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Comparison of Short-Term Outcome of Late Preterm and Term Infants

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ABSTRACT

We aimed to compare the rate of morbidity and mortality of late preterm and term infants during hospitalization in the third-level neonatal intensive care unit (NICU).

743 late preterm and 489 term infants who were born and followed up in the third level NICU were evaluated retrospectively. The birth weight, mode of delivery, gestational week, gender, duration of hospitalization, problems in neonatal and post-discharge period, and rate of mortality were investigated. The rate of mortality and morbidity were compared between the groups.

Respiratory distress syndrome (RDS) was the most common (40.3%) cause of hospitalization. The rate of necrotizing enterocolitis, RDS and bronchopulmonary dysplasia was significantly higher in late preterms. Sixty-two (8.3%) of the late preterms and 88 (18%) of the term babies died. Congenital anomalies (55%) were the major cause of mortality in the term group, whereas RDS (35%), surgical interventions, long-term hospitalization, and infection were the main causes of mortality in the late preterm group.

The high mortality rate in our study was because our study included only the babies hospitalized in the 3rd level NICU. It must be kept in mind that late preterms experience most of the problems of ongoing prematurity; therefore, they should not be delivered unless there is absolute obstetric and/or fetal indication.

Keywords: Late preterm; term newborn; mortality; morbidity

Introduction

Although neonatal deaths declined from 5.0 million in 1990 to 2.4 million in 2019, mortality under the age of 5-years has declined slower than neonatal deaths. Globally the most common causes of neonatal deaths in 2017 according to World Health Organization (WHO) data were preterm birth, intrapartum-related complications, and birth defects (1). The global neonatal mortality rate in 2019 was 17.47 per 1000 live births. The same rate for USA and Turkey were 5.28 and 3.70 per 1000 live births, respectively (2). Prematurity is the most important determinant of neonatal morbidity and mortality. Preterm birth complications are the leading cause of death in children under the age of 5 years, and it was responsible for approximately 1 million deaths in 2015 (3).

Although all newborns born before completing the 37th gestational week (GW) are defined as preterm babies, there is a significant difference in means of the developmental problems between infants born before the 33rd GW and infants born after the 33rd GW. The babies, who are born between the $34^{0/7}$ – $36^{6/7}$ GW, are classified as "late preterm" (4, 5). In 1992, late preterms constituted 7.3% of all deliveries in the USA and it rose by 16% reaching 8.5% in 2002 (6). The worldwide preterm birth rate is estimated to be about 11%, similarly, the preterm birth rate in our country is reported as 10% (7, 8). In 2002, late preterm deliveries constituted 71% of all preterm deliveries in the USA (5, 9).

Most studies related to neonatology are focused on the very low birth weight (VLBW) infants and data regarding late preterms are more limited. In the previous years, late preterms were functionally and developmentally perceived as term babies and

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medical decisions were made accordingly. However, recent clinical experiences have shown that these infants are faced with higher rates of respiratory and feeding problems, sepsis, jaundice, hypoglycemia, and prolonged hospitalization duration. Late preterm infants have a higher mortality rate compared to term infants; although not at the same rate as VLBW infants. Although there is limited number of studies related to the long-term neurological development of late preterm infants, it is recommended to follow up these infants for longer periods for early detection of the morbidities such as learning difficulty, academic failure, and behavioral problems (5, 6, 9, 10).

In this study, we investigated and compared the morbidities and mortalities experienced by late preterms and term infants which were followed up in the 3rd level neonatal intensive care unit.

Material and Methods

The morbidity and mortality of the late preterm and term infants who were born and followed up in Bakırköy Gynecology&Obstetrics and Children's Education and Research Hospital Neonatal Intensive Care Unit (NICU) between January 2005 and December 2015 were investigated. The babies who were born between the $34^{0/7}$ – $36^{6/7}$ GW, were classified as "late preterm", and the babies who were born between $37^{1/7}$-42 GW were classified as "term newborn". The gestational age was calculated by the time of the last menstrual period and/or the new Ballard Score (11). The local ethics committee approved the study.

Patient data were collected from the NICU database, patient files, and birth records. The birth weight, mode of delivery, gender, gestational age, history of surfactant therapy, and mechanical ventilation support were investigated. Morbidities such as respiratory distress syndrome (RDS), air leak syndrome (pneumothorax), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and mortalities in the neonatal and post-discharge period were investigated.

Echocardiography and cranial ultrasonography were performed to all newborns during hospitalization for diagnosis of congenital heart disease and central nervous system (CNS) anomalies. Congenital anomalies were evaluated with their phenotypical characteristics and all cases with congenital anomalies were also evaluated with the department of genetics. Chromosomal analysis was performed when necessary. The diagnosis of BPD was made according to the criteria published by the American National Institute of Health (NIH) in 2001(12). Complete blood count, C reactive protein (CRP), procalcitonin, peripheral blood smear and blood, cerebrospinal fluid (CSF), and urine cultures were obtained for the diagnosis of sepsis (13). International ROP criteria were used for the diagnosis of ROP (14). Modified Bell criteria (15) was used for the diagnosis of NEC and Papille classification (16) was used for the diagnosis of IVH.

Indications for surgery, duration of hospitalization, rate of surgical morbidity, and mortality were also investigated. The rate and causes of morbidity and mortality were compared between the groups.

Statistical Analysis: For statistical analyses, NCSS (Number Cruncher Statistical System) 2007&PASS 2008 Statistical Software (Utah, USA) was used. Mean and standard deviation and ratios were used for descriptive statistics. In the comparison of the qualitative data, the Chi-square test was used. The statistical significance was set at $p<0.05$ and 95% confidence interval.

Results

A total of 2399 newborns were followed up in our NICU between January 2005 and December 2015, and 1167 (49%) of the patients were preterms born before $33^{6/7}$ weeks, 743 (31%) were late preterms and 489 (20%) were term newborns. A total of 1232 newborns; 743 late preterms and 489 term newborns, were enrolled in the study. The mean birth weight was 3080±605 g in the term and 1989±350 g in the late preterm group. The mean GW was 38.02±0.77 and 34.42±1.09 weeks in the term and the late preterm group respectively.

The preterm group consisted of 404 males (54.3%) and 339 females (45.7%), and the term group consisted of 278 males (56.8%) and 211 females (43.2%). There was no statistical difference in terms of gender between the groups. The rate of cesarean section in the late preterm group (65.9%) was significantly higher than the term group (39.7%), and the rate of delivery by C/S increased significantly as the GW decreased ($p=0.000$).

Table 1: Distribution of respiratory problems and early neonatal morbidities in late preterm and term newborns

	Late preterm infants (n:743) N (%)	Term infants (n:489) N (%)	P
Transient tachypnea of newborn	317 (42.7)	179 (36.6)	*0.034*
Respiratory distress syndrome	287 (38.6)	83 (16.9)	*0.001*
Bronchopulmonary dysplasia	15 (2)	3 (0.6)	*0.044*
Congenital anomalies	159 (21.3)	244 (49.9)	*0.001*
Congenital heart disease	55 (7.4)	89 (18.2)	*0.001*
Intraventricular hemorrhage	27 (3.6)	10 (2)	0.109
Necrotizing enterocolitis	21 (2.8)	1 (0.2)	*0.001*
Hyperbilirubinemia	274 (36.9)	128 (26.2)	*0.001*
Sepsis	169 (22.7)	175 (35.8)	*0.001*
Convulsion	32 (4.3)	67 (13.7)	*0.001*

Chi-square test, p<0.005

The most common indication for hospitalization during the neonatal period was respiratory problems. In our study, in ten years, 866 (70.2%) patients were followed up and treated in NICU because of respiratory problems. The frequency of both RDS and transient tachypnea of newborn (TTN) were significantly higher in the late preterm group (p=0.000, p=0.034, respectively). Ventilatory support was given to all patients who were diagnosed with severe RDS. The median time of hospitalization and mechanical ventilatory support were similar between the groups. The distribution of respiratory problems and early morbidities is shown in Table 1.

Hypoglycemia was observed in 12.5% of the late preterms that were hospitalized. The frequency of convulsion was 4.3 %. Asphyxia, IVH, and CNS anomalies were the most common causes of convulsions.

The rate of the congenital anomaly was 21.3% (n:159) in the late preterms and 49.9% (n:244) in the term newborns. As the gestational age increased, the frequency of congenital anomaly increased and there was a positive correlation between the GW and the frequency of congenital anomaly (p=0.000). The distribution of congenital anomalies and the outcomes of the patients are shown in Table 2.

The most frequent malformation was diaphragmatic hernia (82 patients: 6.65%). Thirty-six late preterm and 46 term infants had a diaphragmatic hernia. Forty-six of these infants had surgery. A total of 36 infants died: 3 infants died during surgery, 11 infants died in the early postoperative period, 12 infants who underwent surgery died due to other reasons. Ten infants who did not have surgery also died. Surgical mortality and overall mortality rate for diaphragmatic hernia were 30.5 % and 44 %, respectively. Surgical treatment was performed in 85 (43.4 %) of the late preterm infants and 103 (37.7 %) of the term newborn infants with congenital anomalies. The most common congenital anomalies that required surgical intervention were diaphragmatic hernia (24.4%) and tracheoesophageal fistula (18.6%). There was no difference between the groups in means of surgical treatment.

Sixty-two (8.3%) of the late preterms and 88 (18%) of the term babies died. The most common cause of death in the late preterm group was severe RDS (35%), whereas congenital anomalies (55%) were the most common cause of death in the term newborns. The overall mortality of the term group was significantly higher than the late preterm group (p=0.000). (Table 3).

Discussion

Advances in neonatology and a better understanding of the physiology of preterm babies have significantly contributed to increased survival rates of preterm babies. The most common hospitalization indications in NICU for preterm babies are respiratory problems and sepsis, but on the other hand term newborns are hospitalized because of congenital malformations, sepsis, and metabolic diseases (17, 18). In this study, early morbidity and mortality characteristics of late preterms and term newborns were evaluated.

Table 2: Distribution of Congenital Anomalies and Outcomes

	Late preterm infants N (%)	Term infants N (%)	Total N (%)	Treatment	Outcome
		GIS* anomalies			
Diaphragmatic hernia	36 (4.84)	46 (9.4)	82 (6.65)	46 had surgery	36 exitus
TOF**	14 (1.88)	32 (6.54)	46 (3.73)	35 had surgery	11 exitus
Anal atresia	17 (2.28)	21 (4.29)	38 (3.08)	All had surgery	All healthy
Choanal atresia	6 (0.8)	19 (3.88)	25 (2.03)	All were referred	
Pyloric stenosis	5 (0.6)	17 (3.47)	22 (1.79)	All had surgery	All healthy
Duodenal atresia	12 (1.61)	6 (1.23)	18 (1.46)	16 had surgery	3 exitus
Jejunal atresia	5 (0.6)	6 (1.23)	11 (0.9)	All had surgery	All healthy
Biliary atresia	3 (0.4)	5 (1.02)	8 (0.65)	All were referred	
Omphalocele	2 (0.26)	5 (1.02)	7 (0.57)	All had surgery	1 exitus
Gastroschisis	3 (0.4)	3 (0.6)	6 (0.49)	All had surgery	1 exitus
Total GIS anomalies	103 (13.86)	160 (32.71)	263 (21.35)	181 had surgery	52exitus
CNS*** anomalies					
Microcephaly	15 (2.01)	22 (4.5)	37 (3)	Follow-up	3 exitus
Hydrocephalus	2 (0.26)	3 (0.6)	5 (0.4)	All had surgery	All healthy
Total CNS anomalies	17 (2.28)	25 (5.1)	42 (3.4)	5 had surgery	3 exitus
Urogenital anomalies					
Multicystic kidney	7 (0.94)	2 (0.4)	9 (0.73)	Follow-up	3 exitus
UPJ**** obstruction	5 (0.6)	11 (2.25)	16 (1.3)	Follow-up	All healthy
Hydronephrosis	3 (0.4)	5 (1.02)	8 (0.65)	Follow-up	All healthy
Unilateral agenesis	1 (0.13)	3 (0.6)	4 (0.32)	Follow-up	4 exitus
Posterior urethral valve	1 (0.13)	1 (0.2)	2 (0.16)	All were referred	All healthy
Total urogenital anomaly	17 (2.28)	22 (4.5)	39 (3.17)	-	7 exitus
Cleft palate, lip	12 (1.61)	24 (4.9)	36 (2.92)	All were referred	
Other	10 (1.34)	13 (2.66)	23 (1.86)	2 had surgery	4 exitus
TOTAL	159 (21.3)	244 (49.9)	403(32.71)	188 had surgery	66 exitus

GIS: Gastrointestinal system, TOF**: Tracheoesophageal fistula, CNS***: Central nervous system UPJ****: Ureteropelvic junction*

In our study, the rate of delivery by C/S in hospitalized late preterm babies and term babies was 65.9% and 39.7% respectively. In a study conducted in our country, the rate of delivery by C/S was 83.7% in the late preterm group and 74.6% in the term group (19). Wang et al. (10) reported this rate as 51.8% in the late preterm group and 31.2% in the term group. Refuerzo et al. (20) reported the rate of C/S as 56.7% and 66.5% in late preterm and term twin babies respectively and the difference was not significant. In another study conducted in 2015 in Germany, the rate of C/S was 39% in late preterms and 30% in term newborns (21). The main causes for the high rate of C/S delivery in our study were as follows: The presence of a perinatology unit in our hospital, follow-up of high-risk pregnancies, a previous history of C/S delivery, and pregnancy by assistive reproduction technique.

Many diseases of the respiratory system such as mild TTN, severe RDS, pneumothorax, and pneumonia are indications for hospitalization in NICU. Escobar et al. (22) found the frequency of TTN to be 9.6% and 0.6% in the late preterm and in the term newborns, respectively, while Wang et al. (10) reported these rates to be 28.9% and 4.2%.

Table 3: Mortality Rates and Causes In The Late Preterms and Term Babies

	Late preterm infants N (%)	Term infants N (%)	*P*
Severe RDS*	22 (35.4)	2 (2.2)	*0.001*
Congenital anomalies	18 (29.03)	48 (54.54)	*0.001*
Congenital heart disease	8 (12.9)	22 (25)	*0.001*
Sepsis	10 (16.1)	10 (11.36)	0.342
Other	4 (6.4)	6 (6.81)	0.187
Total	62	88	*0.001*

Chi-square test, p<0.005, *RDS*: Respiratory distress syndrome*

Similarly, Bastek et al. (23) reported that the frequency of TTN was higher in late preterms. In our study, the frequency of TTN was 42.7% in the late preterm group and 36.6% in the term group in accordance with the literature.

The rates of RDS by GW according to the 2009 data of the Turkish Neonatology Association were as follows: 33-34 GW: 19.6%, 35-36 GW: 10.7%, 37-42 GW: 3.2% (24). In the study of Lewis et al. (4), the rate of RDS was 14.9% at the 34th week and 0% at the 36th week. Similarly, Arnon et al. (25) reported that the rate of RDS was 15% at the 34th week and 3.2% at the 36th week. Yoder et al. (26) reported the rate of RDS as 3.9% at the 36th week and as 0.7% and 0.8 at the 39th and 40th weeks respectively and the difference was significant. In our study, the rate of severe RDS was significantly higher in the late preterm (38.6%) group than the term group (17%) (p=0.000).

Prematurity and low birth weight are important risk factors for the development of BPD. Payne et al. (27) reported the rate of BPD to be 36.6% in 2001 and 26.8% in 2003 in babies with a birth weight of 501-1500 g. In one of our previous studies, the rate of BPD was 11% in preterms with a gestational age of >32nd week (28). In our study, 15 (2%) of the late preterms had a diagnosis of BPD. Also, 3 (0.6%) of the term newborns had chronic lung disease. Parenchymal damage and pulmonary hypertension due to diaphragmatic hernia and tracheoesophageal fistula were the causes of chronic lung disease in term newborns.

The frequency of NEC is inversely proportional to gestational age and birth weight. In our study, the rate of NEC was 2.8% in the late preterms and 0.2% in the term babies. Wilson et al. (29) reported the rate of NEC according to birthweight as follows: <1000 g: 42%, 1000-1500 g: 39%, 1501-2000 g: 3.8%, and 1501-2000 g: 0.11%. Kavuncuoğlu et al. (30) reported the rate of NEC in our NICU as 1.1% in the late preterm group and 0.02% in the term group. Factors such as hypoxia, reperfusion, inflammation, and infection may lead to the development of NEC in late preterms in which the intestinal system has not yet completed its maturation.

Although significant developments have been obtained in perinatal care, the development of intracranial bleeding and ischemia can't be prevented in preterm babies. Germinal matrix-intraventricular hemorrhage is the most common lesion and its severity is inversely proportional to gestational week. Melamed et al. (31) reported the rate of IVH to be 2% in the late preterm and 0.02% in the term group. In our study, IVH was found in 27 (3.6%) late preterm and in 10 (2%) term babies and the difference was not significant (p>0.05). Similar risk factors including perinatal asphyxia, ventilatory support, and sepsis were identified in patients with IVH in both groups. In addition to this, chronic hypoxia due to respiratory insufficiency, excessive pulmonary hypertension, and prolonged ventilatory support especially in cases with diaphragmatic hernia were the other causes of IVH in term newborns.

Although ROP is a problem of preterm babies with a gestational age of <32 weeks, it is recommended that high-risk newborns should be screened independent of GW according to the International ROP Screening Program (14). The late preterms and term newborns matching these criteria were screened for ROP while being followed up in the NICU and none of the patients had retinopathy.

While the rate of neonatal sepsis has been reported to be 1-10 per 1000 live births in developed countries, similar or higher rates have been reported in developing countries and the rate of clinical sepsis has been reported to increase from 49 to 170 per 1000 live births (32). In newborns with low birth weight, the rate of early-onset sepsis and the rate of late-onset sepsis have been reported to be 1.5-2% and 21% respectively (33). Generally, low GW, comorbidities, and long-term hospitalization are the most important risk

factors in the etiology of sepsis in preterms (34). Sinha et al. (35) reported that a GW of <36 weeks increased the risk of infection 3.7-fold. Wang et al. (7) and Melamed et al. (31) reported that the incidence of sepsis was (4-fold and 10-fold respectively) higher in the late preterms compared to the term group. Bastek et al. (23) reported that the risk of possible or confirmed sepsis was 7.2% in the late preterm group and 4.5% in the term group. In our study, the diagnosis of sepsis was made in a total of 344 (27.9%) newborns (late preterm and term). 22.7% (169/743) of the late preterms and 35.8% (175/489) of the term newborns were followed up with a diagnosis of clinical or confirmed sepsis. In contrast to the literature, in our study, the rate of sepsis was high in the term group and it is thought to be due to the high rate of surgical problems, preoperative and postoperative follow-up in NICU, and long-term hospitalization.

Hyperbilirubinemia is observed in 60-79% of mature newborns and generally in 80% of the preterms in the first week of life (36). Wang et al. (7) reported that the incidence of hyperbilirubinemia was 1.95-fold higher in the late preterms compared to the term group. Haroon et al. (37) reported that hyperbilirubinemia which required phototherapy developed in 37.9% of the late preterms and 11% of the term babies. In our study, the incidence of indirect hyperbilirubinemia was 26.2% and 36.9% in the term newborns and the late preterms (p=0,000).

An important problem of preterms followed up in NICU is patent ductus arteriosus (PDA). The incidence of PDA is one per 2000 live births in term babies, whereas it is identified in 5-10% of newborns with cardiac problems followed up in NICU (38). Tan et al.(39) reported the rate of PDA as 4.3% and 1.1% in the late preterm and term groups, respectively. In our study, PDA was detected in 41 (5.5%) of the late preterms and 30 (6.1%) of the term newborns. Ibuprofen was administered for three days to twenty of the late preterms with PDA and all were treated successfully. The majority of cases with PDA in the term group had concomitant CHD.

It has been reported that late preterms have significantly higher mortality compared to the term group both in the neonatal and postnatal periods. In the study of McIntire et al. (18), which was conducted with 133.022 single late preterms and term babies who had no malformations, the neonatal mortality rate was 1.1 per 1000 live births at the 34th week, 1.5 per 1000 live births at the 35th week, 0.5 per 1000 live births at the 36th week and 0.2 per 1000 live births at the 39th week. Young et al. (40) reported the mortality rate as 8.2 per 1000 live births at the 34th week, 5.1 per 1000 live births at the 35th week, 3.8 per 1000 live births at the 36th week, and 0.59 per 1000 live births at the 39th week. In this study, the leading cause of mortality was congenital malformations followed by immaturity. The Turkish Neonatology Association reported the rate of mortality in 2017 as 3.1 % at 33-34 GW, 2.7% at 35-36 GW, and 2.1% at 37-42 GW which was 4.7%, 4%, and 3.2% in 2005, respectively (8). In our study, the mortality rate was 8.3% in the late preterm and 18% in the term group. The rate of mortality was high because our study included only the babies hospitalized in the 3rd level NICU. Another important factor was the significant number of patients referred to our center because of congenital anomalies and intensive care support.

In our study, congenital anomalies were the major cause of mortality in the term newborn group, whereas respiratory problems, surgical interventions, long-term hospitalization, and sepsis were the main causes of mortality in the late preterm group. As consanguineous marriages are still frequent in our country, cases with congenital anomalies should be identified early in the prenatal period and termination of pregnancy should be presented as an option in the cases that are not compatible with life. Especially complex cardiac anomalies such as hypoplastic left heart syndrome and severe central nervous system anomalies constitute an important group of disorders that the pregnancy should be terminated; otherwise, should be followed up in a multidisciplinary fashion and delivered in experienced centers capable of performing appropriate interventions and treatment.

The increase in survival rates of preterms has led to increasing rates of prematurity-related problems. Late preterms experience most of the problems of ongoing prematurity because gestational age is the most important determinant of intrauterine growth and maturation. Therefore, late preterms should not be delivered with a perception of "being term" and should be delivered and followed up in experienced centers if there is an absolute obstetric and fetal indication

Limitations: Our study was a retrospective cross-sectional study performed in a single tertiary center. As discussed above, the prevalence of some diseases may be higher than usual, because of the referral of complex cases to our institution. Prospective multi-center studies including a larger

number of subjects are required for more precise data.

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Ethical Standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional ethical committee.

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