Appropriate Use of Antenatal Corticosteroid in Women at Risk for Preterm Birth

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ABSTRACT **Background:** The benefits of corticosteroid administration for suspected premature birth (PTB) are widely accepted. Although a single course of antenatal corticosteroids is generally considered to be safe, there are concerns regarding the safety and benefit of multiple courses. Nevertheless, many women who present with symptoms of PTB do not deliver early.

Objectives: To assess how often we used corticosteroid appropriately in our clinical practice in women who presented with risk of PTB.

Methods: Clinical data were retrospectively collected on patients who were admitted to our clinic between September 2014 and August 2015 due to risk of PTB and who were treated with prenatal corticosteroids.

Results: We identified 305 patients at risk of PTB who were treated with corticosteroids; 42.3% delivered < week 34, 22.5% delivered between weeks 34 and 37, and 35.1% delivered > 37 weeks. In women who delivered after week 37, the more time that elapsed between corticosteroids administration and delivery, the lower the pH and the APGAR scores were. Only 26% of patients delivered 2–14 days after the last steroids course of treatment.

Conclusions: The rate of term deliveries at our center after receiving antenatal corticosteroids due to prior symptoms of preterm labor was 35.1%. The ratio of maternal antenatal corticosteroid administration for potential versus actual PTB at < 37 weeks of gestation was not optimal but acceptable.

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Preterm birth, defined as birth earlier than 37 weeks of gestation, is associated with neonatal morbidities, including respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, and infections [1].

The mechanisms underlying preterm labor have been extensively studied over the years and are now recognized as a syndrome associated with multiple pathological outcomes such as infection, decidual hemorrhage and vascular disease, disruption of maternal-fetal tolerance, decline in progesterone action, uterine overdistension, and maternal distress [1].

In preterm deliveries, the administration of antenatal corticosteroids (ACS) to combat the effects of prematurity between 24 and 34 weeks gestation is firmly established as the standard of care and has been shown to significantly reduce infant morbidity and mortality [2].

Corticosteroid administration is associated with reduction of neonatal mortality (RR=0.69), cerebroventricular hemorrhage (RR=0.6), necrotizing enterocolitis (RR=0.46), respiratory distress (RR=0.6), systemic infection during the first 48 hours of life (RR=0.56) and the need for invasive intubation (RR=0.8) [3,4]. Due to the results of the ALPS trial [5], late preterm ACS administration was recommended by obstetrical societies worldwide [6,7].

Studies have been conducted to check the long-term childhood outcomes for babies who were exposed to ACS [8]. A retrospective cohort study of 5 year olds born later than 37 weeks gestation to mothers diagnosed with threatened preterm labor during pregnancy who took ACS showed increased odds of being in a lower growth percentile than those not exposed [9]. Räikkönen and colleagues [10] found that infants exposed to ACS at 34–39 weeks gestation and delivered at term showed an increase in psychiatric and behavioral diagnoses in childhood [10].

In early preterm infants, the long-established short-term benefits of ACS are likely to override any potential long-term adverse effects. However, if the short-term benefits of ACS are minimal (as in late preterm administration) or absent (as in term-born infants), the balance between benefits and harm may change [11].

The aim of our research is to determine how often we correctly administered corticosteroids in women who were admitted with threatened early preterm labor between 2014–2015, before the ALPS trial.

PATIENTS AND METHODS

For this retrospective cohort study, data were collected retrospectively on pregnant women with singleton and multiple pregnancies admitted to Rambam Health Care Campus, between September 2014 and August 2015. All had potential precursors for delivery between 24 + 0 and 34 + 0 weeks of gestation and all were treated with ACS.

The collected data included the week of gestation when the ACS was administered, the gestational week of delivery, the time elapsed between the last dose of corticosteroid and delivery, and the neonatal complications. Patients with missing data such as unknown gestational age and those who received ACS or delivered in other hospitals were excluded.

The risk for preterm delivery was determined according to different factors, including the presence of regular contractions, preterm premature rupture of membranes, cervical dilation and effacement, and antepartum hemorrhage.

The indications of preterm inductions included placental abruption, gestational hypertension, intra-uterine growth restriction, and other active maternal diseases. Patients presenting with suspected preterm labor were admitted to the labor ward and the diagnosis of imminent preterm birth was determined on the basis of history and examination. Those at risk were treated with course of corticosteroid (two 12-mg doses of betamethasone given intramuscularly 24 hours apart). Some were treated with two courses of ACS (2 weeks apart at least). Tocolytic treatments were administered to some patients, depending on clinical consideration.

The primary outcome was the ratio of women who were treated with ACS to those who were treated and subsequently had a preterm delivery before 34 and 37 weeks. The secondary outcomes were the time elapsed from the last dose of corticosteroid until the time of delivery and the correlation with neonatal complications.

The study protocol was approved by the Helsinki committee at Rambam. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA). We measured the correlation between neonatal outcome and time of corticosteroid administration. Methods of comparison and analysis included Pearson's chi-square test, *t*-test, and ANOVA. In addition, Mann–Whitney and Kruskal–Wallis tests were used for variables that do not have normal distribution. A P-value < 0.05 was considered statistically significant. Last, power analysis of the sample size was determined to detect the effectiveness and degree of confidence. The analysis for this study was based on preterm birth in Rambam between September 2014 and August 2015. ACS was 70% of the sample.

RESULTS

Between September 2014 and August 2015, 305 pregnant women were admitted to Rambam due to threatened preterm labor. They were treated with at least one course of ACS. Of those, 40 patients with missing and those who received corticosteroid or delivered at other hospitals were excluded.

The remaining 265 patients in the cohort were included in the study. D demographic data are presented in Table 1. Women were divided into three groups: women who de-

Table 1. Demographic and clinical characteristics of the participants (n=305)

Maternal characteristics	Values
Age at diagnosis, mean ± SD	30.3 ± 5.5
Ethnicity, n (%)	
Jewish	203 (66.6%)
Other	102 (33.4%)
Smoking, n (%)	21 (6.9%)
Gravidity, mean ± SD	3 ± 2
Parity, mean ± SD	2 ± 1
Type of pregnancy, n (%)	
Singleton	221 (72.5%)
Twins	84 (27.5%)
Number of courses of ACS, n (%)	
1	258 (84.5%)
2	47 (15.5%)
Gestational age at first ACS dose, mean ± SD	29.5 ± 3.2
Contractions, n (%)	172 (56.6%)
Preterm premature rupture of membranes, n (%)	25 (8.3%)

ACS = antenatal corticosteroids, SD = standard deviation

livered before 34 weeks of gestation (42.3%), women who delivered between 34 and 37 weeks (22.6%), and women who delivered after 37 weeks (35.1%). Table 2 presents the frequency of women in each group. As can be seen from the table, most women gave birth before 34 weeks of gestation [Table 2].

Table 2. Week of delivery in patients in the study cohort

	N	%
Before 34 weeks	112	42.3
Between 34–37 weeks	60	22.6
After 37 weeks	93	35.1

The ratio of women who were treated with ACS to those who were treated and subsequently had a preterm delivery before 37 weeks was around 5:3 (64.9%) and the ratio of women who treated with steroids to those who were treated and subsequently had a preterm delivery before 34 weeks of gestation was 5:2 (42.3%).

Table 3 presents the means and standard deviations of time elapsed, in weeks, from the last dose of corticosteroid and the delivery. Women who gave birth prior to 34 weeks' gestation, gave birth on average less than one week after receiving the second dose (last dose) of corticosteroid treatment.

Our study showed that 26% of the women in the sample gave birth 2–14 days after receiving the last dose of corticosteroid treatment, which is the most effective window of corticosteroids treatment.

Table 3. Mean ± standard deviation of time elapsed from administration of antenatal corticosteroids to delivery

	Minimum	Maximum	Mean ± SD
Before 34 weeks	0.00	7.43	0.77 (1.05)
Between 34–37 weeks	0.29	12.71	4.94 (3.22)
After 37 weeks	0.00	16.86	7.97 (2.88)

EFFECT OF TIME BETWEEN CORTICOSTEROID ADMINISTRATION TO DELIVERY ON NEONATAL COMPLICATIONS

To examine the effect of time elapsed on fetal complications in each of the three groups, linear regressions were employed for the continuous complication variables and for the categorical complication variables. The regressions were conducted on the data of first and second fetuses.

RESULTS OF LINEAR REGRESSION:

In the preterm delivery groups (before week 34 and between weeks 34 and 37), there were no significant linear regression models for any of the fetuses. In other words, for women with a preterm delivery, the length of time between corticosteroid administration and delivery did not predict fetal complications. However, in the group after week 37, we found several significant linear regression models for the first fetus. The results are presented in Table 4.

The findings in the group of women who delivered after week 37 gestation (at term) illustrate that the extent of time elapsed from ACS administration to delivery has a direct correlation with pH and APGAR score. The longer the time elapsed, the lower the pH and APGAR scores (at 1 minute and at 5 minutes). The more time that elapsed between corticosteroid administration and delivery, the more neonatal complications presented.

Table 4. Results of linear regressions to predict complications by time elapsed, in the after week 37 group

	B	SE	B-beta	T
PH				
Time elapsed	-0.02	0.01	-0.58	-3.62*
Weight				
Time elapsed	25.02	14.47	0.18	1.73
APGAR1				
Time elapsed	-0.15	0.04	-0.37	-3.77**
APGAR5				
Time elapsed	-0.12	0.04	-0.32	-3.15*
Days in neonatal intensive care unit				
Time elapsed	-0.08	0.04	-0.18	-1.72

*$P < 0.01$
**$P < 0.001$

B = unstandardized regression coefficient, SE = standard error; B-beta = standardized regression coefficient, T = *t*-statistic

LOGISTIC REGRESSION RESULTS

In the women who gave birth before 34 weeks of gestation, there was no statistical significance in all the logarithmic models. For the group who delivered between week 34 and week 37 no statistics could be calculated for the complications because of small sample size. For those who delivered after 37 weeks of gestation or later neonatal mortality was not significant, and no statistics could be calculated for neonatal morbidity due to the small sample size.

DISCUSSION

Several articles have dealt with the effects of ACS on the risk of neonatal death, the risk of respiratory distress syndrome, and the need for respiratory support. ACS de-

creases the risk of other complications of prematurity, including intraventricular hemorrhage and necrotizing enterocolitis, but not bronchopulmonary dysplasia [1-4].

Moreover, findings showed that repeated courses of corticosteroids reduced the occurrence and severity of neonatal lung disease and the risk of serious health problems in the first few weeks of life. However, these benefits were associated with reduced weight and head circumference at birth. There is still insufficient evidence on the long-term benefits and risks. These limitations highlight the importance of wise use of ACS [12-17].

In our research, we investigated how often we correctly used ACS in women with suspected preterm labor. We noted an acceptable but not optimal use of ACS. Besides the minority of treated women gave birth between 2 and 14 days following the ACS administration: 42.3% delivered before 34 weeks, 22.6% between 34–37 weeks, and 35.1% after 37 weeks. This finding shows that 64.9% among the pregnant women who was treated with ACS delivered before 37 weeks. The ratio of women given corticosteroids to the number who delivered before 37 weeks gestation was approximately 5:3, and the ratio of women given ACS to the number who delivered before 34 weeks gestation was 5:2 overall.

Few studies have investigated corticosteroid administration. One prospective study conducted in Ireland in 2010 dealt with 414 women who were admitted due to threatened preterm labor prior to week 34. Of those women, 67% were given ACS. Of the women who delivering at < 34 weeks gestation, 93% received any corticosteroid and 76% received a complete course. The ratio of women given a complete course of corticosteroids to the number who actually delivered before 34 weeks gestation was 4:1 overall [18]. Another retrospective study performed in Qatar in 2009 investigated the ratio between women who received corticosteroid and those who delivered prior to 34 weeks gestation. This study illustrated that two-thirds of the women who received a full course of corticosteroid treatment gave birth before 37 weeks gestation [19]. Compared with those studies, we found that the administration of corticosteroids in our hospital was acceptable, but not optimal.

The beneficial effects of a complete course of antenatal corticosteroid are greatest if more than 24 hours and less than 7 days elapsed between initial administration of therapy and actual delivery [20]. Our study showed that 26% of the women in the sample gave birth 2–14 days after receiving the last dose of corticosteroid treatment, and those who gave birth prior to 34 weeks gestation delivered on average less than 7 days after receiving the second dose of corticosteroids, which is the most effective window of corticosteroids treatment.

When examining the effect of time elapsed on fetal complications, the study showed that for women with preterm delivery before 37 weeks of gestation, the length of time between corticosteroid administration and delivery did not predict fetal complications. However, in those who delivered after 37 weeks of gestation, the time from corticosteroid administration to delivery impacted pH levels and APGAR scores (at 1 minute and at 5 minutes). This finding may be incidental or may be the result of a maximal effect of steroids lasting between 2 and 14 days. Battarbee and colleague [20] found that the optimal timing of ACS administration and preterm neonatal and early childhood outcomes was ≥ 14 days before delivery. This timing increased odds for severe neonatal morbidity (aOR 1.57, 95%CI 1.12–2.19) and early childhood morbidity (aOR 1.74, 95%CI 1.02–2.95), compared to those exposed 2 to < 7 days before delivery [20].

CLINICAL IMPLICATIONS

The suboptimal use of ACS could be due to the over diagnosis of the risks for deliveries for preterm labor and the need for criteria with more sensitivity and specify for preterm delivery diagnosis.

The more inappropriate use of ACS, the more possibility of repeated doses and the more risk of reduction in weight and head circumference at birth.

The maximal effective therapeutic window of the corticosteroid is 1–7 days from its administration [20].

RESEARCH IMPLICATIONS

On one hand, further research is required to evaluate the criteria used for diagnosing preterm delivery, with the aim of reducing the incidence of unnecessary ACS treatment. On the other hand, this study could serve as a reference for quality control measures regarding the appropriate use of steroids in women with suspected preterm labor and could provide a basis for future studies and meta-analyses on this subject.

STRENGTHS AND LIMITATIONS

Our study has several strengths as it is one of the few studies to address how often we use correctly corticosteroids. Moreover, the data were collected from a tertiary hospital. However, there were several limitations The study was a retrospective cohort design from a single hospital in a single country and with a small sample size.

CONCLUSIONS

ACS and glucocorticoids should be administered wisely to women at risk of preterm birth. More research is needed to check the appropriate use of ACS after the ALPS trial.

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Capsule

TNF and type I interferon crosstalk controls the fate and function of plasmacytoid dendritic cells

Hornero and colleagues used single-cell omics and functional experiments to show that activated human plasmacytoid dendritic cells (pDCs) can lose their identity as IFN-I-secreting cells and acquire the transcriptional, epigenetic and functional features of a professional antigen-presenting conventional dendritic cell (cDCs). This pDC fate-switching process is promoted by tumor necrosis factor but blocked by IFN-I. Importantly, it occurs in vivo during human skin inflammatory diseases and injury, and physiologically in elderly people. This work identifies the pDC-to-cDC reprogramming trajectory and unveils a mechanistic framework for harnessing it therapeutically.

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