

# Effects of antenatal steroids on the incidence and severity of respiratory distress syndrome in an Iranian hospital

F. Nayeri,<sup>1</sup> K. Movaghar-Nezhad<sup>1</sup> and F. Assar-Zadegan<sup>1</sup>

تأثير العلاج بالأدوية الستيرويدية أثناء الحمل على وقوع وشدة الإصابة بمتلازمة الضائقة التنفسية في أحد المستشفيات الإيرانية  
فاطمة نيري، كوروش موقرنراد، فرهاد عصارزادگان

**الخلاصة:** لازال استخدام الأدوية الكورتيكوستيرويدية أثناء الحمل لا يتم بشكل روتيني في جمهورية إيران الإسلامية لتعزيز نضج الرئتين في المواليد الخدج. ففي دراسة بحثية استعادية، تمت من خلال مراجعة السجلات الطبية للمرضى، في مستشفى الإمام بطهران، قمنا بمقارنة 140 خديجاً ولدوا في عام 2000، كانت أمهاتهم قد عولجن بعقار الستيرويدي أثناء الحمل، مع 142 طفلاً ولدوا في العام 1995 ولم تتلق أمهاتهم أي علاج. ولم تكن هناك فروق يُعتدُّ بها إحصائياً بين المجموعتين من حيث عمر الأمهات، أو وزن الخديج عند الولادة، أو العمر الحملي للجنين، أو جنس الخديج، أو طريقة الولادة، أو تعدد الأجنة، أو وجود مرض مستبطن لدى الأم، أو وقوع أحداث ضائرة أثناء المخاض. وكانت الإصابة بمتلازمة الضائقة التنفسية أقل بنسبة يُعتدُّ بها إحصائياً في مجموعة الذين عولجت أمهاتهم بالستيرويديين (18.6% مقابل 35.9%). في حين أن معدل الوفيات (5.7% مقابل 14.8%) وضرورة استخدام وحدة الرعاية المركزة للولدان (12.9% مقابل 21.1%) فقد كانت أقل بنسبة يُعتدُّ بها إحصائياً في أولئك الذين لم تتلق أمهاتهم أي علاج.

**ABSTRACT** Antenatal corticosteroids are still not routinely used in the Islamic Republic of Iran to promote lung maturity in premature neonates. In a retrospective review of records at Imam Hospital, Tehran, we compared 140 premature neonates born in 2000 whose mothers received dexamethasone antenatally with 142 born in 1995 whose mothers did not receive treatment. There were no significant differences between the groups in mothers' age; neonates' birth weight, gestational age or sex; route of delivery and multiple gestation; underlying maternal disease; or adverse events in labour. The incidence of respiratory distress syndrome was significantly lower in the dexamethasone-treated group (18.6% versus 35.9%). Mortality (5.7% versus 14.8%) and use of the neonatal intensive care unit (12.9% versus 21.1%) were also significantly lower among those who had received treatment.

## Effets des stéroïdes administrés en prénatal sur l'incidence et la gravité du syndrome de détresse respiratoire dans un hôpital iranien

**RÉSUMÉ** La corticothérapie prénatale n'est pas encore utilisée systématiquement en République islamique d'Iran pour accélérer la maturation pulmonaire chez les prématurés. Au cours d'une étude rétrospective des dossiers à l'hôpital Imam de Téhéran, nous avons comparé 140 prématurés nés en 2000 de mère ayant reçu de la dexaméthasone pendant la période prénatale avec 142 enfants nés en 1995 de mère n'en n'ayant pas reçu. Il n'y avait aucune différence significative entre les groupes pour ce qui concerne l'âge de la mère, le poids de naissance du nouveau-né, l'âge gestationnel ou le sexe, le mode d'accouchement et la grossesse multiple, une maladie maternelle sous-jacente ou un événement indésirable durant les couches. L'incidence du syndrome de détresse respiratoire était significativement plus faible dans le groupe traité par dexaméthasone (18,6 % contre 35,9 %). La mortalité (5,7 % contre 14,8 %) et le recours à l'unité néonatale de soins intensifs (12,9 % contre 21,1 %) étaient significativement moindres chez ceux du groupe n'ayant pas reçu de traitement.

<sup>1</sup>Neonatal Intensive Care Unit Ward, Vali-e-Asr Reproductive Health Research Centre, Imam Hospital Complex, Tehran Medical University, Tehran, Islamic Republic of Iran (Correspondence to F. Nayeri: fatemehnayeri@hotmail.com).

## Introduction

Respiratory distress syndrome (RDS) is present in 1% of all deliveries and 10% of preterm neonates [1]. Its incidence and severity is generally higher in low-birth-weight neonates (less than 2500 g), among boys, infants with gestational age less than 35 weeks, infants of diabetic mothers, asphyxiated neonates and cases of multiple gestation and feto-maternal haemorrhage. However, it is less common in infants of heroin-addicted mothers or mothers suffering pre-eclampsia, eclampsia or hypertension [1-4].

Although measures have been developed for managing respiratory distress syndrome, effective preventive methods should also be considered. One of the most effective methods of prevention is to promote lung maturity by inducing the synthesis of lung surfactant. Antenatal treatment with the corticosteroids dexamethasone or betamethasone increases phosphatidylcholine synthesis and morphologic remodelling of alveolar structures (including thinning of interstitial tissues of the lung) in the fetus [3]. Corticosteroids are also believed to regulate several genes associated with the differentiation of the fetal lung, including the genes encoding enzymes involved in the synthesis of phosphatidylcholine and surfactant proteins [3]. Corticosteroids stabilize capillaries and consequently maintain the integrity of the lungs. As a result, these drugs prevent the progression of RDS to pulmonary oedema [2].

Antenatal corticosteroid treatment is a simple and accessible method in which 4 doses of 5 mg dexamethasone (2 days, 2 doses per day) are prescribed for mothers of gestational age less than 35 weeks who are at-risk of preterm labour [5]. The procedure has not been widely used routinely in the management of preterm labour, as the matter is still controversial. In Europe,

almost two-thirds of countries were reported to make use of this method routinely [6]. In the Islamic Republic of Iran, no consensus has yet emerged among obstetricians.

Up to 1996, antenatal steroids were not used for mothers with preterm labour in Imam Khomeini General Hospital in Tehran, Islamic Republic of Iran. After 1996, however, the use of dexamethasone gradually increased so that by the year 2000 antenatal steroids were used for all cases of preterm labour except those with obstetric contraindications. This retrospective study was therefore carried out to compare the characteristics of premature neonates born in the years 1995 and 2000, i.e. the periods before and after dexamethasone was used to treat mothers at-risk of preterm labour.

## Methods

This retrospective study was carried out at Imam Khomeini General Hospital, which is the largest educational hospital in Tehran, consisting of obstetric, gynaecology and perinatology wards as well as routine and intensive neonatal care. It handles between 1500 to 2000 deliveries annually.

Neonates of gestational age 37 weeks or less were included in the study. The following information about the neonate and mother were extracted from the hospital records: mother's age; neonate's sex, gestational age and birth weight; Apgar score < 6 in the 1st minute; presence of placenta praevia or placenta abruptio; presence of underlying maternal disorders (diabetes, eclampsia, pre-eclampsia, hypertension) and multiple gestation.

Out of 2530 newborns in the year 1995 and 1649 in 2000, 177 and 172 premature babies were selected respectively. These 2 groups matched each another in the following respects: mean gestational age, mean

birthweight, mean maternal age, sex, route of delivery (caesarean section or vaginal), mother's underlying disease (diabetes, hypertension, eclampsia or pre-eclampsia, considering one disease for each mother) and problems during labour and delivery (low Apgar score, placenta praevia, placenta abruptio). Neonates with unknown gestational age (16 in 1995 and 12 in 2000) and those with meconium staining were excluded. In addition, the newborns of 20 mothers in 2000 for whom antenatal steroids had not been used were excluded. Thus we compared 142 premature neonates whose mother did not receive dexamethasone antenatally in 1995 (group 1) with 140 whose mothers received dexamethasone in 2000 (group 2).

The diagnostic criteria of RDS in this study were as follows:

- Clinical: the appearance of progressive respiratory distress at birth or up to 6 hours after birth requiring the use of O<sub>2</sub> by means of hood (fractions of inspired oxygen FIO<sub>2</sub> > 60%) or respirator.
- Paraclinical: (1) arterial blood gas showing progressive hypoxia and metabolic acidosis; (2) chest X-ray showing white lung or typical view of RDS (hy-poeration, fine reticulogranular pattern and air bronchogram).

In our study, the severity of RDS was classified as follows:

- Mild or moderate RDS: use of O<sub>2</sub> as applied by hood (5 L/minute FIO<sub>2</sub> > 60%) or hood and nasal cannula (2 L/min).
- Severe RDS: use of ventilator and neonatal intensive care unit or leading to states such as death, pulmonary haemorrhage and white lung view in chest X-ray.

The information extracted from the records was analysed using SPSS, version 9 software, and after computing the re-

quired prevalence, *t*-test was used for comparing means and chi-squared test for comparing ratios. We took a *P*-value less than 0.05 as statistically significant.

## Results

There were no significant differences between the 2 groups in terms of gestational age, birth weight, mother's mean age, route of delivery (caesarean section or vaginal) and neonate's sex (Table 1) (*P* > 0.05).

In group 1, 51 (35.9%) of 142 premature neonates developed RDS compared with 26 of 140 (18.6%) in group 2 (Table 2). This difference was statistically significant (*P* < 0.05). The incidence of severe RDS was also reduced; RDS-related mortality (5.7% versus 14.8%) and use of the neonatal intensive care unit (12.9% versus 21.1%) were significantly lower in group 2 than group 1 (Table 2).

When the 2 groups were compared for the presence of predisposing factors for RDS, there was no significant difference between the 2 groups (*P* > 0.05); 39 mothers in group 1 and 31 mothers in group 2 had problematic labour and delivery (placenta praevia, placenta abruptio, low Apgar score) (Table 2). However, among mothers who had problems during labour, the incidence of RDS in group 2 was significantly lower than in group 1 (*P* < 0.05) (Table 3).

In group 1, 47 mothers and in group 2, 30 mothers were found to have an underlying disease present (diabetes mellitus, hypertension, eclampsia or pre-eclampsia), but the difference was not significant (Table 2). However, among mothers who had underlying disease, group 2 showed significantly lower RDS rate (*P* < 0.05) (Table 3). (A few mothers in both groups had more than one problem concurrently, but for the purpose of this study we analysed only one problem.)

Table 1 Characteristics of the 2 groups of premature births

| Variable                          | Group 1<br>(n = 142) |      | Group 2<br>(n = 140) |      | P-value |
|-----------------------------------|----------------------|------|----------------------|------|---------|
| Mean (SD) gestational age (weeks) | 34.5 (1.2)           |      | 33.6 (1.8)           |      | NS      |
| Mean (SD) birth weight (g)        | 2376 (760)           |      | 2329 (543)           |      | NS      |
| Mean (SD) mother's age (years)    | 24.8 (2.5)           |      | 25.8 (3.2)           |      | NS      |
| Neonate's sex (No., %)            |                      |      |                      |      |         |
| Male                              | 77                   | 54.2 | 71                   | 50.7 | NS      |
| Female                            | 65                   | 45.8 | 69                   | 49.3 | NS      |
| Route of delivery (No., %)        |                      |      |                      |      |         |
| Caesarean section                 | 52                   | 36.6 | 63                   | 45.0 | NS      |
| Vaginal delivery                  | 90                   | 63.4 | 77                   | 55.0 | NS      |

n = total number of premature births.

NS = not significant.

SD = standard deviation.

Group 1: born in 1995, mother not treated with dexamethasone.

Group 2: born in 2000, mother treated with dexamethasone.

## Discussion

Prematurity is one of the most important factors predisposing a neonate to RDS. Due to the complexities and expense of sophisticated treatments for RDS [1-3], preventive measures, particularly the promotion of surfactant synthesis antenatally, are more practical in developing countries. Antenatal treatment with steroids for at-risk mothers has been shown to be highly effective. Elimian et al. in 1999 [7], and Dacosta et al. in 2000 [8] reported that mortality and morbidity of preterm neonates decreased as a result of using corticosteroids before birth. Another study showed a 50% decrease in incidence and severity of RDS [9]. Kari et al. reported that using corticosteroids can reduce the incidence of RDS, the use of exogenous surfactant and the duration of ventilator support. This has increased survival rate of

preterm neonates even without special ventilator care [10].

The incidence of RDS and its complications such as chronic lung disease differ among different races. For example, black newborns are less prone to the risk of developing RDS than white newborns [4]. On the other hand, corticosteroids regulate those genes that encode enzymes involved in the synthesis and secretion of surfactant [3]. Consequently, the response to the use of antenatal steroids in different races with diverse genetic backgrounds might be different. Despite these possible differences, our study in this hospital in the Islamic Republic of Iran agrees with other studies showing that antenatal use of dexamethasone may decrease the rate of RDS.

In this study we sought to consider all those factors that positively or negatively affect the incidence of RDS. As our results

**Table 2 Incidence and severity of respiratory distress syndrome (RDS), adverse events during labour and underlying maternal disease in the 2 groups of premature births**

| Variable                           | Group 1<br>(n = 142) |      | Group 2<br>(n = 140) |      | P-value |
|------------------------------------|----------------------|------|----------------------|------|---------|
|                                    | No.                  | %    | No.                  | %    |         |
| RDS                                | 51                   | 35.9 | 26                   | 18.6 | < 0.05  |
| RDS-related death                  | 21                   | 14.8 | 8                    | 5.7  | < 0.05  |
| Use of NICU                        | 30                   | 21.1 | 18                   | 12.9 | < 0.05  |
| <i>Events during labour</i>        |                      |      |                      |      |         |
| Placenta abruptio                  | 8                    |      | 9                    |      |         |
| Placenta previa                    | 1                    |      | 8                    |      |         |
| Low Apgar score                    | 30                   |      | 14                   |      |         |
| Total                              | 39                   | 27.5 | 31                   | 22.1 | NS      |
| <i>Underlying maternal disease</i> |                      |      |                      |      |         |
| Diabetes mellitus                  | 5                    |      | 6                    |      |         |
| Hypertension                       | 4                    |      | 4                    |      |         |
| Pre-eclampsia                      | 38                   |      | 20                   |      |         |
| Total                              | 47                   | 33.1 | 30                   | 21.4 | NS      |

n = total number of premature births.

NICU = neonatal intensive care unit.

NS = not significant.

Group 1: born in 1995, mother not treated with dexamethasone.

Group 2: born in 2000, mother treated with dexamethasone.

**Table 3 Adverse events during labour and underlying maternal disease according to incidence of respiratory distress syndrome (RDS) in the 2 groups of premature births**

| Variable                           | Group 1      |      | Group 2      |      | P-value |
|------------------------------------|--------------|------|--------------|------|---------|
|                                    | No. with RDS | %    | No. with RDS | %    |         |
| <i>Events during labour</i>        |              |      |              |      |         |
|                                    | (n = 39)     |      | (n = 31)     |      | < 0.05  |
| No                                 | 8            | 20.5 | 19           | 61.3 |         |
| Yes                                | 31           | 79.5 | 12           | 38.7 |         |
| <i>Underlying maternal disease</i> |              |      |              |      |         |
|                                    | (n = 47)     |      | (n = 33)     |      | < 0.05  |
| No                                 | 27           | 57.4 | 24           | 80.0 |         |
| Yes                                | 20           | 42.6 | 6            | 20.0 |         |

n = number of premature births.

Group 1: born in 1995, mother not treated with dexamethasone.

Group 2: born in 2000, mother treated with dexamethasone.

show, predisposing factors such as being male, having a caesarean section, lower gestational age and birthweight, maternal diabetes, asphyxia and low Apgar score and vaginal bleeding were the same. On the other hand, protective factors such as maternal hypertension and eclampsia were distributed uniformly in the 2 groups. However, the use of antenatal steroids in group 2 significantly decreased the incidence and severity of RDS, which accords well with the findings reported in Elimian et al. [7], Da Costa et al. [8] and Iarukova et al. [9]. It also led to a decrease in the frequency of ventilator use, as well as reducing NICU admission, confirming the findings reported by Kari et al. [10].

It is worth noting that management protocols regarding this disease and ward facilities in the hospital remained the same during the years 1995 to 2000. Due to the small number of newborns, the comparison of subgroups of these RDS patients with similar status (such as infants of diabetic mothers, asphyxiated patients, etc.)

was not possible in this study. This could be done in studies with a much larger number of cases.

In our study, predisposing factors for RDS were similar in the 2 groups. However, the incidence of death and use of the neonatal intensive care unit (and hence ventilator use) were significantly decreased in neonates born after maternal dexamethasone treatment compared with those born before the use of corticosteroids for mothers at risk of preterm labour. During the years that this study was carried out, antenatal steroids were rarely used in the Islamic Republic of Iran. The extent to which the treatment is used in Eastern Mediterranean Region countries is not documented, but it seems that antenatal steroids were still not routinely used in around one-third of European countries by the year 2000 [6]. In view of the benefits as well as the low cost of treatment, we suggest the use of antenatal steroids on a routine basis for at-risk mothers.

### References

1. Martin RJ, Fanaroff AA, Klaus MH. Respiratory problems. In: Klaus MH, Fanaroff AA, eds. *Care of the high risk neonate*, 4th ed. Philadelphia, WB Saunders, 1993:238–40.
2. Martin RJ et al. The respiratory system. In: Fanaroff AA, Martin RJ, eds. *Neonatal-perinatal medicine*, 6th ed. St Louis, Missouri, Mosby Yearbook, 1997:1007–22.
3. Whitsett JA et al. Acute respiratory disorders. In: Avery GB, ed. *Neonatology*, 5th ed. Philadelphia, JB Lippincott, 2000: 490–3.
4. Stoll BJ, Kliegman RM. Respiratory tract disorders. In: Behrman RE, Kliegman R, Jenson HB, eds. *Nelson's textbook of pediatrics*, 16th ed. Philadelphia, WB Saunders, 2000:498–505.
5. Cunningham FG, MacDonald PC. Preterm birth. In: Cunningham FG et al., eds. *Williams obstetrics*, 20th ed. Norwalk, Connecticut, Appleton & Lange, 1997:812.
6. Empana JP et al. Use of antenatal corticosteroids in Europe. *Prenatal and neonatal medicine*, 2001, 6(suppl. 2):1–7.
7. Elimian A et al. Effectiveness of antenatal steroids in obstetric subgroups. *Obstetrics and gynecology*, 1999, 93(2): 174–9.
8. Da Costa DE, Nair PA, Al Khusaiby SM. Effect of antenatal steroids on the complications of prematurity in an era of surfactant replacement therapy in Oman. *Journal of tropical pediatrics*, 2000, 46(6):375–7.

9. Iarukova N et al. Efekt ot antenatalnata kortikosteroidna profilaktika pri preamturni novorodeni sus surfaktant terapiia. [The effect of antenatal corticosteroid prophylaxis in premature newborns with the use of surfactant therapy.] *Akusherstvo i ginekologija*, 1998, 37(2): 20–3.
10. Kari M et al. Prenatal dexamethasone treatment in conjunction with rescue therapy of human surfactant: a randomised placebo controlled multi-center study. *Pediatrics*, 1994, 93(5): 730–6.

### Implementing Best Practices Initiative (IBP)

The goal of the IBP Initiative is to improve access and quality of reproductive healthcare through a systematic approach focused on developing and supporting strategies that introduce, adapt and apply evidence-based practices in reproductive health.

Initiated by the World Health Organization and USAID, and supported by an increasing number of international and local reproductive health agencies, the IBP Initiative responds to several challenges in the reproductive health community in low resource settings, among them:

- The lack of targeted and coherent information on what works and what does not work
- Costly duplication of efforts
- Costly implementation of ineffective programmes
- Limited access to evidence-based tools, materials and strategies
- Limited opportunities to share new knowledge with local and international colleagues.