Factors Affecting Antenatal Corticosteroid Administration from the Obstetricians' Viewpoint

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ABSTRACT

OBJECTIVE: We aimed to investigate the factors affecting antenatal corticosteroid administration from the obstetricians' viewpoint.

STUDY DESIGN: The pregnant women who delivered between 24 and 34 weeks of gestation were divided into two groups: Group 1, pregnant patients given corticosteroid therapy; Group 2, pregnant patients who were not given corticosteroid therapy. The indications for delivery, gestational week at administration, dosing, residence and manner of transfer of the patients to the tertiary center, and the interval between admission to hospital and delivery were evaluated.

RESULTS: The percentage of patients who received antenatal corticosteroid treatment was 68.4%, whereas 31.6% of the pregnant women didn't receive corticosteroid therapy. The most common indications for preterm delivery were preterm labor and severe preeclampsia. The interval between admission to hospital and delivery was significantly higher in group 1.

CONCLUSION: Even though obstetricians are aware of the importance of corticosteroid treatment in preterm deliveries, indications for impending delivery can affect administration of the therapy.

Keywords: Preterm delivery, Antenatal corticosteroid administration, Affecting factors, Obstetrician, viewpoint

Gynecol Obstet Reprod Med 2015;21:4-9

Introduction

Preterm delivery is still the most common cause of neonatal mortality and morbidity associated with complications such as respiratory distress syndrome (RDS), necrotizing enterocolitis and intraventricular hemorrhage.[1,2] Among these complications, RDS, which occurs in cases of lung immaturity and surfactant deficiency, is the major complication leading to neonatal loss.[3]

Antenatal corticosteroid treatment, which is administered to women at risk for preterm delivery between 28 and 34 weeks of gestation, was first reported by Liggins and Howie in 1972; it is believed to be the most effective intervention for reducing mortality and morbidity associated with RDS.[4,5] It is currently the standard treatment in cases in which preterm delivery (between 24 and 34 weeks of gestation) is suspected. However, since the introduction of this treatment, it has been a topic of debate among pediatricians and obstetricians.

The corticosteroid dose and interval between its administration and delivery are affected by several factors such as the indications for preterm labor and the hospitalization period.[6] The objective of this study was to investigate the factors affecting the features and the rate of antenatal corticosteroid administration from the obstetricians' viewpoint at a university hospital in Turkey.

Material and Method

This retrospective study included 114 pregnant women who delivered between 24 and 34 weeks of gestation at Ondokuz Mayıs University Hospital between January 2012 and January 2013.

The subjects were divided into two groups based on the antenatal treatment given: Group 1, pregnant patients given corticosteroid therapy and tocolytic treatment (indomethacine for patients with 28-32 weeks of gestation, nifedipine for patients with 32-34 weeks of gestation) until the completion of

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Submitted for Publication: *04. 11. 2014*
Accepted for Publication: *18. 02. 2015*

✍: *This original study was presented as a poster at the 9th National Congress of Turkish Maternal Fetal Medicine and Society of Perinatology.*

corticosteroid therapy; group 2, pregnant patients who did not receive corticosteroid therapy and tocolytic treatment owing to impending delivery and informed about the risk/benefit for corticosteroid treatment. Data for the indications for preterm delivery, the place of administration, dosing (single or two doses) and completion of the corticosteroid therapy (it was considered to be complete 48 h after the first corticosteroid dose was administered), the gestation week at administration, residence and the manner of transfer of the patient to the hospital, the mode of delivery and the interval between corticosteroid administration and delivery.

A single course was defined as betamethasone given at a dose of 12 mg intramuscularly 24 h apart.[7] Preterm delivery and indications for preterm delivery were defined according to the guidelines of the American College of Obstetricians and Gynecologists (ACOG).[8-14]

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). The Kolmogorov-Smirnov test was used to determine whether the distribution of continuous variables was normal or not. The homogeneity of variances was analyzed using the Levene test. Discriminative statistics and continuous and intermittent variables were expressed as mean (±standard deviation) or median (min–max), and categorical variables were expressed as case numbers and percentages (%).

The mean differences between two independent groups were compared using the Student's t test while one-way analysis of variance (one-way ANOVA) was applied to compare the mean differences among more than two independent groups. The median differences between two independent groups were compared using the Mann-Whitney U test. The Kruskal-Wallis test was applied to compare the median differences among more than two independent groups. When the result of the Kruskal-Wallis test was found to be statistically significant, the factor causing the difference was searched using Conover's nonparametric multiple comparison test. Categorical variables were investigated by Pearson's chi-square, Fisher's exact or probability ratio tests.

A p value less than 0,05 was considered to indicate statistical significance.

Results

The study included 114 pregnant women who delivered between 24 and 34 weeks of gestation. The most common indications for preterm delivery were preterm labor (n=29 [25.4%]), severe preeclampsia (n=29 [25.4%]) and preterm membrane rupture (n=26 [22.8%]), and cesarean section was much more common than vaginal delivery. The demographic and clinical features of the study group are shown in Table 1.

Table 1: Demographic and clinical features of the study group

Features	**n = 114**
Age (y)	29.6 ± 6.2
Gravida	1 (1-7)
Parity	0 (0-6)
Multiple pregnancy	**17 (14.9%)**
Indications for preterm delivery	
Preterm labor	29 (25.4%)
Severe preeclampsia	29 (25.4%)
Preterm membrane rupture	29 (25.4%)
Fetal distress	17 (14.9%)
Eclampsia	5 (4.4%)
Placenta previa	4 (3.5%)
HELLP	2 (1.8%)
Intrahepatic cholestasis	2 (1.8%)
Gestational week	30.8±2.3
Delivery mode	
Vaginal delivery	6 (5.3%)
Cesarean section (C/S)	108 (94.7%)
Residence of the patient	
Urban	58 (50.9%)
Rural	56 (49.1%)
Manner of transfer of the patient to the tertiary center (university)	
Self referred	66 (57.9%)
By ambulance	48 (42.1%)

The percentage of patients who received antenatal corticosteroid administration was 68.4% (group 1, n=78), whereas 31.6% (group 2, n=36) of the pregnant women did not receive corticosteroid therapy. Tocolysis was administered to group 1 including patients with preterm labor (n=17), severe preeclampsia (n=18), preterm membrane rupture (n=29), fetal distress (n=11), placenta previa (n=4), intrahepatic cholestasis (n=2) until completion of the corticosteroid therapy, while group 2 including patients with preterm labor (n=12), severe preeclampsia (n=11), eclampsia (n=5), HELLP (n=2), fetal distress (n=6), did not receive tocolytic treatment due to the impending delivery. In group 1, a single dose was administered to 24 (21%) pregnant women, while two doses were administered to 54 (47.4%) patients. The rate of administration and completion of the therapy was higher at the university hospital than at the previous hospital from which the patient had been transferred (Table 2).

When the pregnant women who were administered corticosteroid therapy (group 1) were divided into three groups on the basis of gestational week at administration, no statistically siginificant difference was found in the features of the therapy (Table 3).

A significant difference was found between group 1 and group 2 with regard to the interval between steroid administration and delivery ($p<0.001$). The interval was 48 (0.3-336) h in

the former, whereas it was 0.5 (0.08-4) h in the latter. Although cesarean section (C/S) delivery was much more common than vaginal delivery in both groups (p<0.001), C/S was more common in group 1 than in group 2. No significant difference was found between the two groups with regard to the place of administration, the gestational week at administration, and the residence and manner of transfer of the patients to the hospital (Table 4).

When the group that received corticosteroid therapy was divided on the basis of the dose, the interval between corticosteroid administration and delivery was significantly shorter in the single-dose group than in the double-dose group (p<0.001). The incidence of C/S delivery was also found to be significantly higher in the single-dose group than in the double-dose group (p=0.018) (Table 5).

Table 2: Features of the corticosteriod therapy

Features	**n = 114**
Corticosteroid administration	
Yes (group 1)	*78 (68.4%)*
Single dose	*24 (21.0%)*
Two doses	54 (47.4%)
No (group 2)	36 (31.6%)
Dose status	
Incomplete	3 (5.6%)
Complete	51 (94.4%)
Place of administration	
University hospital	59 (75.6%)
Previous hospital	19 (24.4%)
Place of completion of the dose	
University hospital	38 (74.5%)
Previous hospital	13 (25.5%)

Table 3: Relationship between the features of the corticosteroid therapy and gestational week at administration

	24-28 (n= 9)	**28-32 (n=44)**	**32-34 (n=25)**	**p-value**
Corticosteroid administration				0.277
	9 (52.9%)	44 (73.3%)	25 (67.6%)	
Dosing				0.719
Single dose	2 (22.2%)	13 (29.5%)	9 (36.0%)	
Two doses	7 (77.8%)	31 (70.5%)	16 (64.0%)	
Dose status				0.651
Incomplete	-	2 (6.5%)	1 (6.3%)	
Complete	7 (100.0%)	29 (93.5%)	15 (93.7%)	
Interval between corticosteroid administration and delivery (h)	3 (0.33–96)	24 (0.17–336)	8 (0.08–120)	0.241

Table 4: Comparison of the demographic and clinical features of Group 1 and Group 2

Features	**Group 1 (with steroid therapy)n = 78**	**Group 2 (without steroid therapy) n = 36**	**p-value**
Age (y)	29.9±6.1	29.0±6.4	0.523
Gravida	1 (1-7)	2 (1-6)	0.919
Parity	0 (0-6)	0 (0-4)	0.586
Gestational week	30.9±2.2	30.6±2.6	0.667
			0.277
24-28	9 (11.5%)	8 (22.2%)	
28-32	44 (56.4%)	16 (44.4%)	
32-34	25 (32.1%)	12 (33.3%)	
Interval between admission to hospital and delivery (h)	48 (0.3-336)	0.5 (0.08-4)	**<0.001**
Mode of delivery			**0.012**
Vaginal	1 (1.3%)	5 (13.9%)	
C/S	77 (98.7%)	31 (86.1%)	
Residence of the patient			0.783
Urban	39 (50.0%)	19 (52.8%)	
Rural	39 (50.0%)	17 (47.2%)	
Manner of transfer of the patient to the tertiary center (university			0.731
Self referred	46 (59.0%)	20 (55.6%)	
By ambulance	32 (41.0%)	16 (44.4%)	

Table 5: Comparison of the demographic and clinical features of the single-dose and double-dose corticosteroid therapy group

Features	One dose (n = 24)	Two doses (n = 54)	p-value
Age (y)	29.1±6.6	30.2±5.9	0.643
Gravida	1 (1-7)	2 (1-7)	0.421
Parity	0 (0-6)	1 (0-5)	0.489
Gestational week	31.4±1.8	30.8±2.3	0.453
			0.532
24-28	2 (8.3%)	7 (13.0%)	
28-32	13 (54.2%)	31 (57.4%)	
32-34	9 (37.5%)	16 (29.6%)	
Interval between corticosteriod administration and delivery	4 (0.33-24)	48 (3-336)	**<0.001**
Mode of delivery			**0.018**
Vaginal	-	1 (1.9%)	
C/S	24 (100.0%)	53 (98.1%)	
Residence of the patient			0.963
Urban	12 (50.0%)	27 (50.0%)	
Rural	12 (50.0%)	27 (50.0%)	
Manner of transfer of the patient to the tertiary center (university)			0.112
Self referred	10 (41.7%)	36 (66.7%)	
By ambulance	14 (58.3%)	18 (33.3%)	
Place of corticosteroid administration			0.629
University hospital	19 (79.2%)	40 (74.1%)	
Previous hospital	5 (20.8%)	14 (25.9%)	

Discussion

Despite all the advances in maternal and neoanatal care, preterm birth is the leading cause of neonatal mortality and morbidity around the world. Antenatal corticosteroid treatment is currently the most effective treatment that is used to reduce the mortality and morbidity resulting from direct complications of preterm delivery.[5]

Several studies have investigated the maternal and neonatal effects of antenatal steroid therapy.[15] The features of the treatment, such as dosing, choice of drug, timing before delivery, and additional therapy, were evaluated in order to find the association of these factors with the outcomes. This topic has never been examined from the obstetricians' viewpoint. In this study, we investigated the patient-, physician-, and hospital-related factors that affect the outcome of antenatal corticosteriod therapy and discuss the findings from the viewpoint of obstetricians.

Certain indications require emergency delivery, such as severe preeclampsia, eclampsia and fetal distress; it may be difficult and sometimes impossible to administer and complete corticosteroid therapy in such cases. In this study, we found that preterm labor, severe preeclampsia and preterm membrane rupture are the most common indications for preterm delivery, and our administration rate was 68.4%. Betamethasone given at a dose of 12 mg intramuscularly 24 h apart was the treatment administered to our study group; 21% of the pateints in the group were treated with a single dose and 47.4% were given two doses. In the subgroup given two doses, the dose was completed in 94.4% of the patients.

The features of the patients were evaluated in order to determine whether they had an effect on the treatment rates and dosing. The study group was divided on the basis of the treatment status. There was no significant difference in gestational weeks in terms of treatment status. The residence (urban or rural) was not found to have a significant effect on the therapy either. Since preterm neonates require intensive care, such cases should be transferred to tertiary care centers. Therefore, we investigated corticosteroid administration and completion of the therapy outside our tertiary university hospital, but found no statistically significant difference. In addition, the manner of transfer of the patients was found to be important, because it is likely that in cases of self-referral, there may have been some delay in the corticosteroid treatment. However, we did not find a significant difference between the patients who came by themselves and those who were brought in by an ambulance.

The duration of the interval between corticosteroid administration and delivery has been also investigated in order to determine the optimal treatment-delivery interval.[16-20] In vitro studies have shown that choline begins to get incorporated into phospholipids at 6 h and peaks at 48 h after the first dose of antenatal corticosteroid is administered.[21] The optimal

treatment-delivery interval for administration of antenatal corticosteroids has been found to be more than 24 h but >7 days after the start of treatment.[22] In the present study, this interval was only 30 min in the group without therapy whereas it was 48 h in the group administered treatment.

In conclusion, this study shows that indications for preterm delivery, particularly impending delivery, seem to be the most influential factors that determine the effectiveness of antenatal corticosteroid administration. Despite the fact that obstetricians are aware of the importance of corticosteroid therapy in preterm deliveries, certain indications can affect administration of the therapy.

Obstetrisyenlerin Bakış Açısıyla Antenatal Kortikosteroid Uygulamasını Etkileyen Faktörler

ÖZET

AMAÇ: Obstetrisyenlerin bakış açısıyla, antenatal kortikosteroid uygulamasını etkileyen faktörleri araştırmayı hedefledik.

GEREÇ VE YÖNTEM: Ondokuz Mayıs Üniversitesi'nde 24-34 gebelik haftaları arasında doğum yapmış olan hastalar iki gruba ayrıldı: Grup 1, kortikosteroid tedavisi verilenler; Grup 2: kortikosteroid tedavi verilmeyenler. Doğum endikasyonları, steroid uygulama sırasındaki gebelik haftası, kortikosteroid dozu, uygulama yeri, hastaların tersiyer merkeze transfer şekilleri ve hastaneye kabul ile doğum arasında geçen süre değerlendirildi.

BULGULAR: Antenatal kortikosteroid tedavisi alanlar %68,4, almayanların yüzdesi ise %31,6 idi. En sık görülen preterm doğum endikasyonları, preterm eylem ve şiddetli preeklampsiydi. Hastaneye kabul ile ile doğum arasındaki süre grup 1'de grup 2'den daha uzundu.

SONUÇ: Obstetrisyenler antenatal kortikosteroid uygulamasının öneminin farkında olmalarına rağmen, doğumun kaçınılmaz olduğu endikasyonlar tedaviyi etkileyebilmektedir.

Anahtar Kelimeler: Preterm doğum, Antenatal kortikosteroid uygulaması, Etkili faktörler, Obstetrisyen, Bakış açısı

References

1. Eichenwald EC. Care of the extremely low-birth-weight infant. In: Taeusch HW, Ballard RA, Gleason CA, eds. Avery's Diseases of the Newborn. 8th ed. Philadelphia: Saunders 2005:410-26.
2. Creasy RK, Lams JD. Preterm labor and delivery. In: Creasy RK, Resnik R, eds. Maternal-Fetal Medicine. 4th ed. Philadelphia: Saunders 1999:498-531.
3. Avery ME, Mcad J. Surface properties in relation to atelectasis and hyaline membrane disease. Am J Dis Child 1959;97:517-93.
4. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972 Oct;50:515-25.
5. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006;(3):CD004454.
6. Report on the Consensus Development Conference on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. U.S. Department of Health and Human Services, Public Health Service, NIH Pub 1994;95-3784.
7. Ballard PL, Granberg P, Ballard RA. Glucocorticoid levels in maternal and cord serum after prenatal betamethasone therapy to prevent respiratory distress syndrome. J Clin Invest 1975;56:1548-54.
8. ACOG Committee Opinion No 579: Definition of term pregnancy. Obstet Gynecol 2013;122:1139.
9. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122.
10. American College of Obstetricians and Gynecologists. Antepartum fetal surveillance. ACOG practice bulletin #9. ACOG, Washington DC 1999.
11. American College of Obstetricians and Gynecologists. Viral hepatitis in pregnancy. ACOG Educational Bulletin number 248. Washington DC: ACOG 1998.
12. Placenta accreta. Committee Opinion No. 529. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120:207-11.
13. ACOG Practice Bulletin No. 80: premature rupture of membranes. Clinical management guidelines for obstetrician-gynecologists. Obstet Gynecol 2007;109:1007-19.
14. American College of Obstetricians and Gynecologists. Intrauterine growth restriction. ACOG Practice Bulletin 12. American College of Obstetricians and Gynecologists, Washington, DC 2000.
15. Antenatal Corticosteroid Revisited: Repeat Courses. National Institutes of Health Consensus Development Conference Statement August 17-18, 2000. http://consensus.nih.gov/2000/2000 Antenatal Corticosteroid Revisited 112html.htm
16. Sekhavat L, Firouzabadi RD, Karbasi SA. Comparison of interval duration between single course antenatal corticosteroid administration and delivery on neonatal outcomes. J Turk Ger Gynecol Assoc 2011;12:86-9.
17. Peaceman AM, Bajaj K, Kumar P, Grobman WA. The interval between a single course of antenatal steroids and delivery and its association with neonatal outcomes. Am J Obstet Gynecol 2005;193:1165-9.

18. Waters TP, Mercer B. Impact of timing of antenatal corticosteroid exposure on neonatal outcomes. J Matern Fetal Neonatal Med 2009;22:311-4.

19. Ay H, Tosun M, Malatyalioglu E, et al. Comparison of single and double courses of antenatal corticosteroid administration on neonatal mortality and morbidity. J Turk Ger Gynecol Assoc 2011;11:38-43.

20. Thorp JA, Jones AM, Hunt C, Clark R. The effect of multidose antenatal betamethasone on maternal and infant outcomes. Am J Obstet Gynecol 2001;184:196-202.

21. Gross I, Ballard PL, Ballard RA, Jones CT, Wilson CM. Corticosteroid stimulation of phosphatidylcholine synthesis in cultured fetal rabbit lung: evidence for de novo protein synthesis mediated by glucocorticoid receptors. Endocrinology 1983;112:829-37.

22. Royal College of Obstetricians and Gynaecologists (RCOG), Antenatal Corticosteroids To Prevent Reapiratory Distress Syndrome. Guideline No. 7, February 2004.