A META-ANALYSIS OF THE USE OF CORTICOSTEROIDS IN PREGNANCIES COMPLICATED BY PRETERM PREMATURE RUPTURE OF MEMBRANES

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A systematic review of the literature has been undertaken with regard to the use of corticosteroids in women with preterm premature rupture of membranes (PPROM). The benefit of corticosteroids clearly outweighs their potential harmful effects. Antibiotics should probably be included in any management protocol for women with PPROM. There is no reason to suggest that use of corticosteroids in women with PPROM needs to be restricted in developing countries.

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Considerable concern has been expressed regarding the use of corticosteroids to enhance fetal lung maturity in women with preterm premature rupture of membranes (PPROM) in South Africa.[1,2] A meta-analysis published as early as 1990[3] demonstrated a significant reduction in the prevalence of respiratory distress syndrome (RDS), with no concomitant increased infectious morbidity in mothers or neonates. However, the concern has persisted.[4] It is centred around the fact that the studies were performed in developed countries, and that in South Africa the conviction exists that infection plays a major role as a causative factor in PPROM.[5] Can the data from the meta-analysis, therefore, be safely extrapolated to the management of patients in South Africa?

The Dexiprom Study,[6] a multicentre, placebo-controlled, double-blind, randomised trial (this issue), was performed to address these issues. The study was conducted in six South African hospitals. This systematic review places the Dexiprom Study in context with world experience and makes recommendations regarding the use of corticosteroids in South Africa.

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METHOD

The literature was searched for other randomised trials where corticosteroids were given in the presence of PPROM. A Medline search was conducted and considerable use was made of the Cochrane Database of Trials. Where the references were only available in conference proceedings, the data quoted in *The Cochrane Library*[7] were used. Only randomised studies were included and none of these studies were excluded from the meta-analysis. Studies were not excluded because of the paucity of information where maternal or neonatal infectious complications were reported as outcome measures. The effect of using the weaker trials gives a bias against the use of corticosteroids. Where problems in the study structure exist they are pointed out in the tables.

THE EFFECT OF CORTICOSTEROIDS ON MATERNAL INFECTION IN WOMEN WITH PPROM

Very few studies have reported on the effect of corticosteroids on women with PPROM. There are two aspects to study, i.e. antenatal infection, most likely clinical chorio-amnionitis, and postpartum infection, namely endometritis. Each is poorly defined, and is essentially a clinical diagnosis. Chorio-amnionitis is really a histological diagnosis, but this was performed in only one study.[8] Protocols used varied, compounding the difficulties of analysis. Garite *et al.*[9] and Iams *et al.*[10] electively delivered the fetuses 48 hours after administration of corticosteroids. Only Morales *et al.*[8] and the Dexiprom Study[6] used antibiotics. The Dexiprom Study was the only study to use prophylactic antibiotics for all participants in the study. The meta-analysis is shown in Tables I and II. There is no clear evidence of increased maternal infections. In the studies where antibiotics were used in conjunction with corticosteroids[6,8] more women in the control group experienced infections.

No study reported that it was necessary to perform a hysterectomy for sepsis. Absence of evidence is not evidence of absence of occurrence. The risk of a patient developing a severe but rare complication is dependent on the sample size. It is possible to estimate the maximum risk (upper 95% confidence interval (CI) of a patient developing a rare complication that has not been reported in the literature.[11] This information gives the clinician an idea of the risk his patient has of developing the complication, despite its not being reported. For a woman with PPROM treated with corticosteroids the maximum risk (upper 95% CI) of developing severe sepsis is approximately 1%.[11]

Table I. The effect of using corticosteroids in women with PPROM on the clinical diagnosis of chorio-amnionitis

Study	Corticosteroid	Control	OR (95% CI)
Garite *et al.*, 1981[9]*	11/80	11/80	1 (0.37 - 2.68)
Morales *et al.*, 1986[20]	16/121	18/124	0.45 (0.17 - 1.16)
Morales *et al.*, 1989[8]‡	9/87	19/78	0.45 (0.17 - 1.16)
Carlan *et al.*, 1991[22]†	3/11	0/13	10.9 (1.01 -117.5)
Dexiprom, 1999[6]‡	11/102	8/102	1.44 (0.51 - 4.12)
Total	50/401	56/397	0.86 (0.53 - 1.38)

*Study has co-intervention of elective delivery.
† Abstract.
‡ Studies used antibiotics concomitantly, Morales *et al.*[8] for only a subset of patients.

Table II. The effect of using corticosteroids in women with PPROM on the diagnosis of endometritis

Study	Corticosteroids	Control	OR (95% CI)
Garite *et al.*, 1981[9]*	23/80	11/80	2.53 (1.07 - 6.09)
Schmidt *et al.*, 1984[12]	17/34	6/17	1.79 (0.56 - 5.70)
Iams *et al.*, 1985[10]*	9/38	2/35	5.12 (0.91 - 29.8)
Nelson *et al.*, 1985[15]*	1/22	4/22	0.21 (0.01 - 2.40)
Dexiprom, 1999[6]†	4/102	7/102	0.55 (0.13 - 2.19)
Total	54/276	33/256	1.66 (0.97 - 2.83)

* Study has co-intervention of elective delivery.
† Studies used antibiotics concomitantly.

THE EFFECT OF CORTICOSTEROIDS ON NEONATAL OUTCOME IN WOMEN WITH PPROM

The most studied effect has been that of RDS. This end-point, rather than that of hyaline membrane disease (HMD), has been used because of problems with regard to definitions and diagnoses. Ideally one would want to differentiate between HMD and congenital pneumonia. Theoretically, if corticosteroids increase the chances of neonatal infection, then one would expect the incidence of HMD to be decreased by corticosteroids, but that of congential pneumonia to be increased. Neonatologists have considerable difficulty in differentiating between the two. This was also the case in the Dexiprom Study.[6] Ultimately one is forced to use RDS as an end-point. Early studies found no difference in the prevalence of RDS between groups.[9,10,12-15] This was originally thought to be due to lung maturity being enhanced by the stress of rupture of membranes. It could equally have been due to an increase in congenital pneumonia. Coupled with lack of change in the prevalence of RDS, an increase in neonatal infection was observed.[9,15-17] Table III shows the meta-analysis in which the effect of corticosteroids on RDS is clearly demonstrated. Neonates born to the women who received corticosteroids have approximately 40% less chance of developing RDS than those whose mothers did not receive it.

The effects of corticosteroids are not restricted to the respiratory system but also benefit other organ systems. A trend towards a reduction in necrotising enterocolitis (NEC) and intraventricular haemorrhage (IVH) has been observed in

Table III. The effect of using corticosteroids in women with PPROM on respiratory distress syndrome in the neonate

Study	Corticosteroids	Control	OR (95% CI)
Block *et al.*, 1977[13]	3/25	5/26	0.58 (0.13 - 2.60)
US Trial, 1981[14]	15/153	17/135	0.75 (0.36 - 1.57)
Garite *et al.*, 1981[9]*	14/80	17/79	0.77 (0.35 - 1.69)
Schmidt *et al.*, 1984[12]	7/24	6/17	0.75 (0.20 - 2.83)
Iams *et al.*, 1985[10]	10/38	12/35	0.68 (0.25 - 1.85)
Nelson *et al.*, 1985[15]*	10/22	11/22	0.83 (0.25 - 2.65)
Morales *et al.*, 1986[20]	30/121	63/124	0.33 (0.19 - 0.55)
Parsons *et al.*, 1988[21]†	3/23	3/22	0.95 (0.17 - 5.20)
Morales *et al.*, 1989[8]‡	23/87	41/78	0.33 (0.17 - 0.62)
Cararach *et al.*, 1990[23]†	1/12	0/6	2.63 (0.06 - 99.13)
Carlan *et al.*, 1991[22]†	1/11	4/13	0.28 (0.04 - 1.96)
Dexiprom, 1999[6]‡	32/105	27/103	1.24 (0.64 - 2.38)
Total	149/701	206/660	0.59 (0.46 - 0.76)

* Study has co-intervention of elective delivery.
† Abstract.
‡ Studies used antibiotics concomitantly, Morales *et al.*[8] for only a subset of patients.

Table IV. The effect of using corticosteroids in women with PPROM on necrotising enterocolitis in the neonate

Study	Corticosteroids	Control	OR (95% CI)
Morales *et al.*, 1986[20]	1/121	4/124	0.25 (0.01 - 2.42)
Morales *et al.*, 1989[8]*	1/87	4/78	0.21 (0.01 - 2.11)
Dexiprom, 1999[6]*	6/105	8/103	0.72 (0.21 - 2.4)
Total	8/313	16/305	0.47 (0.12 - 1.23)

* Studies used antibiotics concomitantly, Morales *et al.*[8] for only a subset of patients.

neonates where corticosteroids were administered to women with preterm labour.[7] There is a trend towards a reduction in NEC in neonates of women with PPROM who receive corticosteroids (odds ratio (OR) 0.47, 95% CI 0.12 - 1.23) (Table IV).

The diagnosis of infection in the neonate is difficult and is based mainly on a raised or lowered neutrophil count, an increase in the immature to mature neutrophil ratio, a positive C-reactive protein, or a positive culture. In most studies it has been left to the neonatologists to diagnose neonatal infections based on their clinical interpretation of the clinical signs and results of laboratory investigations. Most neonatologists agree that signs of neonatal infection must be present within 72 hours of delivery in order to relate the infection to the pregnancy complication. Thereafter, the possibility of nosocomial infection makes interpretation of the origin of sepsis very difficult.

Table V gives the data for neonatal infections. In the studies of Taeusch *et al.*[16] and Papageorgiou *et al.*,[17] only data for the subset of neonates where the membranes were ruptured for longer than 24 hours before delivery were reported (Table VI). There was no increased risk of neonatal infection, although in earlier studies there was a trend towards increased infection.

Table V. The effect of using corticosteroids in women with PPROM on neonatal infection

Study	Corticosteroids	Control	OR (95% CI)
Garite *et al.*, 1981[9]*	4/80	0/79	6.51 (0.97 - 43.69)
Schmidt *et al.*, 1984[12]	4/24	3/17	0.93 (0.18 - 4.77)
Nelson *et al.*, 1985[15]*	5/22	0/22	8.03 (1.34 - 48.09)
Iams *et al.*, 1985[10]*	4/38	3/35	1.24 (0.26 - 5.87)
Morales *et al.*, 1986[20]	11/121	11/124	1.02 (0.42 - 2.46)
Morales *et al.*, 1989[8]‡	3/43	4/41	0.54 (0.12 - 2.34)
Cararach *et al.*, 1990[23]†	0/12	1/6	0.08 (0.00 - 3.21)
Dexiprom, 1999[6]‡	11/105	11/103	0.98 (0.36 - 2.54)
Total	42/445	33/427	1.23 (0.71 - 2.14)

* Study has co-intervention of elective delivery.
† Abstract.
‡ Studies used antibiotics concomitantly, Morales *et al.*[8] for only a subset of patients.

Table VI. The effect of using corticosteroids in women with membranes ruptured for longer than 24 hours on neonatal infection

Study	Corticosteroid	Control	OR (95% CI)
Papageorgiou *et al.*, 1979[17]	4/17	2/19	2.48 (0.44 - 14.03)
Taeusch *et al.*, 1979[16]	5/56	3/71	2.20 (0.52 - 9.27)
Total	9/73	5/90	2.31 (0.77 - 6.99)

In the studies[6,8] where antibiotics were concomitantly administered, there were 14/147 cases of neonatal infection where corticosteroids were given, compared with 15/146 cases where a placebo was given (Table V).

Ultimately the most important and meaningful end-point is perinatal survival. The positive and negative effects of the aspects discussed above are important in themselves, but combined they determine the survival of the fetus/neonate. There was a significant reduction in perinatal mortality, with the fetus/neonate having approximately 50% less chance of dying if its mother received corticosteroids (Table VII).

As outlined above, antibiotics were not used in the earlier trials, and were used only partially in the 1989 trial of Morales *et al.*,[8] but were used for all cases in the Dexiprom Study.[6]

Table VII. The effect of using corticosteroids in women with PPROM on perinatal deaths

Study	Corticosteroids	Control	OR (95% CI)
Garite *et al.*, 1981[9]*	2/80	5/80	0.38 (0.03 - 2.33)
Nelson *et al.*, 1985[15]*	1/22	1/22	1 (1 - 1)
Iams *et al.*, 1985[10]*	1/38	1/35	0.91 (0.71 - 1.18)
Morales *et al.*, 1986[20]	7/121	13/124	0.52 (0.18 - 1.47)
Morales *et al.*, 1989[8]†	7/87	8/78	0.77 (0.23 - 2.47)
Dexiprom, 1999[6]†	4/105	10/103	0.37 (0.09 - 1.34)
Total	22/453	38/442	0.54 (0.30 - 0.95)

*Study has co-intervention of elective delivery.
† Studies used antibiotics concomitantly, Morales *et al.*[8] for only a subset of patients.

Systematic reviews of the use of antibiotics in women with PPROM[18,19] have demonstrated that with antibiotics the latency period from rupture of membranes to onset of labour is prolonged, the fetus/neonate is significantly less likly to die in the perinatal period, and women have fewer episodes of infection. The Dexiprom Study[6] is the only trial to use antibiotics concomitantly with corticosteroids or placebo. Contrary to earlier trials involving corticosteroids,[9,10,12,15,-17] there was no indication of any increase of infection in the Dexiprom Study,[6] either with regard to the woman or her fetus/neonate. Consequently antibiotics are probably indicated in any management protocol of women with PPROM where corticosteriods are administered.

Conclusion

A summary of the important end-points is given in Table VIII. It is clear that the benefit of corticosteroids outweighs their potential harmful effects when given to women with PPROM. However, antibiotics should probably be included in any management protocol for women with PPROM. There is no reason to suggest that use of corticosteroids in women with PPROM needs to be restricted in developing countries.

Table VIII. Summary analyses of the effect of the use of corticosteroids in women with PPROM

End-point	Corticosteroids	Control	OR (95% CI)
Maternal complications			
Chorio-amnionitis	50/401	56/397	0.86 (0.53 - 1.38)
Endometritis	54/276	33/256	1.66 (0.97 - 2.83)
Perinatal complications			
Respiratory distress	149/701	206/660	0.59 (0.46 - 0.76)
Necrotising enterocolitis	8/313	16/305	0.47 (0.12 - 1.23)
Neonatal infection	42/445	33/427	1.23 (0.71 - 2.14)
Perinatal death	22/453	38/442	0.54 (0.30 - 0.95)

There are still some important unresolved problems. The place of corticosteroids and antibiotics in the management of women with PPROM complicated by AIDS, tuberculosis, or diabetes mellitus is unknown. Future research should concentrate on these problems.

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