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EXTREMELY LOW BIRTH WEIGHT INFANT, LATE MORBIDITIES AND HEALTH OUTCOMES

ANET PAPAZOVSKA CHEREPNALKOVSKI, MARIJA BUCAT, IVANKA FURLAN, VESNA PAVLOV, MILA DRUŽIĆ, MAJDA BUDIMIR, LUKA BRAJKOVIC*

Extremely low birth weight infants (ELBW) are those of birth weight of less than 1000 g and are usually born at ≤27 weeks' gestation. We identified several major contributors to late morbidity in this group, namely bronchopulmonary dysplasia (BPD), late-onset infections, necrotizing enterocolitis, central nervous system manifestations, retinopathy (ROP) and anemia of prematurity. We estimated incidence and severity for each of these manifestations among our 41 study subjects of ELBW. We found low incidence of BPD- 7%. Severe ROP requiring laser photocoagulation and/or bevcizumab treatment was observed in 17.1% patients. Intraventricular hemorrhage (any grade) was noted in 11 (29%) of the patients. Diffuse cystic periventricular leucomalacia was present in only 1 patient (2.4%) of the deceased group. We showed high incidence of late-onset infection (73%), most frequent pathogens were Meticilin Resistant Staphylococus Epidermidis and Acinetobacter baumanii. Candida was infrequently present in hemoculture due to the strict policy of prophylaxis with fluconazole. No cases of hydrocephalus or necrotizing enterocolitis were described. A larger study group is needed to draw conclusions on morbidities' incidences and association with departments' treatment strategies. We concluded that, specific follow up goals should be set for these ELBW infants upon discharge, most importantly for early identification of developmental disabilities and identification and treatment of medical complications. Close cooperation is required between neonatologists and the subspecialties further involved in follow up of these children.

Descriptors: EXTREMELY LOW BIRTH WEIGHT INFANTS, LATE MORBIDITIES, FOLLOW UP, UNIVERSITY HOSPITAL OF SPLIT

Aim of the study was to analyze the incidence of late morbidities in infants born with an extremely low birth weight (ELBW), for a period of 2 years at the Unit of neonatology, Department for obstetrics and gynecology, University Hospital of Split, and to compare our results with the available literature data.

In addition, we present an overview of the long-term health outcomes of this vulnerable group and their impact on the quality of life.

*University Hospital of Split
Clinic for obstetrics and gynecology

Address:
Dr. sci. Anet Papazovska Cherepnalkovski, dr. med.
University Hospital of Split
Department for obstetrics and gynecology
21000 Split, Spinčićeva 1
E-mail: anet.cherepnalkovski@gmail.com

Background

Extremely low birth weight infants (ELBW) are by definition those of birth weight of less than 1000 g and are also the youngest premature newborns usually born at 27 weeks' gestation or younger. Attention has been turned to the improvement of the intact survival rate of ELBW infants born at the frontier of current perinatal medicine at 22-23 weeks' gestation (GW) (1). Survival rates of ELBW infants are above 80% for the advanced gestations and greater than 50% between 23-24 weeks gestation (2-4). The smaller the birth weight the bigger are the observed neurological, neurodevelopmental, neurosensory and functional morbidities (5). In the ELBW population, poorer outcomes are observed in infants who had bronchopulmonary dysplasia (BPD), periventricular leucomalacia (PVL) and/or grade III/IV intracranial haemorrhage, necrotizing enterocolitis requiring surgery, postnatal steroids, neonatal infections, retinopathy of prematurity and male gender (5-7). On the contrary, factors associated with decreased morbidity are increased birth weight, female gender, higher maternal education, and white race (7). Major later morbidities of the ELBW infants include:

- Bronchopulmonary dysplasia (BPD) is defined as a need for supplemental oxygen or ventilator support at 36 weeks' postmenstrual age. In 2000, the National Institute of Child Health and Human Development (NICHD) refined the definition of BPD categorizing the severity of BPD as mild, moderate, or severe (8). Infants with BPD are found to have higher rates of adverse neurodevelopmental outcomes and cognitive impairment in early childhood compared to those without BPD (9).

- Late-onset infections (LOI) (nosocomial) typically occur after the first week of life and result from the inner hospital flora. Frequent nosocomial pathogens are coagulase-negative staphylococci, Klebsiella and Pseudomonas species as well as methicillin-resistant Staphylococcus aureus (MRSA) and fungi (10, 11). Predisposing factors include immaturity of the immune system, ventilator care, total parenteral nutrition, central venous catheters, and exposure to extensive handling. Association is found in a large cohort study between neonatal infection in ELBW infants and poor neurodevelopmental and growth outcomes in early childhood (6).

- Necrotizing enterocolitis (NEC) is a gastrointestinal disorder selectively affecting the intestinal mucosa and vasculature of the sick premature infants' gut; risk factors include intestinal immaturity, poor intestinal motility, hypoxemia, ischemia, PDA, umbilical catheter placement, IUGR, feeding practices, exchange transfusion, and systemic infections (12). The antenatal administration of steroids and early enteral nutrition are found to offer protection against NEC to the prematurely born infant (13, 14). The incidence of NEC varies between centers, and is estimated at between 9% and 25% for ELBW infants (15). Treatment options depend on the clinical presentation and vary from medical to surgical. Post-NEC intestinal strictures can present several weeks after the initial episode, with milk intolerance, vomiting, and abdominal distension.

- Intraventricular haemorrhage (IVH) is bleeding in the brain that begins in the subependimal germinal matrix and progresses into the ventricular system; most IVHs occur within the first 3 days of life (16). The incidence and severity of IVH are inversely related to gestational age, with infants on the lowermost scale of gestations and weight being most heavily affected. IVH is being recognized as one of the key morbidities for the ELBW infant, with serious potential sequelae in survivors such as hemorrhagic periventricular infarction, posthemorrhagic hydrocephalus, seizures, periventricular leukomalacia (PVL) and, in the long term, neurosensory and neurodevelopmental impairments (17). IVH incidences of up to 40% in ELBW cohorts have been described (18, 19).

- Periventricular leukomalacia (PVL) represents damage to cerebral white matter that can result in severe motor and cognitive deficits, with an estimated incidence of 4-15% in ELBW babies. It is believed to be a consequence of hypoxic-ischemic events, leading to necrosis of the white matter (20).

- Retinopathy of prematurity (ROP). The disruption of the natural cause of vascularization of the premature retina caused by exposure to oxygen has been postulated as the core pathogenesis mechanism of ROP. Risk factors for ROP include prematurity and exposure to oxygen, however the optimal oxygen saturation target ranges remain controversial (21, 22). Results from multiple studies suggest that although hiperoxia with higer oxygen saturation targets of 91-95% can be harmful, lower target ranges of 85-89% can increase mortality (21, 23, 24). Severe ROP is defined as unilateral or bilateral stage 4 or 5 disease or disease requiring laser or bevacizumab treatment (anti-vascular endothelial growth factor (anti-VEGF monoclonal antibody) in at least one eye. Schmidt et al report an incidence of about 7% in a surviving ELBW cohort (25). The timing of onset of ROP is related to both gestational age and chronological age. Current joint statement by the American Academy of Pediatrics, the American Academy of Ophthalmology, the American Association for Pediatric Ophthalmology and Strabismus, and the American Association of Certified Orthoptists recommend screening for ROP to begin by 31 weeks postmenstrual age (PMA) for infants born at 22-27 weeks (26).

- Anaemia of prematurity. All premature infants, including those of ELBW experience earlier and more profound anaemia compared to term counterparts. Proposed causes are frequent phlebotomies for laboratory studies, low iron stores, decreased survival of erythrocytes, immature erythropoietic response, deficiencies of vitamins B12, E or folate, and rapid growth. Treatment of anemia consists of transfusions with packed red blood cells. The administration of erythropoietin with iron supplementation has not been shown to significantly reduce the need for transfusions in the first few weeks of life (27, 28). To decrease the risk of transfusion-related infection, one unit of packed red blood cells from a single donor, divided into several small bags (satellite bags), can be used for the same infant for several weeks (29). Positive association has been described between number of blood transfusions and duration of anemia in the first weeks of life and ROP (30). Proposed mechanism of advancing ROP is by replacing HbF with HbA during transfusion and rapidly increasing oxygen availability to the retina (31).

Materials and methods

Study design was retrospective analytical. We analyzed medical records of all ELBW newborns delivered at the Department for Gynecology and obstetrics, University Center Split for the period of 2 years (January 1, 2016 through December 31, 2017) and were hospitalized and treated at the Clinical department of neonatology. The cohort consisted of 41 examinees with a birth weight of 500-999 g, of which 51.2% male, and 48.8% female. A computer data base was kept for purposes of clinical audit. Multiple data were retrieved from the data base such as maternal and infant data, relevant clinical presentations as well relevant laboratories, and compared between the two major outcome groups (survival or death). For the purpose of this study analysis was performed on the above mentioned later morbidities associated with ELBW. Data were entered onto an MS-Excel spreadsheet and imported to the statistical software package. Statistical analyses were performed using the statistical package Statistical

Package for the Social Sciences (SPSS) 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were presented with absolute numbers and percentages whereas quantitative variables were presented with minimum, maximum, and median (M). Testing of significance between groups regarding the analyzed parameters was performed with: Fisher exact test, and Mann-Whitney U test. The result was considered significant if probability value (p) <0.01 for high significance. The study has been approved by an institutional Ethics Committee in accordance with the Declaration of Helsinki.

Results

The study group consisted of 41 examinees with a birth weight of 500-999 g, of which 51.2% male, and 48.8% female. The median (min-max) gestational age (GA) of the group was 26 (22-32), the median (min-max) birth weight (BW) was 780 (500-990), and the median (min-max) head circumference (HC) was 24 (18-29). Of the later morbidities BPD was present in 7% of patients (2 of the surviving, and one of the deceased). Late-onset infection (LOI) was present in 30 patients (73%) and was treated with reserve antibiotics (meropenem+vancomycin and/or collistin, depending on the antibiotic sensitivity test). The most frequent pathogens isolated from later hemocultures suggesting intrahospital infection were: Meticilin Resistant Staphylococus Epidermidis (7, 23%) and Acinetobacter baumanii (7, 23%) followed by Klebsiella (6, 20%) and Koagulase Negative Staphylococcus sp. (5, 17%), than Meticilin Sensitive Staphylococus Epidermidis (2, 7%), Streptococcus viridans (2, 7%), and Candida (1, 3%).

Severe ROP requiring laser photocoagulation and/or bevcizumab treatment was observed in 7 (17.1%) patients. IVH (any grade) was noted in 11 (29%) of the patients with no statistical significance between the two major outcome groups. PVL grade 3 which is associated with poor neurodevelopmental outcome was present in only 1 patient (2.4%) of the deceased group. Among the survivors, 2 (4.8%) patients had grade 2 PVL and one had unilocular periventricular cystic lesion. Blood transfusions with packed and irradiated RBC were performed on average 4.8 (5) times until discharge or death. In the ROP group requiring laser photocoagulation and/or bevcizumab treatment, the average transfusion count was 7. We did not observe patients with post-hemorrhagic hydrocephalus in our study group, nor did we have patients with necrotizing enterocolitis.

Table 1
Comparison of the analyzed late morbidities between the two major outcome groups (survival and death)

		Outcome		
General data	Total (N=41) 100%	Survival (N=19) 46%	Death (N=22) 54%	P value
Gender N (%)				
Male	21 (51.2%)	9	12	0.785*
Female	20 (48.8%)	10	10	
GA (weeks); M (min-max)	26 (22-32)	28 (25-32)	24 (22-31)	0.001**
BW (g); M (min-max)	780 (500-990)	840 (500-990)	700 (500-940)	<0.001**
HC (cm); M (min-max)	24 (18-29)	25 (22-29)	22.5 (18-26)	<0.001**
Morbidity	N (%)	Survival	Death	P value
1. BPD	3 (7)	2	1	
2. LOI	30 (73)	17	13	
Backup antibiotics (Meropenem + Vancomycin and/or Colistin)	32 (79)	18	14	
Candida profilaxis	29 (71)	16	13	0.098*
3. IVH				
Any grade	11 (29)	4	7	0.0476*
No IVH	27 (71)	15	12	
4. PVL	8 (19)	3	5	
Grade 2 (Ventriculomegalia)	6 (14.6)	2	4	
Grade 3	1 (2.4)	0	1	
Unilocular cyst	1 (2.4)	1	0	
5. ROP	7 (17.1)	7	0	

Discussion

ELBW and extreme preterm birth warrant further follow up of general health outcomes as well as specific evaluations of cognitive development, vision and hearing ability, and neurodevelopmental progress. In our study group, we identified major late morbidities that would require further developmental follow up. The incidence of BPD is about 30% for infants with birth weights <1000 g (9). Despite maximum therapy, some infants remain dependent on supplemental oxygen beyond 40 weeks of postmenstrual age and after discharge should be evaluated and followed by a pediatric pulmonologist. Re-hospitalizations are common especially during the first 2 years of life, mostly as a result of respiratory illnesses including lower respiratory tract infections and RSV bronchiolitis (32). We found low incidence of BPD in our group i.e. 7% for the whole group, and 5% for survivors. A larger study group is needed to establish association between certain ventilation preventive strategies performed and low incidence of BPD.

Coordination with a pediatric pulmonologist at the time of discharge is essential. Late-onset infections were present in 30 patients (73%) as evidenced by the positive late blood cultures. Most frequent intrahospital pathogens identified were: Meticilin Resistant Staphylococus Epidermidis and Acinetobacter baumanii followed by Klebsiella and Koagulase Negative Staphylococcus sp. We identified only one case of Candida sepsis in the study group. Fungi, most commonly Candida albicans are frequent causes of LOI in ELBW infants, especially related to the central venous catheters' placement (33). The literature supports targeting infants <1000 g and ≤27 weeks for antifungal prophylaxis with fluconazole, because this group has high infection-related mortality and neurodevelopmental impairment in 73% of survivors (10, 11, 34). The low incidence of fungal sepsis in our study (3%) is attributable to the departments' adherence to policy for fluconazole prophylaxis of Candida. Grade of IVH is correlated with its prognosis. However, infants with grades I and II IVH require close neurodevelopmental follow-up due to possibility for impaired cortical development and reduced cortical volume at near term age (35). Association has been found of grade I-II IVH with adverse neurodevelopmental outcomes in follow up studies (17). Forty four percent of children with grades III and IV intracranial hemorrhage (ICH) manifest disabling cerebral palsy (CP), and 45-85% of children with grade IV intracranial hemorrhage have mental retardation and CP (5). We did not find such high incidence of IVH in our study group as described by other authors (18, 19). Our incidence for all grades IVH was 29%. All these patients were scheduled for close neurodevelopmental follow up upon discharge. We did not find any patients with post-hemorrhagic hydrocephalus, however we demonstrated 6 (14.6%) with grade 2 PVL (Ventriculomegalia), 1 (2.4%) with cystic PVL grade 3 among the deceased and 1 (2.4%) with a unilocular cyst in the parietooccipital white matter. While diffuse cystic PVL shows strong correlation with later cerebral palsy, the clinical correlates of diffuse white mater injuries and localized cysts are not so straightforward and require future follow up (5, 20).

Our center complies with the recommendation for ROP screening to start at 31 weeks' postconceptual age, and depending on the results, weekly thereafter until the retina is fully vascularized (26). We found incidence of 17.1% of severe ROP among survivors. The average transfusion count in the ROP patients was 7. We did not find any patients with necrotizing enterocolitis. In our center, we adhere to policy of early initiation of enteral feeds and gradual increase in volume of feeds, carefully monitoring for subtle signs of gut compromise.

We found low incidences of almost all ELBW-associated late morbidities. We speculate that this is due to the small study sample. A larger study group is needed to determine whether certain actions performed at our clinical center, particularly associated with ventilation strategies might be beneficial to long-term morbidities.

Conclusion

ELBW infants experience more than a few late morbidities. Specific follow up goals should be set for these infants upon discharge, most importantly early identification of developmental disabilities and identification and treatment of medical complications. Close collaboration is required between neonatologists and the pediatric subspecialties involved in follow up of these children.

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Sažetak

NOVOROĐENČAD EKSTREMNO NISKE RODNE MASE, KASNI MORBIDITETI I ZDRAVSTVENI ISHODI

Anet Papazovska Cherepnalkovski, Marija Bucat, Ivanka Furlan, Vesna Pavlov, Mila Družić, Majda Budimir, Luka Brajković

Novorođenčad ekstremno niske rodne mase (ELBW) su ona s rodnom masom manjom od 1000 g i obično ≤27 tjedana gestacije. Pronašli smo nekoliko glavnih uzroka kasnog morbiditeta u ovoj skupini a to su bronhopulmonalna displazija (BPD), kasna infekcija, nekrotizirajući enterokolitis, komplikacije sa strane središnjeg živčanog sustava, retinopatija (ROP) i anemija prematuriteta. Procjenjujemo učestalost i ozbiljnost za svaki od tih morbiditeta među našim ispitanicima ELBW-a. Pronašli smo nisku učestalost BPD-e od 7%. Ozbiljni ROP koji zahtijeva lasersku fotokoagulaciju i/ili tretman bevcizumabom zabilježen je u 17,1% pacijenata. Intraventrikularna hemoragija (bilo koji stupanj) zabilježena je u 11 (29%) pacijenata. Difuzna cistična periventrikularna leukomalacija prisutna je u samo jednog pacijenta (2,4%) iz skupine umrlih. Pokazali smo visoku incidenciju kasne infekcije (73%), najčešći patogeni bili su meticilin rezistentni Staphylococus epidermidis i Acinetobacter baumanii. Candida je rijetko prisutna u hemokulturi zbog stroge politike profilakse flukonazolom. Nije opisan ni jedan slučaj hidrocefalusa niti nekrotizirajućeg enterokolitisa. Potrebna je veća studijska skupina za zaključke o incidencijama i povezanosti morbiditeta sa strategijama liječenja odjela. Zaključili smo da bi za ovu ELBW novorođenčad trebalo postaviti posebne ciljeve praćenja nakon otpusta, što je važno za ranu identifikaciju razvojnih poteškoća i identifikaciju i liječenje medicinskih komplikacija. Potrebna je bliska suradnja između neonatologa i subspecijalista koji su uključeni u daljnje praćenje ove skupine djece.

Deskriptori: NOVOROĐENČAD EKSTREMNO NISKE RODNE MASE, KASNI MORBIDITET, PRAĆENJE, KLINIČKI BOLNIČKI CENTAR SPLIT

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