ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Clinical Features of Late-preterm vs. Term Newborns: A Case-control Study

Geç Preterm ve Term Yenidoğanların Klinik Özellikleri: Bir Vaka Kontrol Çalışması

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ABSTRACT

Aim: *This study aimed to compare the morbidity and mortality of preterm and term neonates who were admitted to the neonatal intensive care unit.*

Material and Method: *In this study, we compared the neonatal problems and mortality rates of 250 late-preterm newborns (gestational age: 34 0/7 – 36 6/7 weeks) and 250 term newborns (gestational age: 37–42 weeks) who were admitted to the Neonatal Intensive Care Unit of Zeynep Kamil Women and Children's Diseases Training and Research Hospital from 01.05.2009 to 01.05.2010.*

Results: *Respiratory distress, feeding problems, hypoglycemia, hypothermia, necrotizing enterocolitis, jaundice, and sepsis were significantly more frequent in late-preterms compared to term newborns. While respiratory distress was observed in 25.2% of late-preterms, only 7.2% of terms had respiratory distress. Cesarean delivery, male gender, LGA status, and late-prematurity were statistically significant risk factors for respiratory distress. The late-preterm newborns were 2.96 times more likely than term newborns to experience feeding problems, 1.12 times more likely to exhibit hypoglycemia, and 2.24 times more likely to have indirect hyperbilirubinemia.*

Conclusion: *We conclude that late-preterm newborns have a significantly higher risk of morbidity and mortality than term newborns. We believe clinicians should be aware of this fact, and the evaluation and follow-up of these newborns, which are usually considered to be 'term' for all intents and purposes, should be carried out with greater care.*

Key words: *late preterm infant; newborn; morbidity and mortality*

ÖZET

Amaç: *Bu çalışmada yenidoğan yoğun bakım ünitesine başvuran erken doğmuş yenidoğanların morbidite ve mortalite oranlarının karşılaştırılması amaçlandı.*

Materyal ve Metot: *Bu çalışmada Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi Yenidoğan Yoğun Bakım Birimi'ne 01.05.2009 ile 01.05.2010 tarihleri arasında başvuran 250 geç preterm yenidoğan (gebelik yaşı: 34 0/7 – 36 6/7 hafta) ve 250 term yenidoğan (gebelik yaşı: 37–42 hafta) yenidoğan sorunları ve ölüm oranları açısından karşılaştırıldı.*

Bulgular: *Solunum sıkıntısı, beslenme sorunları, hipoglisemi, hipotermi, nekrotizan enterokolit, sarılık ve sepsis geç preterm yenidoğanlarda term yenidoğanlara göre anlamlı olarak daha sık görülmüştür. Geç pretermlerin %25,2'sinde solunum sıkıntısı görülürken, termlerin yalnızca %7,2'sinde solunum sıkıntısı vardı. Sezaryen doğum, erkek cinsiyeti, gebelik yaşına göre ağır olma durumu ve prematürite solunum sıkıntısı için istatistiksel olarak anlamlı risk faktörleriydi. Geç pretermler, term yenidoğana göre beslenme problemlerinin 2,96 kat, hipogliseminin 1,12 kat ve indirekt hiperbilirubineminin 2,24 kat daha fazla olduğu görülmüştür.*

Sonuç: *Geç preterm yenidoğanların morbidite ve mortalite riskinin term yenidoğanlara göre anlamlı derecede yüksek olduğu sonucuna vardık. Klinisyenlerin bu gerçeğin farkında olarak genellikle term gibi kabul edilen geç preterm yenidoğanların değerlendirilmesi ve takibinin daha dikkatli yapılması gerektiğine inanıyoruz.*

Anahtar kelimeler: *geç preterm bebek; yenidoğan; morbidite ve mortalite*

Introduction

It is a known fact that the risk for mortality and morbidity is increased in preterm infants compared to term infants[1]. Preterm delivery is defined as a delivery that occurs before 37 weeks (259th day) gestation. However, due to the need for a more definitive classification in order to differentiate mortality and morbidity risks and to plan customized healthcare services among infants born in different gestation weeks, deliveries were further classified. Accordingly, infants born between 32 0/7 – 33 6/7 weeks gestation are defined

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as moderate-preterm infants, while late preterm infants (LPIs) are defined as those born between 34 0/7 – 36 6/7 weeks of gestational age[2].

LPIs are more likely to have complications such as hypothermia, hypoglycemia, Respiratory Distress Syndrome (RDS), apnea, hyperbilirubinemia, feeding difficulty, low APGAR (<4) scores, intraventricular hemorrhage and necrotizing enterocolitis (NEC) compared to term infants[3–5].

The numerical and proportional increase in the number of LPIs and the increase in treatment costs have elevated the interest in identifying appropriate maintenance and follow-up in this group of newborns. It is now evident that performing the usual follow-up and treatment approaches utilized in term newborns is insufficient for LPIs and may lead to recurrent hospitalizations and increased treatment costs[6,7]. Therefore, morbidity and common problems that may occur in LPIs should be well defined, and the follow-up and treatment plans of these patients should be established accordingly.

This study was planned with the aim to determine the differences between term infants and LPIs regarding clinical characteristics associated with morbidity and mortality. Our research questions were as follows: 1) Is there a difference between the general characteristics and the maternal epidemiological characteristics of preterm and term babies? 2) Is there a difference between preterm and term babies in terms of neonatal complications such as hypoglycemia, hypothermia, jaundice, feeding difficulties, necrotizing enterocolitis, respiratory distress, and sepsis? 3) Is there a difference in the length of hospital stay between preterm and term babies? 4) What are the mortality risks in late-preterm and term babies?

Material and Method

Study Group

This study was conducted between May 2009 and May 2010 in Zeynep Kamil Training and Research Hospital, Pediatrics Department. In this period, there were a total of 265 LPIs in our NICU. Among these, eight infants were excluded from the study due to transferring to other hospitals, and seven were excluded because their parents declined to participate in the study. The remaining 250 LPIs were included in the case group. Randomly selected 250 term infants who were born in the same period were included in the study as a control group.

Ethics

Before starting the study, verbal and written consent was obtained to the families who were sufficiently informed about the study and its protocol. During the conduct of the study, the principles put forth by the Good Clinical Practices Guideline and the Declaration of Helsinki were respected. The study was approved by Zeynep Kamil Training and Research Hospital Ethics Committee.

Measurements

All data were obtained through follow-up forms which included the following parameters: epidemiological characteristics of the mother (age, history of premature birth, type of delivery, multiple gestations, consanguinity, antenatal problems, smoking, steroid use before birth), characteristics of the baby (gender, birth weight) and neonatal complications (respiratory problems, nutritional problems, hypoglycemia, hypothermia, necrotizing enterocolitis [NEC], jaundice, sepsis), respiratory problems (meconium aspiration syndrome [MAS], respiratory distress syndrome [RDS], pneumonia, transient tachypnea of the newborn [TTN], pneumothorax, apnea), interventions (intubation, nasal continuous positive airway pressure [NCPAP], HOOD), use of total parenteral nutrition (TPN), length of hospital stay of the baby and outcome.

Statistical Analysis

All data obtained from the study were transferred to SPSS version 15.0 computer software for windows. Continuous data were expressed as mean ± standard deviation, and categorical data were expressed as a percentage. The normality of distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test. The Mann-Whitney-U test was used to compare continuous data. The Chi-square test was used to compare categorical data. Logistic regression analysis was performed to determine the difference between the two groups in terms of neonatal complications. The significance level was accepted as $p<0.05$.

Results

The mean birth weight of the case group was 2111.9±503.6 grams, and the mean birth weight of the control group was 3078.8±586.5 grams ($p=0.001$). The mean gestational age in the case group was 34.64±0.82 weeks, while the mean gestational week of the control group was 38.88±1.24 ($p=0.001$).

Table 1. *The maternal and birth features of study group*

		Case group (n=250)		Control group (n=250)		p value
Gender	Female	116	46.4%	125	50.0%	χ^2: 0.649
	Male	134	53.6%	125	50.0%	p=0.421
Delivery type	NVD	65	26.0%	117	46.8%	χ^2: **23.3**
	C/S	185	74.0%	133	53.2%	**p=0.001**
Maternal age	<18 years	1	0.4%	4	1.6%	
	18–35 years	216	86.4%	213	85.2%	χ^2: 1.82
	>35 years	33	13.2%	33	13.2%	p=0.402
Birth weight	AGA	199	79.6%	191	76.4%	
	SGA	39	15.6%	36	14.4%	χ^2: 3.74
	LGA	12	4.8%	23	9.2%	p=0.154
Multiple gestation	Absent	201	80.4%	238	95.2%	χ^2: **25.5**
	Present	49	19.6%	12	4.8%	**p=0.001**
History of premature birth	Absent	230	92.0%	243	97.2%	χ^2: **6.6**
	Present	20	8.0%	7	2.8%	**p=0.010**
Consanguinity	Absent	206	82.4%	205	82.0%	χ^2: 0.014
	Present	44	17.6%	45	18.0%	p=0.907
Antenatal problem	Absent	79	31.6%	131	52.4%	χ^2: **22.2**
	Present	171	68.4%	119	47.6%	**p=0.001**
Smoking	Absent	221	88.4%	230	92.0%	χ^2: 1.8
	Present	29	11.6%	20	8.0%	p=0.176
Steroid use before birth	Absent	219	87.6%	250	100.0%	χ^2: **33**
	Present	31	12.4%	0	0.0%	**p=0.001**

NVD, normal vaginal delivery; C/S, cesarean section; AGA, appropriate gestational age; SGA, small gestational age; LGA, large gestational age.

Maternal Features

The mean maternal age of the study group was 28.24±6.56 years, and the mean maternal age of the control group was 27.5±5.8 years. The frequency of caesarian delivery (p=0.001), multiple pregnancies (p=0.001), history of giving premature birth (p=0.010), presence of antenatal problems (p=0.001), and steroid use (p=0.001) were found to be more frequent in the case group compared to the control group. The maternal features of the study group are shown in Table 1.

Neonatal Complications

In LPIs, the frequency of respiratory problems (OR: 4.26, p=0.001), nutritional problems (OR: 2.96, p=0.001), hypoglycemia (OR: 1.12, p=0.015), jaundice (OR: 2.24, p=0.048), the use of total parenteral nutrition (TPN) (OR: 15.11, p=0.001), hypothermia (p=0.008), and NEC frequency (p=0.045) were found to be higher compared to the control group (Table 2).

When the diagnoses leading to respiratory distress were examined, Transient tachypnea of the newborn (TTN) was the most common respiratory problem in LPIs (21.2%) and also term infants (5.2%). The frequency of pneumonia (p=0.001) and TTN (p=0.001) was higher in LPIs compared to term infants (Table 3).

In terms of interventions, intubation (p=0.001), nCPAP (p=0.001) and HOOD (p=0.001) were found to be more frequent in the LPI group compared to the control group (Table 4).

Length of Stay

The mean length of hospital stays in the LPI group (9.45±5.78 days) was longer than the mean hospital stays (6.65±4.38 days) of term infants (p=0.001).

Table 2. *The distribution of neonatal problems*

	Case group (n=250)		Control group (n=250)		OR (95% CI)	p value
Respiratory problems	63	25.2%	18	7.2%	4.26 (2.24–8.11)	**0.001**
Nutritional problems	213	85.2%	18	47.2%	2.96 (1.65–5.31)	**0.001**
Hypoglycemia	5	18.0%	6	10.4%	1.12 (0.55–2.25)	**0.015**
Apnea	0	0.0%	1	0.4%	-	0.317
Hypothermia	7	2.8%	0	0.0%	-	**0.008**
Necrotizing enterocolitis	4	1.6%	0	0.0%	-	**0.045**
Jaundice	47	58.8%	25	50.0%	2.24 (1.3–3.87)	**0.048**
Sepsis	3	29.2%	3	25.2%	0.87 (0.49–1.54)	0.315
Total parenteral nutrition	45	58.0%	3	5.2%	15.11 (7.66–29.8)	**0.001**

Table 3. *The distribution of respiratory problems*

Respiratory problem		Case group (n=250)		Control group (n=250)		p value
Meconium aspiration syndrome	Absent	249	99.6%	247	98.8%	χ^2: 1
	Present	1	0.4%	3	1.2%	p=0.315
Respiratory distress syndrome	Absent	242	96.8%			
	Present	8	3.2%			
Pneumonia	Absent	234	93.6%	246	98.4%	χ^2: **7.5**
	Present	16	6.4%	4	1.6%	**p=0.006**
Transient tachypnea of the newborn	Absent	197	78.8%	237	94.8%	χ^2: **27.9**
	Present	53	21.2%	13	5.2%	**p=0.001**
Pneumothorax	Absent	248	99.2%	250	100.0%	χ^2: 2
	Present	2	0.8%	0	0.0%	p=0.156
Apnea	Absent	250	100.0%	249	99.6%	χ^2: 1
	Present	0	0.0%	1	0.4%	p=0.317

Table 4. *The distribution of intubation, nCPAP and HOOD applications*

		Case group (n=250)		Control group (n=250)		p value
Intubation	Absent	228	91.2%	249	99.6%	χ^2: **20**
	Present	22	8.8%	1	0.4%	**p=0.0001**
nCPAP	Absent	203	81.2%	245	98.4%	χ^2: **40.1**
	Present	47	18.8%	4	1.6%	**p=0.0001**
HOOD	Absent	176	70.4%	229	91.6%	χ^2: **36.5**
	Present	74	29.6%	21	8.4%	**p=0.0001**

nCPAP, nasal continuous positive airway pressure.

Mortality

The mortality rate was 1.6% in LPIs. In terms of infants, the mortality rate was 0.4%. No difference was observed between the case and control groups in terms of respiratory problems prevalence (p=0.147), culture positivity prevalence (p=0.646). and NEC prevalence (p=0.840). Clinical sepsis was found to be a significant risk factor for mortality (p=0.001) (Table 5).

Discussion

In this study, it was aimed to determine the differences between the characteristics of neonatal complications among LPIs and term infants, and to determine appropriate follow-up and treatment plans for LPIs.

In our study, between preterm infants and term babies; there was a significant difference between cesarean

Table 5. *Distribution of risk factors for mortality among preterm and term infants*

		Discharged (n=495)		Exitus (n: 5)		p value
Respiratory problems	Absent	416	84.0%	3	60%	χ^2: 2
	Present	79	16.0%	2	40%	p=0.147
Sepsis	Absent	364	73.5%	0	0.0%	χ^2: **13.5**
	Present	131	26.5%	5	100.0%	**p=0.0001**
Culture positivity	Absent	475	96.0%	5	100.0%	χ^2: 0.2
	Present	20	4.0%	0	0.0%	p=0.646
Necrotizing enterocolitis	Absent	491	99.2%	5	100.0%	χ^2: 0.4
	Present	4	0.8%	0	0.0%	p=0.840

birth rate, multiple pregnancy history, the history of premature birth, presence of antenatal problems, and prenatal steroid use. Maternal age was similar in preterm and term groups. Studies in the literature show that the history of preterm labor increases the possibility of late-preterm births by 20–30%. This rate is further increased after the second preterm labor[8–10]. The increase in the number of repeat cesarean section births (including obstetric indications and family/physician choice), gestational age of 30 and above, multiple pregnancies, gestational diabetes, hypertension, the presence of infection during pregnancy in the mother and the use of assisted reproductive techniques increase the frequency of preterm births[11]. Later studies have shown that antenatal steroids increase circulatory stability and therefore reduce the risk of NEC and intraventricular bleeding[12].

In our study, the frequency of respiratory problems was found to be 25.2% in LPIs and 7.2% in term infants. Accordingly, respiratory problems were 4.26 times more common in LPIs than term infants and showed that almost one of every four LPIs are affected by respiratory problems. When the literature is examined, Scheuchenegger et al.[13] reported that the rate of respiratory distress was 14.3%. At the same time, Çelik et al.[14] found this rate to be 46.5% in a study involving 605 late preterm cases. In an extensive study that included 19334 preterm infants in the USA between 2002 and 2008, it was found that respiratory insufficiency leading to NICU requirement was significantly more frequent in preterm infants compared to terms (36.5% vs. 7.2%). When RDS development rates are examined, the frequency is 10.5% in those with 34 weeks of gestation, 6% in 35 weeks, 2.8% in 36 weeks, 1% in 37 weeks, and 0.3% in those born after 38 weeks of gestation. In line with these results, it was found that the need for interventions such as nasal oxygen supplementation, intubation, surfactant use, and ventilator support are significantly reduced by the 39th week [15].

In our study, the frequency of oxygen administration with endotracheal intubation, nasal CPAP, and HOOD was significantly higher in LPIs than in terms. Mally et al.[16] found the rate of RDS in late preterm infants to be between 3% and 9% according to their week of birth. Whereas in a study reported that RDS was present in 51 of 2437 (2.1%) late preterm infants[17]. However, these studies did not report a significant difference in the requirement for the interventions mentioned above.

In our study, feeding problems were observed in 85.2% of LPIs and 47.2% of terms. TPN was used in 58.0% of LPIs and only 5.2% of term infants. Furthermore, in late preterms, hypoglycemia was found to be 1.12 times more frequent than terms. Hypoglycemia is associated with breastfeeding problems in LPIs, and hypoglycemia has been reported to be present in 6–8% of LPIs in different studies. During breastfeeding, these newborns tire easily, and because metabolic mechanisms of glucose homeostasis are not fully developed, LPIs may be at higher risk of malnourishment, which increases hypoglycemia frequency. Furthermore, the presence of intrauterine growth retardation also increases the risk of hypoglycemia in these infants[13,18].

In our study, the frequency of jaundice was 2.24 times higher among late premature newborns. Although there is a limited number of studies in the literature, available data show that late premature babies are re-admitted to the hospital more frequently than terms due to jaundice[19].

Lubow et al.[20] reported that the length of stay in the NICU among LPIs born at 34, 35, 36 weeks of gestation were 8±7, 3±4, and 3±4 days, respectively. Melamed et al.[21] reported hospitalization time to be 9.4±8.8 days for 34-week, 6.5±6.3 days for 35-week, and 4.7±3.9 days for 36-week LPIs. Similarly, in our study, the mean length of stay at the hospital was calculated as 9.45±5.78 days in LPIs and 6.65±4.38 days in term infants. These data demonstrate that LPIs have more extended hospitalization compared to terms, and the gestational week is also an important factor that contributes to the length of stay.

The large 2013 study performed in the US reported that the mortality rates of neonatal infants according to a gestational week of birth were as follows: 1.75% at 40 weeks, 2.41% at 37–39 weeks, 7.23% at 34–36 weeks. Risk factors for mortality included bronchopulmonary dysplasia, brain injury, sepsis, and NEC[22]. Tomashek et al.[23] reported that the risk of mortality in preterm infants is three times higher than term babies. In our study, neonatal mortality was 1.6% (4 patients) in LPIs, and mortality in term infants was 0.4% (1 patient). Clinical sepsis was found to contribute to the increase in mortality risk.

There are some limitations to our study. Firstly, infants were not followed in the long-term. Secondly, this study was a case-control study. It may not reflect the effects of all parameters involved in the differences among newborns, such as physicians' approach, which may be directly affected by gestational week and could have caused a more cautious approach to LPIs. However, the inclusion of all LPIs that were born at our center during the study period and the fact that the control group was randomly selected by SPSS randomization are factors that increase the objectivity of our results.

Similar to other studies in the literature, late premature subjects were found to have a higher frequency of significant respiratory problems as well as nutritional problems, hypothermia, hypoglycemia, NEC, jaundice, hospital stay, and mortality compared to term newborns. These results indicate that LPIs (born between 34 0/7 and 36 6/7 weeks of gestation) have higher possibilities for many problems that cause significant morbidity and mortality. As a result, late premature babies, who constitute 84% of all premature babies, should be considered at higher risk for morbidities, and it is important to acknowledge that these patients may have higher treatment costs compared to term newborns. At the time of delivery, the obstetrician and neonatal specialists should consider these characteristics and decide for birth about the health of the mother and baby as a whole. Also, we believe there may be benefits in extending the follow-up duration of LPIs, or they should be monitored closely after discharge, especially during the first week.

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