

# PREMATURE BIRTH AND COMPLICATIONS OF PREMATURE BIRTH ARE LEADING CAUSES FOR INCREASED NEONATAL MORTALITY

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## Abstract

**Introduction:** Neonatal mortality (NNM) is a mortality in newborns in within the first 28 days after birth. Prematurity and the complications from prematurity are the leading cause for higher NNM rates. A premature newborn is born less than 37 gestational weeks of pregnancy. Low birth weight and low gestational age at delivery and their complications are the leading causes of NNM.

**Aim of the study:** The aim of this paper is to present our results gathered from the material of the newborns treated at the Neonatal Intensive Care Unit (NICU) at the University Clinic of Gynecology and Obstetrics in Skopje (UGOC- Skopje), demonstrating that prematurity and complications of prematurity have been the main causes of increased mortality among newborns, in the analyzed period of 9 months.

**Material and methods:** The study is a cross-sectional prospective research that included 445 newborns who were transferred to the NICU for resuscitation, monitoring and treatment after birth, over a period of 9 months or the period from May 1, 2019 to January 31, 2020, at the University Clinic of Gynecological and Obstetric (UGOC) in Skopje. In this paper, we focused on prematurity and complications of prematurity, which had a significant impact on the NNM of newborns in the NICU, in the analyzed period.

**Results:** The study shows that the leading causes for NNM at UGOC- Skopje were prematurity and complications from prematurity: low gestational age at birth, low birth weight, asphyxia, ARDS, NEC, intracranial hemorrhage, sepsis, congenital anomalies etc. Cesarean delivery, prenatal administration of corticosteroids, higher APGAR score in the 1st and 5th minutes, have a significant impact on the survival of newborns and reduction of mortality in newborns.

**Conclusion:** For a long period of time N. Macedonia was a country with one of the highest NNM rates in Europe. Prevention of prematurity and complications from prematurity, improved health and prenatal service, all this reduce the prematurity and NNM. The reasons for higher NNM are preventable and need programs for health care and education of patients, and better public health service.

**Key words:** Acute respiratory distress syndrome; gestational week; intracranial hemorrhage; low birth weight; neonatal intensive care unit, neonatal mortality; necrotizing enterocolitis.

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## Introduction

Neonatal mortality (NNM) is a mirror of a country's health system. The care for mothers, newborns, and children is among the highest priorities in the health policies of all countries in the modern world (1).

The neonatal period is the most sensitive period in human life and mortality is highest during this period of life, in the first 28 days after birth (2).

Neonatal mortality is the percentage of newborn deaths of live births, in the neonatal period in the first 28 days after birth, or born after 22 weeks of gestation and with a birth weight greater than 500 g, per thousand live births (3) (4).

In 2023, 2.3 million newborns died in the neonatal period globally, or 6500 newborns per day. The neonatal mortality rate stood at 17 newborns per 1000 live births globally, representing a significant decrease in the NMR rate, from 37 neonatal deaths per 1000 live births in 1990 (5). More than 90% of neonatal deaths occur in developing countries, especially in sub-Saharan Africa and Southeast Asia (5) (6). Japan, Iceland, Singapore, Finland, and Slovenia have the lowest neonatal mortality rates in the world, with 1 neonatal death per 1,000 live births (7).

For many years after gaining independence in 1990, N. Macedonia was among the countries in Europe with the highest neonatal mortality rate. It was often at the top or near the top, right after countries such as Turkey, Albania, Kosovo, and Moldova (**Picture 1**). N. Macedonia was a European country with a high rate of neonatal mortality, among the highest in Europe, and in 2017, with 7.4 neonatal deaths per 1,000 live births, it was the second country with the highest rate of neonatal mortality in Europe, right after Moldova (8).



**Picture 1.** Neonatal mortality in N. Macedonia from 1982- 2018

From 2012 to 2017, there was an increasing trend that ranged from 7 to 9.5 neonatal deaths per 1000 live births, while a new decreasing trend of 7-9.5 ‰ was observed from 2018 and 2019 to the present (7). From 2020, the NNM rate in N. Macedonia began to further decrease and approach the European average and was reduced to 2 ‰ in 2022.

The Neonatal Intensive Care Unit (NICU) at the University Clinic of Gynecology and Obstetrics in Skopje (UGOC-Skopje) is the largest neonatal and perinatal center in N. Macedonia, where about 70% of these newborns are cared for, since the largest percentage of these complicated and pathological pregnancies and newborns from the entire country are treated and cared for in this Clinic (9).

The participation of the Clinic's NNM in the total NNM of the country, accounts for about 70% or 2/3, and makes this Clinic the most relevant center for research and studies related to NNM (9).

A lower gestational age at delivery and a low birth weight (LBW) are two of the most important factors that increased NNM rate(10).

Prematurity accounts for 12% or more in developing countries and 9% in developed countries. Prematurity is also high in some developed countries, such as the USA, but the survival rate of premature infants is higher in highly developed countries, than in developing countries. Leading causes of death in developing countries are prematurity, LBW, and infections, while in developed countries are congenital anomalies (10).

Premature newborns are divided into two groups: premature by gestational week and premature by birth weight. A premature newborn or a premature child, is a newborn born between 22-37 weeks of gestation or with a birth weight greater than 500 g at birth (11) (12) . Low birth weight (LBW) infants are at higher risk of neonatal mortality and morbidity, and up to 60% of all neonatal mortality is associated with low birth weight (LBW) (13) (14).

According to birth weight, newborns are divided into: Newborns with extremely low birth weight - less than 1000 g. (from 500 to 999 g.); newborns with very low birth weight - less than 1500 g. (from 1000-1499 g.); newborns with low birth weight - less than 2500 g. (from 1500-2499 g.) and newborns with a weight greater than 2500 g. (11) (13) (15).

According to gestational age at the time of delivery, premature newborns can be divided into several groups: born at 22-27 weeks of pregnancy - extremely premature, the highest risk group; born at 28-32 weeks of pregnancy - very premature, a risk group of premature babies; born at 33-36 weeks of pregnancy - moderately to late premature, a lower risk group of premature babies; born over 37 weeks of pregnancy - term newborns, the group where the neonatal mortality rate is the lowest (11) (16) (17).

The purpose of this paper is to presents the results from our material gathered at the UGOC – Skopje, which show that prematurity and complications of prematurity have been the main causes of increased mortality among newborns at the clinic, and throughout the country for many years. The study was conducted in a transitional year and during a period when the situation with NNM rates at the Clinic and in the country was starting to significantly improve in 2019/20. The study extensively examined a significant number of reproductive, maternal, neonatal, and socio-demographic factors, which collectively have an impact on NNM rates and the main reasons which increase it, both at the Clinic and in the country (9).

In this paper, we focus only on prematurity and complications of prematurity, as the most important factors for increasing the NNM rate.

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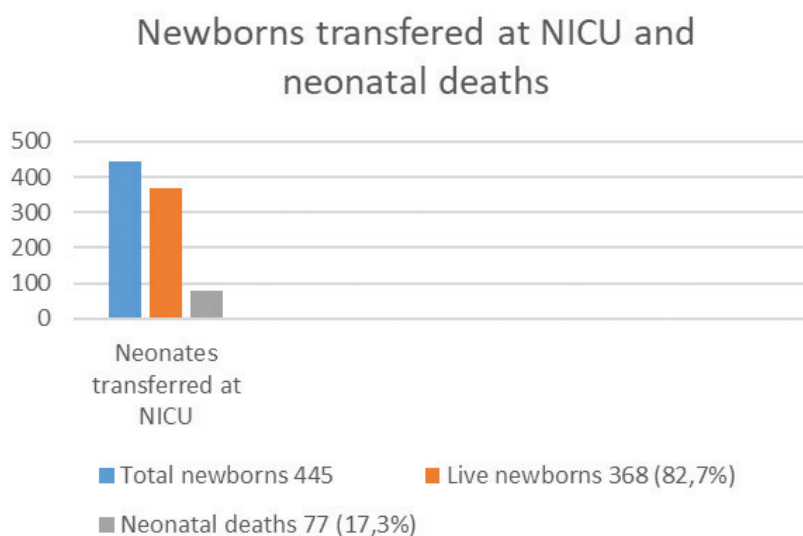
## Material and methods

The study is a cross-sectional prospective research that included 445 newborns, who were transferred to the NICU for resuscitation, monitoring and treatment, over a period of 9 months or the period from May 1, 2019 to January 31, 2020. at the University Clinic of Gynecological and Obstetric (UGOC) in Skopje. For the study, all mothers of newborns signed consent and completed a questionnaire about the course of pregnancy and childbirth, and hospital histories of the mothers and newborns who were transferred to the NICU were also used for data. In this paper, we focused, on the results that are related to prematurity and complications of prematurity, which had a significant impact on the NNM rates of newborns in the NICU, in the analyzed period.

## Results

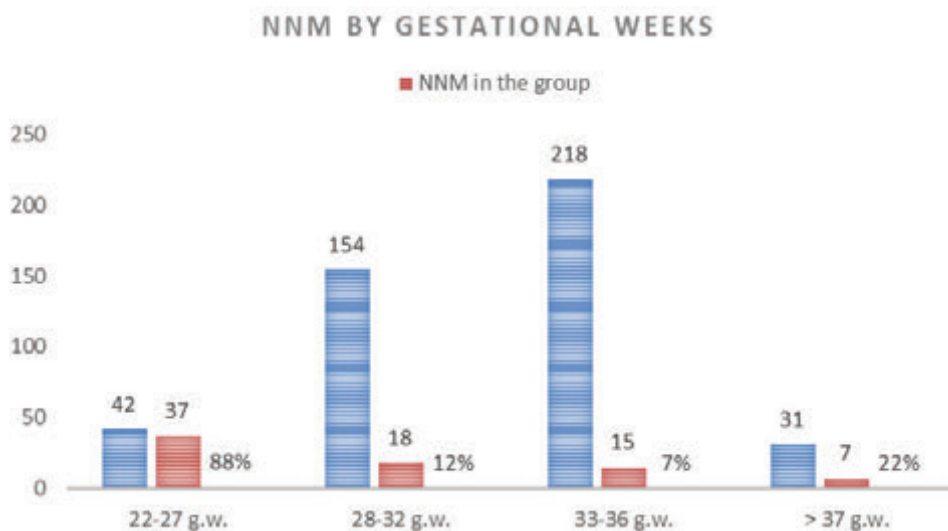
In the analyzed period of 9 months at the UGOC in Skopje, there were a total of 3453 live births. 445 (12.9%) of these newborns were transferred and treated at NICU. Of all newborns treated at NICU, 368 (82.7%) of newborns remained alive and 77 (17.3%) were neonatally deceased newborns in the first 28 days after birth ( Fig.1).

Prematurity in newborns was the main reason for transferring newborns at NICU and accounted for 93% of the total number of newborns transferred for treatment, or 414 premature newborns, out of the total number of 445 newborns treated at NICU.



**Fig. 1.** Neonates transferred at NICU/ UGOC- Skopje and neonatal deaths

The highest mortality rate was identified in the group of extremely preterm newborns, where 88% of newborns died during NICU treatment, followed by the group of 28-32 gestational weeks, where the mortality rate was significantly reduced to 12% and the survival rate in this group of newborns was greatly improved, compared to previous years. The group of late preterm infants consisted of a smaller number of newborns transferred to the NICU, and in this group, the mortality rate was higher due to insufficiently monitored pregnancies, delivery complications such as placental abruption and other bleeding, or due to undetected serious congenital anomalies prenatally (**Fig.2**).



**Fig. 2.** Presentation of the neonatal mortality rate by gestational age at NICU/ UGOC- Skopje

In relation to low birth weight, the results showed a higher mortality rate among newborns born with a low birth weight, as well as with lower gestational age. The highest mortality rate was among newborns weighing less than 1000 grams - 77.8%, and the mortality rate decreased as the weight of newborns increased. Premature newborns and newborns with lower birth weight are more fragile and their adaptation and survival after birth are much riskier, compared to those born with higher weight and higher gestational age ( **Table 1**).

**Table 1.** Birth weight and neonatal mortality at NICU/ UGOC- Skopje

Neonatal deaths	500-999 gr.	100-1499 gr.	1500-2499 gr.	>2500 gr..	Total newborn
1- 7 day NNM	30	12	8	6	56
8-28 day NNM	12	3	3	3	21
Total NNM	42 (77,8%)	15 (18%)	11 (4,3%)	9 (17,65%)	77 (17,3%)
Survived newborns	12 (22,2%)	68 (82%)	246 (96%)	42 (82,35%)	368 (82,7%)

Premature newborns are born with lower APGAR scores at birth, due to their immaturity and are more likely to be exposed to RDS, NEC, asphyxia and brain hemorrhage, infections and sepsis, compared to term newborns.

On the other hand, the method of delivery and administration and prenatal maturation with corticosteroids also had a significant impact on the survival of these newborns.

In relation to the APGAR score obtained in the 1st and 5th minute after birth in newborns, the mortality rate of newborns with a lower APGAR score at birth was significantly higher. With an APGAR score < 3 in the 1st minute after birth, the mortality rate was 75%. With an APGAR

score of 4-6 in the 1st minute after birth, the mortality rate in newborns was 20% and with an APGAR score of 7-10, the mortality rate was the lowest at 4.4% (Fig.3).

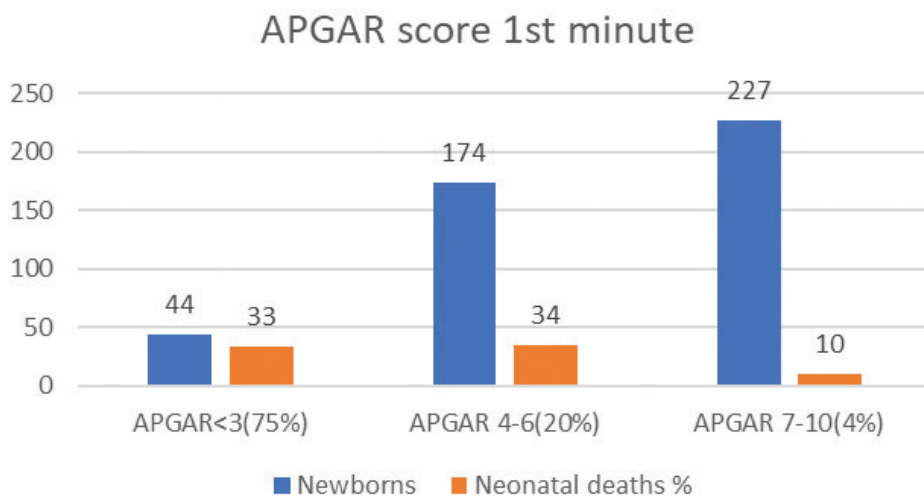


Fig. 3. APGAR score at 1st minute and NNM at the NICU/ UGOC- Skopje

The mortality rate of newborns is even higher with a lower APGAR score at the 5th minute after birth, when the newborn does not accept the initial adaptation and resuscitation after birth and the APGAR score remains low. A low APGAR score < 3 at 5th minute, led to a mortality rate of 89% in newborns; an APGAR score of 4-6 at 5th minute resulted in a fatal outcome in 31% of newborns; and with an APGAR score of 7-10 at 5 minutes, the mortality rate of newborns was significantly lower at 7% (Fig.4).

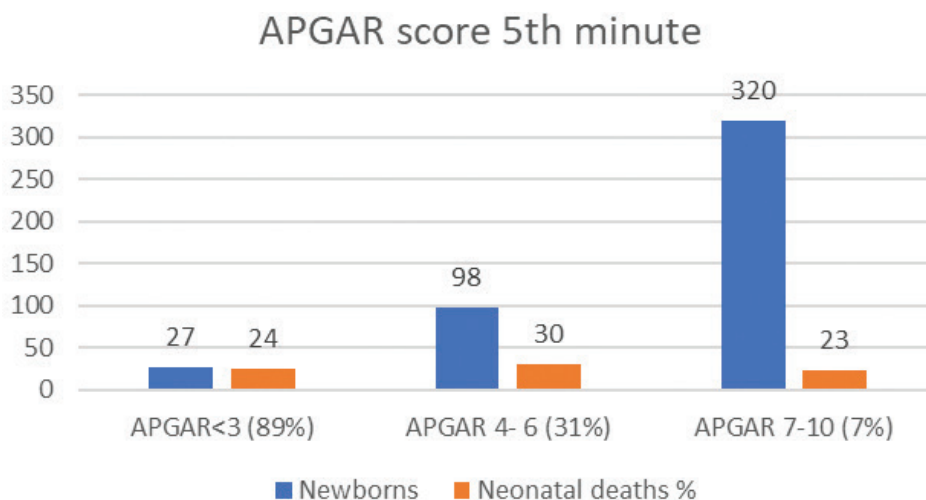
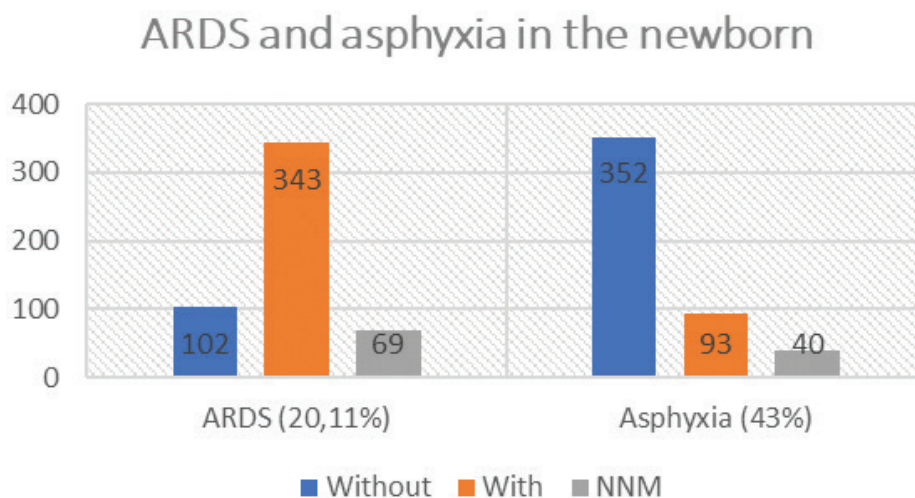


Fig. 4. APGAR score at 5th minute and NNM at the NICU/ UGOC- Skopje

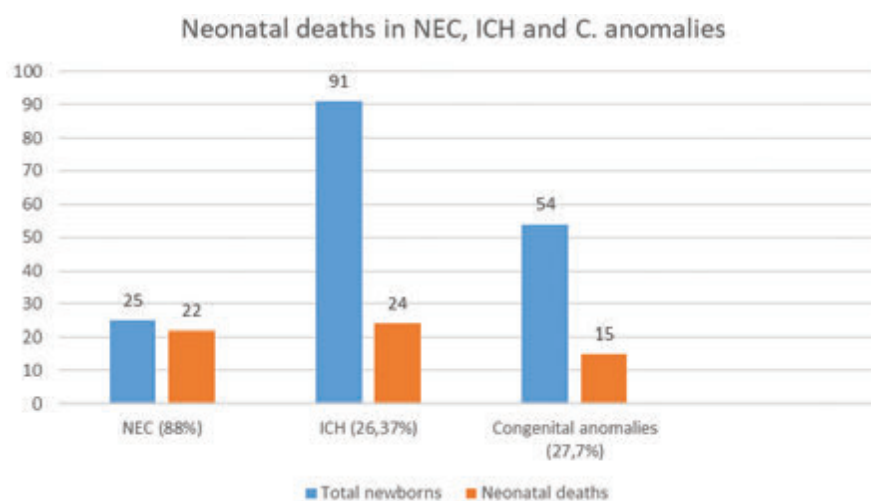
Regarding ARDS (acute respiratory distress syndrome) and asphyxia in newborns who were transferred to the NICU during this period, an increased mortality rate was also observed after birth in newborns who developed ARDS or had asphyxia during birth. Out of 445 newborns transferred to the NICU, 343 newborns developed mild or severe ARDS, and 69 newborns died, or 20.11% of the total number with ARDS (Fig.5).



**Fig. 5.** ARDS and asphyxia in newborn at the NICU/ UGOC- Skopje

Of the total number of newborns transferred to the NICU during this period, 93 newborns from all gestational groups and newborns of different birth weights had asphyxia during delivery. Of these, 40 newborns died, or a high 43% of all newborns with asphyxia transferred to the NICU.

The neonatal mortality rate was the highest in the group of neonates who developed NEC (necrotizing enterocolitis) after delivery, which most often occurs in the group of extremely premature neonates up to 28 weeks of age. Of the 25 neonates who developed NEC after delivery and were transferred to the NICU, 22 (88%) of the neonates died in the neonatal period (**Fig.6**).



**Fig. 6.** Neonatal deaths in NEC, ICH and cong. anomalies at the NICU/ UGOC- Skopje

Intracranial hemorrhages ( ICH) occurred in 91 newborns out of a total of 445 transferred to the NICU during this period, while 24 newborns from all gestational groups died from ICH, or 26.37% of all newborns who had intracranial hemorrhages (Fig.6).

54 newborns transferred to the NICU had complex or single congenital anomalies, most of which belonged to late premature newborns over 32 weeks of gestation, and 15 of those newborns or 27.7% died (Fig.6).

Many of the 445 neonates transferred to the NICU during this period developed neonatal infections and mild or more serious septic conditions. Of the total number of neonates transferred to the NICU, 321 (72.1%) did not develop sepsis, while 124 (27.7%) developed mild or more serious symptoms of sepsis. Of these, 124 neonates who developed symptoms of sepsis, 32 neonates or 25.8% died in the NICU within the first 28 days after birth (Fig.7).

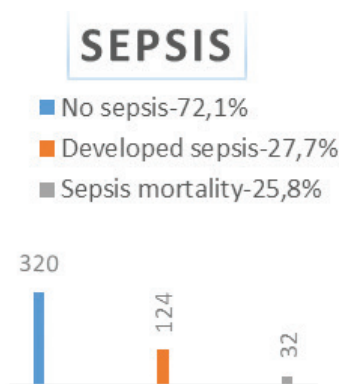


Fig. 7. Neonatal deaths caused by sepsis at the NICU/ UGOC- Skopje

Newborns at risk of preterm birth who had successfully completed maturation with corticosteroids at least 24 hours before delivery had a higher chance of survival in the group of newborns transferred to the NICU. From 279 premature newborns which received corticosteroids for pulmonary maturation before delivery, only 28 (10%) of the newborns died, and 251 (90%) survived. It was not possible to perform prenatal maturation with corticosteroids in 166 newborns, and of these, 49 or 29.5% of them died. The mortality rate in the group where prenatal maturation with corticosteroids was not performed was three times higher than the mortality rate of the newborns who received prenatal maturation with corticosteroids (Fig.8).

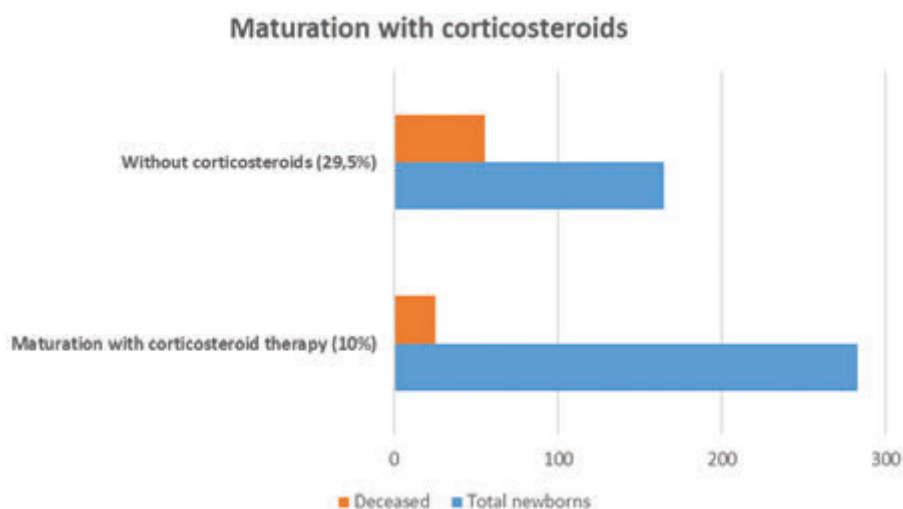


Fig. 8. Maturation with corticosteroids and neonatal deaths at the NICU/ UGOC- Skopje

The way of delivery of these newborns - spontaneous, with intervention (vacuum, forceps) or by cesarean section, also showed a significant impact on the survival rate of newborns. The chances of injury to the mother and the newborn are the lowest during a cesarean section delivery. This was also demonstrated by the examined group of newborns transferred to the NICU

during this period, i.e., the mortality rate was lower among those delivered by a cesarean section (13,6%), unlike newborns delivered spontaneously (26%), where the mortality rate was higher.

## Discussion

The study concluded that prematurity and complications of prematurity and low birth weight, such as: lower APGAR score at birth, RDS, NEC, cerebral hemorrhage, infections and sepsis, are the main factors for increasing the NNM rate in newborns transferred to the NICU at the UGOC in Skopje. The study also determined that the neonatal mortality rate is lower in newborns who received prenatal maturation with corticosteroids and in those born by a cesarean section. Each of these factors individually affects the increase in the NNM rate in newborns in the group, and of course the combination of multiple factors together affects the increase in NNM in the group (9).

The mortality rate of newborns transferred at the NICU during the study period is high. Of the 445 newborns transferred at NICU, 77 (17.3%) died. There are studies that have concluded that are very high mortality rates of newborns in Neonatal Intensive Care, with 58.8% neonatal deaths of treated newborns in Ethiopia (18) and with low mortality rates of 4% and 6% in Canada and Brazil (19) (20). A large proportion of newborns born in less developed countries are born out-of-hospital settings (often at home), 20-60% who were then transferred to hospitals. In our study, all analyzed newborns transferred and treated at the NICU were born in hospital.

Prematurity is the main reason for treating newborns in the NICU and of all 445 treated newborns, 414 (93%) were premature, born before 37 weeks of gestation. The majority of extremely premature newborns, less than 28 weeks of gestation, treated in the NICU died, almost 88% of them, as well as newborns with extremely low birth weight under 1000 grams, almost 78% of them. The significant survival rate of newborns born between 28-32 weeks of gestation is notable, with only 12% of newborns treated in the NICU dying, as well as significantly lower mortality rate among newborns born with weight over 1000 grams.

The survival rate of premature infants varies greatly between developed and developing countries. A study conducted by the American College of Obstetricians and Gynecologists, in the United States as a highly developed country as of 2020, reported a survival rate in extremely premature infants at 24 weeks of age in more than 60% of infants, the survival rate of 80% in infants born at 26 weeks of age, more than 90% survival rate in infants born at 28 weeks of age, and about 99% survival rate in infants over 30 weeks of age (21).

The APGAR score at 1st minute <3 and at 5th minute less than 7 has a significant association with the survival rate in newborns. Many studies refer to the APGAR score at 1 and 5 minutes as a direct factor, which has a significant association with the NNM rate. The predictive role of a higher APGAR score at 1 minute, in the survival rate of newborns and in reducing the NNM rate was also demonstrated in the study of Worku B. et al.(22). The predictive role of a higher APGAR score at 5 minutes, in the survival rate of newborns and reducing the NNM rate was found in several other studies (18-20) (24).

Asphyxia in newborns showed a significant association with the NNM rate. Newborns with birth asphyxia have an increased mortality rate, especially in the first 24 h. after birth and in the early neonatal period of up to 7 days after birth, during which period 88% of newborns with

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signs of asphyxia died. In a considerable number of studies, asphyxia is associated with a low APGAR score in the 1st and especially with an APGAR score in the 5th minute <7 (18-20). Asphyxia plays one of the most significant roles in the NNM rate, as well as terms of the morbidity and the consequences it leaves in newborns who survive (18-20) (22).

Our study also demonstrated that ARDS - acute respiratory distress syndrome the second leading reason for transferring newborns to the NICU, following prematurity. Of the 445 treated newborns at the NICU, 343 (77.10%) had signs of mild or severe ARDS. The study showed that ARDS had a significant association with the NNM rate. All studies that analyze ARDS confirm that it plays a significant role in the NNM rate and the transfer of newborns to Intensive Care Units, especially in developing countries, with a participation of 27% to 94.5% (57-61). The most common complications of ARDS are intracranial hemorrhage, pneumothorax, bronchopulmonary dysplasia, NEC, sepsis, and death (9) (13) (14) (22).

Our research demonstrated that NEC (necrotizing enterocolitis) had a significant association with the NNM rate. Of the 25 infants who developed NEC, 22 infants died. NEC has been identified as a predictive factor for increased neonatal mortality rate, which other studies have highlighted (9) (13) (23). Intracranial hemorrhages play a significant role in increasing the neonatal mortality rate. Congenital anomalies play a leading role in the neonatal mortality rate in developed countries compared to other causes, unlike in developing countries (19-20).

During the newborns' treatment at the NICU, the clinical and laboratory signs of sepsis were developed in 124 newborns, out of a total of 445 treated newborns during this period, and 32 (25,8%) newborns died. Sepsis is one of the leading causes of neonatal mortality in developing countries, with a share of 30-50% in neonatal mortality shown in several studies (9).

Newborns who received prenatal corticosteroids had a significantly lower risk of NNM compared to newborns who did not receive prenatal corticosteroids, at a ratio of 1:3. Prenatally prescribed corticosteroids showed a predictive role for reducing the NNM rate in this study.

A Japanese multicenter study conducted by JSOG, in 133 level-3 hospitals in Japan, reported an 80% survival rate for premature infants born at 24 weeks of gestation and a birth weight > 500 g. There was a significant difference in the survival rate between infants delivered by a cesarean section and those delivered vaginally at 24–31 weeks of age, favoring cesarean section. In the same study, prenatal corticosteroids and a high 5-minute APGAR score significantly influenced the survival rate of infants (24).

ACOG makes the same recommendations for deliveries at 24 weeks of gestation and beyond, for termination of labor by a cesarean section, use of tocolysis to induce antenatal maturation with corticosteroids, use of antibiotics in PROM, and use of magnesium sulfate as a neuroprotectant (21).

Prematurity and low birth weight, as well as complications of prematurity, are responsible for over 60% of neonatal mortality worldwide (10).

## **Conclusion**

The decline in the NNM rate in N. Macedonia and in the UGOC - Skopje in recent years is largely due to the increase in the survival rate among newborns in the group of 28-32 weeks of

gestation. N. Macedonia still does not have an effective mechanism to increase the survival rate of extremely premature newborns, born during 24-27 weeks of gestation.

Further activities to reduce the NMR rate should be directed towards: prevention of prematurity; strengthening the antenatal primary health care; detection of maternal comorbidities in high-risk pregnancies and timely referral to tertiary centers; proper treatment of infections during pregnancy, childbirth and postpartum in mothers and newborns; as well as reducing complications during childbirth and choosing the most appropriate mode of delivery. The goal of all of these is to obtain a more vital and healthy newborn at birth, who will not need to receive or will receive minimal neonatal care after delivery.

The neonatal mortality rate is a mirror of the health system of a country that sublimates the work, and the functionality in primary, secondary and tertiary health care. The reasons for the increase in the NNM rate are always multifactorial and come from antenatal care, maternal comorbidities, the mode of delivery and the hospital treatment of newborns after delivery. Most of the causes of NNM are preventable.

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