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Is There a Place for an Individual Approach to Late Preterm Newborns According to Gestational Age?

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ABSTRACT

Introduction: *Late preterm infants (LPT) are at high risk for perinatal acute morbidity and mortality. This risk seems to be lower with increasing gestational age (GA). We aim to discuss if an individual approach to the LPT according to GA is justified.*

Materials and Methods: *A secondary analysis of a retrospective study on antenatal corticosteroids in LPT birth was performed. Singleton, nonanomalous, delivered at 34–36 weeks infants born between January 1 2012, and December 31 2017 were included and classified into three groups according to GA at birth: 34+0 to 34+6 weeks; 35+0 to 35+6; 36+0 to 36+6. Primary outcomes included neonatal morbidity at birth and neonatal respiratory morbidity in the first 72 hours. Maternal demographic and obstetric data were analyzed as possible confounders.*

Results: *From a total of 390 LPT, 58.4% were born at 36 weeks, 24.9% at 35 and 16.7% at 34. Respiratory morbidity was 7 times higher in 34w than in 36w neonates. Comparing with 36w, 34w neonates reported 2.6 times more jaundice and 9 times more NICU admission. Neonates born at 34 weeks were more likely to present, with statistical significance: need of oxygen supplementation at birth and in the first 72 hours of life; need for non-invasive respiratory support; RDS of newborn; TTN; NICU admission; prolonged hospital stay for more than seven days; need for nutrition through nasogastric tube; jaundice with need for phototherapy; sepsis evaluation; treatment with antibiotics; hypoglycemia. Respiratory and non-respiratory outcomes decreased with increasing GA.*

Discussion: *These findings suggest that one week makes a difference in neonatal outcomes. Whenever possible efforts should be made to postpone preterm delivery. A discussion about individual approach to LPT according to GA should be raised. GA-specific guidelines could be justified to anticipate and prevent morbidity in perinatal life.*

Keywords

Late preterm, Gestational age, Neonatal respiratory morbidity.

Introduction

Late preterm (LPT) describe infants born between 34 weeks + 0/7 days and 36 weeks + 6/7 days of gestation [1]. The number of premature births have been increasing over the last decades, mostly due to LPT [1,2], which represents 7.4-9.1% of all deliveries [4-5]. Estimated rates in Portugal are slightly lower (5.4-6.1% of all deliveries and 68% of all preterm newborns) [6–7]. Although the morbidity is less severe than in early preterm newborns, LPT represent the largest burden of prematurity-associated disease [8-9]. In fact, these newborns have an increased rate of resuscitation at birth, respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), pneumonia, apnea and pneumothorax, which lead to an increased need for respiratory support [8-11]. Other associated morbidities include temperature instability, feeding problems, hypothermia, hyperbilirubinemia and hypoglycemia

[1,9]. Therefore, LPT infants are more likely to be admitted into Neonatal Intensive Care Units (NICU) and have a longer length of hospital stay compared to full-term infants [1,9,12]. This consequently leads to significant neonatal hospital costs as well as disability-specific lifetime associated costs, highlighting the economic point of view of the need to reduce prematurity [14-15]. Recent studies have suggested that the gestational age (GA) at delivery of LPT can influence the risk of major complications [15,16].

The purpose of this study is to analyze whether there are significant differences in morbidity within each of the age groups of LPT born in our center in a period of 6 years. Additionally, we aim to understand if there is place for discussion about individual approach to LPT according to GA.

Materials and Methods

A secondary analysis of a retrospective study on antenatal corticosteroids in late preterm birth [17] was performed. The primary study has been approved by the authors' Institutional Review Board. As this was a clinical audit, informed written consent was not required.

The present study included all neonates born between 34 + 0/7 and 36 + 6/7 weeks of gestation delivered at our center. The exclusion criteria were unknown pregnancy until time of birth, pregnancy with known congenital and/or chromosomic disorders, multifetal pregnancy and mothers on chronic systemic corticotherapy. Selected newborns were classified into three groups, according to gestational age: (a) born at 34 + 0/7 to 34 + 6/7 weeks of GA, henceforth designated "34w"; (b) "35w": born at 35 + 0/7 to 35 + 6/7 weeks of GA; (c) "36w": born at 36 + 0/7 to 36 + 6/7 weeks of GA.

Primary outcomes included newborn morbidity at birth and respiratory morbidity in the first 72 hours of life. Newborn morbidity at birth included APGAR score (AS) at first and fifth minute of life and the need for resuscitation/support of transition at birth such as: oxygen supplementation, continuous positive airway pressure or/and endotracheal intubation. Respiratory morbidity in the first 72 hours of life included: occurrence of RDS, occurrence of TTN, the need for ongoing respiratory support including oxygen, invasive and/or noninvasive respiratory support. As for secondary outcomes, we evaluated: additional hospital stay, need for admission in NICU, occurrence of hypoglycemia, sepsis evaluation (any of complete blood count, blood culture, C-reactive protein), treatment with antibiotics for presumed sepsis, need for gavage feeding and hyperbilirubinemia with need for phototherapy.

Maternal demographic characteristics and obstetric data were included in this study as possible confounders, namely: mother's age, race, short cervix (defined as cervix length < to 25mm); precipitate delivery; threatened preterm labor; premature rupture of membranes; vaginal hemorrhage during the first, second or third trimester; oligohydramnios and fetal growth restriction; prior history of premature delivery, prior history of cesarean delivery; type of delivery; maternal hypertensive disease (chronic, gestational or preeclampsia) and maternal diabetes (pre-existing or gestational). Other possible confounders were birth weight, newborn's gender and exposure to antenatal corticotherapy (ACS) for lung maturation.

Data were analyzed using SPSS Statistics 23.0. Differences between groups for categorical variables were tested using either χ^2 or Fisher's exact test. Multivariable logistic regression was used to estimate the odds of neonatal outcomes adjusting for known confounders with statistical differences between groups.

Results

A total of 390 newborns were included: 58.4% (n = 228) in 36w group, 24.9% (n = 97) in 35w group and 16.7% (n = 65) in 34w group. No statistically significant differences were found between groups concerning type of delivery nor gender (Table 1). Not surprisingly, we observed a higher rate of low birth weight and exposure to ACS for lung maturation in the 34w group. When considering maternal obstetric data, particularly pregnancy complications, there were no statistically significant differences between groups (Table 2).

Regarding morbidity at birth, neonates born at 34 weeks of GA needed more support of transition at birth compared to 35w and specially 36w (Table 3). When comparing to 36w, 34w neonates reported 2.2 times more oxygen supplementation, 1.8 times more intermittent positive pressure ventilation (IPPV) and 3.5 times more endotracheal intubation (EOT). Those parameters showed statistically significance. There were no statistically significant differences between groups regarding AS at first and fifth minutes of life (Table 3).

As for respiratory morbidity in the first 72 hours of life, 34w neonates presented three times more RDS and TTN than 35w neonates and seven times more than 36w neonates. This trend was also found in need for oxygen supplementation, invasive or non-invasive respiratory support (Table 3). Similar results were observed in all secondary outcomes, with considerable differences between GA groups regarding hospital stay longer than a week and admission in NICU (Table 4).

Even after the adjustment for birth weight, neonates born at 34 weeks were more likely to present, with statistical significance: need of oxygen supplementation at birth and in the first 72 hours of life; need for non-invasive respiratory support; RDS of newborn, TTN; NICU admission; prolonged hospital staying for more than seven days; need for nutrition through nasogastric tube; jaundice with need for phototherapy; sepsis evaluation; treatment with antibiotics and hypoglycemia (Table 5).

We report no deaths at birth or during the hospital stay. There was no record of pharmacological advanced resuscitation at birth. We report no cases of congenital pneumonia, pneumomediastinum or pulmonary hypertension.

Table 1: Perinatal data of all the newborns and comparison between groups of interest.

Perinatal Data	**All N=390**	**34 weeks GA n = 65 (16.7%)**	**35 weeks GA n = 97 (24.9%)**	**36 weeks GA n= 228 (58.4%)**	***P*-value***
Type of delivery					0.065
Vaginal delivery	227 (58.4%)	35 (53.8%)	48 (50.0 %)	144 (63.2%)	
Cesarean transversal section	162 (41.6%)	30 (46.2%)	48 (50.0%)	84 (36.8%)	
Weight at birth (grams)					< 0.001
≥2500	192 (49.2%)	8 (12.3%)	33 (34.0%)	151 (66.2%)	
Low birth weigth (<2500)	198 (50.8%))	57 (87.7%)	64 (66.0%)	77 (33.8%)	
Gender					0.272
Female	190 (48.7%)	29 (44.6%)	54 (55.7%)	107 (46.9%)	
Male	200 (51.3%)	36 (55.4%)	43 (44.3%)	121 (53.1%)	
ACS	189 (48.5%)	57 (87.7%)	59 (60.8%)	73 (32.0%)	< 0.001

GA: gestational age. ACS: antenatal corticotherapy. * *P* -value represents χ^2 of comparison among groups for categorical variables.

Table 2: Maternal demographic and obstetric data of the mothers of all newborns and comparison between groups of interest.

Maternal and obstetrical data	**All N=390**	**34 weeks GA n = 65 (16.7%)**	**35 weeks GA n = 97 (24.9%)**	**36 weeks GA n= 228 (58.4%)**	***P*-value***
Age					0.136
>34 years old	80 (20.6%)	16 (25.0%)	17 (17.5%)	47 (20.6%)	
20-34 years old	272 (69.9%)	40 (62.5%)	66 (68.1%)	166 (72.8%)	
<20 years	37 (9.5%)	8 (12.5%)	14 (14.4%)	15 (6.6%)	
Ethnicity					0.806
Caucasian	371 (99.2%)	61 (100%)	95 (100%)	215 (98.6%)	
African American	2 (0.5%)	0 (0%)	0 (0%)	2 (0.9%)	
Others	1 (0.3%)	0 (0%)	0 (0%)	1 (0.5%)	
Short cervix	27 (6.9%)	5 (7.7%)	10 (10.3%)	12 (5.3%)	0.251
Threatened Preterm birth	120 (30.8%)	20 (30.8%)	33 (34.0%)	67 (29.4%)	0.710
Precipitate delivery	42 (10.8%)	5 (7.7%)	11 (11.3%)	26 (11.5%)	0.898
Premature Rupture of Membranes	132 (33.9%)	23 (35.4%)	27 (27.8%)	82 (36.1%)	0.340
Uterine bleeding during pregnancy	54 (13.8%)	6 (9.2%)	18 (18.5%)	30 (13.2%)	0.217
Oligohydramnios	39 (10.0%)	8 (12.3%)	10 (10.3%)	21 (9.2%)	0.759
Fetal Growth Restriction	76 (19.5%)	14 (21.5%)	24 (24.7%)	38 (16.7%)	0.219
Previous Preterm birth	42 (10.9%)	6 (9.2%)	10 (10.4%)	26 (11.6%)	0.857
Previous birth by C-section	45 (11.7%)	6 (9.2%)	10 (10.5%)	29 (12.9%)	0.655
Arterial Hypertension	69 (17.7%)	13 (20.0%)	13 (13.4%)	43 (18.9%)	0.432
Diabetes	28 (7.2%)	4 (6.2%)	4 (4.1%)	20 (8.8%)	0.312

GA: gestational age. * *P* -value represents χ^2 statistic of comparison among groups for categorical variables.

Table 3: Primary outcomes in all newborns and comparison between groups of interest.

Variables	**All N=390**	**34 weeks GA n = 65 (16.7%)**	**35 weeks GA n = 97 (24.9%)**	**36 weeks GA n= 228 (58.4%)**	***P*-value***
Morbidity at birth					
Need for oxygen supplementation	66 (17.1%)	19 (29.2%)	17 (17.9%)	30 (13.3%)	0.010
Need for IPPV	43 (11.1%)	12 (18.5%)	8 (8.4%)	23 (10.1%)	0.001
Need for EOT	13 (3.3%)	6 (9.2%)	1 (1.0%)	6 (2.6%)	0.022
AS 1st minute of life					0.389
AS 7-10	371 (95.1%)	60 (92.3%)	94 (96.9%)	217 (95.2%)	
AS 0-6	19 (4.9%)	5 (7.7%)	3 (3.1%)	11 (4.8%)	
AS 5th minute of life	386 (99.0%)	63 (96.9%)	96 (99.0%)	227 (99.6%)	0.124
AS 7-10 AS 0-6	4 (1.0%)	2 (3.1%)	1 (1.0%)	1 (0.4%)	
Morbidity in the first 72 hours of life					
Need of oxygen supplementation	48 (12.3%)	26 (40.0%)	11 (11.3%)	11 (4.8%)	<0.001
Need for non-invasive respiratory support	28 (7.2%)	16 (24.6%)	6 (6.2%)	6 (2.6%)	<0.001
Need for invasive respiratory support	7 (1.8%)	3 (4.6%)	3 (3.1%)	1 (0.4%)	0.022
Need for surfactant therapy	4 (1.0%)	2 (3.1%)	2 (2.1%)	0 (0%)	0.047
Respiratory distress syndrome	54 (13.8%)	27 (41.5%)	13 (13.4%)	14 (6.1%)	<0,001
Transient tachypnea of the newborn	28 (7.2%)	14 (21.9%)	7 (7.2%)	7 (3.1%)	<0,001

AS: Apgar Score. EOT: endotracheal intubation. GA: gestational age. IPPV: intermittent positive pressure ventilation. * *P* -value represents $\chi 2$ statistic of comparison among groups for categorical variables.

Table 4: Secondary outcomes in all newborns and comparison between groups of interest.

General neonatal morbidity	All N=390	34 weeks GA n = 65 (16.7%)	35 weeks GA n = 97 (24.9%)	36 weeks GA n= 228 (58.4%)	*P*-value*
Hospital stay <3 days 3-7 days >7 days	 296 (75.9%) 39 (10.0%) 55 (14.1%)	 18 (27.7%) 11 (16.9%) 36 (55.4%)	 74 (76.3%) 14 (14.4%) 9 (9.3%)	 204 (89.5%) 14 (6.1%) 10 (4.4%)	<0.001
Admission in NICU	29 (7.4%)	16 (24.6%)	7 (7.2%)	6 (2.6%)	<0.001
Nutrition through nasogastric tube	55 (14.1%)	30 (46.2%)	10 (10.3%)	15 (6.6%)	<0.001
Jaundice with need for phototherapy	145 (37,2%)	45 (69.2%)	40 (41.2%)	60 (26.3%)	<0.001
Sepsis evaluation	136 (34,9%)	50 (76.9%)	32 (33.0%)	54 (23.7%)	<0.001
Treatment with antibiotics	37 (9.5%)	11 (16.9%)	13 (13.4%)	13 (5.7%)	0.008
Hypoglycemia	43 (11.0%)	13 (20.0%)	18 (18.6%)	12 (5.3%)	<0.001

GA: gestational age. NICU: neonatal intensive care units. * *P* -value represents χ2 statistic of comparison among groups for categorical variables.

Table 5: Risk of neonatal outcomes in neonates born at 34 weeks of gestational age after adjusting for weight at birth and antenatal corticotherapy for lung maturation.

Variables	Crude Odds Ratio (95% IC; *P*-value)	Adjusted Odds Ratio (95% IC; *P*--value)
Morbidity at birth		
Need for oxygen supplementation	3.419 (1.755 – 6.659; <0.001)	2.62 (1.173 – 5.87; 0.019)
Need for IPPV	2.008 (0.939 – 4.297; 0.072)	3.802 (0.591 – 1.498; 0.395)
Need for EOT	3.763 (1.171 – 12.092; 0.026)	4.244 (0.904 – 19.916; 0.067)
1st minute AS <7	0.608 (0.203 – 1.818; 0.374)	0.663 (0.169 – 2.596; 0.555)
5^{ft} minute AS <7	0.139 (0.012 – 1.555; 0.109)	0.158 (0.008 – 3.015; 0.220)
Respiratory Morbidity in the first 48 hours of life		
Need for oxygen supplementation	13.152 (6.010 – 28.777; <0.001)	10,707 (4.125 – 27.791; <0.001)
Need for non-invasive respiratory support	12.082 (4.498 – 32.448; >0.001)	7.183 (2.200 – 23.455; 0.001)
Need for invasive respiratory support	10.984 (1.123 – 107.443; 0.039)	10.371 (0.723 – 148.700; 0.085)
Respiratory distress syndrome	10.861 (5.224 – 22.581; <0.001)	12.542 (4.962 – 31.701; <0.001)
Transient tachypnea of the newborn	8.840 (3.392 – 23.037; <0.001)	7.440 (2.308 – 23.986; 0.001)
General neonatal morbidity		
NICU admission	12.082 (4.498 – 32.448; <0.001)	10.556 (3.156 – 35.304; <0.001)
Prolonged hospital staying (7 or more days)	21.854 (10.380 – 46,015; <0.001)	10.370 (4.447 – 24.184; <0.001)
Nutrition through nasogastric tube	12.171 (5.951 – 24.893; <0.001)	7.808 (3.324 – 18.340; <0.001)
Jaundice with need for phototherapy	6.300 (3.445 – 11.521; <0.001)	5.625 (2.811 – 11.255; <0.001)
Sepsis evaluation	10.741 (5.592 – 20.632; <0.001)	12.579 (5.851 – 27.045; <0.001)
Treatment with antibiotics	3.369 (1.140 – 5.748; <0.001)	2.771 (0.998 – 7.694; 0.051)
Hypoglycemia	4.500 (1.941 – 10.434; <0.001)	3.776 (1.398 – 10.200; 0.009)

AS: Apgar Score. EOT: endotracheal intubation. GA: gestational age. IPPV: intermittent positive pressure ventilation. NICU: neonatal intensive care units. * *P* -value represents χ^2 statistic of comparison among groups for categorical variables.

Discussion

Data analyses demonstrated increasing incidence of morbidity with decreasing GA, irrespective of pregnancy complications (Tables 3 and 4).

Correia et al. drew attention to the fact that newborns delivered after 35 weeks, whose mothers are not given ACS, have considerable respiratory morbidity [11]. Nonetheless, our results show that respiratory morbidity is higher in 34w when compared to 35w and 36w neonates regardless of ACS, excluding this as a confounding factor (Table 3). RDS and TTN are more frequent in LPT in general than in full-term newborns, due to the underdevelopment of lung function and immature surfactant system [1,9,20-21]. A retrospective evaluation on a large American study reported a 40 times greater risk of RDS in 34 week neonates when compared to 38 week neonates [18]. Marrocchella et al. showed an increased incidence of RDS in LPT of 34w (7.04%) and 35w (2.82%), with no statistically significant incidence in 36w (1.4%) [15]. Accordingly, our data showed a significant decrease in RDS with increasing GA (Table 3). Rates of RDS have been reported over a wide range of incidence, depending on the centers and the type of samples studied, but this GA-dependent pattern has been constantly described [7,18]. A similar pattern was found in TTN (Table 3). These results enhance the importance of delaying delivery for some days or weeks, whenever possible. A GA-dependent pattern has also been reported in non-invasive and invasive respiratory support, although rates vary across studies [5,7,18]. Escobar et al. inferred that 35w newborns were nine times and 36w newborns five times more likely to be ventilated than full-term newborns (born from 38 to 40 weeks) [7]. This need for respiratory support may be a direct consequence of the pattern showed in general respiratory morbidity, reflecting pulmonary immaturity that increases with prematurity.

Higher incidence of non-respiratory morbidity has been described in 34w newborns compared to the other LPT infants [5,16]. It is well established that jaundice is more frequent in LPT than in full-term newborns [1,20]. Jaundice with need for phototherapy was the most frequent non-respiratory complication in our LPT sample, with a rate of 37.2% of all (Table 4). By stratified GA, we report jaundice in almost 70% of 34w newborns in the first 72h versus little more than a quarter in 36w newborns (Table 4). Our rates are higher than what is reported in other studies but this GA-dependent pattern has been described as well [5,15]. We also demonstrate a similar pattern in hypoglycemia and feeding difficulties inferred by the need for nasogastric tube (Table 4). This is in accordance with other studies on stratified GA [5,15]. Notwithstanding, García-Reymundo et al. reported high rates but no significant changes within GA groups of LPT [21]. Hypoglycemia can result from immaturity and difficulty to adequate transition to extrauterine life, especially in the first 12 hours of life live [1], hence it should be a focus of attention mainly in more premature LPT.

Both respiratory and general morbidity naturally contribute to prolonged hospitalization [1,9,12]. In the present study, hospitalization longer than one week was more frequent in 34w newborns, which is in agreement with similar reports [5,21]. In the absence of specific evidence-based guidelines for LPT newborns, which should include admission and discharge planning strategies, some infants may be inappropriately treated using guidelines defined for full-term infants, according to their birth weight and presumed asymptomatic status [7]. Based on our results, we consider that this tendency should be modified, and further research on this subject should be done.

In our hospital, LPT are not systematically admitted in NICU due to GA, but only if there are some clinical criteria. Several studies have described association between lower GA and need for NICU admission [5,16]. We reported an overall 7.4% rate of NICU admission with statistically significance between GA groups: three times higher in 34w neonates than in 35w, and nine times higher than in 36w (Table 4). Those rates are substantially lower than those reported by other Portuguese studies in a similar year period (~34%) [6–7]. That difference may be explained by our exclusion of pregnancies with known congenital/chromosomic disorders and multifetal pregnancy, factors that could contribute to more admissions.

Admission criteria of LPT infants in Local Neonatal Units (LNU) varies widely [1]. Some alert has emerged about the protective effect of NICU admission on LPT due to greater supervision on early jaundice and feeding difficulties [7]. The Portuguese Neonatal Society (SPN) published in 2018 a consensus regarding late prematurity, in which admission to LNU is recommended to 34w and 35w neonates and/or if there is risk for increased morbidity [22]. Our center's LNU admits infants born before 34w and/or with low birth weight. However, LPT are only admitted to LNU when there are some clinical criteria, similarly to some other centers [20]. Our center has been unable to apply SPN orientations since LNU and NICU work as non-individualized units and so: 1) capacity for non-intensive care is reduced; 2) attempts are made to avoid separating clinically well infants from their mothers, which supports breastfeeding and early bonding.

Our results corroborate that major attention, specially to 34w and 35w neonates, must be paid in the first hours of life to any type of breathing difficulty, which may correspond to RDS and TTN. The same must be done in the first 72 hours of life to identify signs of jaundice, feeding difficulties and hypoglycemia. Phototherapy and nasogastric feeding are examples of supplementary postnatal support that can be applied in the regular postnatal ward, as occurs in our center. Some centers have 'transitional care' units, where the mother provides normal care to the newborn with support from professionals; however the safety of this units must be better explored [20]. The impact of such differences in neonatal care should be further investigated.

Early discharge of LPT, if similar to what is commonly applied to full-term newborns, carries a serious risk for bilirubin-induced brain injury due to potentially inadequate evaluation of jaundice [23]. SPN's consensus recommends criteria for clinical discharge such as hospitalization of at least 72 hours in 34w and 35w newborns and 48 hours in 36w newborns, if clinical stable in the previous 24 hours [22]. We emphasize that early follow-up after discharge with any health service should be ensured for early detection of these complications. Feeding difficulties may lead to poor weight gain and dehydration during early postnatal weeks [1,8].

The present study is not without limitations, and its retrospective nature is to take in account. The strengths include the wide period of data (6 years) and that sample represents the whole region, since all deliveries occurs in our hospital. Additionally, this one and the primary study are the first approach to the LPT theme in our region and are one of the very few in our country, so it adds relevant information on this matter.

In conclusion, our stratified data for GA at birth and early days allows a better understanding of the contribution of each GA to neonatal morbidity in LPT. We observed that increasing GA within LPT group was accompanied by decreasing respiratory (RDS, TTN) and non-respiratory (jaundice, hypoglycemia) morbidity, more medical procedures (invasive and non-invasive respiratory support, nasogastric tube, sepsis evaluation, treatment with antibiotics), more frequent NICU admission and longer hospital stay. These findings suggest that one week makes a difference on neonatal outcomes and, whenever possible, efforts should be made to postpone preterm delivery. A discussion about individual approach to the LPT according to GA should be raised and GA-specific guidelines in perinatal care of LPT could be justified. We suggest that for LPT infants admitted in common nursery there should be specialized staff alerted to the above-mentioned signs. Also, these infants should not be discharged before 72 hours of life. Future studies should focus on strategies to anticipate and prevent morbidity in perinatal life, particularly in preventable prematurity.

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