Contribution to the assessment of steroid Therapy in the prevention of respiratory distress syndrome in the neonate

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Summary: The respiratory distress syndrome (RDS) is a physiological manifestation of neonatal pulmonary immaturity and it is still the major cause of neonatal morbidity and mortality. In order to promote early fetal lung maturity when a preterm delivery is anticipated, a number of pharmacological agents have been investigated. Corticosteroids, in particular, have been extensively used and the results of several trials are reported in literature.

A cohort of 246 consecutive singleton preterm infants, liveborn at the Obstetric Clinic of Ferrara University during a 5-year period, was studied to assess whether antenatal steroid therapy reduces the incidence of RDS.

Respiratory distress developed in 18.6% of 102 babies who received treatment and in 15.3% of 144 controls, without difference at the statistical analysis. According to previous studies, a lower incidence of RDS was only observed in the treated females compared to non-treated controls (35% vs 46%) at the gestational age of 28-33 weeks.

Since the efficacy of steroids seems to be restricted to a very small and specific group of babies, who, moreover are relatively mature by modern intensive care standards, the Authors suggest that the prevention of RDS and its related complications should rely much more on appropriate surveillance and management of the mother and infant than on specific pharmacological interventions.

INTRODUCTION

There are many forms of respiratory failure from which newborn infants suffer in their first days of life, the most common and the most important of which worldwide is hyaline membrane disease. This condition, commonly termed also respiratory distress syndrome (RDS), has an incidence hard to assess because of the difficulties of making a precise diagnosis and for the lack of accurate statistics ([1]).

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In neonates born between the 28th and 35th week of gestation, RDS ranges from 14% to 60% and is associated with 30% of all neonatal deaths and with 50% to 70% of premature deaths ([2]).

RDS occurs in infants who are born before term, but susceptibility depends more on the stage of lung maturation at the time of delivery than on precise gestational age. The disease has become synonymous with deficiency and abnormality of the pulmonary surfactant, which lines the alveolar surface of healthy lungs. However, it is important to recognise that there are many other abnormalities in the

lungs of premature babies which compound the surfactant abnormality and exacerbate the RDS. Immature lung structure, cell damage and protein exudation onto alveolar surface are also very important. If surfactant is inadequate, the lungs do not expand easily, once expanded they readily collapse, the epithelial cells become damaged and protein exudes onto the surface so that alveolar gas exchange becomes ineffective ([1]).

Since Liggins and Howie ([3]) first suggested that glucocorticoids might accelerate fetal lung maturation, steroids have been widely administered in women who are threatening to deliver prematurely. The role of antenatal steroid administration in stimulating lung maturation and surfactant synthesis has been extensively investigated. The results of several trials have been reviewed in detail by Roberts ([4]) and Zachmann ([5]). Today it is well accepted that antenatal steroid treatment is not associated with short and long-term adverse effects; however its efficacy in preventing neonatal RDS is limited to very specific groups of babies who are relatively mature by modern neonatal intensive care standards ([6, 7, 8]).

During the last decade, the number of infants at high risk for RDS, born before 32-33 weeks of gestation, has not changed in our hospital. However, the neonatal mortality rate has more than halved and we have experienced a significant fall of the neonates with severe RDS we were accustomed to see in the past.

At present, we are in favour of explaining the improvement in neonatal prognosis more by the amelioration of perinatal care as the whole rather than by specific pharmacological intervention. In particular, this improvement can hardly be ascribed to the antenatal steroid therapy which has never been changed since its introduction more than 15 years ago.

To assess whether steroids given to accelerate fetal lung maturation continue to have a significant role in the prevention of neonatal RDS, we studied a cohort of preterm babies born over the 5-year period from January 1, 1982 to December 31, 1986 at the Clinica Ostetrica of Ferrara University.

METHODS

The perinatal data of 295 consecutive, nonmalformed single live births delivered before 37 weeks of gestation were retrospectively evaluated. Throughout the study period, mothers admitted to the hospital with threatened premature delivery received steroids at the discretion of the physician on duty.

For the purpose of the study, fetuses were considered to have received therapy if their mothers had had at least two doses of betamethasone 12-24 hours apart within the week before the delivery. Those who received only one dose were not considered. Fetuses from mothers not treated with steroids were controls.

The treated population and control population were compared for maternal age, illnesses complicating the pregnancy, gestational age, type of delivery, sex, and birth weight. The diagnosis of RDS was based on standard clinical, radiological, and blood gas findings. These included chest retraction, grunting, cyanosis, increased ambient oxygen requirement, hypercarbia, and a groundglass appearance on chest x-ray with air bronchograms and elevated diaphragms. The RDS was defined absent when infants were spontaneously breathing air or low-concentration supplemental oxygen, present when in addition to oxygen some form of respiratory support (CPAP or mechanical ventilation) was needed.

Chi-square test and Student's t test were used for statistical analysis where appropriate.

RESULTS

Of 294 neonates screened, 48 (16%) were inelegible because steroid treatment was incomplete and did not meet the study criteria. The steroid group was constituted of 102 neonates whose mothers received at least two doses of betamethasone within the week before the delivery. The control group was constituted of 144 neonates whose mothers were not treated with steroids.

The baseline comparison of the two groups of neonates suggests no difference

Table 1. – *Comparison of groups on mother and infant baseline data.*

Variables	Treated (n. 102)	Controls (n. 144)	P value
Maternal age (yr)	27.7±6.2	27.4±5.9	n.s.
Gestational age (wk)			
– at hospital admission	32.2±0.9	32.4±3.4	n.s.
– at delivery	33.1±2.0	32.9±3.8	n.s.
Mode of delivery			
– vaginal	74 (72.5%)	113 (78.4%)	n.s.
- cesarean	28 (27.5%)	31 (21.6%)	n.s.
Sex			
– male	41 (40.2%)	65 (45.1%)	n.s.
– female	61 (59.8%)	79 (54.9%)	n.s.

Table 2 – *Illnesses complicating the pregnancy.*

Membranes ruptured > 24 hours	40 (16.3%)
Preeclampsia	21 (8.5%)
Placental insufficiency	2 (0.8%)
Gestational diabetes	12 (4.9%)
Antepartum hemorrhage	8 (3.3%)

Table 3. – *Infants with RDS in gestational age subgroups.*

G.A. (weeks)	Treated	Controls	P value
All	19/102 (18.6%)	22/144 (15.3%)	n.s.
⩽ 27	–	8/8 (100%)	–
28-33	14/30 (46.7%)	12/24 (50%)	n.s.
34-36	5/72 (6.9%)	2/112 (1.8%)	n.s.

in perinatal variables, such as maternal age, gestational age at hospital admission and at delivery, type of delivery, and sex of the neonates (Tab. 1).

Also the medical conditions that may affect the incidence of RDS, present in 83 pregnancies (34%), were distributed into the two groups without significant difference (Tab. 2).

Forty-one neonates of the study population (16.7%) developed RDS requiring some form of respiratory support. The percentage of infants with RDS was approximately the same in steroid and control group and correlated with the gestational age. No difference existed in the gestational age subgroups (Tab. 3).

The incidence of RDS was 17.1% in vertex delivered infants and 15.3% in cesarean section, without differences in steroid and control group (Tab. 4).

In Tab. 5 the well known higher prevalence of RDS in the male sex was confirmed. In Tab. 6 the relationship of sex, RDS, and steroid treatment is presented. The statistical analysis of the data did not

Table 4. – *Infants with RDS by treatment in mode-of-delivery subgroups.*

Mode of delivery	Treated	Controls	P value
Vaginal	14/74 (18.9%)	18/113 (15.9%)	n.s.
Cesarean	5/28 (17.9%)	4/31 (12.9%)	n.s.

Table 5. – *Percentage of infants with RDS by sex.*

	Male	Female	P value
RDS	22.6% (24/106)	12.1% (17/140)	<0.005

Table 6. – *Infants with RDS by treatment in sex and gestational age subgroups.*

G. A. (weeks)	Male sex		P value
	Treated	Controls	
⩽ 27	–	6/6 (100%)	–
28-33	7/10 (70%)	6/11 (54.5%)	n.s.
34-36	4/31 (12.9%)	1/48 (2.1%)	n.s.
Total	11/41 (26.8%)	13/65 (20%)	n.s.

G. A. (weeks)	Female sex		P value
	Treated	Controls	
⩽ 27	–	2/2 (100%)	n.s.
28-33	7/20 (35 %)	6/13 (46.2%)	n.s.
34-36	1/41 (2.4%)	1/64 (1.6%)	n.s.
Total	8/61 (13.1%)	9/79 (11.4%)	n.s.

show any significant difference between the groups considered and there was no evidence that in either sex the incidence of RDS was modified by steroid treatment. A lower incidence of RDS was only observed in treated females compared to non treated controls (35% vs 46%) at the gestational age of 28-33 weeks.

DISCUSSION

Among the several studies on the effect of antenatal steroid administration to prevent neonatal RDS, the most important and authoritative is that of the Collaborative Study of Bethesda sponsored by the National Institutes of Health ([8]). There the Authors confirmed the findings of Liggins and Howie, that prenatal steroid administration is effective in reducing the overall incidence of RDS. The greatest effect was seen in the group with gestational age of 30-34 weeks delivered between 24 hours and 7 days after initiation of maternal therapy. However, in this study the effect of treatment was dependent upon sex, race, and other characteristics of the infant and mother and, therefore, its potential usefulness was dictated by those limitations.

Since it has been hypothesized that steroid dynamics are different in multiple births and dexamethasone did not appear to reduce the incidence of RDS in newborn twins and tripletts ([8]), in our study we considered only singleton neonates. Moreover, our population of twins (46 neonates) was too small to be studied separately.

Also the relationship between mortality and steroid treatment was not considered. RDS is certainly a risk factor for mortality; however, early and intensive maternal, fetal, and neonatal surveillance and intervention may have reduced the impact of treatment with steroids on the mortality rate. Moreover, more tiny babies die today from complications, such as cerebral hemorrhage, sepsis, or necrotising enterocolitis, than from respiratory failure, also when RDS is present.

Although our study has confirmed the wellknown higher prevalence of RDS in the male sex, it has not demonstrated that maternal steroid treatment prior to premature delivery reduces the incidence of RDS in the newborn infants. In the female population of 28-33 weeks of gestation, steroid treatment is associated with a lower incidence of RDS and, although this result does not reach statistical significance, it is in accordance with the results of other studies.

We are aware that our figures are small and results should be interpreted with caution; however they suggest that steroids play today, if anything, a minor role in the prevention of RDS of preterm babies. It is our opinion that the prevention of RDS, and its related complications, must rely more on appropriate surveillance and intervention on the mother and infant.

Uncomplicated delivery, opportune resuscitation with early lung expansion, constant positive airways pressure and appropriate ventilation, good hemodynamics and, finally, the prevention of hypoxic or hypercarbic episodes are all very effective means for avoiding or reducing the severity of RDS, also in the smallest babies. Recent results obtained with natural surfactant replacement therapy appear much more promising and allow the hypothesis that in the near future this will be the most effective intervention for preventing or treating RDS in the preterm neonate ([9, 10, 11]).

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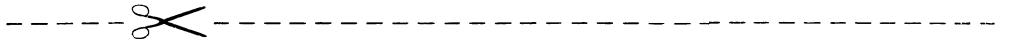

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