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# Prediction of Respiratory Morbidities in Late Preterm Neonates Using Cord Blood Arterial Lactate and Base Excess

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## ABSTRACT

***Background:*** Late preterm neonates may have the external appearance and behavior similar to their counterparts. However, they are susceptible to various neonatal morbidities , due to their physiological and metabolical immaturity. To assess the correlation between cord blood arterial lactate levels and base excess with the development of respiratory distress in late preterm neonates.

***Methods:*** All inborn neonates born at Kasturba hospital Manipal, satisfying the criteria of late preterm infants (34-36 6/7 weeks) were included in this prospective observational study.The data recorded included gender, birth weight, multiple births, presence of major congenital anomalies, mode of delivery, APGAR score at minute 5, need for resuscitation, admission to the neonatal intensive care unit (NICU), and days of hospitalization. Lactate and base excess were estimated using blood obtained from umbilical artery sampling. The primary outcome assessed was the requirement of delivery room resuscitation. The secondary outcomes assessed were the development of respiratory distress, requirement of invasive/non- invasive ventilation, and respiratory support.

***Results:*** Cord blood base excess levels were significantly higher in late preterm neonates requiring delivery room resuscitation compared to those who did not require resuscitation (median: -8 vs -4mEq/L, p-value: 0.002).In terms of respiratory morbidities, cord blood base excess levels were significantly higher in neonates with respiratory distress syndrome (RDS)(median: -8.5 vs -3.4 mEq/L, p-value 0.001), and transient tachypnea of newborn (TTNB) (median: -8 vs -3.4 mEq/L, p-value 0.004), compared to those without RDS and TTNB.However,there was no significant association between cord blood lactate levels and the outcomes assessed.

***Conclusion:*** Estimation of arterial base excess levels obtained from umbilical cord blood sampling during delivery may serve as a sensitive marker for predicting respiratory morbidities in late preterm neonates.

***Keywords:*** Base excess, Cord blood, Lactate, Late preterm, Respiratory morbidities

## Introduction

Late preterm birth is defined as birth between 34 -36 6/7 weeks of gestation from the first day of the last menstrual cycle(1). Late preterm neonates are at a higher risk of respiratory distress immediately after birth, due to,TTNB, persistent pulmonary hypertension (PPHN), pneumonia, along with an increased need for surfactant therapy, continuous positive airway pressure (CPAP), and ventilator support when compared to term neonates(2).

This study aimed to assess the correlation between cord blood arterial lactate levels, base excess (BE) in late preterm neonates and the development of respiratory distress.The primary outcome assessed was the requirement of delivery room resuscitation. The secondary outcome assessed was the development of respiratory distress, requirement of invasive/non-invasive ventilation or other modalities of respiratory support and the time taken to establish breast-feeding.

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## Methods

All inborn neonates born at Kasturba hospital, Manipal, satisfying the criteria of late preterm neonates (34-36 6/7 weeks) were included in this prospective observational study. The study lasted from October 1st 2014 to June 30th 2016. Institutional ethical committee approval was obtained prior to the commencement of the study (IEC number: 655/2014).Late preterm neonates with congenital anomalies like congenital diaphragmatic hernia, complex congenital heart diseases, esophageal atresia, hydrocephalus, and neural tube defects were excluded from the study.

Gestational age was estimated by the assessment of ultrasound examination at first trimester of gestation. The data including, gender, birth weight, multiple births, presence of major congenital anomalies, mode of delivery, APGAR score at 5 minutes, need for resuscitation, admission to the neonatal intensive care unit (NICU), and days of hospitalization were recorded at the time of birth.

One ml of blood was collected from the umbilical artery after double clamping in a pre heparinized syringe immediately after delivery and the sample was sent for blood gas analysis and lactate level estimation.Blood samples were analyzed in GEM Premier 3000 blood gas analyzer in the neonatal intensive care unit. Hyperlactatemia was defined as an arterial blood lactate concentration greater than2.5 mmol/l or 25 mg/dL(3).The mean umbilical artery base excess was taken as -4.8meq/L(4).

Invasive ventilation was considered for those neonates with respiratory distress requiring intubation in the delivery room or neonates with Downe's score(5)>6 or requiring $FiO_2$> 40% on noninvasive ventilation. Extubated neonates were managed with non-invasive ventilation using nasal continuous positive airway pressure (N-CPAP)/, heated humidified high flow nasal cannula (HHHFNC), or humidified oxygen through headbox.The data on respiratory support such as oxygen therapy either invasive or non-invasive method was documented. The need for specific adjunctive therapies, such as surfactant administration, duration of respiratory support and highest level of respiratory support were analyzed. Blood glucose levels were monitored every 6 hours for a 72-hour period.

Statistical analysis was done using IBM SPSS statistics, version 23. Descriptive statistics was reported using mean ± standard deviation or median(range) for the continuous variables. Numbers and percentage were used for the categorical variables.

## Results

There were 1558deliveries during the study that 156 late preterm neonates were included in the study. The demographic and clinical features of the study population are depicted in Table 1.

Nearly 50% of the late preterm neonates were born at 36 weeks of gestation and 82.7% were born AGA. The majority of them (75%) were delivered by emergency LSCS and the most common indication was fetal distress. Resuscitation in the delivery room was required in 22 (14.1%)

**Table 1.** Demographic and clinical features of the study population

| Variable | Late preterm neonates(156)- n (%) |
|---|---|
| Gestational age in weeks:34 | 44(28.2) |
| 35 | 35(22.4) |
| 36-6/7 | 77(49.4) |
| Gender: | |
| Male | 75(48.1) |
| Female | 81(51.9) |
| Weight for gestation: | |
| AGA | 129(82.7) |
| SGA | 24(15.4) |
| LGA | 3(1.9) |
| Mode of delivery: | |
| Vaginal | 16(10.2) |
| Elective LSCS | 21(13.6) |
| Emergency LSCS | 118(75.6) |
| Assisted vaginal delivery | 1(0.6) |
| Pregnancy order: | |
| Singleton | 123(78.9) |
| Twins | 30(19.2) |
| Triplets | 3(1.9) |
| APGAR score<7 at 5min | 2(1.3) |
| Steroid prophylaxis: | |
| Received | 53(34.0) |
| Not received | 103(66.0) |
| Delivery room resuscitation: | |
| Requirement: | 22 (14.1) |
| Type of resuscitation: | |
| Bag and mask | 17(10.9) |
| Intubation and bag | 4(2.6) |
| Intubation and mechanical ventilation | 1(0.6) |
| Chest compressions | Nil |
| Respiratory morbidity: | |
| Present: | 28(17.9) |
| Types: | |
| RDS | 14 (9.0) |
| TTNB | 9 (5.7) |
| Congenital pneumonia | 2 (1.3) |
| MAS | 3 (1.9) |

AGA: appropriate for gestational age, SGA: small for gestational age, LGA: large for gestational age, LSCS: lower segment cesarean section. MAS: meconium aspiration syndrome.

neonates and mostly by bag-mask ventilation. Subsequently, respiratory morbidities were observed in 28 (17.9%) neonates and the most common was RDS. Only 34% of mothers had received steroid prophylaxis prior to delivery. As depicted in table 2, the arterial base excess levels were significantly higher in neonates requiring resuscitation in the delivery room than those who did not require resuscitation.

The cord blood lactate and base excess levels in RDS and TTNB were elevated as depicted in table 3. Similarly, 2 neonates had congenital pneumonia with median lactate/base excess values of 4mmol/L /-6.5meq/L,and 3 neonates had MAS with median lactate/base excess of 7.6mmol/L /-12.1meq/L.

Neonates with RDS had significantly higher levels of base excess (-8.5), compared to those without respiratory morbidities (-3.4) as depicted in table 4.

Similarly neonates with TTNB had significantly higher levels of base excess (-8), compared to those without respiratory morbidities (-3.4) as depicted in table 5.

Of the total 156 late preterm neonates, 99(62.9%) newborns had cord blood lactate more than 2.5mmol/L, out of whom 19(19.2%) neonates had respiratory morbidities. Moreover, 57(36.3%) newborns had cord blood lactate less than 2.5mmol/L, out of whom 8(14%) neonates had respiratory morbidities. Similarly, 87(55.7%) neonates had base excess more than -4.8. Respiratory morbidities were observed in 27 (37.7%) neonates out of whom 69 newborns had cord blood base excess less than -4.8meq/L among whom none had respiratory morbidities.

The majority of the neonates requiring respiratory support, needed CPAP for a median duration of 36 hours as depicted in Table 6.

**Table 2.** Association of cord blood lactate and base excess with resuscitation requirement.

| n = 156 | Noresuscitation(134) | Resuscitation(22) | P value |
|---|---|---|---|
| Lactate (mmol/L) (Median, IQR 25th /75th) | 2.8 (2.2, 3.6) | 4.0 (2.0, 6.5) | 0.35 |
| Base excess (meq/L) (Median, IQR 25th/75th) | -4 (-6.6, -2.0) | -8 (-10.4, -2.0) | 0.002 |

**Table 3.** Cord blood lactate and base excess in respiratory morbidities.

| Variables | TTNB (n= 9) | RDS (n= 14) |
|---|---|---|
| Lactate (mmol/L) (median, IQR 25th /75th ) | 4.0 (2.5, 5.5) | 3.0 (2, 6) |
| Base excess (meq/L) (median, IQR 25th /75th ) | -8 (-10, -7.5) | -8.5 (-10, -7) |

**Table 4.** Association between cord blood lactate /base excess in babies with RDS and without respiratory morbidities

| Variable | RDS (n= 14) | No respiratory morbidity (n=128) | P-value |
|---|---|---|---|
| Lactate (mmol/L) median IQR 25th/75th | 3.0 (2, 6) | 2.7 (3.7, 2.2) | 0.733 |
| Base excess (meq/L) median IQR 25th/75th | -8.5 (-10, -7) | -3.4 (-6.3, -1.7) | 0.001 |

**Table 5.** Association between cord blood lactate /base excess in babies with TTNB and without respiratory morbidities

| Variable | TTNB (n=9) | No respiratory morbidity (n=128) | P-value |
|---|---|---|---|
| Lactate (mmol/L) median, IQR 25th/75th | 4(2.5, 5.5) | 2.7 (3.7, 2.2) | 0.361 |
| Base excess (meq/L) median, IQR 25th/75th | -8 (-10, -7.5) | -3.4 (-6.3, -1.7) | 0.004 |

**Table 6.** Late preterm infants requiring respiratory support

| Respiratory support | n= 28 | Duration of $O_2$ requirement in Hours, Median (IQR 25th/75th) |
|---|---|---|
| Non-invasive ventilation | 27 | |
| CPAP | 20 (9.2) | 36 (24, 72) |
| Oxygen by nasal cannula | 2 (1.2) | 24 |
| HHHFNC | 5 (4.6) | 72 (24,72) |
| Invasive ventilation | 1 | |
| <24 hours | 1 (0.6) | 24 |
| 24-48 hours | 0 | 0 |
| >48 hours | 0 | 0 |

Among the late preterm neonates, those with 34 weeks gestational age required maximum duration of hospital stay for a mean duration of 8.7 days. The time taken to establish breastfeeding was maximum among late preterms of 34 weeks gestation, requiring a median duration of 7 days as depicted in table 7.

**Table 7.** Duration to establish breast-feeding and NICU stay

| Gestational age in weeks | 34 (n=44) | 35 (n=35) | 36-6/7 (n=77) |
|---|---|---|---|
| Duration of NICU stay –mean(SD) | 8.7 (7.7) | 6.9 (2.7) | 2.7 (1.1) |
| Duration to establish breastfeeding in days, Median (IQR 25$^{th}$/75$^{th}$) | 7 (4,12) | 1 | 1 |

## Discussion

Since the late 90s the preterm birth rate across the globe has increased by 33%,out of whom 72% constitutes late preterm neonates(6).Multiple factors have been attributed to the increasing incidence of late preterm (LPT) deliveries,such as the increase in the mean age of childbearing mothers,changes in infertility treatments, rising incidence of multiple gestation pregnancies, increasing use of labor induction, and cesarean delivery at 34-36 weeks of gestation(6). Due to the advances in reproductive technologies, there has been increasing surveillance of mother and fetus. Accordingly, fetuses who are considered at the risk of stillbirth, intrauterine growth retardation, and intrapartum asphyxia are identified earlier, resulting in more deliveries at 34-36 weeks gestation(7).Earlier studies on the outcomes of infants with respiratory distress have mainly focused on extremely premature infants, leading to a gap in knowledge and understanding of the physiology and mechanism of pulmonary diseases in late preterm neonates. A large study performed in USA(8) has reported respiratory morbidities in 9% of late preterm births and added that this risk decreased with each advancing week of gestation up to 38 weeks.

There is paucity of data on respiratory morbidities in late preterm neonates from India. In the present study, nearly 18% of late preterm neonates developed respiratory morbidities immediately after birth out of which 50% constituted RDS followed by TTNB. Additionally, our findings were consistent with the results of a study from USA which showed RDS as the most common respiratory morbidity among the late preterm deliveries(8). Studies have demonstrated that surfactant deficiency is the most common etiology of RDSin very preterm and moderately preterm neonates, while cesarean section and lung infection play major roles in RDS development in both late preterm and term neonates(9). It has been observed that neonates born at 34-36 weeks gestation are more likely to be delivered via cesarean than by labor induction, leading to increased rates of respiratory compromise(10). Neonates born by cesarean section have a larger residual volume of lung fluid and secrete less surfactant to the alveolar surface thereby increasing the risk of developing RFS(11). The detrimental effects of cesarean section without trial of labor on the development of RDS is more prominent in LPT and term infants(11). In our study 89% of LPT neonates were delivered by cesarean section.Studies have shown that administration of antenatal corticosteroids to mothers with the risk of imminent delivery between 34-36 weeks of gestation could significantly reduce the acute respiratory morbidity associated with LPT birth(12). In our study only 34% of late preterm neonates received steroid prophylaxis prior to delivery.Studies have shown that the efficacy of surfactant therapy in LPT neonates is not as good as it is for preterm neonates(9) and none of the neonates in our study received surfactant.

Cord blood lactate has been identified as a more specific factor than pH in the prediction of adverse neonatal outcomes(13). However, the present research indicated no significant correlation between cord blood arterial lactate and the outcomes assessed.Studies have demonstrated umbilical artery base excess ( cut off value ≥ 12 mmol/l) as a reliable indicator of intrapartum asphyxia with best correlation to long term morbidities(14).A study performed by Victory et al.from Canada has shown a significant correlation between umbilical cord base excess values at birth (mean artery BE -5.6±3.0 mmol/l) and adverse neonatal outcomes, such as APGAR score less than 7 at 5 min, NICU admission and the need for assisted ventilation(15). In the current study, the umbilical artery BE increased significantly (median -8meq/L) in late preterms requiring resuscitation in the delivery room, compared to those who did need resuscitation. Moreover, this study demonstrated significantly increased BE values in late preterms with RDS (median -8.5meq/L) and TTNB (median -8meq/L), compared to those without any respiratory morbidities. The umbilical artery BE is directly related to fetal production of carbon dioxide and lactate which contributes to metabolic acidosis(15) and is significantly related to long term morbidities including death(16).

In this research,17.9% of late preterms required respiratory support predominantly in the form of CPAP, which is in line with the study conducted in the US(8)wherein the majority received oxygen via nasal cannula followed by

CPAP.The late preterm babies were reported to have significantly increased respiratory morbidities, increased use of intensive care, longer stay of hospitalization (17), increased rates of rehospitalization, and increased cost of health care(18), compared to term babies.

## Conclusion

To the best of our knowledge,this study has been one of the first performed in literature that have assessed the prediction of respiratory morbidities in the late preterm neonates using cord blood lactate and arterial base excess levels. This research provided a significant insight into various respiratory morbidities, requirement of resuscitation, including respiratory support and the time taken to establish breastfeeding among LPT neonates. The estimation of umbilical arterial base excess levels at birth in late preterm neonates may serve as the most reliable parameter in assessing the severity of respiratory morbidities.

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## Conflicts of interests

No conflict of interests is declared by the authors in this study.

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