The effect of antenatal corticosteroid therapy on pregnancies complicated by premature rupture of membranes

H. S. Qublan[1], H. Y. Malkawi[1], M. S. Hiasat[1], I. M. Hindawi[1], M. I. Al-Taani[1], S. A. Abu-Khait[1], J. F. Al-Maaitah[2]

[1]Department of Obstetrics and Gynecology; [2]Department of Pediatrics Royal Medical Services (Jordan)

Summary

This study was carried out to examine the effect of antenatal corticosteroid therapy on pregnancies complicated by premature rupture of membranes (PROMs). For this purpose, 139 patients with a singleton pregnancy (27-34 weeks of gestation) complicated by PROMs were evaluated prospectively during the period January 1997 to February 1999 at two Jordanian military hospitals (Prince Rhashed and Prince Zaid). Patients were allocated into two groups; Group 1 included 72 patients treated with dexamethsone (24 mg divided into 4 doses 12 hours apart), and Group 2 which included 67 patients who received no treatment (control group). All women were examined clinically and the diagnosis of PROMs was demonstrated using vaginal speculum, nitrazine paper examination and ultrasonography. All neonates were evaluated clinically, radiologically, and by laboratory investigations. Pearson's Chi-square and Fisher's exact tests were used to assess the significance of differences between the two study groups. Respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH), and days of hospital stay were significantly reduced in premature infants of the corticosteroid treated women compared with the controls ($p<0.04$, $p<0.04$, $p<0.04$, and $p<0.05$, respectively). The perinatal mortality was significantly decreased among the corticosteroid treated group in the gestational subgroups 31-32 and 33-34 weeks ($p<0.04$), and in all birth weight subgroups ($p<0.03$). RDS was statistically a significant factor which resulted in increased perinatal mortality in the control group ($p=0.02$). Regarding the occurrence of postpartum endometritis there was a statistically significant increase among the corticosteroid treated group compared with the controls ($p<0.04$).

Conclusion: Antenatal corticosteroid therapy in pregnancies complicated by PROMs has a positive influencing effect on premature infants between 31 and 34 weeks of gestation, decreasing significantly the perinatal morbidity and mortality. It should be used with particular relevance to the developing world where surfactant is not available or where neonatal intensive care units are lacking.

Key words: Premature rupture of membranes; Premature delivery; Corticosteroids; Perinatal morbidity and mortality.

Introduction

Premature rupture of membranes (PROMs) is a significant obstetric problem. It affects 1%-15% of all pregnancies, and in most cases happens spontaneously and without apparent cause [1-5]. The reported incidence of PROMs has varied greatly, likely reflecting population demographics, the study type (prospective or retrospective), the study interval, the method of diagnosis and the gestational age at which PROMs was diagnosed [6]. It is one of the most common complications of pregnancy that has a major impact on neonatal mortality and morbidity [3-5]. It is responsible for approximately 30% of all preterm deliveries and causes important maternal morbidity [5]. Preterm birth is the most important consequence of PROMs and the development of respiratory distress syndrome (RDS) and its complications affecting therefore perinatal morbidity and mortality [7, 8]. Many studies [9-12], reported that the antenatal corticosteroid therapy in pregnancies complicated by PROMs is associated with a significant reduction in the incidence of RDS, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) and perinatal infection. We conducted this study to determine the effect of corticosteroids administered antenatally on pregnancies complicated by PROMs.

Revised manuscript accepted for publication April 10, 2001

Patients and Methods

All singleton pregnancies between 27-34 weeks of gestation complicated by PROM at Prince Rhashed (PRAH) and Prince Zaid Hospital (PZH) between 1 January 1997 and 31 February 1999 were studied. Inclusion criteria were: gestational age between 27-34 weeks, proved rupture of membranes, no lethal congenital abnormality or fetal death, no clinically apparent infection (fever >38°C, maternal or fetal tachycardia, uterine tenderness and foul-smelling vaginal discharge) or expected delivery within 12 hours (antepartum hemorrhage, chorioamnionitis, and progressive dilatation or cord prolaps). PROMs was defined as rupture of the membrane before completing 37 weeks of gestation. The diagnosis of PROMs was based on sterile speculum examination to confirm fluid leakage from the cervical os, nitrazine-positive fluid in the posterior fornix (nitrazine paper quickly will turn deeply blue because of the alkaline PH of the amniotic fluid) and the ultrasonographic findings (decreased amniotic fluid). During the speculum examination, cervical and vaginal cultures were obtained. Digital examination was not performed unless labor was well established. Ultrasonography was used to document the gestational age, the amount of fluid and to rule out any fetal congenital abnormality. Gestational age determination was based on a detailed menstrual history with dates consistent with previous ultrasonographic examinations. All pregnancies were managed with continuous external fetal heart rate (FHR) and uterine monitoring in the labor and delivery room for a minimum of 12 hours. Those without evidence of labor, infection or fetal distress were then transferred to the antenatal ward for the duration of preg-

nancy, where they were followed with daily physical examinations, temperature recordings every four hours, serial white blood cell count and C-reactive protein every other day, and daily non-stress tests (NSTs). Occurrence of infection and non-reactive NST were reasons to stop dexamethasone treatment, to start the patient on antibiotics and to induce labor or to perform cesarean section (depending on the fetal condition and presentation). Randomization was carried out using a random-table number in the two groups. The dexamethasone-treated group, comprised of 72 women in whom PROMs was diagnosed, were started on corticosteroids (dexamethasone) 24 mg intramuscularly (IM) divided in four doses 12 hours apart, and repeated if the patient had not delivered after one week; 58% of the dexamethasone treated group received more than two doses of dexamethasone during their stay in the hospital. Sixty-seven women with proved PROM were randomized as a control group. They had the same maternal characteristics and did not receive dexamethasone.

Cesarean section was performed after the onset of labor for non-vertex presentation fetuses and those with cephalic presentation when there was evidence of fetal distress. All fetuses were monitored continuously throughout labor. A pediatrician was present at the time of delivery and was responsible for performing any resuscitation and to assign an Apgar score. All neonates were admitted to the neonatal unit, where cultures of skin, oropharynx, urine blood and cerebrospinal fluid and chest X-ray were obtained for those who were suspected of having any sequelae of PROMs and prematurity. Brain ultrasound was performed by the third day to detect intracranial hemorrhage despite its deficient sensitivity in all neonates under 1,500 g. All infants were started on ampicillin and gentamycin intravenously (IV) immediately after cultures were obtained for 10-14 days depending on culture results and clinical improvement.

Diagnosis of chorioamnionitis was based on clinical and histological (placenta) findings, while for the post-partum endometritis it was based on clinical and laboratory findings (fever >38°C, uterine tenderness, mucopurulent vaginal discharge and positive endometrial culture). Neonatal sepsis diagnosis was based on clinical signs and positive cultures for blood, urine and skin. Diagnosis of respiratory distress syndrome was based on the characteristic radiological findings and clinical assessment by the attending pediatrician. Statistical analysis of the data was performed using Pearson's Chi-Square and Fisher's exact tests. Differences were considered significant when $p<0.05$.

Table 1. — *Maternal characteristics of the study groups with PROMs.*

Characteristics	Dexamethasone-treated n=72	%	Control n=67	%	p value
Age (years)					
<20	6	8.3	6	9	NS
20-24	17	23.6	18	26.8	NS
25-30	20	27.8	17	25.4	NS
30-34	16	22.2	15	22.4	NS
>35	13	18.1	11	16.4	NS
Parity					
0	56	8.3	5	7.5	NS
1	10	13.9	8	11.9	NS
2	16	22.2	16	23.9	NS
3	18	25	14	20.9	NS
>3	22	30.6	24	35.8	NS
Mode of delivery					
Vaginal	53	73.6	51	76.1	NS
Cesarean section	19	26.4	16	23.9	NS

Table 2. — *The effect of antenatal corticosteroids on perinatal and maternal morbidity in women with PROMs.*

Characteristics	Dexamethasone-treated n=72	%	Control n=67	%	p value
Fetal					
RDS*	14	19.4	24	35.8	<0.04
IVH**	2	2.8	8	11.9	<0.04
NEC***	0	0	5	10.2	<0.04
Neonatal sepsis	10	13.9	9	18.4	NS
Pneumonia	6	8.3	3	6.1	NS
PDA⁺	1	1.4	3	6.1	NS
Mean no. of hospital stay (days)	15.9		32.8		<0.05
Maternal					
APH▲	3	4.2	3	4.5	NS
Chorioamnionitis	6	8.3	3	4.5	NS
Postpartum endometritis	9	12.5	2	3	<0.05

RDS* = Respiratory distress syndrome; IVH** = Intraventricular hemorrhage; NEC*** = Necrotizing enterocolitis; PDA⁺ = Patent ductus arteriousus; APH▲ = Antepartum hemorrhage.

Results

Table 1 summarizes the maternal characteristics of the study groups. There were no significant differences in age, parity and mode of delivery between the corticosteroid treated group and the controls.

Table 2 shows the effect of corticosteroids administered antenatally on the premature infants. A statistically significant decrease in RDS, NEC, IVH, and duration of hospital stay among the corticosteroid treated group compared with the controls was observed ($p<0.04$, $p<0.04$, $p<0.04$, and <0.05, respectively). No significant differences in the occurrence of neonatal infectious morbidity were noted. A statistically significant increase in postpartum endometritis among the corticosteroid treated group was noted ($p<0.04$).

Perinatal mortality showed a statistically significant reduction in the corticosteroid treated group compared with the controls ($p<0.05$). RDS was a statistically significant factor responsible for the increase in perinatal mortality in the control group ($p<0.05$) as shown in Table 3. A statistically significant reduction in perinatal mortality among the corticosteroid treated group compared with the controls was found in the gestational subgroups 31-32 and 33-34 ($p<0.04$), and in all birth weight subgroups ($p<0.03$) (Table 4). Infants of the corticosteroid treated group showed a statistically significant increase in an accumulating Apgar score ≥ 7 compared to the control group at 1 and 5 minutes ($p<0.05$) as shown in Table 5.

Discussion

Preterm birth is the most important consequence of preterm PROMs, and the development of respiratory distress syndrome and its complications are key factors affecting morbidity and mortality, both immediate and

Table 3. — *The effect of antenatal corticosteroids on perinatal mortality in women with PROMs.*

Characteristics	Dexamethasone-treated n=21/72	%	Control n=41/67	%	p value
IUFD*	2	2.8	2	3	NS
RDS	8	11.1	15	22.4	<0.05
IVH	2	2.8	8	7.5	NS
NEC	1	1.4	4	6	NS
Neonatal sepsis	5	6.9	8	11.9	NS
Pneumonia	3	4.2	3	4.5	NS
PDA	0	0	1	1.5	NS

IUFD* = Intrauterine fetal death.

Table 4. — *Perinatal mortality according to gestational age and birth weight.*

Characteristics	Dexamethasone-treated n=21/72	%	Control n=41/67	%	p value
Gestational age					
27-28	5	6.9	7	10.4	NS
29-30	7	9.7	11	16.4	NS
31-32	5	6.9	12	17.9	p<0.04
33-34	4	5.5	11	16.4	p<0.04
Birth weight					
<1,500 g	14	19.4	26	38.8	<0.03
≥1,500 g	7	9.7	15	22.4	<0.02

Table 5. — *1-minute and 5-minute Apgar scores in corticosteroid treated and control groups.*

Characteristics	Dexamethasone-treated n=72	%	Control n=67	%	p value
1-min Apgar score					
0-3	10	13.9	15	22.4	NS
4-6	23	31.9	29	43.3	NS
≥ 7	39	54.2	23	34.3	<0.05
5-min Apgar score					
0-3	5	6.9	11	16.5	NS
4-6	15	20.9	21	31.3	NS
7	52	72.2	35	52.2	<0.05

long-term [7, 8]. Thus PROMs is clearly one of the most common events that turns a traditional pregnancy into a high-risk situation for both the fetus and mother. Hack *et al.* [13] defined major neonatal morbidity as having at least one of the following complications of prematurity: respiratory distress syndrome, necrotizing enterocolitis, or a grade III or IV intraventricular hemorrhage (IVH). The neonatal morbidity and mortality secondary to PROMs are strongly affected by the gestational age at the time of delivery [3].

Antenatal corticosteroids are associated with maturation of the fetal lung which results in a decreased incidence of RDS [9, 14, 15]. Also, their use is associated with a reduction in the risk of IVH, which appears likely to be independent of the pulmonary effect, and a reduction in the risk of NEC [7, 10, 14-16]. There may also be an effect on the cardiovascular system maturation as manifested by the infants ability to sustain higher blood pressure [17]. The preferred corticosteroids for antenatal therapy are dexamethasone and betamethasone. These two compounds are identical in biological activity and readily cross the placenta in their biological active forms. They are devoid of mineralocorticoid activity, relatively weak in immunosuppressive activity and exert a longer duration of action than cortisol and methylprednisolone [15].

The issue is whether corticosteroids should be used during the latent period of PROMs to accelerate pulmonary maturation. In cases of preterm labor with intact membranes there is evidence that the use of prenatal corticosteroids reduces the morbidity and mortality caused by RDS with minimal maternal risk [18]. The use of corticosteroids in cases of PROMs has been a source of controversy because of their immunosuppressive effects. There has been concern that the inherent susceptibility to infection of women with PROMs might be increased or that the signs of infection might be masked, thereby causing a delay in its diagnosis [19]. Randomized controlled trials reported no increase in perinatal infection in corticosteroid treated groups compared with control groups [8, 10, 17, 20, 21]. A summary of randomized controlled trials assessing the efficacy of antenatal corticosteroid administration concluded that infants born to women with PROMs benefit less than those born with intact membranes [4]. Many studies [2, 18, 22] failed to demonstrate the efficacy of antenatal corticosteroids in decreasing perinatal mortality, but other investigators [11, 23-25] indicated that antenatal corticosteroid use was associated with a greater than 50% reduction in the incidence of RDS.

Our study revealed a significant reduction in the incidence of RDS and NEC, and IVH. These findings are in agreement with those reported by other investigators [9-12] who demonstrated the same findings in the corticosteroid treated group complicated by PROMs. A significant increase in postpartum endometritis was noted in the dexamethasone treated group as compared with the controls. The same finding was reported by Garite *et al.* [19], Ohlsson *et al.* [11] and Iams *et al.* [26]. Premature infants of women treated with dexamethasone showed a significant reduction in hospital stay and a significant decrease in perinatal mortality in those with very low birth weight infants (≤ 1,500 g); such findings are supported by Morales [7] and Wright [23] *et al.*, respectively. In our study, 1 and 5-minute Apgar scores were higher among dexamethasone-treated group. Similar findings have been reported by other investigators [7, 14, 18, 20, 21].

In light of the available data, we conclude that corticosteroid therapy should be initiated in all cases of PROMs in pregnancies between 31-34 weeks, unless immediate delivery is indicated due to antepartum hemorrhage, chorioamnionitis, progressive dilatation or cord prolapse. This is of great value in decreasing perinatal mortality in developing countries like Jordan where surfactant therapy is not available. There is no significant increase in perinatal infection, but the risk of postpartum endometritis has increased significantly in women with PROMs who received dexamethasone for which antibiotic therapy merits being studied in association with corticosteroid administration.

References

[1] Gibbs R. S., Blanco J. D.: "Premature rupture of membranes". *Obstet. Gynecol.*, 1982, *60*, 671.

[2] Nelson L. H., Meis P. J., Hatjis C. G. *et al.*: "Premature rupture of membranes: a prospective randomized evaluation of steroids, latent phase and expectant management". *Obstet. Gynecol.*, 1985, *66*, 55.

[3] Taylor J., Garite T. J.: "Premature rupture of membranes before fetal viability". *Obstet. Gynecol.*, 1984, *64*, 615.

[4] Kennedy K. A., Clark S. L.: "Premature rupture of membranes: Management controversies". *Clin. Perinatol.*, 1992, *19*, 385.

[5] Arias F., Tomich P.: "Etiology and outcome of low birth weight and preterm infants". *Obstet. Gynecol.*, 1982, *60*, 277.

[6] Bourgeois F. J., Harbert G. M., Anderson W. A.: "Early versus late tocolytic treatment for premature rupture of membranes". *Am. J. Obstet. Gynecol.*, 1988, *159*, 742.

[7] Morales W. J., Diebel N. D., Lazar A. J. *et al.*: "The effect of antenatal dexamethasone administration on prevention of respiratory distress syndrome in preterm gestations with premature rupture of membranes". *Am. J. Obstet. Gynecol.*, 1986, *154*, 591.

[8] Schmidt P. L., Sims M. E., Strassner H. T. *et al.*: "Effect of antepartum glucocorticoid administration upon neonatal respiratory distress syndrome and perinatal infection". *Am. J. Obstet. Gynecol.*, 1984, *148*, 178.

[9] National Institutes of Health (NIH) Consensus Development Conference Statement: "Effect of corticosteroids for fetal maturation on perinatal outcome". *Am. J. Obstet. Gynecol.*, 1994, *173*, 246.

[10] Crowley P.: "Up date on the antenatal steroids meta-analysis". *Am. J. Obstet. Gynecol.*, 1995, *173*, 322.

[11] Ohlsson A.: "Treatment of premature rupture of membranes: A meta-analysis". *Am. J. Obstet. Gynecol.*, 1989, *160*, 890.

[12] Morales W. J., Angel J. L., O'brien W. F., Knuppel R. A.: "Use of ampicillin and corticosteroids in premature rupture of membranes: A randomized study". *Obstet. Gynecol.*, 1989, *73*, 721.

[13] Hack M., Horber J. D., Malloy M. H. *et al.*: "Very low birth weight outcome of the National Institute of Child Health and Human Development National Network". *Pediatrics*, 1991, *87*, 587.

[14] Gardner M. O., Goldenberg R. L.: "Use of antenatal corticosteroids for fetal maturation". *Curr. Opin. Obstet. Gynecol.*, 1996, *8*, 106.

[15] NIH Consensus Conference: "Effect of corticosteroids for fetal maturation on perinatal outcome". *JAMA*, 1995, *273*, 413.

[16] Scottish Neonatal Consultants' Collaborative Study Group, International Neonatal Network: "Trends and variations in use of antenatal corticosteroids to prevent neonatal respiratory distress syndrome: recommendations for national and international comparative audit". *Br. J. Obstet. Gynecol.*, 1996, *103*, 534.

[17] Kari M. A., Hallman M., Eronen M. *et al.*: "Prenatal dexamethasone treatment in conjunction with rescue therapy of human surfactant: A randomized placebo-controlled multicenter study". *Pediatrics*, 1994, *93*, 730.

[18] Crowley P., Chalmers I., Keirrs M. J. N. C.: "The effect of corticosteroid administration before preterm delivery: An overview of the evidence from controlled trials". *Br. J. Obstet. Gynecol.*, 1990, *97*, 11.

[19] Garite T. J., Freeman P. K., Linzey E. M. *et al.*: "Prospective randomized study of corticosteroids in the management of premature rupture of membranes and premature gestation". *Am. J. Obstet. Gynecol.*, 1981, *141*, 508.

[20] Garite T. J., Rumnes P. J., Briggs G. G. *et al.*: "A randomized placebo-controlled trial of betamethasone for the prevention of RDS at 24-28 weeks' gestation". *Am. J. Obstet. Gynecol.*, 1992, *166*, 646.

[21] Gamsu H. R., Mullinger B. M., Donnal P., Dash C. H.: "Antenatal administration of betamethasone to prevent respiratory distress syndrome in preterm infants: Report of a UK multicenter trial". *Br. J. Obstet. Gynecol.*, 1989, *96*, 401.

[22] Simpson G. F., Harbert G. M.: "Use of betamethasone in management of preterm gestation with premature rupture of membranes". *Obstet. Gynecol.*, 1985, *66*, 168.

[23] Wright L. L., Verter J., Younes N., Stevenson D. *et al.*: "Antenatal corticosteroids administration and neonatal outcome in very low birth weight infants: The NICHD Neonatal Research Network". *Am. J. Obstet. Gynecol.*, 1995, *173*, 269.

[24] Gunkel J. H., Mitchell B. R.: "Observational evidence for the efficacy of antenatal steroids from randomized studies of surfactant replacement". *Am. J. Obstet. Gynecol.*, 1995, *173*, 281.

[25] Gardner M. O., Papile Lu-Ann, Wright L. L.: "Antenatal corticosteroids in pregnancies complicated by premature rupture of membranes". *Obstet. Gynecol.*, 1997, *90*, 851.

[26] Iams J. D., Talbert M. L., Barrows H., Sachs L.: "Management of preterm prematurely ruptured membranes: A prospective randomized comparison of observation versus use of steroids and timed delivery". *Am. J. Obstet. Gynecol.*, 1985, *151*, 32.

Address reprint requests to:
HUSSEIN S. T. QUBLAN
Irbid - Aidun
P.O. Box 97 (Jordan)