006. This corresponds to literature data on their higher prevalence in female children, related primarily to developmental hip dysplasia, which is dominated by the anomalies of musculoskeletal system [18−21].

Worldwide, the incidence of premature live births varies widely, depending on geographic location, racial origin and development of the country, so in the UK it is 4.6% [10, 20, 21], 12−13% in the USA, while in other developed countries is 5−9%. Certainly, premature labor is an important factor for fetal damage and it is reasonable for the greater number of congenital anomalies in premature than in term newborns. Increased risk of preterm delivery was found in congenital anomalies such as anencephaly, renal agenesis, atresia of the small intestine, omfalocela, gastroschisis, tracheoesophageal fistula, oesophagal atresia etc [11, 22, 23].

Intrauterine growth restriction is one of the most common disorders in pregnancy, which significantly increases the risk of intrauterine mortality and morbidity in newborns. The frequency of IUGR in Europe ranges from 4.1% in Finland to 9.5% in Romania, while in developing countries it exceeds 10%, and the values obtained in this study are close to those in Europe. Twin pregnancies account for about 20% of cases of IUGR, chromosomal abnormalities were detected in approximately 15% of cases of IUGR, uteroplacental insufficiency, fetal infection and fetal exposure to radiation together constitute about 10% of IUGR, while the remaining

55% of cases are bone dysplasias (achondroplasia), osteogenesis imperfecta, immune and other reasons [12, 24, 25].

Hypertrophic intrauterine growth was seen in 10% of births. In hypertrophic newborns the occurrence of hip subluxation and talus calcaneovalgus was more frequent. Hypertrophic growth is common with hydrocephalus and the syndromes with hyperinsulinism (Beckwith-Wiedemann syndrome, Sotos syndrome, infants of diabetic mothers) [12, 13, 26]. In 1996 hypertrophic intrauterine growth was more frequent and associated with anomalies of the locomotor system, than the cardiovascular system and anomalies of the anterior abdominal wall, abdominal organs, and urogenital system. In 2006, hypertrophic intrauterine growth was mostly present in newborns with anomalies of the cardiovascular system, musculoskeletal system, anterior abdominal wall, abdominal organs and the urogenital system.

Apgar scores (both the first and fifth minute) were higher in 1996, showing the more severe clinical pattern of anomalies in 2006. In both observed years, Apgar score was higher in the fifth minute of life, indicating a good adaptability of infants with major congenital anomalies to the extrauterine life.

The association of multiple organ system anomalies indicates the effect of teratogenic agents during the first trimester of pregnancy. A small number of live born infants with associated major anomalies was found in this study, as in others with the prevalence of 0.7% [18, 27].

The incidence of breech presentation in the world is 3−4%, and in the newborns with congenital anomalies it is often present because the malformed fetus is not able to take a stand head and pelvic posture may be an indicator for the presence of anomaly [14, 28]. Breech presentation was more common in newborns with musculoskeletal, cardiovascular and chromosomal abnormalities, in accordance with the reference data [15, 29, 30].

The fact that more deliveries with cardiovascular and urogenital congenital anomalies in newborns in 2006 were completed with intervention (compared to 1996), speaks in favor of the better prenatal diagnosis of these defects. Caesarean section, as an intervention during childbirth, except for the usual obstetric indications, should be used with breech fetal presentation in primipara or in imminent preterm deliveries, regardless of parity. It is, however, believed that about 40% of breech deliveries can be performed vaginally without compromising neonatal outcomes [17].

In relation to parity, no differences in the frequency of anomalies were found which is consistent with the reference data.

Comparing to 1996, in 2006 the increased number of the newborns was transferred from the Department of Gynecology and Obstetrics to the Institute for Children and Youth Health Care in Novi Sad, on further examination and treatment, indicating the greater severity of anomalies. The largest number of the newborns with structural defects was in the age group of mothers between 18 and 35 years, which requires changes in attitudes in prenatal screening. Introduction of amniocentesis in women older than 35 years has led to a significant reduction in the birth of children with chromosomal abnormalities in this age group, but it still remained a problem among young pregnant women who were not covered by mandatory screening [31].

A significantly higher number of stillbirths and neonatal deaths in 2006 compared to 1996 year speaks for the severity of anomalies.

Conclusion

In the span of ten years, covering the period of the NATO campaign in Novi Sad and the environment, the frequency of major congenital anomalies in the newborns was not increased.

The most frequent anomalies observed during both years implied the musculosketelal, cardiovascular, urogenital and central nervous system. In the year 2006 there was a significant eruption of cardiovascular anomalies and a significant decrease of musculoskeletal anomalies, chromosomal and central nervous system abnormalities, while the number of urogenital anomalies declined from one third in 1996 to one fourth in 2006.

In the year 2006 there was an obvious increase in breech presentation in the newborns with major congenital anomalies, compared to the year 1996. Higher Apgar score in the fifth minute of life in the year 2006 indicated a good adaptability of infants with major congenital anomalies, but also a higher level of perinatal care.

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