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The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials

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Summary. Continuing differences of opinion among obstetricians and neonatologists about the place of corticosteroid administration before preterm delivery have prompted us to carry out a systematic review of the relevant controlled trials, using methods designed to minimize systematic and random error. Data from 12 controlled trials, involving over 3000 participants, show that corticosteroids reduce the occurrence of respiratory distress syndrome overall and in all the subgroups of trial participants that we examined. This reduction in respiratory morbidity was associated with reductions in the risk of intraventricular haemorrhage, necrotizing enterocolitis and neonatal death. There is no strong evidence suggesting adverse effects of corticosteroids. The risks of fetal and neonatal infection may be raised if they are administered after prolonged rupture of the membranes, but this possibility is not substantiated by the results of the available trials. The available data on long-term follow-up suggest that the short-term beneficial effects of corticosteroids may be reflected in reduced neurological morbidity in the longer term.

In the course of investigating the initiation of labour in sheep, Liggins (1969) observed that lambs born preterm after exposure to corticosteroids *in utero* survived longer than control lambs. A subsequent randomized, placebo-controlled trial of betamethasone administration in women who were expected to be give birth preterm found a statistically significant reduction in the frequency of respiratory distress in babies born before 32 weeks gestation and a fivefold reduction in neonatal mortality among preterm babies born after corticosteroid compared with placebo administration (Liggins & Howie 1972).

Since these classic studies, several further investigations have suggested that antenatal administration of corticosteroids reduces neonatal morbidity. However, 18 years after the trial described by Liggins & Howie (1972) there continues to be variation in obstetricians' use of antenatal corticosteroids in women who are expected to give birth preterm. A survey of practice among fellows and members of the Royal College of Obstetricians and Gynaecologists resident in the UK showed that 42% used this

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treatment 'frequently', 40% 'sometimes', and 18% 'never' (Lewis *et al.* 1980). In a similar study of obstetricians in northern Belgium and the Netherlands, Keirse (1984) also found a wide variation in practice, with only 32·5% of respondents using the treatment 'routinely'.

These variations in practice among obstetricians reflect differing interpretations of the evidence of efficacy and safety of antenatal corticosteroid therapy. Differences of opinion also exist among neonatologists. Roberton (1982) for example suggested that corticosteroids only benefit white, male infants, and that, even for them, the benefit is mainly among those born between 30 and 32 weeks gestation. Avery (1984) by contrast has condemned the obstetric community's failure to accept antenatal corticosteroid administration as 'an essential intervention to prevent respiratory distress syndrome'.

These differences of opinion may, in part, result from overemphasis on the results of a single trial, or a secondary analysis within a particular trial. Because the sample sizes of individual trials are relatively small, estimates of the effects of corticosteroids are likely to vary widely as a result of the play of chance (random error). Investigators may sometimes have concluded that differences between corticosteroids and placebo did not exist because the differences were not statistically significant in these trials and subgroup analyses.

In an attempt to clarify the extent to which these phenomena have led to conflicting opinions, which obviously exist among clinicians, we have incorporated data derived from as high a proportion as possible of all relevant placebo-controlled, randomized trials in a single analysis. In this way, we have attempted to minimize not only systematic error (bias), but also random error (the play of chance).

Materials and methods

Identification and selection of relevant studies

We attempted to locate all published reports of controlled trials of corticosteroid use in threatened or planned preterm delivery using the Oxford Database of Perinatal Trials (Chalmers 1988). (Details of the database and the completeness of its coverage of perinatal trials are available elsewhere: Dickersin *et al.* 1985; Chalmers *et al.* 1986, 1989.) In an attempt to locate unpublished trials, letters were sent to 42 000 obstetricians and paediatricians in 18 countries (Hetherington *et al.* 1989).

Using these two approaches, we identified a total of 23 potentially relevant trials. On closer analysis, four of these proved not to be randomized controlled trials (Baillie *et al.* 1976; Dluholucky *et al.* 1976; Kleinschmidt *et al.* 1977; Szabo *et al.* 1977), and one had amalgamated randomized with non-randomized cases (Simpson & Harbert 1985); so these five trials were excluded. Three trials (Farrell *et al.* 1983; Gunston & Davey 1978; Whitt *et al.* 1976) assessed the effects of antenatal corticosteroid administration only in terms of the results of laboratory tests (e.g. lecithin: sphyngomyelin ratios); these were also excluded from our analysis, since clinical data were not available.

In three of the remaining 15 trials, allocation had not been simply to either corticosteroid administration or no administration of corticosteroids, but to a larger 'package of care' of which corticosteroid administration was but one component (Garite *et al.* 1981; Iams *et al.* 1985; Nelson *et al.* 1985); these trials were excluded from the main analysis. All three of the trials in this last category involved women with prelabour rupture of the membranes (PROM) preterm who were not in labour at the time of admission to the study. Data from these trials have therefore been included in a secondary analysis, restricted to women with PROM.

Data presented in multiple reports of the same trial have been amalgamated (*the New Zealand trial:* Liggins & Howie 1972, 1973, 1974; Howie & Liggins 1973, 1977, 1980, 1982; Liggins 1976; *the (US) Collaborative Group on Antenatal Steroid Therapy* 1981, 1984; Bauer *et al.* 1984; Burkett *et al.* 1986; Schneider *et al.* 1988; and *the Amsterdam trial:* Schutte *et al.* 1979, 1980, 1983). Because failure to report the outcome of all cases randomized and selective reporting of data on relevant outcomes may lead to biased estimates of treatment effects, we contacted investigators in an effort to obtain missing data. We are indebted to the investigators who helped us in this way (see Acknowledgments).

A total of 12 trials, involving over 3000 women, was thus available for the main analysis. Table 1 lists the entry and exclusion criteria, treatment and diagnostic regimens and completeness of reporting for these 12 trials. Four of the 12 trials (Block *et al.* 1977; Collaborative Group on Antenatal Steroid Therapy 1981; Schmidt *et al.* 1984; Morales *et al.* 1986) pro-

Table 1. Characteristics of the randomized controlled trials of corticosteroid administration

Authors and date	Entry criteria	Exclusion criteria	Treatment regimen	No. reported: no. randomized
Liggins & Howie (1972); Howie & Liggins (1977)	Threatened or planned preterm delivery 25–37 weeks	Imminent delivery; 'clinical decision not to randomize'	Betamethasone 12 mg i.m. in 2 doses 24 h apart	1070:1135 (65 with lethal malformations)
Block *et al.* (1977)	Women judged to be in preterm labour	Not stated	Betamethasone 12 mg i.m. in 2 doses 24 h apart	155:175
Morrison *et al.* (1978)	Threatened or planned preterm delivery if <34 weeks or immature L/S ratio	Imminent delivery; mature L/S ratio; medical contraindication to corticosteroids	Hydrocortisone 500 mg i.v. in 4 daily doses at 12-h intervals	126–196
Papageorgiou *et al.* (1979)	Preterm labour or PROM at 26–33 weeks	Diabetes; hypertension; pre-eclampsia; rhesus disease; retarded fetal growth	Betamethasone 12 mg i.m. in 2 doses 12 h apart	131:146
Schutte *et al.* (1979)	Preterm labour 27–31 weeks 'if it seemed possible to postpone labour for 12 h'	Diabetes; severe hypertension; retarded fetal growth; hyperthyroidism; cardiac disease; fetal distress; infection	Betamethasone phosphate 8 mg + betamethasone acetate 6 mg in 2 doses i.m. 24 h apart	122:122
Taeusch *et al.* (1979)	Preterm labour or PROM either <34 weeks with immature L/S ratio or with previous infant with RDS	Cervix 5 cm dilated; severe bleeding; chorioamnionitis; severe pre-eclampsia; pre-existing glucocorticoid therapy	Dexamethasone 4 mg i.m. in 6 doses at 8-h intervals	127:127
Doran *et al.* (1980)	Preterm labour or PROM, or planned preterm delivery at 25–33 weeks	Pre-eclampsia; medical contraindication to corticosteroid therapy	Betamethasone 6 mg i.m. in 4 doses at 12-h intervals	144:144
Teramo *et al.* (1980)	Preterm labour at 29–35 weeks, cervix <4 cm dilated, no precipitous progression after 12 h observation	Diabetes; pre-eclampsia	Betamethasone 12 mg i.m. in 2 doses 24 h apart	80:80

PROM, Prelabour rupture of the membranes.

Table 1 (continued). Characteristics of the randomized controlled trials of corticosteroid administration

Authors and date	Entry criteria	Exclusion criteria	Treatment regimen	No. reported: no. randomized
Collaborative Group on Antenatal Steroid Therapy (1981)	Women with 'high risk for premature delivery' at 27–33 weeks; with 'high risk' >34 weeks and L/S ratio ≤2·0	Cervix 5 cm dilated; delivery anticipated in <24 h or >7 days; intrauterine infection; previous corticosteroid therapy in pregnancy; medical contraindication to corticosteroid therapy; infant unavailable for follow-up	Dexamethasone 5 mg i.m. in 4 doses	739:757
Schmidt *et al.* (1984)	Preterm labour or PROM at 25–33 weeks or with estimated fetal weight 750 g	Cervix 5 cm dilated; medical contraindication to corticosteroid therapy; 'deemed unsafe to delay delivery for 24 h'	Betamethasone 12 mg in 2 doses 24 h apart; methylprednisolone 125 mg in 2 doses 24 h apart; hydrocortisone 250 mg in 2 doses 24 h apart	97:149
Morales *et al.* (1986)	Women with PROM	Labour on admission; foul-smelling amniotic fluid; retarded fetal growth; phosphatidyl glycerol present	Dexamethasone 6 mg i.m. in 4 doses at 12-h intervals	245:250
Gamsu *et al.* (1989)	Spontaneous labour or elective induction at <34 weeks	Diabetes; chorioamnionitis; contraindication to corticosteroid therapy; when delay of delivery for 24 h was not in the maternal or fetal interest	Betamethasone 4 mg i.m. in 6 doses at 8-h intervals over 48 h	251:251 (268 babies)

PROM, Prelabour rupture of the membranes.

Table 2. Characteristics of the randomized controlled trials of corticosteroid administration combined with other treatment options for women with prelabour rupture of the membranes (PROM)

Study	Entry and exclusion criteria No. treated and controls	Corticosteroid group	Control group
Garite *et al.* (1981)	Entry: 28–34 weeks Excluded: chorioamnionitis; advanced labour; fetal distress; mature L/S or positive Gram stain on amniocentesis No. treated: 80 No. control: 80	Betamethasone 12 mg in 2 doses 24 h apart + tocolytic treatment (ethanol or magnesium sulphate) for 48 h; delivery effected after 48 h by discontinuing tocolytic treatment, inducing labour, or caesarean section	'Expectant management'; delivery was performed only when either labour, chorioamnionitis or fetal distress occurred
Iams *et al.* (1985)	Entry: 28–34 weeks; singleton pregnancy; not in labour and not infected Excluded: mature amniotic fluid L/S ratio or phosphatidyl glycerol determination No. treated: 38 No. control: 35	Hydrocortisone 500 mg i.v. in 4 doses at 8-h interval; tocolytics if necessary to delay delivery until 12 h after corticosteroid treatment; delivery effected at 48–72 h by discontinuing tocolysis, induction of labour or caesarean section	No corticosteroids; no tocolysis; delivery only when labour, amnionitis or fetal distress developed
Nelson *et al.* (1985)	Entry: 28–34 weeks; not in labour and not infected Excluded: cervix >3 cm; fetal distress; sensitivity to tocolytics; membranes ruptured for >24 h No. treated: 22 No. control: 22* + 24	Betamethasone 6 or 12 mg in 2 doses 12 hours apart + ritodrine or terbutaline for 24 h; delivery effected after full 24 h corticosteroid treatment	Non-steroid group treated identically (including delivery)* Second control group without steroid and tocolytic treatment followed expectantly

* Only this control group was used for the data shown in Tables 9 and 10.

vided separate data on women with PROM. These data have been incorporated in the secondary analysis of this subgroup of women, along with data from the three additional trials referred to above (Table 2).

Methodological quality of the published studies

In addition to the requests for missing data, authors were asked, where necessary, to provide information on their study methods. This enabled us to assess the methodological quality of each study in terms of control of bias at entry, control of selection bias after entry, and control of observer bias in assessing outcomes. The criteria we used to assess the likely influence of these three sources of bias have been described elsewhere (Prendiville *et al.* 1988; Chalmers *et al.* 1989). The trials included in this overview are generally of high methodological quality; but in each array of trial results presented below, studies have been ranked according to our assessment of the likelihood that the comparisons may have been biased. Trials of equivalent quality were ranked by date of publication.

Statistical methods

The results of each trial have been presented using the odds ratio together with its 95% confidence interval (CI). The odds ratio is the ratio of the odds of a negative outcome (for example, respiratory distress) *versus* a positive outcome (no respiratory distress) among those allocated to corticosteroids, to the odds of the negative outcome *versus* the positive outcome among the controls. Because random variation may lead the odds ratio in individual trials to be overestimated or underestimated, we used methods described by Peto and his colleagues (Peto *et al.* 1976; Collins *et al.* 1985; Yusuf *et al.* 1985) to analyse data within the framework of an overview (meta-analysis) of information derived from each of the relevant trials identified (Chalmers *et al.* 1989). The effect of corticosteroids in each trial is measured by $O-E$, where O is the observed number of individuals suffering the outcome in question among those allocated corticosteroids, and E is the number that would have been expected on the basis of the experience of the corticosteroid and placebo groups combined. The sum of the differences derived from each individual trial [$\Sigma\,(O-E)$], combined with the sum of the variances of these differences [Σ Var $(O-E)$], have been used to provide an estimate of a 'typical odds ratio':

$$\text{Exp}\,(\Sigma\,(O-E)/[\Sigma\ \text{Var}\,(O-E)]).$$

This statistic is an expression of any tendency that may exist for those receiving steroids to do better or worse than those who received placebo. Its 95% CI is calculated as follows:

$$\text{Exp}\,[\Sigma\,(O-E)/\Sigma\ \text{Var}\,(O-E)] + 1{\cdot}96/\Sigma\ \text{Var}\,(O-E)$$

Results

Neonatal respiratory distress

The occurrence of neonatal respiratory distress is the principal outcome reported in the 12 eligible trials identified. The data presented in Table 3 show that antenatal corticosteroid administration is associated with an overall reduction of about 50% in the odds of this form of neonatal morbidity (typical odds ratio 0·49, 95% CI 0·41–0·60).

In a secondary analysis stratified by time interval between trial entry and delivery, the point estimate of a 70% reduction in the odds of developing respiratory distress (typical odds ratio 0·31, 95% CI 0·23–0·42) among babies born between 24 h and 7 days after corticosteroid administration suggests that the protective effect is more marked in these circumstances, and this is biologically plausible. Nevertheless, babies born outside this time interval also benefit, albeit to a lesser extent (typical odds ratio 0·69, 95% CI 0·50–0·94) (Fig. 1).

There is no evidence to support the view that the effect on the incidence of respiratory distress is confined to babies born within a particular gestational age range. Most of the babies randomized in these trials were born between 30 and 34 weeks gestation; the overall results thus tend to reflect the experiences of these babies in particular. Nevertheless, analyses based on data derived from the seven trials from which data are available show that corticosteroid administration is followed by an unambiguous and important reduction in the risk of respiratory morbidity among babies born at less than 31 weeks gestation (typical odds ratio 0·38, 95% CI 0·24–0·60) (Table 4). Respiratory distress is such a rare condition among babies born after 34 weeks gestation that the available data yielded only 29 affected babies from eight trials. The

Table 3. Effect of corticosteroids before preterm delivery on respiratory distress, overall

Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical
Liggins & Howie (1972)	49/532	(9·21)	84/538	(15·61)	0·56 (0·39–0·80)
Block *et al.* (1977)	5/69	(7·25)	12/61	(19·67)	0·34 (0·12–0·94)
Schutte *et al.* (1979)	11/64	(17·19)	17/58	(29·31)	0·51 (0·22–1·18)
Taeusch *et al.* (1979)	7/56	(12·50)	14/71	(19·72)	0·60 (0·23–1·52)
Doran *et al.* (1980)	4/81	(4·94)	10/63	(15·87)	0·29 (0·10–0·88)
Teramo *et al.* (1980)	3/38	(7·89)	3/42	(7·14)	1·11 (0·21–5·83)
Gamsu *et al.* (1989)	7/131	(5·34)	16/137	(11·68)	0·45 (0·19–1·05)
Collaborative Group (1981)	42/371	(11·32)	59/372	(15·86)	0·68 (0·45–1·03)
Morales *et al.* (1986)	30/121	(24·79)	63/124	(50·81)	0·33 (0·20–0·56)
Papageorgiou *et al.* (1979)	7/71	(9·86)	23/75	(30·67)	0·28 (0·13–0·63)
Morrison *et al.* (1978)	6/67	(8·96)	14/59	(23·73)	0·33 (0·13–0·87)
Schmidt *et al.* (1984)	9/34	(26·47)	10/31	(32·26)	0·76 (0·26–2·20)
Typical odds ratio					0·49 (0·41–0·60)

Odds ratios and 95% CI: Graphical (0·1, 0·5, 1, 2, 10)

typical odds ratio of 0·62 and its 95% CI (0·29–1·30) is, however, consistent with those derived from other subgroups, although (because it includes 1·0) it is also compatible with chance variation.

There is no evidence from the few available data that infant gender influences the protective effect of corticosteroids on the risk of neonatal respiratory distress described above. The typical odds ratio for males is 0·43 (95% CI 0·29–0·64); for females it is 0·36 (95% CI 0·23–0·57) (Fig. 1).

The separate analysis of corticosteroid administration after PROM (see below) indicates a reduction in neonatal respiratory morbidity of a similar order to that described for other subgroups.

In summary, we have not been able to identify any subgroup of babies for which it can be con-

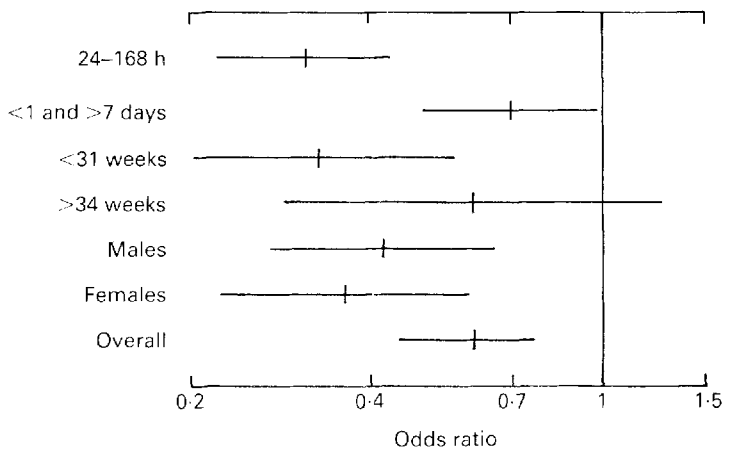


Fig. 1. Effects of corticosteroid administration before preterm delivery on the occurrence of neonatal respiratory distress, by interval between corticosteroid administration and delivery, gestational age at delivery, and infant gender (typical odds ratio and 95% confidence interval).

Table 4. Effect of corticosteroids before preterm delivery on respiratory distress in babies <31 weeks gestation

Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical	Graphical (0·01 0·1 0·5 1 2 10)
Liggins & Howie (1972)	10/36	(27·78)	15/26	(57·69)	0·29 (0·11–0·82)	
Taeusch *et al.* (1979)	1/3	(33·33)	4/6	(66·67)	0·30 (0·02–4·18)	
Gamsu *et al.* (1989)	4/29	(13·79)	7/39	(17·95)	0·74 (0·20–2·70)	
Collaborative Group (1981)	6/10	(60·00)	7/16	(43·75)	1·87 (0·40–8·80)	
Morales *et al.* (1986)	17/53	(32·08)	32/52	(61·54)	0·31 (0·14–0·66)	
Papageorgiou *et al.* (1979)	2/5	(40·00)	11/12	(91·67)	0·07 (0·01–0·73)	
Morrison *et al.* (1978)	6/36	(16·67)	11/28	(39·29)	0·32 (0·11–0·97)	
Typical odds ratio					0·38 (0·24–0·60)	

cluded that corticosteroid administration before preterm delivery is *not* associated with a reduction in the risk of neonatal respiratory morbidity (Fig. 1).

Other forms of neonatal morbidity

In addition to promoting functional maturation of the fetal lungs, corticosteroids may have similar 'primary' effects on other organs. Furthermore, because corticosteroids reduce the risk of respiratory morbidity, they might be expected to have 'secondary' effects by reducing those complications of respiratory morbidity and its treatment which involve other organ systems. The data available for examining this possibility are limited, but they suggest that the odds of both periventricular haemorrhage and necrotizing enterocolitis are reduced by anything between 10 and 80% after corticosteroid administration (Fig. 2). The reduction in serious neonatal morbidity is likely to explain the statistically significantly shorter mean durations of hospital stay among cortiscosteroid-treated infants in the two trials for which these data were reported (Collaborative Group on Antenatal Steroid Therapy 1981; Morales *et al.* 1986).

Early neonatal mortality and morbidity in later infancy

These significant reductions in serious forms of neonatal morbidity are reflected in a substantial reduction in the risk of early neonatal mortality (typical odds ratio 0·59, 95% CI 0·47–0·75) (Table 5).

It is important to assess whether this reduction in the risk of death was achieved at the cost of an increased prevalence of morbidity among survivors. Because of the reduced neonatal mortality rate in corticosteroid-treated babies, survivors in the corticosteroid arms of these trials had a lower mean gestational age at delivery than survivors in the control groups. In the light of this difference, one might expect survivors in the corticosteroid groups to be more likely to have impaired function than survivors in the control groups.

Three follow-up studies have been published (Butterfill & Harvey 1979; MacArthur *et al.* 1981, 1982, 1989; Collaborative Group on Antenatal Steroid Therapy, 1984). Unfortunately, the study reported by Butterfill & Harvey (1979) amalgamated non-randomized with randomized cohorts, and it is not now possible to disaggregate the data to allow unbiased comparisons to be made between the steroid-treated and the control groups (Harvey, personal communication). Data from the two studies that followed up surviving members of randomized cohorts are reassuring. If anything, they suggest that neurological abnormalities are less frequent among babies whose mothers received corticosteroids than among controls (typical odds ratio 0·61, 95% CI 0·34–1·08) (Table 6).

Possible fetal, neonatal and maternal risks

The randomized trials analysed here do not provide any evidence that fetal exposure to corticosteroids is accompanied by any increased risk of fetal death: stillbirth occurred with almost identical frequency in the two groups (odds ratio 1·03, 95% CI 0·68–1·54). In the subgroup of participants who had pre-eclampsia in the Auckland trial (Howie & Liggins 1977), there were 12 fetal

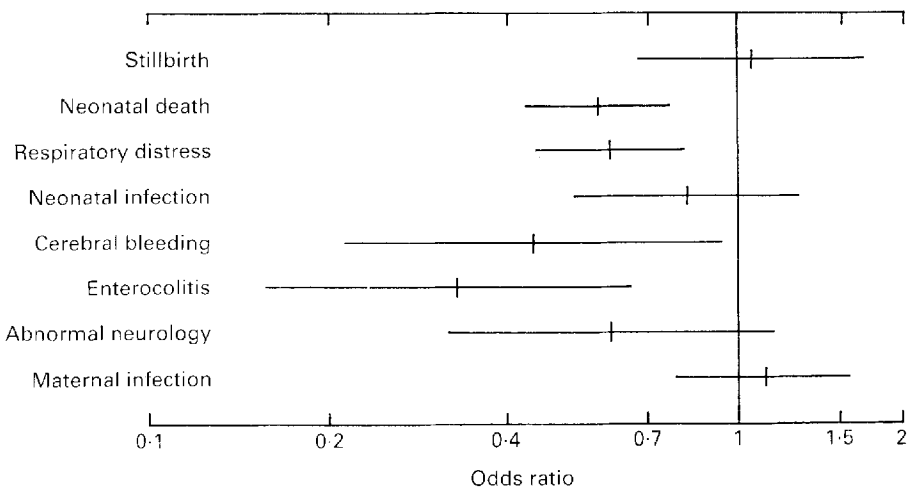


Fig. 2. Effects of corticosteroid administration before preterm delivery (typical odds ratio and 95% confidence interval).

deaths in participants who had received corticosteroids, and none among controls. All these 12 deaths were associated with proteinuria of >2 g/24 h for more than 14 days, a severity of disease that was not found in any of the placebo-treated women. The investigators recognized that this unpredicted difference may have arisen by chance, and recommended that the hypothesis it had generated should be tested in further research. Although similar numbers of hypertensive women have participated in later trials (Morrison *et al.* 1978; Collaborative Group on Antenatal Steroid Therapy 1981; Gamsu *et al.* 1989), there have been no further fetal deaths among their babies, so the hypothesis remains unsubstantiated.

The point estimate of the typical odds ratio for maternal infection is just above 1, that for fetal or neonatal infection just below 1 (Tables 7 and 8), but the 95% CI of both point estimates are quite wide. A further analysis, restricted to women with prolonged rupture of the mem-

Table 5. Effect of corticosteroids before preterm delivery on early neonatal deaths

Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical	Odds ratios and 95% CI: Graphical (0·1 0·5 1 2 10)
Liggins & Howie (1972)	36/532	(6·77)	60/538	(11·15)	0·58 (0·38–0·89)	
Block *et al.* (1977)	1/69	(1·45)	5/61	(8·20)	0·22 (0·04–1·12)	
Schutte *et al.* (1979)	3/64	(4·69)	12/58	(20·69)	0·23 (0·08–0·67)	
Taeusch *et al.* (1979)	5/56	(8·93)	7/71	(9·86)	0·90 (0·27–2·96)	
Doran *et al.* (1980)	2/81	(2·47)	10/63	(15·87)	0·18 (0·05–0·57)	
Teramo *et al.* (1980)	0/38	(0·00)	0/42	(0·00)	1·00 (1·00–1·00)	
Gamsu *et al.* (1989)	14/131	(10·69)	20/137	(14·60)	0·70 (0·34–1·44)	
Collaborative Group (1981)	36/371	(9·70)	37/372	(9·95)	0·97 (0·60–1·58)	
Morales *et al.* (1986)	7/121	(5·79)	13/124	(10·48)	0·54 (0·22–1·33)	
Papageorgiou *et al.* (1979)	1/71	(1·41)	5/75	(6·67)	0·27 (0·05–1·36)	
Morrison *et al.* (1978)	2/67	(2·99)	7/59	(11·86)	0·26 (0·07–1·03)	
Schmidt *et al.* (1984)	5/34	(14·71)	5/31	(16·13)	0·90 (0·24–3·42)	
Typical odds ratio					0·59 (0·47–0·75)	

Table 6. Effect of corticosteroids before preterm delivery on neurological abnormality at follow-up

Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical	Graphical (0·1 0·5 1 2)
MacArthur *et al.* (1982)	12/139	(8·63)	15/111	(13·51)	0·60 (0·27–1·35)	
Collaborative Group (1984)	9/200	(4·50)	15/206	(7·28)	0·61 (0·27–1·38)	
Typical odds ratio					0·61 (0·34–1·08)	

branes in these 12 trials, suggests that the risk of infection may be increased or may be decreased by steroids in these circumstances, since, once again, the confidence interval is wide (typical odds ratio 1·26, 95% CI 0·66–2·40).

Secondary analysis on women with prelabour rupture of the membranes

Separate data referring to women with prelabour rupture of the membranes are available from seven trials (four from the main analysis and the three others listed in Table 2). These show that corticosteroid administration also reduces the risk of respiratory distress syndrome in these circumstances. The point estimate of a 45% reduction in the odds (typical odds ratio 0·55, 95% CI 0·40–0·75 Table 9) indicates an effect of similar magnitude to that observed among infants of all corticosteroid-treated mothers (Table 3).

The incidence of neonatal infection, albeit available for only five of these trials, was not statistically significantly higher in the corticosteroid-treated group than in the control group, but the available data (typical odds ratio 1·61, 95% CI 0·87–2·98) suggest that corticosteroid administration is more likely to increase than to decrease the occurrence of neonatal infection (Table 10).

Discussion

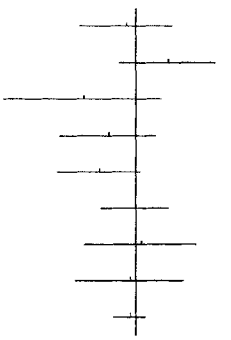
This overview of randomized trials of antenatal corticosteroid administration (24 mg betamethasone, 24 mg dexamethasone, or 2 g hydrocortisone) has shown that corticosteroid administration leads to statistically and clinically significant reductions in neonatal morbidity and mortality, and that these are very unlikely to be outweighed by unwanted effects of these drugs (Fig. 2). Overall, the reduction in the odds of neonatal respiratory morbidity is of the order of 40–60%. Further, the beneficial effects of antenatal corticosteroids appear to apply to babies born at all gestational ages at which respiratory distress syndrome may occur, and regardless of whether or not there has been prelabour rupture of the membranes. Although babies born >24 h and <7 days after beginning steroid administration may well benefit most from prophylaxis, the evidence suggests that babies born outside

Table 7. Effect of corticosteroids before preterm delivery on maternal infection

Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical	Graphical (0·1 0·5 1 2 10)
Liggins & Howie (1972)	5/108	(4·63)	6/91	(6·59)	0·69 (0·20–2·32)	
Taeusch *et al.* (1979)	14/56	(25·00)	8/71	(11·27)	2·59 (1·03–6·51)	
Gamsu *et al.* (1989)	6/126	(4·76)	6/125	(4·80)	0·99 (0·31–3·16)	
Collaborative Group (1981)	27/349	(7·74)	29/347	(8·36)	0·92 (0·53–1·59)	
Morales *et al.* (1986)	16/121	(13·22)	18/124	(14·52)	0·90 (0·44–1·85)	
Papageorgiou *et al.* (1979)	9/71	(12·68)	9/75	(12·00)	1·06 (0·40–2·85)	
Morrison *et al.* (1978)	4/67	(5·97)	2/59	(3·39)	1·76 (0·34–9·03)	
Schmidt *et al.* (1984)	13/32	(40·63)	9/29	(31·03)	1·51 (0·53–4.25)	
Typical odds ratio					1·11 (0·81–1·51)	

Table 8. Effect of corticosteroids before preterm delivery on fetal or neonatal infection

Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical
Howie & Liggins (1977)	5/532	(0·94)	6/538	(1·12)	0·84 (0·26–2·76)
Taeusch *et al.* (1979)	7/56	(12·50)	4/71	(5·63)	2·37 (0·68–8·18)
Doran *et al.* (1980)	1/81	(1·23)	3/63	(4·76)	0·27 (0·04–2·01)
Gamsu *et al.* (1989)	4/126	(3·17)	7/125	(5·60)	0·56 (0·17–1·88)
Collaborative Group (1981)	4/371	(1·08)	10/372	(2·69)	0·42 (0·15–1·21)
Morales *et al.* (1986)	11/121	(9·09)	11/124	(8·87)	1·03 (0·43–2·46)
Papageorgiou *et al.* (1979)	4/71	(5·63)	4/75	(5·33)	1·06 (0·26–4·39)
Schmidt *et al.* (1984)	5/34	(14·71)	5/31	(16·13)	0·90 (0·24–3·42)
Typical odds ratio					0·83 (0·54–1·26)



this optimum period can also benefit. There is no evidence to support the view that the gender of the baby modifies these effects. Indeed, we have been unable to identify any subgroup of babies at risk of respiratory morbidity for which there are data to justify a conclusion that corticosteroids have no beneficial effects.

The clear-cut reduction in the risk of respiratory distress is, as far as we can judge from the admittedly limited data available, accompanied by reductions in periventricular haemorrhage and necrotizing enterocolitis. All of this results in a reduced early neonatal mortality rate, and reductions in the duration, and thus the costs, of hospital neonatal care.

The significant reduction in the duration of neonatal hospitalization has obvious social and economic implications. Avery (1984) has estimated that appropriate use of antenatal corticosteroids could save 35 million dollars per year in intensive care costs in the United States. Morales *et al.* (1986) reported an average saving of $17 300 per woman treated.

A number of possible short-term and long-term risks of antenatal corticosteroid administration have been considered (Taeusch 1975). The immunosuppressive effects of corticosteroids could result in an increased susceptibility to fetal, neonatal or maternal infection, or to a delay in its recognition. Over the 11 years following the introduction of corticosteroids for fetal lung maturation in England and Wales, there were two maternal deaths from septicaemia associated with their use (Department of Health and Social Security 1979, 1982, 1986, 1989). It is these two deaths that underlie the opposition of some British obstetricians to the use of corticosteroids for fetal lung maturation.

In the presence of intact membranes, there is no clear evidence of an increase in the risk of

Table 9. Effect of corticosteroids after prelabour rupture of the membranes on respiratory distress

Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical
Block *et al.* (1977)	3/25	(12·00)	5/26	(19·23)	0·59 (0·13–2·61)
Morales *et al.* (1986)	30/121	(24·79)	63/124	(50·81)	0·33 (0·20–0·56)
Collaborative Group (1981)	15/153	(9·80)	17/135	(12·59)	0·75 (0·36–1·57)
Nelson *et al.* (1985)	10/22	(45·45)	11/22	(50·00)	0·84 (0·26–2·70)
Schmidt *et al.* (1984)	7/24	(29·17)	6/17	(35·29)	0·76 (0·20–2·84)
Garite *et al.* (1981)	14/80	(17·50)	17/79	(21·52)	0·78 (0·35–1·70)
Iams *et al.* (1985)	10/38	(26·32)	12/35	(34·29)	0·69 (0·25–1·86)
Typical odds ratio					0·55 (0·40–0·75)

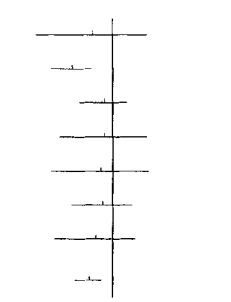
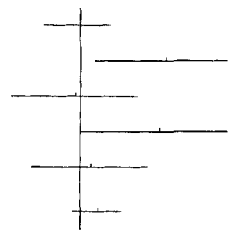


Table 10. Effect of corticosteroids after prelabour rupture of the membranes on neonatal infection

Study	Treated *n*	Treated (%)	Control *n*	Control (%)	Odds ratios and 95% CI: Numerical
Morales *et al.* (1986)	11/121	(9·09)	11/124	(8·87)	1·03 (0·43– 2·46)
Nelson *et al.* (1985)	5/22	(22·73)	0/22	(0·00)	9·07 (1·44–57·16)
Schmidt *et al.* (1984)	4/24	(16·67)	3/17	(17·65)	0.93 (0·18– 4·78)
Garite *et al.* (1981)	4/80	(5·00)	0/79	(0·00)	7·58 (1·05–54·87)
Iams *et al.* (1985)	4/38	(10·53)	3/35	(8·57)	1·25 (0·27– 5·88)
Typical odds ratio					1·61 (0·87– 2·98)



maternal, fetal or neonatal infection. In the presence of prolonged rupture of the membranes, the absolute risk of fetal and neonatal infection may be greater, but again, controlled trials provide no strong evidence that corticosteroids increase this risk. Follow-up data from the Dutch trial (Smolders-de Haas *et al.* 1990) suggest that there may be an increased occurrence of pharyngeal and ear infections in infancy among infants in the corticosteroid group during the first 2 years of life. Similar data from other follow-up studies are needed to establish whether or not this is a consistent finding.

Instances of pulmonary oedema have been reported in pregnant women receiving a combination of corticosteroids and tocolytic drugs (Stubblefield & Kitzmiller 1980). Here again, the trials provide little in the way of information to assess the extent to which corticosteroids, *per se*, may be responsible for this serious condition. In the trial reported by Morales *et al.* (1986), pulmonary oedema occurred in two women among 44 women treated with magnesium sulphate and corticosteroids. Pulmonary oedema was not reported by the authors of the other randomized trials, so the magnitude of this risk cannot be estimated with any confidence from these data.

There is no evidence that antenatal corticosteroid administration increases the overall risk of stillbirth. The higher risk of fetal death in pregnancies complicated by hypertension noted in one trial (Liggins & Howie 1972) may reflect chance. Alternatively, it may reflect undue delay in delivering women with severe proteinuric hypertension, an explanation that is supported by the fact that no such risk was recorded in the other trials that included hypertensive women. However, the possibility that corticosteroid administration may have a specific adverse effect on the evolution of pre-eclampsia cannot be excluded using the available data.

It is important to recognize that neonatal respiratory distress syndrome is common in infants of mothers with pre-eclampsia delivered preterm: for example, it affected 36% of babies of women with pregnancy-induced hypertension in the placebo arm of the Collaborative Group trial (Schneider *et al.* 1988). In the light of the available data, it would seem reasonable to use corticosteroids to reduce this considerable neonatal morbidity, provided the commitment to early delivery implied by corticosteroid treatment is carried through. Those obstetricians who remain uncertain that the demonstrable advantages of this policy would be outweighed by possible disadvantages in hypertensive women, or in other circumstances, should collaborate in further randomized trials to provide evidence on which to base their practice more firmly.

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