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Neonatal Survival Rate following Premature Rupture of Membranes at Gestational Age 15-30 Weeks

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ABSTRACT

Objectives: To determine neonatal survival rate and associated factors in pregnancies with preterm premature rupture of membranes (PPROM) at gestational age (GA) between 15 and 30 weeks.

Materials and Methods: This retrospective descriptive study was conducted by reviewing the medical records of the pregnant women with premature rupture of membranes (PROM) at 15-30 weeks' gestation admitted at King Chulalongkorn Memorial Hospital between 1st January 2002 and 31st December 2013. Logistic regression analysis was used to determine association between factors and neonatal survival.

Results: The total number of pregnancies in this study was 99 and neonatal survival rate was 80.8% (95% confidence interval 71.4-87.8%). Women with PPROM at GA between 15 and 19^{+6} weeks had neonatal survival rate of 16.7% while neonatal survival rates of cases with PPROM at 20-23^{+6} weeks and 24-30 weeks were 50.0% and 92.2%, respectively. Factors associated with increased neonatal survival from logistic regression analysis included GA at PROM ≥ 24 weeks and tocolytic administration.

Conclusion: Neonatal survival in pregnancies with midtrimester PPROM depended on GA when PROM started. Neonates in women with PPROM at ≥ 24 weeks' gestation had more chances to survive than those with PROM at GA less than 24 weeks. Use of tocolysis was associated with increase neonatal survival.

Keywords: neonatal survival, preterm premature rupture of membranes, previable

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อัตราการรอดชีวิตของทารกแรกเกิดภายหลังภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์ที่อายุครรภ์15-30 สัปดาห์

รุจิรา มโนรมย์ภัทรสาร, ญดา คุนผลิน, สุรสิทธิ์ ชัยทองวงศ์วัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาอัตราและปัจจัยที่เกี่ยวข้องของการรอดชีวิตของทารกแรกเกิดในการตั้งครรภ์ที่มีภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์ที่อายุครรภ์ระหว่าง 15 ถึง 30 สัปดาห์*

วิธีการวิจัย: *เป็นการศึกษาเชิงพรรณาแบบย้อนหลัง โดยทบทวนข้อมูลจากเวชระเบียนของสตรีตั้งครรภ์ที่มีภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์ที่อายุครรภ์ 15-30 สัปดาห์ ที่ได้รับไว้รักษาในโรงพยาบาลจุฬาลงกรณ์ ตั้งแต่ 1 มกราคม 2545 ถึง 31 มกราคม 2556 โดยใช้การวิเคราะห์ถดถอยลอจิสติกทดสอบความสัมพันธ์ระหว่างปัจจัยต่างๆ และการรอดชีวิตของทารกแรกเกิด*

ผลการวิจัย: *จากสตรีตั้งครรภ์ทั้งหมดในการศึกษานี้ 99 ราย พบอัตราการรอดชีวิตของทารกแรกเกิดเท่ากับร้อยละ 80.8 (ช่วงความเชื่อมั่นร้อยละ 95 เท่ากับ 71.4-87.8) สตรีตั้งครรภ์ที่มีภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์ที่อายุครรภ์ 15-19^{+6} สัปดาห์ มีอัตราการรอดชีวิตคิดเป็นร้อยละ 16.7 ในขณะที่พบอัตราการรอดชีวิตของทารกแรกเกิดร้อยละ 50 และร้อยละ 92.2 ในรายที่เกิดภาวะนี้ที่อายุครรภ์ 20-23^{+6} สัปดาห์ และ 24-30 สัปดาห์ ตามลำดับ การวิเคราะห์ถดถอยลอจิสติกพบว่า อายุครรภ์ที่มีภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์ที่อายุครรภ์มากกว่า 24 สัปดาห์ และการใช้ยายับยั้งการเจ็บครรภ์คลอด เพิ่มอัตราการรอดชีวิตของทารกอย่างมีนัยสำคัญทางสถิติ*

สรุป: *การรอดชีวิตของทารกแรกเกิดในรายที่มีภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์ในไตรมาสที่สอง ขึ้นกับอายุครรภ์ที่เกิดภาวะนี้ ทารกแรกเกิดในสตรีตั้งครรภ์ที่มีภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์หลังอายุครรภ์ครบ 24 สัปดาห์ มีโอกาสมีชีวิตรอดมากกว่ารายที่เกิดก่อนอายุครรภ์ 24 สัปดาห์ การใช้ยายับยั้งการเจ็บครรภ์คลอด สัมพันธ์กับการเพิ่มอัตราการรอดชีวิตของทารกแรกเกิด*

คำสำคัญ: *อัตราการรอดชีวิตของทารก, ภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์ที่อายุครรภ์น้อยกว่า 37 สัปดาห์, อายุครรภ์ก่อนวัยเลี้ยงรอด*

Introduction

Preterm premature rupture of membranes (PPROM), defined as spontaneous rupture of the membranes at less than 37 weeks' gestation before the onset of labor, complicates around 3% of all pregnancies and is one of major causes of preterm birth. Preterm PROM during previable period or at less than 24 weeks' gestation has an incidence of 0.37% and can result in significant maternal and perinatal morbidity and mortality[1].

Management of midtrimester PROM, especially previable PROM, is still controversial because of insufficient evidences to support which management having better maternal and neonatal outcomes. The American College of Obstetricians and Gynecologists (ACOG) recommends the expectant management for patients with PROM at gestational age (GA) of 24-33^{+6} weeks[2]. The treatment consists of antibiotics to prolong latency period and single-course of corticosteroids. Termination of pregnancy and expectant management are the options of treatment for patients with PROM before 24 weeks of gestation. However, antibiotic, tocolysis, and corticosteroid are not recommended if a previable PROM is expectantly managed.

Neonatal survival rate after previable or midtrimester PROM with expectant management has been reported between 20.3% and 69.4%[1,3-9]. All prior studies are from developed countries where having high standard facilities of neonatal intensive care. Because most of Thai pregnant women refuse to terminate pregnancy in this controversial condition, we conducted the study to determine rate and associated factors of neonatal survival among Thai pregnant women who having preterm PROM at the GA of 30 weeks or less.

Materials and Methods

This study was a retrospective descriptive study by reviewing medical records of pregnant women with PROM at the GA of 15 to 30 weeks who was admitted at King Chulalongkorn Memorial Hospital (KCMH) during the 1st January 2002 to the 31st December 2013. Maternal data were collected from hospital records for demographic data, GA at PROM, treatment received, length of latency period, GA at delivery, mode of delivery and obstetric complications. Collected newborn data were birth status, birth weight, neonatal complications, neonatal death, admission to neonatal intensive care unit (NICU) and neonatal length of hospital stay. The study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University.

Standard treatment protocol of KCMH for pregnancy with PROM at GA of 24 weeks or more consisted of four 6-mg doses of dexamethasone given intramuscularly every 12 hours and antibiotics to prolong latency period. The antibiotic regimen used during study period contained intravenous ampicillin (2 g every 6 hours) for 48 hours followed by oral amoxicillin (500 mg every 8 hours) for 5 days and oral azithromycin (1 g at diagnosis and followed by 500 mg daily) or oral erythromycin (500 mg every 6 hours) for a 7-day course. Expectant management was given to patient with gestational age less than 24 weeks. The antibiotic for prolong latency period and corticosteroid were postponed until after 24 weeks of gestation. Tocolysis was prescribed only in patients with regular contraction after prolong-latency antibiotic administration. In cases with active labor less than 37 weeks' gestation, intrapartum antibiotic for group B streptococcus prophylaxis was provided. Neonatal care was supervised by the neonatologists from the Department of Pediatrics, Faculty of Medicine, Chulalongkorn University.

The primary outcome was neonatal survival rate and the secondary outcomes were factors which associated with neonatal survival. Neonatal survival was defined as livebirth neonates who survived beyond 28 days of life[10]. The statistical analysis was performed with IBM SPSS Statistics V22.0 (IBM Corp, Armonk, NY, USA). Data were presented as mean ± standard deviation, median (range) for continuous variables and percentage with 95% confidence interval (CI) for categorical variables. The student t-test or Mann-Whiney U test were used to compare continuous data between survival group and non-survival group while chi-square test or Fisher's exact test were used to compare proportions between the groups. Logistic

regression analysis was used to determine an association between factors and neonatal survival adjusted for covariates that found significant association from univariate analysis. A p-value of < 0.05 was considered statistically significant.

Results

A total of 111 pregnant women with history of PPROM between 15 and 30 weeks' gestation with expectant management were identified from the hospital database during the 1st January 2002 to the 31st December 2013. Nine cases were excluded due to incomplete neonatal information because they did not deliver in KCMH. Another three women were excluded because preterm PROM occurred within 48 hours after second-trimester amniocentesis. Finally, a total of 99 pregnant women were recruited in this study.

Maternal characteristics are shown in Table 1. Mean maternal age was 30.6 years. The mean GA at presentation was 27.0 weeks (range 17.1-30.0 weeks) and 22 cases (22.2%) had PROM at less than 24 weeks' gestation. Amniotic fluid index (AFI) at maternal admission ranged from 0 to 18 centimeters with the median of 3.2 centimeters. Eight patients (8.2%) presented with anhydramnios and 57 cases (58.2%) were found to have oligohydramnios (AFI 1-5 centimeters) at the admission.

Antibiotics for prolong latency period were prescribed to 88 patients (88.9%) when preterm PROM was diagnosed. Eleven patients who did not receive antibiotics for prolong latency period because they were diagnosed as previable PROM, preeclampsia with severe features and chorioamnionitis. Eighty-three patients (83.8%) received corticosteroid for fetal pulmonary maturation. Tocolysis were given to 49 patients (49.5%). The most commonly prescribed tocolytic agent was terbutaline.

The median of latency period was 8 days (range 0-87 days). The median GA at delivery was 28.4 weeks (range 19.0-40.9 weeks) and 5 cases (5.1%) delivered at less than 24 weeks' gestation. Cesarean section was the most common mode of delivery (50 women, 50.5%). Chorioamnionitis was the most common maternal complication and found in 26 patients (26.3%).

Neonatal outcomes are shown in Table 2. The overall neonatal survival rate was 80.8 (95% CI 71.4-87.8). There were 11 stillbirths (11.1%). These cases had PROM between 17.4 and 24.6 weeks' gestation (7 cases with GA less than 24 weeks) and delivered between 19.0 and 25.6 weeks' gestation (4 cases with GA less than 24 weeks). Eight neonatal deaths were found among 88 livebirths. The contributory causes of death were immaturity in 5 cases (62.5%), respiratory distress syndrome in 2 cases (25%) and sepsis in one case (12.5%). All of the 5 cases who died at the first day of life had PROM at less than 24 weeks' gestation. The increasing survival rate was well associated with the greater GA at diagnosis ($p<0.001$) and also with the GA at delivery ($p<0.001$) as shown in Table 2.

Body mass index, oligohydramnios, antibiotics use and duration of latency period were not significantly different between surviving and non-surviving newborn groups. GA at presentation and delivery, corticosteroids administration, tocolysis usage and neonatal birthweight were significantly different between the groups as shown in Table 3. After logistic regression analysis adjusted for factors including GA at PROM ≥ 24 weeks, corticosteroid administration, tocolytic administration, GA at delivery ≥ 28 weeks and neonatal birthweight ≥ 1000 grams, the significant factors associated with increased neonatal survival were GA at PROM ≥ 24 weeks ($p = 0.005$) and tocolytic administration ($p = 0.015$).

Of the 80 surviving newborns, 87.5% (n = 70) were admitted to NICU with the median length of stay in NICU of 36.5 days (range 2-176 days). The median length of hospital stay was 52.5 days (range 4-213 days). Seventy nine neonates (98.8%) could be discharged to home. One infant died at approximately 5 months of age due to immaturity. Morbidities of livebirth newborns are shown in Table 4. Three most common complications were respiratory distress syndrome (58 cases, 65.9%), sepsis (43 cases, 48.9%) and pneumonia (24 cases, 27.3%), respectively.

Table 1. Demographic and clinical characteristics of the participants.

Characteristics	N=99
Maternal age (years)	30.6 ± 6.4
Gravida (number)	2 (1-6)
Antenatal care visit (number)	5 (0-11)
Body mass index (kilogram/meter^2)	20.7 (14.1-34.0)
GA at PPROM (weeks)	27.0 (17.1-30.0)
AFI (centimeters)	3.2 (0-18.0)
Antibiotics for prolong latency period (cases)	88 (88.9%)
Corticosteroid administration (cases)	83 (83.8%)
Tocolytic administration (cases)	49 (49.5%)
Latency period (days)	8 (0-87)
GA at delivery (weeks)	28.4 (19.0-40.9)
Mode of delivery (cases)	
Cesarean delivery	50 (50.5%)
Spontaneous vertex delivery	38 (38.4%)
Breech assisted delivery	11 (11.1%)
Obstetric complications (cases)	
Chorioamninitis	26 (26.3%)
Fetal distress	9 (9.1%)
Postpartum hemorrhage	6 (6.1%)
Placental abruption	2 (2.0%)

Data were presented as mean ± SD, median (range) or n (%)

Table 2. Neonatal outcomes.

	Cases/Total	Percentage (95%CI)
Stillbirth rate	11/99	11.1 (5.9-19.4)
Neonatal death	8/99	8.1 (3.8-15.8)
Surviving neonate	80/99	80.8 (71.4-87.8)
Surviving neonate when categorized by GA at PROM		
15-19^{+6} weeks	1/6	16.7 (0.9-63.5)
20-23^{+6} weeks	8/16	50.0 (25.5-74.5)
24-27^{+6} weeks	38/43	88.4 (74.1-95.6)
28-30 weeks	33/34	97.1 (82.9-99.9)
Surviving neonate when categorized by GA at delivery		
< 24 weeks	0/5	0 (0-53.7)
24-27^{+6} weeks	26/35	74.3 (56.4-86.9)
28-31^{+6} weeks	48/53	90.6 (78.6-96.5)
> 32 weeks	6/6	100 (51.7-100)

Table 3. Comparison of factors between survival and non-survival neonates.

Characteristics	Survival cases (N=80)	Non-survival cases (N=19)	p value
Body mass index (kilogram/meter^2)	20.6 (14.1-34.0)	22.6 (16.7-29.2)	0.447
GA at PPROM (weeks)	27.2 (19.0-30.0)	23.0 (17.1-28.0)	< 0.001*
Oligohydramnios (cases)	32 (40.0%))	4 (22.2%)	0.186
Antibiotics for prolong latency period (cases)	73 (91.3%)	15 (78.9%)	0.214
Corticosteroid administration (cases)	73 (91.3%)	10 (52.6%)	< 0.001*
Tocolytic administration (cases)	47 (58.8%)	2 (10.5%)	< 0.001*
Latency period (days)	7 (0-87)	18 (1-68)	0.065
GA at delivery (weeks)	28.9 (24.7-40.9)	25.3 (19.0-31.7)	< 0.001*
Neonatal birthweight (grams)	177 (620-3780)	795 (300-1755)	< 0.001*

Data were presented as mean ± SD, median (range) or n (%)
* $p < 0.05$ was considered statistically significant

Table 4. Morbidities and interventions in livebirth neonates (N=88).

Characteristics	Survival cases (N=80)	Non-survival cases (N=19)	Total (N=88)
NICU admission	70 (87.5%)	8 (100%)	78 (88.6%)
Mechanical ventilator	42 (52.5%)	8 (100%)	78 (56.8%)
Oxygen therapy	68 (86.1%)	8 (100%)	76 (87.4%)
Length of stay in NICU (days)	28.5 (0-176)	1 (1-10)	24 (0-176)
Length of hospital stay (days)	52.5 (4-213)	1 (1-10)	50.5 (1-213)
Neonatal complications			
- Respiratory distress syndrome	51 (63.8%)	7 (87.5%)	58 (65.9%)
- Sepsis	37 (46.2%)	6 (75.0%)	43 (48.9%)
- Pneumonia	24 (30.0%)	-	24 (27.3%)
- Retinopathy of prematurity	20 (25.0%)	-	20 (22.7%)
- Bronchopulmonary dysplasia	14 (17.5%)	1 (12.5%)	15 (17.0%)
- Intraventricular hemorrhage	11 (13.8%)	2 (25.0%)	13 (14.8%)
- Necrotizing enterocolitis	4 (5.0%)	-	4 (4.5%)
- Pulmonary hypoplasia	3 (3.8%)	-	3 (3.4%)

Data were presented as median (range) or n (%)

Discussion

Our study revealed that the neonatal survival rate among Thai pregnant women having preterm PROM at the GA ≤ 30 weeks was 80.8%. The high proportion of survival in our study might be explained by advance in GA at PROM (median 27.0 weeks) when compared to those of the previous studies (≤ 25 weeks) [1, 3-7, 9]. When focusing on previable PROM or PROM at the GA ≤ 24 weeks, the neonatal survival rate in our study was reduced to 40.9% which comparable to those from previous reports (40.5%-44.4%)[1,5].

González-Mesa E, et al[8] demonstrated a trend

to increase perinatal survival as gestational age at diagnosis increased. Likewise, our study found that neonatal survival rates in women with preterm PROM depended on GA at diagnosis: 16.7% at GA of 15-19^{+6} weeks' gestation; 50% at 20-23^{+6} weeks' gestation; 88.4% at 24-27^{+6} weeks' gestation; and 97.1% at 28-30 weeks' gestation. Similar to previous study[9], the median GA at diagnosis and median GA at delivery among non-survived neonates were significantly lower than those of survival group. No newborn survived if delivered before 24 weeks of gestation while all newborns delivered after 32 weeks of gestation were survive.

Tocolytic administration was used in 49.5% of all cases which was much higher than those of previous reports[1,3-9]. Interestingly, this intervention was found to be associated with increase neonatal survival from the regression analysis. Because there is a risk of adverse effects of tocolytic agents, we still support to use tocolysis only in women with regular contraction post treatment with antibiotics.

Infectious morbidity is one of major maternal and neonatal complications among women with PROM. Clinical chorioamnionitis was diagnosed in 26.3% of the women in our study while it was stated in the previous studies between 25.0%-39.8%[1,3,5-7]. It was found to be as much as 90.7% of cases when chorioamnionitis was diagnosed by histology[9]. This high rate of amniotic infection may explain high risk of neonatal sepsis. Our study found neonatal sepsis in almost half of the livebirth newborns which was concordant to rates (18.6%-77.2%) from the other reports[1, 3, 6, 7].

Whether to terminate pregnancy or expectant manage of the patients with previable PROM is still controversial. Results from this study could be used for counseling the pregnant women with preterm PPROM. The further study regarding cost-effective analysis should be done to determine the proper management for this group of patients.

In conclusion, neonatal survival in pregnancies with PROM at 15-30 weeks' gestation depended on GA when PROM started. Neonates in women with PROM at ≥ 24 weeks' gestation had more chances to survive than those with PROM at GA less than 24 weeks. Use of tocolysis in these cases was associated with increase neonatal survival.

Potential conflicts of interest

The authors declare no conflict of interest.

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