Original Article

Association of Antenatal Dexamethasone with Maternal and Neonatal Outcomes in Late Preterm Labor in a Tertiary Hospital in Thailand: A Retrospective Cohort Study

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Objective: To study the association of antenatal intramuscular dexamethasone with maternal and neonatal outcomes in women presenting with late preterm labor

Materials and Methods: A retrospective cohort study was performed in pregnant women who had labor pain with or without delivery during the 34 0/7 to 36 6/7 weeks of gestation and admitted in Sunpasitthiprasong Hospital, Ubonratchathani, Thailand between 2016 and 2019. The clinical data such as maternal age, gestational age, gravidity, comorbidities, obstetric complications, dexamethasone, tocolytics, antibiotics administration, and delivery outcomes were recorded. The primary outcome was neonatal composite respiratory complications, defined as having any of respiratory distress, pneumonia, apnea, transient tachypnea of newborn, and bronchopulmonary dysplasia. The secondary outcome was invasive respiratory support including endotracheal intubation and continuous positive airway pressure use. Associations of dexamethasone with primary and secondary outcomes were examined using univariate and multivariate logistic regression.

Results: Among 1,978 pregnant women and 2,089 neonates in the present cohort study, they had median gestational age of 35 weeks 5 days at the time of presentation with preterm labor. Seven hundred and eighty (39.4%) pregnant women received dexamethasone. Nine hundred and forty neonates (45.1%) had composite respiratory complications. The neonates who received antenatal dexamethasone had an increased risk of composite respiratory complications (adjusted odd ratio [OR] 1.275, 95% confidence interval [CI] 1.018 to 1.598) without a significant increased risk of invasive respiratory support (adjusted OR 1.132, 95% CI 0.839 to 1.527). Other factor associated with significantly increased risk of composite respiratory complications was multifetal gestation.

Conclusion: Antenatal dexamethasone administration in late preterm labor increased risk of composite respiratory complications.

Keywords: Dexamethasone; Late preterm; Neonatal respiratory complications

Received 9 May 2022 | Revised 13 June 2022 | Accepted 23 June 2022

J Med Assoc Thai 2022;105(8):768-79

Website: http://www.jmatonline.com

Late preterm birth, defined as delivery duration between 34 0/7 and 36 6/7 weeks of gestation, accounted for more than seventy percent of preterm birth[1]. Preterm birth is the most common cause of death in neonates[2]. In 2010, the worldwide rate of preterm birth was 11.1%[3]. A study investigating rates of preterm birth in 65 developed countries, Latin America, and the Caribbean regions showed an increasing trend, from 7.5% in 1990 to 8.6% in 2010[3]. The estimated rate of preterm birth in Thailand was 10.8% in 2018[4]. Premature neonates suffered from complications such as respiratory, cardiovascular, gastrointestinal, immunologic, neurologic, retinopathy, and endocrine complications[1]. These complications can aggravate morbidity and long-term sequelae of the premature baby. Among these complications, respiratory complication is the most important and commonly found in premature neonates.

Treatment with antenatal corticosteroids, compared with placebo or no treatment, in anticipating preterm delivery before the thirty-fourth week of gestation was reported to be associated with a reduction in the most serious adverse outcomes related to prematurity, including respiratory distress syndrome (RDS), perinatal death, and neonatal

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How to cite this article:

Panthonglapthavee S, Wuttikonsammakit P, Chamnan P. Association of Antenatal Dexamethasone with Maternal and Neonatal Outcomes in Late Preterm Labor in a Tertiary Hospital in Thailand: A Retrospective Cohort Study. J Med Assoc Thai 2022;105:768-79.

DOI: 10.35755/jmedassocthai.2022.08.13480

death[5-7]. Additionally, antenatal corticosteroids had no or few benefits in reducing maternal deaths, chorioamnionitis, and endometritis[7]. However, the benefits remained unclear in specific subgroups such as multiple pregnancies and late preterm labor. Although a pharmacodynamics and pharmacokinetics study suggested that two corticosteroids, betamethasone, and dexamethasone, might be efficacious in promoting fetal lung development with high affinity towards the glucocorticoid receptor and easily crossed placenta[8]. There was conflicting evidence on the clinical efficacy of both corticosteroids in promoting fetal lung maturation. A systematic review and meta-analysis of 12 trials[9] found that treatment with either betamethasone or dexamethasone in preterm labor was unfavorably associated with a higher rate of neonatal RDS and maternal chorioamnionitis compared to placebo.

A large trial in 2831 pregnant women presenting with late preterm labor, showed opposite results as betamethasone reduced risk of severe respiratory complication by 33%[10], although following studies mostly in western populations showed conflicting results with respiratory complications[11,12]. These studies were done in western population and used betamethasone. Results from a systemic review suggested no difference in respiratory distress syndrome and other neonatal outcomes between dexamethasone and betamethasone[13]. In Thailand, dexamethasone is the only corticosteroid used for promoting lung maturity. Evidence on efficacy and safety of antenatal intramuscular dexamethasone in Thai pregnant women with late preterm labor is limited, with only one trial and most studies being relatively small[14-16]. Moreover, there is paucity of evidence on the impact of maternal outcomes of antenatal corticosteroids in late preterm. Therefore, the present study aimed to investigate the association of antenatal dexamethasone in late preterm labor with maternal and neonatal outcomes in a tertiary hospital in Thailand.

Materials and Methods

After approval of Sunpasitthiprasong Hospital Ethics Committee (Ref No. 040/63R), a retrospective cohort study was performed in the Department of Obstetrics and Gynecology, Sunpasitthiprasong Hospital. Subjects were pregnant women presenting with late preterm labor between 2016 and 2019. Late preterm labor was defined as having regular uterine contractions with or without cervical changes at 34 0/7 to 36 6/7 weeks of gestation. During that period, pregnant women received 6-mg intramuscular dexamethasone every 12 hours for four doses for a complete course or until delivery for an incomplete course, while others did not receive antenatal dexamethasone. The study samples were randomly selected through hospital electronic medical records from pregnant women with late preterm labor who did and did not receive antenatal dexamethasone using computer program to represent the pregnant women in both groups. After medical chart review, the pregnant women who had dead fetus in utero (DFIU), stillbirth, Bart's hydrops fetalis, congenital anomaly incompatible with life, and missing data on main outcomes were excluded. Baseline data on maternal age, education, gravidity, abortion, route of delivery, alcohol consumption, smoking, and drug abuse were collected. Data on maternal comorbidities, complications, and treatments were also collected. These included oligohydramnios, fetal growth restriction, preeclampsia, hypertension, gestational diabetes mellitus, ruptured of membrane, doses of dexamethasone, tocolytics, antibiotics for group B streptococcal (GBS) prophylaxis, antibiotics for prolonging latency period, magnesium sulfate administration, and postpartum complications. The primary outcome was neonatal composite respiratory complications, defined as having any of the following outcomes, respiratory distress syndrome (RDS), pneumonia, apnea, transient tachypnea of newborn (TTNB), and bronchopulmonary dysplasia. The secondary outcome was invasive respiratory support including endotracheal intubation and continuous positive airway pressure (CPAP). Other neonatal outcomes including birthweight, Apgar score, pediatric ward or neonatal intensive care unit (NICU) admission, length of stay, hypoglycemia, jaundice, polycythemia, sepsis, and neonatal death were also obtained. The maternal outcomes included postpartum hemorrhage, chorioamnionitis, postpartum fever, postpartum endometritis, wound infection, need for blood transfusion, peripartum hysterectomy, and maternal length of stay.

Maternal and neonatal complications were defined based on the International Classification of Diseases and Related Health Problem Tenth Revision (ICD-10) codes for final diagnoses in the discharge summary. The neonatal outcomes were ascertained until discharge of the neonates.

Statistical analysis

Sample size was determined based on effectiveness of dexamethasone on respiratory distress

and need for respiratory support in Thai population[14]. Therefore, 402 and 550 subjects were required. However, the present study did not investigate composite respiratory complications, which was the present study's primary outcome. Thus, sample size was also calculated according to the findings from a study by Gyamfi-Bannerman et al[10] suggesting that corticosteroid reduced the composite outcome of severe respiratory complications with a relative risk of 0.67 (95% confidence interval [CI] 0.53 to 0.84]. At 80% power and 95% confidence with 10% dropout or missing data assumed, a sample size of 1,978 was required.

Statistics analyses were performed using IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY, USA). Categorical, normally, and non-normally distributed continuous variables were described as number (%) and mean (standard deviation, SD) or median (interquartile range, IQR). Comparison of characteristics between groups were performed using chi-square test for categorical variables and independent sample t-test, Mann-Whitney U test for normally and non-normally distributed continuous variables. Kolmogorov-Smirnov test was used to evaluate the distribution of continuous data. Factors affecting major neonatal outcomes were analyzed using univariate and multivariate logistic regression. Factors potentially associated with the outcomes with a p-value of less than 0.2 from univariate analysis were included in multivariate logistic regression analysis. A p-value of less than 0.05 was considered statistically significant.

Results

There were 2,922 pregnant women at 34 0/7 weeks to 36 6/7 weeks admitted in Sunpasitthiprasong Hospital with preterm labor during the three years of the study period (Figure 1). After excluding 929 cases of incomplete data, 12 cases of DFIU, two cases of stillbirth, and one case of Bart's hydrops fetalis, 1,978 pregnant women were included in the present study. There were 114 cases of multifetal pregnancy with 107 twins, five twins with single fetal demise, and two triplets, and gave birth to 225 neonates. These resulted in 2,089 neonates. Among all subjects, 780 pregnant women and 834 neonates received antenatal dexamethasone, while 1,198 pregnant women and 1,255 neonates did not receive dexamethasone.

Table 1 shows the characteristics of pregnant women, comorbidities, complications, and treatments. Median gestational age at admission was 35 weeks

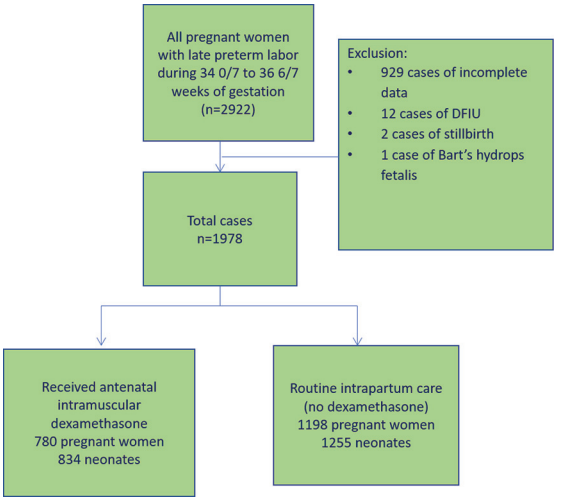

Figure 1. Flow of participants.

5 days. Diabetes mellitus, hypertension, anemia, premature rupture of membrane (PROM), and multifetal pregnancy were found in 171 (8.6%), 268 (13.5%), 340 (17.2%), 610 (30.8%), and 114 (5.8%), respectively. One thousand two hundreds fifty-five (60.1%) neonates did not receive dexamethasone and 834 (39.9%) did receive dexamethasone. Four hundred fourteen (19.8%) neonates received partial dexamethasone course, 361 (17.3%) completed course, and 58 (2.8%) repeated courses. Compared with those who did not receive dexamethasone, pregnant women who received dexamethasone had lower gravidity, gestational age at admission and delivery, and lower prevalence of premature rupture of membrane. Those receiving dexamethasone had a higher prevalence of hypertension, diabetes mellitus, and multifetal gestation and placenta previa, as well as higher percentage of treatment with tocolytics, magnesium sulfate, and antibiotics than those who did not. There were no differences in maternal age, abortion, education, smoking, alcohol consumption, drug abuse, anemia, intrapartum fever, and route of delivery between the two groups.

Among 2,085 neonates, 940 (45.1%) had composite respiratory complications and 361 (17.3%) needed invasive respiratory support whether CPAP or endotracheal intubation (Table 2). Neonates receiving dexamethasone had a higher rate of composite respiratory complications than neonates who did not receive dexamethasone. Similar results were observed for TTNB, RDS, invasive respiratory support, CPAP use, endotracheal intubation, hypoglycemia, and jaundice. Higher rates of NICU admission and longer stay in pediatric wards were observed in neonates

Table 1. Baseline characteristics of 1978 pregnant women, overall and by dexamethasone treatment

	Total (n=1,978)	Received Dexamethasone (n=780)	No dexamethasone (n=1,198)	p-value
Age (years); median (IQR)	27 (22, 33)	27 (21, 33)	28 (23, 33)	0.288
Gravidity; median (IQR)	2 (1, 2)	2 (1, 2)	2 (1, 3)	0.020
Abortion; median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.616
Initial gestational age (weeks); median (IQR)	35.7 (34.9, 36.4)	35.3 (34.6, 36.1)	36.0 (35.3, 36.6)	<0.001
34 0/7 to 34 6/7; n (%)	509 (25.7)	313 (40.1)	196 (16.4)	<0.001
35 0/7 to 35 6/7; n (%)	588 (29.7)	231 (29.6)	357 (29.8)	
36 0/7 to 36 6/7; n (%)	881 (44.6)	236 (30.3)	645 (53.8)	
Gestational age at delivery (weeks); median (IQR)	36.1 (35.3, 36.7)	35.9 (34.9, 36.6)	36.3 (35.6, 36.7)	<0.001
34 0/7 to 34 6/7; n (%)	362 (18.3)	217 (27.8)	145 (12.1)	<0.001
35 0/7 to 35 6/7; n (%)	502 (25.4)	202 (25.9)	300 (25.0)	
36 0/7 to 36 6/7; n (%)	880 (44.5)	268 (34.4)	612 (51.1)	
Term; n (%)	234 (11.8)	93 (11.9)	141 (11.8)	
Education; n (%)				0.148
Primary	276 (13.9)	106 (13.6)	170 (14.2)	
Secondary	975 (49.3)	399 (51.2)	576 (48.1)	
Vocational	116 (5.9)	50 (6.4)	66 (5.5)	
Diploma	81 (4.1)	23 (2.9)	58 (4.8)	
Bachelor or higher	461 (23.3)	181 (23.2)	280 (23.4)	
Unknown	69 (3.5)	21 (2.7)	48 (4.0)	
Smoking; n (%)	7 (0.4)	1 (0.1)	6 (0.5)	0.255
Alcohol consumption; n (%)	83 (4.2)	29 (3.7)	54 (4.6)	0.376
Drug abuse; n (%)	7 (0.4)	4 (0.5)	3 (0.3)	0.445
Hypertension in pregnancy; n (%)	268 (13.5)	138 (17.7)	130 (10.9)	<0.001
Maternal diabetes mellitus; n (%)	171 (8.6)	82 (10.5)	89 (7.4)	0.017
Anemia; n (%)	340 (17.2)	150 (19.2)	190 (15.9)	0.056
Intrapartum fever; n (%)	56 (2.8)	26 (3.3)	30 (2.5)	0.277
Preterm premature rupture of membrane; n (%)	610 (30.8)	220 (28.2)	390 (32.6)	0.041
Rupture of membrane prior to admission; n (%)	667 (33.7)	237 (30.4)	430 (35.9)	0.011
Placenta previa; n (%)	52 (2.6)	37 (4.7)	15 (1.3)	<0.001
Multifetal gestation; n (%)	114 (5.8)	55 (7.1)	59 (4.9)	0.047
Receiving tocolytics; n (%)	404 (20.4)	330 (42.3)	74 (6.2)	<0.001
Type of tocolysis; n (%)				0.017
Terbutaline	284 (14.4)	222 (28.5)	62 (5.2)	
Nifedipine	60 (3.0)	54 (6.9)	6 (0.5)	
Combined	60 (3.0)	54 (6.9)	6 (0.5)	
Magnesium sulfate; n (%)	152 (7.7)	74 (9.5)	78 (6.5)	0.015
Indication for antibiotics use; n (%)				<0.001
Prolong latency	47 (2.4)	46 (5.9)	1 (0.1)	
GBS prophylaxis	761 (38.5)	346 (44.4)	415 (34.6)	
Other indications	99 (5.0)	72 (9.2)	27 (2.3)	
GBS prophylaxis	840 (42.5)	418 (53.6)	422 (35.2)	<0.001
Route of delivery; n (%)				0.496
Normal delivery	916 (46.3)	353 (45.3)	563 (47.0)	
Cesarean section	950 (48.0)	384 (49.2)	566 (47.2)	
Vacuum extraction	97 (4.9)	40 (5.1)	57 (4.8)	
Forceps extraction	8 (0.4)	2 (0.3)	6 (0.5)	
Breech assisting delivery	7 (0.4)	1 (0.1)	6 (0.5)	
Peripartum hysterectomy; n (%)	6 (0.3)	4 (0.5)	2 (0.2)	0.220

IQR=interquartile range; GBS=group B streptococcus

Table 2. Comparison neonatal outcomes between neonate whose mother received and did not receive dexamethasone

	Total (n=2,085)[c]	Antenatal dexamethasone (n=832)	No dexamethasone (n=1,253)	p-value
Birth weight (g); median (IQR)	2,540 (2,260, 2,845)	2,470 (2,170, 2,755)	2,595 (2,337.5, 2,887.5)	<0.001
Apgar score at 1 minute; median (IQR)	9 (9, 9)	9 (9, 9)	9 (9, 9)	0.154
Apgar score at 5 minutes; median (IQR)	10 (10, 10)	10 (10, 10)	10 (10, 10)	NA
Chest compression; n (%)	11 (0.5)	6 (0.7)	5 (0.4)	0.320
Duration of chest compression; median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.312
Type of multifetal gestation; n (%)				0.047
Twin	186 (8.9)	92 (11)	94 (7.5)	
Twin with single fetal demise	5 (0.2)	2 (0.2)	3 (0.2)	
Triplet	6 (0.3)	3 (0.4)	3 (0.2)	
Composite respiratory complications[a]; n (%)	940 (45.1)	435 (52.3)	505 (40.3)	<0.001
Transient tachypnea of newborn	780 (37.4)	364 (43.8)	416 (33.2)	<0.001
Pneumonia	96 (4.6)	36 (4.3)	60 (4.8)	0.622
Respiratory distress syndrome	76 (3.6)	41 (4.9)	35 (2.8)	0.011
Apnea	9 (0.4)	3 (0.4)	6 (0.5)	1.000
Bronchopulmonary dysplasia	5 (0.2)	2 (0.2)	3 (0.2)	1.000
Persistent pulmonary hypertension; n (%)	28 (1.3)	16 (1.9)	12 (1.0)	0.061
Surfactant use; n (%)	25 (1.2)	13 (1.6)	12 (1.0)	0.214
Composite respiratory support[b]; n (%)	361 (17.3)	182 (21.9)	179 (14.3)	<0.001
CPAP	290 (13.9)	147 (17.7)	143 (11.4)	<0.001
Endotracheal intubation	159 (7.6)	77 (9.3)	82 (6.5)	0.022
Duration of respiratory support (days); median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	<0.001
Hypoglycemia; n (%)	469 (26.3)	218 (29.0)	251 (24.3)	0.026
Jaundice; n (%)	895 (42.9)	380 (45.7)	515 (41.1)	0.039
Sepsis; n (%)	115 (5.5)	55 (6.6)	60 (4.8)	0.074
Polycythemia; n (%)	38 (1.8)	19 (2.3)	19 (1.5)	0.200
Preterm birth; n (%)	1850 (88.6)	737 (88.4)	1113 (88.7)	0.824
Pediatric ward admission; n (%)	1312 (62.9)	583 (70.1)	729 (58.2)	<0.001
Neonatal length of stay (days); median (IQR)	3 (3, 5)	3 (3, 5)	3 (3, 4)	0.009
Neonatal death; n (%)	23 (1.1)	10 (1.2)	13 (1.0)	0.725

IQR=interquartile range; CPAP=continuous positive airway pressure; NA=not applicable

[a] Composite respiratory complications: defined as having any of respiratory distress, pneumonia, apnea, transient tachypnea of newborn, and bronchopulmonary dysplasia

[b] Invasive respiratory support including endotracheal intubation and continuous positive airway pressure use

[c] Exclude 4 case undiagnosed Edward syndrome 1 case, undiagnosed Patau syndrome 2 case, death from failed internal podalic version 1 case

who received antenatal dexamethasone. Moreover, neonates in dexamethasone group also had significant lower birthweight than those in no dexamethasone group. However, Apgar score at 1 and 5 minutes, chest compression, sepsis, and polycythemia were not significantly different between the two groups. Overall, 23 (1.1%) neonates died, but there was no difference between the two groups.

Among 1,978 pregnant women, 857 (43.3%), 11 (0.6%), 174 (8.8%), and 30 (1.5%) had postpartum fever, wound infection, postpartum hemorrhage, and required blood transfusion, respectively (Table 3). There was a significantly higher rate of wound infection and longer hospital stay in pregnant women who received antenatal dexamethasone. However, there was no significant difference in postpartum hemorrhage, chorioamnionitis, postpartum fever, blood transfusion, peripartum hysterectomy, and postpartum endometritis. There was no maternal death in the present study cohort.

Table 4 shows factors associated with composite respiratory complications. Univariate logistic regression suggested that gestational age, birthweight, hypertension, diabetes mellitus, tocolysis, magnesium sulfate, antibiotics for GBS prophylaxis, multifetal gestation, and dexamethasone were associated with risk of having composite respiratory complications. The factors associated with the outcome with a

Table 3. Comparison of maternal outcomes between dexamethasone and no dexamethasone groups

	Total (n=1,978)	Received Dexamethasone (n=780)	No dexamethasone (n=1,198)	p-value
Postpartum hemorrhage; n (%)	174 (8.8)	60 (7.7)	114 (9.5)	0.160
Chorioamnionitis; n (%)	7 (0.4)	2 (0.3)	5 (0.4)	0.711
Postpartum fever; n (%)	857 (43.3)	330 (42.3)	527 (44.0)	0.461
Peripartum hysterectomy; n (%)	6 (0.3)	4 (0.5)	2 (0.2)	0.220
Blood transfusion; n (%)	30 (1.5)	16 (2.1)	14 (1.2)	0.116
Wound infection; n (%)	11 (0.6)	8 (1.0)	3 (0.3)	0.030
Postpartum endometritis; n (%)	7 (0.4)	2 (0.3)	5(0.4)	0.711
Maternal length of stay (days); median (IQR)	3 (2, 3)	3 (3, 4)	3 (2, 3)	<0.001

IQR=interquartile range

Table 4. Factors affecting composite respiratory complications[a]

	Crude odd ratio (95% CI)	p-value	Adjusted odd ratio* (95% CI)	p-value
Dexamethasone	1.623 (1.360 to 1.937)	<0.001	1.275 (1.018 to 1.598)	0.034
Initial gestational age, for every week older	0.646 (0.584 to 0.716)	<0.001	1.126 (0.955 to 1.328)	0.157
Gestational age at delivery, for every week older	0.568 (0.519 to 0.621)	<0.001	0.579 (0.502 to 0.668)	<0.001
Birth weight, for every 100 g heavier	0.907 (0.889 to 0.925)	<0.001	0.965 (0.942 to 0.987)	0.003
Hypertension	1.815 (1.410 to 2.336)	<0.001	1.077 (0.734 to 1.579)	0.704
Maternal diabetes mellitus	1.455 (1.070 to 1.979)	0.017	1.315 (0.931 to 1.857)	0.121
Rupture of membrane prior to admission	0.845 (0.704 to 1.015)	0.071	0.742 (0.598 to 0.919)	0.006
Placenta previa	1.553 (0.892 to 2.703)	0.120	1.362 (0.748 to 2.480)	0.312
Tocolysis	1.345 (1.089 to 1.662)	0.006	1.109 (0.839 to 1.466)	0.468
Magnesium sulfate	2.393 (1.707 to 3.354)	<0.001	1.516 (0.932 to 2.466)	0.094
Antibiotics				
No antibiotics	Reference		Reference	
Prolong latency	1.378 (0.773 to 2.456)	0.277	1.020 (0.400 to 2.599)	0.967
GBS prophylaxis	1.291 (1.076 to 1.549)	0.006	1.400 (0.625 to 3.135)	0.414
Other indications	1.433 (0.955 to 2.150)	0.082	1.691 (0.960 to 2.980)	0.069
GBS prophylaxis	1.286 (1.079 to 1.531)	0.005	0.680 (0.305 to 1.516)	0.346
GBS prophylaxis				
No GBS prophylaxis	Reference		Reference	
<4 hours	1.295 (1.048 to 1.600)	0.017	1.119 (0.838 to 1.493)	0.447
>4 hours	1.274 (1.014 to 1.602)	0.038		
Multifetal gestation	2.575 (1.730 to 3.832)	<0.001	1.849 (1.214 to 2.817)	0.004

GBS=group B streptococcus

* Adjusted with gestational age, birthweight, hypertension, diabetes mellitus, ruptured of membranes, placenta previa, tocolysis, magnesium sulfate, antibiotics GBS prophylaxis, dexamethasone, multifetal gestation

[a] Composite respiratory complications: defined as having any of respiratory distress, pneumonia, apnea, transient tachypnea of newborn, and bronchopulmonary dysplasia

p-value of less than 0.2 from univariate analysis were included in multivariate logistic regression analysis. After adjusting for gestational age, birthweight, hypertension, diabetes mellitus, ruptured of membrane, placenta previa, use of tocolytics, magnesium sulfate, antibiotics, multifetal gestation, and dexamethasone, dexamethasone (adjusted OR 1.275, 95% CI 1.018 to 1.598) and multifetal gestation (adjusted OR 1.849, 95% CI 1.214 to 2.817) significantly increased the risk of having composite respiratory complications, while older gestational age at delivery (weeks) (adjusted OR 0.579, 95% CI 0.502 to 0.668), higher birthweight (100 g) (adjusted OR 0.965, 95% CI 0.942 to 0.987), and rupture of membrane prior to admission (adjusted OR 0.742, 95% CI 0.598 to 0.919) significantly lowered the risk.

Table 5 shows the factors associated with the need for invasive respiratory support. Hypertension,

Table 5. Factors affecting composite invasive respiratory support[a]

	Crude odd ratio (95% CI)	p-value	Adjusted odd ratio* (95% CI)	p-value
Dexamethasone	1.680 (1.337 to 2.111)	<0.001	1.132 (0.839 to 1.527)	0.417
Initial gestational age, for every week older	0.549 (0.481 to 0.627)	<0.001	1.231 (0.918 to 1.651)	0.164
Gestational age at delivery, for every week older	0.492 (0.435 to 0.557)	<0.001	0.481 (0.366 to 0.631)	<0.001
Birth weight, for every 100 g heavier	0.872 (0.849 to 0.895)	<0.001	0.943 (0.914 to 0.973)	<0.001
Hypertension	2.574 (1.944 to 3.409)	<0.001	1.145 (0.714 to 1.837)	0.574
Maternal diabetes mellitus	1.634 (1.139 to 2.344))	0.008	1.501 (0.985 to 2.288)	0.059
PPROM	0.771 (0.598 to 0.995)	0.045	1.139 (0.384 to 3.380)	0.815
Ruptured of membrane	0.710 (0.553 to 0.913)	0.008	0.584 (0.200 to 1.705)	0.325
Placenta previa	2.385 (1.321 to 4.306)	0.004	2.276 (1.179 to 4.394)	0.014
Tocolysis	1.423 (1.093 to 1.851)	0.009	1.093 (0.767 to 1.559)	0.621
Magnesium sulfate	3.374 (2.395 to 4.752)	<0.001	2.277 (1.314 to 3.946)	0.003
Antibiotics				
No antibiotics	Reference		Reference	
Prolong latency	1.675 (0.856 to 3.280)	0.132	1.232 (0.560 to 2.710)	0.604
GBS prophylaxis	1.017 (0.798 to 1.297)	0.889	0.828 (0.620 to 1.105)	0.199
Other indications	1.720 (1.073 to 2.756)	0.024	2.014 (1.153 to 3.516)	0.014
Multifetal gestation	2.455 (1.623 to 3.714)	<0.001	1.716 (1.088 to 2.708)	0.020

PPROM=preterm premature ruptured of membrane; GBS=group B streptococcus; CI=confidence interval

* Adjusted with gestational age, birthweight, hypertension, diabetes mellitius, PPROM, ruptured of membrane, placenta previa, tocolysis, magnesium sulfate, antibiotics, dexamethasone, multifetal gestation

[a] Invasive respiratory support including endotracheal intubation and continuous positive airway pressure use

diabetes mellitus, placenta previa, tocolysis, magnesium sulfate, antibiotics for other indications, gestational age, birthweight, preterm premature rupture of membrane (PPROM), ruptured of membrane, and dexamethasone were associated with the need for invasive respiratory support in univariate analysis. In multivariate regression analysis, dexamethasone was not significantly associated with need for invasive respiratory support, after adjusted for gestational age, birthweight, hypertension, diabetes mellitus, PPROM, ruptured of membrane, placenta previa, tocolysis, magnesium sulfate, antibiotics for other indications, multifetal gestation, and dexamethasone. Placenta previa (adjusted OR 2.276, 95% CI 1.179 to 4.394), multifetal gestation (adjusted OR 1.716, 95% CI 1.088 to 2.708), treatment with magnesium sulfate (adjusted OR 2.277, 95% CI 1.314 to 3.946), and antibiotics for other indications (adjusted OR 2.014, 95% CI 1.153 to 3.516) significantly increased the need for invasive respiratory support, while older gestational age at delivery (weeks) (adjusted OR 0.481, 95% CI 0.366 to 0.631), and higher birthweight (100 g) (adjusted OR 0.943, 95% CI 0.914 to 0.973) decreased this risk.

Table 6 shows the maternal and neonatal outcomes by different regimen of dexamethasone. The pregnant women who received repeated and completed course of dexamethasone were more likely to have postpartum fever and wound infection than those who received partial course dexamethasone. Among the four groups, the neonates exposed to repeated course of dexamethasone had the highest risk of composite respiratory complication and need for invasive respiratory support. The neonates who were exposed to repeated course of dexamethasone had higher risk of sepsis, and persistent pulmonary hypertension than those who were not. Lastly, the neonates who received repeated and complete course of dexamethasone had a higher rate of hypoglycemia than those who received partial course or did not receive any dexamethasone.

Table 7 shows the subgroup analysis to compare maternal and neonatal outcomes in multifetal gestation who did receive dexamethasone. Among 114 pregnant women, 55 (48.2%) received dexamethasone. The pregnant women who received dexamethasone had a longer length of stay than those who did not. There was no difference between the two groups in other maternal outcomes. Among 225 neonates, 109 (48.4%) neonates were exposed to antenatal dexamethasone. There was no significant difference in composite respiratory complications, invasive respiratory support, and other neonatal outcomes between the two groups.

Table 6. Doses of dexamethasone affecting maternal and neonatal outcomes

	No dexamethasone	Partial course (1-3 doses)	Complete course (4 doses)	Repeated courses (> 4 doses)	p-value
Maternal outcomes (n=1,978); n (%)	(n=1,199)	(n=396)	(n=331)	(n=52)	
Postpartum hemorrhage	114 (9.5)	27 (6.8)	27 (8.2)	6 (11.5)	0.340
Chorioamnionitis	5 (0.4)	1 (0.3)	1 (0.3)	0	0.927
Postpartum fever	527 (44.0)	146 (36.9)	163 (49.2)	21 (40.4)	0.008
Wound infection	3 (0.3)	2 (0.5)	5 (1.5)	1 (1.9)	0.026
Postpartum endometritis	5 (0.4)	0	2 (0.6)	0	0.510
Blood transfusion	14 (1.2)	5 (1.3)	9 (2.7)	2 (3.8)	0.100
Neonatal outcomes (n=2,085)[c]; n (%)	(n=1,254)	(n=414)	(n=359)	(n=58)	
Birthweight (g); median (IQR)	2,595 (2,338.8, 2,890)	2,422.5 (2,160, 2,690)	2,540 (2,200, 2,840)	2,417.5 (2,047.5, 2,721.3)	<0.001
Apgar score at 1 minute; median (IQR)	9 (9, 9)	9 (9, 9)	9 (9, 9)	9 (8, 9)	0.323
Apgar score at 5 minutes; median (IQR)	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (9, 10)	NA
Chest compression	5 (0.4)	5 (1.2)	1 (0.3)	0 (0.0)	0.189
Composite respiratory complications[a]	505 (40.3)	222 (53.6)	178 (49.6)	35 (60.3)	<0.001
• Transient tachypnea of newborn	416 (33.2)	180 (43.5)	156 (43.5)	28 (48.3)	<0.001
• Pneumonia	60 (4.8)	19 (4.6)	11 (3.1)	6 (10.3)	0.094
• Respiratory distress syndrome	35 (2.8)	27 (6.5)	12 (3.3)	2 (3.4)	0.006
• Apnea	6 (0.5)	2 (0.5)	1 (0.3)	0 (0.0)	0.911
• Bronchopulmonary dysplasia	3 (0.2)	1 (0.2)	1 (0.3)	0 (0.0)	0.983
Persistent pulmonary hypertension	12 (1.0)	10 (2.4)	3 (0.8)	3 (5.2)	0.007
Surfactant use	12 (1.0)	10 (2.4)	2 (0.6)	1 (1.7)	0.067
Invasive respiratory support[b]	179 (14.3)	99 (23.9)	61 (17.0)	22 (37.9)	<0.001
• CPAP use	143 (11.4)	76 (18.4)	53 (14.8)	18 (31.0)	<0.001
• Intubation	82 (6.5)	46 (11.1)	18 (5.0)	13 (22.4)	<0.001
Neonatal hypoglycemia	251 (24.3)	86 (21.7)	109 (36.5)	23 (41.8)	<0.001
Neonatal jaundice	515 (41.1)	194 (46.9)	155 (43.2)	31 (53.4)	0.072
Sepsis	60 (4.8)	32 (7.7)	16 (4.5)	7 (12.1)	0.013
Polycythemia	19 (1.5)	13 (3.1)	4 (1.1)	2 (3.4)	0.088
Pediatric admission	729 (58.1)	295 (71.3))	243 (67.7)	45 (77.6)	<0.001
Neonatal length of stay (days); median (IQR)	3 (3, 4)	3 (3, 6)	3 (3, 5)	5 (3, 8.5)	0.003
Neonatal death	13 (1.0)	7 (1.7)	2 (0.6)	1 (1.7)	0.467

IQR=interquartile range; CPAP=continuous positive airway pressure; NA=not applicable

[a] Composite respiratory complications: defined as having any of respiratory distress, pneumonia, apnea, transient tachypnea of newborn, and bronchopulmonary dysplasia

[b] Invasive respiratory support including endotracheal intubation and continuous positive airway pressure use

[c] Undiagnosed Edward syndrome 1 case, undiagnosed Patau syndrome 2 case, death from failed internal podalic version 1 case

Discussion

The present retrospective cohort study showed that exposure to antenatal dexamethasone was associated with increased risk of neonatal composite respiratory complications, especially TTNB and RDS, but not associated with need for invasive respiratory support. Additionally, antenatal dexamethasone may increase risk of neonatal hypoglycemia, and jaundice. Moreover, the women who received dexamethasone also increased risk of wound infection.

Despite the findings from trials suggesting benefits of antenatal corticosteroids in late preterm labor[10,14,17,18], increasing evidence from more recent studies including the authors' own, showed no benefits or even opposite results. Most early trials[10,14,17] found that treatment with antenatal corticosteroids, both betamethasone and dexamethasone, in late preterm resulted in a reduction in adverse respiratory outcomes. However, other trials[11,12,19,20] showed no benefit of antenatal corticosteroids in respiratory morbidity in this anticipating late preterm labor group. The present study found dexamethasone significantly increased the risk of composite respiratory complications, especially RDS and TTNB. These associations were not altered even after controlling for previously known risk factors

Table 7. Comparison maternal and neonatal outcomes in multifetal gestation

	Total	Dexamethasone	No dexamethasone	p-value
Maternal outcomes; n (%)	(n=114)	(n=55)	(n=59)	
Postpartum hemorrhage	10 (8.8)	4 (7.3)	6 (10.2)	0.744
Chorioamnionitis	1 (0.9)	0 (0.0)	1 (1.7)	1.000
Postpartum fever	71 (62.3)	37 (67.3)	34 (57.6)	0.288
Wound infection	0 (0.0)	0 (0.0)	0 (0.0)	NA
Postpartum endometritis	2 (1.8)	1 (1.8)	1 (1.7)	1.000
Blood transfusion	2 (1.8)	1 (1.8)	1 (1.7)	1.000
Maternal length of stay (days); median (IQR)	3 (3, 4)	4 (3, 5)	3 (3, 3)	0.001
Neonatal outcomes; n (%)	(n=225)	(n=109)	(n=116)	
Birth weight (g); median (IQR)	2,155 (1,870, 2,425)	2,155 (1,850, 2,460)	2,152.5 (1,926.3, 2,417.5)	0.942
Apgar at 1 minute; median (IQR)	9 (8, 9)	9 (8, 9)	9 (8, 9)	0.975
Apgar at 5 minutes; median (IQR)	10 (10, 10)	10 (10, 10)	10 (10, 10)	NA
Chest compression	5 (2.2)	3 (2.8)	2 (1.7)	0.675
Composite respiratory complications[a]	146 (64.9)	71 (65.1)	75 (64.7)	0.940
• Transient tachypnea of newborn	115 (51.1)	58 (53.2)	57 (49.1)	0.541
• Pneumonia	13 (5.8)	5 (4.6)	8 (6.9)	0.458
• Respiratory distress syndrome	17 (7.6)	6 (5.5)	11 (9.5)	0.259
• Apnea	1 (0.4)	0 (0.0)	1 (0.9)	1.000
Bronchopulmonary dysplasia	1 (0.4)	0 (0.0)	1 (0.9)	1.000
Persistent pulmonary hypertension	4 (1.8)	2 (1.8)	2 (1.7)	1.000
Surfactant use	5 (2.2)	1 (0.9)	4 (3.4)	0.371
Neonatal hypoglycemia	79 (35.6)	41 (38.0)	38 (33.3)	0.471
Neonatal jaundice	100 (44.4)	50 (45.9)	50 (43.1)	0.676
Sepsis	16 (7.1)	8 (7.3)	8 (6.9)	0.897
Polycythemia	3 (1.3)	3 (2.8)	0 (0.0)	0.112
Composite respiratory support[b]	70 (31.1)	35 (32.1)	35 (30.2)	0.754
• CPAP use	60 (26.7)	31 (28.4)	29 (25.0)	0.560
• Endotracheal intubation	30 (13.3)	10 (9.2)	20 (17.2)	0.075
Respiratory support (days); median (IQR)	0 (0, 0.58)	0 (0, 0.58)	0 (0, 0.68)	0.865
Pediatric ward admission	180 (80.0)	91 (83.5)	89 (76.7)	0.205
Neonatal length of stay (days); median (IQR)	4 (3, 7.5)	4 (3, 7.5)	4 (3, 7.8)	0.988
Neonatal death	6 (2.7)	4 (3.7)	2 (1.7)	0.434

IQR=interquartile range; CPAP=continuous positive airway pressure; NA=not applicable

[a] Composite respiratory complications: defined as having any of respiratory distress, pneumonia, apnea, transient tachypnea of newborn, and bronchopulmonary dysplasia

[b] Invasive respiratory support including endotracheal intubation and continuous positive airway pressure use

for neonatal outcomes such as diabetes mellitus, hypertension placenta previa, and gestational age at delivery. Dexamethasone also increased risk of maternal wound infection. This is supported by a recent systematic review of 45 trials[13] that indirectly showed dexamethasone increased risk of RDS, and puerperal sepsis. There may be reasons for the difference in such findings. First, different studies used different definitions of neonatal respiratory outcomes. For example, early large trial by Gyamfi-Bannerman[10] defined respiratory outcome as use of invasive respiratory support or neonatal death, while the present study and other recent studies defined respiratory outcomes as having composite respiratory complications including RDS, TTNB, pneumonia apnea, and bronchopulmonary dysplasia. Second, study samples in Gyamfi-Bannerman's study and the present study were different regarding obstetric complications, which could have affected the impact of corticosteroids on primary outcomes. Third, practice in tocolysis in late preterm labor may be different across studies, which could affect the gestational age at delivery and hence respiratory complications.

The benefits of antenatal corticosteroids on need for invasive respiratory support remained controversial. While an early study[10] found that betamethasone decreased the need of invasive respiratory support, other studies[12,14,19,21] reported no such benefit. The present study also found antenatal dexamethasone was not associated with reducing the need for invasive respiratory support, including CPAP and endotracheal intubation, independent of maternal morbidities, treatments received, gestational age, and birthweight. This could be explained by different practice of neonatologists in starting respiratory support across studies. Compared to a previous landmark study[10], the present study had a higher rate of CPAP use in dexamethasone group at 10.2% versus 17.7% and lower rate of CPAP use in non-dexamethasone group at 13.1% versus 11.4%.

Similar to previous studies[10,11,22], the present study showed that dexamethasone increased the risk of neonatal hypoglycemia. In the present study and other observational studies[11,22], this deleterious effect could be explained by those neonates receiving antenatal corticosteroid were those who had lower gestational age at birth and birthweight. Therefore, they were likely to develop hypoglycemia. Similarly, results from trial[10] found a higher risk of neonatal hypoglycemia in betamethasone than placebo groups, given that other factors were balanced. The impact of corticosteroid on risk of neonatal hypoglycemia could lead to long-term psycho-behavioral and cardiovascular problems[23,24].

Further, corticosteroid has been reported to be associated with an increased risk of puerperal infection. The present study found that pregnant women who received dexamethasone had a higher rate of wound infection and a longer length of hospital stay than pregnant women who did not received dexamethasone. The finding from the current study supported the Ciapponi's work[13] showing a potentially increased risk of chorioamnionitis, endometritis, and puerperal sepsis in those who received antenatal corticosteroids.

Potential harms of corticosteroids treatment in late preterm labor should be outweighed by its benefits. In addition to an increased risk of neonatal hypoglycemia[10], a recent registry-based study in 674,877 neonates in Finland found that corticosteroids treatment was associated with a higher risk of any mental and behavioral disorder in the entire cohort of children over a median follow up of almost six years[25]. Hence, concerns over both short- and long-term risks following antenatal corticosteroids in late preterm should be carefully taken.

There is limited evidence on the benefit of antenatal corticosteroid in preterm labor of multifetal pregnancy. Previous studies reported the benefit of reducing risk of having adverse neonatal outcome such as RDS, IVH, and neonatal death in multiple pregnancies exposed to at least one dose of antenatal corticosteroid in pregnant women with gestational age of less than 34 weeks[26,27]. The present study is among studies[26,27] to examine the effect of antenatal corticosteroids on maternal and neonatal outcomes in multifetal pregnancy presenting with late preterm labor. However, the present study did not find the differences in the maternal and neonatal outcomes between those who received and did not receive antenatal dexamethasone, due to the small number of pregnant women in this group.

The present study is among the largest studies and included pregnant women with various complicated conditions that are commonly found in obstetric practice. Standard statistical techniques were used to examine the associations between antenatal corticosteroids and primary outcomes. As this was observational study, there was no risk of experimental intervention and no ethical conflict against the recommendation of antenatal corticosteroids in late preterm from the American College of Obstetrics and Gynecology (ACOG)[28,29]. However, the present study has limitations. Due to the retrospective study design, the results depend on the availability of data in medical records. For example, data on time to delivery after corticosteroids administration were not available. Therefore, the authors were not able to compare benefit of corticosteroids between those who delivered before and after seven days of corticosteroids administration. As neonatal outcomes were ascertained based on ICD-10 diagnostic codes in discharge summary, there might be possibility of misclassification of the outcomes that could have altered their association with antenatal corticosteroids. Although confounding factors were adjusted in the present study, there is still possibility of residual confounding. Furthermore, there might be other confounders, both known and unknown, that the authors did not account for, including cervical progression. In spite of the number of participants being smaller than the calculated sample size, the present study was able to identify the association between corticosteroids and primary outcomes.

The present study had practical implications concerning administration of antenatal dexamethasone in late preterm labor. With an increased risk of

adverse neonatal respiratory outcomes observed in the present study, strict indication for administration of dexamethasone in late preterm labor should be taken. That is, four doses of 6 mg intramuscular dexamethasone 12 hours apart should be administrated only in the impending late preterm birth without tocolytics is used to prolong delivery. In addition, before treatment with dexamethasone, risk of other adverse maternal and neonatal outcomes such as hypoglycemia, jaundice, and puerperal sepsis should be clearly discussed with the pregnant women. Further studies are needed to examine the effects of corticosteroid in specific subgroups such as multiple fetal gestation, diabetes mellitus, and fetal growth restricted, and to follow for long-term outcomes of both mothers and babies. Cautions should be taken when considering treatment of dexamethasone in this group.

Conclusion

Antenatal intramuscular dexamethasone between 34 0/7 and 36 6/7 weeks of gestation was independently associated with increased risk of composite neonatal respiratory complications but not associated with need for invasive respiratory support. Other associated factors included multifetal gestation, magnesium sulfate use, birth weight, gestational age at delivery, rupture of membrane, and placenta previa.

What is already known on this topic?

Treatment with antenatal corticosteroids, as compared with placebo or no treatment, in anticipating preterm delivery before the thirty-fourth weeks of gestation was reported to be associated with a reduction in the most serious adverse outcomes related to prematurity, including respiratory distress syndrome (RDS), perinatal death, and neonatal death. However, the benefits remained unclear in specific subgroups such as multiple pregnancies and late preterm labor. In Thailand, dexamethasone is the only corticosteroid used for promoting lung maturity. Evidence on efficacy and safety of antenatal intramuscular dexamethasone in Thai pregnant women with late preterm labor is limited

What this study adds?

In late preterm group, antenatal dexamethasone was associated with increased risk of neonatal composite respiratory complications, especially TTNB and RDS, but not associated with need for invasive respiratory support. Additionally, antenatal dexamethasone may increase risk of neonatal hypoglycemia, and jaundice. Moreover, the women who received dexamethasone also have increased risk of wound infection. For practical implications concerning administration of antenatal dexamethasone in late preterm labor, strict indication for administration of dexamethasone in late preterm labor should be taken.

Acknowledgement

The authors appreciate all the contributors of Sunpasitthiprasong Hospital for data and funding resource. The authors also appreciated Dr. Charnsak Jungmunkong, head of the Obstetrics and Gynecology Department, Sunpasitthiprasong Hospital, for accommodation of the present study.

Conflicts of interest

The authors declare no conflicts of interest.

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