ARTICLES

A CONTROLLED TRIAL OF ANTEPARTUM GLUCOCORTICOID TREATMENT FOR PREVENTION OF THE RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS

G. C. Liggins, M.B., Ph.D., F.R.C.O.G., *and* R. N. Howie, M.B., M.R.A.C.P.

From the Postgraduate School of Obstetrics and Gynaecology, University of Auckland, New Zealand

ABSTRACT. A controlled trial of betamethasone therapy was carried out in 282 mothers in whom premature delivery threatened or was planned before 37 weeks' gestation, in the hope of reducing the incidence of neonatal respiratory distress syndrome by accelerating functional maturation of the fetal lung.

Two hundred and thirteen mothers were in spontaneous premature labor. When necessary, ethanol or salbutamol infusions were used to delay delivery while steroid or placebo therapy was given. Delay for at least 24 hours was achieved in 77% of the mothers. In these unplanned deliveries, early neonatal mortality was 3.2% in the treated group and 15.0% in the controls (p 0.01). There were no deaths with hyaline membrane disease or intraventricular cerebral hemorrhage in infants of mothers who had received betamethasone for at least 24 hours before delivery. The respiratory distress syndrome occurred less often in treated babies (9.0%) than in controls (25.8%, p 0.003), but the difference was confined to babies of under 32 weeks' gestation who had been treated for at least 24 hours before delivery (11.8% of the treated babies compared with 69.6% of the control babies p. 0.02).

There may be an increased risk of fetal death in pregnancies complicated by severe hypertension-edema-proteinuria syndromes and treated with betamethasone, but no other hazard of steroid therapy was noted.

We conclude that this preliminary evidence justifies further trials, but that further work is needed before any new routine procedure is established. *Pediatrics*, 50:515, 1972, RESPIRATORY DISTRESS SYNDROME, PREMATURITY, PULMONARY SURFACTANT, CORTICOSTEROID THERAPY, HYALINE MEMBRANE DISEASE.

RECENT experimental work showing that functional maturation of fetal animal lungs can be accelerated by stimulation of the fetal adrenal cortex or by administration of glucocorticoids suggests a possible approach to the prevention of disease resulting from pulmonary immaturity in the human. Liggins[1,2] in 1969 noted that lambs delivered prematurely at 118 to 123 (term, 147) days after intrafetal infusions of ACTH, cortisol, or dexamethasone were viable and that, when sacrificed, their lungs remained partially expanded. This evidence of alveolar stability was unusual in view of the studies of Brumley *et al.*[3] which showed that stable pressure-volume curves and low alveolar surface tensions normally developed only after 125 days. Liggins suggested that glucocorticoids caused premature liberation of surfactant into the alveoli, perhaps by induction of an enzyme concerned with the biosynthesis of surfactant. DeLemos *et al.*[4] confirmed these observations by comparing the lungs of cortisol-treated fetal lambs with those of their untreated twins. They found in all animals of more than 100 days of gestation that the lungs of treated lambs had functional evidence of accelerated appearance of surfactant. Similar evidence has been obtained in fetal rabbits following injection of 9α-fluoroprednisolone.[5] In these animals there was also evidence of increased formation of osmiophilic bodies in type II alveolar cells and abundant osmiophilic material in the alveolar spaces of treated fetuses.[6]

Naeye *et al.*,[7] in a study of 387 necropsies on human neonates dying within 72 hours of birth, showed that the mean weight of adrenal glands was 19% lower in neonates dying with hyaline membrane disease than in those free of the disorder. In addition,

(Received May 22; accepted for publication June 8, 1972.)

ADDRESS FOR REPRINTS: (G.C.L.) National Women's Hospital, Claude Road, Auckland 3, New Zealand.

TABLE I

ASSOCIATED DISORDERS OF PREGNANCY

Major fetal malformations	14
Rh isoimmunisation	21
Hypertension-edema-proteinuria syndromes*	32
Placenta previa*	2
Other unplanned premature labor	213
All mothers	282

* Planned deliveries only.

they found that anencephalic neonates with hypoplastic adrenal cortices had, in comparison with neonates without this malformation, less than half the mass of osmiophilic granules in type II alveolar cells.

These previous studies raise the possibility that the same phenomenon of accelerated lung maturation might occur in the human. Unlike the ovine placenta which has high resistance to the passage of corticosteroids,[8] the human placenta is relatively permeable to these compounds and the inhibitory effect of maternally administered corticosteroids on the fetal adrenal production of the estrogen precursor, dehydroepiandrosterone sulphate, is well known.[9,10] Thus, maternal administration is a feasible means of subjecting the human fetus to high levels of glucocorticoid activity. The present study was designed to investigate the effects of large doses of a potent glucocorticoid given to mothers expected to deliver prematurely on the subsequent respiratory adaptation of neonates of less than 37 weeks' gestation.

TABLE II

PERINATAL OUTCOME IN PLANNED DELIVERY FOR HYPERTENSION-EDEMA-PROTEINURIA SYNDROMES

	Betamethasone-Treated Group		*Control Group*	
	No.	*%*	*No.*	*%*
Fetal deaths, antepartum	3	15.8	...	0.0
Fetal deaths, intrapartum	2	10.5	...	0.0
Early neonatal deaths	1	5.3	2	15.4
Perinatal deaths	6	31.6	2	15.4
Survived 7 days	13	68.4	11	84.6
All infants	19	100.0	13	100.0

SUBJECTS AND METHODS

During a period of 22 months from December 1969, women admitted in premature labor at 24 to 36 weeks or in whom premature delivery before 37 weeks was planned because of an obstetrical complication were included in the trial. In a few instances an obstetrician considered that corticosteroid treatment was contraindicated and in others delivery occurred soon after admission; otherwise, few patients who fulfilled the above criteria were omitted.

On admission to the trial, each patient was given an intramuscular injection of the material contained in a numbered vial. The vials contained either a mixture of 6 mg betamethasone phosphate and 6 mg betamethasone acetate or a control of identical appearance consisting of 6 mg cortisone acetate, the latter's glucocorticoid potency being approximately one-seventieth that of the betamethasone preparation. Equal numbers of pairs of ampules of active and control material were arranged in random order by a pharmacist who held the key to identification. Unless delivery had already occurred, a second injection of the same material as the first was given 24 hours later.

An attempt was made to delay delivery for an arbitrarily defined period of 48 to 72 hours from the time of the first injection by inhibiting uterine activity with intravenous infusions of ethanol or, more recently, with salbutamol (2-t-butylamino-1-[4-hydroxy-3-hydroxymethyl] phenylethanol). When spontaneous rupture of the fetal membranes was present on admission, antibiotics were given and the period of attempted suppression of labor was limited to 48 hours. In patients to be delivered prematurely because of obstetric complications, the first injection was given three days before elective induction.

In a few volunteers, amniocentesis was

performed before the first injection of corticosteroid or placebo and was repeated two to seven days later. The lecithin-sphingomyelin ratio of the amniotic fluids was determined by the method of Gluck *et al.*[11] Blood samples were collected daily for seven to eight days from 12 patients and the concentration of cortisol was estimated by the method of Murphy.[12]

Following delivery, the infants' Apgar scores were recorded at one minute and again at five minutes. Medical examinations were carried out at delivery and later as required. Gestational age was assessed from obstetric data including the menstrual history, the estimate of uterine size made on vaginal examination during the first trimester, and the date of quickening, and from the general appearance, body dimensions and neurological development of the neonate.

Observations were made of respiratory rate, grunting, and chest retraction using the Silverman score[13] on admission to the neonatal intensive care unit and again at 3, 6, and 12 hours after delivery. Chest radiographs were taken during the first day, usually during the first six hours of life. Clinical records and radiological findings were assessed separately and independently, the former by one of the authors (R.N.H.), the latter by one radiologist. An infant was regarded as having suffered from RDS only if both clinical and radiological signs were present: clinical signs of grunting respirations and chest retraction present during the first three hours and persisting beyond the first six hours after delivery, and a radiological pattern of having fine generalized granularity of lung fields with air bronchogram.

Umbilical arterial catheters were inserted in infants with signs of respiratory distress who required oxygen in a concentraion of 40% or more to relieve cyanosis, and gas tensions were measured repeatedly on arterial blood samples.

All infants were fed early, and respiratory and circulatory support was given where appropriate by positive end expiratory pressure, mechanically assisted ventilation, and infusions of sodium bicarbonate.

Blood glucose concentrations were estimated at least three times daily for the first three days in all infants delivered before 37 weeks. Serum bilirubin estimations were carried out at approximately 48 hours after delivery and repeated at least twice daily if the infant appeared significantly jaundiced.

Histological sections from necropsies on infants who died were reviewed by one pathologist.

TABLE III

INFLUENCE OF THERAPY ON COURSE OF PREGNANCY IN UNPLANNED PREMATURE LABOR

	Bethamethasone-Treated Group		*Control Group*	
	No.	*%*	*No.*	*%*
Interval Between First Injection and Delivery:				
Under 24 hours	28	23.9	22	22.9
24 hours and under 7 days	44	37.6	43	44.8
7 and under 21 days	6	5.1	4	4.2
21 days and over	39	33.4	27	28.1
All mothers	117	100.0	96	100.0
Mean interval (days)	22.1		14.4	
Median interval	3.7		2.8	

RESULTS

During the first 22 months, 287 mothers entered the trial. Five mothers in whom there was a procedural error, the second

TABLE IV

INFANT SURVIVAL IN UNPLANNED PREMATURE LABOR (ALL INFANTS)

	Betamethasone-Treated Group		*Control Group*		
	No.	*%*	*No.*	*%*	*p**
Fetal deaths, antepartum	3	2.4	...	0.0	NS†
Fetal deaths, intrapartum	1	0.8	3	3.0	
Early neonatal deaths	4	3.2	15	15.0	.01
Perinatal deaths	8	6.4	18	18.0	.02
Survived 7 days	118	93.6	82	82.0	
All babies	126	100.0	100	100.0	

* p values in this and subsequent Tables are derived using the chi-squared test with Yates's correction.

† NS = difference not significant ($p > 0.05$).

TABLE V

OCCURRENCE OF RDS IN LIVEBORN INFANTS RELATED TO ENTRY-DELIVERY INTERVAL IN INFANTS DELIVERED AFTER UNPLANNED PREMATURE LABOR

Entry-Delivery Interval	*Betamethasone-Treated Group*			*Control Group*			
	No.	*RDS*	*% RDS*	*No.*	*RDS*	*% RDS*	*p*
Under 24 hours	29	7	24.1	22	7	31.8	NS
24 and under 48 hours	20	2	10.0	19	7	36.8	NS
2 and under 7 days	28	1	3.6	24	8	33.3	.03
7 days and over	45	1	2.2	32	3	9.4	NS
All live births	122	11	9.0	97	25	25.8	.003
All infants born alive over 24 hours after entry to trial	93	4	4.3	75	18	24.0	.002

dose of steroid or placebo being omitted, were not further considered. The remaining 282 mothers were grouped according to the disorders of pregnancy as shown in Table I.

Rh Hemolytic Disease of the Newborn Infant

Twenty-one babies were delivered from 21 mothers. Perinatal mortality was 25.0% (two of eight) in the betamethasone-treated group and 38.5% (five of 13) in the control group, but the difference is not statistically significant. RDS occurred in none of the seven liveborn infants treated with betamethasone, and in two of the ten liveborn controls, but again the difference is not significant.

Planned Delivery for Hypertension-Edema-Proteinuria Syndromes

Thirty-two babies were delivered from 32 mothers. Infant outcome is shown in Table II.

The betamethasone-treated group had a higher perinatal mortality (31.6%) than the controls (15.4%) due to an excess of fetal deaths in the former group. On the other hand, there was a lower incidence of RDS in liveborn infants in the treated group (one of 14, 7.1%) than in the controls (four of 13, 30.8%). Neither difference is statistically significant.

Unplanned Premature Labor

There were 213 mothers in this group, 117 treated with betamethasone and 96 controls. The influence of therapy on the course of pregnancy is shown in Table III.

A similar proportion (about 23%) of mothers in both groups delivered less than 24 hours after entry to the trial, thus escaping full treatment, but average entry-delivery intervals were longer in the betamethasone-treated group than in the controls. The difference is not significant.

The 213 mothers delivered 226 infants. There were 11 pairs of twins (seven in the betamethasone-treated group) and one set of triplets (also in the treatment group). Infant outcome is shown in Table IV.

The fetal death rate was similar in the two groups (about 3%) but there was a lower perinatal death rate in the treatment group (6.4%) than in the controls (18.0%), due to a lower early neonatal death rate in the former group (3.2% compared with 15.0% of the controls). Both these differences are significant.

The effect of treatment and the duration of treatment on the incidence of RDS in liveborn infants is shown in Table V.

In all babies of unplanned deliveries, the incidence of RDS in the betamethasone-treated group was only one-third that of the controls (9.0% compared with 25.8%). There was little difference between the two

TABLE VI

COMPOSITION AND OUTCOME OF TREATED AND CONTROL GROUPS OF INFANTS OF UNPLANNED DELIVERIES OCCURRING AT LEAST 24 HOURS AFTER ENTRY TO TRIAL

	Betamethasone-Treated Group		*Control Group*		
Mothers	89		74		
Infants	94		78		
Sex: male	52 (55.3%)		48 (61.5%)		
female	42 (44.7%)		30 (38.5%)		
Gestational age (days after LMP, mean ± SD)*					
(a) at entry to trial	222 ± 21		225 ± 20		
(b) at delivery	249 ± 31		244 ± 29		
Birth weight (grams, mean ± SD)	2,350 ± 810		2,280 ± 780		
Infant outcome	*No.*	*%*	*No.*	*%*	*p*
Fetal deaths, antepartum	...	0.0	...	0.0	
Fetal deaths, intrapartum	1	1.1	3	3.8	NS
Early neonatal deaths	3	3.2	11	14.1	.02
Perinatal deaths	4	4.3	14	17.9	.01
Survived 7 days	90	95.7	64	82.1	
All infants	94	100.0	78	100.0	

* LMP = first day of last normal menstrual period; SD = standard deviation.

TABLE VII

DETAILS OF EARLY NEONATAL DEATHS AMONG INFANTS OF UNPLANNED DELIVERIES OCCURRING AT LEAST 24 HOURS AFTER ENTRY TO TRIAL

Case No.	*Sex*	*Gestational Age at Delivery (weeks and days after LMP)*	*Birth Weight (grams)*	*Age at Death*	*Findings*
Betamethasone-Treated Group					
24	F	31:2	1,280	1½ hr	No necropsy, respirations never properly established, clinically, intrapartum hypoxia
146	F	26:?	820	4 days	No abnormality at necropsy, (no RDS or hyaline membrane disease)
276	M	26:6	1,000	10 hr	Pneumonia (no RDS or hyaline membrane disease)
Control Group					
1	M	28:5	1,500	9 hr	RDS, alveolar atelectasis
86	M	28:1	1,110	4 hr	Hyaline membrane disease
108	M	30:6	1,660	¾ hr	Pneumonia, septicemia (*E. coli*)
152	M	26:?	800	¾ hr	Intrapartum hypoxia
167	M	31:3	1,900	13 hr	Hyaline membrane disease, intraventricular hemorrhage
173	F	26:3	806	35 hr	Intraventricular hemorrhage, pneumonia
184	M	29:?	1,040	1½ hr	Intraventricular hemorrhage
236	M	29:6	1,600	4 hr	Hyaline membrane disease, pneumonia
238	F	29:4	1,120	½ hr	Intrapartum hypoxia, pneumonia
251	M	31:?	1,510	12 hr	Hyaline membrane disease
253	F	31:5	1,500	½ hr	Hyaline membrane disease, intraventricular hemorrhage

groups of babies who delivered less than 24 hours after entry to the trial but in those who delivered after this time the difference in incidence of RDS was more marked (4.3% compared with 24.0%).

Further results reported in this section relate only to those babies who were considered to receive full therapy, i.e., two injections of betamethasone or control material 24 hours apart, the first more than 24 hours before delivery. There were 94 babies in the treated group and 78 controls. No differences were apparent in the composition of the two groups with respect to sex, gestational age at entry and at delivery, and birth weight (Table VI).

Three and two-tenths percent of the betamethasone-treated infants died during the first 7 doys of life compared with 14.1% of the controls, a probably significant difference. Details of the early neonatal deaths are given in Table VII. Necropsies were performed on all but one of the babies who died.

Hyaline membrane disease was present at necropsy in five infants in the control group (6.7% of the 75 liveborn infants), and in none of the 93 betamethasone-treated liveborn infants, a difference that is probably significant (p 0.04). Intraventricular hemorrhage was present in four of the control infants (5.3%) and in none of the treated group, but this difference is not significant.

RDS was significantly less frequent in betamethasone-treated liveborn infants than in the controls (4.3% compared with 24.0%, Table VIII), but the difference was confined to infants delivered at less than 32 weeks' gestation (11.8% compared with 69.6%).

Infants of under 30 weeks' gestation are listed in Table IX. Eight of 12 treated with betamethasone survived 28 days, compared with none of the eight controls, a probably significant difference.

The duration of maternal action of the betamethasone regimen is illustrated in Figure 1 which gives results of daily plasma cortisol estimations in seven mothers treated with betamethasone and five given placebo. Endogenous cortisol suppression was evident for three days after the start of betamethasone therapy.

No complication of pregnancy, labor, delivery, or the puerperium was detected that could have been attributed to steroid medication. Notifiable puerperal pyrexia (i.e., any febrile condition within 14 days after delivery in which a temperature of 38°C or more was sustained during a period of 24 hours or recurred during that period) occurred in five of the 108 mothers given two doses of betamethasone (4.9%) and in six

TABLE VIII

INCIDENCE OF RDS ACCORDING TO GESTATIONAL AGE AT DELIVERY IN LIVEBORN INFANTS OF UNPLANNED DELIVERIES AT LEAST 24 HOURS AFTER ENTRY TO TRIAL

	Betamethasone-Treated Group			*Control Group*			
	No. of Infants	*RDS*		*No. of Infants*	*RDS*		*p*
		No.	*%*		*No.*	*%*	
Gestational Age at Delivery:							
26 and under 32 weeks	17	2	11.8	23	16	69.6	0.02
32 and under 37 weeks	43	2	4.7	29	2	6.9	NS
37 weeks and over	33	0	0.0	23	0	0.0	NS
All liveborn infants	93	4	4.3	75	18	24.0	0.002

TABLE IX

INFANTS UNDER 30 WEEKS' GESTATION DELIVERED AT LEAST 24 HOURS AFTER ENTRY TO TRIAL

Case No.	*Sex*	*Gestational Age at Delivery (weeks and days after LMP)*	*Birth Weight (grams)*	*RDS*	*Outcome*
8	F	28:?	1,130	+	Survived
16	M	29:5	1,360	0	Survived
45	F	29:4	1,280	0	Survived
58	F	28:6	1,340	+	Survived
65	M	27:?	910	+	Survived
102	F	29:3	1,220	0	Late NND* 14 days, *E. coli* enteritis
146	F	26:?	820	0	NND 4 days, no abnormality found
153	F	26:3	710	0	Survived
180	M	29:2	1,060	0	Survived
269	M	26:?	940	...	Intrapartum death, no abnormality found
276	M	26:6	1,000	0	NND 10 hr, pneumonia
277	F	29:6	1,220	0	Survived
Control Group					
1	M	28:5	1,500	+	NND 9 hr, alveolar atelectasis
86	M	28:1	1,110	+	NND 4 hr, hyaline membrane disease
152	M	26:?	800	...	NND ¾ hr, no abnormality found
173	F	26:3	800	+	NND 35 hr, intraventricular hemorrhage, pneumonia
184	M	29:?	1,040	+	NND 1½ hr, intraventricular hemorrhage
190	M	28:5	1,450	0	Late NND 12 days, meningitis
236	M	29:6	1,600	+	NND 4 hr, hyaline membrane disease and pneumonia
238	F	29:4	1,120	...	NND ½ hr, intrapartum hypoxia and pneumonia

* NND = neonatal death.

of the 91 controls (6.6%). Betamethasone therapy had no obvious influence on lactation: 29% of the betamethasone-treated mothers were lactating on discharge compared with 23% of the controls.

There was no added risk of fetal or neonatal infection with betamethasone therapy, possibly the reverse. One of 94 infants treated prenatally with two doses of betamethasone died with pneumonia (1.1%) compared with four of 78 controls (5.1%). The difference is not significant.

There were no differences between treated and control groups in Apgar scores at birth (Table X) or in the incidence of hypoglycemia, jaundice, or diarrhea.

DISCUSSION

The results of the trial support the hypothesis that in humans, as in experimental animals previously studied, glucocorticoid administration to the fetus accelerates lung maturation. Relatively brief intrauterine exposure of human infants to pharmacological doses of betamethasone was associated with a substantial reduction in the incidence of RDS which was particularly marked in the most immature group. The duration of exposure as judged both by the incidence of RDS in relation to time from start of treatment and by the time course of betamethasone release from depot injections is consistent with observations made in experimental animals which have shown that functional and morphological maturation of fetal lung occurs within 48 hours of glucocorticoid administration.

How the glucocorticoid acts remains to be determined. The apparent promptness of the effect, even in the most immature fe-

tuses, may be in part due to release of surfactant already stored within the alveolar epithelium since, as shown by Platzker *et al.*,[14] the concentration of surfactant in lung homogenates of human fetuses rises sharply between 18 and 22 weeks to reach levels near those of term infants. However, mechanisms other than enhanced surfactant production or release could be responsible for the improved function of the lungs of treated infants. Factors other than surfactant deficiency that have been incriminated in the pathogenesis of RDS include pulmonary ischemia[15] and fetal hypoxia.[16,17] In the present study, no assessment of pulmonary perfusion could be made and an effect of the glucocorticoid on the pulmonary vasculature cannot be excluded. A reduced incidence of hypoxia, on the other hand, is unlikely to be responsible for the lower incidence of RDS in treated infants since there was no difference in Apgar scores of the treated and control groups.

Our findings have implications for the pathogenesis of RDS, suggesting that alveolar atelectasis is the result rather than the cause of surfactant deficiency, and that the deficiency is primary rather than secondary, at least in those cases occurring in infants of less than 32 weeks' gestation. The difference in steroid effect before and after 32 weeks remains to be explained, and factors other than primary surfactant deficiency may be responsible for RDS in infants delivered nearer term.

It appears that steroids should be given to the fetus at least 24 hours before delivery if therapy is to have any noticeable effect on lung function. Treatment after birth, even if immediate, may be of little value if most of the damage is done before the drug acts. The lack of benefit from cortisone

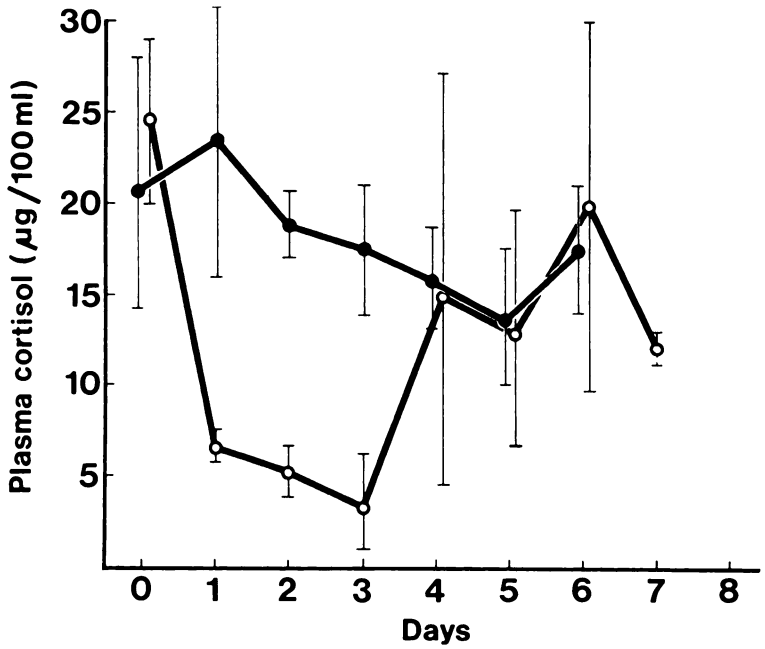

FIG. 1. Maternal plasma cortisol levels after treatment with depot betamethasone (open circles, n = 7) or placebo (closed circles, n = 5). The vertical lines give the range, one standard deviation from the mean.

treatment in a trial in infants of diabetic mothers[18] supports this view.

The use of pharmacological doses of corticosteroids in late pregnancy has a number of potential hazards. In particular, corticosteroids administered to various experimental animals may induce premature labor.[19] This effect, if it occurred in human pregnancy, would militate against any beneficial effects on lung function by causing more premature delivery. It is reassuring that the interval from first injection to delivery is longer in the treated group than in the controls. Although the difference is not significant, it raises the possibility that Van Rensberg's observation[20] of prolonged pregnancy in sheep after brief administration of corticosteroids to the fetus may be relevant to the human. Attention has been drawn to the lethal effects of very large doses of corticosteroids given to sheep fetuses[21] and to increased perinatal mortality in women treated throughout pregnancy with glucocorticoids in daily doses equivalent to 50 mg or more of prednisone.[22] Although the latter observations have not been confirmed in other reported studies,[23-25] it has been important to show in the present trial that, with the exception of one subgroup, there was no increased risk of antepartum or intrapartum fetal death with betamethasone treatment. The exception was noted in women with the syndrome of severe hypertension, proteinuria, fetal growth retardation, and low urinary estrogen excretion in whom labor was to be induced before 36 weeks: in this group there was an excess of fetal deaths in the treated cases compared with the controls. The difference in mortalities of the two groups is not significant but until larger numbers of subjects in the trial establish whether or not the present distribution has occurred by chance the possibility remains that corticosteroids have adverse effects on placentas severely damaged by vascular disease.

Retardation of growth has been described in fetuses of rats given corticosteroids during pregnancy[26] and in children treated with corticosteroids for long periods of time.[27] In the present trial the mean birth weight of treated children was slightly greater than that of controls but not as much as would be expected from the difference in mean gestational age at delivery. This finding could be explained by the larger number of infants of multiple pregnancies in the treated group. Thus, there was no evidence that a short period of exposure to betamethasone retarded growth under the conditions of our study.

TABLE X

APGAR SCORES IN LIVEBORN INFANTS OF UNPLANNED DELIVERIES AT LEAST 24 HOURS AFTER ENTRY TO TRIAL

Apgar Scores	*One Minute*		*Five Minutes*	
	Betamethasone-Treated Group	*Control Group*	*Betamethasone-Treated Group*	*Control Group*
0, 1, 2	10	8	3	6
3, 4	11	11	4	4
5, 6, 7	31	28	13	12
8, 9, 10	40	27	72	51
Not recorded	1	1	1	2
All liveborn infants	93	75	93	75
Mean Apgar score	6.4	6.1	8.0	7.5
Standard deviation	2.3	2.4	1.7	2.3

Lowered resistance to infection in either the mother or the fetus was also considered as a possible adverse reaction to corticosteroid treatment. No difference was found in the incidence of puerperal pyrexia. Furthermore, the incidence of neonatal illness attributable to intrauterine infection was rather lower in the treated group. The data were also examined for evidence of other adverse reactions including acute adrenal insufficiency, neonatal hypoglycemia, and hyperbilirubinemia with negative results.

The success of any attempt at prolonged fetal medication in the presence of premature labor depends on effective control of uterine contractions and delayed delivery. During most of the period of the trial, inhibition of labor was attempted with intravenous ethanol infusions according to the technique described by Fuchs *et al.*[28] The

large number of women delivering within 24 hours of the first injection of steroid is an indication of the limited success achieved with uterine relaxants. More recently, better control of labor has been obtained by the use of salbutamol, a β-adrenergic stimulant which has predominantly β_2 activity.[29] Our experience with salbutamol is described elsewhere.[30] But whichever uterine inhibitor is used, adverse effects arising from its use must be considered a risk of therapy. We were especially concerned that delaying delivery in the presence of ruptured membranes or a dilated cervix might lead to amnionitis. When neonatal death from pneumonia is used as the measure of the incidence of intrauterine infection, the results do not support such an effect in that the incidence of neonatal death from pneumonia was lowest when the membranes were ruptured longest. The difference is not significant but if confirmed by further work it could be due to the use of a broad spectrum antibiotic which is more likely to be prescribed when delivery is delayed.

The results of analyses of samples of amniotic fluid obtained before administration of betamethasone and again two to seven days later will be reported elsewhere. However, it is of some interest in considering both the mode of action of betamethasone and the practical application of corticosteroid treatment in the prophylaxis of RDS that no consistent change has been found in the lecithin-sphingomyelin ratio of amniotic fluid samples taken before and after betamethasone therapy. Although amniotic fluid analysis is likely to be valuable in selecting patients for corticosteroid treatment it is doubtful that it will prove useful in monitoring the response to treatment.

Contrary to expectation, death from intraventricular cerebral hemorrhage in the most immature infants of the treated group did not occur whereas this disorder was found in four infants of the control group. The difference is not statistically significant but nevertheless raises the possibility that RDS predisposes to intraventricular hemorrhage and that prophylaxis of neonatal respiratory disorders may reduce the incidence of the intracranial disorder.

The trial is continuing and it is hoped that firm conclusions can eventually be drawn on such questions as the effects of corticosteroids on placental function, on the incidence of intraventricular hemorrhage and on long-term development of survivors. Meanwhile, from the present results we conclude that there is sufficient evidence of beneficial effects on lung function and of absence of adverse effects to justify further trials. In view of the present trial's empirical basis of selection of the glucocorticoid and its dosage and duration of treatment, it would be surprising if there were no scope for improved results from therapeutic regimens based on a better understanding of the mode of action of glucocorticoids, on better selection of patients and on more effective control of uterine activity.

REFERENCES

1. Liggins, G. C.: The foetal role in the initiation of parturition in the ewe. *In* Wolstenholme, G. E. W., and O'Connor, M., eds.: Foetal Autonomy. London: Ciba Foundation Symposium. J. & A. Churchill Ltd., p. 142, 1969.
2. Liggins, G. C.: Premature delivery of foetal lambs infused with glucocorticoids. J. Endocr., **45**:515, 1969.
3. Brumley, G. W., Chernick, V., Hodson, W. A., Normand, C., Fenner, A., and Avery, M. E.: Correlations of mechanical stability, morphology, pulmonary surfactant and phospholipid content in the developing lamb lung. J. Clin. Invest., **46**:863, 1967.
4. DeLemos, R. A., Shermeta, D. W., Knelson, J. H. Kotas, R., and Avery. M. E.: Acceleration of appearance of pulmonary surfactant in the fetal lamb by administration of corticosteroids. Amer. Rev. Resp. Dis., **102**:459, 1970.
5. Kotas, R. V., and Avery, M. E.: Accelerated appearance of pulmonary surfactant in the fetal rabbit. J. Appl. Physiol., **30**:358, 1971.
6. Wang, N. S., Kotas, R. V., Avery, M. E., and Thurlbeck, W. M.: Accelerated appearance of osmiophilic bodies in fetal lungs following steroid injection. J. Appl. Physiol., **30**: 362, 1971.
7. Naeye, R. L., Harcke, H. T., and Blanc, W. A.: Adrenal gland structure and the development of hyaline membrane disease. PEDIATRICS, **47**:650, 1971.
8. Beitins, I. Z., Kowarski, A., Shermeta, D. W.,

DeLemos, R. A., and Migeon, C. J.: Fetal and maternal secretion rate of cortisol in sheep: Diffusion resistance of the placenta. Pediat. Res., 4:129, 1970.

9. Simmer, H. H., Dignam, W. J., Easterling, W. E., Frankland. M. V., and Naftolin, F.: Neutral C-19 steroids and steroid sulfates in human pregnancy. Steroids, 8:179, 1966.
10. Brown, J. B., Beischer, N. A., and Smith, M. A.: Excretion of urinary oestrogens in pregnant patients treated with cortisone and its analogues. J. Obstet. Gynaec. Brit. Comm. 75:819, 1968.
11. Gluck, L., Kulovich, M. V., Borer, R. C., Brenner, P. H., Anderson, G. G., and Spellacy, W. N.: Diagnosis of the respiratory distress syndrome by amniocentesis. Amer. J. Obstet. Gynec., 109:440, 1971.
12. Murphy, B. E. P.: Some studies of the protein-binding of steroids and their application to the routine micro and ultra-micro measurement of various steroids in body fluids by competitive protein-binding radioassay. J. Clin. Endocr., 27:973, 1967.
13. Silverman, W. A., and Andersen, D. H.: A controlled clinical trial of effects of water mist on obstructive respiratory signs, death rate and necropsy findings among premature infants. PEDIATRICS, 17:1, 1956.
14. Platzker, A., Clements, J., and Tooley, W.: Surfactant development in the human fetal lung. Clin. Res., 19:232, 1971.
15. Chu, J., Clements, J. A., Cotton, E. K., Klaus, M. H., Sweet, A. Y., and Tooley, W. H.: Neonatal pulmonary ischemia: 1. Clinical and physiological studies. PEDIATRICS, 40: 709, 1967.
16. James, L. S.: Physiology of respiration in newborn infants and in the respiratory distress syndrome. PEDIATRICS, 24:1069, 1959.
17. Hey, E., and Hull. D.: Lung function at birth in babies developing respiratory distress. J. Obstet. Gynaec. Brit. Comm. 78: 137, 1971.
18. Haddad, H. M., Hsia, D. Y., and Gellis, S. S.: Studies on respiratory rate in the newborn. Its use in the evaluation of respiratory distress in infants of diabetic mothers. PEDIATRICS, 17:204, 1956.
19. Liggins, G. C., Grieves, S. A., Kendall, J. Z., and Knox, B. S.: The physiological roles of progesterone, oestradiol-17β and prostaglandin $F_2\alpha$ in the control of ovine parturition. J. Reprod. Fertil., suppl. 16, p. 85, 1972.
20. Van Rensberg, S. J.: Gestation in sheep after fetal adrenalectomy and cortisol acetate administration. J. Endocr., 38:83, 1967.
21. Halliday, R., and Buttle, H. R. L.: The effects of cortisone acetate on the length of the gestation period and the survival of fetal Scottish Blackface lambs. J. Endocr., 41:447, 1968.
22. Warrell, D. W., and Taylor, R.: Outcome for the fetus of mothers receiving prednisolone during pregnancy. Lancet, 1:117, 1968.
23. Margulis, R. R., and Hodgkinson, C. P.: Evaluation of the safety of corticotropin (ACTH) and cortisone in pregnancy. Obstet. Gynec., 1:276, 1953.
24. Yackel, D. B., Kempers, R. D., and McConahey, W. M.: Adrenocorticosteroid therapy in pregnancy. Amer. J. Obstet. Gynec., 96:985, 1966.
25. Walsh, S. D., and Clark, F. R.: Pregnancy in patients on long-term corticosteroid therapy. Scot. Med. J., 12:302, 1967.
26. Mercier-Parot, J.: Influence de la cortisone et de l'hormone corticotrope sur la gestation et le développement post-natal du rat. Biologie Méd., 46:672, 1957.
27. Editorial: Corticosteroid therapy and growth. Brit. Med. J., 1:393, 1969.
28. Fuchs, F., Fuchs, A.-R., Poblete, V. F., and Risk, A.: Effect of alcohol on threatened premature labor. Amer. J. Obstet. Gynec., 99:627, 1967.
29. Kennedy, M. C. S., and Simpson, W. T.: Human pharmacological and clinical studies on salbutamol: A specific beta-adrenergic bronchodilator. Brit. J. Dis. Chest., 63:165, 1969.
30. Liggins, G. C., and Vaughan, G. S.: Intravenous infusion of salbutamol in the management of premature labor J. Obstet. Gynaec. Brit. Comm., in press.

Acknowledgment

Thanks are due to Mr. R. G. Laurie who prepared and numbered the drug ampules and to those who assisted in the day-to-day running of the trial: the staff of the Delivery Suite, particularly Sister J. Hare, obstetric and pediatric medical staff, and Sisters A. de Zoete and S. Coenraadts; to Dr. J. H. Stewart, who reviewed the chest radiographs; and to Dr. D. M. O. Becroft, who reviewed the necropsy findings in the infants who died.

The study was supported in part by a grant from the Medical Research Council of New Zealand.

The betamethasone and placebo preparations used in the trial were supplied by Glaxo Laboratories (N.Z.) Ltd., through the courtesy of Dr. Lewis Bieder.

A CONTROLLED TRIAL OF ANTEPARTUM GLUCOCORTICOID TREATMENT FOR PREVENTION OF THE RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS

G. C. Liggins and R. N. Howie

Pediatrics 1972;50;515

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

A CONTROLLED TRIAL OF ANTEPARTUM GLUCOCORTICOID TREATMENT FOR PREVENTION OF THE RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS

G. C. Liggins and R. N. Howie

Pediatrics 1972;50;515