Original Article

Neonatal Short-Term Outcomes in Late Preterm Compared with Term Infants in Srinagarind Hospital

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Objective: To determine short-term morbidities in late preterm infants ($34^{0/7}$ to $36^{6/7}$ weeks of gestation) compared with term infants in Srinagarind Hospital and factors associated with late preterm births.

Materials and Methods: A prospective cohort study conducted by collecting and analyzing clinical data and short-term outcomes of late preterm and term infants born in Srinagarind Hospital during November 2009 to October 2010.

Results: During the study period, there were 2,199 live births. An overall preterm birth rate was 10.5%, and late preterm birth rate was 5.9%. Among 129 late preterm infants with mean gestational age of 35.4±0.7 weeks and mean birth weight of 2,520.2±470.2 grams, hyperbilirubinemia (53.5%) was the most common problem. Neonatal intensive care unit admissions, hyperbilirubinemia, hypothermia, respiratory problems, infections, hypoglycemia and feeding problems in late preterm infants were significantly higher when compared with term infants. The most common diagnosis of respiratory problems included transient tachypnea of the newborn (72.7%) and respiratory distress syndrome (15.2%). Spontaneous premature labor was the most common risk factor associated with late preterm births (38.8%).

Conclusion: Late preterm infants had significantly higher short-term morbidities than term infants. Antenatal and perinatal care for prevention of late preterm births may reduce neonatal morbidities, mortality and costs of hospitalization.

Keywords: Late preterm infants, Term infants, Short-term morbidities, Late preterm birth, Risk factors

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Term infant is the lowest risk factor for neonatal morbidities and mortality. Preterm and post-term births increase the risks[1-3]. In the past, late preterm infants defined by gestational age at $34^{0/7}$ to $36^{6/7}$ weeks were accounted for near term infants and considered to have lower risks comparable to term infants. Many recent studies from variety of continents, mostly north America, demonstrated that late preterm infants had higher rates of short-term morbidities, intensive care requirement, re-hospitalization, long-term developmental impairment and mortality than term infants[1-19]. Since medical resources in high income and low to middle income countries are different, we should have our own data to recognize the burden and anticipate.

The objectives of the present study were to determine short-term neonatal morbidities in late preterm infants compared with term infants in Srinagarind Hospital and factors associated with late preterm births.

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Materials and Methods

The present study was a prospective cohort study conducted by collecting and analyzing of clinical data and short-term outcomes of late preterm and term infants born in Srinagarind Hospital during November 2009 to October 2010. Srinagarind Hospital, a tertiary university hospital with a level-III neonatal intensive care unit (NICU) in the North-eastern part of Thailand, has estimated 2,000 live births a year. Approximately 10% of live births is preterm births and 60% of the preterm births is late preterm births. The equal number of term infants were planned to randomly selected for comparing with all of the late preterm infants. Then every the 15th birth order of term infants was included consecutively. Since hyperbilirubinemia is the most common newborn problem and Srinagarind Hospital has had policy of phototherapy in the newborn nursery to diminish maternal-infant separation and promote breast feeding, the total amount of hyperbilirubinemia requiring phototherapy in both late preterm and term infants was planned to collect.

Statistical analysis was performed by using STATA software. Descriptive data were presented by percent and mean ± SD. Association analysis was performed by using Chi-square test or Fisher's exact test and *p*-value less than 0.05 was considered statistically significant. The present study was approved by the Ethics Committee for Human

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Research of Khon Kaen University.

Results

During the study period, there were 2,199 live births. Of these, 1,969 (89.5%) were term infants and 230 (10.5%) were preterm infants. Among preterm infants, 129 (56.1%) were late preterm infants. One infant with hydrops fetalis was late preterm, however, no one in the late preterm infants die. Characteristics of infants included in the present study were shown in Table 1 and Table 2. Mean maternal age and rate of cesarean section delivery were not different between the late preterm and term infants. Mean gestational age of the late preterm infants was 35.4±0.7 weeks and mean birth weight was 2,520.2±470.2 grams. The late preterm infants significantly required admission to a special care nursery and NICU greater than the term infants (50.4% vs. 19.5%, $p<0.0001$). The rate of admission for special and intensive care was inversely proportional to their gestational age (84.2% at 34 weeks, 80.0% at 35 weeks and 28.0% at 36 weeks) as well as rate of acute respiratory problems (47.4% at 34 weeks, 45.7% at 35 weeks and 10.7% at 36 weeks) and median duration to full enteral feeding (6 days at 34 weeks, 2 days at 35 weeks and 1 day at 36 weeks). Mean length of hospital stay of the late preterm infants was longer than the term infants (8.4±10.4 days vs. 3.8±1.6 days, $p<0.0001$).

Hyperbilirubinemia was the most common problem. There were 53.5% (69/129) of late preterm infants, 21.7% (28/129) of term infants included in the present study and 27.6% (543/1,969) of total term infants developed hyperbilirubinemia requiring phototherapy. Hypothermia (45.0%), acute respiratory distress (25.6%) and infections requiring antibiotic treatment (21.7%) were also common problems in the late preterm infants. The most common diagnosis of acute respiratory distress included transient tachypnea of the newborn (TTN) (72.7%) and respiratory distress syndrome (RDS) (15.2%). RDS was diagnosed only in the late preterm infants (5/33 vs. 0/11) and 60% (3/5) of them received surfactant replacement therapy. Feeding intolerance and definite necrotizing enterocolitis (NEC ≥stage II) were also diagnosed only in the late preterm infants (7/129 vs. 0/129 and 4/129 vs. 0/129, respectively). Late preterm infants required more respiratory (16.3% vs. 3.1%, $p = 0.0001$) and parenteral nutritional supports (8.5% vs. 0%, $p = 0.0007$) than term infants. The short-term outcomes and managements of the late preterm infants presented in Table 3 and Table 4 shown statistically significant differences when compared to the term infants.

From the present study, the most common risk factor associated with late preterm births was spontaneous premature labor (38.8%). The list of risk factors associated with late preterm births presented in Table 5 shown statistically significant differences when compared between the late preterm and term infants, except for placenta previa.

Discussion

The present study demonstrated that Srinagarind Hospital, a tertiary university hospital with a level-III NICU had a similar preterm birth rate (10.5% vs. 8.2 to 18.6%), but a little smaller proportion of late preterm birth (56% vs. 61 to 77%) when compared with previous studies[3-16]. Although late preterm infants had higher mortality rate than term infants[1-3,6-8,17], there was no death of late preterm infants in the present study.

A number of studies reported higher morbidities in late preterm infants than term infants[1-19] since they still remain at risk for prematurity-related complications. From the present study, the most common medical problem in newborn infants was hyperbilirubinemia and late preterm infants had significantly higher rate of hyperbilirubinemia requiring phototherapy than term infants. This result was similar to the studies by Wang ML, et al[18], Vachharajani AJ, et al[9] and Buthani VK, et al[20]. The latter authors explained this issue by the unsuccessful lactation and biologic risk factors for hyperbilirubinemia of immature enterohepatic system. On the other hand, the study in maternal hospital in Turkey by Bulut C, et al[10] showed high rates of hyperbilirubinemia without a difference between the late preterm and term infants (48.1% vs. 46.3%, $p = 0.32$). Hypothermia was the second most common problem in the present study. In contrast, late preterm infants in the present study had higher rate of hypothermia when compared with previous studies by Wang ML, et al[18] and Vachharajani AJ, et al[9] (45% vs. 10% and 16%, respectively). Additionally, 7% of term infants in the present study had hypothermia whereas only 0.05% was found from the study in Taiwan by

Table 1. Characteristics of infants included in the present study

	Late preterm infant (n = 129)	Term infant (n = 129)
Maternal age (year), mean ± SD	28.6±5.3	29.1±4.9
Cesarean section delivery, n (%)	58 (44.9)	56 (43.4)
Gestational age (week), mean ± SD	35.4±0.7	38.4±0.9
Birth weight (gram), mean ± SD	2,520.2±470.2	3,124.4±399.2
Male, n (%)	76 (58.9)	70 (54.3)
Duration to full enteral feeding (day), mean ± SD	3.1±7.4	1.0±0.1
median (IQR)	1 (1, 2)	1 (1, 1)
Length of hospital stay (day), mean±SD	8.4±10.4	3.8±1.6
median (IQR)	5 (4, 8)	3 (3, 4)

Table 2. Characteristics of late preterm infants included in the present study

	Late preterm infant, Gestational age			
	34 weeks (n = 19)	35 weeks (n = 35)	36 weeks (n = 75)	Total (n = 129)
Maternal underlying disease, n (%)				
Thalassemia	0	4 (11.4)	3 (4.0)	7 (5.4)
Heart disease	2 (10.5)	0	1 (1.3)	3 (2.3)
SLE	2 (10.5)	1 (2.7)	0	3 (2.3)
Hyperthyroidism	0	1 (2.7)	1 (1.3)	2 (1.5)
Maternal obstetric complication, n (%)				
None	1 (5.3)	3 (8.6)	16 (21.3)	20 (15.5)
Spontaneous premature labor	7 (36.8)	9 (25.7)	34 (45.7)	50 (38.8)
PPROM	7 (36.8)	8 (22.8)	15 (20.0)	30 (23.3)
GDM	0	5 (14.3)	5 (6.7)	10 (7.7)
PIH	1 (5.3)	6 (17.1)	1 (1.3)	8 (6.2)
IUGR	1 (5.3)	3 (8.6)	3 (4.0)	7 (5.4)
Placenta previa	1 (5.3)	1 (2.9)	1 (1.3)	3 (2.3)
Hydrops fetalis	1 (5.3)	0	0	1 (0.8)
Mode of delivery, n (%)				
Normal delivery	8 (42.1)	14 (40.0)	48 (64.0)	70 (54.3)
Cesarean section	11 (57.9)	21 (60.0)	26 (34.7)	58 (44.9)
Forceps extraction	0	0	1 (1.3)	1 (0.8)
Sex, n (%)				
Male	9 (47.4)	21 (60)	46 (61.3)	76 (58.9)
Female	10 (52.6)	14 (40)	29 (38.7)	53 (41.1)
Type of body, n (%)				
AGA	16 (84.2)	29 (82.9)	71 (94.7)	116 (89.9)
SGA	2 (10.5)	4 (11.4)	3 (4.0)	9 (7.0)
LGA	1 (5.3)	2 (5.7)	1 (1.3)	4 (3.1)
1-minute Apgar score, n (%)				
0 to 3	1 (5.3)	1 (2.9)	1 (1.3)	3 (2.3)
4 to 7	4 (21.1)	4 (11.4)	8 (10.7)	16 (12.4)
>7	14 (73.7)	30 (85.7)	66 (88.0)	110 (85.3)
5-minute Apgar score, n (%)				
0 to 3	1 (5.3)	0	0	1 (0.8)
4 to 7	1 (5.3)	0	0	1 (0.8)
>7	17 (89.5)	35 (100)	75 (100)	127 (98.4)
Admission, n (%)				
Newborn nursery	3 (15.8)	7 (20)	54 (72.0)	64 (49.6)
Special care nursery	12 (63.2)	25 (71.4)	19 (25.3)	56 (43.4)
Level-III NICU	4 (21.1)	3 (8.6)	2 (2.7)	9 (7)
Acute respiratory problem, n (%)	9 (47.4)	16 (45.7)	8 (10.7)	33 (25.6)
Duration to full enteral feeding (day),				
mean ± SD	11.3±17.2	2.8±2.4	1.2±0.8	3.1±7.4
median (IQR)	6 (2, 8)	2 (1, 4)	1 (1, 1)	1 (1, 2)
Length of hospital stay (day),				
mean ± SD	20.4±21.4	9.4±8.8	5.1±2.5	8.4±10.4
median (IQR)	10 (8, 26)	7 (4, 9.5)	4 (4, 6)	5 (4, 8)

SLE = systemic lupus erythematosus, PPROM = preterm prelabor rupture of membranes, GDM = gestational diabetes mellitus, PIH = pregnancy induced hypertension, IUGR = intrauterine growth retardation, AGA = appropriate for gestational age, SGA = small for gestational age, LGA = large for gestational age, NICU = neonatal intensive care unit

Tsai ML, et al[11]. These findings could lead to our urgent quality improvement in newborn care concerning temperature control.

Acute respiratory distress requiring respiratory support, the most common cause of NICU admission, was higher in late preterm infants when compared with term infants (25.6% vs. 8.5%; OR 3.7; 95% CI 1.7 to 8.5; p = 0.0003) which comparable to the previous report by Wang ML, et al[18] (28.9% vs. 4.2%; OR 9.14; 95% CI 2.9 to 37.8; p<0.00001). Nevertheless, numerous studies showed various rates of respiratory distress in late preterm infants from 10.5 to 31.1%[21-24]. Vachharajani AJ, et al[9] from USA.

Table 3. Short-term outcomes

Outcomes, n (%)	Late preterm (n = 129)	Term (n = 129)	OR	95% CI	*p*-value
Hyperbilirubinemia	69 (53.5)	28 (21.7)	4.15	2.33 to 7.43	<0.0001*
Hypothermia	58 (45.0)	9 (7.0)	10.89	4.93 to 26.31	<0.0001*
Acute respiratory problem	33 (25.6)	11 (8.5)	3.68	1.70 to 8.49	0.0003*
TTN	24	8			
RDS	5	0			
Apnea	2	0			
Pneumonia	1	2			
MAS	1	1			
Infection	28 (21.7)	10 (7.8)	3.30	1.46 to 7.96	0.0016*
Clinical sepsis	19	7			
PPROM	7	0			
Pneumonia	1	2			
MAS	1	1			
Hypoglycemia	10 (7.8)	1 (0.8)	10.76	1.48 to 470.28	0.0055*
Feeding intolerance	7 (5.4)	0	-	-	0.0073*
NEC stage ≥II	4 (3.1)	0	-	-	0.0438*
BPD	1 (0.08)	0	-	-	0.3164

TTN = transient tachypnea of the newborn, RDS = respiratory distress syndrome, MAS = meconium aspiration syndrome, PPROM = preterm prelabor rupture of membranes, NEC = necrotizing enterocolitis, BPD = bronchopulmonary dysplasia

Table 4. Short-term managements

Managements, n (%)	Late preterm (n = 129)	Term (n = 129)	OR	95% CI	*p*-value
Admission					
Newborn nursery	64 (49.6)	103 (79.8)	0.25	0.14 to 0.45	<0.0001*
Special care nursery	56 (43.4)	25 (19.4)	3.03	1.69 to 5.52	0.0001*
Level-III NICU	9 (7.0)	1 (0.01)	9.60	1.29 to 423.91	0.0099*
Respiratory support	21 (16.3)	4 (3.1)	6.07	1.95 to 25.04	0.0001*
Oxygen cannula	1	0			
Oxygen flow	6	0			
NCPAP	7	3			
Mechanical ventilation	7	1			
Total parenteral nutrition	11 (8.5)	0	-	-	0.0007*
Surfactant replacement	3 (2.3)	0	-	-	<0.0001*

NICU = neonatal intensive care unit, NCPAP = nasal continuous positive airway pressure

Table 5. Risk factors associated with late preterm births

Risk factors, n (%)	Late preterm (n = 129)	Term (n = 129)	*p*-value
Spontaneous premature labor	50 (38.8)	0	<0.0001*
Preterm prelabor rupture of membranes (PPROM)	30 (23.3)	2 (1.6)	<0.0001*
Advance maternal age (>35 years old)	19 (14.7)	4 (3.1)	0.0010*
Multiple pregnancy	12 (9.3)	0	<0.0001*
Gestational diabetes mellitus (GDM)	10 (7.8)	1 (0.7)	0.0055*
Pregnancy induced hypertension (PIH)	8 (6.2)	0	0.0041*
Intrauterine growth retardation (IUGR)	7 (5.4)	0	0.0073*
Placenta previa	3 (2.3)	5 (3.9)	0.4726

reported 23 to 33% of their late preterm infants required respiratory support and 3.3% of them required mechanical ventilation. The studies in Asia by Ma X, et al from China[12] and Tan JH, et al from Singapore[13] revealed 42.1 and 28.5%

of their late preterm infants had respiratory distress, 36.8 and 8.8% of them required respiratory support, 21.4 and 6.8% required nasal continuous positive airway pressure (NCPAP) and 15.4 and 0.3% required mechanical ventilator, respectively. The incidence of acute respiratory distress and rates of respiratory supports of late preterm infants in the present study were in between the China and Singapore's studies. TTN was the most common cause of acute respiratory distress in both late preterm and term infants (72.7% of all acute respiratory problems in each group). However, the rate of TTN was greater in late preterm infants (18.6% vs. 6.2%; OR 3.5; 95% CI 1.5 to 8.0; $p = 0.0039$) similar to the study by Lubow JM, et al[21] (12.8% vs. 2.7%, $p<0.05$). Because there was no difference in cesarean section rates between the groups, TTN was more likely caused by immature mechanism of late preterm infant that reduced ability to clear lung fluid after birth than route of delivery[8,19]. Furthermore, the incidence of acute respiratory problems in late preterm infants in the present study rapidly declined from more than 45% to 10% when gestational age reached 36 weeks. The rates of RDS requiring surfactant replacement therapy in late preterm infants reported in the present study and the study by Kitsommart R, et al[22] were comparable (60% vs. 55.8%).

Despite the fact that most of infections of late preterm infants were suspected sepsis without culture-proven bacteremia, they underwent sepsis evaluation and received antibiotic treatment. These could prolong the length of hospital stay especially for an at least 7-day course of antibiotic treatment. The rates of suspected sepsis diagnosis and management increased with decreasing gestational age. The study by Wang ML, et al[18] determined that 30.3% of late preterm infants and 16.7% of term infants required blood tests and received 7-day antibiotic treatment. Mean lengths of hospital stay in late preterm infants were similarly reported by Kitsommart R, et al[22] and the present study which significantly longer than term infants. Contrary to the study by Wang ML, et al[18] that the median lengths of hospitalization for their late preterm and term infants were comparable.

Thus fetal glycogen storage, hepatic enzyme function, hormonal regulation and sucking-swallowing coordination are maturity-related evolution. Hypoglycemia and feeding problems were significantly more common in late preterm infants than term infants. The present study found feeding intolerance and definite necrotizing enterocolitis (NEC $\geq$stage II) only in the late preterm infants. The rate of parenteral nutritional support and median duration to full enteral feeding increased with decreasing gestational age. Vachharajani AJ, et al[9] demonstrated median times to full enteral feeding were 10, 6 and 3 days at 34, 35 and 36 weeks of gestation, respectively, similar to the present study. Additionally, Kongwattanakul K, et al[25] reported that mother-infant separation during the first couple months postpartum was a factor associated with exclusive breastfeeding failure in Srinagarind Hospital.

The three majority risk factors associated with the increasing rate of preterm birth were spontaneous premature labor, preterm prelabor rupture of membranes (PPROM) and multiple pregnancy[26]. The present study demonstrated the same association in late preterm births, except for the lower rate of multiple pregnancy (9.3% vs. 12 to 28%)[7,26]. This might be partly explained by the advance of artificial reproductive technologies and delayed child bearing in developed country[7,26], thus developing country needed to anticipate this problem in the future. In addition, some risk factors associated with late preterm births were preventable such as elective cesarean section delivery and induction of labor without obstetric indications[27]. The patients and health care providers' health education including the recognition that late preterm infant could suffer more complications than term infant during antenatal care is important.

Conclusion

Late preterm infants remained at risk for prematurity-related morbidities. Because of these morbidities, they needed more intensive care when compared to infants born at term. Since spontaneous premature labor was the most common risk factor associated with late preterm births, antenatal and perinatal care is essential for early detection and prevention of preterm births. The awareness and advance postnatal care plan is also required for reduction of complications, mortality and costs of hospitalization along with the long-term monitoring of infants' outcomes.

What is already known on this topic?

Late preterm infants are at higher risk for health complications than term infants. The rates of morbidities and mortality in late preterm infants increase with decreasing gestational age. Spontaneous preterm labor is the major cause of preterm delivery. Multiple pregnancy, partly from recent advances in the use of assisted conception techniques, is one of the risk factors associated with the rising rate of late preterm births in developed country.

What this study adds?

Although the rates of late preterm births and morbidities in late preterm infants in the present study were in the same direction with the previous studies, there was more concern about temperature control. The common risk factors associated with late preterm deliveries were spontaneous premature labor, PPROM and multiple pregnancy. The multiple gestations might be the future concern for developing country.

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Potential conflicts of interest

The authors declare no conflict of interest.

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การศึกษาเปรียบเทียบผลที่เกิดในระยะสั้นของทารกเกิดก่อนกำหนดระยะท้ายและทารกครบกำหนดที่เกิดในโรงพยาบาลศรีนครินทร์

จรรยา จิระประดิษฐา, พรพิมล โรจนครินทร์, ผกาพรรณ เกียรติชูสกุล

วัตถุประสงค์: เพื่อศึกษาภาวะแทรกซ้อนในระยะสั้นที่พบในทารกเกิดก่อนกำหนดระยะท้าย (อายุครรภ์ $34^{0/7}$ ถึง $36^{6/7}$ สัปดาห์) เปรียบเทียบกับทารกครบกำหนดที่เกิดในโรงพยาบาลศรีนครินทร์และเพื่อศึกษาปัจจัยที่สัมพันธ์กับการคลอดก่อนกำหนดระยะท้ายในโรงพยาบาลศรีนครินทร์

วัสดุและวิธีการ: เป็นการศึกษาเชิงวิเคราะห์แบบไปข้างหน้าโดยการเก็บข้อมูลทั่วไปและผลลัพธ์ รวมถึงภาวะแทรกซ้อนที่เกิดในระยะสั้นของทารกเกิดก่อนกำหนดระยะท้ายและทารกครบกำหนดที่เกิดในโรงพยาบาลศรีนครินทร์เป็นระยะเวลา 1 ปี ตั้งแต่ เดือนพฤศจิกายน พ.ศ. 2552 ถึง เดือนตุลาคม พ.ศ. 2553

ผลการศึกษา: พบว่ามีทารกเกิดมีชีพทั้งหมด 2,199 คน เป็นทารกเกิดก่อนกำหนดร้อยละ 10.5 โดยมีทารกเกิดก่อนกำหนดระยะท้ายจำนวน 129 คน คิดเป็นร้อยละ 5.9 ของทารกเกิดมีชีพ มีอายุครรภ์เฉลี่ย 35.4±0.7 สัปดาห์ น้ำหนักแรกเกิดเฉลี่ย 2,520.2±470.2 กรัม ปัญหาที่พบมากที่สุดของทารกเกิดก่อนกำหนดระยะท้าย คือ ภาวะตัวเหลือง (ร้อยละ 53.3) ทารกเกิดก่อนกำหนดระยะท้ายต้องเข้ารับการรักษาในหอผู้ป่วยทารกแรกเกิด มีภาวะตัวเหลือง อุณหภูมิกายต่ำ หายใจลำบาก การติดเชื้อ น้ำตาลในเลือดต่ำ และปัญหาการกินนม มากกว่าทารกครบกำหนดอย่างมีนัยสำคัญทางสถิติ สาเหตุของภาวะหายใจลำบากที่พบบ่อย คือ ภาวะหายใจเร็วชั่วคราวในทารกแรกเกิด (ร้อยละ 72.7) และกลุ่มอาการหายใจลำบากจากการขาดสารลดแรงตึงผิว (ร้อยละ 15.2) ภาวะเจ็บครรภ์คลอดก่อนกำหนดโดยไม่ทราบสาเหตุเป็นปัจจัยที่สัมพันธ์กับการคลอดก่อนกำหนดระยะท้ายที่พบบ่อยที่สุด (ร้อยละ 38.8)

สรุป: ทารกเกิดก่อนกำหนดแม้จะเป็นระยะท้ายยังคงมีภาวะแทรกซ้อนมากกว่าทารกครบกำหนด การป้องกันไม่ให้เกิดการคลอดก่อนกำหนดระยะท้ายสามารถลดอัตราป่วย อัตราตายและค่าใช้จ่ายในการรักษาพยาบาล