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The Outcomes of Ampicillin plus Azithromycin to Prolong Latency Period in Preterm Premature Rupture of Membranes between 24 and 33^{+6} Weeks of Gestation at King Chulalongkorn Memorial Hospital

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ABSTRACT

Objectives: To determine the success rate of ampicillin plus azithromycin to prolong the latency period in cases with preterm premature rupture of membranes (PPROM).

Materials and Methods: A retrospective descriptive study was conducted. Medical records of singleton pregnancies between 24 and 33^{+6} weeks of gestation who complicated with PPROM and received ampicillin and oral azithromycin to prolong the latency period at King Chulalongkorn Memorial Hospital between January 2010 and December 2016 were reviewed. Prolonged latency period more than 48 hours was defined as success. Descriptive statistics were used for data analysis.

Results: Eighty eight pregnancies were included in the study with mean ± standard deviation age of 30.4 ± 5.6 years and mean gestational age of 31.3 ± 2.5 weeks. The median of latency period was 96 hours (interquartile range 60-192 hours) and 76 cases (86.4%) reached more than 48 hours of latency period. Seven women (8.0%) complicated by chorioamnionitis with 1 case of maternal sepsis. Regarding neonatal outcomes, respiratory distress syndrome (RDS) complicated in 29 neonates (33.0%) and 12 cases (13.6%) needed ventilator. Forty eight cases (54.5%) found neonatal sepsis along with 3 (3.4%) neonatal deaths.

Conclusion: Antibiotic regimen including ampicillin and azithromycin was effective to prolong latency period in most women presented with PPROM. However, one-third of the neonates complicated with RDS and neonatal sepsis was found in more than half of the cases. Further study is needed to identify regimens that may improve neonatal outcomes.

Keywords: antibiotic, azithromycin, premature rupture of membrane, prolong latency period.

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ผลการรักษาของแอมพิซิลลินร่วมกับอะซิโทรมัยซินเพื่อยืดระยะเวลาก่อนคลอดในภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์ช่วงอายุครรภ์ระหว่าง 24 และ 33^{+6} สัปดาห์ ในโรงพยาบาลจุฬาลงกรณ์

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บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาร้อยละของความสำเร็จในการยืดระยะเวลาก่อนคลอดในผู้ป่วยภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์ช่วงอายุครรภ์ก่อนครบกำหนด*

วัสดุและวิธีการ: *การศึกษาเชิงพรรณนาแบบย้อนหลัง โดยทบทวนเวชระเบียนของหญิงตั้งครรภ์เดี่ยวที่เข้ารับการรักษาตัวในโรงพยาบาลจุฬาลงกรณ์ เนื่องจากมีภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์ช่วงอายุครรภ์ระหว่าง 24 และ 33^{+6} สัปดาห์ และได้รับยาแอมพิซิลลินร่วมกับอะซิโทรมัยซิน เพื่อยืดระยะเวลาก่อนคลอด ระหว่างเดือนมกราคม พ.ศ. 2553 ถึงเดือนธันวาคม พ.ศ. 2559 ความสำเร็จของการยืดระยะเวลาก่อนคลอด นับเมื่อมีระยะเวลาก่อนคลอดนานกว่า 48 ชั่วโมง และวิเคราะห์ข้อมูลโดยใช้สถิติเชิงพรรณนา*

ผลการศึกษา: *การศึกษาข้อมูลหญิงตั้งครรภ์รวม 88 ราย มีอายุเฉลี่ย ± ส่วนเบี่ยงเบนมาตรฐาน เท่ากับ 30.4 ± 5.6 ปี และอายุครรภ์เฉลี่ย 31.3 ± 2.5 สัปดาห์ ค่ามัธยฐานของระยะเวลาก่อนคลอดเท่ากับ 96 ชั่วโมง (ค่าพิสัยระหว่างควอไทล์ 60-192 ชั่วโมง) โดยมี 76 ราย (ร้อยละ 86.4) ที่สามารถยืดระยะเวลาก่อนคลอดได้นานกว่า 48 ชั่วโมง ผู้ป่วย 7 ราย (ร้อยละ 8.0) เกิดการอักเสบของถุงน้ำคร่ำ และพบการติดเชื้อในกระแสเลือด 1 ราย ผลในทารกแรกเกิดพบภาวะกลุ่มอาการหายใจลำบากรวม 29 ราย (ร้อยละ 33.0) และ 12 ราย (ร้อยละ 13.6) ต้องใช้เครื่องช่วยหายใจ และพบทารกติดเชื้อในกระแสเลือดจำนวน 48 ราย (ร้อยละ 54.5) และมีทารกเสียชีวิต 3 ราย (ร้อยละ 3.4)*

สรุป: *สูตรยาปฏิชีวนะประกอบด้วยแอมพิซิลลินและอะซิโทรมัยซินมีประสิทธิภาพในการยืดระยะก่อนคลอดในหญิงตั้งครรภ์ส่วนใหญ่ที่เกิดภาวะถุงน้ำคร่ำแตกก่อนการเจ็บครรภ์ช่วงอายุครรภ์ก่อนครบกำหนดอย่างไรก็ตาม หนึ่งในสามของทารกแรกเกิดพบภาวะกลุ่มอาการหายใจลำบาก และพบทารกติดเชื้อในกระแสเลือดมากกว่าครึ่งหนึ่งของทารกทั้งหมด จำเป็นต้องมีการศึกษาต่อไปเพื่อหาสูตรยาปฏิชีวนะที่อาจช่วยให้ผลลัพธ์ในทารกแรกเกิดดีขึ้น*

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Introduction

Preterm birth, of which the global incidence approximately 15 million each year[1,2], is the leading cause of neonatal morbidity and mortality. In 2010, the estimated preterm birth rates worldwide were ranging from 5% to 18% of all livebirths[2]. Similarly, about 14% of all neonates born at King Chulalongkorn Memorial Hospital (KCMH) during the years 2008-2017 were preterm babies. Preterm premature rupture of membranes (PPROM) is accounted for one-third of spontaneous preterm births and frequently associated with intra-amniotic infection and inflammation[3,4]. PPROM could lead to maternal infectious complications including chorioamnionitis, sepsis and postpartum endometritis, while babies born after PPROM commonly complicated with respiratory distress syndrome (RDS), neonatal sepsis, pneumonia and death[5]. Surviving neonates may pose long-term neurodevelopmental consequences including cerebral palsy[6] that would be a burden to their parents.

The benefits of antibiotic therapy after PPROM were confirmed to prolong latency periods and reduce chorioamnionitis and short-term neonatal morbidities[7]. As a result, several national guidelines[8-10] recommend the use of prophylactic antibiotics in cases of PPROM. For management of PPROM between 24 and 33^{+6} weeks of gestation, the American College of Obstetricians and Gynecologists (ACOG) suggests a 7-day course of therapy with a combination of intravenous ampicillin and erythromycin followed by oral amoxicillin and erythromycin to prolong latency together with a single-course corticosteroids to promote neonatal lung maturity[10].

Erythromycin is endorsed by the ACOG and other national organizations for the first line antibiotic regimen for PPROM[8-10] because it is one of the well-studied regimens[7]. However, clinical use of erythromycin faces problems of poor compliance due to its gastrointestinal side effects and number of dosages per day. In addition, the intravenous erythromycin formulation is not available at KCMH. Azithromycin is a newer macrolide derivatives that has a longer half-life allowing for once a day regimen, excellent tissue distribution, minimal drug interaction and similar pharmacokinetics of intravenous and oral formulations[11-13]. Antibiotic regimens used for prolongation of latency period in cases with PPROM at KCMH includes intravenous ampicillin (2 g every 6 hours) for 48 hours following by 5 days of oral amoxicillin (250 mg every 8 hours) and oral erythromycin (250 mg every 6 hours) for 7 days. Due to easier administration, replacement of erythromycin with oral azithromycin (500 mg on the first day following by 250 mg every 24 hours for 6 days) for PPROM at KCMH is increasing. Because of limited information of azithromycin-included regimen, this study was conducted to determine the effectiveness of the antibiotic regimen including ampicillin plus azithromycin to prolong the latency period in cases with PPROM in term of success rate, maternal and neonatal morbidities.

Materials and Methods

This retrospective descriptive study was approved by The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Medical records of pregnant women who diagnosed as PPROM at gestational age between 24 and 33^{+6} weeks and admitted at King Chulalongkorn Memorial Hospital between January 2010 and December 2016 were reviewed. Singleton pregnancies between 24 and 33^{+6} weeks of gestation with clinical presentation of PROM without labor pain and received ampicillin plus azithromycin to prolong latency period were included. Cases having fetal lethal anomaly, history of fetal surgery or genetic amniocentesis in the current pregnancy were excluded. The perinatal outcomes of PPROM after genetic amniocentesis are significantly better than spontaneous PPROM at a similar gestational age[14] while outcomes of fetal surgery depend on the nature of diseases. Rupture of membranes was primarily diagnosed by combination of history of fluid leakage and visualization of amniotic fluid pooling in the vagina during sterile speculum examination and/or positive arborization test. The patients included in this study received antibiotic regimen using ampicillin plus azithromycin to prolong latency period. The regimen included ampicillin 2 g intravenously every 6 hours for 48 hours then amoxicillin 500 mg orally three times a day and azithromycin 500 mg orally for one day then

250 mg orally once daily for 6 days.

Data collection included demographic and baseline information: maternal age, gravidity, parity, marital status, underlying diseases, history of previous preterm delivery, total number of prenatal care visit, gestational age on admission, and duration from membranes rupture to admission, investigation results on the day of admission: amniotic fluid index, hemoglobin level, white blood cell count, percentage of neutrophils, urine analysis, urine culture, and cervical swab culture, and receiving interventions: tocolysis, and steroids to promote fetal lung maturity. The primary outcome of this study was percentage of women being success on prolongation of the latency period. Latency period was determined by the time interval from membranes rupture to delivery and the latency period of more than 48 hours defined as success. The secondary outcomes were the latency period, maternal complications and neonatal complications. Maternal complications included placental abruption, prolapsed umbilical cord, acute chorioamnionitis, sepsis and death. Neonatal outcomes focused on birthweight, Apgar scores, RDS, use of ventilator, neonatal intensive care unit (NICU) admission, neonatal sepsis, mortality and length of hospital stay.

The sample size was calculated by using the formula for a binary outcome in single population[15]. According to Phupong et al study[16], the proportion of women who success in prolongation of the latency was 0.647. Eighty-eight women were needed when an alpha error was 0.05 and an acceptable error was 0.1. Statistical analysis was performed with SPSS software package version 22.0 (IBM Corp., Armonk, NY, USA). Quantitative data were presented as mean and standard deviation (SD) or median and interquartile range (IQR) and a comparison was done by student t-test or Mann-Whitney U test. Percentages were used to describe qualitative data and compared by chi-square test or Fisher exact test. P value of less than 0.05 was considered statistically significant.

Results

From January 2010 through December 2016, 88 women were met the criteria and included in the study. Seven women having amniocentesis during second trimester for prenatal diagnosis were excluded. Baseline maternal characteristics were shown in Table1. Mean maternal age was 30.4 years and mean gestational age on admission was 31.3 weeks. Most of the women were nulliparous. Median duration from membranes rupture to admission was 4.4 hours.

Table 1. Baseline characteristics of the pregnant women.

Characteristics	N = 88
Age (years)[a]	30.4 ± 5.6
Gravidity[b]	
1	41 (46.6%)
2	23 (26.1%)
3	15 (17.1%)
4	8 (9.1%)
5	1 (1.1%)
Parity[b]	
Nulliparity	55 (62.5%)
Multiparity	33 (37.5%)
Number of prenatal care visit (times)[c]	6 (4-7)
Gestational age on admission (weeks)[a]	31.3 ± 2.5
Duration from membrane rupture to admission (hours)[c]	4.4 (3.0-9.0)
Amniotic fluid index[c]	6.5 (2.9-9.1)

[a] presented as mean ± standard deviation, [b] presented as number (%), [c] presented as median (interquartile range)

Cervical swab cultures were noted in 78 women and most of the cases reported negative results. Among cases with positive culture (N=19), group B streptococcus and Escherichia coli (E. coli) was found in 5 cases and 4 cases, respectively (Table 2).

To promote fetal lung maturity in pregnant women complicated with preterm labor or PPROM at KCMH, a regimen of dexamethasone 6 mg intramuscularly every 12 hours for 4 doses is used. Dexamethasone were prescribed in all study women, but 88.6% of cases received completed course and 62 women (70.5%) received tocolytic agents (Table 3). Tocolysis was used in the cases having regular uterine contraction after admission without any signs of chorioamnionitis, non-reassuring fetal status, or cervical dilatation ≥ 4 centimeters.

Seventy-six women (86.4%) were success to prolong the latency period while the median latency period was 96 hours. Chorioamnionitis occurred in 7 cases (8.0%) who having the latency period between 3 and 596 hours. One out of 88 women showed clinical sepsis. E.coli was found positive in her cervical swab and urine culture. No maternal death was noted.

Table 2. Microbiology of cervical swab culture on admission.

Organism	Number (%) (N = 78)
Yeast	6 (7.7%)
Group B streptococcus	5 (6.4%)
Escherichia coli	4 (5.1%)
Streptococcus viridans	2 (2.6%)
Acinetobacter baumannii	1 (1.3%)
Group D streptococcus	1 (1.3%)
No growth	59 (75.6%)

Table 3. Interventions, pregnancy and maternal outcomes.

Characteristics	N = 88
Tocolytic use[a]	62 (70.5%)
Number of dexamethasone received[a]	
1 dose	4 (4.5%)
2 doses	2 (2.3%)
3 doses	4 (4.5%)
4 doses	78 (88.6%)
Latency period (hours)[b]	96 (60-192)
Prolonged latency period > 48 hours[a]	76 (86.4%)
Chorioamnionitis[a]	7 (8.0%)
Sepsis[a]	1 (1.1%)

[a] presented as number (%), [b] presented as median (interquartile range)

Regarding neonatal outcomes, the mean gestational age at birth was 32.3 weeks with the mean birthweight of 1,837 grams (Table 4). Most of the neonates had Apgar scores at 1 and 5 minutes equal to or greater than 7; however, 29.5% of them needed NICU admission. One-third (29/88) of the

newborns complicated with RDS and ventilation support was needed in 12 cases. Neonatal sepsis was diagnosed in 54.5% of all cases and there were three neonatal deaths. Fetal lung hypoplasia were suspected in all non-survived cases because they were born at between 27 weeks and 31 weeks of gestation with extremely low birth weight after complicated by severe oligohydramnios. Among surviving babies, the median length of stay was 10 days.

Table 4. Neonatal outcomes.

Characteristics	N = 88
Gestational age at birth (weeks)[a]	32.3 ± 2.0
Birthweight (grams)[a]	1,837 ± 425
Apgar score at 1 minute < 7[b]	18 (20.5%)
Apgar score at 5 minute < 7[b]	9 (10.2%)
Neonatal intensive care unit admission[b]	26 (29.5%)
Respiratory distress syndrome[b]	29 (33.0%)
Ventilation support[b]	12 (13.6%)
Neonatal sepsis[b]	48 (54.5%)
Neonatal death[b]	3 (3.4%)
Length of stay (days)[c]	10.0 (7.0-25.5)

[a] presented as mean ± standard deviation, [b] presented as number (%), [c] presented as median (interquartile range)

Discussion

Because neonatal morbidities and survival are associated with gestational age at birth[5], one of the goals in the management of PPROM is to extend latency period[17]. The present study found that ampicillin plus azithromycin could prolong the latency period of more than 48 hours in 86.4% of women presented with PPROM between 24 and 33^{+6} weeks of gestation. The success rate in the present study seem to be higher than those (64.7%) in the prior report[16] that reviewed cases with PPROM between 28 and 34 of gestation at KCMH from 1997 to 2009. During that time period, the antibiotic regimen for PPROM at KCMH consisted of ampicillin plus one of macrolide group: erythromycin, azithromycin or roxithromycin[16].

Although the guidelines[8-10] recommend antibiotic regimen including ampicillin plus erythromycin, an increasing use of oral azithromycin in place of erythromycin has been reported[16,17]. These antibiotics have similar antimicrobial coverage, but azithromycin is easier for administration than erythromycin. Two retrospective studies of women with PPROM between 23 and 34 weeks of gestation reported no difference in latency period between those who received ampicillin plus erythromycin and those who received ampicillin plus azithromycin[18,19]. The median latency period in women receiving ampicillin plus a single oral dose of 1 gram azithromycin in the study by Finneran et al[19] was 5.9 days (IQR 3.1-12.1 days) that comparable to those found in the present study (4 days, IQR 2.5-8 days). The study by Pierson et al[18] did not found difference of maternal and neonatal outcomes between women receiving erythromycin and women receiving azithromycin while cesarean section rate and positive neonatal blood culture were higher in women receiving erythromycin in Finneran et al study[19].

Clinical chorioamnionitis complicated in 8.0% of the women in the present study that similar to 8.6% of women receiving azithromycin reported in the study by Pierson et al[18]. However, the percentage of neonatal sepsis in the present study was much higher than those in the previous studies[18,19]. This disparity may be

explained by diverse criteria used for diagnosis. The neonatologists at KCMH defined neonatal presumed sepsis as neonatal sepsis that were 54.5%, but only 3.4% of all neonates were found positive blood culture. On the other hand, Finneran et al study used blood culture positive for bacteria as criteria to diagnose neonatal sepsis that reported in 4.1% of neonates delivered from women receiving azithromycin.

Two-thirds of the neonates delivered from women in azithromycin group from the previous studies were complicated with RDS[18,19] while it was noted in 33.0% of neonates in the present study. This discrepancy may be due to more advanced gestational age at birth of the newborns in the present study (mean gestational age 32.3 weeks) when compared to the previous studies (30-31 weeks of gestation)[18,19]. Nevertheless, neonatal death rates were not different between the present study (3.4%) and previous studies (2.2% and 4.0%)[18,19].

Drug administration of azithromycin practically is more convenient than erythromycin. If it is not inferior to erythromycin in term of clinical effectiveness, it may be a good choice for an antibiotic regimen in women complicated by PPROM. A recent study focusing on cost analysis of using azithromycin compared with erythromycin in treatment of pregnancies with PPROM demonstrated that azithromycin substituted for erythromycin in the antibiotic regimen had a potential for substantial cost reduction[20].

There was limited information of azithromycin use for antibiotic regimen in the treatment of PPROM. The present study reported outcomes of the regimen including ampicillin plus 7-day course of azithromycin. Since it was a retrospective study, a number of confounding factors may impact the interested outcomes such as tocolytic use. Other limitations of the study were incomplete data of the reviewed medical records and not having a control group. Although cervical swab culture is a routine practice for the management of PPROM at King Chulalongkorn Memorial Hospital, there were 10 medical records (11.4%) in the present study that cervical swab culture results are not available. A randomized controlled trial comparing outcomes between regimen including azithromycin and regimen including erythromycin should be conducted to confirm the non-inferiority of azithromycin. Furthermore, advantages of azithromycin including fewer side effects, better compliance and cost-effectiveness should be investigated.

Conclusion

In conclusion, antibiotic regimen including ampicillin and azithromycin was effective to prolong latency period in most women presented with PPROM. However, one-third of neonates complicated with RDS and more than half of them were presumed sepsis. Further study is needed to identify regimen that may improve neonatal outcomes.

Potential conflicts of interest

The authors declare no conflict of interest.

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