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Effects of Antenatal Dexamethasone on Respiratory Distress in Late Preterm Infant: A Randomized Controlled Trial

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ABSTRACT

Objective: To determine the effects of antenatal dexamethasone on rate of respiratory distress in late preterm infant comparing with non-dexamethasone.

Study design: Opened label randomized controlled trial.

Method: 194 singleton pregnant women who were admitted to Chonburi Hospital due to preterm labor from March 2013 to March 2014 were randomized by block of four method into two groups. The study group (n = 96) was prescribed dexamethasone 6 mg intramuscularly every 12 hours for totally 4 doses or until delivery and control group (n = 98) who not receive dexamethasone. Rate of neonatal respiratory distress, morbidity and mortality were assessed and analyzed by Unpaired T-test, Mann Whitney U-test and Chi-square test between both groups.

Results: The study showed that rate of neonatal respiratory distress was statistically significant lower in study group, 9 cases (9.4%) compared with control group, 20 cases (20.4%). (p = 0.03, relative risk = 0.40, confidence interval = 0.17 to 0.94). Anyway, the need for respiratory support and the need of intensive unit care were not different, (p = 0.07, 0.05, respectively).

Conclusion: Administration of dexamethasone in late preterm labor pregnancies significantly decreased the rate of respiratory distress.

Keywords: Late preterm, respiratory distress, dexamethasone

Introduction

Preterm labor is an important problem worldwide including Thailand. Late preterm defined as labor between gestational ages 34 weeks and 36^{+6} weeks[1], Previous study showed that neonatal complication significant higher in late preterm birth than term birth[2]. The neonatal complications included respiratory complication such as respiratory distress syndrome, transient tachypnea of newborn, pneumonia, pulmonary hypertension[3] and ventilator support needed[4,5].

There is clear evidence about benefit of prescribing corticosteroid to the pregnant woman who are at risk of preterm labor from gestational age 24 weeks to 34[6-8] or 34^{+6} weeks[9]. Before labor pain occurs, there will be a change of fetal hormone to decrease production of pulmonary fluid. After delivery, together with spontaneous breathing of infant, pulmonary fluid are excreted by sodium efflux from interalveolar space into cells which rely on sodium ion channel at apical and basolateral membrane.

Development of pulmonary fluid excretion depends on gestational age. Corticosteroid not only assists these mechanisms but also aids in absorbing fluid out of lungs[5,10].

One course of corticosteroid has not shown any short-term adverse drug reaction for both mother and fetus[7]. Dose, route and duration of corticosteroid are betamethasone 12 mg intramuscularly for 24 hours apart, totally two doses which equivalent to dexamethasone 6 mg intramuscularly for 12 hours apart, totally four doses[7, 9].

However, there are concerns about role of corticosteroid in the prevention of respiratory complication in late preterm birth. Cochrane review revealed that corticosteroid significantly reduced respiratory distress syndrome in preterm birth from gestational age 33 weeks to 34^{+6} weeks but no clear evidence support for gestational age 35 weeks to 36^{+6} weeks[6]. Afterwards, two randomized controlled trials, were conducted to compare the effect of corticosteroid and placebo in late preterm birth. One showed that respiratory distress syndrome significantly lowered in corticosteroid group[11] contrary to the other one that did not show the benefit of corticosteroid in respiratory complication[12]. Both trials used betamethasone regimen.

From existing literatures, there is no clear evidence about benefit of corticosteroid in late preterm birth. So, we aim to conduct a randomized controlled trial to determine the effects of antenatal dexamethasone on rate of respiratory distress in late preterm infant comparing with non-dexamethasone.

Materials and Methods

Study population

We have designed an opened label randomized controlled trial involving all pregnant women who were admitted to Chonburi Hospital due to preterm labor from March 2013 to March 2014 after Chonburi Hospital Ethic Committee approved. Eligible criteria were singleton pregnancy, gestational age 34 weeks to 36^{+6} weeks which determined on the basis of certain last menstrual period and ultrasonography performed at the first ANC before 26 weeks of gestation. Preterm labor pain defined as regular uterine contraction at least 4 times in 20 minutes or 8 times in 60 minutes and cervical dilatation more than 1 centimeter and cervical effacement at least 80 percent.

Participants who had history of corticosteroid administration in current pregnancy, history of dexamethasone allergy, systemic infection, multifetal pregnancy, complicated pregnancy including overt diabetes mellitus, gestational diabetes mellitus (GDM), pregnancy induced hypertension (PIH), placenta previa and abruptio placentae, positive or unknown sexual transmitted disease serology, evidence of fetal amniotic membrane leakage confirmed by two of the following test; pooling, nitrazine test, fern test or cough test, known fetal intrauterine restriction, oligohydramnios, non-reassuring fetal heart rate tracing, fetal death, fetal anomaly, suspicious of chorioamnionitis (fetal tachycardia >160/min, maternal fever > 37.8°C, uterine tenderness, foul smelling amniotic fluid), cervical dilatation more than 7 centimeters, were excluded from our study. All participants were informed and sign the consent before recruitment.

Assessment of outcome

Participants were randomized by block of four method into two groups, the intervention group was prescribed dexamethasone 6 mg intramuscularly every 12 hours for totally 4 doses or until delivery and controlled group who not be prescribed dexamethasone. Both groups were managed follow Clinical Practice Guideline of Chonburi Hospital. The data were retrieved from chart review and all attending hospital staffs who care them were blinded from the study except the labor room's nurse. Primary outcome was rate of respiratory distress defined as grunting, flaring, tachypnea > 60/min, retraction, and/or supplemental oxygen requirement that sustained more than 2 hours after birth[3]. Secondary outcome were neonatal morbidity and mortality including APGAR scores < 7, positive pressure ventilation as basic resuscitation, admission to sick newborn care unit (SNB) or newborn intensive care unit (NICU), need for respiratory support, the diagnosis that occurred within 48 hours of life; respiratory distress syndrome (RDS), transient

tachypnea of newborn (TTNB), apnea, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), early onset sepsis, pneumonia and length of hospital stay. Maternal outcome consisted of chorioamnionitis, postpartum endomyometritis(maternal fever ≥ 38°C, abdominal pain, parametrial tenderness, foul smell lochia, WBC > 15,000) and length of hospital stay.

Statistical analysis

Sample size was calculated to have type one error of 5 percent and 80 percent power to detect a reduction of 50 percent in rate of respiratory distress. Rate of respiratory distress in late preterm infant was assumed to be 28.9 percent based on Wang ML, et al[3]. Accordingly, the number of study population was at least 95 pregnant women in each group. Outcomes were analyzed as intention to treat analysis. All statistical analysis was done using SPSS program version 17.0. The patient's baseline characteristics in each groups was compared. Unpaired T-test for continuous quantitative variables with normal distribution. Mann-Whitney U-test for discrete or non-normal distribution quantitative variables and chi-square test for categorical variables, calculated risk-ratio as a measurement of relative risk, together with 95 percent confidence interval. P-value less than 0.05 was considered as significance.

Results

Eight hundred and six pregnant women were admitted to Chonburi Hospital due to late preterm labor. One hundred ninety four participants met the inclusion criteria and were randomized to dexamethasone group (n = 96) or control group (n= 98). There was no significant difference between groups in baseline characteristics of pregnant women, admission time to delivery, route of delivery, sex and birth weight of infant (Table 1). No local or systemic adverse reactions due to dexamethasone were recorded.

There were significant differences of neonatal respiratory distress rate between dexamethasone and control group. Nevertheless, dexamethasone did not reduce the need for respiratory support or positive pressure ventilation. Apgar scores < 7, rate of admission to sick newborn care unit and neonatal intensive care unit, rate of RDS, early onset neonatal sepsis and TTNB were not different between groups. Furthermore, dexamethasone did not shorten the length of hospital stay for both infant and mother (Table 2).

Table 3. showed neonatal complication other than respiratory problem including hypoglycemia, neonatal jaundice, low birth weight, subgaleal/cephal hematoma and miscellaneous: imperforate anus and congenital measles infection. No neonatal apnea, IVH, NEC, maternal chorioamnionitis and endomyometritis found in our study.

The subgroup analysis was conducted whether any gestational age group have different effects to maternal and neonatal outcome, as shown in Table 4, no statistically significant difference in any gestational age to the rate of respiratory distress and Table 5. showed the rate of respiratory distress according to number of dexamethasone dose.

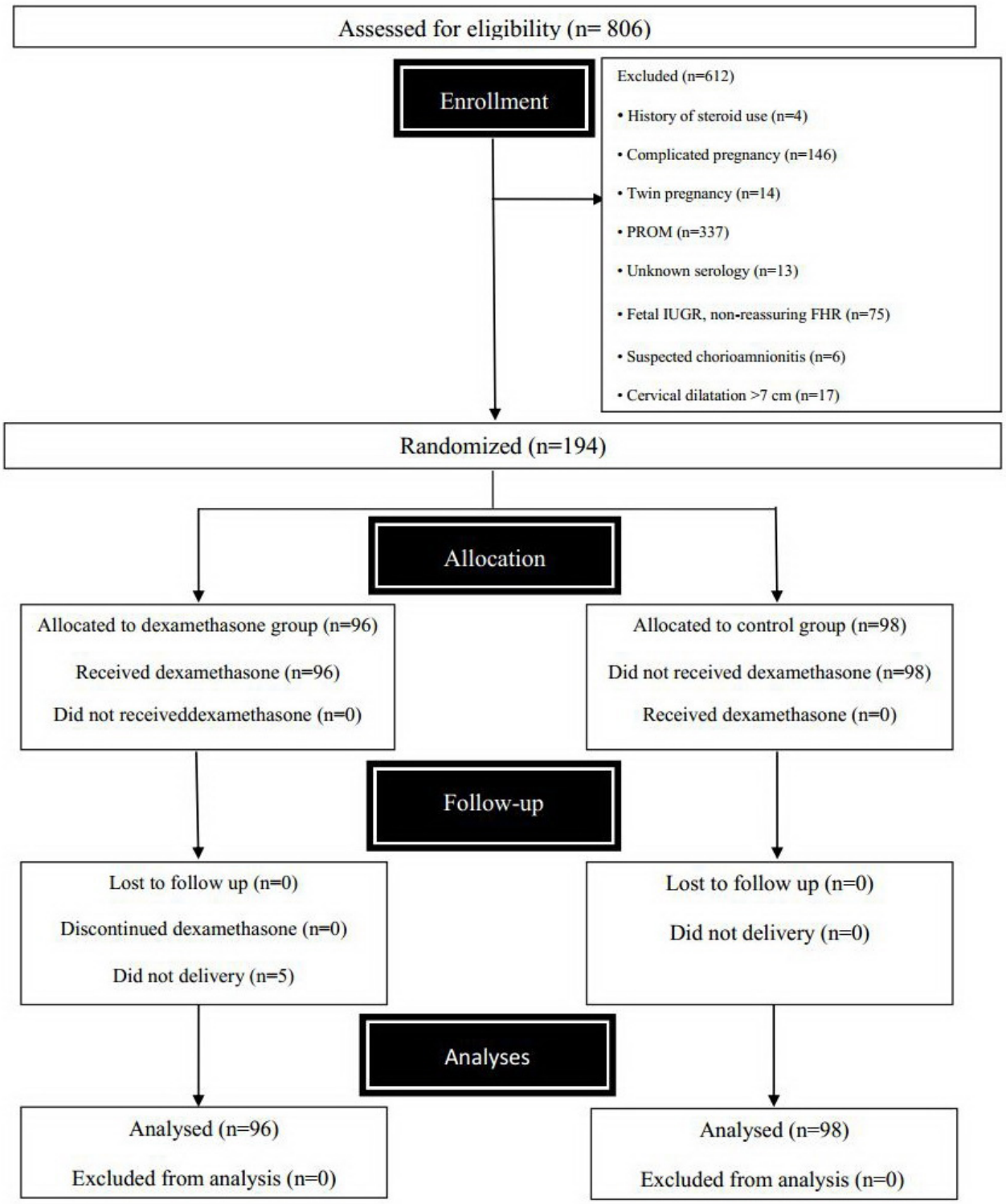

Fig. 1. Enrollment, randomization, treatment and follow-up of patients

Table 1. Baseline characteristics of study population.

	Dexamethasone group (N=96)	Control group (N=98)	P
Maternal age (years)	24.7 (5.6)	26.0 (5.5)	0.11
Nationality, N (%)			
Thai	85 (88.5)	93 (94.9)	0.11
Non-Thai	11 (11.5)	5 (5.1)	
Gravidity, N (%)			
1	47 (49.0)	41 (41.8)	0.32
>1	49 (51.0)	57 (58.2)	
Parity, N (%)			
0	61 (63.5)	51 (52.0)	0.11
≥1	35 (36.5)	47 (48.0)	
Gestational age, N (%)			
34-34^{+6} weeks	24 (25.0)	22 (22.4)	0.81
35-35^{+6} weeks	33 (34.4)	38 (38.8)	
36-36^{+6} weeks	39 (40.6)	38 (38.8)	
History of prematurity, N (%)	4 (4.2)	7 (7.1)	0.37
Smoking, N (%)	2 (2.1)	2 (2.0)	0.98
Route of delivery, N (%)			
Normal delivery	68 (70.8)	64 (65.3)	0.43
Cesarean delivery	23 (24.0)	23 (23.5)	
Vacuum extraction	5 (5.2)	10 (10.2)	
Forceps extraction	0 (0.0)	1 (1.0)	
Time from admit to delivery, N (%)			
<12 hr	74 (77.1)	81 (82.7)	0.14
12-24 hr	14 (14.6)	11 (11.2)	
>24-48 hr	2 (2.1)	5 (5.1)	
>48 hr	6 (6.3)	1 (1.0)	
Sex of infant, N (%)			
Male	53 (55.2)	58 (59.2)	0.58
Female	43 (44.8)	40 (40.8)	
Birth weight of infant (grams)	2,557.2 (367.6)	2,558.1 (340.0)	0.99

Data were presented as mean (SD) or percentage

Table 2. Perinatal outcomes of late preterm infant and maternal outcomes of study population.

Outcome	Dexamethasone group (N=96)	Control group (N=98)	P	Relative risk (95% CI)
Primary outcome, N (%)				
Respiratory distress	9 (9.4)	20 (20.4)	0.03	0.40 (0.17-0.94)
Secondary outcome, N (%)				
APGAR score < 7 at five minutes	1 (1.0)	2 (2.0)	0.57	1.98 (0.18-22.10)
Positive pressure ventilation	1 (1.0)	5 (5.1)	0.10	0.20 (0.02-1.71)
Admit to				
Sick newborn unit	12 (12.5)	23 (23.5)	0.05	0.47 (0.22-1.00)
Neonatal intensive care unit	0 (0.0)	2 (2.0)	0.16	0.50 (0.43-0.58)
Need respiratory support	6 (6.3)	14 (14.3)	0.07	0.40 (0.15-1.09)
Diagnosis of Respiratory distress syndrome (mild)	5 (5.2)	5 (5.1)	0.97	1.02 (0.29-3.65)
Transient tachypnea of newborn	2 (2.1)	1(1.0)	0.55	2.06 (0.18-23.14)
Early onset neonatal sepsis	2 (2.1)	1(1.0)	0.55	2.06 (0.18-23.14)
Length of hospital stay of infants (days)	4.69 (3.60)	4.42 (2.30)	0.53	
Length of hospital stay of pregnant women (days)	3.57 (0.87)	3.58 (0.75)	0.94	

Data were presented as mean (SD) or percentage

Table 3. Neonatal complications other than respiratory problems.

Diagnosis, N (%)	Dexamethasone group (N=96)	Non-dexamethasone group (N=98)	P	Relative risk (95% CI)
Neonatal jaundice	11 (11.5)	7 (7.1)	0.30	1.68 (0.62-4.54)
Hypoglycemia	9 (9.4)	4 (4.1)	0.14	2.41 (0.72-8.18)
Low birth weight	1 (1.0)	3 (3.1)	0.32	0.33 (0.03-3.26)
Subgaleal or cephal hematoma	3 (3.1)	1 (1.0)	0.30	3.12 (0.32-30.62)
Miscellaneous: imperforate anus, congenital measles infection	2 (2.1)	0 (0.0)	0.15	0.49 (0.42-0.57)

Table 4. Other Neonatal Outcome

Gestational age(weeks)	Dexamethasone group (N=96)	Control group (N=98)	P	Relative risk (95% CI)
$34\text{-}34^{+6}$	6 (25.0)	8 (36.4)	0.40	0.58 (0.16-2.00)
$35\text{-}35^{+6}$	2 (6.1)	7 (18.4)	0.12	0.29 (0.06-1.49)
$36\text{-}36^{+6}$	1 (2.6)	5 (13.2)	0.08	0.17 (0.02-1.56)

Table 5. Subgroup analysis: respiratory distress according to number of dexamethasone dose.

	number of dexamethasone dose			
Outcome, N (%)	**1 (N = 75)**	**2 (N = 12)**	**3 (N = 3)**	**4 (N = 6)**
Respiratory distress	8 (10.7)	0 (0.0)	1 (33.3)	0 (0.0)
No respiratory distress	67 (89.3)	12 (100.0)	2 (66.7)	6 (100.0)

Discussion

The late preterm infants were 8 percent of all delivery[1] and incidence of morbidity/mortality was 28.9 percent[3]. Many retrospective cohort studies, comparing rate of respiratory distress in late preterm infants who had received corticosteroid or not, showed statistically significant lower rate of respiratory distress[13,14]. Other studies are randomized controlled trial which evaluated fetal lung maturity by amniocentesis which revealed the corticosteroid group had statistically significant more favorable biological profile than control group[15]. Nevertheless, biological profile did not directly related to the clinical of infants.

Aforementioned, there are only two randomized controlled trials about antenatal corticosteroids in late preterm infants compare with placebo and limited only betamethasone. One study, although limited by small population number, revealed statistically significant lower rate of respiratory distress syndrome in betamethasone group[11]. However, another study showed insignificant results but had high loss of follow up rate[12].

Our study was the first randomized controlled trial that use dexamethasone to determine the effects of dexamethasone on respiratory complication reduction in late preterm infant. The study showed that administration of dexamethasone in gestational age 34 to 36 weeks 6 days women with preterm labor significantly reduce the rate of respiratory distress that possible from excretion of pulmonary fluid was enhanced by the corticosteroid. Contradiction to previous study, this effect was not much enough to decrease the rate of RDS and TTNB in late preterm infant. Moreover, rate of admission in SINB or NICU were not different. These are probably elucidated by the fact that, firstly, the most of participants were delivered within 12 hours because we followed the standard care, no inhibition, and augmentation for delivery if subsequent ruptured of membrane, possible of short duration between 1st injection and delivery, the benefit still not occur. As shown from the previous study, supreme effect of corticosteroid will occur after 24 hour of the 1st dosage. Anyway, some evidences support even receiving corticosteroid less than 24 hours could also minimize neonatal morbidity and mortality in early pretem[7-9,16], but still no evidence support in late preterm group. In our study, 6 participants were retrieved full doses of dexamethasone and all of them revealed no neonatal respiratory distress. Anyway, most of the dexamethasone group retrieved only 1 dosage and 89.3% of them had no respiratory distress. However, we could not conclude whether number of dexamethasone injection will have different effects on respiratory outcome because of limitation of number of participants. Secondly, number of participants in our study was under power to detect the difference of RDS and TTNB.

In addition, 5 late preterm pregnancies in the dexamethasone group did not deliver soon after first admission but delivery after a week. We still concluded these participants and analyzed in intention to treat basis.

There are no short-term complication occurred in our study. We did not assess long-term complication, but other study which followed children to their 11th birthday also show favorable outcomes in corticosteroid group[17]. The other study had followed children 8 to 15 years after antenatal betamethasome administered between 37 to 38 weeks of gestation in ASTECS trial[18], the results did not show any adverse outcomes[19].

The strength of the present study were 1) our study was the first study that use dexamethasone to

evaluate the respiratory complication in late preterm 2) there was no participant that loss to follow up in our study 3) we assessed the effects of dexamethasone in the basis of standard practice because of awareness of hided infection from dexamethasone so no inhibition and augmentation was performed if indicated even the participants will not receive full course of dexamethasone that easier to apply to the clinical practice, nowadays.

This study concluded that dexamethasone tends to have the positive effect to respiratory outcome even in late preterm, although this not much enough to decreased hospital stay or rate of RDS. The further study should be conducted by increased number of participants to have enough power to detect the rate of RDS.

Conclusion

Our study showed that dexamethasone administration in late preterm labor pregnant women significantly decreased the rate of respiratory distresswithout increase in rate of adverse events as same asmany studies. However, there is a need of larger trials to correct limitation in our study.

Conflict of interest

The authors declare that there was no conflict of interest.

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ผลของการให้ยา dexamethasone ก่อนคลอดต่อการหายใจผิดปกติ ในทารกเกิดก่อนกำหนดระยะท้าย: การศึกษาวิจัยแบบสุ่ม

นิภาวรรณ อรรถวัฒนกุล, พิมพิกา ตันสุภสวัสดิกุล

วัตถุประสงค์ *: เพื่อศึกษาผลของการให้ยา dexamethasone ต่อการหายใจผิดปกติ ในทารกเกิดก่อนกำหนดระยะท้ายเปรียบเทียบกับกลุ่มที่ไม่ได้รับยา*

รูปแบบการวิจัย *: การวิจัยเชิงทดลองแบบสุ่มและมีกลุ่มควบคุม*

วิธีการวิจัย *: สตรีตั้งครรภ์เดี่ยวที่อายุครรภ์ตั้งแต่ 34 สัปดาห์ถึง 36 สัปดาห์ 6 วัน ที่เจ็บครรภ์คลอดก่อนกำหนดในโรงพยาบาลชลบุรี ตั้งแต่เดือนมีนาคม 2556 ถึงมีนาคม 2557 รวม 194 คน เข้าร่วมงานวิจัย ถูกกำหนดเป็นสองกลุ่มโดยการสุ่ม กลุ่มทดลอง 96 คนได้รับยา dexamethasone 6 มิลลิกรัม ทุก 12 ชั่วโมง รวม 4 เข็ม หรือจนกว่าจะคลอด และกลุ่มควบคุม 98 คน ไม่ได้รับยา เก็บข้อมูลอัตราการหายใจผิดปกติ และความเจ็บป่วยของทารก วิเคราะห์ข้อมูลโดยใช้ Unpaired T-test, Mann Whitney U-test และ Chi-square test โดยใช้หลักการ intention to treat analysis*

ผลการวิจัย *: อัตราการหายใจผิดปกติของทารกลดลงอย่างมีนัยสำคัญในกลุ่มทดลอง (9 คน, 9.4%) เปรียบเทียบกับกลุ่มควบคุม (20 คน, 20.4%) (p = 0.03, relative risk = 0.40, confidence interval = 0.17 to 0.94) แต่อย่างไรก็ดี อัตราการใช้เครื่องช่วยหายใจและการเข้ารับการรักษาในหน่วยดูแลผู้ป่วยหนัก ไม่มีความแตกต่างกันอย่างมีนัยสำคัญ (p = 0.07, 0.05 ตามลำดับ)*

สรุป *: ผลการวิจัยการได้รับยา dexamethasone ในหญิงเจ็บครรภ์คลอดก่อนกำหนดระยะท้าย มีผลลดอัตราการหายใจผิดปกติอย่างมีนัยสำคัญทางสถิติ*