A comparison of the clinical outcome of late preterm neonates with versus without antenatal corticosteroids*

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ABSTRACT

Background: Preterm birth remains to be the largest cause of neonatal deaths worldwide. Improvement in preterm neonatal outcomes with antenatal corticosteroids (ACS) given to mothers at 24 to 34 weeks gestation who are at risk for preterm birth is well established. Nevertheless, the use of ACS in the late preterm, which comprises the majority of preterm births, remains an area of discussion. Recent international studies have recommended the use of ACS on the late preterm group. However, such studies in a low-income setting are lacking. Moreover, there has been no local studies and guidelines supporting the use of ACS in the late preterm.

Objective: To determine the difference in late preterm neonatal outcomes between neonates of mothers given versus those not given antenatal corticosteroids.

Materials and Methods: This was a cross sectional study done at a tertiary hospital on all singleton late preterm deliveries from 2016 to 2018. The population was divided into the no ACS and with ACS group. Data were presented in means and proportions. T test and Z test were used to determine the significant difference. Test statistic with p value less than 0.05 was considered significant.

Results: The need for intubation was higher in neonates without ACS compared to the those with ACS, whether the course was completed or not (p value=0.024). Furthermore, respiratory distress syndrome and need for surfactant was significantly higher in the no ACS group when compared to those who completed the ACS course (p value=0.024 and 0.044, respectively). Though, no significant difference was noted in the other neonatal outcomes (p values >0.05).

Conclusion: ACS, whether completed or not, resulted in a lesser need for intubation. Furthermore, a complete ACS course results in a decreased risk of respiratory distress syndrome and need for surfactant among late preterm neonates.

Keywords: Late Preterm, Antenatal Corticosteroids

INTRODUCTION

Background of the Study

Preterm birth has been rising every year. It is subdivided into early preterm, those before 33 6/7 weeks, and late preterm, those between 34 and 36 completed weeks. According to UNICEF, there are 15 million preterm births each year, ranging from 5-18%. To date, preterm birth has remained to be the largest cause of neonatal deaths accounting to 35% of 3.1 million deaths in a year.[1] Thus, preterm birth is the single most important determinant of adverse infant outcomes in terms of survival and quality of life.[2]

Interventions to improve preterm neonatal outcomes include the use of antenatal corticosteroids (ACS). It has been reported that corticosteroids stimulate lung maturation and surfactant synthesis.[3] ACS was proven to improve neonatal outcomes to neonates delivered 24 to 34 weeks gestation.

Due to the recognition that late preterm neonates account for majority of preterm births and that these neonates experience more morbidities and mortality compared to their term counterparts[4-5], the use of ACS in the late preterm period was evaluated. Previous studies showed that ACS is ineffective in reducing the respiratory morbidity as well as other complications of prematurity among late preterm neonates.[6-7] However, in the study done by Gyamfi-Bannerman, et al[8], the Antenatal Late Preterm Steroid (ALPS) Trial, reported that the administration of a single course of betamethasone reduces the rate of neonatal respiratory complications

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with no evidence of harm, which is consistent with the findings of other studies.[9-10] These studies were done in international, high-income settings. And it has been shown that neonates have a higher chance of survival in high-income countries.[11] Thus, the World Health Organization is currently looking into the safety and efficacy of ACS in resource-limited settings through the Antenatal Corticosteroids for Improving Outcomes in Preterm Newborns (ACTION) Trial. Presently, there is still lack of studies on the use of ACS in the late preterm period in low income countries. Moreover, there have been no local studies and guidelines on the use of ACS in late preterm. This is the pilot study in our institution.

Significance of the Study

Since the publication of the ALPS trial[8], there has been a shift in the practice of ACS administration. The American College of Obstetrics and Gynecology (ACOG) now recommends a single course of betamethasone for pregnant women between 34 to 36 6/7 weeks gestation who are at risk for preterm birth.[12] However, due to findings of other studies showing no benefit of ACS in the late preterm, plus the lack of local guidelines, the use of ACS in the late preterm group has not been routinely practiced by obstetricians locally.

It is the aim of this study to compare neonatal outcomes among late preterm neonates with versus without ACS. If shown to yield positive results, the study will pave way for obstetricians to consider the administration of ACS to mothers at risk for late preterm births. This in turn may improve the neonatal outcomes in our institution. Moreover, the study will also serve as a benchmark for further and detailed local studies; a small-scale study to detect areas of improvement therefore enhancing a future research plan.

RESEARCH OBJECTIVE

General Objective: To determine the difference in the neonatal outcome among late preterm neonates whose mothers were given versus those not given antenatal corticosteroids

Specific Objectives:

1. To describe and compare maternal characteristics to include age (years), gravidity, weight (kg), height (cm), educational attainment, route of delivery, and comorbidities between late preterm neonates of mothers given and not given antenatal corticosteroids

2. To describe and compare neonatal characteristics to include age of gestation, gender, birth weight, APGAR score, and Ballard Score between late preterm neonates of mothers given and not given antenatal corticosteroids

3. To determine and compare the neonatal outcomes between late preterm neonates of mothers given and not given antenatal corticosteroids; and between late preterm neonates of mothers given a complete course and not given antenatal corticosteroids
   i. Neonatal morbidities
      a. Respiratory Distress Syndrome
      b. Pneumonia
      c. Transient Tachypnea of the Newborn
      d. Sepsis
      e. Jaundice
      f. Surfactant use
      g. Intraventricular Hemorrhage
      h. Necrotizing Enterocolitis

   ii. The need for respiratory support
      a. Mechanical ventilation
      b. Continuous Positive Airway Pressure (CPAP)
      c. Oxygen Modalities

4. To determine and compare the mean length of hospital stay between late preterm neonates of mothers given and not given antenatal corticosteroids

5. To determine and compare the causes of mortality between late preterm neonates of mothers given and not given antenatal corticosteroids

Definition of Terms

1. Late Preterm Neonates – neonates born at 34 1/7 to 36 6/7 weeks gestation
2. Age of gestation – is the estimate age of pregnancy computed using the last menstrual cycle or basing on the early sonologic age
3. APGAR Score – it is a scoring system that assesses the over-all clinical status and response to resuscitation of newborn infants at 1 minute and 5 minutes of life basing on the newborn's appearance, pulse rate, grimace, activity and respiration.
4. Ballard Score – a tool used to determine gestational age through neuromuscular and physical assessment of the newborn.
5. Complete Course Antenatal corticosteroids – either betamethasone 12 mg intramuscularly 2 doses 24 hours apart or dexamethasone 6 mg intramuscularly for 4 doses 12 hours apart
6. Neonatal morbidities – refers to neonatal diseases that are the leading complications of prematurity. In the study, these refers to Respiratory Distress Syndrome,

Pneumonia, Transient Tachypnea of the Newborn, Sepsis, Jaundice, Surfactant use, Intraventricular Hemorrhage, and Necrotizing Enterocolitis as found in the final diagnosis of the neonate.

Ethical Consideration

A research protocol was submitted to the Institution Review Board for approval. Permission to review patients' charts was granted by the Office of the Medical Director. All data were coded to ensure confidentiality of the patient's data during the data collection and in the writing of the manuscript.

REVIEW OF RELATED LITERATURE

The Philippines ranks 8th among the countries with the greatest number of preterm births, and ranks 17th among countries with greatest total number of deaths due to complications from preterm birth.[1] The preterm live birth rate in the Philippines ranges from 7 to 24%, with a preterm neonatal death rate of 12 to 81%.[7]

Preterm newborns suffer morbidities largely due to organ system immaturity. Global efforts to improve preterm neonatal outcomes using cost-effective interventions are continuing. One of the most revolutionary discovery in reducing preterm neonatal morbidities and mortality is the administration of antenatal corticosteroids (ACS) to pregnant women who are at risk for preterm birth. Evidence shows that corticosteroids stimulates fetal lung maturation and augments surfactant synthesis. Furthermore, it also has extrapulmonary effects that contribute to the maturation of different organs and systems.[9] Thus, a complete course of ACS has been proven to improve survival and reduce the morbidity and mortality of early preterm infants.[14] Owing to the fast rise of late preterm birth, now comprising majority of preterm births, the effectivity of ACS in this population has been an area of interest and debate.

A randomized clinical trial done by Porto, et al,[6] involving 320 women at 34 to 36 weeks age of gestation randomized to either receive a complete course of betamethasone or a placebo, showed no significant difference among the 2 groups in terms of baseline maternal and fetal characteristics, respiratory disorders, ventilatory support and neonatal morbidities. The study concluded that ACS is ineffective in reducing the respiratory morbidity as well as other complications of prematurity among late preterm neonates.

In the WHO Preterm Birth Outcomes Guidelines, the evidence presented that ACS was not shown to reduce respiratory distress syndrome when analyzed for all infants born after 34 weeks gestation.[7]

In contrast to above findings, a prospective observational study by Serrano, et al[9] showed that the incidence of admission to a higher care unit, transient tachypnea, ventilatory support, jaundice was higher in the late preterm group that did not receive ACS. The study assessed the effect of ACS on the neonatal outcomes of those at 34-36 6/7 weeks gestation. The neonates were divided into those exposed to ACS, either a single dose or a complete course of betamethasone, and those not exposed at all.

The systematic review with meta-analysis of 6 trials done by Saccone and Berghella,[10] likewise concluded that a complete course of ACS is beneficial in decreasing severe respiratory distress syndrome in late preterm gestation.

Recently, the American College of Obstetricians and Gynecologists recommends a single course of betamethasone for pregnant women in late preterm labor.[12] This recommendation was based on the results of the Antenatal Late Preterm Steroids trial, a double-blind, placebo-controlled, randomized clinical trial by Gyamfi-Bannerman, et al.[8] The study showed that betamethasone led to a significant decrease in the need for respiratory support and rates of respiratory complications such as transient tachypnea of the newborn, bronchopulmonary dysplasia, respiratory distress syndrome, and the need for postnatal surfactant.

Most of the studies mentioned previously compared the use of a complete ACS course to no ACS exposure at all except for the study by Serrano, et al,[9] where in exposure to ACS also included those exposed to an incomplete course. Though investigations on the use of single dose ACS is lacking in the late preterm group, investigations involving the early preterm group has been done. Studies involving single dose ACS in the early preterm showed significantly better neonatal outcomes compared to the no ACS exposure.[15-17] Hence, ACS should still be given even if completion of a single course is not feasible. On the other hand, there is insufficient evidence to make a recommendation for or against the use single dose ACS in the late preterm group.

RESEARCH METHODOLOGY

Study Design: Cross Sectional Prevalence

Study Setting: This study was conducted in a 660-bed capacity tertiary hospital

Study Population:

Inclusion Criteria

1. Singleton
2. Late Preterm Delivery

Exclusion Criteria

1. Congenital anomalies
2. Corticosteroids were given before 34 weeks
3. Incomplete data

Sampling Size and Sampling Method

This study included all late preterm deliveries from January 2016 to December 2018.

Data Collection:

A detailed medical chart review on all late preterm deliveries was done. Data was extracted and recorded in a patient data form. The data was then entered manually into a spreadsheet and was sorted using Excel computer software. The population was divided into 2 groups: Group 1 consisted of late preterm neonates whose mothers did not receive any ACS while Group 2 consisted of those whose mothers received ACS, whether the course has been completed or not. Comparison among the two groups basing on the maternal and neonatal characteristics, neonatal outcomes, and length of hospital stay was done. Further comparison was made between those who received the complete ACS course to those who received none.

Data Analysis:

Data were presented in means and proportions. T test was used to determine the significant difference of 2 population means and Z test for 2 population proportions. Test statistic with p value less than 0.05 is considered significant.

RESULTS

A total of 4,755 live births from January 2016 to December 2018 was recorded. Of these, 606 were preterm births, accounting for 12.7%. There were 390 late preterm deliveries, comprising 8.2% of all live births and 64.4% of all preterm births. There were 67 cases excluded due to: multifetal pregnancy (12); exposure to steroids prior to 34 weeks (30); known fetal congenital anomalies (11); and incomplete data (14). Thus, a total of 323 cases were enrolled. Of the 323 cases, 239 women were not given ACS and 84 were given ACS. Of those given ACS, 45 received an incomplete course and 39 received the complete course.

Maternal characteristics

Mothers of both groups had a mean age of 30 years. The mean weight of group 1 and 2 mothers was 66.5 kg and 65.3 kg, respectively. Majority of mothers of both groups were college graduate (group 1=89.5%, group 2=92.9%). Majority of the neonates were delivered vaginally (group 1=61.9%, group 2=54.8%). In terms of comorbidities, majority of mothers had hypertension (group 1=27.6%, group 2=28.6%), followed by diabetes mellitus (group 1=24.7%, group 2=20.2%), then respiratory diseases (group 1=9.6%, group 2=9.5%), thyroid diseases (group 1=6.7%, group 2=6%), and cardiac diseases (group 1=1.7%, group 2=1.2%). Preterm premature rupture of membranes occurred more in group 2 (31%) than in group 1 (28.9%), however it was not statistically significant (p=0.721). The baseline maternal characteristics, as summarized in Table 1,

Table 1. Comparability of Both Groups based on Maternal Characteristics

Characteristics	No antenatal corticosteroids, n = 239		With antenatal corticosteroids, n = 84		Test Statistic Value	P-Value
Age, in year	30.93	SD + 6.06	30.45	SD + 5.46	0.67A	0.501
Weight, in kg	66.52	SD + 10.90	65.32	SD + 13.12	0.75A	0.455
Height, in cm	153.77	SD + 5.55	153.80	SD + 6.27	-0.04A	0.971
Educational Attainment, n (%)						
Primary	1	0.42%	0	0 %	1.00	0.316
Secondary	24	10.04%	6	7.14 %	0.85	0.396
College	214	89.54%	78	92.86 %	-0.97	0.334
Route of Delivery, n (%)						
Vaginal Delivery	148	61.92%	46	54.76%	1.14[B]	0.254
Abdominal Delivery	87	36.40%	38	45.24%	-1.41[B]	0.158
Comorbidities, n (%)						
Hypertension	66	27.62%	24	28.57%	-0.17[B]	0.867
Cardiac Diseases	4	1.67%	1	1.19%	0.33[B]	0.738
Diabetes Mellitus	59	24.69%	17	20.24%	0.86[B]	0.392
Respiratory Diseases	23	9.62%	8	9.52%	0.03[B]	0.979
Thyroid Diseases	16	6.69%	5	5.95%	0.24[B]	0.807
PPROM	69	28.87%	26	30.95%	-0.36[B]	0.721

Note: ** Significant at 0.05, A Using T Test Two Independent Samples, B Using Z Test Two Proportions
PPROM – preterm premature rupture of membranes

Table 2. Comparability of Both Groups based on Neonatal Characteristics

Characteristics	No antenatal corticosteroids, n = 239		With antenatal corticosteroids, n = 84		Test Statistic Value	P-Value
Sex, n (%)						
Male	129	53.97%	50	59.52%	-0.89[B]	0.375
Female	110	46.03%	34	40.48%	0.89[B]	0.375
Birth Weight, in grams	2516.46	SD ± 402.37	2328.45	SD ± 442.46	3.43[A]	0.001**
APGAR Score						
1 minute	8.26	SD ± 1.17	8.14	SD ± 1.17	0.78[A]	0.435
5 minutes	9.28	SD ± 5.84	8.88	SD D ± 0.39	1.05[A]	0.295
Age of Gestation, in weeks	36.16	SD ± 0.83	35.37	SD ± 0.80	7.66[A]	0.000**
Ballard Score, in weeks	37.01	SD ± 1.07	36.29	SD ± 1.03	5.47[A]	0.000**

Note: *** Significant at 0.05;* [A] *Using T Test Two Independent Samples;* [B] *Using Z Test Two Proportions*

Table 3. Comparison of Neonatal Outcomes Among Those With and Without ACS

Characteristics	No antenatal corticosteroids, n = 239		With antenatal corticosteroids, n = 84		Test Statistic Value	P-Value
Morbidities, n %						
RDS, n (%)	8	3.35%	3	3.57%	-0.10[B]	0.924
Pneumonia, n (%)	26	10.88%	13	15.48%	-1.04[B]	0.299
TTN, n (%)	15	6.28%	3	3.57%	1.0[6B]	0.291
Sepsis, n (%)	42	17.57%	22	26.19%	-1.60[B]	0.110
Jaundice, n (%)	16	6.69%	6	7.14%	-0.14[B]	0.890
Surfactant, n (%)	4	1.67%	1	1.19%	0.33[B]	0.738
IVH, n (%)	1	0.42%	0	0%	1.00[B]	0.316
NEC, n (%)	1	0.42%	0	0%	1.00[B]	0.316
Respiratory Support						
Intubation, n (%)	5	2.09%	0	0%	2.26	0.024**
CPAP, n (%)	22	9.21%	12	14.29%	-1.20[B]	0.232
Oxygen, n (%)	34	14.23%	13	15.48%	-0.27[B]	0.783

Note: *** Significant at 0.05;* [A] *Using T Test Two Independent Samples* [B] *Using Z Test Two Proportions*
RDS – Respiratory Distress Syndrome, TTN – Transient Tachypnea of the Newborn, PHN – Pulmonary Hypertension, NEC – Necrotizing Enterocolitis, IVH – Intraventricular Hemorrhage, CPAP – Continuous Positive Airway Pressure

Table 4. Comparison of Neonatal Outcomes Among Those With Completed ACS vs Without ACS

Characteristics	No antenatal corticosteroids, n = 239		Complete Course antenatal corticosteroids, n = 39		Test Statistic Value	P-Value
Morbidities, n %						
RDS, n (%)	8	3.35%	0	0%	2.88[B]	0.004**
Pneumonia, n (%)	26	10.88%	4	10.26%	0.12[B]	0.906
TTN, n (%)	15	6.28%	1	2.56%	1.25[6B]	0.213
Sepsis, n (%)	42	17.57%	10	25.64%	-1.09[B]	0.276
Jaundice, n (%)	16	6.69%	1	2.56%	1.38[B]	0.169
Surfactant, n (%)	4	1.67%	0	0%	2.02[B]	0.044**
IVH, n (%)	1	0.42%	0	0%	1.00[B]	0.316
NEC, n (%)	1	0.42%	0	0%	1.00[B]	0.316
Respiratory Support						
Intubation, n (%)	5	2.09%	0	0%	2.26	0.024**
CPAP, n (%)	22	9.21%	4	10.26%	-0.20[B]	0.840
Oxygen, n (%)	34	14.23%	6	15.38%	-0.19[B]	0.852

Note: *Note: ** Significant at 0.05;* [A] *Using T Test Two Independent Samples;* [B] *Using Z Test Two Proportions*
RDS – Respiratory Distress Syndrome, TTN – Transient Tachypnea of the Newborn, PHN – Pulmonary Hypertension, NEC – Necrotizing Enterocolitis, IVH – Intraventricular Hemorrhage, CPAP – Continuous Positive Airway Pressure

DISCUSSION

Consistent with the literatures reviewed, the preterm birth in our institution comprised 12.7% of all live births, in which majority, at 64.4%, are late preterm neonates.

Maternal characteristics of both groups are comparable thus, it will minimize bias and will not influence the findings of this study. Though neonatal characteristics in terms of gender and APGAR scores were shown to be comparable, of note, fetal aging and birthweight were significantly lower in group 2 neonates. Due to lack of local studies and guidelines on the beneficial effects of ACS on the late preterm, not all obstetricians in our institution give ACS to mothers in late preterm labor. And if they do, they are more likely to give it nearer to 34 weeks. This may explain the findings that the group 2 neonates had lower fetal aging and subsequently lower birthweights.

In this study the incidence of respiratory distress syndrome, pneumonia, transient tachypnea of the newborn, need for surfactant, jaundice, intraventricular hemorrhage, necrotizing enterocolitis were similar in group 1 and 2 neonates, similar to the findings of Porto, et al[6] and the WHO Preterm Birth Outcomes Guidelines[7]. However, group 2 neonates have significantly lesser need for intubation. Further investigating the effect of a complete ACS course, this study showed that these neonates had a significantly reduced risk of respiratory distress syndrome and need for surfactant, which are similar to the findings of Serrano, et al[9], Saccone and Berghella[10], and Gyamfi-Bannerman, et al[8]. Though it is known that the fetal lungs mature after 32 to 34 weeks gestation, the late preterm period is still associated with immaturity and lesser number of the sodium transport channels across the alveolar epithelium, which is involved in the clearance of fetal lung fluid.[18] Hence, respiratory disorders are still frequent in the late preterm. Corticosteroids stimulate the synthesis and activity of the sodium channels therefore, they contribute to the reabsorption of fetal lung fluid. This may explain as to why respiratory distress syndrome and need for surfactant is lower in the neonates exposed to ACS and stresses the importance of a complete course for its benefit to be seen.

One of the concerns on ACS administration in the preterm period is the risk of perinatal infection owing to the immaturity of the immune system especially in the setting of ruptured membranes. In this study, preterm premature rupture of membranes as well as the incidence of sepsis are comparable in both groups. Hence, it supports that ACS will not increase the risk of sepsis in the late preterm neonates, a finding similar to the study done by Serrano, et al.[9]

CONCLUSION

The benefit of ACS in the late preterm is supported in this study as shown by the evidence that ACS exposed neonates, whether the course has been completed or not, showed significantly lesser need for intubation. Furthermore, a complete course of ACS results in a significantly decreased risk of respiratory distress syndrome and need for surfactant. Lastly, the study reinforce that ACS does not increase the risk of sepsis even in the setting of preterm premature rupture of membranes.

LIMITATIONS

The data obtained relied on the accuracy of record data keeping. More on, this study did not dwell on the time of delivery from ACS administration, the indications of delivery, and reasons for incomplete course administration, which may have a bearing on the neonatal outcome. Since a non-random probability sampling was done and only minority of local obstetricians practice ACS administration in the late preterm group, adequate representation might not be fully known.

RECOMMENDATIONS

To better recognize the effects of ACS on the late preterm neonates in the local setting, further studies in a controlled setting, such as a randomized controlled trial, is recommended as this will increase the statistical power of this study. A longer study period with larger population is suggested as this will yield a stronger significance. The topic on the role of single dose ACS in the early preterm group is still debatable, more so, its role in the late preterm group is not yet known. This would be a promising study since not all mothers are able to complete the dose of ACS due to presence of indications to terminate pregnancy early or in cases of imminent delivery. ■

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