Research Article

Perinatal outcomes of spontaneous and medically-indicated late preterm infants

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Abstract

Objective: The aim of the study was to compare the perinatal results of spontaneous and medically-indicated late-preterm infants.

Methods: We conducted a retrospective cohort study including all singleton late-preterm infants born at our University Hospital between January 2009 and December 2010 (n=171). Neonates with congenital infections, major congenital malformations and chromosomal abnormalities were excluded. Late-preterm infants were classified into two groups, spontaneous and medically-indicated, according to delivery indication. Obstetric complications and short-term neonatal outcomes were investigated.

Results: 145 late-preterm infants were eligible for analysis. Obstetric complications were more frequent in medically-indicated late-preterm infants. However, when neonatal results were compared no differences were found between groups. Both spontaneous and medically-indicated late-preterm infants were at risk to develop respiratory morbidity (14.5% vs 24.2%, p=0.195), hyperbilirubinemia (15.7% vs 11.3%, p=0.478), excessive weight loss (2.4% vs 4.8%, p =0.651), infectious complications (1.2% vs 8.1%, p =0.084) and central nervous system morbidity (2.4% vs 0%, p=0.507). Only length of hospital stay was significantly higher among medically-indicated late-preterm infants.

Conclusions: Both spontaneous and medically-indicated late-preterm infants are at risk for perinatal morbidity. Obstetric management of pregnancies at risk for late-preterm prematurity should be clarified, and specific strategies of care for these infants need to be improved.

Introduction

Neonates born between 34 0/7 and 36 6/7 weeks' gestation, also referred as late-preterm infants, represent nearly three-quarters of premature infants [1]. Over the past decade several countries have observed a significant increase in late-preterm birth rates, these births accounting for about 8% of all births [2-5]. The majority of late-preterm deliveries are due to spontaneous onset of labour (SoL) or preterm premature rupture of the membranes (PPROM), while only less than one third of these births occur as the result of a medical indication to terminate the pregnancy [6]. It has been argued that the increase in late-preterm births has been mostly due to the increase of medically-indicated births [7].

Late-preterm infants have poorer neonatal results when compared to term neonates. Multiple studies have already stated that late-preterm birth is associated with significantly higher rates of respiratory morbidity, neonatal jaundice, feeding difficulties, and other severe morbidities such as intraventricular haemorrhage or sepsis [8-10]. Long-term neurodevelopmental outcome and mortality rates are also worse in this group of neonates [11,12]. Several obstetric morbidities have also been linked to poorer perinatal results. Intrauterine growth restriction (IUGR) and preeclampsia have been related with both short-term and long-term morbidities [13]. These findings have encouraged the obstetric community to reduce late-preterm prematurity rates, and preventive actions have mainly focused on elective deliveries. However, late-preterm births are not easily avoidable [14].

Late-preterm medically-indicated deliveries are the result of a maternal or obstetric condition that will benefit from ending the pregnancy. Pregnancies with preterm SoL or PPROM are usually actively managed beyond 34 weeks to avoid unnecessary risks from continuing the pregnancy. However, infants born late preterm are usually equally managed, and differences between the neonatal results of spontaneous and medically-indicated late-preterm infants remain unknown. We conducted a retrospective cohort study to compare the perinatal results of late-preterm infants according to cause of prematurity.

Methods

We performed a retrospective cohort study of all singleton infants delivered between 34 0/7 and 36 6/7 weeks' gestation at Hospital de la Santa Creu i Sant Pau in Barcelona, a tertiary university hospital, between January 1, 2009 and December 31, 2010. This study was approved by the ethics committee of the Institutional Review Board at Hospital de la Santa Creu i Sant Pau.

Eligible cases were identified from the delivery room logbook, and maternal and neonatal data were reviewed. Well-dated and well-controlled singleton pregnancies with a live fetus at hospital admission were included in the study. Only pregnancies with first-trimester

ultrasound assessment of gestational age were considered well-dated. Exclusion criteria were major anatomic malformations, chromosome abnormalities and congenital infections.

Data were extracted from patient's medical records, and information on maternal age and parity was recorded. Presence of obstetric complications was reviewed. Pregnancy-related complications analysed were hypertensive disorders of pregnancy (gestational hypertension and preeclampsia), intrauterine growth restriction (IUGR), intrahepatic cholestasis of pregnancy, gestational diabetes, and bleeding in the second half of pregnancy (abruptio placentae, placenta previa). Other obstetric complications (e.g. urinary tract infections, ovarian hyperstimulation syndrome, alterations in the quantity of amniotic fluid, maternal anemia) were considered as "others" for the analysis. We also recorded maternal antenatal care requirements such as admission to the High Risk Obstetric Unit, antenatal corticosteroid and tocolytic treatment. Finally, indication for delivery and mode of delivery were noted.

For comparative purposes late-preterm infants were classified into two groups according to cause of prematurity. We considered the birth was spontaneous when PPROM or SoL occurred between 34 0/7 and 36 6/7 weeks, as in these cases our protocols recommended immediate delivery. Women admitted to hospital for SoL or PPROM in the late preterm period were included in the spontaneous group even if other obstetric complications were present. We considered the birth as medically-indicated when delivery occurred following an obstetric or maternal complication. In cases where PPROM occurred before 34 0/7 week's gestation and no infection criteria were found, conservative management was adopted until 34 weeks. If 34 weeks were reached, labor was induced and prematurity was thus classified as medically-indicated.

We recorded immediate neonatal information on sex, birth weight, APGAR score and umbilical artery pH. Trained neonatologists collected data on neonatal outcome. We analysed respiratory morbidity (defined as the occurrence of respiratory distress, transient tachypnea of the newborn or hyaline membrane disease), need for respiratory support methods (defined as the use of oxygen therapy, nasal continuous positive pressure (nCPAP), nasal intermittent mandatory ventilation (nIMV) or endotracheal intubation), neonatal jaundice and need for phototherapy treatment. Other morbidities such as small-for-gestational age (SGA), central nervous system morbidity (seizure or intraventricular haemorrhage), neonatal infection (defined as clinical signs of infection with positive blood culture) and admission to the neonatal intensive care unit (NICU) were also investigated. Our admission to NICU criteria are: gestational age at delivery less than 35 0/7 weeks, birth weight less than 2000g and occurrence of one or more neonatal complication (respiratory distress symptoms, jaundice, feeding difficulties and infection suspicion or diagnose). We created a composite variable to measure neonatal results. This variable, composite neonatal outcome, was defined as the presence of one or more adverse neonatal outcome. We recorded information on mortality, length of hospital stay and readmissions to hospital within the neonatal period (0-28 days). Neonatal results were also analysed according to gestational age at birth.

By institutional protocol, infants born in the late-preterm period have a different discharge policy from those born at term, and discharge is only considered when weight gain is established. Our institution also benefits from a follow-up program for late-preterm infants after hospital discharge. This program is based on two conditions. First, a specific website designed to evaluate the wellbeing of the infant and to support the parents for a well-adapted breastfeeding [15]. Second, a trained nurse performing home visits and follow-up in selected cases. Data on neonatal evolution after hospital discharge were thus obtained from this program.

All uncertainties or discrepancies in the patient's medical record were jointly resolved by at least two study investigators. A specific database was created, and a spreadsheet format was used for statistical analysis. Statistical analysis was performed using SPPS (version 17.0, SPSS Inc., Chicago IL). Associations between categorical variables were evaluated using either Chi-square or Fisher's exact test. The Mann–Whitney U test was used for ordinal variables, and continuous variables were compared using the Student's t-test. For further evaluation of respiratory morbidity, a multivariate logistic regression analysis was performed. This analysis included both the variables that were statistically significant in the univariate analysis and the variables that were considered clinically relevant.

Results

During the study period, there were 3545 singleton live births at our hospital, including 6.43% (n=228) premature births. Of these, 74.9% (n=171) were late-preterm births, but only 145 cases met selection criteria and were thus considered for analysis. Among the 145 late-preterm births included in the study, 57% (n=83) were spontaneous late-preterm births, and 43% (n=62) were medically-indicated late-preterm births. There were no differences in the distribution by gestational age at birth between the two groups. In the spontaneous group, 13 (16%) infants were born at 34 weeks, 27 (32%) at 35 weeks, and 43 (52%) at 36 weeks; in the medically-indicated group, 15 (24%) infants were born at 34 weeks, 13 (21%) at 35 weeks, and 34 (55%) at 36 weeks (p=0.207).

Results concerning maternal and obstetric characteristics of late-preterm births are presented in Table 1. Women with a medically-indicated delivery were older and more frequently nulliparous than women with a spontaneous late-preterm birth. All pregnancy-related complications were more frequent in the group of medically-indicated births, and hypertensive disease, IUGR and intrahepatic cholestasis accounted for more than 70% of the obstetric conditions complicating these pregnancies. However, both groups had equal requirements of maternal antenatal care such as admission to the High Risk Obstetric Unit, tocolysis treatment and corticosteroid therapy for fetal lung maturation. As for mode of delivery, caesarean section rate was significantly higher in the medically-indicated group (74.2% vs 19.3%, p<0.001).

Medically-indicated late-preterm infants had lower scores in the Apgar test at 1 minute, but these differences were no longer observed at minute 5. Mean value of umbilical artery pH was also similar in both study groups. With regard to neonatal outcome, we found comparable frequency rates between groups for all morbidities analysed in the study, and no significant differences in admission to NICU were either noticed. 34.9% and 46.8% of infants in the spontaneous and medically-indicated groups, respectively, presented at least one neonatal complication (p=0.172). Table 2 illustrates these results. Neonatal morbidities more frequently observed in both groups were respiratory complications and neonatal jaundice. However, the occurrence of these morbidities significantly decreased with advancing gestational age at birth: 46.4% of infants born at 34 weeks presented respiratory difficulties, but only 11.7% of infants born at 36 weeks developed this complication; 28.6% of infants born at 34 weeks presented neonatal jaundice, compared to 7.8% of infants born at 36 weeks (data not shown in tables).

Table 1. Maternal and obstetric characteristics of the spontaneous and medically-indicated late-preterm infants

Maternal and Obstetric characteristics	Spontaneous Late Preterm (n=83)	Medically-indicated Late Preterm (n=62)	P value
Maternal age, y[a]	31.07 ± 5.18	33.69 ± 5.19	0.003[b]
Nulliparity, n (%)	41 (49.4)	47 (75.8)	0.002[b]
Maternal admission to the High Risk Obstetric Unit, n (%)	12 (14.6)	13 (21)	0.377
Corticosteroid therapy, n (%)	13 (15.7)	11 (17.7)	0.823
Tocolytic therapy, n (%)	13 (15.7)	6 (9.7)	0.330
Obstetric complications			
Hypertensive disease, n (%)	0 (0)	11 (17.7)	<0.001b
Intrauterine growth restriction, n (%)	2 (2.4)	20 (32.3)	<0.001[b]
Intrahepatic cholestasis of pregnancy, n (%)	1 (1.2)	14 (22.6)	<0.001[b]
Gestational diabetes, n (%)	6 (7.2)	8 (12.9)	0.270
Bleeding in the second half of pregnancy, n (%)	2 (2.4)	5 (8.1)	0.138
Other, n (%)	2 (2.4)	8 (12.9)	0.019[b]
Cesarean section, n (%)	16 (19.3)	46 (74.2)	<0.001[b]

[a]Data are given as mean ± SD
[b]$p < 0.05$

Table 2. Neonatal results of the spontaneous and medically-indicated late-preterm infants

Neonatal results	Spontaneous Late Preterm (n = 83)	Medically-Indicated Late Preterm (n = 62)	p value
Male sex	31 (37.3)	34 (38.4)	1.0
Birth weight, g[a]	2625 ± 356	2438 ± 534	0.008[b]
Apgar ≤ 7 at 1 minute, n (%)	4 (4.9)	12 (19.7)	0.011[b]
Apgar ≤ 7 at 5 minutes, n (%)	0 (0)	2 (3.3)	0.180
Umbilical artery pH [a]	7.24 ± 0.07	7.21 ± 0.1	0.222
Admission to NICU	29 (34.9)	29 (46.8)	0.172
Respiratory morbidity, n (%)	12 (14.5)	15 (24.2)	0.195
Need for respiratory support	10 (12)	11 (17.7)	0.351
Jaundice, n (%)	13 (15.7)	7 (11.3)	0.478
Phototherapy treatment, n (%)	15 (18.1)	11 (17.7)	1.0
SGA, n (%)	6 (7.2)	11 (17.7)	0.068
Excessive weight loss, n (%)	2 (2.4)	3 (4.8)	0.651
Central nervous system morbidity, n (%)	2 (2.4)	0 (0)	0.507
Infectious morbidity, n (%)	1 (1.2)	5 (8.1)	0.084
Other, n (%)	2 (2.4)	8 (12.9)	0.019[b]
Composite neonatal outcome, n (%)	29 (34.9)	29 (46.8)	0.172
Length of hospital stay [a]	5.2 ± 4.7	8.4 ± 8.1	0.001[b]
Readmission to hospital, n (%)	5 (6)	0 (0)	0.071

[a]Data are given as mean ± SD
[b]$p < 0.05$

Obstetric complications, antenatal corticosteroid treatment, gestational age at delivery, mode of delivery and birth weight were included in the multivariate regression analysis to further assess respiratory morbidity among late-preterm infants. The only variable significantly associated with respiratory morbidity in this model was gestational age at delivery, and the association was the highest at 34 weeks (OR=6.54; CI: 2.37-18.11) (data not shown in tables).

Length of hospital stay was significantly longer in medically-indicated late-preterm births than in spontaneous late-preterm births (8.4 days vs 5.2 days, $p=0.001$). As for readmission to hospital, no differences were found between groups, but all cases occurred in the spontaneous group (6% vs 0%, $p=0.071$). Indications for readmission were mainly neonatal jaundice and infectious complication.

Discussion

Previous studies have shown that late-preterm infants have more neonatal complications than term infants [8-10]. Even infants born at term (between 37 0/7 weeks and 42 0/7 weeks) have heterogenous results, with poorer outcomes at 37 weeks compared to 39 or 40 weeks

[16]. It has thus been advised that the definition of term pregnancy should be redefined [17,18], and the risks of prematurity at the late-preterm period have mainly been attributed to a physiologic immaturity of several organ systems [19].

In our study, we found that spontaneous and medically-indicated late-preterm infants were at similar risk for neonatal morbidity, regardless to the higher rate of obstetric complications observed in the medically-indicated group. This contrasts with previous studies suggesting that the underlying cause for prematurity might be responsible for the higher rate of morbidities observed in some of these infants, such as IUGR infants [20]. This suggests that, even though the subjacent cause for prematurity has probably an influence on neonatal outcome at this stage of gestation, prematurity itself is the most important risk factor for morbidity among these infants. Pregnancy-related complications might have a more important role at lower gestational ages.

Our findings are consistent with previous studies reporting respiratory morbidity and jaundice as the most frequent complications in late-preterm infants [8,9,11]. Our results also suggest that, within the late-preterm period, the risk for these morbidities is higher at

lower gestational age. As regards of hospitalization length, previous data showed that late-preterm infants had longer hospital stays than full-term neonates [21]. In the present study we found that length of stay in medically-indicated late-preterm infants was longer than in spontaneous late-preterm infants, although neonatal results were similar between groups. Considering that the rate of IUGR was significantly higher among medically-indicated deliveries (32.3% vs 2.4%, *p*<0.001), birth weight was subsequently lower among these infants compared to spontaneous late-preterm infants. Weight being a discharge criteria, our result might be attributable to lower birth weight in the medically-indicated group rather than to other neonatal factors. We also found that all readmissions to hospital after discharge occurred in the spontaneous late-preterm group, although these differences were not statically significant. This suggests that discharge criteria for late-preterm infants should be carefully considered both in medically-indicated and spontaneous deliveries. Factors affecting length of stay in late-preterm infants have previously been evaluated [22]. Aly et al. showed that both demographic and clinical factors may affect length of stay in late-preterm neonates. These associations were not specifically assessed in our study, but its evaluation might help to determine other factors affecting length of stay in medically-indicated late-preterm infants as compared to spontaneous late-preterm infants.

The rate of medically-indicated late-preterm deliveries in our study (43%) tended to be slightly higher than the rate reported by other authors (approximately 32%) [23]. Our center is a tertiary referral hospital for high-risk pregnancies, which might explain this result. However, indications for delivery were only recorded for the study, and no further evaluation was performed. Better knowledge of the specific obstetric conditions that led to medically-indicated births might contribute to a better evaluation of the indication of the delivery.

Whether or not late-preterm deliveries are avoidable is a highly controversial topic [14,23]. The concern about the neonatal results of late-preterm infants has led to evaluate the indications for delivery in the late-preterm period. It has been suggested that several conditions such as isolated oligohidramnios or mild preeclampsia might not justify an early delivery in most cases [24]. Our study shows that the results of spontaneous late-preterm infants should also raise concern, as they do not differ from those of infants born as a consequence of a pregnancy-related complication. It has been observed that obstetric practice can influence the rate of late-preterm births [25]. PPROM and preterm SoL are usually expectantly managed until 34 weeks. Would it be possible to continue this management beyond this stage of the pregnancy if conditions are stable? Several paediatric societies have adopted specific protocols of care for late-preterm infants, considering the particular risks this neonates are at [26,27]. Obstetric protocols should also consider the management of pregnancy-related complications at this gestational age.

To our knowledge, this is the first study evaluating the neonatal results of late-preterm infants according to the indication of the delivery. We believe our results can contribute to define and improve the obstetric management of pregnancies at risk for a late-preterm birth. The chart review of all cases included in the study allowed a more precise data assessment than abstraction from large databases. Additionally, data concerning the evolution after discharge of these infants was obtained from a follow-up program specifically designed for late-preterm births. This contributed to obtain reliable on the neonatal period.

However, our study has also some limitations. Data regarding hypoglycaemia were not available for most of the infants, and this neonatal complication could not be assess for the outcome evaluation.

This constitutes an important limitation for the study, as hypoglycaemia is a common complication in late-preterm infants. Another possible limitation is the size of the study groups. It might be of interest to confirm our findings with larger and prospective studies. Finally, the medically-indicated group constitute an heterogenous group that included several pregnancy-related complications, some of which might have greater impact on the neonatal outcome than others. This heterogeneity could thus be considered as a confounding factor. However, the aim of the study was not to evaluate the impact of a specific obstetric condition in the neonatal outcome, but to compare the neonatal results of medically-indicated and spontaneous births.

Conclusions

Prematurity is the main contributor to neonatal morbidity in the late-preterm period. Spontaneous late-preterm infants does not seem to have a better outcome than infants born at this gestational age following pregnancy-related complications. This study highlights the need of evidence-based protocols for the management of pregnancies complicated by SoL or PPROM, as well as other obstetric complications, at this gestational age. Future research on late-preterm prematurity should focus on elucidating whether or not a conservative management of obstetric complications in the late-preterm period would reduce neonatal morbidity without increasing maternal or fetal risks.

Declaration of interest statement

The authors report no declarations of interest.

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