

# NEONATAL OUTCOMES OF PRETERM INFANTS DEPENDING ON THE CARE APPROACHES

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## ABSTRACT

**Introduction.** With the improvement in perinatal care management, the survival rate of very and extremely preterm infants increased, while the incidence of neonatal morbidity remained constant.

**The aim of the study** was to analyse and compare two cohorts of Neonatal Intensive Care Unit-admitted preterm infants with gestational age <32 weeks (from Ukraine and Poland), and to identify the key problems of neonatal care, to improve the management of preterm infants.

**Material and methods.** The comparative analysis included survival rates and neonatal outcomes as intraventricular hemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia, late-onset sepsis, necrotizing enterocolitis (NEC), duration of parenteral feeding, breast-feeding rate and infants' growth parameters. Mann-Whitney U-test and Chi-square test were used for statistical analysis.

**Results.** The survival rate of preterm infants was lower in the cohort from Ukraine compared with Poland ( $p=0.0076$ ). The late-onset infection rates were higher in extremely and very preterm newborns ( $p<0.05$ )

## RÉSUMÉ

**Résultats néonataux des nouveau-nés prématurés selon les soins périnataux**

**Introduction.** Avec l'amélioration de la prise en charge des soins périnataux, le taux de survie des nourrissons prématurés a augmenté, tandis que l'incidence de la morbidité néonatale est restée constante.

**Le but de l'étude** était d'analyser et de comparer deux cohortes de prématurés d'âge gestationnel <32 semaines admis à l'unité des soins intensifs (de l'Ukraine et de Pologne), et d'identifier les grands problèmes des soins néonataux dans le but d'améliorer la prise en charge des prématurés.

**Matériel et méthodes.** L'analyse comparative comprenait les taux de survie et les résultats néonataux comme l'hémorragie intraventriculaire, la rétinopathie de la prématurité, la dysplasie bronchopulmonaire, la septicémie tardive, l'entérocolite nécrosante (ECN), la durée de l'alimentation parentérale, les taux d'allaitement et les paramètres de croissance des nourrissons. Le test U de Mann-Whitney et le test du Chi-carré ont été utilisés pour l'analyse statistique.

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and NEC prevailed in very preterm infants ( $p=0.000$ ) among neonates of Ukraine; the duration of parenteral feeding was significantly higher in both age groups in this cohort. Postnatal growth failure was observed in 57.1% and 29.4% in extremely preterm infants of Ukraine and Poland, respectively ( $p=0.035$ ).

**Conclusions.** The comparative analysis of short-term outcomes of very and extremely preterm infants in different perinatal centers identified key problems in their management and the possible ways to improve the quality of care. Regular auditing of clinical outcomes and identification of main problems could facilitate quality improvement in preterm infants' management and help to implement new interventions and approaches.

**Keywords:** extremely preterm infants, very preterm infants, survival rate, morbidity, preterm infants' care.

**List of abbreviations:**

BPD – bronchopulmonary dysplasia  
ELBW – extremely low birth weight  
GA – gestational age  
IVH – intraventricular hemorrhage  
IQR – inter-quartile range  
KMC – Kangaroo mother care  
LOS – late-onset sepsis  
NEC – necrotizing enterocolitis  
PGF – postnatal growth failure  
ROP – retinopathy of prematurity  
SGA – small for gestational age

**INTRODUCTION**

Preterm birth is an important public health issue all over the world<sup>1</sup>. The incidence of preterm deliveries varies from 5 to 12% in the developed countries of Europe and the USA and may reach 40% in less developed regions. About 15% of preterm births occur before 32 weeks of gestation<sup>2,4</sup>. With the improvement in perinatal care management, the survival rate of very and extremely preterm infants increased, while the incidence of neonatal morbidity and complications associated with premature birth remained constant or even has tendency to grow. Infants born extremely and very preterm have a high risk of multiple neonatal morbidities, strongly associated with poor long-term outcomes<sup>1,3</sup>. It is crucial to analyze and compare the local data of clinical outcomes with the international standards.

**THE OBJECTIVE OF OUR STUDY** was to analyse and compare two cohorts of Neonatal Intensive Care Unit-admitted preterm infants with gestational age

**Résultats.** Le taux de survie des nourrissons extrêmement prématurés était plus faible dans la cohorte de l'Ukraine que dans celle de la Pologne ( $p=0,0076$ ). Les taux d'infection tardive étaient plus élevés chez les nouveau-nés extrêmement et très prématurés ( $p<0.05$ ) et la ECN prévalait chez les nourrissons très prématurés ( $p=0,000$ ) parmi les nouveau-nés de l'Ukraine; la durée de l'alimentation parentérale était significativement plus élevée dans les deux groupes d'âge de cette cohorte. Un retard de croissance postnatal a été observé chez 57,1% et 29,4% des nourrissons extrêmement prématurés de l'Ukraine et de Pologne, respectivement ( $p=0,035$ ).

**Conclusions.** L'analyse comparative des résultats à court-terme des nourrissons très et extrêmement prématurés dans différents centres de périnatalité a identifié des problèmes clés dans leur prise en charge et les moyens possibles d'améliorer la qualité des soins. Un audit régulier des résultats cliniques et l'identification de grands problèmes pourraient faciliter l'amélioration de la qualité de la prise en charge des prématurés et aider à mettre en œuvre de nouvelles interventions et approches.

**Mots-clés:** nourrissons extrêmement prématurés, nourrissons très prématurés, taux de survie, morbidité, soins aux nourrissons prématurés.

(GA) < 32 weeks (from developed and developing countries), and to identify the key problems of neonatal care, to improve the management of preterm infants.

**MATERIAL AND METHODS**

**Study design and participants.** Standardized perinatal/neonatal data of 152 infants with gestational age of 24+0 to 31+6 weeks, who were born in Ternopil Regional Perinatal Center (Ukraine), were collected for this study (Ternopil Group). These data were compared with the database of the Clinic of Neonatology and Intensive Neonatal Care, Warsaw Medical University (Poland) that included 130 infants with the same GA (Warsaw Group). The data were collected between January 2016 and December 2017 in the Ternopil Group and between January 2014 and December 2016 in the Warsaw Group.

This is a retrospective analysis, that included antenatal risk factors, peculiarities of delivery, birth-weight, clinical characteristics of infants in the early

neonatal period and early outcomes as intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), late-onset sepsis (LOS), necrotizing enterocolitis (NEC), duration of parenteral feeding, breast-feeding rates and infants' growth parameters.

Small for gestational age (SGA) was defined as a birth weight of <10<sup>th</sup> percentile for gender and GA and further growth dynamics were evaluated with Olsen growth calculator<sup>5</sup>. Postnatal growth failure (PGF) was defined as a discharge weight <10<sup>th</sup> percentile for post-conceptual age<sup>6</sup>.

The survival rate was defined as neonates who survived to the time of discharge. BPD was diagnosed at the post-conceptual age of 36 weeks or at hospital discharge, whichever one comes first<sup>7</sup>. The early-onset infection was defined as positive cultures from blood or cerebrospinal fluid or a combination of clinical symptoms and laboratory biomarkers occurring within 72 hours of life. The late-onset infection was defined as bacterial or fungal infection after the 3<sup>rd</sup> day of life. NEC was suspected or definite, which was confirmed by clinical and radiological or ultrasound abnormalities.

The definition and classification of IVH was based on the Papille IVH classification. ROP was defined according to the International Classification of Retinopathy of Prematurity and includes the highest level of ROP in either eye.

All the children guardians signed an informed consent to participate in the study.

**Human research statement.** The ethical approval was obtained from the local ethical committee of the I. Horbachevsky Ternopil National Medical University (No 43 issued 23.10.2017) and the research was conducted in accordance with the World Medical Association's Helsinki Declaration.

**Statistical analysis.** All computations were performed using "EXCEL FOR WINDOWS" and "STATISTICA 13.0. FOR WINDOWS". The quantitative data are presented as the median and inter-quartile range (IQR; 25<sup>th</sup> to 75<sup>th</sup> percentiles), depending on the distribution of the data. For qualitative parameters, absolute and relative frequencies are presented. The Mann-Whitney U-test (for two independent groups) was used to compare numerical data. Proportions were compared between the two groups using the Chi-square test. Significance was assumed at  $p < 0.05$ .

## RESULTS

### Demographic data and peculiarities of anamnesis of the study groups

The data were obtained for 152 newborns of Ternopil Group and 130 of Warsaw Group. The

Ternopil Group included 83 boys (54.6%) and 69 girls (45.4%) and the Warsaw Group included 61 boys (46.9%) and 69 girls (53.1%), respectively.

The mean GA was 30.0 [28.0; 31.0] weeks in the Ternopil Group and 28.0 [26.0; 30.0] weeks in the Warsaw Group ( $p < 0.001$ ). A significantly greater number of infants were born as an extremely preterm (GA < 28 weeks) in the Warsaw Group compared with Ternopil Group, 68 (52.3%) vs 43 (28.3%),  $p = 0.0001$ . The GA of the largest group in the Warsaw Group was 27 weeks (14.6%;  $p = 0.006$ ), while in the Ternopil Group was 32 weeks (22.37%;  $p = 0.003$ ).

The mean birth weight was 1095.0 [840.0; 1370.0] grams in the Warsaw Group and 1370 [1050; 1705] grams in the Ternopil Group ( $p < 0.001$ ). The extremely low birth weight (ELBW) infants (< 1000 g) constituted 41.6% of Warsaw Group and 22.4% of Ternopil Group ( $p = 0.016$ ) (Table 1).

There was no significant difference in pregnancy-associated diseases such as preeclampsia, eclampsia, gestational hypertension and gestational diabetes, and thyroid gland disorders among the study groups. Deliveries by cesarean section were significantly less frequent in the Ternopil Group compared with Warsaw Group,  $p = 0.001$  (Table 1).

The characteristics of infants in the early neonatal period are presented in Table 1. Fewer children in the Ternopil Group needed primary resuscitation after birth compared with Warsaw Group (44.1% vs 86.9%,  $p = 0.000$ ). Significantly more infants among those who needed resuscitation from the Ternopil Group were intubated in the delivery room compared with Warsaw Group (56.7 % vs 29.2%,  $p = 0.000$ ).

**Table 1.** Proportions of preterm infants born at different GA in Ternopil and Warsaw groups.

GA (weeks)	TG (n=152)	WG (n=130)	P
	n (%)	n (%)	
22	1 (0.66)	2 (1.54)	0.596
23	2 (1.32)	6 (4.61)	0.149
24	2 (1.32)	6 (4.61)	0.149
25	9 (5.92)	6 (4.61)	0.791
26	10 (6.58)	14 (10.77)	0.284
27	7 (4.61)	19 (14.61)	0.006*
28	12 (7.89)	15 (11.54)	0.317
29	22 (14.47)	16 (12.31)	0.727
30	22 (14.47)	17 (13.08)	0.863
31	31 (20.39)	17 (13.08)	0.114
32	34 (22.37)	12 (9.23)	0.003*

\* $p < 0.05$

**Survival rates and short-term outcomes (morbidity indices) in the study groups**

The overall survival rate in the Ternopil Group was 78.29% (119 infants), with no significant difference in comparison with the Warsaw Group – 84.61% (110 infants),  $p=0.221$ . The survival rate of extremely preterm infants was lower in the Ternopil Group compared with Warsaw Group (48.84% vs 75.0%;  $p=0.0076$ ), in very low preterm category – no difference (89.09% and 95.16%, respectively;  $p=0.261$ ).

The evaluation and analysis of short-term outcomes and morbidity indices were provided among surviving infants according to their GA (extremely preterm infants with GA < 28 weeks and very preterm infants with GA 29-32 weeks). One infant from the Warsaw Group was excluded from further evaluation because of the multiple congenital malformations of gastro-intestinal tract and heart.

The mean birth weight in extremely preterm newborns in the Ternopil Group was 1050.0 [900.0; 1220.0] grams, in the Warsaw Group it was 980.0 [790.0; 1190.0] grams,  $p=0.4206$ . All infants from the Ternopil Group were born with appropriate weight for GA, and there were 5 (9.8%) infants with SGA in the Warsaw Group,  $p=0.3150$ .

The birth weight in very preterm infants' groups was also without significant difference – 1585.0 [1320.0; 1800.0] grams in Ternopil Group and 1495.0 [1200.0; 1810.0] grams in Warsaw Group,  $p=0.2802$ .

GA in extremely preterm newborns of Ternopil and Warsaw groups was 28.0 [27.0; 28.0] and 27.0

[26.0; 28.0] weeks, respectively,  $p=0.137$ ; in very preterm infants 31.0 [30.0; 32.0] and 30.0 [30.0; 31.0],  $p=0.0812$ . Newborns with GA of 28 weeks prevailed among the surviving extremely premature infants of the Ternopil Group, while in the Warsaw Group the newborns with GA of 24-27 weeks were more frequent. The subgroup of very premature babies in the Ternopil Group was dominated by infants with 31-32 weeks of gestation, in the Warsaw Group – by infants with GA of 30-31 weeks.

Major neonatal morbidities and short-term outcomes in extremely and very low- birth weight preterm infants in study groups are displayed in Table 2.

Fewer extremely preterm infants from the Ternopil Group were given surfactant therapy in comparison with the Warsaw Group, but without statistical significance; invasive ventilation rates were approximately equal. Significantly fewer very preterm infants from the Ternopil Group compared with Warsaw Group were given surfactant therapy for RDS management (18.4% vs 51.7%,  $p=0.000$ ) and were treated with mechanical ventilation (31.6% vs 50.0%,  $p<0.027$ ). The rate of continuous positive airway pressure therapy in Ternopil Group was 76.2% in extremely preterm newborns and 65.3% in very preterm infants, while in Warsaw Group – 100% and 86.2%, respectively ( $p=0.001$  and  $p=0.005$ ).

There was no significant difference in postnatal steroids usage for BPD between Ternopil Group

**Table 2.** Characteristics of infants of the study groups

Parameter	Statistical indicators	TG (n=152)	WG (n=130)	p value
<b>Maternal factors</b>				
Preeclampsia, eclampsia, gestational hypertension	[n (%)]	23 (15%)	16 (12.3%)	0,604
Gestational diabetes	[n (%)]	1 (0.65%)	6 (4.31%)	0.051
Thyroid gland disorders	[n (%)]	18 (11.84%)	9 (6.92%)	0.223
<b>Mode of delivery</b>				
C-section	[n (%)]	(34.9%)	(69.2%)	0.001*
<b>Birth weight characteristics of infants</b>				
Mean birth weight (g)	Me [Lq; Uq]	1370.0 [1050.0; 1705.0]	1190.0 [850.0; 1480.0]	0.000*
Percentile of birth weight for GA	Me [Lq; Uq]	63.0 [42.0; 85.5]	58.0 [22.0; 76.0]	0,017*
SGA	[n (%)]	12 (7.89)	13 (10.0)	0.538
ELBW	[n (%)]	34 (22.4)	41.6 46 (35.4)	0.016*
<b>Characteristics of infants in the early neonatal period</b>				
Apgar score at 1 min	Me [Lq; Uq]	7.0 [5.0; 7.0]	6.0 [4.0; 7.0]	0.000*
Apgar score at 5 min	Me [Lq; Uq]	7.0 [6.0; 7.0]	7.0 [6.0; 7.0]	0.256
Primary resuscitation	[n (%)]	67 (44.1)	113 (86.9)	0.000*
Surfactant replacement therapy	[n (%)]	54 (35.5)	85 (65.4)	0.000*

and Warsaw Group, with similar rates of BPD indices within all gestational age groups ( $p>0.05$ ).

The incidence of early-onset infection was 33.7% in very preterm infants from Ternopil Group and 15.5% in the Warsaw Group ( $p=0.015$ ). These indices were similar ( $p=1.00$ ) in both extremely preterm newborns groups. Late-onset infections were diagnosed more frequently in the Ternopil Group in extremely and very preterm newborns compared with Warsaw Group (76.2% vs 35.3%,  $p<0.05$  and 22.4% vs 8.6%,  $p<0.05$ ). The overall frequencies of NEC were higher in very-low-birth weight preterm infants from the Ternopil Group (21.4% vs 1.7%,  $p=0.000$ ). The duration of parenteral feeding was higher in both age groups in Ternopil Group compared with Warsaw Group ( $p=0.005$  and  $p=0.001$ ).

The incidences of severe IVH (grades III) and periventricular hemorrhagic infarction were similar in extremely and very preterm infants of both centers. There were few extremely preterm newborns with severe ROP ( $\geq$ stage 3) in Warsaw Group (7.8%) than in Ternopil Group (23.8%), but the difference was not statistically significant ( $p=0.117$ ).

The rate of exclusive breast-feeding in the Ternopil Group was significantly lower compared with Warsaw Group (2.5% and 95.6%, respectively,  $p<0,000$ ). Overall, 19.3% of Ternopil Group infants got mixed feeding, including mother's milk and formula for preemies, the rest of them received only formula. The postnatal growth failure at discharge was observed in 57.1% of extremely preterm infants from the Ternopil Group and in 29.4% from the Warsaw Group ( $p=0.035$ ).

## DISCUSSION

The comparative analysis of preterm infants' management in two tertiary centers from Ukraine and Poland showed significant differences in the outcomes of these patients. A detailed analysis of these differences will allow to identify the main reasons for their occurrence and to study the current experience of both centers, in order to improve the early outcomes of preterm infants. To date, there is insufficient data regarding the in-depth analysis of survival rates and morbidities in extremely and very preterm infants from Ukraine, in comparison with European indicators.

Our study revealed that the overall survival rate of preterm infants with GA less than 32 weeks from the Ternopil Group was similar with that of Warsaw Group. However, the analysis of these indicators showed that the survival rate among extremely preterm infants in the Warsaw Group significantly exceeded the Ternopil Group (75.0% vs 48.8%;  $p=0.0076$ ), despite the fact that Warsaw Group had a significantly higher number of children with a GA less than 28 weeks (52.3% vs 28.3%;  $p=0.0001$ ).

The analysis of primary resuscitation showed that a much larger proportion of infants from the Ternopil Group were intubated in the first minutes of life in the delivery room. The invasive ventilation compared to non-invasive techniques used in the delivery room for respiratory support of preterm infants increases the risk of further need for invasive ventilation, with its consequences: BPD development<sup>8</sup>, and nosocomial infection<sup>9</sup>.

**Table 3.** Neonatal morbidities and outcomes in extremely and very preterm infants in Ternopil and Warsaw groups

	Extremely preterm infants (GA<28 weeks)			Very preterm infants (GA>28 weeks)		
	TG (n=21)	WG (n=51)	<i>p</i> value	TG (n=98)	WG (n=58)	<i>p</i> value
Early-onset infection, n (%)	5 (23.8)	13 (25.5)	1.000	33 (33.7)	9 (15.5)	0.015*
Late-onset infection, n (%)	16 (76.2)	18 (35.3)	0.002*	22 (22.4)	5 (8.6)	0.030*
NEC, n (%)	1 (4.8)	4 (7.8)	1.000	21 (21.4)	1 (1.7)	0.000*
BPD, n (%)	11 (52.4)	32 (62.7)	0.424	6 (6.12)	7 (12.1)	0.186
ROP, n (%)	13 (61.9)	24 (47.1)	0.305	24 (24.5)	9 (15.5)	0.226
Severe ROP ( $\geq$ stage 3), n (%)	5 (23.8)	4 (7.8)	0.117	3 (3.1)	0	0.295
IVH (III-IV stages)	2 (9.5)	5 (9.8)	1.000	2 (2.0)	2 (3.4)	0.628
Surfactant administration, n (%)	13 (61.9)	43 (84.3)	0.059	18 (18.4)	30 (51.7)	0.000*
Mechanical ventilation, n (%)	12 (57.1)	38 (74.5)	0.168	31 (31.6)	29 (50.0)	0.027*
CPAP-therapy, n (%)	16 (76.2)	51 (100.0)	0.001*	64 (65.3)	50 (86.2)	0.005*
PGF at discharge, n (%)	12 (57.1)	15 (29.4)	0.035*	37 (37.8)	17 (29.3)	0.302
Parenteral nutrition duration, days	21.0 [13.0; 32.0]	13.0 [9.0; 19.0]	0.005*	13.0 [8.0; 18.0]	8.0 [7.0; 13.0]	0.001*

Nosocomial infections remain a significant health problem among the major morbidities in extremely and very preterm infants hospitalized in Neonatal Intensive Care Units and neonatal departments for a long period of time. The late-onset infection was diagnosed more frequently in the Ternopil Group, in both extremely and very preterm newborns, compared with Warsaw Group. The combination of several risk factors could potentially have an impact on the late-onset infection development: infection control in the department, hand hygiene peculiarities, control of bacterial colonization in newborns and venous catheter care that should be improved in Ukraine. Additionally, Ternopil Group children had standard care, where parents were not involved in the care process, in contrast to Warsaw Group, where the Kangaroo mother care (KMC) with skin-to-skin contact was widely used.

KMC shows positive results for nosocomial infection prevention in term and preterm infants<sup>10</sup>. The Cochrane Database of Systematic Reviews results stated that preterm infants who received KMC in comparison with neonates who had standard care in the incubator were more likely to have decreased likelihood of nosocomial infection<sup>10</sup>. It was revealed that early, regular and prolonged skin-to-skin contact successfully prevents the nosocomial infection in very and extremely preterm infants<sup>11,12</sup>. KMC with skin-to-skin contact prevents the nosocomial infection in several ways. Early and long-lasting skin-to-skin contact helps infants to become colonized with parents' non-pathogenic flora, and therefore decreases the risk of nosocomial infection. Skin-to-skin contact improves the preterm infant's skin hydration and protective barrier function<sup>13</sup> and prevents the development of hypothermia, which is a significant trigger factor of severe infections<sup>14</sup>. Also, it ameliorates stress, reduces the sympathetic nervous system activity that leads to corticosteroid secretion reduction and therefore decreases the risk of stress-induced infections<sup>14</sup>.

Other factor influencing the nosocomial infection development is the type of feeding. Thus, children from the Warsaw Group were fed mainly with human milk – 95.6% (breast and donor milk), while infants from Ternopil Group had artificial feeding from the first days of life. Human milk improves the infant's immune protection and digestive processes, preventing the occurrence of NEC and sepsis. In addition, complete enteral nutrition starts earlier because of better tolerance to breast milk, reducing the duration of parenteral feeding and, thus, the risk of catheter-associated bloodstream infection<sup>10,15</sup>. In support to this fact, the duration of parenteral feeding was higher in both age groups of Ternopil Group compared with Warsaw Group.

The rate of NEC in very preterm infants was higher in Ternopil Group compared with Warsaw Group. We suppose that human milk feeding is a major protective factor in reducing NEC, which is consistent with other studies<sup>16</sup>. Bovine proteins of formula, leading to intestinal inflammation together with the absence of human milk that has protective properties contribute to the increased risk of NEC development<sup>17</sup>. In support to this, the rates of exclusive own mother's breast-feeding in the Ternopil Group compared to the Warsaw Group were significantly lower (2.5%), only 19.3% of Ternopil Group infants got mixed feeding, including mother's milk and formula for preemies. Most of the infants from the Warsaw Group had human milk. Moreover, there is no human milk bank available in the Ternopil region. KMC, which is usually accompanied by breast-feeding, also plays a significant protective role in NEC development in preterm infants<sup>18</sup>.

Despite significant advances in the neonatal care of premature infants, the incidence of BPD is not reduced<sup>19</sup>. The rate of BPD showed no difference among the study groups according to the GA, however these rates were quite high among extremely preterm infants in both study groups (52.4% and 62.7%). According to the Vermont Oxford Network, the rate of BPD is 40% in preterm newborns with GA<29 weeks<sup>20</sup>. Atalay et al. reported an incidence of BPD of 35% in the <1000 g group<sup>21</sup>. So, it is crucial to influence the modifiable risk factors, thus preventing and decreasing BPD development<sup>19</sup>. It is necessary to initiate the resuscitation in the delivery room with minimal FiO<sub>2</sub> using a T-piece resuscitator to provide continuous positive airway pressure or non-invasive intermittent positive pressure ventilation, to use pulse oximetry in the delivery room to assess "normal" oxygen saturation values after birth, followed by further avoidance of high oxygen concentrations, to use non-invasive ventilation and as early as possible extubation, to ensure adequate nutrition (parenteral and enteral), preferably using breastmilk, and to prevent the infection<sup>22,23</sup>.

The type of nutrition affects not only the morbidity, but also the physical development of preterm infants. These children should increase their body weight several times in extrauterine life conditions before reaching the full gestational age to achieve the correct parameters of physical development. Thus, their physical development depends entirely on the environmental factors, including appropriate nutrition and medical care<sup>24</sup>. Approximately half of the extremely and very preterm infants' population worldwide suffers from PGF. Fenton et al.<sup>25</sup> reported about 55-65% and Clark et al.<sup>26</sup> about 23-71% incidence of PGF in preterm infants of 23-32 and 23-34 weeks of gestation, respectively.

A significant proportion of infants in the Ternopil Group had PGF at discharge (57.1% of extremely preterm and 37.8% of very preterm infants). Various factors affect the postnatal growth. Nutrition is a key factor of the postnatal growth development of preterm infants. The main problems that led to the PGF in infants from the Ternopil Group are feeding intolerance to formulas in the first days of life and the lack of multi-nutrient human milk fortifiers. On the other hand, total parenteral nutrition, although starting from the first days of life, does not always meet the infant's caloric requirements and it doesn't contain vitamins and microelements.

Unlike infants from the Ternopil Group, all Warsaw Group newborns received colostrum from the first days of life, with continued breast-feeding (maternal or donor milk) during the hospital stay. Li YW et al. reported that breast-feeding plays an important role in reducing the incidence of feeding intolerance and NEC, increasing the body weight<sup>27</sup>.

The lack of breast-feeding and human milk fortification, together with inadequate parenteral nutrition and calorie intake in preterm infants may lead to subsequent impairment of growth and development. Thus, intense nutrition should be recommended to prevent PGF<sup>28</sup>. Aggressive nutrition, both enteral and parenteral, started since the first postnatal day, reduced the incidence of PGF by 23%<sup>29</sup>. The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee recommends enteral nutrient supplementation for very preterm infants, providing an adequate range of energy intake of 110–135 kcal/kg/day and daily weight gain of 17–20 g/kg<sup>30</sup>.

Factors such as GA, birth weight, presence of RDS, BPD, sepsis, and NEC, duration of parenteral nutrition and ventilation have also been associated with slower post-natal growth and development in preterm infants<sup>29</sup>. Majority of these factors prevailed in the Ternopil Group infants (mainly high rates of sepsis and BPD), requiring great efforts to reduce these morbidities, and this will in turn contribute to better physical development of children.

The authors are aware of the study limitations – the significant difference between the GA of the study groups in both centers, and lack of prenatal steroid analysis that reflects the quality of the obstetric care in the country.

## CONCLUSIONS

Identification of the key differences between preterm infants' care approaches is a challenge to improve the early outcomes and survival rates of very and extremely preterm newborns in Ukraine. To reduce the incidence of the most prevalent morbidities,

modifiable risk factors need to be addressed. All procedures that can decrease the incidence of late-onset neonatal sepsis should be implemented. Postnatal growth failure at discharge can be reduced by the early onset of trophic feeding using colostrum, adequate enteral (fortified mother or donor milk), and parenteral nutrition.

Regular auditing of clinical outcomes and identification of main problems could facilitate the quality improvement in preterm infants' management and help to implement new interventions and approaches.

## Author Contributions:

*Conceptualization, H.P., R.B., M.B-K., I.S., I.H.; methodology, H.P., M.B-K., I.S.; software, I.S., I.H.; validation, H.P., M.B-K.; formal analysis, R.B., I.S., I.H.; investigation, H.P., R.B., I.S.; resources, H.P., M.B-K.; data curation, I.S., I.H.; writing–original draft preparation, H.P., I.S.; writing–review and editing, R.B., M.B-K., I.H.; visualization, H.P., I.S.; supervision, H.P., M.B-K.; project administration, H.P., I.S. All the authors have read and agreed with the final version of the article.*

## Compliance with Ethics Requirements:

*“The authors declare no conflict of interest regarding this article”*

*“The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the guardians of all the patients included in the study”*

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