ORIGINAL ARTICLE

Late Preterm Newborns: Do We Already Know Everything About Them?

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Abstract

Introduction: The preterm birth rate is on the rise, and late preterm deliveries account for 75% of preterm deliveries. Late preterm newborns were for many years considered full-term newborns; however, their particularities have been recognized in the last decade, particularly in terms of the higher rate of complications in the neonatal period. This study aimed to analyze the factors associated with greater morbidity in late preterm newborns.

Methods: In this cross-sectional study we reviewed the medical records of mothers and their late preterm infants born at our hospital during a four-year period. Logistic binary regression analysis was used to identify predictors of morbidity and control the confounding variables.

Results: The study included 576 newborns, of whom 28% (n = 164) had some morbidities, the most common of which included respiratory distress syndrome and hyperbilirubinemia. The morbidity rate varied inversely with gestational age. A lower gestational age, being small for gestational age, and the incomplete use of antenatal corticosteroids were identified as risk factors for morbidities ($p < 0.01$). Antenatal corticosteroids were apparently more used on the newborns who later developed respiratory distress syndrome ($p < 0.01$). In contrast, type of delivery, medically assisted reproduction, and pregnancy morbidity did not influence neonatal morbidity.

Discussion: Some well-known risk factors were confirmed for neonatal morbidity; however, there was no evidence to confirm the association between other determinants mentioned in previous studies and the increased risk of morbidity in our study samples, such as cesarean section, gemelarity, or fetal growth restriction.

Keywords: Infant, Newborn; Infant, Premature; Infant, Premature, Diseases/epidemiology; Risk Factors; Morbidity

Keypoints

What is known:

- Late preterm neonates are physiologically immature and are at greater risk of morbidity and adverse outcomes in the neonatal period.
- Previous studies identified some independent determinants of morbidity, such as gestational age, intrauterine growth restriction, and multiple gestations.

What is added:

- Fetal growth restriction, multiple gestations, cesarean section, and assisted reproductive technology were not associated with an increased neonatal morbidity rate.
- The use of antenatal corticosteroids did not significantly influence respiratory morbidity in neonates with a gestational age of 34 weeks.

Introduction

Late preterm infants are born at a gestational age between 34 weeks and 36 weeks and six days. In high-income countries, low preterm births occur in up to 6% of all births and account for 75% of preterm deliveries.[1] Risk factors for the delivery of preterm newborns are similar among low preterm births, preterm births between 32-33 weeks gestation, and very preterm births. The risk factors include a history of a previous preterm delivery, infection, maternal stress, increased maternal age, uterine, placental, or fetal anomalies, short cervix, and multifetal pregnancies.[2,3]

After nearly a decade of steady decreases, the preterm birth rate is increasing again.[3] This increase has been attributed to the rise in assisted reproductive therapy (ART), increased obstetric interventions, multiple births,

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and such maternal factors as advanced maternal age.[1]
Two-thirds of preterm deliveries occur as a result of spontaneous preterm labor and/or premature rupture of membranes.[4] Low preterm neonates are usually heavier than other premature neonates and are often mistaken as term infants who are developmentally mature. However, there is increasing recognition of their physiological immaturity and greater risk of morbidity and adverse outcomes.[5,6] The long-term consequences of late prematurity on neurodevelopment are also a major problem.
Several independent determinants of low preterm morbidity include gestational age, intrauterine growth restriction, multiple gestations, and specific maternal medical conditions. According to some studies, gestational age is the most important risk factor since the newborn morbidity rate doubles for every gestational week less than 38 weeks. It is noteworthy that the morbidity rate is as high as 51% for 34-week newborns.[1,5]
During birth hospitalization, low preterm infants are more likely to suffer from such complications as hypoglycemia, respiratory distress, apnea, hyperbilirubinemia, feeding difficulties, infections and sepsis, low Apgar score, and hypothermia, compared with term infants.[2]
This study aimed to raise awareness about this public health issue and determine the risk factors associated with greater morbidity and the clinical outcomes in this special group of preterm infants.

Methods

Study population and period

In this cross-sectional study, medical conditions and procedures evaluation was performed on low preterm infants during their stay in the neonatology or maternity hospital unit with differentiated neonatal care (level II) and more than 2500 births per year. The study period was four years (2015-2018) and included low preterm infants born at our hospital. Low preterm newborns were defined as newborns born at a gestational age between 34 weeks, and 36 weeks and 6 days. The newborns who were transferred to other hospitals were excluded from the study as there was a high risk of losing valuable information.

Variables and definitions

Data were collected on maternal medical history, gestational events, birth, perinatal occurrences, early comorbidities, and medical procedures performed. Gestational age was determined from the first trimester ultrasound or from the date of the last menstruation in the absence of the ultrasound. Weight for gestational age was classified as small (< 10th percentile), adequate, or great (> 90th percentile), using Fenton curves. Preterm births after either spontaneous labor with intact membranes or preterm premature rupture of the membranes were considered spontaneous, and those following induction or cesarean section delivery for maternal or fetal indications were considered iatrogenic. Morbidity was defined as death or hospital stay of more than three days with one of such clinical conditions as respiratory distress, apnea, feeding difficulties, hyperbilirubinemia requiring phototherapy, hypoglycemia, sepsis, or neonatal pneumonia.

Statistical analysis

Demographic and clinical data were assessed, and values were reported as average and standard deviation (SD) for quantitative variables and percentages for qualitative variables. The data collected were analyzed and categorized. Logistic binary regression analysis was used to identify predictors of morbidity and control the confounding variables. Clinical and demographic characteristics were included in the model. Results are shown for all samples and divided by groups, according to gestational age. The data were analyzed using SPSS software (version 22). A *p*-value less than 0.05 ($p < 0.05$) was considered statistically significant.

Results

Study population characteristics

During the study period, 588 low preterm births occurred, accounting for 5.6% of the total 10 589 births at our hospital. Twelve cases were excluded from the study due to their transfer to another hospital. Four, five, and three newborns completed 34, 35, and 36 weeks of gestational age, respectively. Monetary issues were the reason for transferring seven out of the 12 excluded neonates, and the remaining five needed a higher level of care. They all needed some respiratory support, and four neonates were transferred under mechanical ventilation. The total number of neonates included was 576, belonging to 499 mothers (77 multiple gestations). Almost half of the mothers had some obstetric morbidities. Demographic and clinical data are presented in Table 1.

Morbidity and the need of procedures

In total, 28.5% (n = 164) of all newborns had some morbidities (Table 2). Respiratory distress syndrome (RDS) was the most frequent morbidity identified (n =

Table 1. Demographic and clinical newborn and maternal data

Newborn data (n = 576)		**Maternal data (n = 499)**	
	n (%)		n (%)
Sex		**Maternal age**	
Female	266 (46.2)	Mean (± SD)	34.3 (± 4.7)
Male	310 (53.8)	Minimum	20
Antenatal ccorticosteroids		Maximum	56
No	290 (50.3)	**Parity**	
Complete	224 (38.9)	Nulliparous	223 (44.7)
Incomplete	62 (10.8)	Multiparous	276 (55.3)
Gestational age (completed weeks)		**ART**	55 (11.0)
34	86 (14.9)	**Mode of delivery**	
35	169 (29.3)	Eutocic	91 (18.2)
36	321 (55.7)	Dystocic (vacuum/forceps)	63 (12.6)
Birth weight (g)		Cesarean section	345 (69.1)
Mean (± SD)	2502.2 (± 385.9)	**Pregnancy morbidity**	
Minimum	1450	Total	228 (45.6)
Maximum	3600	Fetal growth restriction	58 (11.6)
Weight for gestational age		Gestational diabetes	46 (9.2)
SGA	70 (12.2)	Arterial hypertension	36 (7.2)
AGA	493 (85.6)	Oligohydramnios	30 (6.0)
LGA	13 (2.3)	Preeclampsia / eclampsia	23 (4.6)
Apgar score 5 minutes		Cholestasis of pregnancy	20 (4.0)
≥ 8	572 (99.3)	Hypothyroidism	21 (4.2)
< 8	4 (0.7)	Others	79 (15.9)
Multiple gestation	154 (26.7)	**Labor**	
Age at hospital discharge (day of life)		Spontaneous	246 (49.3)
Median	4	Iatrogenic	253 (50.7)
Minimum	2		
Maximum	25		
Type of feeding at discharge			
Exclusive breastfeeding	267 (46.4)		
Non-exclusive breastfeeding	277 (48.1)		
No breastfeeding	30 (5.2)		
NSCU admission	306 (53.1)		
> 3 days	180 (31.3)		
Length of hospitalization (days)			
Median	5		
Minimum	1		
Maximum	25		
Morbidity	164 (28.5)		
Mortality	2 (0.3)		

AGA - adequate for gestational age; ART - assisted reproductive therapy; LGA - large for gestational age; SGA - small for gestational age; NSCU - newborn special care unit; SD - standard deviation.

Table 2. Newborn morbidity and applied procedures			
Newborn morbidity	**n (%)**	**Procedures**	**n (%)**
RDS	138 (23.9)	Respiratory support	
Hyperbilirubinemia	123 (21.4)	Oxygen	168 (29.2)
Feeding difficulty	104 (18.1)	Non-invasive ventilation	97 (16.8)
Apnea	10 (1.7)	Mechanical ventilation	13 (2.3)
Hypoglycemia	49 (8.5)	Phototherapy	123 (21.4)
Sepsis	7 (1.2)	Antibiotics	49 (8.5)
		Central venous catether	57 (9.9)
Caffeine citrate		40 (6.9)	
Surfactant		8 (1.4)	

Table 3. Morbidity rate according with different factors	
Factors	**n (%)**
Gestational age	
34 weeks	61 (70.9)
35 weeks	52 (36.7)
36 weeks	41 (12.8)
Gemelarity	
Single gestation	117 (27.7)
Multiple gestation	47 (30.5)
Parity	
Nulliparous	72 (28.7)
Multiparous	92 (28.3)
Conception	
Spontaneous	145 (29.4)
Assisted reproductive therapy	19 (22.9)
Growth restriction	
Fetal growth restriction	31 (52.5)
No fetal growth restriction	133 (25.7)
Labour	
Spontaneous	72 (26.7)
Iatrogenic	92 (30.1)

138, 23.9%), followed by hyperbilirubinemia (n = 123, 21.4%). Accordingly, respiratory support (oxygen mainly) and phototherapy were the most used procedures for low preterm neonates. Sepsis was diagnosed in seven (1.2%) patients. However, antibiotics were used on 49 (8.5%) patients, mainly due to the presence of infection risk factors. There were two cases of deaths in the study sample. One was a two-hour newborn with 36 weeks and one day gestational age who had a cardiorespiratory arrest, according to the evidence from the autopsy of metabolic storage disease. The other case of death was a newborn with 34 completed weeks of gestational age, who died on the second day of life with massive cardiac tamponade and gastric and pulmonary hemorrhage.

The comparison of morbidity across subgroups showed that the morbidity rate was 12.8%, 36.7%, and 70.9% in the 36 weeks, 35 weeks, and 34 weeks gestational age groups, respectively (Table 3).

Risk factors for morbidity

It was possible to identify some independent morbidity determinants that were statistically significant after joint effects of the others (Table 4). A lower gestational age, being small for gestational age (SGA), and the incomplete use of antenatal corticosteroids (not using all doses) were identified as risk factors for morbidity.

The exclusive analysis of the impact of antenatal corticosteroids on the occurrence of respiratory distress syndrome among the late preterm population showed an odds ratio of 1.878 with a 95% confidence internal (95% CI) of 1.232-2.863 ($p = 0.003$). We individualized the analyses by completed weeks of gestational age which yielded p values of 0.702, 0.965, and 0.068 for 34, 35, and 36 weeks, respectively, failing to prove any impact.

Discussion

The results of the present study showed that lower gestational age, incomplete use of antenatal corticosteroids, and small for gestational age are independent risk factors for morbidity in low preterm newborns.

The relation found between an earlier gestational age and newborn morbidity is aligned with previous studies. It was shown that neonatal morbidity was inversely related to gestational age both for singletons born between 34 and 39 completed weeks of gestational age,

Table 4. Risk factor for morbidity in late preterm newborns

Tested risk factors	*p*	Odds ratio (95% CI)
Gestational age		
36 weeks	Reference category	
35 weeks	**< 0.001**	**4.510 (2.608-7.798)**
34 weeks	**< 0.001**	**21.514 (10.683-43.325)**
Maternal age > 35 years old	0.276	1.290 (0.816-2.039)
Pregnancy morbidity		
Arterial hypertension	0.563	1.297 (0.537-3.133)
Gestational diabetes	0.885	0.947 (0.452-1.983)
Oligohydramnios	0.221	1.809 (0.700-4.673)
Preeclampsia / eclampsia	0.509	1.451 (0.481-4.371)
Fetal growth restriction	0.268	1.564 (0.709-3.453)
Cholestasis of pregnancy	0.497	0.687 (0.233-2.027)
Hypothyroidism	0.864	0.902 (0.275-2.959)
Nulliparity	0.605	1.136 (0.701-1.841)
Assisted reproductive therapy	0.116	0.554 (0.265-1.158)
Multiple gestation	0.460	1.254 (0.688-2.284)
Spontaneous labour	0.999	1.000 (0.594-1.683)
Mode of delivery		
Eutocic	Reference category	
Dystocic	0.324	0.620 (0.240-1.602)
Cesarean section	0.487	0.799 (0.425-1.503)
Birth weight < 2500 g	0.534	1.193 (0.684-2.082)
Apgar score 5 minutes < 8	0.307	2.893 (0.378-22.167)
Weight for gestactional age		
AGA	Reference category	
SGA	**< 0.001**	**5.975 (2.791-12.792)**
LGA	0.725	0.727 (0.122-4.311)
Antenatal corticosteroids		
No	Reference category	
Complete	0.299	1.299 (0.793-2.129)
Incomplete	**< 0.001**	**3.227 (1.589-6.552)**

AGA - adequate for gestational age; LGA - large for gestational age; SGA - small for gestational age.

and for twins born between 34 and 37 completed weeks of gestational age.[7] A review study performed in 2015 also emphasized this tendency, particularly concerning respiratory morbidities.[6] Despite this trend, morbidity in low preterm newborns with a higher gestational age is also significant (12.8% at 36 weeks of gestation in the present study). Therefore, they should not be systematically managed as full-term newborns.

Interestingly, the low birth weight did not prove to be a determinant of morbidity in this study. A possible reason for this unexpected result is that the cut-off used for the definition of low birth weight almost equalizes the birth weight mean of samples. The association between preterm morbidity and low birth weight is well-known.[8] Regarding the concepts of birth weight and gestational age, it was found that small for gestational age newborns were also at an increased risk for neonatal morbidity.

Highlighting the importance of the discussion on the

administration of antenatal corticosteroids in the low preterm newborns, the results revealed it as a risk factor for respiratory morbidity when analyzing all samples. However, no statistical significance was found when analyzing within each subgroup of gestational age. Although the administration of antenatal corticosteroids is associated with decreased incidence of respiratory distress syndrome in very low birth weight and early preterm infants, the risk-benefit ratio is unclear in low preterm newborns.[9,10] The use of antenatal corticosteroids in low preterm newborns is controversial given the absence of a survival benefit, less absolute respiratory benefit, and greater concern about short-term adverse effects, such as neonatal hypoglycemia and long-term adverse effects.[11] Current recommendations point to the use of antenatal corticosteroids only for those at risk of preterm birth before 34 weeks and six days.[9,12]

The mode of delivery did not prove to be an independent risk factor. This was an unexpected result in this study since most previous studies identified cesarean section, especially delivery without labor, as a risk factor for neonatal morbidity, particularly respiratory distress syndrome. In this regard, an Italian study on more than 300 000 infants showed that cesarean section delivery increased the risk of respiratory distress syndrome both for the term and preterm newborns.[13]

Similarly, advanced maternal age and maternal comorbidities, such as gestational diabetes, were not associated with an increased risk of low preterm morbidity in this study. Older women have a significantly higher risk of prematurity and unfavorable global neonatal outcomes.[14] Advanced maternal age also poses a higher risk of gestational diabetes, which is solely a risk factor for neonatal morbidity. However, studies involving only low preterm newborns are missing. A recent study found that gestational diabetes is not a major contributor to respiratory distress syndrome in low preterm newborns. A possible theory is that this factor contributes to prematurity and, consequently, to a higher morbidity rate, with minor impact in the group of low preterms.[15]

Moreover, neither assisted reproductive therapy nor gemelarity was associated with higher rates of morbidity. Some previous studies found an increased risk of neonatal morbidity in the assisted reproductive therapy groups in comparison with the control (spontaneous conception) groups.[16,17] However, this risk is particularly affected by the higher rate of twin pregnancy and prematurity.[18] The results of analyzed studies, which included only preterm infants, showed that preterm infants conceived with assisted reproductive therapy did not have a poorer neonatal outcome, compared to those from spontaneous pregnancies, with neonatal morbidity in the assisted reproductive therapy group being even less frequent in more immature infants.[19] Although there is no pathophysiological explanation for these findings, the most accepted theory is that this difference could be related to better monitoring of assisted reproductive therapy pregnancies and multiple gestations, in which mothers often have earlier contact with the obstetric team and are monitored more closely.[20]

Neither spontaneous nor iatrogenic labor had an influence on the risk of neonatal morbidity in the present study sample. A recent retrospective study on very preterm neonates also did not find a significant difference in terms of short-term complications and mortality between spontaneous and iatrogenic labor. The exceptions were the higher risk of intraventricular hemorrhage in neonates born from spontaneous labor, whereas iatrogenic preterm birth was associated with a higher risk of necrotizing enterocolitis and coagulopathy.[21]

Regarding the limitations of the present study, one can refer to the transferring of newborns to other units which was mainly due to monetary concerns of the parents who could not afford the cost of more or less long-term care in our unit. However, the basic analysis of transferred patients (namely the five newborns who were transferred due to the need for a higher level of care) showed that they had the potential to meet the morbidity criteria. In fact, their exclusion led to the elimination of some patients with severe morbidities. It should also be noted that our unit provides both intermediate and intensive levels of care, which makes it difficult to accurately distinguish patients who need an only intermediate level of care from those who need intensive care. This distinction could have facilitated the characterization of morbidity in this group.

In conclusion, the increasing number of low preterm births necessitates the need for gaining more knowledge about morbidity in this age group. This study confirmed some previously known risk factors for morbidity in low preterm infants, allowing the relaunch of the discussion on the use of antenatal corticosteroids in this population. The fact that multiple gestations, assisted reproductive therapy, low birth weight, cesarean section, and fetal growth restriction did not prove to be morbidity determinants was among the major highlights of this study and should promote more investigation in this field. Further studies with larger sample size and a prospective design are needed to better characterize morbidity in late prematurity births.

Author Contribuitions

MPP, CF, ARF, ML, AR, CM and ASN participated in the study conception or design. MPP participated in acquisition of data. MPP, CE and CF participated in the analysis or interpretation of data. MPP and CE participated in the drafting of the manuscript. MPP, CF, ML, CM and ASN participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013).

Provenance and peer review

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Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Recém-Nascidos Prematuros Tardios: Já Sabemos Tudo Sobre Eles?

Introdução: A taxa de nascimento prematuro está a aumentar, e os recém-nascidos prematuros tardios correspondem a 75% de todos os partos prematuros. Os recém-nascidos prematuros tardios foram durante muitos anos considerados como recém-nascidos de termo, mas na última década as suas especificidades foram reconhecidas, principalmente no que se refere ao maior índice de complicações no período neonatal. O nosso objetivo é analisar quais os fatores associados a maior morbilidade neonatal nesta população.
Métodos: Realizámos um estudo de coorte com revisão dos registos médicos dos prematuros tardios (e respetivas mães) nascidos no nosso hospital durante um período de quatro anos. A análise de regressão logística binária foi usada para identificar preditores de morbilidade e controlar as variáveis confundidoras. Nível de significância considerado foi $p < 0,05$.
Resultados: Foram incluídos 576 recém-nascidos. Destes, 28% (n = 164) apresentaram alguma morbilidade, sendo a síndrome de dificuldade respiratória e a hiperbilirrubinemia as mais frequentes. A taxa de morbilidade variou inversamente com a idade gestacional. Ter uma menor idade gestacional, ser leve para a idade gestacional e a utilização incompleta de corticoterapia pré-natal foram identificados como fatores de risco para morbilidade ($p < 0,01$). A corticoterapia pré-natal foi aparentemente mais utilizada nos recém-nascidos que vieram a desenvolver síndrome de dificuldade respiratória ($p < 0,01$). Em contraste, o tipo de parto, reprodução medicamente assistida e morbilidade obstétrica não influenciaram a morbilidade neonatal.
Discussão: Confirmámos alguns fatores de risco bem conhecidos para morbilidade neonatal, contudo, outros determinantes citados em estudos anteriores não apresentaram evidência relativamente ao aumento do risco de morbilidade na nossa amostra, como o parto por cesariana, a gemelaridade ou a restrição do crescimento fetal.

Palavras-Chave: Doenças do Prematuro Fatores de risco; Morbilidade; Recém-Nascido; Recém-Nascido Prematuro