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Analysis of neonatal morbidity and mortality in late-preterm newborn infants

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Abstract

Objective: To compare mortality and the principal intercurrent clinical conditions suffered by late-preterm newborn infants born with gestational ages of 34 full weeks to 36 weeks and 6 days, and full term newborns.

Methods: This was a cross-sectional study of all preterm newborn infants born at a public hospital from August 2010 to August 2011. The study sample comprised late-preterm infants (cases) and a group of full term newborns (controls). Three controls were enrolled for each case. Maternal, gestational and neonatal variables were analyzed. Means and standard deviations were used to compare numerical variables between case and control groups using Student's *t* test and the Mann-Whitney test; Pearson's chi-square was used for categorical variables. Odds ratios and 95% confidence intervals were calculated to estimate risk.

Results: The study sample comprised 239 late-preterm infants and 698 full term newborns. Mothers aged over 35 years and/or with a history of previous premature deliveries had a higher proportion of late-preterm children. The following gestational variables were associated with late-preterm delivery: hypertension, infectious diseases, rupture of membranes more than 18 hours previously and multiple pregnancies. When compared with full term newborns, late-preterms were statistically more likely to be subject to hypothermia/hyperthermia, hypoglycemia, respiratory pathologies, resuscitation in the delivery room, phototherapy, supplementary feeding, mechanical ventilation, venous infusions, antibiotics and admission to the neonatal intensive care unit, resulting in a nine times greater neonatal mortality rate. Intercurrent conditions were inversely related to gestational age.

Conclusions: Late-preterm newborn infants had a mortality rate nine times that of full term infants and were exposed to a greater risk of intercurrent conditions during the neonatal period. These intercurrent conditions were inversely related to gestational age.

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Introduction

Prematurity is the principal cause of infant mortality and of several serious neurocognitive, respiratory and ophthalmic morbidities. As a result, prematurity has been recognized as a severe public health problem.[1-3]

The incidence of premature birth has been increasing over recent decades and in the United States incidence increased from 10.6% in 1990 to 12.8% in 2006.[4] The observed increase is primarily the result of the inclusion of a group of borderline preterm infants who have been classified as late-preterm infants (LPTI) since 2005,[5] when the definition of LPTI was established as those infants born with gestational ages (GA) of 34 full weeks to 36 weeks and 6 days. This new classification was created in order to focus on this group of borderline infants who are still

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premature and, as a result, should not receive the same care as full term infants (FTI).

There were approximately 4 million live births in the United States in 2003 and 12.3% of these were preterm infants, while 75% of these preterms were, in turn, classified as LPTI.[6] The LPTI group increased by around 40% between 1998 and 2003 in the United States, with 31% of preterms and 11% of extreme PTI.[7]

A number of factors have been linked with the increase in premature births: new fertilization methods have increased the number of twin and multiple pregnancies; an increasing number of women are having children after the age of 35; and there is an increasing number of medical indications for interrupting pregnancy, which are the result of increased use of technology to monitor pregnancies.[8]

However, it is only in recent years that this group has been studied systematically, with the results of some population studies showing that morbidity and mortality is significantly higher in this population than among FTI, with a seven times greater risk of intercurrent conditions during the neonatal period. Related findings include lower Apgar scores, hypothermia/hyperthermia, suction and deglutition deficiencies, hypoglycemia, hyperbilirubinemia, respiratory pathologies, increased risk of infections and a higher rate of neurological disorders.[6,9-13]

Multiple fetus pregnancies are 15 times more common among LPTI because the majority of twins and multiples are born at 34 to 36 weeks.[14] Infant and neonatal mortality among children born with GA from 34 to 36 weeks is three times that observed in FTI.[11]

The objective of thus study was therefore to identify and compare mortality rates and the frequency of principal intercurrent clinical conditions of the neonatal period between LPTI and FTI from a low-income population in Brazil's South administrative region.

Methods

This was a cross-sectional study of all LPTI infants born from August 2010 to August 2011 at the Gynecology and Obstetrics Department of the Caxias do Sul Hospital Geral (HG) in Rio Grande do Sul state, Brazil. This hospital only treats patients on the Brazilian National Health Service (Sistema Único de Saúde, SUS).

The study population is a convenience sample comprising neonates born in the HG maternity unit during the study period. For the purposes of analysis, the sample was divided into an LPTI group (cases) and a FTI group (controls). Three infants were enrolled into the control group immediately after each LPTI was born.

The investigators followed the infants in the sample throughout their stays in the maternity unit and/or neonatal intensive care unit (NICU), up until hospital discharge.

Data were collected from infants' and mothers' medical records and supplemented with additional information collected at discharge using a structured form covering the variables of interest. These data were input to a database using the Statistical Package for the Social Sciences, version 18.0, for later statistical analysis.

Variables relating to the mothers, their pregnancies and their infants were analyzed.

The maternal and gestational variables studied were: age (years), educational level, family income, number of pregnancies, prior history of miscarriages, still births and premature deliveries; type of delivery (normal or caesarean); intercurrent clinical conditions observed during gestation – diabetic syndromes, hypertensive syndromes, urinary infections at any point during pregnancy, syphilis, human immunodeficiency virus (HIV), toxoplasmosis, heart disease, hepatitis B; premature rupture of membranes (PROM) for longer than 18 hours; placental abruption (PA); umbilical cord pathologies (cord coiling, true knot, cord prolapse); drug use (alcohol, cocaine, crack, marijuana); smoking.

The neonatal variables studied were: days in hospital; sex; birth weight; GA (calculated from date of last menstruation and early obstetric ultrasonography and/or pediatric assessment using the Capurro method); ratio between GA and birth weight; admission to NICU; resuscitation in the delivery room; 1 and 5-minute Apgar scores; hypothermia/hyperthermia (hypothermia: body temperature below 36 ºC, hyperthermia: temperature above 37.5 ºC); hypoglycemia (glucose below 40 mg/dL); hyperbilirubinemia requiring phototherapy; breastfeeding problems, problems requiring dietary supplementation; mechanical ventilation; parenteral nutrition; respiratory pathologies – transient tachypnea of the newborn (TTNB), hyaline membrane disease (HMD), pneumonia, pulmonary hypertension, apnea of prematurity; infection; venous infusion; and deaths and their causes.

The variable maternal hypertension included preexisting hypertension, mild and severe pre-eclampsia, preexisting hypertension in combination with severe pre-eclampsia and gestational hypertension, according to criteria described in the Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.[15] The variable diabetes included cases of gestational diabetes mellitus and diabetes mellitus types 1 and 2.

Data on syphilis, HIV, toxoplasmosis, hepatitis B, illicit drug use and DPP were taken from mothers' Expectant Mother's Records or from the Perinatal Records held at the High Risk Expectant Mothers' Clinic at the HG. Means and standard deviations were used to compare numerical variables between case and control groups, using Student's *t* test and the Mann-Whitney test, and Pearson's chi-square

was used for categorical variables. Odds ratios and 95% confidence intervals were calculated to estimate risk. The significance level adopted was 5%.

This study was approved by the Teaching and Research Committee at the Caxias do Sul HG and by the Research Ethics Committee at the Universidade de Caxias do Sul.

Results

A total of 937 infants were recruited for the study, 239 LPTI in the case group and 698 FTI in the control group. There were no differences between the two groups in terms of mean maternal age; 26.6±7.4 years in the LPTI group vs. 25.6±6.9 years in the FTI group (p = 0.055). Notwithstanding, mothers over 35 years old were associated with a higher rate of LPTI (p = 0.04).

There was no difference between the groups in terms of family income: R$ 1,303.10±751.00 vs. R$ 1,312.93±722.00 in the control group (p = 0.86). There was no difference in mothers' educational level either and in both groups the largest subset comprised mothers who had not completed primary education, at 39.7% of the mothers of LPTI and 32.9% of the mothers of FTI.

With regard to obstetric history, the LPTI mothers had had 2.44±1.7 previous pregnancies and the FTI mothers had had 2.38±1.5 previous pregnancies. There was no statistical difference between the groups in terms of history of miscarriages (17.2 vs. 15.0%) or still births (1.3 vs. 1.4%). However, the mothers of LPTI had had twice as many previous premature deliveries (5.4 vs. 2.7%) than the mothers of FTI (p = 0.04).

Table 1 shows the results of the comparison of the groups in terms of variables relating to pregnancy and delivery.

Premature birth was associated with hypertension, PROM and maternal infections.

There was a predominance of cesarean deliveries in the LPTI group and umbilical cord pathologies were more common in the FTI group.

There were no differences between the LPTI and the controls in terms of the variable sex of infant (49.8 vs. 49.1%). Mean weight of the LPTI was 2,346±486 g, versus

Table 1 - Distribution of live births by characteristics of pregnancies and deliveries

Variables	Cases* (n = 239)		Controls* (n = 698)		OR (95%CI)	p
	n	%	n	%		
Maternal hypertension	65	27.2	99	14.2	2.25 (1.58-3.22)	0.0001
Diabetes	19	7.9	67	9.6	0.81 (0.47-1.38)	0.51
Heart disease	2	0.8	3	0.4	1.95 (0.32-11.75)	0.60
Urinary infection	63	26.5	148	21.2	1.33 (0.95-1.87)	0.1
HIV	10	4.2	7	1.0	4.30 (1.62-11.43)	0.003
Other infections†	19	7.9	26	3.7	2.23 (1.21-4.11)	0.01
Smoking	51	21.3	137	19.6	1.11 (0.77-1.59)	0.57
Drug use when pregnant‡	51	21.3	143	20.5	1.05 (0.73- 1.50)	0.78
PA	3	1.3	3	0.4	2.94 (0.59-14.69)	0.17
Umbilical cord pathologies	28	11.7	139	19.9	0.53 (0.34-0.82)	0.004
PROM > 18 h	32	13.4	15	2.1	7.03 (3.73-13.25)	0.0001
Caesarean	141	59.0	275	39.7	2.18 (1.62-2.95)	0.0001
Multiple birth	27	11.3	5	0.7	17.6 (6.7-46.40)	0.0001

95%CI = 95% confidence interval; HIV = human immunodeficiency virus; OR = odds ratio; PA = placental abruption; PROM = premature rupture of membranes.
* Differences are the result of incomplete or lost records.
† Variable includes cases of hepatitis B, syphilis and toxoplasmosis.
‡ Variable includes alcohol, cocaine, crack and marijuana use.
Hypertension: variable includes preexisting hypertension, mild and severe pre-eclampsia, preexisting hypertension in combination with severe pre-eclampsia and gestational hypertension.
Diabetes: includes cases of gestational diabetes mellitus and diabetes mellitus types 1 and 2.

3,220±476 g for controls. Mean GA was 35.5 weeks for cases and 39 weeks for controls.

Table 2 shows a comparison of the two groups in terms of neonatal variables.

Mean 1-minute Apgar scores were 7.4 for the LPTI and 8.0 for the control group ($p < 0.0001$). Mean 5-minute Apgar scores also differed between the groups: 8.5 for LPTI vs. 9.0 for FTI ($p < 0.0001$).

There was a higher proportion of small for GA (SGA) infants among the LPTI, whereas in the control group large for GA (LGA) infants predominated.

The LPTI had higher rates of resuscitation in the delivery room, more frequent episodes of hypoglycemia and greater hypothermia/hyperthermia, with statistically significant differences in relation to the control group.

A higher proportion of the LPTI needed phototherapy to treat neonatal jaundice and LPTI were more likely to need formula to supplement their diets. The members of the LPTI group were also more likely to need parenteral nutrition and venous infusions.

With regard to neonatal diseases, it was observed that incidence rates of HMD, TTNB, pneumonia and apnea of prematurity were all higher among the cases. Almost 25% of the premature infants needed to be given antibiotics whilst in the maternity unit, compared with 3% of the FTI.

Table 3 lists the results for the most important neonatal variables studied, stratified by GA. We observed that frequency and relative risk (compared with the control group) of intercurrent neonatal conditions reduced with each extra week of GA. Even so, LPTI born at 36 weeks gestational age were still significantly different from the FTI in terms of a large number of variables.

Nine of the 12 deaths observed during the study were in the LPTI group. Severe malformations were the basic cause of death in 10 cases, seven of which were in the LPTI group. In two cases sepsis was the cause of death.

Table 2 - Distribution of live births by neonatal characteristics

	Cases* (n = 239)		Controls* (n = 698)			
Variables	**n**	**%**	**n**	**%**	**OR (95%CI)**	**p**
SGA infants	58	26.1	42	7.4	4.4 (2.85-6.79)	0.0001
LGA infants	13	7.3	132	20.2	0.31 (0.17-0.57)	0.0001
5 minute Apgar < 7	10	4.2	11	1.6	2.71 (1.13-6.46)	0.03
Resuscitation in DR	45	18.9	65	9.3	2.27 (1.50-3.43)	0.0001
Temperature < 36 ºC	106	44.7	151	21.7	2.92 (2.13-3.99)	0.0001
Temperature > 37.5 ºC	29	12.2	19	2.7	4.96 (2.72-9.03)	0.0001
Glycemia < 40	48	20.3	29	4.2	5.85 (3.59-9.54)	0.0001
Phototherapy	85	35.9	33	4.8	11.2 (7.22-17.37)	0.0001
Complementary feeding	146	62.1	73	10.5	13.97 (9.77-19.9)	0.0001
Mechanical ventilation	18	7.5	5	0.7	11.28 (4.14-30.75)	0.0001
Parenteral nutrition	28	11.7	8	1.1	11.44 (5.13-25.49)	0.0001
Venous infusion	112	46.9	23	3.3	28.88 (15.9-42.12)	0.0001
HMD	7	2.9	0	0	4.00 (3.56-4.48)	0.0001
Transient tachypnea	62	25.9	5	0.7	48.5 (19.23-122.5)	0.0001
Pneumonia	10	4.2	7	1.0	4.31 (1.62-11.45)	0.003
Pulmonary hypertension	3	1.3	1	0.1	8.86 (0.91-85.5)	0.053
Apnea of prematurity	15	6.3	2	0.3	23.3 (5.28-102.6)	0.0001
Antibiotics given	59	24.7	20	2.9	11.11 (6.52-18.93)	0.0001
NICU admission	129	54.0	31	4.4	25.19 (16.21-39.1)	0.0001
Death	9	3.8	3	0.4	9.10 (2.44-33.91)	0.0001

95%CI = 95% confidence interval; DR = delivery room; HMD = hyaline membrane disease; LGA = large for gestational age; NICU = neonatal intensive care unit; OR = odds ratio; SGA = small for gestational age.
* Differences are the result of incomplete or lost records.

More than half of the LPTI needed to be admitted to the NICU and LPTI had a mean hospital stay of 8.1 days, vs. 2.9 days for the control group (p < 0.0001).

Discussion

This study has demonstrated the importance and magnitude of the risks of intercurrent conditions to which infants born at 34 to 36 weeks' gestation are subject.

The etiology of LPTI births needs to be studied in greater depth. Reddy et al. classified premature births in a United States cohort into one of the four groups according to cause of premature delivery: maternal medical conditions, obstetric complications, major congenital anomalies or isolated spontaneous deliveries, assigning the remaining 23% of births that did not fit any of these categories to a fifth group entitled "no recorded indications."[16] Laughon et al. reported similar findings, showing that a considerable

Table 3 - Distribution of live births by neonatal characteristics, stratified by gestational age

	Gestational age (weeks)					
	34		35		36	
Variables	n (%)	RR (95%CI)	n (%)	RR (95%CI)	n (%)	RR (95%CI)
Resuscitation in DR	11 (26.8)	3.5 (1.7-7.4)	22 (21.4)	2.63 (1.54-4.49)	12 (12.6)	1.40 (0.72-2.70)
Temperature < 36 ºC	25 (62.5)	5.9 (3.0-11.6)	50 (48.1)	3.32 (2.17-5.08)	31 (33.0)	1.76 (1.10-2.81)
Temperature > 37.5 ºC	6 (15.0)	6.2 (2.3-16.6)	12 (11.5)	4.62 (2.17-9.82)	11 (11.7)	4.69 (2.15-10.20)
Glycemia < 40	8 (20.5)	5.8 (2.5-13.9)	19 (18.3)	5.10 (2.74-9.49)	21 (22.3)	6.56 (3.56-12.10)
Phototherapy	20 (50.0)	19.9 (9.8-40.6)	39 (37.5)	11.96 (7.04-20.30)	26 (27.7)	7.62 (4.30-13.50)
Supplement in addition to milk	32 (82.1)	39.9 (17.0-93.9)	62 (59.6)	12.91 (8.13-20.50)	52 (55.9)	11.09 (6.88-17.88)
Venous infusion	30 (73.2)	79.6 (35.5-178)	50 (48.1)	27.05 (15.35-47.66)	32 (33.7)	14.84 (8.18-26.90)
Hyaline membrane disease	3 (7.3)	19.2 (14.1-26.3)	3 (2.9)	7.88 (6.56-9.45)	1 (1.1)	8.39 (6.94-10.14)
Transient tachypnea	15 (36.6)	79.6 (26.8-235)	30 (28.8)	55.94 (21.06-148.5)	17 (17.9)	30.07 (10.80-83.76)
Pneumonia	1 (2.4)	2.45 (0.29-20.4)	7 (6.7)	7.09 (2.43-20.65)	2 (2.1)	2.11 (0.43-10.32)
Apnea of prematurity	5 (12.2)	48.1 (9.0-256.5)	6 (5.8)	21.21 (4.22-106.5)	4 (4.2)	15.23 (2.75-84.32)
Antibiotics given	16 (39.9)	21.6 (10.0-46.6)	24 (23.1)	10.12 (5.35-19.14)	19 (20.0)	8.43 (4.31-16.50)
Admitted to NICU	34 (82.9)	103.8 (42.6-252.8)	58 (55.8)	26.96 (15.89-45.75)	37 (38.9)	13.64 (7.89-23.58)
Death	3 (7.3)	18.2 (3.5-93.2)	4 (3.8)	9.22 (2.03-41.83)	2 (2.1)	5.01 (0.82-30.40)

95%CI = 95% confidence interval; DR = delivery room; NICU = neonatal intensive care unit; RR = relative risk.

number of preterms are born by caesarean with no record of any indication for caesarean delivery, which suggests that they are potentially avoidable.[17]

Caesarean deliveries predominated in this study too, which is probably because high-risk expectant mothers are referred to the HG maternity unit from the entire Northeast region of the state.

The research conducted at the HG found that LPTI births were associated with expectant mothers over the age of 35, with maternal pathologies during pregnancy, including hypertension and infections, and with multiple births, all of which have also been described by other authors.[8,18-20]

On the subject of intercurrent neonatal conditions, the medical literature is unanimous in describing a large number of neonatal problems among LPTI, both soon after birth and over the long term; in this group morbidity and mortality are inversely related to GA, as can be observed in Table 3.

Carrie et al. found that the risk of morbidity among LPTI was seven times the risk to which FTI were exposed. This risk doubled with every week that GA reduced, to the extent that a premature infant's risk of morbidity was 51.7% at 34 weeks' GA, 25.6% at 35 weeks and 12.1% at 36 weeks.[6]

A large number of the infants in this study had respiratory pathologies, with TTNB predominating, and recurrent episodes of apnea and HMD were also important, which demonstrates the immaturity of these newborns' respiratory systems and has also been described by other authors.[21-24]

A significant number of infants had hypothermia/hyperthermia, hypoglycemia and/or hyperbilirubinemia requiring phototherapy. Hyperbilirubinemia tends to be more intense and longer-lasting among LPTI and there is a risk of cerebral involvement. Infants born at 36 weeks' GA are at eight times the risk of developing hyperbilirubinemia beyond 20 mg/dl than infants born at 41 weeks' GA.[25]

One quarter of the LPTI in this study were also classified as SGA. Pulver et al. reported that the risk of death during the first month of life was 44 times greater among LPTI classified as SGA than among LPTI with weights appropriate for their GA.[26]

The Caxias do Sul HG has Baby Friendly Hospital certification and so any dietary supplementation is given in adherence to very strict standards and can only be used in specific circumstances. Notwithstanding, a large proportion of the LPTI (62%) needed to be given formula to supplement breastmilk.

In addition to feeding problems caused by neonatal pathologies, the immaturity of preterms' gastrointestinal tracts and the consequent lack of coordination of suction and deglutition mechanisms are often barriers to establishing successful breastfeeding, which in turn leads to excessive weight loss and dehydration during the first days of life.[10] The indications for giving supplementary formula were not investigated, which constitutes a limitation to this study.

Almost half of the LPTI required some type of venous infusion while in hospital and 54% of them were admitted to the NICU.

Risk of death was nine times greater for LPTI than for FTI. Other authors have reported relative risks of death ranging from 1.5 to 6.3, which are lower than the figure calculated here.[26,27]

Tomashek et al. conducted a study that showed that early neonatal mortality, late neonatal mortality and postneonatal mortality were respectively six, three and two times greater among LPTI.[28] Three times as many LPTI than FTI die during infancy and the most common causes of death are malformations, sepsis and sudden infant death syndrome.[26] Similar data were observed in this study, with 10 deaths attributed to congenital malformations and two to sepsis.

The erroneous concept of LPTI as almost full term infants means that they are discharged prematurely, following the routine protocols set out for FTI. Discharging these infants before 48 hours precludes the opportunity of identifying morbidities early enough to allow timely intervention. It is not therefore surprising that these infants have a much higher rate of hospital readmission. Common causes of readmission are jaundice, infection, feeding problems and excessive weight loss.[29]

In view of the above, there is a clear need for discharge criteria developed specifically for LPTI. These criteria should include: discharge after a minimum of 48 hours; normal vital signs for 12 hours before discharge; 24 hours feeding successfully; weight loss below 7% while in the maternity unit; a breastfeeding assessment conducted by an experienced pediatrician or nurse; a hyperbilirubinemia risk assessment; and an evaluation of social and family risk factors.

It is important to explain to parents the vulnerabilities to which their children are subject and to stress to them the importance of monitoring feeding, weight gain, jaundice and apnea. These intercurrent conditions are frequently responsible for a pediatric visit within 48 hours of discharge.

It was beyond the scope of this study to investigate causes of rehospitalization or the long-term risks to which these infants are exposed.

Another limitation of this study is that the reason for premature delivery was not investigated. Recent studies have shown that more than 50% of LPTI deliveries are not the result of scientific, evidence-based, medical indications. This subset is made up of older mothers, mothers with health insurance and mothers of twins and multiples and their deliveries are very often by caesarean. It is notable

that 56% of LPTI deliveries that are not medically indicated result in infants being admitted to NICUs, compared with 31% of infants delivered prematurely when medically indicated.[30]

It is therefore important that further studies be conducted to: (1) establish and evaluate strategies, routines and protocols for premature interruption of pregnancy that are more rigorous and are based on scientific evidence, thereby reducing the number of premature births and (2) develop obstetric protocols that increase the precision of methods for estimating GA, such as, for example, routine ultrasound in the first trimester, which is important to decision-making when considering interrupting a pregnancy before full term.

Another intervention that merits greater study is the possibility of using antenatal corticoid after 34 weeks to reduce respiratory pathologies and prevent a significant number of deaths in this group of neonates.[5]

Analysis of the data shows that LPTI suffer a large number of intercurrent conditions during the neonatal period, especially increased likelihood of resuscitation in the delivery room, hypothermia/hyperthermia, hypoglycemia, jaundice requiring phototherapy, respiratory pathologies, antibiotic use, supplementary feeding, mechanical ventilation, venous infusion and admission to a NICU, contributing to a neonatal mortality rate nine times greater than that of FTI.

Late-preterm infants are therefore a high-risk group of children and need special attention while in hospital, including delayed discharge and pediatric follow-up very soon after discharge.

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