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The change of morbidity and mortality rates in very low birth weight infants over time

Ömer Güran, Ali Bülbül, Sinan Uslu, Mesut Dursun, Umut Zubarioğlu, Asiye Nuhoğlu

Şişli Etfal Education and Research Hospital, Division of Neanotology, İstanbul, Turkey

Summary

Aim: The aim of this study is to determine mortality and morbidity changes in very low birth weight infants in the last decade in our intensive care unit.

Material and Method: Infants with birth weights of 500-1500 g and gestational age of <36 weeks admitted to our clinic between January 2007 and December 2011 (2. period) were examined retrospectively. The obtained data were compared to the results of 2002-2006 (1. period) years. In addition, effects of antenatal steroids on the prognosis of the babies were also investigated in the last group.

Results: Two hundred fourty six very low birth weight infants between 2007 and 2011 were studied. The mean gestational age, birth weight and male ratio were 28.9±2,97 weeks, 1119±283 g and 46.7%, respectively. Only the mean gestational age was significantly lower in the second period (p<0,001). Cesarean delivery, regular pregnancy monitoring, and antenatal steroid usage rates were increased significantly in the present study (p values are 0,011, 0.002, 0.001, respectively). Compared with the previous period,the mortality rate significantly decreased from 35.7% to 25.2% (p=0.013). There was no significant difference between the two periods in terms of the incidence of respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, parenchymal hemorrhage, retinopathy of prematurity, and sepsis (p>0.05). Severe respiratory distress syndrome and advanced retinopathy of prematurity were observed with a significantly lower rate in infants whose mothers received antenatal steroids.

Conclusions: While early morbidity rates have not changed, mortality rates have been reduced in infants under 1500 g over time. Severe respiratory distress syndrome and advanced retinopathy of prematurity were observed less commonly in the babies whose mothers were given antenatal steroid. *(Turk Arch Ped 2013; 48: 102-109)*

Key words: Antenatal steroid, mortality, very low birth weight infants

Introduction

Although very low birth weight (VLBW) infants and extremely low birth weight (ELBW) infants are observed with low rates among all live births (1.5% and 0.7%, respectively), they constitute a significant proportion of the morbidity and mortality rates in the neonatal and infancy period (1). While severe diseases including cerebral palsy, visual, auditory and conceptual disorders may be observed in survivor infants, premature infants constitute half of the hospital expenses spent for neonatal jaundice (1,2,3,4).

Technological advances in respiratory support devices, less invasive interventions and less blood sampling and widespread use of surfactant have resulted in higher survival rates in VLBW infants. Although a marked increase in the survival rates of ELBW infants is observed, no significant change has occured in the frequency of complications including respiratory distreess syndrome (RDS), intraventricular bleeding (IVB), nectrotizing enterocolitis (NEC), nasocomial infections, retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) (1).

In neonatal units, the number of low birth weight infants cared and the level of intensive care effect the mortality rates (5). In studies performed in different regions in our country, the mortality rates in infants below 1500 g have been reported to be 16.4-37.3% (6,7,8,9,11,12). In our unit, the mortality rate in infants below 1500 g between 2002 and 2006 was reported to be 35.7% (13). In our study, we aimed to determine the morbidity and mortality rates in VLBW infants hospitalized in our clinic between 2007 and 2011 and compare these rates with the previous period and the rates found in other studies.

Yazışma Adresi/Address for Correspondence: Dr. Ömer Güran, Şişli Etfal Education and Research Hospital, Division of Neanotology, İstanbul, Turkey
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Material and Method

Our unit offers service as a reference hospital with a total of 35 beds which are composed of 20 third-level intensive care beds, 10 second-level intensive care beds and 5 primary-level intensive care beds. The files of the infants with a birth weight between 500 g and 1 500 g and a gestational age below 36 weeks who were hospitalized in the Intensive Care Unit between January 2007 and December 2011 were examined retrospectively. Adjusted chronological age of one month was considered as the early period. Patients who were referred to different divisions in the first month of life beause of different reasons (cyanotic congenital heart disease, intestinal atresia, anal atresia etc.) were not included in the study. Familial histories, demographic properties, problems related with prematurity, perinatal risk factors, mortality rates and reasons and treatments performed were recorded. Pregnant women who were examined in any health institution at least three times during pregnancy were considered as monitored women. While the gestational age was calculated according to the last mensturation date and modified Ballard score, intrauterine growth was assessed using the Lubchenco curve. Infants with a birth weight above the 90th percentile were considered large for gestational age (LGA), infants with a birth weight below the 10^{th} percentile were considered small for gestational age (SGA) and infants with a birth weight between the 10^{th} and 90th percentile were considered appropriate for gestational age (AGA).

Respiratory disress syndrome was classified as mild, moderate and severe according to clinical findings, lung graphy and blood gases (13). Infants with diffuse increased density, need for mechanical ventilation and respiratory acidosis according to blood gases were considered to have severe RDS, infants with pathcy areas of increased density on lung graphy and need for continuous positive airway pressure (CPCP) were considered to have moderate RDS and infants with scattered areas of increased density and/or air bronchogram for whom mask oxygen support was sufficient and who had no respiratory acidosis according to blood gases were considered to have mild RDS. The criteria for respiratory acidosis included a pH of <7,25, a PCO_2 of >55 mmHg and a HCO_3 of >15 mmol/L. Classification of retionopathy was made according to the international ROP classification (14), IVB was classified according to cranial ultrasonography findings (Papile classification) (15), perinatal asphyxia was classified according to the Sarnat classification (16) and NEC was classified according to the modified Bell classification (17).

The mortality and early morbidity rates were compared between infants whose mother received and did not receive antenatal steroid treatment. The results of the VLBW infants in our neonatology unit obtained in the early period between 2002 and 2006 were considered as the results of the first period (13) and the data obtained in this study which we conducted between 2007 and 2011 were considered as the results of the second period. The early mortality and morbidity rates in VLBW infants were compared between the two periods.

Statistics

Quantitative data were expressed as mean±standard deviation and categorical data were expressed as percentages. The differences between the groups were investigated using chi-square test and independent simple t-test. In comparison between the periods, chi-square test was used for categorical data and one simple t-test was used for continuous numerical data. A p value of <0,05 was considered significant.

Results

A total of 3847 infants were internalized and monitored between 2007 and 2011 in our Neonatal Intensive Care Unit and there were 258 infants whose birth weight ranged between 500 g and 1500 g. Four infants whose file data were missing and 8 infants who were referred to other divisions in the first month of life (three infants with intestinal atresia, two infants with anal atresia, one infant with esophagus atresia, one infant with Fallot tetralogy and one infant with transposition of the great arteries) were not included in the study. The study was completed with 246 (6.4%) infants. In the first period, the total number of infants internalized was 2 735 and 224 (8.2%) VLBW infanst were included in the assessment. The prenatal risk factors and demographic properties of the infants in both periods are summarized in Table 1. When the periods were compared, no difference was found between the infants in terms of the mean birth weight, mean Apgar scores and gender, but the mean gestational week was found to be significantly lower in the infants who were born in the second period (29.8±3.0 vs 28.9±2.9, p=0.0001). It was observed that use of antenatal steroid, regular pregnancy monitoring and deliveries by cesarean section were significantly increased in the second period (Table 1). In our current study, the most common prenatal risk factors included eclampsia/preeclampsia (21%), inappropriate maternal age (19.5%) and multiple pregnancy (18.3%). It was observed that there was no statistically significant change in terms of prenatal risk factors compared to the previous period (Table 1). In contrast, the mortality rates were found to be significantly reduced in the second period (35.7% vs 25.2%, p=0.013). Comparison of the treatments applied in the infants and short-term morbidities is summarized in Table 2. No significant difference was found between the two periods in terms of the rates of development of RDS, PDA, IVB, NEC, ROP, BPD and sepsis (p>0.05). When the patients were analysed by their grades, it was observed that mild RDS

significantly increased in the second period and severe RDS decreased (Table 2). While the frequency of grade 1 IVB was significantly high in the second period, an insignificant reduction was found in the frequency of grade 2 and 3 IVB. Similarly, it was observed that the frequency of grade 1 NEC increased statistically insignificantly in the second period. While mechanical ventilation and CPAP were applied more frequently in the second period, statistical significance was found only for mechanical ventilation (Table 2). It was observed that the rates of surfactant administration significantly increased compared to the previous period (20.7% vs 57.7%, p=0.0001) (Table 2). Among the infants who received surfactant in the second period, it was found that surfactant was administered for one time in 34.3%, for two times in 18,2% and for three times in 7.6%.

Laser therapy was applied in 11 patients who developed grade 3 and higher ROP in the second period. In the same period, oral and/or intravenous ibuprofen treatment was administered in 23 (12.6%) of 31 infants who were diagnosed with PDA on echocardiography. Four patients (4/24, 21%) were treated by surgical ligation. In the second period, the mean number of transfusions per patient was 1.41+1.58 (range:0-6). The rate of infants who received at least one transfusion significantly increased compared to the first period (36.6% vs 49.6%, p=0.005). 49 (19.9%) of the infants in the second period were diagnosed with clinical sepsis and 50 (20.3%) were diagnosed with confirmed sepsis. The most commonly isolated microorganisms included Staphyloccoccus spp. (40%), Klebsiella spp. (16%) and other gram negative bacilli (28%). In our current study, the mean hospitalization time was 32 days in the patients who were not diagnosed with sepsis and 51 days in the patients with sepsis. No significant difference was found between the two periods in terms of the rates of clinical sepsis and confirmed sepsis (Table 2).

Comparison of the infants who did and did not receive antenatal steroid in the second period is shown in Table 3. The rate of pregnant women who received antenatal steroid was 34,1% (84 pregnant women). The rates of cesarean section and female gender were found to be significantly higher in the group who received antenatal steroid. In the group who received antenatal steroid, the rates of severe RDS and advanced grade retinopathy were found to be significantly lower. No significant difference was found between the groups in terms of rates of other morbidities including PDA, IVB and BPD and in terms of mortality rates (Table 3). There was a nearly statistically significant increase in the mortality rates in the infants of the mothers who did not receive antenatal steroid [Odds Ratio: 1.6 (95% confidence interval; 1-2.7), p=0.056].

While the total number of infants lost was 62 in the second period, the distribution of the infants by the time of loss is shown in Table 4. It was found that 38.7% of the infants who were lost (n=24) died in the first day. In 40 of the patients who were lost, RDS was accompanying. Sepsis was accompanying (culture positive in 6, clinical sepsis in 13) in 19 infants, moderate-severe asphyxia was accompanying in 14 infants, NEC was accompanying in 9 infants, grade 3-4 IVB was accompanying in 12 infants and PDA was accompanying in 10 infants. Birth weights

Table 1. Comparison of the demographic properties and prenatal risk factors of the infants in both periods

	2002-2006 (n=224)	2007-2011 (n=246)	p
	%, (n)		
Male gender	43.8 (98)	46.7 (115)	0.753
Birth weight. g*	1122±294	1119±283	0.865
Gestational week. weeks*	29.8±3.0	28.9±2.9	***0.0001***
SGA†	25.8 (58)	14.6 (36)	***0.020***
Apgar 1st min.*	4.2±1.7	4.7±3.3	0.085
Apgar 5th min*	7.4±1.2	7.2±2.0	0.386
Perinatal asphyxia	23.7 (53)	19.9 (44)	0.076
Mortality rate	35.7 (80)	25.2 (62)	***0.013***
Cesarean	46 (103)	74.4 (183)	***0.011***
Delivery in an external center	10.7 (24)	5.3 (13)	***0.029***
Regular pregnancy monitoring	46 (103)	80.5 (198)	***0.002***
Antenatal steroid	12.1 (27)	34.1 (84)	***0.001***
Maternal age (<18. >35)	--	19.5 (48)	-
Preeclampsia	21.8 (49)	19.5 (48)	0.758
Eclampsia	3.5 (8)	1.6 (4)	0.414
Placenta disorders	6.3 (14)	6.9 (17)	0.157
Multiple pregnancy	17 (38)	18.3 (45)	0.866
Hypertension in the mother	--	2.8 (7)	-
Oligohydramniosis	5.4 (12)	6.9 (17)	0.564
Gestational diabetes	--	3 (5)	-
Other		14.2 (35)	-

*mean±standard deviation †SGA. Small for gestational age infant

and gestational weeks were found to be significantly lower in the infants who were lost compared to the infants who survived (for both, p=0.0001).

When the infants in both periods were grouped by birth weight, the comparison of the mortality rates is shown in Figure 1. A significant reduction was found in the mortality rates in the infants with a birth weight between 750 g and 1000 g compared to the first period. The data of our study, our results of the first period, the mortality rates of the infants with a birth weight below 1 500 g by weight ranges reported from our country and other countries are compared in Table 5. Our mortality rates by gestational week in the first and second period are compared in Figure 2. It was observed that the mortality rates significantly decreased in the infants with a gestational age between 27 and 30 weeks in the second period.

Table 2. Comparison of the treatments applied and short-term morbidity rates in both periods

	2002-2006 (n=224)	2007-2011 (n=246)	p
	% (n)		
Need for mechanical ventilation	44,6 (100)	59.3 (146)	***0.001***
Rate of application of CPAP	17.4 (39)	24.8 (61)	0.051
Surfactant application	20.7(47)	57.7 (142)	***0.0001***
Respiratory distress syndrome	72.3(162)	70.3(173)	*0.063*
Mild	27.7 (62)	39 (96)	***0.009***
Moderate	16.5 (37)	14.6 (36)	*0.573*
Severe	28.1 (63)	16.7 (41)	***0.003***
Patent ductus arteriosus	11.6 (26)	12.6 (31)	0.841
Intraventricular bleeding	27.2 (61)	25.3 (62)	0.971
Grade 1	6.7 (15)	12.2 (30)	***0.043***
Grade 2	10.3 (23)	6.5 (16)	*0.140*
Grade 3	7.1 (16)	3.3 (8)	*0.056*
Grade 4	3.1 (7)	3.3 (8)	*0.938*
Necrotizing enterocolitis	11.1 (25)	15.9 (39)	0.138
Grade1	6.7 (15)	11.8 (29)	0.058
Grade 2-3	4.4 (10)	4.1 (10)	0.830
Retinopathy of prematurity	72.3(162)	22.4 (55)	0.276
Grade 1		11.8 (29)	*0.126*
Grade 2		6.1 (15)	*0.411*
Grade 3 and above		4.5 (11)	*0.298*
Sepsis*	44.2 (99)	40.2 (99)	0.663
Need for transfusion	36.6 (82)	49.6 (122)	***0.005***

*Includes both clinical sepsis and sepsis confirmed with cultur

Table 3. Comparison of short-term morbidity rates between the infants who received and did not receive antenatal steroid between 2007 and 2011

	Antenatal steroid Yes (n=84)	No (n=162)	p
	% (n)		
Male gender	36.9 (31)	51.9 (84)	**0.026**
Cesarean section	85.7 (72)	68.5 (111)	**0.013**
Gestational week. weeks*	28.9±2.3	28.9±3.3	0.972
Birth weight. g *	1136±252	1109±298	0.488
Mortality rate	17.9 (15)	29 (47)	0.056
Respiratory distress syndrome			
None	20.5 (17)	32.7 (52)	
Mild	49.4 (41)	34.6 (55)	
Moderate	18.1 (15)	13.2 (21)	
Severe	12 (10)	19.5 (31)	**0.036**
Mechanical ventilation support	63.9 (53)	58.1 (93)	0.239
Necrotizing enterocolitis			
None	81 (68)	85.8 (139)	
Grade1	14.3 (12)	10.5 (17)	
Grade 2-3	4.8 (4)	3.7 (6)	0.612
Patent ductus arteriosus	15.5 (11)	15.9 (20)	0.944
Intraventricular bleeding			
None	73.8 (62)	75.3 (122)	
Grade 1-2	21.4 (18)	17.5 (28)	
Grade 3-4	4.8 (4)	7.4 (12)	0.571
Retinopathy of prematurity			
None	65.8 (48)	79.1 (106)	
Grade 1-2	31.5 (23)	14.2 (19)	
Grade 3-4	2.4 (2)	5.5 (9)	**0.009**
Asphyxia	12.8 (10)	32 (22.4%)	0.283
Sepsis	53.3 (41)	39.4 (58)	0.123

*mean±standard deviation

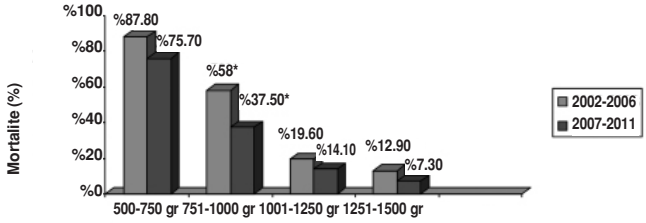
Discussion

In our study in which the short-term outcomes of VLBW infants hospitalized and treated in our unit between 2007 and 2011, it was observed that the mortality rate significantly decreased compared to the previous period. While the mortality rate was found to be 35,7% in the first period in our infants with a birth weight between 500 g and 1500 g, it was found to be 25,2% (a reduciton of 30%) in the second period (2007-2011). Especially the increase in survival rates in infants with a birth weight between 751 g and 1000 g was efficient in this improvement. Although the mortality rate was decreased in the second period in the infants with birth weight <750 g, it was found that the reduction rate was not significant compared to the first period.

In VLBW infants, the mortality rates were observed to range between 10% and 60% according to the developmental level of countries (18,19). In recent years, it was noted that the mortality rates in VLBW infants stayed stable and could not be reduced with a significant rate despite all efforts. In USA, the mortality rate in VLBW infants was 16% between 1995 and 1996 and 15% between 1997 and 2002. Only a 1% improvement was noted in a period of ten years (19). In studies performed from different regions of our country, the mortality rates in VLBW infants were reported to range between 16% and 38% (6,7,8,9,10,11,12). In the study of the Turkish Neonatology Association which included 35 centers and which was performed in 2009, it was observed that the mean mortality rate in infants below 1500 g for the whole country was 26% and ranged between 10% and 54% by centers (20). In our study, our mortality rate in the second period was compatible with the data reported from our country. We think that the reasons for different mortality rates found in different centers include the properties, technological infrastructures, differences in healthcare service and the number of employees and education of the employees in the units in which the infants were cared. It is known that as the level of the unit in which the delivery takes place and the number of infants addmitted increase, the mortality rate decreases (21). In our unit, approximately

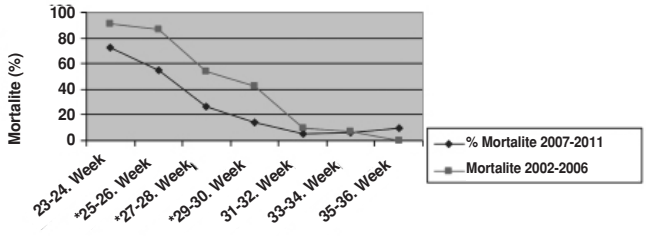
Table 4. Distribution of death times in the infants lost in both periods

Time of death	2002-2006 n (%)	2007 -2011 n (%)	p
1st day	33 (41.3)	24 (38.7)	0.823
2-7th day	32 (40.0)	25 (40.3)	1
8-30th day	15 (19.7)	8 (12.9)	0.223
>30th day	--	5 (8.1)	--



* While a reduction was found in the mortality rate in all weight ranges, it was found that the reduction in the mortality rate in infants with a birth weight of 751-1000 g in the second period was statistically significant (p=0.41).

Figure 1. Comparison of morbidity rates by birth weights between the two periods



*It was observed that the mortality rate was significantly reduced in infants born at the 25-30th gestational week between 2007 and 2011 compared to the previous period (p<0.05)

Figure 2. Comparison of mortality rates by gestational week between the two periods

Table 5. Comparison of mortality rates (%) by birth weights between our first period (13), the Turkish Neanotology Association data (TNA) (20) and the data of developed countries (19)

Birth wieght	Şişli Etfal	Şişli Etfal 2007-2011	TND 2009	Data of developed countries 1997-2002
500-750 g	87.8	75.7	30.8-90.9	45
751-1000 g	58	37.5	6.3-66.7	12
1001-1250 g	19.6	14.1	0-48.1	6
1251-1500 g	12.9	7.3	0-28.6	4

TND: The Turkish Neanotology Association

37 VLBW infants were internalized annually between 2002 and 2006. In our stıudy which covered the period of 2007-2011, this number increased and reached 50.

In international publications, the frequency of RDS in VLBW infants has been reported to range between 44% and 73% (19,22,23). According to the Vermont Oxford Network data, RDS was observed with a rate of 90% in infants with a birth weight below 1000 g. The same frequency was found be decreased to 60% in infants with a birth weight of 1000-1500 g (22). In our clinic, the frequency of RDS was found to be 70.3% in infants with a birth weight below 1500 g which was similar to these data. Compared with the data of the first period, it was observed that no significant change occured in our RDS rates. In other studies performed in our country, lower rates for the incidence of RDS have been reported in VLBW infants (36% and 47%) (7,10,11,12). Since there is no certain measurement or assessment method in the definition of respiratory distress syndrome, the different RDS rates found in the studies are an expected result. In our unit, certain classification criteria which were described in our previous study are applied regularly (13). We think that this classification can be used as an established method in determining the severity of RDS, because the RDS rates found in the studies in both periods were similar to the rates found in inernationally reported infants with the same birth weight.

It is thought that increased use of antenatal steroid and surfactant application in recent years has reduced the IVB rates (24). While IVB is observed in 20% of VLWB infants currently, most of these are grade 1-2 bleedings (24). In infants with a birth weight of <1 500 g, intraparenchymal bleeding is observed with a rate of 5-11% (24). When the studies reported from our country were examined, it was observed that the frequency of grade 3-4 bleeding ranged between 6.4% and 20% (6,7,8,9,10,11,12). In our study, the frequency of grade 3-4 bleeding was found to be 10.2% in the first period and 6.6% in the second period which was a significant reduction. The incidence of necrotizing enterocolitis may range between 6% and 28% in infants with a birth weight below 1500 g (25). Differences in definitions lead to the differences in the incidences of NEC. In the studies performed in our country, the incidence of confirmed and advanced grade NEC (grade 2-3) has been reported to be 3.2%-5% (7,8). Although the rates of confirmed and advanced stage NEC in the second period of our study were similar to the rates reported in our country, it was observed that the frequency of grade 1 NEC increased compared to the previous period. This showed that the diagnosis is made at an earlier time in infants who are suspicious in terms of the disease as a result of increased awareness of NEC in healthcare providers and the disease can be cured with appropriate follow-up and treatment before the disease progresses.

Retinopathy of prematurity is the most common cause of vision loss and blindness in the childhood. In developed countries, ROP is the main problem predominantly in preterm infants below the 28th gestational week and 1000g. In developing countries, severe ROP has been reported up to the 34th gestational week (26). The mean prevelance of advanced ROP (grade III and above) in VLBW infants has been reported to be 9.3% in our country (range: 24.7%-0.7%) (27). In our unit, it was observed that the prevelance of advanced ROP was lower compared to the mean value of our country and the rate of ROP did not change in the two periods. It is known that infections increase the morbidity and mortality rates in VLBW infants in the short-term and affect the neurodevelopmental prognosis negatively in the long-term. Stoll et al. (28) found the prevelance of sepsis confirmed with culture to be 21% in VLBW infants who could survive longer than three days. Similarly, the rate of culture positive sepsis was found to be 20.3% in VLBW infants in our unit. In the same study, the incidence of coagulase negative staphyloccoccus was found to be 48% (in the first order) which was similar to our unit (28). In our country, Atasay et al. (9) found the incidence of late sepsis to be 25% in VLBW infants and Türkmen et al. (6) found the incidence of sepsis confirmed with culture to be 32%. Sepsis increases the mortality rate in VLBW infants and is known to prolong hospitalization durations (28). Sepsis accompanied in 19 of the infants who were lost in our unit (6 culture positive and 13 clinical sepsis). In addition, the mean hospitalization time in the infants who were not diagnosed with sepsis was 32 days, while it was 51 days in the infants with a dignosis of sepsis. These results once again show that late sepsis increases both the duration of hospitalization after the early period is survived and the mortality risk in these infants.

It was observed that 68% of our patients had at least one prenatal risk factor which could lead to preterm delivery. In developed countries, it has been reported that prenatal risk factors belonging to the mother or the infant accompany in 20-30% of preterm deliveries (2). The fact that most pregnant women admitted to our unit had a risk factor may be related with our hospital being a reference hospital in our province.

It has been reported that antenatal use of steroid decreases the frequency of RDS, mortality rate, NEC and IVB in VLBW infants (29). Therefore, continuous steroid treatment at least 24 hours before delivery is currently recommended in all pregnant women who have premature labour before the 34th gestational week. In our country, the rates of use of antenatal steroid have been reported to range between 8% and 55,6% (7,9,10). In our study, the rate of use of antenatal steroid (34.1%) was compatible with the rates reported from our country. When compared with developed countries, however, the rates of antenatal

steroid use were observed to be at very low levels in our country and in our unit (19). In our second period study, the incidences of RDS and advanced ROP were found to be significantly lower in the infants whose mothers received antenatal steroid compared to the infants whose mothers did not receive antenatal steroid. The data of our unit and other studies reported from our country show that large-scale studies related with increasing administration of prenatal steroid are needed.

In the second 5-year period, it was observed that the rate of pregnancy with regular monitoring, the rate of delivery with cesarean section and the rate of use of antenatal steroid increased significantly. In both periods, it was found that the frequencies of severe RDS and advanced ROP significantly decreased in the infants who received antenatal steroid. In the second 5-year period, the mortality rate was found to be decreased by 30% compared to the first period and especially the 50% decrease in the mortality rate in infants with a birth weight of 751-1000 g was considered as a significant improvement. It was observed that 80% of the VLBW infants hospitalized in our unit were lost in the first week and 50% of these were lost in the first day. The times of losses did not change in both periods. Therefore, it should be our priority to perform early and appropriate intervention in VLBW infants in the delivery room in addition to improvement of healthcare starting from the perinatal period in order to increase survival rates.

Conflict of interest: None declared.

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