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**Neonatal outcome associated with singleton birth at 34 to
41 weeks of gestation.**



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4 **Neonatal outcome associated with singleton birth at 34 to 41 weeks of**
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6 **gestation.**
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58 **Short running head: outcome of late-preterm and early-term neonates.**
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SUMMARY

Background: Approximately 75% of preterm births are late-preterm (34^{0/7} to 36^{6/7} weeks' gestation). This group has usually been considered as a whole in studies assessing the outcome of these preterm infants by comparison with term infants. However, the respective contribution to prognosis of each week of gestation has not been fully clarified.

Methods: A population-based study of 150,426 live-born singleton neonates with gestational ages ranging from 34 to 41 weeks of gestation.

Results: The rate of severe respiratory disorders (treated by mechanical ventilation and/or nasal continuous positive airway pressure) markedly declined with gestational age from 19.8% at 34 weeks to 0.28% at 39-41 weeks. Between 34 to 38 weeks, each additional week diminished the relative risk (crude or adjusted) of severe respiratory disorders by a factor varying from 2 to 3. The rate of poor prognosis (death and/or severe neurological condition) significantly declined between 34 to 38 weeks and remained stable thereafter. A multivariate analysis showed that antepartum hemorrhage and hypertensive disorders during pregnancy were significantly associated with severe respiratory disorders and poor outcome. Diabetes was an additional factor associated with severe respiratory disorders.

Conclusions: Future studies should delineate more precisely the respective contribution of gestational age, maternal complication and induced delivery in the prognosis of infants born between 33 and 39 weeks' gestation.

KEY WORDS

Late-preterm; early-term; late-term; respiratory disorders; mortality; poor prognosis.

INTRODUCTION

The preterm birth rate has increased in developed countries over the past decade (1) and the US rate reached 12.7% in 2005 (2). Most studies have focused on infants born before 33 weeks of gestation because they are at high risk of mortality and serious morbidity. However, approximately 75% of preterm births are late-preterm (34^{0/7} to 36^{6/7} weeks of gestation) (3).

Late-preterm infants are 3.5 times more likely to have clinical problems than term infants and their neonatal mortality is 4.6 times higher (4). Therefore, these infants represent a substantial proportion of hospitalizations after delivery (5). The outcome of late-preterm infants can be related to physiological immaturity but also to maternal complications leading to a preterm birth (6, 7), a condition making the antenatal assessment of prognosis more difficult.

Moreover, early-term neonates (37^{0/7} to 38^{6/7} weeks' gestation) account for 17.5% of live born infants (8) and were found to experience more transient tachypnea of the newborn, persistent pulmonary hypertension and a longer hospital stay than infants born at 39 weeks of gestation (9 - 13).

Even though a continuum for both mortality and morbidity according to gestational age has been underlined by the National Institute of Child Health and Human Development (14), the respective contribution to prognosis of each week above 33 weeks' gestation has not been fully clarified, as recently pointed out by Kashu et al. (15). Analysis of perinatal morbidities, on the basis of each week of gestation rather than grouping infants by weeks of gestation at delivery (as late-preterm, early-term and late-term infants) could be more relevant.

Therefore, the aim of this study was to assess the neonatal outcome associated with each week of gestational age over 33 weeks.

METHODS

We used a population-based cohort of neonates delivered in all hospitals of Burgundy, a French region with approximately 18,000 births per year. The perinatal network of Burgundy included 18 public and private hospitals that were categorized into 3 levels: (a) level III for neonatal intensive care (n = 1); (b) level II for high dependency care (n = 7); and (c) level I for normal care (n = 10).

Data on the population of all mother-infant pairs cared for in Burgundy hospitals between January 1, 2000, and December 31, 2008, were obtained from a regional database which was set up with the approval of the National Commission for Data Protection (CNIL ## 98003718). The Burgundy perinatal data system is a longitudinally linked data system of mothers and their children up to discharge from maternity and neonatal units (16, 17). The list of variables under study included those presented in Tables 1 and 2, congenital malformations and multiplicity. The gestational age in completed weeks was assessed on the basis of the mother's last menstrual period, as confirmed or modified when necessary by routine early antenatal ultrasound examination. In Burgundy, as in other French regions, 90% of pregnant women experience an early ultrasound examination (18). Data on gestational age was missing in 0.30% of cases. Moreover, gestational age was implausible considering birth weight in 0.37%, using a method developed by Platt et al. (19). Corrections regarding implausible gestational ages were obtained from medical files.

Multi-fetal births, severe congenital malformations, chromosomal abnormalities and metabolic diseases were not included in the study because gestational age - related morbidity and mortality in those infants significantly differ from that of singletons (10, 20).

Definitions

Prematurity

Late-preterm, early-term and late-term infants were defined respectively by gestational age at 34^{0/7} - 36^{6/7} ; 37^{0/7} - 38^{6/7} ; 39^{0/7} - 41^{6/7} weeks of gestation, (14).

Maternal conditions

We examined maternal age and complications of pregnancy including hypertensive diseases of pregnancy (combining chronic hypertension, pregnancy-induced hypertension, pre-eclampsia and eclampsia), diabetes (combining gestational and established diabetes), placental abruption, placenta praevia, preterm and premature rupture of membranes (PPROM), antenatal diagnosis of fetal weight restriction and chorioamnionitis.

Premature rupture of membranes was defined by rupture of membranes before the first stage of labour (by more than 18 hours). PPRM referred to rupture of membranes before 37 weeks of gestation.

Chorioamnionitis was defined as infection or suspected infection of the amniotic cavity as determined by clinical criteria by the attending physician.

Small-for-gestational-age newborns were identified when birth weight was below the 10th percentile according to neonatal growth standards based on a healthy population of mothers (21).

Birth conditions

Abnormal fetal heart rate recordings, mode of delivery (vaginal or caesarean section) and instrumental maneuvers at delivery were recorded. Asphyxia at birth was defined as an Apgar score below or equal to 3 at 1 min of life.

Outcomes

Poor prognosis was defined at the end of neonatal hospitalization by death and/or severe neurological condition (ischemic encephalopathy; intraventricular hemorrhage grades 3-4 according to Papile et al. (22) and/or cystic periventricular leukomalacia in preterm infants and/or seizures). Transfontanelar echography was systematically performed in newborns with neurological symptoms.

Severe respiratory disorder was defined as a respiratory distress treated by mechanical ventilation and/or nasal continuous positive airway pressure.

Statistical Analyses

Qualitative variables were presented as percentages and continuous variables as mean and standard deviations. Bivariate analyses were conducted using chi-square test or Fisher's exact test for comparisons of percentages, and Student's t-test or Mann-Whitney's test for comparisons of means.

Multivariate analyses were conducted using modified Poisson regression models (23) with correction for overdispersion, separately for each outcome. The final multivariate models were obtained using backward selection procedure. The covariates with a p-value ≤ 0.20 in bivariate analyses, and covariates considered as risk factors in the literature, were included in the initial model, and removed if they did not reach a p-value below 0.05. First order interactions between each covariate were systematically tested in the final models and excluded if they did not reach statistical significance at alpha level of 0.05. Crude and adjusted relative risks (cRR and aRR, respectively) and their 95% Confidence Intervals (CI) were estimated.

Statistical analyses were performed using SAS 8.2 (SAS Institute Inc).

RESULTS

Among 161,748 neonates born during the study period, 6,083 (3.76%) were excluded for gestational age at delivery of less than 34^{0/7} weeks or more than 41^{6/7} weeks, 384 (0.24%) for stillbirth, 298 (0.18%) for major fetal anomaly, 4,166 (2.58%) for multiple births and 391 (0.24%) for lack of information on neonatal outcome. Overall, 150,426 newborns were included in this study.

Table 1 shows the characteristics of the study population. Late-preterm, early-term and late-term infants represented respectively 4.0%, 20.7% and 75.3% of the study population. The incidence of all antenatal complications declined linearly from 34 to 39-41 weeks of gestation. The incidence of mothers without gestational complication was significantly different among the late-preterm, early-term and late-term groups (43.4% vs 69.6% vs 84.2%, $p < 0.0001$). Gestational age was positively correlated with vaginal delivery with or without instrumental maneuver and negatively correlated with emergency caesarean section ($p < 0.0001$).

Figure 1 shows the rates of severe respiratory disorders and poor prognosis for each week of gestational age. A poor prognosis was recorded in 0.80% of late-preterm infants, 0.18% of early-term infants and 0.16% of late-term infants ($p < 0.0001$). When examining each week of gestation, the rate of poor prognosis significantly declined from 1.69% at 34 weeks to 0.27% at 37 weeks and remained stable thereafter. The rate of severe respiratory disorders was 8.3% of late-preterm, 0.84% of early-term and 0.28% of late-term infants ($p < 0.0001$). Furthermore, the rate of severe respiratory disorders continuously declined with gestational age from 19.8% at 34 weeks to 0.28% at 39-41 weeks.

Table 2 shows crude and adjusted relative risks for the two outcomes. Between 34 and 37 weeks of gestation, the risk of poor prognosis gradually diminished, but nevertheless remained higher than for infants born at 39-41 weeks of gestational age. Even after

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3 adjustment for antenatal diseases, the risk of poor prognosis was higher (aRR= 1.6; 95% CI =
4 1.1 – 2.3) at 37 weeks of gestation compared with infants born at 39-41 weeks. The adjusted
5 relative risk for poor prognosis was 3.6 (95 % CI: 2.5 – 5.3) in late-preterm infants and 1.1
6 (95% CI: 0.8 – 1.4) in early-term infants, compared with the late-term infants.
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13 Between 34 and 38 weeks, each additional week decreased the relative risk (crude or
14 adjusted) of severe respiratory disorders by a factor varying from 2 to 3 (Table 2). The
15 adjusted relative risk for severe respiratory disorders was 23.9 (95% CI: 20.5 – 27.8) in late-
16 preterm infants and 2.7 (95% CI: 2.3 – 3.2) in early-term, compared with late-term infants.
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23 Poor prognosis was associated with severe respiratory disorders in 37.5% for late-
24 preterm, 37.5% for early-term and 19.7% for late-term infants. The rate of poor prognosis
25 among the neonates with severe respiratory disorders was 6.8% versus 0.1% in infants
26 without respiratory disorders ($p < 0.0001$).
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33 The rate of hospitalization at birth was: 96.9% at 34 weeks of gestational age; 80.1% at
34 35 weeks; 43.2% at 36 weeks; 17.8% at 37 weeks; 8.8% at 38 weeks and 5.8% at 39-41
35 weeks ($p < 0.0001$).
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43 DISCUSSION

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46 This study confirmed that late-preterm infants ($34^{0/7}$ to $36^{6/7}$ WG) were more likely to
47 have severe respiratory disorders (i.e. treated with ventilator and/or nasal continuous positive
48 airway pressure) and poor prognosis than late-term infants born at 39-41 weeks of gestation.
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51 Furthermore, this study provided important additional information showing that: birth at 37
52 weeks of gestation was associated with an increased incidence of poor prognosis; infants born
53 at 37 and 38 weeks of gestation were at increased risk of severe respiratory disorders; up until
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3 39 weeks of gestation, each additional week contributed to improve the clinical condition of
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5 the newborns.
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9 The strengths of this study lie in the large population-based cohort of infants and an analysis
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11 by week of gestation. However, its limitation was the retrospective analysis of maternal and
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13 neonatal data, collected prospectively. That condition was previously associated with a lack of
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15 sufficient information on antenatal corticosteroids (1). The 9 year-period of this study might
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17 have been associated with slight changes in clinical practice. However, the study period has
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19 not been associated with overt changes in clinical practice or changes in the distribution of
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21 gestational age in this regional population.
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27 In this study, the incidence of severe respiratory conditions steadily decreased from the late-
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29 preterm group (8.3%), to the early-term group (0.84%) and to the late-term group (0.28%).
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31 This data matches the gestational age-related decline in incidence of respiratory disorders
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33 (respiratory distress syndrome, transient tachypnea of the newborn, persistent pulmonary
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35 hypertension) and need for mechanical ventilation reported in previous epidemiological
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37 studies (11; 24 - 27). This trend may be illustrated by comparison to incidences recorded in
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39 the United States (26) and Italy (27): respectively 20.6% and 22.1% among babies born at 33-
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41 34 weeks; 7.3 and 8.3% at 35-36 weeks; 0.6 and 2.9% at 37-42 weeks.
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47 Compared to at term infants (37-40 weeks), the occurrence of respiratory distress has been
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49 previously evaluated at 4.5-fold higher in the 33-36 week infants (15) and even at 9.1-fold
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51 higher in the 35-36 week infants (25). Compared with late-term infants (39-41 weeks), the
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53 adjusted relative risk for severe respiratory disorders in this study was 2.7 in early-term and
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55 23.9 in late-preterm infants. These results suggest that the risk for respiratory morbidity in
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57 late-preterm infants has been previously underestimated because early-term infants were
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59 included in the control group.
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3 This study also showed that the rate of severe respiratory diseases approximately doubled for
4 each reduced week of gestation from 39 to 34 weeks. Similarly, Shapiro-Mendoza et al. (7)
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6 also observed that the rate of life-threatening conditions doubled for each reduced week of
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8 gestation before 38 weeks' gestation. The Kaiser Permanente Cohort showed that an increased
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10 risk of respiratory disease was associated with decreasing gestational age before 37 weeks (9),
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12 while our cohort disclosed that an increased risk of severe respiratory disease was still
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14 apparent at 38 weeks. These overall data strongly support that birth before 39 weeks of
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16 gestation cannot be considered as low-risk, and emphasize the need to consider each week of
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18 gestation separately.
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26 This study found that the incidence of poor prognosis (severe neurological disease and/or
27 death) was not higher at 38 weeks, while it increased steadily below 38. Furthermore, a 3.5-
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29 fold higher poor prognosis was observed in the late-preterm group compared to the late-term
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31 group. Sources from Canada (29), the United States and Europe (15, 30 - 32) disclosed
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33 comparable profiles for gestation-specific neonatal mortality rates. For instance, a Canadian
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35 study (15) found that the neonatal mortality rate was 5.5 times higher in a 33-36 week group
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37 compared with a 37-40 week group. Another study (30) highlighted that mortality in the late-
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39 preterm group contributed to 10 % of overall neonatal mortality, a finding close to the 12.2%
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41 observed in the Burgundy population (personal data).
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49 Recently, Shapiro-Mendoza et al. (7) contributed important information by showing that both
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51 late-preterm birth and, to a lesser extent, maternal medical conditions are each independent
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53 risk factors for severe newborn morbidity, especially when late-preterm infants have been
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55 exposed to antepartum hemorrhage and hypertensive disorders of pregnancy. Using a more
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57 precise classification of clinical neonatal conditions, our study confirmed that antepartum
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59 hemorrhage and hypertensive disorders of pregnancy were associated with severe respiratory
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3 disorders and poor prognosis. Diabetes was an additional factor associated with severe
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5 respiratory distress.
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9 The need for admission in a neonatal unit linearly increased from 39-41 weeks of gestational
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11 age (5.8%) to 37 weeks (17.8%) and to 34 weeks (96.9%). Similarly, a large epidemiological
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13 study conducted in the United States previously found an increase in the neonatal unit
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15 admission rate from 2.6% in infants born at 38-40 weeks to 12% at 37 weeks of gestation and
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17 88% at 34 weeks (5). It can be assumed that the differences in absolute rates of admission
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21 between the studies may result from different care systems at national or regional levels.
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CONCLUSIONS

This study confirmed that late-preterm infants are a population at risk of increased respiratory morbidity and poor prognosis, while an intermediate risk of respiratory morbidity was observed in the early-term infants. Therefore birth at 37 and 38 weeks of gestation is not low-risk for the newborn, and this information should lead to avoidance of caesarean section or labor induction without medical indication in early-term infants as well as in late-preterm infants.

The continuous pattern of improvement from one week to the following is a limitation of the current terminology which delineates late-preterm, early-term and late-term infants. Future studies should identify more precisely the respective contribution of each week of gestation, of maternal complications and of induced delivery in the prognosis of infants born between 34 and 39 weeks of gestation.

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Table 1: Characteristics of live-born singleton neonates with gestational age ranging from 34 to 41 weeks of gestation.

GA (weeks)	34 (n = 948)	35 (n = 1655)	36 (n = 3406)	37 (n = 8732)	38 (n = 22394)	39 - 41 (n = 113291)	P
Characteristics							
Maternal age, years							
< 20	5.1%	4.2%	4.1%	3.5%	2.7%	2.9%	
20-24	17.8%	19.1%	18.2%	17.9%	16.0%	16.6%	
25-29	32.6%	34.8%	33.1%	34.6%	34.1%	36.0%	< 0.0001
30-34	27.8%	26.3%	29.0%	27.8%	30.3%	30.2%	
35-39	12.9%	12.8%	13.1%	13.4%	13.9%	12.1%	
≥ 40	3.8%	2.7%	2.6%	2.8%	2.9%	2.3%	
Birthweight (g)	2195 (426)	2452 (432)	2687 (421)	2913 (428)	3122 (419)	3380 (424)	< 0.0001
SGA	17.0%	11.8%	11.0%	9.4%	8.2%	9.0%	< 0.0001
Gender, Male	55.8%	54.3%	56.2%	53.3%	52.6%	50.6%	< 0.0001
Antenatal complications							
HDP	19.6%	13.2%	9.5%	7.7%	5.4%	2.8%	< 0.0001
Preterm labour	39.0%	42.5%	18.1%	13.8%	7.6%	3.5%	< 0.0001
PPROM	28.2%	25.7%	21.1%	12.5%	8.2%	6.4%	< 0.0001
Antepartum hemorrhage	6.3%	5.0%	2.4%	1.2%	0.5%	0.2%	< 0.0001
Clinical chorioamnionitis	1.4%	0.7%	0.3%	0.1%	0.1%	0.1%	< 0.0001
Antenatal diagnosis of IUGR	13.5%	10.0%	9.4%	6.4%	3.4%	1.3%	< 0.0001
Diabetes	7.2%	9.2%	7.6%	7.6%	7.1%	3.5%	< 0.0001
Number of antenatal complications							
0	32.7%	37.6%	49.3%	61.2%	72.9%	84.2%	
1	43.7%	44.2%	38.1%	30.6%	22.8%	14.2%	< 0.0001
≥ 2	23.6%	18.2%	12.6%	8.2%	4.3%	1.6%	
Birth conditions							
Abnormal fetal heart rate	19.9%	17.3%	13.1%	12.3%	11.0%	17.6%	< 0.0001
Asphyxia at birth	3.4%	1.3%	0.9%	0.5%	0.4%	0.4%	< 0.0001
Mode of delivery							
Elective C-section	4.9%	4.9%	5.9%	8.0%	14.1%	5.5%	
Emergency C-section	42.7%	30.7%	20.0%	14.3%	10.2%	8.7%	
Vaginal delivery with instrumental maneuver	5.9%	6.6%	7.3%	8.0%	7.5%	11.4%	< 0.0001
Vaginal delivery without instrumental maneuver	46.5%	57.8%	66.8%	69.7%	68.1%	74.4%	

Data are % or mean (SD).

GA = Gestational Age. SGA = Small for Gestational Age. HDP = Hypertensive Disease of pregnancy. PPRM = preterm and premature rupture of membranes. IUGR = intrauterine growth restriction.

Table 2: Crude and adjusted relative risks for severe respiratory disorders and poor prognosis according to gestational age, gender and maternal conditions.

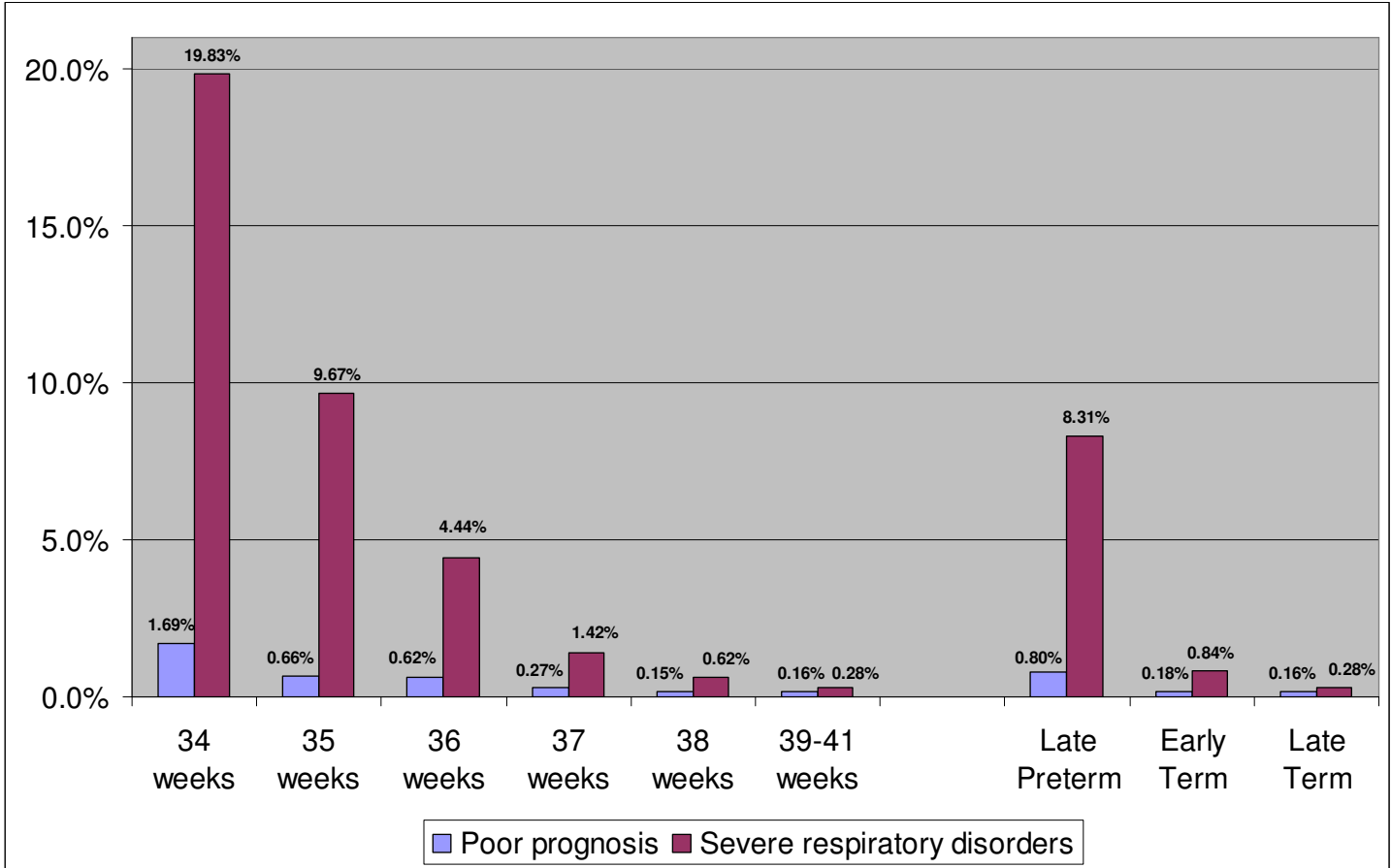
	Poor prognosis				Severe Respiratory Disorders				
	cRR	95% CI	aRR	95% CI	cRR	95% CI	aRR	95% CI	
34 weeks	10.5	6.7 – 16.6	6.8	4.1 – 11.1	68.6	54.1 – 86.9	61.0	49.7 – 74.8	
35 weeks	4.2	2.4 – 7.2	3.0	1.7 – 5.2	33.6	26.2 – 43.1	31.0	25.1 – 38.3	
36 weeks	3.9	2.6 – 5.8	3.1	2.1 – 4.7	15.3	11.9 – 19.7	14.2	11.6 – 17.4	
37 weeks	1.7	1.2 – 5.5	1.6	1.1 – 2.3	4.9	3.8 – 6.5	4.7	3.8 – 5.8	
38 weeks	0.9	0.7 – 1.3	0.9	0.6 – 1.2	2.1	1.7 – 2.8	2.1	1.7 – 2.5	
39-41 weeks	1.0	-	1.0	-	1.0	-	1.0	-	
Maternal Age, years									
< 20	1.2	0.6 – 2.4	NA	NA	1.1	0.8 – 1.6	NA	NA	
20-24	1.0	0.7 – 1.4	NA	NA	0.8	0.7 – 1.1	NA	NA	
25-29	1.0	-	NA	NA	1.0	-	NA	NA	
30-34	1.0	0.8 – 1.4	NA	NA	1.1	0.9 – 1.2	NA	NA	
35-39	0.9	0.6 – 1.4	NA	NA	1.2	1.0 – 1.5	NA	NA	
≥ 40	1.3	0.7 – 2.7	NA	NA	1.5	1.1 – 2.1	NA	NA	
Gender, Male	1.3	1.1 – 1.6	1.3	1.0 – 1.6	1.5	1.4 – 1.7	1.5	1.3 – 1.6	
HDP	2.2	1.5 – 3.4	1.6	1.1 – 2.5	4.1	3.4 – 4.8	1.4	1.2 – 1.7	
Preterm labour	1.4	0.9 – 2.2	NA	NA	3.1	2.6 – 3.7	NA	NA	
PPROM	0.9	0.5 – 1.4	NA	NA	2.0	1.7 – 2.4	NA	NA	
Antepartum hemorrhage	13.0	7.6 – 22.5	6.3	3.5 – 11.3	15.2	11.5 – 20.8	2.4	1.8 – 3.2	
Clinical chorioamnionitis	3.1	0.4 – 22.1	NA	NA	6.7	3.3 – 13.6	NA	NA	
Diabetes	1.4	0.8 – 2.2	NA	NA	2.4	1.9 – 2.9	1.5	1.2 – 1.9	

*Poor prognosis = death and/or severe neurological condition at the end of neonatal hospitalization.

** Severe respiratory disorder = respiratory distress treated by mechanical ventilation and/or nasal continuous positive airway pressure.

cRR = Crude Relative Risk. aRR = Adjusted Relative Risk, calculated only for covariates present in the final multivariate model. CI = Confidence Intervals. HDP = Hypertension Disease of Pregnancy. PPROM = Preterm and Premature Rupture of Membranes. NA = Non Applicable.

Figure 1: Proportions of newborns with severe respiratory disorders and poor prognosis, according to gestational age.



*Poor prognosis = death and/or severe neurological condition at the end of neonatal hospitalization.

** Severe respiratory disorder = respiratory distress treated by mechanical ventilation and/or nasal continuous positive airway pressure.

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KEY MESSAGES

Birth at 37 weeks of gestation was associated with an increased incidence of poor prognosis;

Infants born at 37 and 38 weeks of gestation were at increased risk of severe respiratory disorders;

Before 39 weeks of gestation, each additional week contributed to improve the clinical condition of the newborns.

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