

## HYPOGLYCAEMIA IN THE NEWBORN

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### ABSTRACT

**Aim:** Severe neonatal hypoglycaemia (HG) leads to neurologic damage, mental retardation, epilepsy, impaired cardiac performance and muscle weakness. The aim was to assess the frequency and severity of HG in a population of newborns.

**Patients and methods:** We investigated 739 patients with neonatal hypoglycaemia (HG) (M:F=370:369) born at the University Clinic for Gynaecology and Obstetrics in Skopje in the period 2014-2016 and treated at the neonatal intensive care unit (NICU). 1416 babies were treated in the same period in NICU, and HG was observed in 52.18%. The birth weight was dominated by children with low birth weight: very low birth weight (VLBW)(<1500g) 253 children, (34,23%), low birth weight (1500-2500g) 402 (54.39%), appropriate for gestational age (AGA) 78(10.55%), and high birth weight (>4000g) 6 babies (0.81%). The gestational age was also dominated by children with low gestational age: gestational week (GW) 20-25 four children (0.54%), 26-30 GW 133 babies (17.99%), 31-35 GW 472 (63.87%), and 36-40 GW 130 neonates (17.59 %).

241 mothers (32.61%) have had an infection during pregnancy, 82 preeclampsia or eclampsia (11.09%), 20 diabetes mellitus (2.70%), 78 placental situations (placenta previa, abruption) (10.55%). In this study 47 babies (6.35%) with HG and co-morbidities died.

There was a significant positive correlation between HG birth weight ( $p<0.01$ ), gestational age ( $p<0.05$ ), and the lowest Apgar score ( $p<0.01$ ). Neonatal deaths were significantly correlated with GA ( $p>0,01$ ), co-morbidities of the mothers ( $p>0,05$ ) but not with the birth weight ( $p>0,05$ ). In contrast, a significant positive correlation was found between convulsions and body weight ( $p<0.05$ ). The lowest Apgar score was positively correlated with the gestational age (0.01), but not with the birth weight (0.05).

**Conclusion:** Low birth weight, low gestational age, maternal risk factors, hypoxic-ischemic encephalopathy and neonatal infections are associated with HG and are a significant factor in overall neonatal mortality. Those results indicate that diminishing the frequency of the neonatal HG and the rates of neonatal mortality requires complex interaction of prenatal and postnatal interventions.

**Key words:** neonatal hypoglycaemia, co-morbidities, mortality.

## INTRODUCTION

There is well documented increased risk of HG and seizures in newborn babies [1-3]. Both conditions increase long term invalidity and neonatal mortality. Neonatal HG and seizures are especially frequent in neonatal intensive care units (NICU): 10-25% of babies manifest seizures, 15% of newborns with seizures die, while and 35- 40% will have significant neurological consequences [3].

There are multiple other factors that predispose for HG: infections, intracranial hemorrhage, hypoxic-ischemic encephalopathy (HIE) (~50% of the patients). Some of them are the cause for neonatal HG: birth trauma, CNS malformations, metabolic disorders [1,3].

Timely and appropriate treatment will hinder a poor neurological outcome (Howden 4, Merhta; 5). Persistent and recurrent severe hypoglycaemia results in worst outcomes [3, 6].

We evaluated 739 babies in the NICU at the Clinic for Gynecology and Obstetrics in Skopje, Macedonia.

## PATIENTS AND METHODS

This study was done in the NICU of the UCGO at the Medical Faculty Skopje, Macedonia. The study was approved by the Ethics Committee at the Medical faculty Skopje.

This is the applied classification of neonatal HG: capillary blood glucose (CBG) values were considered normal when  $\geq 2.5$  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)(1). There were multiple measurements of CBG (from the first hour after birth, than consecutively the 3<sup>rd</sup>, 6<sup>th</sup> hour of life, and/or until the resolution of the HG episode).

The seizures were investigated by clinical examination, laboratory results, and/or imaging (ultrasound).

The Diagnosis of birth asphyxia HIE was done at the basis of criteria given by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists [1]: 1) Profound metabolic or mixed acidemia ( $\text{pH}<7.00$ ) 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). Almost all the babies were breast-fed, occasionally formulas were used.

Clinical examination, blood cell count, C reactive protein, and positive blood culture resulted

in the diagnosis of sepsis. Pulmonary infections were assessed clinically and confirmed by microbiological analysis of the deep tracheal aspiration. The clinical suspicion for existence of intracranial hemorrhage was confirmed with US or CT scan.

ARCHITECT plus c4000, Integra 400 system was used for biochemical analysis.

The statistical analysis included non-parametric statistics (Spearman rank test) as the distribution of variables was not normal.

## RESULTS

In this study, we investigated 739 patients with neonatal hypoglycaemia (HG)(M:F=370:369) born at the University Clinic for Gynaecology and Obstetrics (UCGO) in Skopje in the period 29.9.2014-28.10.2016 and who were treated at the neonatal intensive care unit (NICU). The total hospitalized in this period was 1416, which amounts to 52.18% of the patients having HG. The birth weight was dominated by children with low birth weight: very low birth weight (VLBW)( $<1500$ g) 253 children, (34,23%), low birth weight (1500-2500g) 402 (54.39%), appropriate for gestational age (AGA) 78(10.55%), and high birth weight ( $>4000$ g) 6 babies (0.81%).

The gestational age was also dominated by children with low gestational age: gestational week (GW) 20-25 – 4 children (0.54%), 26-30 GW – 133 babies (17.99%), 31-35 GW – 472 (63.87%), and 36-40 GW – 130 neonates (17.59 %).

The delivery was Caesarean in 450 (60.89%) babies, while 289 (39.10%) neonates were delivered virginally.

In this series there were no inborn errors of metabolism. Asymptomatic hypoglycaemia was found in 550 (25.57%) children, while symptomatic HG with seizures was observed in 189 (74.43%).

241 mothers (32.61%) have had an infection during pregnancy, 82 preeclampsia or eclampsia (11.09%), 20 diabetes mellitus (2.70%), 78 placental situations (previa, abruption)(10.55%).

In this group, 145 babies had (19.62%) hypoxic-ischemic encephalopathy, 139 had infections (18.80%), 30 intracranial hemorrhage (4.059%), and 45 hypocalcemia (6.08%)(Fig.3).

47 babies (6.35%) with HG and co-morbidities died. Thus neonatal HG has in important contributing role in the general neonatal mortality.

There was a significant correlation between NH birth weight (at the level of 0.01), gestational age (at the level of 0.05), and the lowest Apgar

score (at the level of 0.01). Interestingly, there wasn't a positive correlation between the lowest glycaemia and convulsions ( $p > 0.05$ ), as well as with the gestational age ( $p > 0.05$ ) maternal co-morbidities ( $p > 0.05$ ). Neonatal deaths were significantly correlated with GA ( $p > 0.01$ ), maternal co-morbidities ( $p < 0.05$ ) but not with the birth weight ( $p > 0.05$ ). In contrast, significant positive correlation was found between convulsions and body weight ( $p < 0.05$ ). The lowest Apgar score was positively correlated with the gestational age (0.01), but not with the birth weight ( $p > 0.05$ ).

## DISCUSSION

Avoiding neonatal HG is critical as even transient moderate HG can result in some neurological sequelae [7]. In spite of plentiful research, the nadir glucose concentrations and the duration of HG that causes brain damage in new-borns are not adequately elucidated [1,3]. Moreover, the specific value of serum glucose for hypoglycaemia is not universally accepted [8-12]. The title "is the sixty the new forty" (mg/dl) is a striking example of the lack of solid evidence in defining the neonatal HG [13].

Among 1416 babies treated in the same period in NICU, we observed HG in 52.18%. In Japan, among the neonates born at 35-36 week of gestation >80% of the admissions to the NICU after birth were due to apnea or HG [14]. USA reported the HG frequency is estimated to 1.3-3 per 1000 live births. Other publications [15-20] have observed an incidence between 7-11%. In Harris county, USA, an incidence of 1-3.5/1000 live birth was reported [1, 18]. NICU have high incidence of HG: 10-25% [21]. The difference in the frequency in the neonatal HG between this study and others can be contributed to the population studied: NICU or delivery ward, and the population studied Aga non-AGA, normal birth weight or various degrees of LBW.

In our study the prevalent number of babies had not AGA, but had some form of LBW: 88.62%. As could be expected there was a significant correlation between NH birth weights ( $p < 0.01$ ). Interestingly, significant positive correlation was found between convulsions and body weight ( $p < 0.05$ ). In a seminal study, children born with a birth weight < 1850 g had worse development at 18 months [22]. Adamkin (2011; 23) has found that LGA, SGA, IUGR are at special risk. Increased BW was also found to be HG risk factors in babies in whom the mother did not have DM [24].

Gestational age among children with HG was also dominated by babies with low gestational age – 82.40%. This finding is characteristic for developing countries (1, NCHS). It is of note that there was a significant correlation between HG and gestational age ( $p < 0.05$ ).

There was a significant correlation between HG and the lowest Apgar score ( $p < 0.01$ ). The lowest Apgar score was positively correlated with the gestational age ( $p < 0.01$ ), but not with the birth weight ( $p > 0.05$ ). Interestingly, there was not a positive correlation between the lowest glycaemia and convulsions ( $p > 0.05$ ). Asymptomatic hypoglycaemia was found in 550 (25.57%) children, while symptomatic HG with seizures was observed in 189 (74.43%).

In 145 babies (19.62%) hypoxic-ischemic encephalopathy (HIE) was diagnosed. Other publications have also observed that HIE was also the most frequent factor [15, 25, 26]. This condition may aggravate the role of HG in causing brain damage. HIE was observed to be the leading factor in neonatal convulsions [15, 27, 28].

Adamkin (2011; 23) has found that and infants of diabetic mothers (DM) are at special risk. In this study 9 mothers were diabetic (type 1 or 2), while 11 mothers had gestational diabetes (2.70%). Maternal risk factors are well known to contribute to neonatal HG and neonatal mortality [1, 3].

Neonatal infections were common among babies with seizures in this study: 139 had infections (18.80%). This observation was shared in other publications in which new-born infections ranged between 24.5% [25], 28.2 [21].

In this study intracranial hemorrhage was observed in 30 patients (4.05%). Other studies have also reported a high percentage of intracranial bleeding: 6.9% -9.0% [2, 15, 23]. This study also observed 45 babies with hypocalcemia (6.08%), which is a reported common metabolic disturbance in new-borns [3, 21].

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% [3, 15]. 47 babies (6.35%) with HG and co-morbidities died. Thus, neonatal HG has a contributing role in the general neonatal mortality. Neonatal deaths were significantly correlated with GA ( $p > 0.01$ ), maternal co-morbidities ( $p > 0.05$ ) but not with the birth weight ( $p > 0.05$ ).

In general, differences in the observed frequency of various co-morbidities and outcomes in children with HG originate from the different

types of new-born populations: full-term versus pre-term, LBW versus ABW, patients from neonatal wards versus NICU.

Lowering the frequency of neonatal HG would lower the neonatal mortality. Prematurity remains a main risk for neonatal HG and the main cause of death in newborns: prematurity-related deaths are 51% of the deaths among children less than 5 years of age (WHO, 2015) [29]. In USA the overall neonatal mortality is 4.2 (NCHS) [30], perinatal mortality in Macedonia is 7.4/1000 live births [31]. In addition, the under age 5-year mortality was higher in Macedonia than in many neighboring countries [29, 31]. Lowering the frequency of neonatal HG would lower the neonatal mortality.

**In conclusion,** neonatal HG is frequent metabolic event in new-borns. Neonatal HG is an important co-factor in neonatal mortality. This study strongly recommends the need for comprehensive, team approach in the efforts to lower the rates of prematurity, low birth weight, birth asphyxia and infections. An improvement in the follow-up of pregnancies and mothers is strongly needed and recommended.

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## ХИПОГЛИКЕМИЈА НА НОВОРОДЕНИТЕ

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### Резиме

Длабоката неонатална хипогликемија (ХГ) резултира во невролошко оштетување, ментална ретардација, епилепсија, намалена срцева моќност и мускулна слабост. Целта на трудот е да се утврдат фреквенцијата и тежината на ХГ кај новородени деца во неонатална интензивна нега. Анализирани се 739 бебиња со неонатална хипогликемија (ХГ) (М:Ф=370:369) родени на Универзитетската клиника за гинекологија и акушерство во Скопје во двегодишен период и лекувани на одделот за интензивна нега. Во истиот период третирани се 1416 деца, а ХГ е опсервирана кај 52.18%. Доминираа деца со намалена родилна тежина: многу ниска родилна тежина (VLBW)(<1500g) 253 деца, (34,23%), ниска родилна тежина (1500-2500g) 402 (54.39%). Тежина соодветна за возраста (AGA) имаа 78 (10.55%), а деца со висока родилна тежина (>4000g) беа (0.81%). Доминираа деца со намалена гестациска возраст (недела) (ГН) 20-25 кај четири деца (0.54%), 26-30 ГН кај 133 бебиња (17.99%), 31-35 ГН кај 472 (63.87%), и 36-40 ГН кај 130 новородени (17.59 %).

241 мајки (32.61%) имаа инфекција за време на бременоста, 82 прееклампсија и еклампсија (11.09%), 20 дијабетес мелитус (2.70%), 78 плацентални неправилности (placenta previa, abruption) (10.55%). 47 деца (6.35%) со ХГ и ко-морбидности завршија летално.

Постоеше сигнификантна позитивна статистичка корелација меѓу ХГ и родилната тежина ( $p < 0.01$ ), гестациската недела на раѓање ( $p < 0.05$ ), и нискиот Апгар скор ( $p < 0.01$ ). Неонаталните смртни исходи беа сигнификантно поврзани со гестациската возраст ( $p > 0.01$ ), ко-морбидностите кај мајката ( $p > 0.05$ ), но не и со родилната тежина ( $p > 0.05$ ). Сигнификантна позитивна корелација е најдена помеѓу конвулзиите и родилната тежина ( $p < 0.05$ ). Нискиот Апгар скор беше позитивно корелиран со гестациската возраст ( $p > 0.01$ ), но не и со родилната тежина ( $p > 0.05$ ).

Ниска родилна тежина, мајчините фактори на ризик, хипооксично-исхемичната енцефалопатија и неонаталните инфекции беа асоцирани со неонаталната ХГ. Истите се сигнификантни фактори за неонаталниот морталитет. Заради ова намалување на фреквенцијата на неонаталната ХГ и намалување на неонаталниот морталитет бара комплетна интерреакција на пренатални и постнатални медицински интервенции.

**Клучни зборови:** неонатална хипогликемија, неонатален морталитет, ко-морбидности.