# NEONATAL HYPOGLYCEMIA:
# RISK FACTORS AND OUTCOMES

Orhideja Stomnaroska[1], Elizabeta Petkovska[1], Snezana Jancevska[1], Dragan Danilovski[2]

[1] University Clinic for Gynecology and Obstetrics, Medical Faculty Skopje, Macedonia
[2] Institute for Epidemiology and Statistics, Medical Faculty Skopje, Macedonia

**Corresponding author**: Orhideja Stomnaroska, University Clinic for Gynecology and Obstetrics, Medical Faculty Skopje, Vodnjanska BB, 1000 Skopje, Macedonia; e-mail: stomnaroskao@yahoo.com

## ABSTRACT

**Background and aims:** Severe neonatal hypoglycemia (HG) leads to neurologic damage, mental retardation, epilepsy, personality disorders, impaired cardiac performance and muscle weakness. We aimed to assess the clinical characteristics of children with hypoglycemia in a random population of newborns.

**Patients, methods and results:** We investigated 84 patients (M:F=35:48) born at the University Clinic for Gynecology and Obstetrics in Skopje (hospitalized in the NICU) who were found to have hypoglycemia. In total 89.25% of the babies were premature. The mean birth weight was 1795.95 +/596.08 grams, the mean birth length was 41.92+/- 4.62 cm, while the mean gestational age was 33.05±3.19 weeks. 32 children (38.08%) were very low birth weight (<1500g), 38 (45.22%) were low birth weight (1500-2500g), while there were 8 children (9.52%) appropriate for age BW and no high BW for age patients (>4000 g).

HG duration was 2.42+/-2.41 hours. In the group as a whole, hypoxic-ischemic encephalopathy (HIE) was found in 3 children (3.57%), infections in 22 (26.18%), respiratory distress syndrome (RDS) in 9 patients (10.62%), intracranial haemorrhage in 2 patients (2.38%). There were no inborn errors of metabolism. There were two deaths (2.38%).

**Conclusion:** Neonatal HG is a significant factor in the overall neonatal mortality. HG can also cause severe invalidity. We found that infections, LBW and low gestational age were most commonly associated with neonatal HG. However the Spearman test showed weak direct correlation, without statistical significance. Neonatal HG requires complex and team interaction of prenatal and postnatal approaches to reduce the incidence of seizures, their consequences and the overall mortality. Special consideration is to be taken in measures that avoid neonatal infections, HIE, LBW and low gestational age. Further studies on a larger population are needed to fully understand and prevent the phenomenon of HG in newborns.

**Keywords:** neonatal hypoglycemia, co-morbidities, low birth weight, HIE, mortality.

## INTRODUCTION

The neonatal period is marked by increased risk of HG and seizures (1-3). Neonatal HG is the most common form of a metabolic disturbance in newborns, while seizures are the most common symptom of neurological dysfunction (2,3). The incidence of neonatal seizure is high: 10-25% in neonatal intensive care units (NICU). Strikingly in NICU 15% of newborns with seizures will die and 35- 40% will have significant neurological defects (2).

Hypoxic-ischemic encephalopathy (HIE) is found in ~50% of the patients with neonatal HG (1). HIE may potentiate the permanent brain damage caused by HG (3). In neonates there are multiple other causative factors for HG: intracranial hemorrhage, infections, metabolic disorders, CNS malformations, birth trauma, and metabolic disorders (2, 3).

Delay in therapy often results in poor neurological outcome (4, 5). It is of note that the worst neurological outcome in large number of children is

observed in neonates and infants with persistent and recurrent severe hypoglycemia (3, 6).

We aimed to assess the incidence, etiology, and outcome of HG in newborns hospitalized at the neonatal ward and NICU of the University Clinic for Gynecology and Obstetrics.

## PATIENTS AND METHODS

This study was carried out in the neonatal intensive care unit of University Clinic for Gynecology and Obstetrics in Skopje, Macedonia.

The following classification of neonatal HG was applied: capillary blood glucose (CBG) values were considered normal when ≥ 2.5 mmol/l, or HG was mild (2.2-2.4 mmol/l), moderate (1.6-2.1 mmol/l) or severe HG (<1.6 mmol/l)(7).

The diagnosis of neonatal seizures was based on clinical observation, multiple measurements of CBG (from the first hour after birth, than consecutively the 3rd, 6th hour of life, and/or until the resolution of the HG episode. The etiology of the seizures was assessed using clinical examination, laboratory results, and/or imaging (ultrasound).

The Diagnosis of HIE was determined by analyzing data from the medical history and physical examination, taking into regard the Apgar score, arterial blood gas results, and neuroimaging. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists defined those features for the diagnosis of birth asphyxia: 1) Profound metabolic or mixed acidemia (pH<7.00) in umbilical arterial blood. 2) Apgar score of 0-3>5 minute after birth. 3) Signs of neonatal encephalopathy (seizures, coma, or hypotonia), 4) Multiple organ involvement (kidney, lungs, liver, heart, intestines). Children were breastfed, rarely formulas were used..

Clinical examination, blood cell count, C reactive protein, and positive blood culture lead to the diagnosis of sepsis. Pulmonary infections were diagnosed clinically and confirmed by microbiological analysis of the deep tracheal aspiration. The existence of intracranial hemorrhage was demonstrated with US or CT scan.

The biochemical analysis was performed using the ARCHITECT plus c4000, Integra 400.

The statistical analysis included parametric and non-parametric statistics using SPSS software.

## RESULTS

We investigated 84 patients (M:F=35:48) as a random group born at the University Clinic for Gynecology and Obstetrics and admitted to the NICU in

Skopje. The delivery in 33 (39.27%) cases was vaginal, and in 51 (60.69%) caesarean section. Among all the patients 89.25% were preterm.

The mean birth weight was 1795.95 +/596.08 grams, the mean birth length was 41.92+/- 4.62 cm. 32 children (38.08%) were very low birth weight (<1500g), 38 (45.22%) were low birth weight (1500-2500g), while there were 8 children (9.52%) appropriate for age BW and no high BW for age patients (>4000 g) (Fig 1).

The Apgar score was 6.65 +/-1.11 at 0 minutes and 7.17+/-1.19 at 5 minutes.

The blood glucose level at 0 hours was 2.17+/-0.17, at one hour 4.08+/- 1.9. at 2 hours 4.37+/-1.74, at 3 hours 4.17+/-2.002, at 4 hours 4.39+/-1.89 and at 5 hours the glycaemia was 4.28+/-1.86 mmol/l. HG duration was 2.42+/-2.41 hours. In the group as a whole, hypoxic-ischemic encephalopathy (HIE) was found in 3 children (3.57%), infections in 22 (26.18%), respiratory distress syndrome (RDS) in 9 patients (10.62%), intracranial hemorrhage in 2 patients (2.38%) (Fig.2).

There were no inborn errors of metabolism. There were two deaths (2.38%) in children with infections, low birth weight and hypoglycemia.
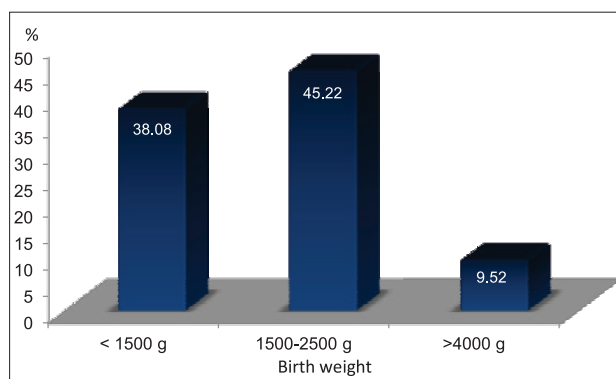


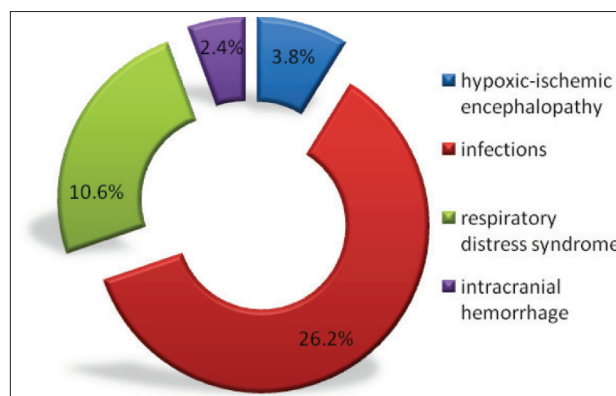**Figure 1:** Birth weight distribution



**Figure 2:** Co-morbidities in children with neonatal hypoglycaemia

Although the Spearman test showed weak direct correlation, there was not statistical significance for the association among HG and infections (multiple R = 0,752101; p=0,526683), gender (multiple R = 0,782301; p=0,577641), LBW (0,114932 weak direct correlation, but no statistical significance p=0,347025)(Fig.1) and low gestational age (-0,112608 weak direct correlation, but no statistical significance p=0,307799) (Fig. 3). HIE and HG were not correlated, probably due to the low number of patients with HIE (3 patients).



24  26  28  30  32  34  36  38  40  42  Weeks
(-0,112608 weak direct correlation, but no statistical significance p=0,307799)
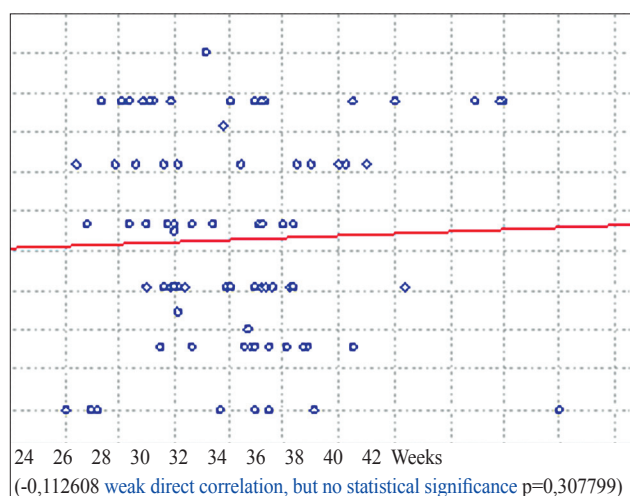
**Figure 3:** Birth age and hypoglycaemia

## DISCUSSION

In neonates long term sequelae can occur within a wide range of low serum glucose values. Even transient moderate HG can result in neurological damage (8). The duration and severity of NH greatly influences the creation of permanent neurological damage, although the nadir glucose concentrations and the duration of HG that can damage newborn brain are not precisely determined (2, 3).

Serum glucose levels in neonates normally decline until age 1-3 hours and spontaneously increase afterwards. In fact, there is no rigorously determined specific blood glucose concentration for a definition of NH for infants (9-15).

The definition of neonatal HG that we used for the study was that of the clinical settings. HG in newborns was defined by a plasma glucose level of less than 30 mg/dL (1.65 mmol/L) in the first 24 hours of life and less than 45 mg/dL (2.5 mmol/L) thereafter. Many experts recommend that values of blood glucose <50 mg/dL in neonates should be vigorously treated (3).

As previous studies have already reported estimating the frequency of neonatal HG many factors can be influenced by many factors: the definition used, the type of glucose assay, the compartment measured (serum, whole blood), the population investigated, the method and timing of feeding.

In the USA NHG is estimated to 1.3-3 per 1000 live births (2), while in Japan, among neonates born at 35-36 weeks' gestation >80% of admissions to the NICU after birth were due to apnea or HG (16). Other authors (17-22) report an incidence between 7-11%. Population-based studies (Harris County, USA) reported an incidence of 1-3.5/1000 live birth (I 3). There is an expected high incidence in NICU: 10-25% (23).

We also observed that all the neonates had HG of early onset (before 72 hours). Mostly neonatal HG was early: 59.6% and 81% of neonates had early onset seizure in reports by different authors (23, 26).

In addition we also found that HIE was not the most frequent factor in NHG seizures (3.57%). HIE was the most frequent factor described by other authors (17, 24, 25). HIE may potentiate the role of HG in causing brain damage. Contrary to our results many authors reported that the HIE is the leading cause of neonatal HG and seizures (27-29).

Infections were the most common finding in children our study: 26.18%. Reported prevalence of seizures among children with infections is between 24.5 and 28.7% (17, 23). This difference might be due to the high number of risk deliveries in our hospital. Exact causes remain to be determined.

Intracranial bleeding in this series of patients was found in 2.38% of newborns. Others have found a higher percentage of intracranial bleeding: 6.9% -9.0% (1, 17, 23). Differences in the observed frequency stem from the different populations of patients: full-term versus pre-term, LBW versus ABW, patients from neonatal wards versus NICU.

The overall mortality remains high, especially in children with co-morbidities. HIE and infections are the most common leading causes of death. The mortality rates ranged between 9 and 14.7% (2, 17). We had a mortality of 2.38%.

The most common risk factors for neonatal HG were asphyxia, birth weight less than 1500 g, sepsis, convulsion, and meningitis (2, 3, 31). EEG is a gold standard for neonatal epilepsy (32). Among many other measures in lowering the neonatal HG, there is no evidence that the universal screening of glucose levels in the first hours should be applied to all newborn infants (33).

In conclusion, neonatal HG is a major factor in neonatal mortality (34). Neonatal HG is also a major factor in permanent neurological consequences. It is of note that major contributing factors for neonatal

HG should be actively searched and preventive measures must be taken in a timely manner. In this study LBW, low gestational age, HIE and high percentage of neonatal infections were the most frequent conditions associated with neonatal HG. It is of note that a larger group of patients is needed for more reliable data. Nevertheless it is obvious that preventive measures should address the LBW, HIE, infections and the low gestational age.

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**Резиме**

## НЕОНАТАЛНА ХИПОГЛИКЕМИЈА: РИЗИК-ФАКТОРИ И ПОСЛЕДИЦИ

**Орхидеја Стомнароска[1*], Елизабета Петковска[1], Снезана Јанчевска[1], Драган Даниловски[2]**

[1] Универзитска клиника за гинекологија и акушерство, Медицински факултет Скопје, Македонија

[2] Институт за епидемиологија и статистика, Медицински факултет Скопје, Македонија

**Апстракт**

Тешката неонатална хипогликемија (НХ) води до невролошки оштетувања, ментална ретардација, нарушувања на личноста, епилепсија, намалување на срцевата функција и мускулна слабост. Нашата цел беше да ја ги анализираме клиничките карактеристики на група новородени со хипогликемија, избрани по случаен избор.

Во ова ретроспективна студија иследивме 84 пациенти (м : ж=35 : 48), кои беа родени во Универзитетската клиника за гинекологија и акушерство и лекувани на Одделот за неонатална интензивна нега. Средната родилна тежина беше 1795,95+/-596,08 грама, средната родилна должина 41,92+/-4,62 цм, средната гестациска возраст 33,05±3,19 недели. 32 деца (38,08%) имаа многу ниска родилна тежина (>1500g), 38 (4,22%) беа со многу ниска родилна тежина (1500–2500g), родени со соодветна гестациска тежина беа 8 (9,52%), а родени со зголемена телесна тежина немаше.

Траењето на ХГ беше 2,42+/-2,41 часа. 94,4% од децата беа предвремено родени. Во целост, хипооксично исхемична енцефалопатија имаа 3 деца (3,57%), инфекции – 22 деца (26,18%), респираторен дистрес-синдром – 9 деца (10,62%), интракранијална хеморагија имаше кај двајца пациенти (2,38%). Не беа најдени деца со вродени грешки во метаболизмот. Две деца (2,38%) завршија летално.

Неонаталната ХГ може да предизвика тежок инвалидитет и е значителен фактор во вкупната неонатална смртност. Студијата покажува дека инфекциите, ниската родилна тежина, малата гестациска возраст се често асоцирани со ХГ. Неонаталната ХГ бара комплексна и тимска соработка и во пренаталниот и во постнаталниот пристап за да се редуцира фреквенцијата и последиците на неонаталната ХГ. Специјална грижа треба да се посвети на намалувањето на бројот и сериозноста на неонаталните инфекции, хипооксично исхемичната енцефалопатија, ниската родилна тежина и малата гестациска возраст. Понатамошни студии со поголеми примероци се потребни за да се разбере целосно феноменот на неонаталната ХГ и за да се преземат мерки за нејзина превенција.

**Клучни зборови**: неонатална хипогликемија, коморбидности, ниска родилна тежина, морталитет