Reduction of incidence and mortality of respiratory distress syndrome by administration of hydrocortisone to mother

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Dluholucký, S., Babic, J., and Taufer, I. (1976). *Archives of Disease in Childhood*, 51, 420. **Reduction of incidence and mortality of respiratory distress syndrome by administration of hydrocortisone to mother.** Hydrocortisone (100 mg in a single injection) was given to 120 pregnant women with threatened premature delivery. None was given to a control group of 40 mothers. Orciprenaline was also given to all the mothers to inhibit uterine activity. The administration of hydrocortisone did not accelerate delivery and in the treated group 55 babies were eventually born at term; none died or had perinatal complications. 65 babies were born prematurely, and yielded these conclusions: if the mother received hydrocortisone less than 24 hours before delivery it had little or no influence on the incidence of and mortality from the respiratory distress syndrome (RDS). If birth occurred more than 24 hours after hydrocortisone injection, the incidence and mortality from RDS were lowered. Prolonged rupture of membranes had no effect on the mortality rate from RDS. It was concluded that hydrocortisone administered to mothers with threatened delivery is an effective means of mitigating the incidence and severity of RDS in infants.

The important role of surfactant deficiency in the respiratory distress syndrome (RDS) is well accepted (Avery and Mead, 1959; Gluck and Kulovich, 1973a; Rorman, 1973). Works with animals led to the conclusion that an increased level of glucocorticoid in fetal blood accelerates lung maturation (Kotas and Avery, 1971; Chiswick, *et al.*, 1973).

Certain stresses have also been thought to increase the production of surfactant. For example, Kotas, (1973) showed that in the fetal rabbit intraperitoneal injection of *Staphylococcus aureus* caused accelerated maturation of the lung. In man, premature rupture of the membranes (Yoon and Harper, 1973; Bauer *et al.*, 1974) and antenatal infection (Gluck and Kulovich, 1973b) have been associated with a lower than expected incidence of RDS, though Jones *et al.*, (1975) found no such effect. Such stresses may cause fetal glucocorticoids to rise and surfactant synthesis to increase. On the other

hand, postnatal administration of glucocorticoids has no favourable effect (Baden *et al.*, 1972).

Liggins and Howie (1972) first reported the use of betamethasone in 282 mothers in whom premature delivery threatened or was planned before 37 weeks' gestation; RDS occurred less often in the babies of treated mothers (9%) than in controls (25.8%). Fargier *et al.* (1974) published similar results. However, there are unfavourable side effects from the antenatal use of glucocorticoids. In sheep they may induce preterm delivery (Liggins, 1969). Methylprednisolone does not affect lung maturation but does induce labour (Taubes, Avery, and Sugg, 1972).

We have sought to determine whether administering hydrocortisone to a woman in premature labour (1) is as safe and effective as betamethasone; (2) accelerates delivery; (3) decreases the incidence of RDS; (4) needs to be given at least 24 hours before delivery in order to be effective; (5) produces differences in acid-base balance and in mortality between a treated and an untreated control sample.

Material and method

The study was carried out over a period of 21 months, from January 1973 to September 1974. Of 160 mothers admitted to hospital because of threatened premature delivery, hydrocortisone was given to 120 while a control group of 40 received none. Gestational age was 37 weeks or less. Treated and control subjects were chosen at random. A single intramuscular injection of 100 mg hydrocortisone was given to the treated group. To inhibit uterine activity we used a preparation of orciprenaline (Alupent, Boehringer), 0.5 mg in an infusion of 400 ml 5 % dextrose at a rate of 1.5–10 µg/min (Babic *et al.*, 1974; Baillie, Meehan, and Tyack, 1970; Di Terlizzi, 1973).

When the infant was delivered the umbilical cord was tied and sodium bicarbonate (4.2 % solution, 2.5 mEq/kg with dextrose) was given via the umbilical vein in order to treat any postnatal acidosis. The Apgar score was recorded and the infant was moved to the intensive care unit of the paediatric department, where its condition was further recorded (maturity, Silverman score, acid-base balance), and the gestational age was estimated from the date of mother's last menstrual period, and the clinical and neurological status.

The diagnosis of RDS was made on the clinical findings (Silverman score), the acid-base balance, and in the case of deceased infants by lung histology. Depending on the severity of disease, infants were treated with bicarbonate and oxygen, the temperature maintained in an incubator, while severe cases were treated with continuous positive airway pressure using Gregory's box, or by intermittent positive pressure breathing by Bird respirator Mark 8. These infants received a 10% solution of dextrose together with fresh frozen plasma via an umbilical vein catheter or via a peripheral vein by using an infusion pump.

Of the 120 mothers admitted with threatened premature labour, in 55 after orciprenaline therapy pregnancy continued to term, with delivery of 55 term infants. The remaining 65 mothers delivered 65 preterm infants. This sample was divided into two groups (Table I). In group C (31 mothers) the hydrocortisone was given >24 hours before delivery, in group B (24 mothers) it was given <24 hours before delivery (mean 12.4, range ±8 hours). Group A (40 mothers) did not receive hydrocortisone and served as a control. There was no difference between the 3 groups as to sex, weight, gestational age, method of delivery, or treatment after delivery. There were no stillbirths.

In order to evaluate the influence of premature rupture of membranes on the mortality rate from RDS we studied retrospectively all preterm deliveries during the previous 3 years. This group consisted of 308 preterm infants, which included the groups A, B, C. In 88 of the deliveries the membranes had ruptured after the onset of labour.

Results

Children born at term of mothers who had received hydrocortisone. There were 55 such mothers and these delivered 55 infants at term. The average birthweight of the infants was 3.128 g and gestational age was 38.6 weeks; they had no perinatal complications, and none died. All were discharged from hospital after the normal 5 days.

Incidence of RDS in infants born preterm of mothers who had received hydrocortisone. The incidence and mortality from RDS are given in Table II. The incidence of RDS was 45% in

TABLE I
Preterm infants delivered from 65 hydrocortisone-treated and 40 untreated mothers

Group	n	Sex M/F	Birthweight (g) (mean ± SE)	Gestational age (w) (mean ± SE)
A	40	15/25	1682.4 ± 494.6	31.3 ± 3.4
B	34	13/21	1579.7 ± 548.3	31.6 ± 3.8
C	31	17/14	1671.8 ± 788.7	31.4 ± 2.7

Group A, Untreated controls.

Group B, Treated <24 hours before delivery.

Group C, Treated >24 hours before delivery.

TABLE II
Incidence and mortality of RDS

Group*	n	Incidence of RDS		Mortality in RDS	
		Cases	%	Cases	%
A	40	18	45	14	35
B	34	11	32	8	23
C	31	5	16	3	9.7

* See Table I.

group A, 32% in group B, and 16% in group C. The difference between groups A and C was significant ($P < 0.001$)* but not between groups A and B, or B and C. The mortality from RDS was 35% in group A, 23% in group B, and 9.7% in group 3, the difference between groups A and C being significant ($P < 0.05$)*. pH and PCO_2 values are shown in Table III. pH values were

TABLE III

Mean values and range of pH and PCO_2 in infants

Group*	n	pH	PCO_2 (mmHg)
A	38	7.259 ± 0.158	61.3 ± 31.1
B	31	7.283 ± 0.158	56.6 ± 31.2
C	29	7.302 ± 0.240	52.0 ± 21.4

Statistical significance (Student's 't' test)

Groups	pH	PCO_2
A:B	$P < 0.05$	NS
B:C	$P < 0.01$	NS
A:C	$P < 0.001$	NS

*See Table I.

significantly different among all 3 groups. There was no statistical difference in PCO_2 values, though those in group C were lower than in groups A and B.

Effect of premature rupture of membranes on mortality from RDS. Table IV summarizes results which show that premature rupture of membranes had no significant effect on the mortality rate from RDS (cases lacking histological verification of hyaline membrane disease were excluded).

TABLE IV

Prolonged rupture of membranes and mortality from RDS

Group	n	RDS deaths
Prolonged rupture	88	24 (27%)
Control	220	51 (23%)

Discussion

Our results are similar to those of Liggins and Howie (1972) and Fargier *et al.*, (1974), and show that a single injection of 100 mg hydrocortisone had practically the same effect as betamethasone. Previous authors have thought that in man hydro-

cortisone does not cross the placenta (Liggins, 1969; Motoyama *et al.*, 1971), and hence it has not been used in clinical practice. Our results suggest that it does cross the placenta and is effective in speeding lung maturation.

Our treated groups had a lower birthweight and gestational age than those reported by Liggins and Fargier *et al.* Perhaps this is why our treatment did not cause as great a reduction of incidence and mortality, while betamethasone may also be more effective. As with betamethasone, the effect of hydrocortisone is greatest when it is given at least 24 hours before delivery. Hydrocortisone did not appear to accelerate delivery since 55 mothers with threatened premature delivery who received it delivered at term.

Although Carson, Tauesch and Avery, (1973) reported that hydrocortisone inhibited division of lung cell in rabbit, Kotas, Mims, and Hart (1974) showed such inhibition to be transient, and to be more than compensated by the advantages of a mature lung at birth.

We have concluded that (1) hydrocortisone given to the mother did not accelerate delivery; (2) hydrocortisone must be given to the mother with threatened premature delivery earlier than 24 hours before delivery in order to be effective. The incidence and mortality of RDS will then be about one-quarter that in infants born to mothers who have not received hydrocortisone. (3) Prolonged rupture of fetal membranes has no favourable effect on mortality rate from RDS.

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*Pearson's χ^2 test.

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