Araştırma Makalesi
Research Article

Morbidity and mortality in VLBW: A comparison of two 5-year periods with a 15-year interval

YENİDOĞAN YOĞUN BAKIM ÜNİTESİNDE İZLENEN ÇOK DÜŞÜK DOĞUM AĞIRLIKLI BEBEKLERDE MORBİDİTE VE MORTALİTE SONUÇLARI: 15 YIL ARAYLA İKİ BEŞ YILLIK DÖNEMİN KARŞILAŞTIRILMASI

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ABSTRACT

Introduction and methods: Improvements in both perinatal and neonatal healthcare have contributed to increased survivability of premature babies. Depending on the development level of countries and units, some of the morbidity rates may increase, while others may decrease. In this retrospective cross-sectional study, the mortality and morbidity results of very low birth weight (VLBW) infants were evaluated by comparing the outcomes of the babies in our earlier research and the data of developed countries.

Results: A total of 203 newborns were enrolled in the final group. The average weight at birth of these babies was 976±308g, and the average gestational age was 27.8±2.5 weeks. The proportion of babies at or above 28 weeks gestational age was significantly lower than the first group containing 173 infants. Regarding major morbidities, the incidence of bronchopulmonary dysplasia (moderate to severe) and necrotizing enterocolitis (> Stage 2) was greater in the final group. However, the incidence of retinopathy of prematurity (> grade 2), intraventricular hemorrhage (> grade 2), and periventricular leukomalacia were similar among the two groups. While survival rates were found to be similar, the survival rate without major morbidity was significantly lower in the last group.

Conclusion: While the survival rates remained unchanged despite the observation of smaller babies in terms of weight at birth and gestational age in the last period when mortality and morbidity data were compared with developed countries, the study demonstrated a need for improvement in mortality rates, especially in small gestational weeks. However, the major morbidity rates were generally encouraging.

Keywords: morbidity, VLBW, mortality

ÖZ

Gereç ve Yöntem: Perinatal ve neonatal bakımdaki gelişmeler sayesinde prematüre bebeklerin yaşama oranları artmıştır. Ülkelerin ve birimlerin gelişmişlik düzeyine bağlı olarak bazı morbidite oranları artabilir, bazılarında ise azalabilir. Bu retrospektif kesitsel çalışmada; çok düşük doğum ağırlıklı (ÇDDA) bebeklerin morbidite ve mortalite sonuçları önceki çalışmamızdaki bebeklerin sonuçları ile gelişmiş ülke verileri karşılaştırılarak değerlendirildi.

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Bulgular: Son gruba 203 bebek dahil edildi. Bu bebeklerin ortalama doğum ağırlıkları 976±308 gr ve ortalama gebelik haftaları 27,8±2,5 hafta idi. Gebelik yaşı 28 hafta ve üzerinde olan bebeklerin oranı, 173 bebek içeren ilk gruba göre anlamlı derecede düşüktü. Majör morbiditelerle ilgili olarak, bronkopulmoner displazi (orta ila şiddetli) ve nekrotizan enterokolit (>evre 2) oranları son grupta anlamlı olarak daha yüksekti; prematüre retinopatisi (>derece 2), intraventriküler kanama (>derece 2) ve periventriküler lökomalazi oranları da iki grup arasında benzerdi. Sağkalım oranları benzer bulunurken, majör morbidite olmaksızın sağkalım oranı son grupta anlamlı olarak daha düşüktü.

Sonuç: Mortalite ve morbidite verileri gelişmiş ülkelerle karşılaştırıldığında son dönemde doğum ağırlığı ve gebelik yaşı açısından daha küçük bebeklerin görülmesine rağmen sağkalım oranları değişmedi. Çalışma, özellikle küçük gebelik haftalarında ölüm oranlarında iyileşmeye ihtiyaç olduğunu gösterirken, majör morbidite oranları genellikle cesaret vericiydi.

Anahtar Kelimeler: Morbidite, mortalite, çok düşük doğum ağırlığı, yenidoğan

Concurrent with the positive developments in the field of perinatal and neonatal healthcare in the world and in our country, the survival rate of high-risk newborns has increased, but the rate of morbidity and chronic diseases in these babies has also increased (1, 2). Perinatal risk factors and problems encountered in the neonatal period pave the way for the formation of neurodevelopmental problems in the future. For this reason, the primary objective of neonatal intensive care units is preventing morbidities that may occur or managing them with minimal sequelae (3).

Continuous monitoring of the mortality and morbidity rates and the factors affecting them, and reviewing clinical practices accordingly by comparing them with the data of developed countries/units, will positively affect the outcomes of very low birth weight (VLBW) infants.

MATERIALS AND METHOD

This retrospective cross-sectional study utilized information from specific records of very low birth weight (VLBW) infants born at Dokuz Eylul University Hospital between 01.01.2014 and 31.12.2018. Following this, we compared the results with our previous study conducted between 01.01.1996-31.12.2000. Data on morbidity, mortality, and potential risk factors of the infants were prospectively recorded and archived using relevant forms in the unit. Infants who were referred to another center before completing the follow-up for any reason or those with major congenital anomalies were excluded from the study. The research obtained ethics committee approval.

The weight at birth, head circumference, and height percentiles of the patients according to their gestational age were evaluated based on the Intergrowth-21 birth body curve standards routinely used in the clinic4. Extra-uterine growth retardation (EUGR) was defined as having a weight below the 10th percentile at the time of discharge (5, 6).

The Turkish Neonatology Society Diagnostic and Treatment Guidelines, aligned with international definitions, were followed for the diagnosis and monitoring of respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), early and late neonatal sepsis, and retinopathy of prematurity (ROP), which were considered as morbidities (7-11). The ICROP staging for ROP, Papile staging for IVH, De Vries staging for PVL and Modified Bell Scoring system for NEC were used (7, 12, 13).

Positive pressure ventilation in the delivery room or the application of the next steps were defined as resuscitation.

Data analysis was performed using SPSS 18.0 (SPSS Inc., published in 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.). Categorical variables were presented as frequencies and percentages, and cross-tabulations were used for variable comparisons. Independent groups were compared using Chi-square and Fisher's Exact test methods. Normality analysis was conducted for comparisons, and parametric methods were preferred if appropriate, while non-parametric methods were preferred if not. In all statistical comparative tests, the significance level was set at α: 0.05, tested in both directions. A difference among groups was considered statistically significant if the "p" value was below 0.05..

RESULTS

In our study, 203 cases were included in the last group, and detailed demographic and clinical features of the cases are summarized in Table 1.

Table 1. Demographic and clinical characteristics of patients

Properties	**Average ± SD or n (%)**
Gestational age (weeks)$^{\alpha}$	27.8 ±2.5
Apgar score 1st / 5th min$^{\alpha}$	5 ±2.4 / 7 ±1.7
Cesarean delivery	169 (83%)
Gender (girl)	109 (53.6%)
Resuscitation	99 (48.8%)
Intrauterine growth	
- Birth weight (g)$^{\alpha}$	976 ± 308
- Birth weight percentile$^{\alpha}$	37.4 ±29.3
- Birth weight by gestational week	
o SGA (percentile <10)	51/203 (25.1)
o AGA (percentile 10-90)	144/203 (70.9)
Surfactant therapy	
- Non-recipients	80 (%39.4)
- Those receiving a single dose	40 (%19.7)
- Those receiving multiple doses	69 (%34)
Ventilation support	
- Non-invasive mechanical ventilation	167 (82.3%)
- Invasive mechanical ventilation	142 (70%)
- Not receiving	36 (17.7%)
Duration of ventilation and oxygen treatments (days)	
- Non-invasive ventilation*$^{\alpha}$	18.4 ±13.3
- Invasive mechanical ventilation*$^{\alpha}$	16.7 ±15.7
- Total oxygen*$^{\alpha}$	30.4 ±27.3
Postnatal steroid treatment	25 (12%)
Total parenteral nutrition time (days)*$^{\alpha}$	22.7 ±15.4
Extrauterine growth retardation	
- Weight at discharge (gr)*$^{\alpha}$	2245 ± 385
- EUGR rate*	60 (38.7%)
Length of hospitalization (days)*$^{\alpha}$	53.4 ±24.3
RDS (at least one dose of surfactant)	109/203 (53.7)
PDA (hemodynamically significant)	60/195 (30.7)
IVH	47/193 (24.4)
- Grade 1	26/193 (13.4)
- Grade 2	10/193 (5.2)
- Grade 3 & 4	11/193 (5.6)
Early neonatal sepsis	14/203 (6.8)
Late neonatal sepsis	71/179 (39.6)
NEC	32/203 (15.8)
- Stage 1	22/203 (10.8)
- Stage 2	4/203 (1.9)
- Stage 3	6/203 (2.9)
PVL (Cystic)	11/193 (5.6)
BPD	54/155 (34.8)
- Mild	22/155 (14.1)
- Moderate	7/155 (4.5)
- Severe	25/155 (16.1)
ROP	38/162 (23.5)
- Without treatment	33/162 (20.4)
- With treatment	5/162 (3.1)
Mortality	48/203 (26.3)

*Excluding those resulting in mortality, αaverage ± SD value

The data were compared with the data of the published study conducted in our unit between 1996 and 2000, which included 173 VLBW infants (14). The patients in the study conducted between 1996-2000 were defined as the "First Group" and the patients in the current study conducted between 2014-2018 were defined as the "Last Group".

When demographic and clinical features were compared between the two groups (Table 2).

Table2. Demographic and clinical characteristics of the two groups

	First group (%)	**Last group (%)**	**p value**
22-27 gestational weeks	17.4	46,7	**p<0.05**
≥ 28 gestational weeks	82,6	53,2	**p<0.05**
Gestational age (weeks)*	29.8 ± 2.7	27.8 ± 2.5	**p<0.05**
Birth weight (grams)*	1218 ± 248	976 ± 308	**p<0.05**
Small for gestational age infants	15	25.1	**p<0.05**
Antenatal steroid treatment rate	19	69	**p<0.05**
Multiple births	23	28	p = 0.15
Caesarian section births	77	83	p = 0.12
Intubation in the delivery room	24	44	**p<0.05**
1st minute Apgar score <6	45	46.7	p = 0.75
5th minute Apgar score <6	10	30	**p<0.05**
Gender (girl)	49	53	p = 0.31
Respiratory distress syndrome	36	53.7	**p<0.05**
Invasive ventilation support	54	70	**p<0.05**
Surfaktan treatment	36	53.7	**p<0.05**
Length of stay on ventilator (days)*	8.5± 16.4	16.7 ± 15.7	**p<0.05**
Air leakage syndrome	5	11.3	**p<0.05**
Total parenteral nutrition time (days)*	19.3± 19.2	22.7 ± 15.4	p = 0.05
Growth retardation at discharge	22.5	38.7	p = 0.12
Length of hospital stay (days)*			
- In the deceased cases	18.9± 30.3	9.9 ± 15.5	p = 0.08
- In the survivors	39.9± 20.4	53.4 ± 24.3	**p<0.05**
Overall survival	82	76.4	p = 0.25
Major morbidity-free survival	91	76.2	**p<0.05**

*Average ± SD values

The ratio of antenatal steroid administration, average weight at birth, and gestational age, the rate of small for gestational age (SGA) infant births, the ratio of intubated babies in the delivery room, and the rate of babies with Apgar score <6 at the 5th minute were significantly higher in the last group. The ratio of babies younger than 28 weeks was significantly higher in the last group, while the ratio of babies 28 weeks and older was significantly higher in the first group. The rate of multiple births, cesarean delivery, infants with Apgar score <6 at the 1st minute, and gender distribution were similar between the two groups.

In the last group, the number of patients diagnosed with respiratory distress syndrome (RDS), receiving surfactant and ventilator support, was higher. The duration of ventilator support and hospitalization was longer in living patients, and air leakage was observed more frequently. Total parenteral nutrition time and the

rate of growth retardation at discharge were similar between the two groups. In terms of major morbidities, the rates of bronchopulmonary dysplasia (BPD) (moderate to severe) and necrotizing enterocolitis (NEC) (>stage 2) were significantly higher in the last group, whereas the rates of retinopathy of prematurity (ROP) (>grade 2), intraventricular hemorrhage (IVH) (>grade 2), and periventricular leukomalacia (PVL) (cystic) were similar between the two groups (Table 3). Although the survival rates were similar, the survival rate without major morbidity was significantly lower in the last group (Table 2).

Table 3. Comparison of mortality and major morbidity data

	First group (%)	**Last group (%)**	**Data of similar studies (%)**				**p value***
References	(14)		(3)	(15)	(16)	(18)	
Mortality	18	23.6	22	14.1	12.5	18	p = 0.25
Major Morbidities							
BPD (moderate-severe)	2	20.6	23.7	27.7	26.3	41	**p<0.05**
NEC (≥stage 2)	0	4.8	9.1	4.9	5.3	11	**p<0.05**
ROP (>grade 2)	0.6	2.4	11.1	10.2	6.8	16	p = 0.2
IVH (>grade 2)	9	5.6	5.4	6.5	6.1	16	p = 0.31
PVL	9	5.6		3	2.7		p = 0.31
Early neonatal sepsis	-	6.8		2.0	1.7	2	-
Late neonatal sepsis	-	39.6	42.4	21	15	36	-

*: First and last group comparison results

DISCUSSION

Advances in antenatal, perinatal and neonatal healthcare over the years have led to significant improvements in the outcomes of VLBW infants. These changes are revealed intermittently through national and international databases with different studies. In addition, it is very important for clinics to periodically monitor their own results locally and to audit and compare them with international standards (15, 16). This data is essential for neonatologists, perinatologists and families when taking quality improvement steps, exchanging information and making important decisions.

In the present study, there was no noteworthy difference in mortality rates among the two groups. This rate was 18% in the first group and 23.6% in the last group. At first glance, this result, which may be interpreted as no significant change or even a decrease in survival despite the recent developments in neonatal intensive care, provides contrary information when the demographic characteristics of the two groups were analyzed in detail. The most important demographic differences between the two groups are average of weight at birth and gestational age, which are the main predicators of mortality and morbidity. Infants in the last group had significantly lower mean birth weight and gestational age than those in the first group. Mortality reported in the data of the Turkish Neonatology Society in the same year, in the South American Neonatal Study Group (NEOCOSUR) and the American National Institute of Child Health and Human Developmental-Neonatal Network-(NIH) rates were similar to our recent data (Table 3) (3, 17, 18). Vermont Oxford Network (VON) mortality ratio was lower than our results (15, 16).

When the infants among the two groups were compared in respect of additional clinical features in our clinic, it was confirmed that more risky babies were observed in the last group. Although most of these risks were associated with low birth weight and gestational age, the higher SGA rates in the last group might be related to the use of different standards. In the first group, the percentiles of the patients were calculated according to the Lubchenco curve, while in the last group they were evaluated according to the Intergrowth-21 curves. In the study comparing the two methods, 24% of infants who were considered SGA according to Intergrowth-21 standards were evaluated as having a birth weight

appropriate for gestational age (AGA) according to Fenton preterm growth charts19. Although there is no study comparing Lubchenco and Intergrowth-21 curves in this sense, in general, Lubchenco curves show more similarity to Fenton curves.

In the 2014-2018 period, resuscitation in the delivery room was defined as positive pressure ventilation and the next steps, and it was applied to 48% (99) of infants. The rate of infants to whom intubation and post-intubation steps were applied was 44% in the last group and was significantly higher compared to the first group. This difference could be explained by the smaller infant ratio in the last group. However, when this high rate was compared with the data of developed countries in the recent period, it revealed similar or even a lower ratio. According to 2003-2007 NIH data, 67% of VLBW infants were intubated in the delivery room, 5% recieved adrenaline, and 8% had chest compressions18. In the study of the Turkish Neonatology Society, the rate of resuscitation at birth was reported as 52.4% in VLBW infants 3.

The rates of multiple births, caesarean section and sex, which may affect mortality and morbidity, were found to be similar between the two groups. Antenatal steroid administration was significantly higher in the last group. The recent increase in our antenatal steroid application rate had an important contribution to providing similar survival and morbidity rates, despite a higher rate of high-risk babies followed. While reported frequency of antenatal steroid administration was over 80-90% in developed countries, this rate was reported as 42.9% in Turkey (3, 20).

When other clinical characteristics of the groups were compared, it was observed that the number of patients receiving surfactant and ventilator support was higher, the duration of ventilator support and hospitalization in living patients was longer, and air leakage was higher in the last group compared to the first group. According to the electronic patient database conducted by the Turkish Neonatology Society in 2016-2017, the incidence of RDS was 69.9% in 3381 premature babies weighing less than 1500 g, while the rate of surfactant use was 58.2% 3. According to 2003-2007 NIH data, the rate of RDS in VLBW infants was 93%, and surfactant was applied to 76% of the infants 18. The high rates of RDS and surfactant use in our country might be associated with the very low rate of antenatal steroid treatment even in third-level perinatal centers. However, in recent years, surfactant usage rates have been declining globally with the earlier and more effective use of noninvasive ventilation support as well as the increasing usage of antenatal steroids. Effective non-invasive ventilation has been applied to VLBW babies from the beginning of the very first breaths in recent years in our clinic. On the other hand, the use of surfactant and the longer duration of ventilation and hospitalization duration in the last period had been associated with the follow-up of younger and babies with more risk factors in this period.

According to 2003-2007 NIH data, extrauterine growth retardation frequency was 80%, twice as high as our incidence of growth retardation in the last group at discharge 18. This rate was considered encouraging for the accuracy of our enteral and parenteral nutrition protocols.

Among the major morbidities, BPD showed a great difference with a rate of 2% in the first group and 20% in the last group. However, it was very clear that the abnormal rate here was 2%. The low survival rates in infants weighing less than 1000 g in the first group and the fact that most of the infants were 28 weeks and above were thought to be the reasons for the low BPD rate. As a result of volume-guaranteed ventilation strategies and noninvasive ventilation practices, the 20% BPD rate in the recent period was quite similar or even lower than the rates of developed countries (Table 3) (15, 16, 18).

Another major morbidity that showed a significant difference between the two groups was NEC, which could be explained by the distribution of birth weight and gestational age. The recently observed 4.8% NEC (≥stage 2) rate was lower than the NIH rate and similar to VON rates (15, 16, 18).

ROP (>grade 2), IVH (>grade 2) and PVL rates were not statistically different between the two groups and were low compared to similar studies (Table 3) (15, 16, 18). These comparison results were considered encouraging as IVH is an important neurodevelopmental marker.

The definition of major morbidity differs between two studies. Sepsis has been accepted as a major morbidity in recent years. However, since these data were not available in the first group, sepsis was not included in the definition in this study. In the first group, survival without major morbidity was found to be 91%. In the last group, when major morbidities were interpreted according to the same definition, survival without major morbidity was 76.2%, and the difference between the two groups was statistically significant. The reason why the survival without major morbidity was found to be lower in the last group was thought to be the transformation of our university into a center where more risky babies were referred in the second period.

According to VON data, in which early and late neonatal sepsis were included in major morbidities, the rate of survival without major morbidity was 53.6% in 2000, 58.6% in 2009, and according to NIH data, the rate of survival without major morbidity was 37% in 2003 and 36% in 2007 15, 16, 18. In our study, if early and late neonatal sepsis were included in the major morbidities in the last group, the survival rate without major morbidity was 51.8%, which is similar to the data of developed countries.

In conclusion, when the data of the studies conducted at 15-year intervals were compared, it was observed that care was given to increasingly more risky babies in our unit over time, and although smaller infants were followed up in terms of birth weight and gestational age in the last period, the survival rates remained unchanged. Among the major morbidities, the rates of BPD and NEC were higher, while the rates of ROP, IVH and PVL were similar. When mortality and morbidity data were compared with developed countries, it was observed that there was a need for improvement in mortality rates, especially in small gestational weeks, while major morbidity rates were generally satisfactory. In this way, monitoring the course of clinical outcomes by conducting regular internal audits and comparing them with data from developed countries will help to review current practices and improve the quality of the healthcare services in units.

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Author contribution:

The authors confirm contribution to the paper as follows: study conception and design: FT, BD, ND, YDA; data collection: YDA, CA; analysis interpretation of results: YDA, CA, BD, FT, HO, ND, draft manuscript preparation: CA, CA YDA, BD, FE,.

REFERENCES

1. Horbar JD, Wright EC, Onstad L. Decreasing mortality associated with the introduction of surfactant therapy: an observational study of neonates weighing 601 to 1300 grams at birth. The Members of the National Institute of Child Health and Human Development Neonatal Research Network. Pediatrics. 1993;92(2):191-6.
2. Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. lancet 2008;371(9607):164-75.
3. Koc E, Demirel N, Bas AY, Ulubas Isik D, Hirfanoglu IM, Tunc T, et al. Early neonatal outcomes of very-low-birth-weight infants in Turkey: A prospective multicenter study of the Turkish Neonatal Society. PLoS One. 2019;14(12):e0226679.
4. Villar J, Giuliani F, Fenton TR, Ohuma EO, Ismail LC, Kennedy SH, et al. INTERGROWTH-21st very preterm size at birth reference charts. lancet 2016;387(10021):844-5.
5. Giuliani F, Cheikh Ismail L, Bertino E, Bhutta ZA, Ohuma EO, Rovelli I, et al. Monitoring postnatal growth of preterm infants: present and future. AmJ Clin Nutr. 2016;103(2):635S-47S.
6. Villar J, Giuliani F, Bhutta ZA, Bertino E, Ohuma EO, Ismail LC, et al. Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-

up Study of the INTERGROWTH-21(st) Project. Lancet Globe Health. 2015;3(11):e681-91.

7. Lee JS, Polin RA. Treatment and prevention of necrotizing enterocolitis. Semin Neonatol. 2003;8(6):449-59.

8. Koç E YBA, Özdek S, Ovalı F, Başmak H. Turkish Neonatal and Turkish Ophthalmology Societies consensus guideline on the retinopathy of prematurity. Turk Pediatrics Ars. 2018;53(Suppl 1):151-60.

9. Köksal N AC, Uras N. T Turkish Neonatal Society guideline on the management of patent ductus arteriosus in preterm infants. Turk Pediatrics Ars. 2018:76-87.

10. Özkan H EÖ, Kanmaz Kutman HG. Turkish Neonatal Society guideline on the management of respiratory distress syndrome and surfactant treatment. Turk Pediatrics Ars. 2018;53(Suppl 1)(53(Suppl 1)):45-54.

11. Satar M EAA, Çelik İH. Turkish Neonatal Society guideline on neonatal infections - diagnosis and treatment. Turk Pediatrics Ars 2018; 53(Suppl 1):88-100.

12. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92(4):529-34.

13. de Vries LS, Dubowitz LM, Dubowitz V, Kaiser A, Lary S, Silverman M, et al. Predictive value of cranial ultrasound in the newborn baby: a reappraisal. lancet 1985;2(8447):137-40.

14. Duman N, Kumral A, Gulcan H, Ozkan H. Outcome of very-low-birth-weight infants in a developing country: a prospective study from the western region of Turkey. J Matern Fetal Neonatal Med. 2003;13(1):54-8.

15. Horbar JD, Plsek PE, Leahy K, Nic/Q. NIC/Q 2000: establishing habits for improvement in neonatal intensive care units. Pediatrics. 2003;111(4 Pt 2):e397-410.

16. Horbar JD, Carpenter JH, Badger GJ, Kenny MJ, Soll RF, Morrow KA, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. Pediatrics. 2012;129(6):1019-26.

17. Grandi C, Gonzalez A, Zubizarreta J, Red Neonatal N. Perinatal factors associated with neonatal mortality in very low birth weight infants: a multicenter study. Arch Argent Pediatr. 2016;114(5):426-33.

18. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010;126(3):443-56.

19. Tuzun F, Yucesoy E, Baysal B, Kumral A, Duman N, Ozkan H. Comparison of INTERGROWTH-21 and Fenton growth standards to assess size at birth and extrauterine growth in very preterm infants. J Matern Fetal Neonatal Med. 2018;31(17):2252-7.

20. H. William Taeusch SEJ. Care of the extremely low-birth-weight infant. Avery's diseases of the newborn. Amsterdam: Elsevier; 2017.