

# Evaluation of the timing and indications of antenatal corticosteroid administration

## *Antenatal kortikosteroid uygulama zamanlamasının ve endikasyonlarının değerlendirilmesi*

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### ABSTRACT

**Objective:** To investigate the timing of antenatal corticosteroid administration for pregnant women who were anticipated for preterm birth.

**Material and Method:** This retrospective cohort study was conducted between September 2016 and September 2017 on cases treated with antenatal steroids and then performed birth in our hospital. The first 113 patients with 23-37 weeks of singleton or twin pregnancy, whose birth records could be accessed, were included in the study. Those who gave birth in another hospital, patients with incomplete records, and those carrying more than one of the indication types were excluded from the study.

**Results:** The median interval between antenatal steroid administration and childbirth was 1.00 (0.02-97.00, IQR: 17.77) days. The interval from the first dose until birth was less than 2 days in 57.5% of cases (n=65), 2-7 days in 11.5% of cases (n=13), and more than 7 days in 31% of cases (n=35). Totally, this period was 7 days or below in 69% of cases (n=78). A significant correlation was found between spontaneous preterm labour as indication of steroid administration and appropriate timing (p=0.001, Odds Ratio:4.62, Confidence Interval: 1.90-11.19).

**Conclusion:** The number of patients giving birth within optimal 2-7 days following the first dose of antenatal steroid administration, is very low. Attempts to improve timing are needed.

**Keywords:** Antenatal corticosteroid, preterm birth, indication, optimal timing, administration

### ÖZ

**Amaç:** Preterm doğumu öngörülen gebelere yapılan antenatal kortikosteroid uygulama zamanlamasının incelenmesidir.

**Gereç ve Yöntem:** Eylül 2016- Eylül 2017 tarihleri arasında, antenatal steroid uygulaması yapılan ve ardından doğumu da hastanemizde gerçekleştiren olgular üzerinde yapılan bir retrospektif kohort çalışmadır. Doğum kaydına ulaşılabilen, tekil ya da çoğul, 23-37 hafta gebeliğe sahip, ilk 113 hasta çalışmaya dahil edildi. Başka bir hastanede doğum yapanlar, kayıtları eksik olan ve endikasyon tiplerinden birden fazlasını taşıyan hastalar çalışma dışı bırakıldı.

**Bulgular:** Antenatal steroid uygulaması ile doğum arasında ortanca geçen süre 1,00 (0,02-134,00), IQR:17,77 gündü. Olguların %57,5'inde (n=65) ilk doz ile doğuma kadar geçen süre 2 günün altında, %11,5 inde (n=13) süre 2-7 gün arasında, %31'inde (n=35) süre 7 günün üzerinde tespit edildi. Toplamda olguların %69'unda (n=78) bu süre 7 gün ve altındaydı. Steroid yapıma endikasyonlarından spontan preterm eylem ile uygun zamanlama arasında bir ilişki tespit edildi (p=0,001, odds oranı: 4,62, güven aralığı: 1,90-11,19).

**Sonuç:** Antenatal steroid uygulamasının ilk dozunu takip eden 2-7 gün içinde doğuran hasta sayısı oldukça azdır. Zamanlamanın iyileştirilmesine ait girişimlere ihtiyaç vardır.

**Anahtar Kelimeler:** Antenatal kortikosteroid, preterm doğum, endikasyon, uygun zamanlama, uygulama,

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## INTRODUCTION

Preterm birth is a significant cause of perinatal mortality and morbidity (1-3). Although preventing preterm birth is not always succeeded, it is possible to delay the birth and allow the baby to be better prepared for childbirth (4,5). Administration of antenatal steroids has been shown to reduce perinatal mortality and morbidity (6,7). Administration of antenatal corticosteroids is the best available treatment that improves perinatal outcomes in patients who are anticipated for preterm birth with various indications (8). It is thought that the fetus receives the maximum benefit from the administration of antenatal steroids between 2 and 7 days after the first dose (8,9). Since it is known that antenatal steroid administration is protective against important and common causes of neonatal mortality, such as respiratory distress syndrome, intraventricular bleeding, and necrotizing enterocolitis (6), the aim is to ensure that each preterm fetus benefits from therapy. However, studies have shown that mothers who give preterm birth receive treatment at the optimal time at a lower rate than expected (10,11).

In the present study, we wanted to investigate the timing of antenatal corticosteroid administration in our hospital. Our goal is to determine the rate of patients in our hospital who receive antenatal steroids for preterm delivery at the optimal time and investigate the relationship between optimal application and indications.

## MATERIAL AND METHOD

This study was approved by the university /local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics committee approval for the study was received from the institutional review board (Zekai Tahir Burak Women's Health Training and Research Hospital's institutional review board, Admission Date:5th December 2017, decision number:10).

This retrospective cohort study was conducted at Zekai Tahir Burak Women's Health Training and Research Hospital between September 2016 and September 2017 on pregnant women who received antenatal steroid administration for preterm birth. Patients who received antenatal steroids at 23-37 gestational weeks were accessed from the hospital pharmacy database. Among these patients, subjects who had steroid treatment and gave birth at the same hospital were sought. The first 113 patients with accessible birth records, either singleton or twin pregnancy, and with steroid administration at 23-37 weeks of pregnancy were included in the study. Patients who gave birth in another hospital, with missing records, or those carrying more than one of the indication types were excluded from the study.

The period from the initial dose of antenatal steroid administration to birth was calculated in days. For the rescue cure, the interval between the first dose of the rescue cure and birth was calculated. The patients were divided into two groups: those with optimal timing (less than 7 days) and those with suboptimal timing (above 7 days). The demographic characteristics of the groups were obtained from patient files.

Antenatal steroid is applied to pregnant women who are anticipated to give preterm birth with various indications to ensure lung maturation of the fetus, reduce neonatal mortality and morbidity. As standard, 24 mg of betamethasone is administered as twice 12mg doses with an interval of 24 hours. Rescue cure is administered in pregnancies under 34 weeks, 14 days after the first dose. It is known that the fetus receives maximum benefit from the administration of antenatal steroids between 2-7 days after the first dose (8).

There are several indications for the administration of antenatal steroids. In the present study, indications for the administration of antenatal steroids were classified as maternal causes, fetal causes, spontaneous preterm labor, and preterm premature rupture of membranes (PPROM). Maternal indications included maternal conditions such as preeclampsia, gestational hypertension, placental abruption, placenta previa, and other maternal diseases. Fetal indications included conditions related to the fetus such as isolated fetal growth restriction and abnormal Doppler findings, oligohydramnios, and nonreactive nonstress test (NST). Spontaneous preterm labor was defined by the presence of cervical changes accompanying regular painful contractions in the NST, in pregnant women under 37. gestational week. PPRM was defined as membrane rupture before the onset of uterine contractions in pregnant women under 37. gestational week. In case of any of the abovementioned indications, decision for labor was made if the situation threatened the life of the mother or baby.

### Statistical Analysis

IBM SPSS statistical 22 program was used for data analysis. Normality of data was examined by Shapiro-Wilk test. The demographic data of groups were presented by mean±standard deviation for numerical variables with normally distribution and median (minimum-maximum) for numerical variables with not-normally distribution. Categorical variables were presented as number and percentage. The difference between groups was evaluated by Student's t test for numerical data with normally distribution, Mann-Whitney U test for numerical data without normally distribution, and Chi-square test for categorical data. Logistic regression analysis was performed to assess whether the groups showed difference according to the indications. Correlation between indications and optimal timing of steroid administration was evaluated by using logistics regression analysis. The data were examined at 95% confidence level and  $p < 0.05$  was considered statistically significant in all analyses.

## RESULTS

Totally 113 cases who gave birth in our hospital and who were previously administered with antenatal steroids during the same pregnancy were included in the study. The median interval between antenatal steroid administration and childbirth was 1.00 (0.02-97.00) and IQR: 17.77 days. The interval from the first dose until birth was less than 2 days in 57.5% of cases (n=65), 2-7 days in 11.5% of cases (n=13), and more than 7 days in 31.0% of cases (n=35). In total, this period was 7 days and below in 69.0% of cases (n=78). In 47.8% of cases (n=54), the dose of steroids was limited to the initial dose of 12 mg, while in 52.2% (n=59) of the cases, the dose was 24 mg. Rescue cure was administered in 4 (3.5%) cases. All these cases gave birth within 7 days after the administered dose.

Seventy eight cases with optimal timing formed one group and 35 cases with suboptimal timing formed the other group. There was no difference between the two groups in terms of age, gravida, parity, smoking, twin pregnancy and previous cesarean section (p=0.7, p=0.8, p=0.6, p=0.9, p=0.8, p=0.1, respectively). Gestational

week at steroid administration was higher in the optimal timing group [34.1 (23.0-37.0) weeks vs. 32.5 (24.3-36.0) weeks, p=0.001]. Birth weight was higher in the suboptimal timing group [2970 (660-4280) grams vs. 2350 (500-3690) grams, p=0.001] (**Table 1**)

According to the indications for steroid administration, 57 cases were listed as spontaneous preterm labor (50.4%), 21 as early membrane rupture (18.6%), 18 as fetal causes (15.9%), and 17 as maternal causes (15.0%). (**Table 2**) A correlation was found between the indications for steroid administration and appropriate timing (p=0.003). When the relationship between the types of indications and optimal timing was evaluated individually, a significant correlation was found only for spontaneous preterm labor. It was found that spontaneous preterm labor status significantly affected the optimal timing group (p=0.001, Odds Ratio: 4.62, Confidence Interval: 1.90-11.19). When the effect of indication types on steroid dose of 12 and 24 mg was examined, it was found that only spontaneous preterm labor significantly affected the dose to remain at 12 mg (p=0.001, Odds ratio: 3.61, Confidence Interval:1,66-7.87).

**Table 1.** Demographics characteristics of groups

Variables	Optimal timing (≤7 days), N=78, 69%	Suboptimal timing (>7 days), N=35, 31%	P
Age (years)	27.3 (±5.6)	27.8 (±7.4)	0.7
Gravidity	2 (1-6)	2 (1-5)	0.8
Parity	2 (0-4)	0 (0-4)	0.6
Smoking	2 (2.6%)	1 (2.9%)	0.9
Previously cesarian section	25 (32.1%)	7 (20.0%)	0.1
Twin pregnancy	5 (6.4%)	2 (5.7%)	0.8
Additional medical condition	8 (10.3%)	1 (2.9%)	0.2
Gestational age (weeks) at the steroid administration	34.1 (23.0-37.0)	32.5 (24.3-36.0)	0.001
Time between first dose and birth, (days)	0.41 (0.02-6.0)	38.0 (10.0-134.0)	0.000
Time between first dose and birth, (hours)	10.0 (0.5-144.0)	888.0 (240.0-3216.0)	
Dose, mg	12 (12-24)	24 (12-24)	0.000
Birth weight, gr	2350 (500-3690)	2970 (660-4280)	0.001
Rescue cure	4 (3.5%)	0 (0%)	0.2

**Table 2.** Comparison of indications for antenatal corticosteroids administration between optimal vs suboptimal timing groups

	Optimal timing (≤7 days) N=78. 69%	Suboptimal timing (>7 days) N=35. 31%	P
Maternal indications	11 (14.1%)	6 (17.1%)	0.003
Preeclampsia/gestational hypertension	5 (6.5%)	5(14.3%)	
Abruptia placenta	3 (3.9%)	0 (0%)	
Intrahepatic cholestasis of pregnancy	2 (2.6%)	0 (0%)	
Placenta accreta	0 (0%)	1 (2.9%)	
Fetal indications	8 (10.3%)	10 (28.6%)	
FGR <sup>a</sup> and abnormal doppler findings	5(6.5%)	7 (20.0%)	
Nonreactive NST <sup>ε</sup>	1 (1.3%)	1 (2.9%)	
Oligohydramnios	1 (1.3%)	2 (5.7%)	
Spontaneous preterm labor	48 (61.5%)	9 (25.7%)	
PPROM <sup>δ</sup>	11 (14.1%)	10 (28.6%)	

<sup>a</sup>FGR: Fetal growth restriction, <sup>ε</sup>NST: nonstress test, <sup>δ</sup>PPROM: premature preterm rupture of membranes

In the present study, the birth of 13 patients took place between 2-7 days after the first dose. Steroid administration was performed for spontaneous preterm labor in 7 (53.8%), for fetal causes in 3 (23.1%), for maternal causes in 2 (15.4%), and for early membrane rupture in 1 (7.7%) of these patients.

## DISCUSSION

The present study showed that the targeted 2-7 day period between the first dose of antenatal steroid administration and childbirth was met in 11.5% of the cases, while the timing of less than 7 days was met in 69% of cases. Optimal application was most often achieved when antenatal corticosteroid was performed with the indication of spontaneous preterm labor. In 47.8% of the cases, the doses could not be completed.

Optimal application rate varies in the literature. Vis et al. (5) included 439 patients with spontaneous preterm labor and PPROM in their study, and found that the dose was completed in 79% of cases, 41% of these patients gave birth within 7 days, and median interval was 11 days (12). In the present study, median interval was 1 day. Boesveld et al. (13) included patients with preterm labor, PPROM, maternal and fetal indications, and vaginal bleeding, and found that 45.4% of cases gave birth within 7 days and this rate was 61.5% in patients with maternal indications. In 2015, Adams (10) conducted two studies on this topic. In the first study, Adams examined timing only in patients with spontaneous preterm labor, and found that median interval was 41 (0-119) days and 20% of patients gave birth within 7 days after antenatal steroid administration. In the other study, Adams et al. (14) excluded patients with preterm labor and included maternal and fetal indications, and found that median interval was shorter with 9 (0-83) days and 48% of the patients gave birth within 7 days. Only maternal and fetal indications were included in the recent study of Rottenstreich et al. (15); the ratio of patients receiving optimal application was 32.4%, rescue dose was performed in one third of patients in this study. In the present study, this ratio was 3.5%. In conclusion, the indications of patients included and the rates of achieving optimal timing differ between studies. Various studies have reported that the ideal period of 2-7 days can be achieved in 20-40% of women (12,13). Similarly, another study reported that rate of women receiving steroid administration within the 2-14 day period was 45% (16). In the present study, this rate (11.5%) was considerably lower compared to other studies. This low rate shows the needs for efforts to improve timing of steroid administration.

Factors affecting the rate can be diverse. Conditions before hospitalization which lead late admission and various other factors such as unawareness to disease,

uncertainty in diagnosis or unstandardized inpatient application etc. may affect the success of the timing of steroid administration (17). In our study, the gestational week at which steroid administration was performed was lower in the suboptimal timing group. Decision of steroid administration can be made more liberally in cases with small gestational age where the possible effects of prematurity may be more severe. In this study, relation of indications with optimal timing was sought. Only relation was seen with spontaneous preterm labor as indication. Some of maternal or fetal indications such as intrauterine fetal growth restriction or preeclampsia without acute presentation or placenta previa may partially allow optimal timing with respect to labor. Larger studies including subgroups with other indications may reveal various criteria to predict optimal timing accurately. Hence a study suggests use of some criteria such as amount of bleeding, presence of contractions and cervical canal length to predict time of labor in women to whom steroid was administered with the indication of placenta previa (11). It is clear that uncovering the reasons for the various rates obtained in different studies of optimal timing rates will contribute to the improvement of steroid administration timing.

The administration of antenatal corticosteroids is the best available antenatal treatment, which improves neonatal outcomes in patients planned for preterm birth (4). Therefore, the aim is to ensure that all premature infants benefit from this treatment. Patients giving birth before the optimal period benefit less from steroid administration (9). Conversely, in those giving birth after the optimal period both fetus and mother are exposed to the toxic effects of the drug without benefit (18,19). In cases of acute conditions, which may be life threatening for mother or fetus, emergency of labor results in time restrictions, while the insufficiency of tests to accurately predict the timing of birth as in spontaneous preterm labor may lead to prolongation of this interval. In the present study, when the optimal timing was taken as under 7 days, it was found that optimal timing could be achieved 4.6 times more when steroid administration was performed with the indication of spontaneous preterm labor. Full dose could be administered in 52.2% of cases. However, when patients with an interval of less than 24 hours were examined, the effect of spontaneous preterm labor indication was observed with 3.6 times. Additionally, these patients mostly delivered within 2 days. It was observed that spontaneous preterm labor could also lead to extreme shortening of the interval. In addition, 25.7% of patients in the suboptimal timing group also consisted of patients with spontaneous preterm labor indication. Therefore, although the effect of spontaneous preterm labor indication on optimal timing is observed in the present study, the likelihood of planning birth correctly



seems to be low in patients with this indication. Strategies that encourage timely administration of corticosteroids to women at risk of premature birth within 7 days and avoid excessive use of corticosteroids in women with low risk is important. Measures should be taken to monitor the use of prenatal corticosteroids for infants born before the 34<sup>th</sup> week of gestation, and quality improvement measures should be supported to optimize appropriate and timely corticosteroid administration regarding childbirth.

The strength of the present study is that it demonstrates the antenatal corticosteroid administration tendencies of a tertiary hospital. Relatively small sample size can be considered as one of the limitations of this study. A larger sample would increase the size of subgroups (complete/incomplete dose, optimal application/suboptimal application) and better reveal the affecting factors.

## CONCLUSION

The number of patients giving birth within 2-7 days following the first dose of antenatal steroid administration, which is our primary target, is very low. Attempts to improve timing are needed.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** Ethics committee approval for the study was received from the institutional review board (Zekai Tahir Burak Women's Health Training and Research Hospital's institutional review board, Admission Date: 5th December 2017, decision number: 10).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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