Original Article

Trends and Causes of Neonatal Mortality in Serbia, 1997-2016

Running Title: Lazarević et al. Neonatal Mortality in Serbia, 1997-2016

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Background: Regardless to notable reduction of child deaths worldwide over the last 30 years, the proportion of neonatal mortality in total child mortality is increasing.
Aims: Trends analysis of neonatal mortality in Serbia.
Study design: Observational descriptive surveillance system evaluation study.
Methods: Join-point regression was used to analyze neonatal mortality data for the 1997-2016 period, obtained from the Statistical Office of Serbia.
Results: Trend in neonatal mortality rate (NMR) decreased significantly, by -5.6% (95% CI: -6.5 to -4.6) per year from 1997 to 2007, and by -2.6% (95% CI: -3.7 to -1.5) per year from 2007 to 2016. NMR from certain conditions originating in the perinatal period decreased by -6.2% (95% CI: -7.5 to -4.9) per year in the 1997-2006 period and by -1.9% (95% CI: -3.1 to -0.7) per year yearly in the 2006-2016 period. Among these conditions, disorders related to short gestation and low birth weight, not elsewhere classified, showed an upward trend by 8.5% (95% CI: 6.2 to 10.8) per year during the entire study period. From 1997 to 2016, a significant decrease in NMR was detected in cases of congenital malformations, deformations and chromosomal abnormalities, by -5.0% (95% CI: -6.1 to -4.0) per year. NMR for cases of symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified, decreased by -8.1% (95% CI: -11.0 to -5.2) yearly.
Conclusions: In the 1997-2016 period, neonatal mortality in Serbia decreased, with the exception of disorders related to short gestation and low birth weight, whose prevention should be therefore given the highest public health priority.

In the 1990-2015 period, the implementation of the Millennium Development Goals (Goal 4) had a goal to decrease world mortality of children under age of 5 (93 deaths per 1,000 live births) by two thirds. At the end of this fifteen-year period (2000-2015), the mortality rate of children under the age of 5 was almost halved (43 deaths per 1,000 live births) while neonatal mortality also decreased (from 33 deaths to 19 deaths per 1,000 live births). However, the share of neonatal deaths in the mortality rate of children under 5 years old showed an upward trend, from 36 % in 1990 to 44% in 2015 (1).
Obviously, the reported decline in neonatal mortality is insufficient when we take into account great variations in rates and causes of neonatal mortality between regions and countries. Southern Asia and sub-Saharan Africa are world regions with highest neonatal mortality rate, with more than three quarters (79%) of world neonatal mortality. Among the countries with the highest neonatal mortality rates is Pakistan (46 deaths per 1,000 live births), while the lowest is in Iceland and Japan (1 death per 1,000 live births) (2). In sub-Saharan Africa and South Asia, infectious diseases account for approximately a quarter of all neonatal deaths, while in high income countries they account for only 7 percent of neonatal deaths (3).

The Republic of Serbia is an upper middle-income country, located in Southeast Europe (Balkan Peninsula). According to the latest 2011 census, Serbia had a population of 7,186,862 inhabitants, out of which almost 60% live in urban areas. More than 1,600,000 inhabitants or 23% of the total population of the Republic of Serbia live in Belgrade, the country's capital. Between the two censuses, 2002 and 2011, the population decreased by 4% (311,139 inhabitants) (4).

Serbia ranks among the European countries with the oldest population. Aging index (number of people over age of 60 per 100 youths under age of 19) was 96.44 in 2000 and 139.54 in 2016. Also, total mortality rate (per 1,000 people) increased from 13.84 in 2000 to 14.29 in 2016, while live birth rate decreased from 9.81 in 2000 to 9.17 in 2016. The number of females in age group of 15-49 years was reduced from 24.4% in 2000 to 22% of total population in 2016 (5,6).

As a political response to this negative demographic trend in Serbia, and to encourage women to have children, in 2000 the Law on Financial Support for Families with Children was introduced (amended in 2005 and 2009). This Law was financed from the national budget and it regulated child benefits, parental allowance, maternity leave payments and leave of absence payments for the special care of children. Nevertheless, in 2016, fertility rates in Serbia were still low (1.46), and only 15.6% of live-born children were third or higher in birth order (5).

To decrease the financial burden of parenthood and for the sake of reconciling work and parenting, starting from December, 2017, Serbia has been applying the new Law on Financial Support for Families with Children (2017). Amendment of this Law from July 1, 2018 significantly increased parental allowances (especially for the third or fourth child) (7).

Since the beginning of the 21st century, mortality rates of children under age of 5 in Serbia decreased more than half (from 13.0 in 2000 to 6.0 per 1,000 live births in 2016) (8). Although neonatal mortality rate also dropped from 7.3 in 2000 to 4.0 per 1,000 live births in 2016 (10), the contribution of neonatal mortality in mortality under 5 years of age increased from 60.4% (567 of 939 deaths) in 2000 to 65.2% (257 of 394 deaths) in 2016 (5,6).

The aim of this nationwide study was to analyze the mortality trends and causes of neonatal deaths in Serbia in the 1997-2016 period. These results may help identify groups of newborns who require specialty healthcare, as well as help prevent risk factors for neonatal mortality.

METHOD

This observational descriptive surveillance system evaluation study included all live-born children in Central Serbia and the Province of Vojvodina for the 1997-2016 period, excluding the Province of Kosovo and Metohija (data unavailable) which declared itself independent in 2008. Annual data on all live births and neonatal deaths were obtained from the Statistical Office of the Republic of Serbia. In Serbia, nearly 99% of births are registred. They occur in health institutions and with medical attendance (9,10).

Neonatal death is defined as death of a newborn occurring during the first 28 days of life (0-27 days). Early neonatal mortality occurs during the first seven days of life (0-6 days) and late neonatal mortality occurs after the seventh day of life and before the 28th day of life (7-27 days) (11). The International Classification of Diseases, 10th revision (ICD-10) was applied to classify diagnosis of causes of neonatal deaths.

We used descriptive statistic (numbers, percentages and rates) to indicate the share of causes of death according to gender in total neonatal mortality. To compare NMRs between boys and girls Chi square test was performed. Data were classified in accordance with the diagnosis of neonatal death and analyzed in terms of annual neonatal mortality rates (NMRs) per 1,000 live-born children and the annual percent change (APC) in neonatal mortality rates. NMRs were calculated as the number of neonatal deaths per 1,000 live births (11).

The trends in NMRs were analyzed using the joinpoint regression model. This analysis fits a series of straight lines (time periods) on a log scale to the NMRs, and detect the points in time (joinpoints) where significant changes in trend occur, using NMR as the dependent variable and calendar year as the independent variable. The optimal number of join points was identified using the Monte Carlo permutation method, starting with zero join points and testing whether more join points must be added to the model. APCs in NMRs and the corresponding 95% confidence intervals (CIs) are computed for each defined time period using generalized linear model assuming a Poisson distribution. P values <0.05 were considered significant. Average annual percentage change (AAPC) was also calculated for the 1997-2016 period using the average of the APCs from the joinpoint model (12). Joinpoint analyses were effectuated by means of the Joinpoint Regression Program version 4.2.0.2. (Statistical Methodology and Applications Branch, Surveillance Research Program, US National Cancer Institute).

RESULTS

In the twenty-year period in the Republic of Serbia there were 1,437,631 births out of which 1,430,005 were live-born children (737,854 boys and 692,151 girls). Out of these, 8,431 (0.6%) of newborns died during the neonatal period (4,985 boys or 59.1% and 3,446 girls or 40.9%).

During the 1997-2016 period, NMR decreased from 10.2 per 1,000 live births to 4.5 among boys, and from 7.3 to 3.3 among girls. On the whole, boys had a somewhat higher neonatal mortality rate when compared to girls (Figure 1).

Figure 1. Trend of neonatal mortality rate (NMR) per 1,000 live births in Serbia, 1997-2016, by gender

The total NMR decreased more than two-fold, from 8.8 in 1997 to 3.9 neonatal deaths per 1,000 newborns in 2016. The joinpoint analysis defined two segments in APC trend. The first period, from 1997 to 2007, showed a significant decline in NMR, with APC value of -5.6% (95% CI: -6.5 to -4.6%). In the second period, from 2007 to 2016, NMR significantly decreased with APC value of -2.6% (95% CI: -3.7 to -1.5) (Table 1).

Values of NMR for early neonatal period had two segment trends. The first period, from 1997 to 2006, showed a significant decline in early NMR, with APC value of -6.5% (95% CI: -8.1 to -4.8%). In the second period, from 2007 to 2016, NMR significantly decreased with APC value of -2.8% (95% CI: -4.2 to -1.3%).

During the whole 1997–2016 period, late NMR showed a significant decline in NMR, with APC value of -3.2% (95% CI: -4.1 to -2.3%) (Table 1).

Table 1. Changes in the early neonatal mortality rates (0-6 days of life) and late neonatal mortality rates (7-27 days of life) per 1,000 live births in Serbia, 1997-2016

Certain conditions originating in the perinatal period (77.6%), congenital malformations, deformations and chromosomal abnormalities (15%) and symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (5.3%) accounted for approximately 98% of neonatal deaths.

The distribution of neonatal deaths according by causes of death among boys and girls was not significantly different. (Table 2).

Table 2. Distribution of neonatal deaths by causes of death and gender

The majority of neonatal deaths were caused by respiratory distress syndrome (P22.0; 1737 deaths or 20.6%), disorders related to short gestation and low birth weight, not elsewhere classified (P07; 1612 deaths or 19.1%) and birth asphyxia (P21; 1110 or 13.2%). Allocation of the 3 most frequent causes of neonatal deaths was not significantly dissimilar for both boys and girls (Table 3).

Table 3. Distribution of the main causes of neonatal deaths according to gender

In the 1997-2016 period, NMR for certain conditions originating in the perinatal period decreased with average APC of -4% (95% CI: -4.8 to -3.1) (Table 4).

Joinpoint analysis defined two segment trends in NMR for certain conditions originating in the perinatal period changes. During the first period (1997 - 2006), NMR showed a significant decline with APC value of -6.2% (95% CI: -7.5 to -4.9). In the second period, from 2006 to 2016, NMR decreased three times, with APC value of -1.9% (95% CI: -4.2 to -1.3%).

The NMR associated with congenital malformations, deformations and chromosomal abnormalities, and NMR associated with symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified, showed a decreasing trend throughout all of the study years (APC: -5.0; 95% CI: -6.1 to -4.0 and APC: -8.1; 95% CI: -11.0 to -5.2, respectively). NMR associated with all other causes of neonatal mortality according to ICD-10 also showed a decreasing trend (APC: -5.1; 95% CI: -8.1 to -2.1).

Table 4. Change of neonatal mortality rates (NMR) per 1,000 live births according to causes of death

During the 1997-2016 period, NMR values decreased for respiratory distress syndrome (P22) by -11.6% (95% CI: -13.2 to -9.9), and for birth asphyxia (P21) by -6.2% (95% CI: -7.6 to -4.8). NMR values for disorders related to short gestation and low birth weight, not elsewhere classified (P07), increased from 0.6 to 1.9 deaths per 1,000 live births, with APC of 8.5% (95% CI: 6.2 to 10.8) (Table 5).

Table 5. Changes of neonatal mortality rates (NMR) per 1,000 live births according to 3 most common causes of death

DISCUSSION

Despite the fact that considerable progress in reduction of total neonatal mortality in Serbia has been made in the last twenty years, the rate of neonatal mortality remains high (3.9 per 1,000 newborns) when compared to other European countries (1.4 per 1,000 newborns in Slovenia, 1.9 in Spain, 2.8 in Greece) including neighboring countries (Croatia, Montenegro, Hungary (3.0; 2.0; 2.5 per 1,000 newborns). Similar to Serbia, neonatal mortality rates in Bulgaria and Romania are 3.9 per 1,000 newborns for both countries (13).

In Serbia, total NMR was higher among the boys than the girls, but distribution of neonatal causes of deaths according to gender was not significantly different, and preterm birth and congenital anomalies were among the main causes of neonatal mortality as noted in other studies from high income countries (14). During our study period, the diagnosis of neonatal death in Serbia has been improved and there have been fewer causes of neonatal deaths related to conditions regarding which no diagnosis classifiable elsewhere is recorded (R00-R99).

Starting with 2005, the Republic Public health Institute of Serbia with the network of 24 local Public health Institutes has begun the organization of procedure for coding of causes of death in the Republic of Serbia (15). Changes in

trend of early NMR in 2006 might be an effect of these changes in reporting of deaths in Serbia, as well as trend changes in total NMR in 2007.
Unfortunately, neonatal mortality rates from disorders related to short gestation and low birth weight in Serbia have shown an increasing trend. Mortality linked to the preterm births presents a severe public health issue, with contribution of 35% in global neonatal mortality (2). Worldwide, preterm birth rate was 10.6% in 2014 (16). Premature birth interrupts normal fetal lung development (17), so it is not surprising that respiratory distress syndrome (18,19) and birth asphyxia (20,21) were still important causes of mortality. In our study, one-third (33.8%) of the causes of total neonatal deaths were respiratory distress syndrome (20.6%) and birth asphyxia (13.2%). According to WHO data, the percentage of premature births in Serbia was growing from 7.23% in 2000 to 11.97% in 2014 (22). Data from a few studies conducted in Serbia indicate the existence of some of the premature birth risk factors such as maternal age (23), smoking (24) and obesity and overweight of mothers (25).
Delayed maternity is often present among women in Serbia, which increases the risk for preterm delivery. In Serbia, mothers in the age group of 35 or more gave birth to 7.7% of all live newborns in 2000, while in 2016, this percentage surged to 17.2%. In 2000, the mean age of mothers of live-born children was 26.5, and in 2016 it increased to 29.6 years (5).
Krstev et al. observed that smoking during pregnancy in Serbia was two- to three-fold higher than in the most affluent western countries (26), which reduced birth weight, birth length and head circumference of newborns, and increased risk for low birth weight (27). In a study conducted in five countries of Central and Eastern Europe (Czech Republic, Hungary, Romania, Slovakia, and Ukraine), smoking, preeclampsia, hypertension and body mass index were identified as risk factors for the occurrence of preterm births (28). Results from the study by Rudic-Grujic show that every fifth pregnant woman in this study was overweight or obese before pregnancy (29).
Recent studies worldwide showed that after the use of assisted reproductive technologies (ART), women _have a significantly higher risk of preterm birth, and more frequent occurrence of low and very low birth weight of the newborn (30).
First National Program of ART in Serbia "One free in vitro fertilization attempt (IVF) for 1,000 couples" was initiated by Ministry of Health of the Republic of Serbia (October 2006). Results of this Program for the period between 1st of March 2007 and 1st of March 2009 showed that prematurity, low birth weight, perinatal asphyxia and systemic infection contribute significantly to morbidity of IVF conceived newborn (31). Starting from March 2017, Serbia adopted the new Law on Treating Infertility through a procedure of Biomedical Assisted Fertilization (the older law was from 2009). The introduction of this Law had a goal to increase the number of IVF attempts implemented, as well the success rate of the procedures performed (32).
Current research suggests that the survival of newborns can be improved by the use of antenatal and perinatal therapies and reanimation of newborns in specialized health care institutions (14). The coverage of pregnant women by antenatal medical care in the first trimester of pregnancy is similar between the Serbia (79.8% in 2017) (33) and other high-income countries (around 81.9%) (34). In Serbia, health care of newborns is applied in pediatric departments of general hospitals, outpatient clinics and specialized hospitals as well as in five major university children's clinics (35).
It has been observed that breastfeeding during the first month of life (36) as well as implementation of Kangaroo Mother Care method (37) lead to a significant reduction in neonatal mortality. In order to improve the neonatal outcome and healthcare potential and skill of medical professionals taking care of sick children and children at risk of premature birth, in 2018, the Government of the Republic of Serbia adopted the Decree on the National Program for Support of Breastfeeding, Family and Developmental Care of Newborns (38) which includes treatment and care based on the principles of individualized developmental care (NIDCAP), application of the Kangaroo Mother Care method and the early start of natural nutrition (breastfeeding) (39).
Our study has some limitations, which affect the final conclusion about the results of medical care of newborns. A national register of congenital abnormalities does not exist in Serbia (40), and we cannot claim that decline of neonatal mortality from congenital abnormalities is caused by advanced neonatal care instead of reducing the incidence of congenital abnormalities in newborns.
Data on the rate of premature births, gestational age and body weight of newborns will contribute to an easier assessment of the effectiveness of antenatal and prenatal care measures for pregnant women and neonatal care of newborns. These data are not available or may be incomplete for some years during the study period, because until 2005 in the Republic of Serbia there was no prescribed and unique birth application (41).
In conclusion, during the investigated period of 20 years, health care in Serbia contributed to the decline of total neonatal mortality, excluding mortality from disorders related to short gestation and low birth weight.

Further investigation and prevention of risk factors of birth prematurity in Serbia, as well as implementation of the National Program for Support of Breastfeeding, Family and Development Care will be required in order to continue the decline of neonatal mortality.

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TABLE 1. Changes in the early neonatal mortality rates (0-6 days of life) and late neonatal mortality rates (7-27 days of life) per 1,000 live births in Serbia, 1997-2016							
Day of life	NMR 1997 2016	1st period trend			2nd period trend		
		Period	APC (95%CI)	P value	Period	APC (95%CI)	p value
0-6	7.3 2.8	1997 2006	-6.5 (-8.1 to -4.8)	<0.001	2006 2016	-2.8 (-4.2 to -1.3)	0.001
7-27	1.5 1.1	1997 2016	-3.2 (-4.1 to -2.3)	<0.001			
0-27	8.8 3.9	1997 2007	-5.6 (-6.5 to -4.6)	<0.001	2007 2016	-2.6 (-3.7 to -1.5)	<0.001

TABLE 2. Distribution of neonatal deaths according to causes of death and gender				
Causes of death (ICD-10)	All deaths n (%)	Girls n (%)	Boys n (%)	p value
Certain conditions originating in the perinatal period (P00-P96)	6545 (77.6)	2668 (77.4)	3877 (77.8)	0.704
Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	1265 (15.0)	535 (15.5)	730 (14.6)	0.265
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	443 (5.3)	181 (5.2)	262 (5.3)	0.999
Other (A00-B99; G00-G99; C00-D48; I00-I99; J00-J99; D50-D89; E00-E90; K00-K93; L00- L99; N00-N99; S00-T98; V00-Y98)	178 (2.1)	62 (1.8)	116 (2.3)	0.097
All causes of death	8431 (100)	3446 (40.9)	4985 (59.1)	<0.001

TABLE 3. Distribution of the main causes of neonatal deaths according to gender				
Causes of death (ICD-10)	All deaths n (%)	Girls n (%)	Boys n (%)	p value
Respiratory distress syndrome (P22)	1737 (20.6)	685 (19.9)	1052 (21.1)	0.171
Disorders related to short gestation and low birth weight, not elsewhere classified (P07)	1612 (19.1)	689 (20.0)	923 (18.5)	0.089
Birth asphyxia (P21)	1110 (13.2)	422 (12.3)	628 (12.6)	0.631

TABLE 4. Change of neonatal mortality rates (NMR) per 1,000 live births according to causes of death			
Causes of death ICD-10	NMR 1997 2016	APC (95%CI)	p value
Certain conditions originating in the perinatal period (P00-P96)	7.1 3.3	-4.0 (-4.8 to -3.1)*	<0.001
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	0.4 0.1	-8.1 (-11.0 to -5.2)	<0.001
Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	1.1 0.5	-5.0 (-6.1 to -4.0)	<0.001
Other (A00-B99; G00-G99; C00-D48; I00-I99; J00-J99; D50-D89; E00-E90; K00-K93; L00- L99; N00-N99; S00-T98;V00-Y98)	0.2 0.1	-5.1 (-8.1 to -2.1)	0.002
*: Average annual percentage change (AAPC)			

TABLE 5. Changes of neonatal mortality rates (NMR) per 1,000 live births according to 3 most common causes of death			
Causes of deathICD-10	NMR 1997 2016	APC (95%CI)	P value
Respiratory distress syndrome (P22)	2.6 0.2	-11.6 (-13.2 to -9.9)	<0.001
Disorders related to short gestation and low birth weight, not elsewhere classified (P07)	0.5 1.9	8.5 (6.2 to 10.8)	<0.001
Birth asphyxia (P21)	1.0 0.5	-6.2 (-7.6 to -4.8)	<0.001

FIG. 1. Trend of neonatal mortality rate (NMR) per 1,000 live births in Serbia, 1997-2016, by gender