Thai Journal of Obstetrics and Gynaecology
April 2020, Vol. 28, No. 2, pp. 103-111

OBSTETRICS

The Effect of Single Dose Antenatal Dexamethasone in Reducing Respiratory Complications in Late Preterm

Adisak Waiketkarn, M.D.*,
Charintip Somprasit, M.D.*,
Chamnan Tanprasertkul, M.D., Ph.D.*,**.

** Department of Obstetrics and Gynecology, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand*
*** Center of excellence in Applied Clinical Epidemiology, Thammasat University, Pathum Thani, Thailand*

ABSTRACT

Objectives: To determine the effect of a single dose of dexamethasone in reducing respiratory complications in late preterm newborns.

Materials and Methods: This was a prospective cohort study. Pregnant women who were at risk of preterm births at $34^{0/7}$ - $36^{6/7}$ weeks of gestation were prospectively observed. The first group was given single dose of antenatal dexamethasone, while the second group received only the standard treatment without dexamethasone as the control group. The main outcomes are rate of respiratory complications in newborns.

Results: A total of 205 pregnant women who were enrolled with complete data for analysis. Sixty-eight and 137 were in the single dose and control groups, respectively. The rates of respiratory complications in all gestational ages between the two groups were not significantly different (22.1% and 32.8%, respectively: $p = 0.11$). Multivariate logistic regression model was utilized to adjust confounders for independent factors of respiratory complications in late preterm newborns. A single dose of dexamethasone and gestational age at $36^{0/7\text{-}6/7}$ weeks became significant factors in order to decrease respiratory complication rate and received an adjusted odds ratio of 0.45 and 0.29 at $p = 0.03$ and $p = 0.001$, respectively.

Conclusion: Administration of a single dose of dexamethasone is a factor in reducing rate of respiratory complications in late preterm newborns without any seriously adverse effects.

Keywords: late preterm, respiratory complications, corticosteroids, dexamethasone.

Correspondence to: *Charintip Somprasit, M.D., Department of Obstetrics and Gynecology. Faculty of Medicine, Thammasat University, Pathum Thani 12120, Thailand, E-mail: csomprasit@gmail.com*

Received: 24 September 2018, **Revised:** 24 December 2018, **Accepted:** 26 December 2018

ผลของการได้ยาเด็กซาเมทธาโซนก่อนคลอดเพียงหนึ่งครั้งในการลดภาวะแทรกซ้อนทางระบบทางเดินหายใจในทารกที่คลอดก่อนกำหนดระยะท้าย

อดิศักดิ์ ไวเขตการณ์, จรินทร์ทิพย์ สมประสิทธิ์, ชำนาญ แท่นประเสริฐกุล

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลของการได้รับยาเด็กซาเมทธาโซน 1 ครั้ง ในการลดภาวะแทรกซ้อนทางระบบทางเดินหายใจในทารกที่คลอดก่อนกำหนดระยะท้าย*

วัสดุและวิธีการ: *เป็นการศึกษาเชิงเปรียบเทียบแบบไปข้างหน้า โดยทำการติดตามศึกษาในสตรีตั้งครรภ์ที่มีอายุครรภ์ระหว่าง 34 สัปดาห์ ถึง 36 สัปดาห์ 6 วัน ที่มีภาวะเสี่ยงต่อการคลอดก่อนกำหนด โดยกลุ่มแรกได้รับยาเด็กซาเมทธาโซน 1 ครั้งก่อนคลอด ในขณะที่กลุ่มที่สองได้รับการดูแลตามมาตรฐาน และไม่ได้รับยาเป็นกลุ่มควบคุม โดยทำการศึกษาเปรียบเทียบผลการลดการเกิดภาวะแทรกซ้อนทางระบบทางเดินหายใจในทารก*

ผลการศึกษา: *อาสาสมัคร 205 คน ที่ข้อมูลครบถ้วนเพียงพอต่อการวิเคราะห์ เป็นกลุ่มที่ได้รับยาเด็กซาเมทธาโซน 68 คน และไม่ได้รับยา 137 คน เมื่อเปรียบเทียบการเกิดภาวะแทรกซ้อนทางระบบทางเดินหายใจโดยรวมพบว่า ไม่แตกต่างกันระหว่างทั้งสองกลุ่ม (ร้อยละ 22.1 และร้อยละ 32.8 ตามลำดับ, p = 0.11) แต่เมื่อวิเคราะห์โดยความสัมพันธ์ถดถอยแบบพหุปัจจัย โดยการกำจัดปัจจัยรบกวนพบว่า การได้รับยา 1 ครั้ง และการคลอดที่อายุครรภ์ 36 สัปดาห์ ถึง 36 สัปดาห์ 6 วัน เป็นปัจจัยอิสระที่ทำให้ทารกแรกเกิดมีภาวะแทรกซ้อนทางระบบทางเดินหายใจลดลง อย่างมีนัยสำคัญทางสถิติ โดยมีอัตราความน่าจะเป็นที่ปรับแล้ว เท่ากับ 0.45 และ 0.29 ที่ค่า p = 0.03 และ 0.001 ตามลำดับ*

สรุป: *การให้ยาเด็กซาเมทธาโซน 1 ครั้งก่อนคลอด ในสตรีตั้งครรภ์ที่มีความเสี่ยงต่อการคลอดก่อนกำหนดระยะท้าย เป็นปัจจัยที่สามารถช่วยลดภาวะแทรกซ้อนทางระบบทางเดินหายใจในทารกได้ โดยไม่พบผลข้างเคียงที่รุนแรง*

คำสำคัญ: *คลอดก่อนกำหนดระยะท้าย, ภาวะแทรกซ้อนทางระบบทางเดินหายใจ, คอร์ติโคสเตียรอยด์, ยาเด็กซาเมทธาโซน*

Introduction

Antenatal corticosteroids have been recommended to pregnant women who were diagnosed of possible preterm births before 34 weeks of gestation for fetal lung maturity acceleration[1-3]. However, in pregnant women who were diagnosed of preterm birth at gestational age more than 34 weeks, the administration of antenatal corticosteroids was in controversy[3].

In Thailand, some obstetricians prescribed antenatal corticosteroids in pregnant women with preterm labor at gestational age more than 34 weeks while some obstetricians did not prescribe it. A single course of betamethasone (antenatal corticosteroids) for pregnant women between $34^{0/7}$ and $36^{6/7}$ weeks was recommended by The Society for Maternal-Fetal Medicine in year 2016[4] and the American College of Obstetricians and Gynecologists (ACOG) in year 2017[1]. However, betamethasone is not widely available in Thailand. Intramuscular 6 mg dexamethasone every 12 hours for 4 consecutive doses were alternative used. The Cochrane database review demonstrated that betamethasone was not superior to dexamethasone for accelerating lung maturation for women at risk of preterm birth[5]. At Thammasat University Hospital, most late preterm cases did not receive a complete course of dexamethasone per protocol. Advanced progression of labor and lack of recommendations being made for inhibiting labor in late preterm cases were still controversial. The practice of antenatal corticosteroids administration in these cases heavily depended on the personal preference of individual obstetricians. The aim of this study was to evaluate the effects of a single dose of antenatal dexamethasone in late preterm cases in reducing respiratory complications in newborns.

Materials and Methods

The prospective cohort study was conducted in the labor room and newborn-care unit of Thammasat University Hospital, a tertiary medical care center outskirt of Bangkok. We enrolled singleton pregnant women at $34^{0/7}$ weeks to $36^{6/7}$ weeks of gestation who had preterm labor pain and received only one dose of dexamethasone before delivery between November 2016 and May 2018. Preterm labor is defined as a regular uterine contraction of at least 4 times in 20 minutes or 8 times in 60 minutes with at least 1 cm. cervical dilatation, and /or at least 80% effacement. Their gestational ages (GA) were confirmed by ultrasonography during their first trimesters or by their last menstrual periods on the basis of certain dates. Participants who had fetuses with growth restriction or fetal anomalies and patients who received corticosteroids during current pregnancy, advanced cervical dilatation more than 8 cm., pregnancy complications such as pre-gestational diabetes mellitus (DM) gestational diabetes mellitus (GDM), pregnancy-induced hypertension or placenta previa, or evidence of maternal or fetal infection were excluded from the study. All eligible participates consecutively enrolled in the study during the studied period and were divided into two groups based on physicians' decisions. The study group was the pregnant women who received only a single dose of 6 mg dexamethasone intramuscularly before delivery. Those who were not given dexamethasone were defined as the control group. The standard care for pregnant women with preterm labor was applied by working up for specific causes of preterm labor such as infection or premature ruptured of membranes. The assessment of fetal well-beings and maternal conditions were conducted in every patients. Tocolytic medications were not utilized in these groups of patients.

The research protocol was reviewed and approved by the Institutional Review Board of Faculty of Medicine at Thammasat University, Thailand (IRB: MTU-EC-OB-2-167/59). The inform consent was obtained from all participants. Demographic data including maternal age, parity, body mass index, number of antenatal visits and gestational age at admittance and delivery were recorded. Primary outcomes consisted of respiratory complications and its prevalence. It included the respiratory-distress

syndrome (RDS) defined as tachypnea development, the chest wall retracts and expiration accompanied by grunting and nostril flaring, the chest radiograph shows a diffuse reticulogranular infiltrate and air bronchogram[6]. Transient tachypnea of the newborn (TTNB) is a clinical diagnosis. Chest radiograph finding were used to look at increased lung volumes with flat diaphragms, mild cardiomegaly, prominent vascular markings in a sunburst pattern originating at the hilum, fluid often seen in the interlobar fissures, possible pleural effusions, and possibility of alveolar edema appeared as fluffy densities. Tachypnea is defined as respiratory rate > 60 breaths per minute[7]. Grunting and retraction of newborns who need ventilators or oxygen support after birth as diagnosed by neonatologist on the basis of standard criteria were also included. The secondary outcomes were prevalence of neonatal hypoglycemia and length of hospital stay.

The sample size was calculated based on result of an earlier study by Balci et al[8]. By testing two independent proportions with two-tailed test, with an α error of 5%, 80% power and ratio at 2:1. The number of participants in study and control group were approximately 67 and 134, respectively. For statistical analysis, baseline characteristics were analyzed and presented as frequency, percentage, mean with standard deviation or median with interquartile range. Continuous data were compared among groups using unpaired T-test or Wilcoxon rank-sum test. Chi- squared or Fisher exact tests were used to compare categorical data. Each variable was analyzed for outcome of respiratory complications, all significant factors were then included in the multivariate logistic regression.

Results

During the period of study, 210 cases of pregnant women were enrolled. Of these, 140 women not receiving antenatal dexamethasone were in the control group. Seventy participants who received single dose dexamethasone were classified as the study group. In the control group, 3 participants had incomplete data, 137 participants had enough data for the analysis. In the study group 2 participants had incomplete data. As a result, 68 participants were providing complete data for further analysis (Fig. 1).

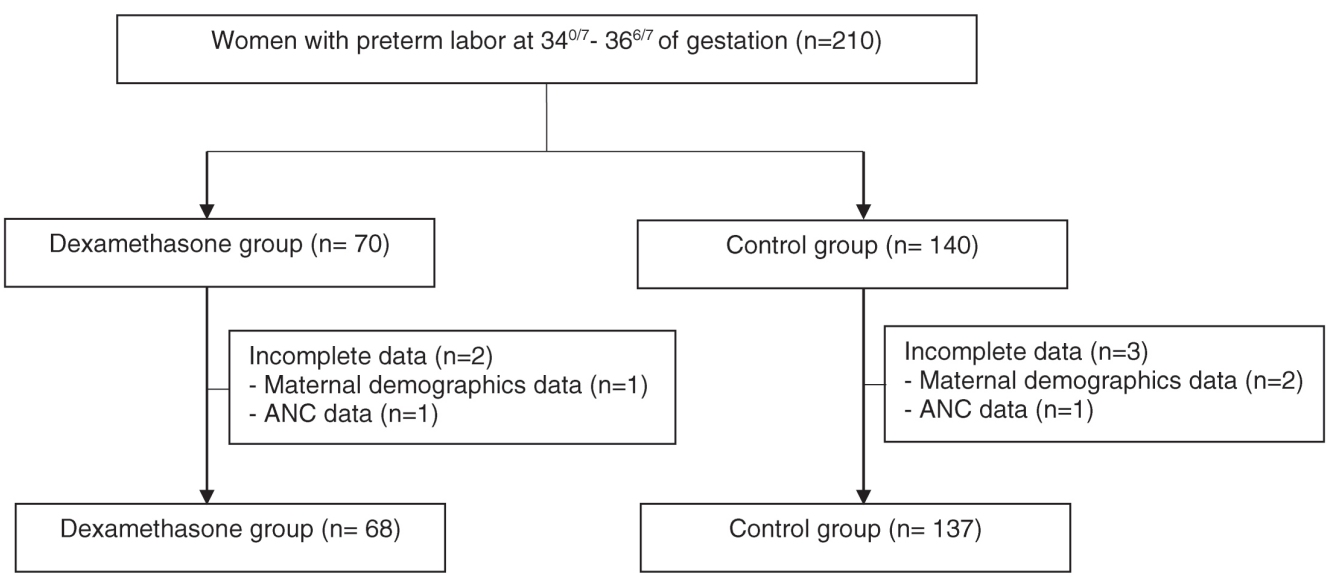

Fig. 1. Participant flow diagram.

As shown in Table 1, demographic data consisted of maternal age, parity, pre-pregnancy body mass index (BMI) and number of total antenatal visits (ANC). The two groups revealed no significant differences in these baseline clinical characteristics. Most of the participants in both groups were nulliparous and had more than 4 antenatal visits. However, the gestational age at delivery between both groups were statistically different ($p < 0.001$).

Table 1. Clinical characteristics of patients participating.

	Study (n=68)	Control (n=137)	p value
Age (year)*	28.3±6.5	28.7±6.9	0.53
Parity**			
Nulliparous	43 (63.2)	74 (54.0)	
Multiparous	25 (36.8)	63 (46.0)	
BMI (kg/m^2)*	26.2±3.9	26.8±5.0	0.39
ANC (time)**			0.29
< 4	15 (22.1)	22 (16.1)	
≥ 4	53 (77.9)	115 (83.9)	
GA at delivery (week)**			< 0.001
340/7-6/7	14 (20.6)	17 (12.4)	
350/7-6/7	28 (41.2)	28 (20.4)	
360/7-6/7	26 (38.2)	92 (67.2)	
all***	35 (35,36)	36 (35,36)	< 0.001

* mean±SD (standard deviation), ** n(%), *** median (iqr).

As shown in Table 2, the rate of respiratory complications in all gestational ages between the two groups were not significantly different (22.1% and 32.8%, respectively: p=0.11). When stratified to each gestational age, respiratory complications between the two groups at $34^{0/6-6/7}$ and $35^{0/6-6/7}$ weeks gestational age were not different. However, at $36^{0/6-6/7}$ weeks of gestational age, the rate of respiratory complications was 7.7 and 28.3% which was significantly different (p=0.047). The mean newborn birth weight (BW), mode of delivery, hypoglycemia and length of hospital stay (LOS) of newborn of both groups were not significantly different.

Factors related with respiratory complications in newborns were analyzed by multivariate logistic regression. After adjusting the confounders, a gestational age of $36^{0/7-6/7}$ weeks and the administering of a single dose of dexamethasone before delivery could independently decreased the risk of respiratory complications by 55%. The adjusted odd ratios were 0.29 and 0.45 with p-values at 0.001 and 0.03, respectively as showed in Table 3.

Table 2. Comparison of neonatal and maternal outcomes.

	Study (n=68)	Control (n=137)	p value
Respiratory			
Complications**			
All	15 (22.1)	45 (32.8)	0.11
$34^{0/7-6/7}$	5/14 (35.7)	9/17 (52.9)	0.55
$35^{0/7-6/7}$	8/28 (28.6)	10/28 (35.7)	0.68
$36^{0/7-6/7}$	2/26 (7.7)	26/92 (28.3)	0.047
Mode of delivery**			
Normal labor	49 (72.1)	94 (68.6)	
Cesarean section	19 (27.9)	43 (31.4)	
BW (grams)*	2,606±312.4	2,668.2±478.7	0.45
Time (hour)*	6.47±2.0	6.56±4.81	0.27
Hypoglycemia**	11 (16.2)	18 (13.1)	0.56
LOS (days)***	3 (3)	3 (3)	0.48

* mean±SD, ** n(%), *** median (iqr), Time: Time from injection of dexamethasone to delivery.

Table 3. Independent factors of respiratory complications by multivariate logistic regression analysis.

Factors	Adjusted odd ratio	p value	95% CI
Parity			
Nulliparous	1.00 (ref)		
Multiparous	0.77	0.27	0.48-1.23
Mode			
Normal labor	1.00		
Cesarean section	1.2	0.124	0.95-1.52
GA (week)			
$34^{0/7-6/7}$	1.00 (ref)		
$35^{0/7-6/7}$	0.59	0.19	0.27-1.3
$36^{0/7-6/7}$	0.29	0.001	0.14-0.62
Dexamethasone (dose)			
0	1.00 (ref)		
1	0.45	0.03	0.22-0.93

* mean±SD, ** n(%), *** median (iqr), Time: Time from injection of dexamethasone to delivery.

Discussion

Respiratory complications rate in control group was 32.8%. The result of this finding is similar to data from the Consortium on Safe Labor that reported

respiratory morbidity rate in late preterm infants at nearly 40%[9]. The respiratory complications rate progressively decreased with an increasing gestational age. Our data showed that half of this complications occurred in the 34th weeks of gestational age, then continuously decreased to 28.3% at the 36th weeks of gestational in the control group. This finding was consistent with the study of Porto et al[10]. In their study, Porto and coworkers demonstrated that respiratory morbidity was substantially reduced according to gestational age, at the rates of 47, 21 and 18% in newborns at $34^{0/7\text{-}6/7}$, $35^{0/7\text{-}6/7}$ and $36^{0/7\text{-}6/7}$ weeks, respectively. Their data strongly supported that increased gestational age as the main factor leading to less newborn respiratory complications. The more advanced the gestational age of newborn, the less are the chances of neonatal morbidity. It was estimated that there was a 23% decrease in adverse outcomes with each additional week of GA[11].

In our study, the rates of respiratory complications was rather high. The reason is that our data combined all severity of respiratory problems that needed oxygen support or monitoring, including such problems as RDS, TTNB, tachypnea or grunting. The rational for the effect of the use of dexamethasone associated with non-severe respiratory complications such as tachypnea or grunting are that corticosteroids could stimulate pneumocyte type 2 and decrease lower alveolar surface tension including the prevention of alveolar collapse[3]. This proposed mechanism could possibly be used to explain the benefit of steroid to the reduction of non-severe respiratory problems.

Despite the fact that some of these complications were non-severe, they could still have effects on long-term growth and the development of infants. All these respiratory complications required meticulous care by pediatricians. Indeed, our data showed low rates of severe respiratory complications after 36 weeks of gestation, as established in the previous literature[9].

Our study demonstrated that the overall rates of respiratory complications in late preterm newborns between the study and control group were comparable. However it is in contrast to the data from the meta-analysis work done by Saccone et al[12]. Their work demonstrated the decrease neonatal respiratory morbidity rate of near term fetus when corticosteroid was used. Because our study consisted of single dose antenatal corticosteroid and it was observational study. The practice of whether to give dexamethasone to late preterm patients was not in anyone's control due to the controversial issue of late preterm management[3].

The National Institute of Health (NIH) panel recommended the use of antenatal corticosteroids prophylaxis with inhibition of labor for deliveries that were anticipated prior to the 34th week of gestation. It would have the most beneficial effects on patients the sooner they received this medication more than 24 hours before the time of delivery[2]. However, ACOG stated that the tocolytic medication's usage is tentative in late preterm[13]. In our study, most patients had delivery within 12 hours after administration of dexamethasone. This is because this study did not include the administering of the tocolytic drug in the standard care of late preterm.

Consequently, we evaluated the benefits of administering a single dose of dexamethasone for reducing respiratory complications in late preterm infants. Our multivariable logistic regression model showed a single dose of dexamethasone before delivery and gestational age $36^{0/7\text{-}6/7}$ weeks were the protective factors against respiratory complications in late preterm newborns after adjustment of other confounders. By the administration of a single dose of dexamethasone, the risk of respiratory complications could be decreased similar to the data from Attawattanakul et al[14] and Balci et al[9] that demonstrated the benefit of antenatal corticosteroids which had decreased the rates of respiratory distress and the need for ventilator support after birth in these late preterm newborns. The benefit of receiving one shot of corticosteroids during late preterm could be explained as involving part of the maturation effects of the fetal lung. There was evidence that it stimulated a surge of endogenous steroids in term newborns when their mothers had gone into spontaneous labor[15].

Neonatal hypoglycemia was the most common of neonatal complications. It was a serious concern. The newborn condition was closely monitored following antenatal corticosteroids use. In our study, neonatal hypoglycemia did not increase in both groups. Our findings were similar to those of studies carried out by Bannerman et al[16] and Attawattanakul et al[14].

The strength of this study is based on the prospective data that dexamethasone usage, which was more available than betamethasone in many countries. The current study was conducted on the basis of standard practice, in which no tocolytic drugs were used as a means of delaying delivery. There are several limitations of this study. Firstly, causes of preterm were unknown in most cases. These could be important baseline characteristics and may possibly be confounder. Secondly, this study lacks randomization and has bias results. The confounding bias is adjusted by multivariate logistic regression analysis. However, there is still some selection bias from corresponding physicians and the underlying diseases of the pregnant women that lead the attending physicians to use corticosteroids.

Conclusion

In conclusion, our study demonstrated the benefit of receiving one dose dexamethasone in reducing rates of respiratory complications in late preterm newborns without any serious neonatal adverse outcomes. Still larger trials with randomization are warranted and ought to be conducted. Also, a study into the long-term effects are needed in order to produce more substantial evidence of these possible beneficial effects.

Acknowledgments

The authors would like to thank Associate professor Kornkarn Bhamarapravatana and Associate professor Komsun Suwannarurk for their support and intensive consultation in this study.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Committee on Obstetric Practice. Committee Opinion No. 713: Antenatal Corticosteroid Therapy for Fetal Maturation. Obstet Gynecol 2017;130:e102-9.
2. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2017;3:CD004454.
3. Cunningham FG, Lenovo JK, Bloom SL, Dashe JS, Hoffman BL, Casey BM, et al. Willliams Obstetrics. 25th ed. New York: McGraw-Hill 2018:803-34.
4. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery. Am J Obstet Gynecol 2016; 215:B13-5.
5. Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2013;8:CD006764.
6. Cunningham FG, Lenovo JK, Bloom SL, Dashe JS, Hoffman BL, Casey BM, et al. Willliams Obstetrics. 25th ed. New York: McGraw-Hill 2018:619-35.
7. Cunningham FG, Lenovo JK, Bloom SL, Dashe JS, Hoffman BL, Casey BM, et al. 8. Willliams Obstetrics. 25th ed. New York: McGraw-Hill 2018:606-18.
8. Balci O, Ozdemir S, Mahmoud AS, Acar A, Colakoglu MC. The effect of antenatal steroids on fetal lung maturation between the 34th and 36th week of pregnancy. Gynecol Obstet Invest 2010;70: 95-9.
9. Consortium on Safe Labor, Hibbard JU, Wilkins I, Sun L, Gregory K, Haberman S, et al. Respiratory morbidity in late preterm births. JAMA 2010;304:419-25.
10. Porto AM, Coutinho IC, Correia JB, Amorim MM. Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. BMJ 2011;342:d1696.
11. Bastek JA, Sammel MD, Paré E, Srinivas SK, Posencheg MA, Elovitz MA. Adverse neonatal outcomes: examining the risks between preterm, late preterm, and term infants. Am J Obstet Gynecol 2008;199:367.e1-8.
12. Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. BMJ 2016;355:i5044.
13. ACOG Committee on Practice Bulletins Obstetrics. ACOG practice bulletin no. 171: Management of preterm labor. Obstet Gynecol 2016;128: 931-3.
14. Attawattanakul N, Tansupawatdikul P. Effects of antenatal dexamethasone on respiratory distress in late preterm infant. Thai J Obstet Gynaecol 2015;23:25-33
15. Jain L, Eaton DC. Physiology of fetal lung fluid clearance

and the effect of labor. Semin Perinatol 2006;30:34-43.
16. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, et al. NICHD Maternal–Fetal Medicine Units Network. Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. N Engl J Med 2016;374:1311-20.