

Neurodevelopmental problems of late preterm fetuses and the factors affecting neurological morbidity

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Abstract

Objective: We aimed to investigate neurodevelopmental prognosis of late premature infants (between 32 and 37 weeks) and to determine antenatal, natal and postnatal risk factors affecting prognosis.

Methods: The study was carried out on a total of 200 children (100 premature and 100 mature born) with no known chronic disease from 6-month-old up to 6-year-old born between January 2008 and January 2013 in the obstetrics clinic of Health Ministry Dr. Sami Ulus Training and Research Hospital and being followed up routinely in the Pediatric Psychiatry Clinic. The information of the children was obtained by a questionnaire form completed by their first degree relatives. Antenatal and natal risk factors were listed by analyzing the files. Psychosocial and motor developments of the children were assessed with Ankara Development Screening Inventory (AGTE), and premature and mature babies were compared in terms of neurological development.

Results: While there was no statistically significant difference between the groups in our study in terms of chronological age and 1-minute and 5-minute Apgar scores ($p>0.05$), the difference between delivery week and birth weight was statistically significant ($p<0.05$). It was found that late premature babies had significantly high level of RDS, hypothermia, hypoglycemia, jaundice, apnea and hospitalization period compared to mature babies ($p<0.05$). There was no significant relation between AGTE and the week of gestation, birth weight, antenatal steroid prophylaxis, 1-minute and 5-minute Apgar score, maternal educational level, and socio-economical level ($p>0.05$). Among the groups, there was statistically no significant difference in terms of general development, language development, fine and gross motor development and personal-social development ($p>0.05$).

Conclusion: Although there was no significant difference between late premature and mature groups in terms of neurological development, late premature babies are under risk in terms of neonatal morbidity and mortality, and they encounter many problems. Therefore, delivery schedule should be planned carefully by considering prematurity risks against the maternal and fetal complication risks if it is decided to maintain pregnancy. In addition, either the periods of follow-up besides mothers for late premature babies should be extended or these babies should be followed-up more closely in the first days after discharge.

Keywords: AGTE, late preterm, neurological development.

Özet: Geç preterm fetüslerin nörogelişimsel sorunları ve nörolojik morbiditeye etki eden faktörler

Amaç: Bu çalışmada geç prematüre bebeklerin (32–37. hafta arası) nöro-gelişimsel prognozunu araştırmak, prognoza etki eden antenatal, natal ve postnatal risk faktörlerini belirlemeyi amaçladık.

Yöntem: Çalışma, Sağlık Bakanlığı Dr. Sami Ulus Eğitim ve Araştırma Hastanesi psikiyatri çocuk polikliniğinde rutin takibi olan, aynı hastanenin kadın doğum kliniğinde Ocak 2008 – Ocak 2013 tarihleri arasında doğan, 6 ay – 6 yaş arası, bilinen herhangi bir kronik hastalığı olmayan, 100 adet prematüre ve 100 adet matür doğmuş çocuk olmak üzere toplam 200 çocuk üzerinde gerçekleştirildi. Çocuga ait bilgiler birinci derece yakınlarının doldurduğu anket formu ile elde edildi. Antenatal ve natal risk faktörleri dosyalar incelenerek çıkarıldı. Çalışmaya alınan çocukların psiko-sosyal ve motor gelişimleri Ankara Gelişim Tarama Envanteri (AGTE) ile değerlendirilerek prematür ve matür bebekler nörolojik gelişim açısından karşılaştırıldı.

Bulgular: Çalışmamızda gruplar arasında kronolojik yaş, 1. ve 5. dk Apgar skorları açısından istatistiksel olarak anlamlı fark bulunmamışken ($p>0.05$), doğum haftası ve doğum ağırlığı arasındaki farkın istatistiksel olarak anlamlı olduğu saptandı ($p<0.05$). Geç prematürelerin daha sık RDS, hipotermi, hipoglisemi, sarılık, apne ve hastanede kalış sürelerinin termlerden anlamlı ölçüde yüksek olduğu belirlendi ($p<0.05$). Gestasyonel hafta, doğum ağırlığı, antenatal steroid profilaksisi, 1. ve 5. dk Apgar skoru, anne eğitim düzeyi ve ailelerin sosyo-ekonomik düzeyi ile AGTE arasında anlamlı bir ilişki bulunmadı ($p>0.05$). Gruplar arasında genel gelişim, dil gelişimi, ince ve kaba motor gelişim ve kişisel-sosyal gelişim açısından istatistiksel olarak anlamlı bir fark saptanmadı ($p>0.05$).

Sonuç: Geç prematüre ve matüre gruplar arasında nörolojik gelişim açısından anlamlı fark bulunmamış olmakla birlikte geç prematüre bebekler neonatal morbidite ve mortalite açısından risk taşımakta ve birçok sorunla karşılaşmaktadır. Dolayısıyla doğum zamanlamasına prematürünün getireceği risklere karşılık gebeliğin devam ettirilmesi halinde anne ve fetüste oluşabilecek komplikasyonların riskini düşünerek dikkatlice karar verilmelidir. Bunun yanı sıra geç prematürelerin ya anne yanında izlem süreleri uzatılması ya da taburculuk sonrası ilk günlerde yakından izlenmeleri sağlanmalıdır.

Anahtar sözcükler: AGTE, geç preterm, nörolojik gelişim.

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Introduction

Preterm labor is one of the leading reasons of neonatal mortality and morbidity in the world including developed countries. Thanks to the recent scientific and technological developments on neonatology and the increase in the quality of newborn intense care units, the survival rates of premature babies have increased. However, despite all the improvements in neonatal and perinatal care, premature birth has still been a significant problem not prevented so far. Premature babies are the largest group under risk among newborns due to various reasons such as their different biological structures, various problems belonging to early neonatal period, their need for longer hospitalization and their tendencies to infections. Due to many risk factors associated, preterm labor increases both morbidity rates during natal and postnatal periods and neuro-developmental problems in the long-term. In premature babies, germinal matrix-intraventricular hemorrhage (GM-IVH) is the most significant factor which has a direct association with neurological development. GM-IVH has an impact on neonatal mortality, morbidity and long-term neuro-developmental problems.^[1] In the studies carried out, cerebral palsy, mental retardation, convulsion, blindness, hydrocephalia and deafness are considered as the major neurological sequelae. Except such neuromotor dysfunctions, some minor neurological problems such as speech delay, visual or verbal perception problems, learning disability, school and behavioral problems, hyperactivity and lack of attention may also be observed in some preterm cases.^[2,3] Since permanent sequelae which develop depending on the complications cause serious social and economical problems for patients and their families, it is important to diagnosis the baby under risk as early as possible, to follow up regularly and to lead to the rehabilitation programs.^[4] By early diagnosis and support, the child can become more independent in the daily life and has the ability to deal with problems in school and game life, and many secondary social and emotional problems can be prevented or fixed.^[5]

This study was planned to investigate the neuro-developmental prognosis of premature babies (between 32 and 37 weeks) born in the obstetric clinic and followed up in the pediatric psychiatry clinic of Health Ministry Dr. Sami Ulus Obstetrics, Gynecology and Pediatrics Training and Research Hospital, and to determine antenatal, natal and postnatal risk factors affecting prognosis.

Methods

Çalışma, Sağlık Bakanlığı Dr. Sami Ulus Eğitim ve The study was carried out on a total of 200 children (100 premature and 100 mature born) chosen randomly regardless of gender and with no known chronic disease from 6-month-old up to 6-year-old born between January 2008 and January 2013 in the obstetrics clinic of Health Ministry Dr. Sami Ulus Training and Research Hospital and being followed up routinely in the Pediatric Psychiatry Clinic of the same hospital. Risk factors during prenatal, natal and postnatal periods of the babies in study and control groups were obtained from the computer database and their medical files, and recorded to the forms. Babies with syndromes, congenital hydrocephaly, asphyxia and metabolic disease were excluded from the study. The approval of the ethics committee was obtained before the study. The families of premature babies included in the study were asked to visit the hospital. The families were informed about the research and the tests, and their written informed consents were received.

Information about the child was obtained preferably from the mother and/or father, otherwise from the first degree relatives who have the possibility to follow-up the child closely; and the information about child was obtained through a questionnaire form including questions such as child's age, gender, birth weight, antenatal tests, birth information, previous diseases if any, the degree of person providing information (mother, father, grandmother etc.), their educational levels, educational level of mother, her profession and her current professional status. Antenatal and natal risk factors were listed by analyzing their files.

Psychosocial and motor developments of children included in the study were evaluated by Ankara Development Screening Inventory (AGTE) which is an assessment tool providing systematic and detailed information on the development of babies and children and applied to patients by physicians trained on this tool. This inventory, which is unique to our culture, can be applied to many participants in a short time and organized as reflecting the development of child in health screenings, consists of 154 items which are arranged according to various age groups and responded with "Yes / No / I don't know" replies. The questions were arranged as representing different but associated parts of the development (a general assessment of abilities such as Language-Cognitive [LC]: language expressions, understanding the language and clearly expressing it; Fine Motor [FM]: visu-

al-motor skills; Gross Motor [GM]: movement and movement-related strength, balance and coordination; Social Skill - Self-Care [SS-SC]: Self-care habits [eating, drinking, toilet use and wearing] and independency, social interaction and initiative). The results reflect the current development of 0–6 y/o babies and children as 4 sub-tests stated above and total development scores. When applying AGTE in our study, only the questions relevant to the ages of children were asked and most appropriate responses were aimed by using an understandable language as much as possible and providing examples when necessary. Ages of children were calculated through months. In this calculation, AGTE recommendation was taken into consideration. If child have passed 15 days or more from one-month as of the date of questionnaire assessment, the age of that child was obtained by adding one to that month (the age of a child who was 20-month and 18-day-old was considered as 21-month-old, and age of a baby who was 8-month and 14-day-old was considered as 8-month-old). After questionnaire was completed, sub-test scores for Language-Cognitive [LC], Fine Motor [FM], Gross Motor [GM] and Social Skill - Self-Care [SS-SC] were calculated first, and General Development (GD) raw score was obtained by summing up these four scores. Raw score profile was used to interpret the raw scores of LC, FM, GM, SS-SC and GD. AGTE was preferred since it was a tool with completed validity studies, compared with the results of validity studies by other clinics which was easy to apply and easy to assess.^[6]

Data entries and analyses were done by SPSS software, version 15 (SPSS, Inc., Chicago, IL, USA). When analyzing the study data in terms of quantitative data comparison, one-way ANOVA test was used for intergroup comparisons and Student-t test for two-group comparison of the parameters displaying normal distribution and Kruskal-Wallis test for intergroup compar-

Table 1. Demographic information.

	Term 37≤week<41		Preterm 32≤week<37		Total	
	n	%	n	%	n	%
Gender						
Male	55	55	48	48	103	51.5
Female	45	45	52	52	97	48.5
Delivery type						
Vaginal	75	75	65	65	140	70
C/S	25	25	35	35	60	30
Educational level of mother						
No education	25	25	18	18	43	21.5
Secondary education	50	50	56	56	106	53
Higher education	25	25	26	26	51	25.5
Professional status of mother						
Not working	65	65	75	75	140	70
Working	35	35	25	25	60	30
Smoking during pregnancy						
Yes	16	16	22	22	38	19
No	84	84	78	78	162	81

isons and Mann-Whitney U test for two-group comparison of the parameters not displaying normal distribution. Spearman correlation analysis was used for the comparison of the correlation among the parameters. For the qualitative data comparison, Chi-square test was used. The results were evaluated within 95% confidence interval and according to $p < 0.05$ significance level.

Results

Information about genders and birth types of children in the study group and educational and professional status of their mothers and smoking habit during pregnancy is shown in the **Table 1**. Comparison of the groups in terms of delivery data and maternal age are shown in the **Table 2**, and statistically no significant

Table 2. Distribution of fetal findings.*

	Group 1 (≥37 weeks)		Group 2 (<37 weeks)		p
	Mean±SD	Min.–Max.	Mean±SD	Min.–Max.	
Delivery week (week)	39±0.93	37–41	35±1.31	32–37	$p < 0.05$
Birth weight (g)	3700±302.0	2550–4250	2360±368.1	1630–3300	$p < 0.05$
Maternal age	31±2.16	25–36	28.50±4.99	17–36	$p > 0.05$
Apgar score (1-minute)	7±0.65	5–8	6±0.88	5–8	$p > 0.05$
Apgar score (5-minute)	9±0.65	7–10	8±0.67	7–9	$p > 0.05$

* χ^2 : chi-square test; SD: standard deviation

Table 3. The comparison of the groups in terms of fetal results and maternal findings.

	Group 1 (≥37 weeks)				Group 2 (<37 weeks)			
	Yes		No		Yes		No	
	n	(%)	n	(%)	n	(%)	n	(%)
Resuscitation	6	6	94	94	20	20	80	80
RDS	0	0	100	100	22	22	78	78
Apnea	20	20	80	80	26	26	74	74
Bradycardia	8	8	92	92	23	23	77	77
Phototherapy	10	10	90	90	21	21	79	79
Hypoglycemia	0	0	100	100	14	14	86	86
Pneumonia	6	6	94	94	8	8	92	92
Anemia	2	2	98	98	5	5	95	95
Rh incompatibility	18	18	82	82	20	20	80	80
Mechanic ventilation	0	0	100	100	12	12	88	88
Hypothermia	0	0	100	100	12	12	88	88
PROM	0	0	100	100	14	14	86	86
Celeston application	12	12	88	88	24	24	76	76
Gestational HT	8	8	92	92	6	6	94	94

difference was found between the groups in terms of chronological age and 1-minute and 5-minute Apgar scores ($p>0.05$). It was found that the difference between the delivery weeks and birth weights of the groups was statistically significant ($p<0.05$). The comparison of the groups in terms of fetal results and maternal findings is shown in the **Table 3**. The comparisons of the groups according to the AGTE development test was shown in the **Table 4** and statistically no significant difference was found among the groups

in terms of general development, language development, fine and gross motor development and personal-social development ($p>0.05$).

Discussion

Unlike mature babies, premature babies are the largest group under risk among newborns due to various reasons such as their different biological structures, various problems belonging to early neonatal period, their

Table 4. The distribution of AGTE test results. *

AGTE parameters		Group 1		Group 2		p
		Normal	Abnormal	Normal	Abnormal	
General development	n	92	8	84	16	$p>0.05$
	%	92	8	84	16	
Language development	n	92	8	84	16	$p>0.05$
	%	8	8	84	16	
Thin motor development	n	96	4	92	8	$p>0.05$
	%	96	4	92	8	
Gross motor development	n	96	4	92	8	$p>0.05$
	%	96	4	92	8	
Personal social development	n	96	4	92	8	$p>0.05$
	%	96	4	92	8	

* χ^2 : chi-square test

need for longer hospitalization and their tendencies to infections. In the international literature, there are many studies on long-term follow up of the premature babies. Due to the decreasing mortality rates of premature babies with very low birth weight, neurodevelopment retardation cases are seen frequently in the developed countries. On the other hand, morbidity rates and treatments of premature babies become more important increasingly as the number of neonatology units grows and mortality rates reach to the western levels in Turkey. It is crucial to reduce morbidity rate in terms of diagnosing the baby under risk as early as possible and the disabilities that would occur later. In the last two decades, premature birth rates increased significantly. Late premature births are the major reason for this increase. In 2003, 71% of all premature births in the USA were late premature cases. This study was planned to identify the developmental problems of late premature babies born in our hospital and followed up in the pediatric psychiatry clinic, and to reveal the correlation between these problems and risk factors during antenatal, natal and postnatal periods.

In our study group, RDS incidence in 32–36 week babies in our study group was consistent with the literature. While RDS incidence decreased significantly after 34 weeks of gestation, the risk continued in 35- and 36-week babies.^[7] Escobar et al. reported that male gender, cesarean delivery, antenatal problem, being SGA and low week of gestation were among the risk factors which have a role in the development of respiratory distress syndrome.^[8] In our study, the risk factors in terms of respiratory distress were similarly found as male gender, cesarean delivery, antenatal problem and being late premature. Before 37 weeks of gestation, the risk of respiratory distress occurrence increases together with each weekly decreases in the week of gestation, and this risk continues even gender, being SGA or LGA, race, antenatal problem, multiple pregnancy and birth weight are controlled.^[8] Although respiratory distress is frequent in late premature cases, the reason is unclear. Insufficiency in fetal alveolar fluid resorption or having underdeveloped lungs may be the reason. Late premature babies are born when their lung developments are in saccular-alveolar period. In physiological development, the number of alveoli significantly increases after 32 weeks. These physiological insufficiencies in the lungs may also have a role in the respiratory distress of these babies.^[9] Since respiratory distress (RDS in particular) is a significant

morbidity reason in late premature babies, timing of the births of late premature babies becomes even more important. There is no sufficient study on the applicability and effectiveness of antenatal corticosteroid treatment after 34 weeks of gestation. Lewis et al. suggest to evaluate fetal lung maturity in the presence of PROM or early labor at 34 weeks of gestation and to delay delivery (conservative approach); however, state that such a practice is not necessary since RDS incidence is very low (0.6%) as of 35 weeks of gestation.^[7] In our study, it is seen that antenatal corticosteroid application does not decrease respiratory distress problem. However, since the late premature rate applied antenatal corticosteroid is only about %10, the current data is insufficient to explain the relationship between antenatal corticosteroid application and respiratory distress. Our study and further studies including many late premature babies may clarify whether late premature babies will be candidates for antenatal corticosteroid applications.

In our studies, the jaundice rate was two times higher in late premature cases than mature cases. While phototherapy was applied to all patients with jaundice, none of them required blood transfusion. Jaundice was the second frequent reason for re-admitting to the hospital. Although there are few studies on this matter in the literature, current studies show that late premature babies compared to mature ones re-admitted to the hospitals and hospitalized more frequently due to jaundice.^[8,10,11] Similarly, Wang et al. found in their study that late premature cases had jaundice 1.95 times more than mature cases.^[12]

While 6% of late premature cases had hypothermia in our study, no hypothermia was observed in mature babies. Wang et al. reported hypothermia incidence as 10% in late premature cases and 0 in mature cases.^[12] While it is possible that hypothermia may be the first finding of neonatal sepsis as well as it may develop depending on just prematurity, it should be cautious in terms of unnecessary sepsis evaluations and antibiotic treatment.

In accordance with the literature, hypoglycemia was 6 times higher in late premature cases than mature cases.^[12] Carbohydrate metabolism is unclear in late premature cases and it is considered that glucose regulation has not grown to sufficient maturity in these babies since hypoglycemia is more frequent in them compared to mature cases.

The studies in the literature show that apnea incidence varies between 4 and 12% in late premature cases but it is below 1% in mature cases.^[12-14] In the study of Wang et al., there was statistically no significant difference, and apnea incidence was found higher in late premature cases (4.4%) than mature cases (0%).^[12] Although there was statistically no significant difference between the groups, the apnea incidence was found to be more frequent in late premature cases than mature cases but the apnea incidence we found in late premature cases was lower than those reported in the literature.

In the literature, major neuromotor sequela rate in the premature cases is higher in the group with low birth weight and varies between 7 and 30%.^[15-17] Cerebral palsy is indicated among the most common major neurological disorders.^[18] In 1997, McCormick reported cerebral palsy rate as 7.7% in babies with low birth weights.^[19] There is no clear consensus in the literature on the correlation between birth weight, week of gestation and development sequela. In the study of Thompson et al., no difference was found between birth weights below 1000 g and those above 1000 g in terms of neurodevelopmental problem.^[20] Özbek et al. stated in their study that mental scale was not affected in cases with low birth weight (LBW); however, motor function was affected by DDA negatively. In the same study, no difference was observed between 38–32 weeks and 32–36 weeks in terms of the impact of week of gestation.^[21] Lya den Ouden et al. carried out a study on 555 premature babies born below 32 weeks of gestation, and found neuromotor retardation in 60% of those born at 24–25 weeks of gestation, in 16% of those born at 26–27 weeks of gestation, in 22% of those born at 28–29 weeks of gestation, and in 15.5% of those born at 30–31 weeks of gestation.^[22] In the study of Chaudhari et al., neurodevelopmental status of 172 premature babies and 36 mature babies were compared at 18–24 weeks of gestation by Bayley Scales of Infant Development-II, and a positive correlation was found between birth weight and motor development.^[23] According to the study of Talge et al. carried out in the USA in 2012 on 6-year-old children of which 473 were born with low birth weight and 350 were born with normal birth weight, preterm labor is statistically and significantly associated with growth retardation and focusing problem.^[24] Unlike these studies, we found that the week of gestation of late preterm cases was not significant in terms of neuro-developmental growth.

We found in our study that week of gestation and birth weight did not make any difference in terms of general development, gross motor development, social development, mental scale and language development. Similar to our study, Vries et al. grouped preterm cases as those below 32 weeks and those above 32 weeks, and reported CP rate of those below 32 weeks as 5% and of those at 32–35 weeks as 6%, and therefore showed that week of gestation was insignificant in terms of neurodevelopmental prognosis.^[25] Similarly, in the study of Nepomnyaschy et al. carried on 315 cases between 1–5 y/o and born through late preterm labor and published in 2012, differences similar to our results were found which are not significant statistically.^[26]

Conclusion

The results of our study show that many problems are still unsolved for late premature babies in Turkey despite all progress in neonatal care. Prematurity is one of the most significant reasons of perinatal and neonatal morbidity and mortality. Delivery time should be determined by obstetricians and newborn experts jointly by considering the health of mother and baby, and in case that pregnancy is maintained despite the risks of prematurity, a profit-loss assessment should be done by considering the risk of complications that may occur in mother and fetus. In addition, either the periods of follow-up besides mothers for late premature babies should be extended or they should be followed-up more closely in the first days after discharge.

Conflicts of Interest: No conflicts declared.

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