THE USE OF DEXAMETHASONE IN WOMEN WITH PRETERM PREMATURE RUPTURE OF MEMBRANES — A MULTICENTRE, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMISED TRIAL

THE DEXIPROM STUDY GROUP

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Objective. To assess whether administration of dexamethasone in women with preterm premature rupture of membranes (PPROM) has an effect on the prevalence of maternal sepsis, neonatal respiratory distress syndrome (RDS), perinatal mortality and neonatal sepsis in a developing country.

Setting. Six public hospitals in South Africa that deal mainly with indigent women.

Method. A multicentre, double-blind, placebo-controlled, randomised trial was performed on women with PPROM and fetuses of 28 - 34 weeks' gestation or clinically estimated fetal weight between 1 000 and 2 000 g if the gestational age was unknown. Women were randomised to receive either dexamethasone 24 mg intramuscularly or placebo in two divided doses 24 hours apart. All women received amoxycillin and metronidazole and were managed expectantly. Hexoprenaline was administered if contractions occurred within the first 24 hours after admission to the trial.

Outcome measures. The maternal outcome measures were clinical chorio-amnionitis and postpartum sepsis. The outcome measures for infants were perinatal death, RDS, mechanical ventilation, necrotising enterocolitis, and neonatal infection within 72 hours.

Results. One hundred and two women who delivered 105 babies were randomised to the dexamethasone group and 102 women who delivered 103 babies, to the placebo group. The groups were well balanced with regard to clinical features. There was a trend towards fewer perinatal deaths in the dexamethasone group: 4 compared with 10 ($P = 0.16$, odds ratio 0.37, 95% confidence intervals 0.09 - 1.34). A sub-analysis of mothers who delivered more than 24 hours after admission to the study and their infants revealed a significant reduction in perinatal deaths; 1 death in the dexamethasone group and 7 in the placebo group, $P = 0.047$ (Fisher's exact test). No woman in either group developed severe sepsis, and the incidence of sepsis in the women did not differ significantly. Eleven infants in each group developed sepsis.

Conclusion. This is the first randomised trial in women with PPROM to compare the effects of the use of corticosteroids with placebo, where all women received prophylactic antibiotics concomitantly with the corticosteroids. A trend towards an improved perinatal outcome was demonstrated in the women who received dexamethasone. There was no increased risk of infection in the women or their infants where dexamethasone was administered. Administration of corticosteroids to women with PPROM has more advantages than disadvantages in developing countries.

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Preterm premature rupture of membranes (PPROM) is a common problem in women admitted to antenatal and labour wards in South Africa. At Kalafong Hospital, Pretoria, women with PPROM occupy 7% of bed space in the antenatal wards (audit data 1995, Kalafong Maternity Unit yearly statistics), and PPROM accounts for 11.1% of perinatal deaths.[1] All the deaths occurred in infants below 2.5 kg, and 96% occurred in infants below 2.0 kg. The majority of these deaths were due to complications of prematurity, although congenital infection was responsible in some cases.

The use of corticosteroids in the management of women with PPROM has been controversial in South Africa. Ballot *et al.*[2] stated: 'We would argue that in South Africa, the use of a cheap effective preventive measure such as antenatal corticosteroids should be strongly encouraged at every opportunity, unless there is definite evidence to the contrary'. This view was countered by Tregoning,[3] who stated that 'until there is evidence from larger randomised controlled trials of adequate study design, it could be potentially hazardous to emphatically advocate their [antenatal corticosteroids] routine use in this [South African] setting'. The dilemma facing both authors is to establish the balance between advantage to the infant and increased risk of infection in mother and infant. Paediatricians will prioritise improved neonatal survival, whereas obstetricians will not want to jeopardise the well- being of the mother, while trying to improve the outcome of the infant. It is clear that the use of antenatal corticosteroids promotes fetal lung maturity, but it is not clear whether this increases the risk of neonatal or maternal infection rate.[4] The main concern expressed in South Africa is a perceived greater risk of infection to women and infants. This is because the majority of cases of PPROM occur in indigent women and in the vast

majority of these women, preterm labour has been associated with sub-clinical infection.[5]

A multicentre, double-blind, placebo-controlled, randomised trial was conducted to answer these questions in the South African setting. The study was called the Dexiprom Trial.

METHODS

The trial took place in six hospitals in South Africa, namely Kalafong and Pretoria Academic hospitals in Gauteng, Pelanomi Hospital in the Free State, and Tygerberg, Groote Schuur and Somerset hospitals in the Western Cape. All these hospitals deal mainly with indigent populations. The trial was pragmatic in nature, and aimed to disrupt the routine management of the women with PPROM as little as possible.

A woman was invited to participate in the trial if she: (*i*) had proven rupture of membranes; (*ii*) was not in labour (or if experiencing contractions her cervix was not more than 4 cm dilated, as assessed visually during a speculum examination); (*iii*) was between 28 and 34 weeks' gestation (or if the gestational age was unknown, she was clinically estimated to have a fetus weighing between 1 000 g and 2 000 g); (*iv*) had no clinical evidence of infection or antepartum haemorrhage; and (*v*) was older than 18 years of age.

A woman who agreed to participate in the trial was allocated the number of the next 'Dexiprom' treatment box available at the participating hospital. The Dexiprom treatment box contained six vials of either dexamethasone (4 mg) or normal saline. The vials and their contents looked identical. Randomisation took place centrally and each hospital received a package of numbered Dexiprom treatment boxes.

All women admitted to the trial were managed as follows: three vials from the Dexiprom treatment box were administered intramuscularly, and repeated 24 hours later when the remaining three vials were opened and administered intramuscularly; amoxycillin 500 mg and metronidazole 400 mg were given orally every 8 hours for 5 days; bed rest was advised; and 6-hourly maternal temperature, pulse and fetal heart rate measurements were taken. If the woman was in labour on admission or went into labour within 24 hours of admission, an attempt was made to suppress the contractions for 24 hours using intravenous hexoprenaline. Hexoprenaline was not used 24 hours after admission to the trial.

The maternal outcome measures were clinical chorio-amnionitis and postpartum sepsis. Clinical chorio-amnionitis was taken to be present if the clinician managing the case terminated the pregnancy for that indication. The clinical signs usually present were a raised maternal temperature, tachycardia, a tender uterus, foul-smelling discharge, and fetal tachycardia. A clinical diagnosis of postpartum sepsis was made if there were clinical signs of endometritis postpartum. Before discharge the highest postpartum temperature of each woman was noted, as well as whether she had a tender uterus and/or a foul-smelling discharge recorded. Whether she had had an episiotomy, whether it was septic or not, and any other sites of sepsis were also noted before discharge. If the woman had an increased temperature, a urine culture was also requested.

The occurrence of perinatal death, respiratory distress syndrome (RDS), mechanical ventilation, necrotising enterocolitis (NEC), and neonatal infection within 72 hours were the outcome measures for each infant. There is considerable variation in the criteria and resources for making the diagnosis of neonatal infection and identifying the cause of RDS in the various neonatal units in South Africa. Specifically, there are difficulties with regard to the differentiation between hyaline membrane disease (HMD) and congenital pneumonia. Participating neonatal units were requested to perform a chest radiograph on any infant with RDS, and to record the duration of any mechanical ventilation and any oxygen support involving a head box or nasal prongs. They were also asked to perform blood cultures at birth, and to do platelet and neutrophil counts and a C-reactive protein (CRP) daily for the first 3 days after birth. These tests were decided upon during the protocol development stage since the neonatologists regarded performance of these tests to be routine in infants.

Other tests were also performed by the participating neonatal units. For example, Groote Schuur Hospital used microscopy of gastric aspirates and an increase in the immature to mature neutrophil ratio as an aid for diagnosing congenital infections. The attending neonatologists were also requested to document whether any respiratory complications were present and to record a definitive diagnosis. RDS was defined as central cyanosis on room air plus the presence of one of the following: tachypnoea, recession or expiratory grunting. The use of mechanical ventilation also depended on available resources and the individual neonatal unit's indications for respiratory support. Infection related to PPROM was regarded as any sign of sepsis in the neonate within 72 hours of delivery. The clinical diagnosis of sepsis was made by the attending neonatologist and supported by positive blood cultures, low platelet and neutrophil counts, raised CRP and signs of infection on the chest radiograph. NEC was diagnosed when a neonate developed a distended abdomen with bloody stools and had the classic radiograph signs or necrotic bowel at laparotomy.

The sample size was calculated using a 30% prevalence of HMD; halving of this prevalence was regarded to be clinically important. A sample of 134 women per limb was estimated to be required for the study to have a power of 80% and an error risk of 0.05 of detecting this difference. This was in keeping with the typical odds ratio (OR) of 0.55 obtained from the meta-analysis of Crowley *et al.*[6] when comparing the effect of corticosteroids versus controls on the prevalence of HMD women with PPROM. The calculation was made using HMD because the magnitude of infectious complications could not be determined.

Statistical analysis was performed using Student's *t* -test for normally distributed data and the Chi-square test for categorical data. Fisher's exact test was used when the expected value in one or more of the cells was less than 5. The OR and 95% confidence intervals (CIs) were calculated for categorical data.

Ethical approval was obtained from the Ethics Committee of each participating hospital, and each woman who participated in the trial gave written informed consent.

RESULTS

Data were collected on 211 women before the study was stopped. There were 7 cases of protocol violations, 3 women did not have rupture of membranes, 2 women had pregnancies of less than 26 weeks' gestation and were incorrectly randomised, 1 woman received Celestone Soluspan (a corticosteroid) prescribed by another clinician who was not aware that the patient was in the trial, and 1 was excluded because there was no neonatal bed available and the clinicians did not follow the protocol for this reason. There were no further data collected on these patients and they were excluded from further analysis. Data of 204 women (102 in each group) were analysed. Two-hundred and eight babies were analysed including four sets of twins.

The groups were well balanced clinically (Table I). No differences between the dexamethasone group and the saline (placebo) group were noted with regard to maternal outcome, specifically with regard to the complication of infection (Table II). No woman in either group was reported to have developed severe sepsis.

Table I. Demographic data of the dexamethasone and saline groups

	Dexamethasone	Saline
Number		
Mothers	102	102
Babies	105 (3 twins)	103 (1 twin)
Hospitals (mothers)		
Kalafong	30	25
Pretoria Academic	7	7
Tygerberg	26	26
Somerset	16	18
Groote Schuur	10	14
Pelanomi	13	12
Age (yrs) (mean ± SD)	27 ± 6	27 ± 6
Parity (median, range)	2 (0 - 5)	1 (0 - 9)
Gravidity (median, range)	3 (0 - 7)	3 (0 - 9)
On admission to trial		
Gestational age (yrs)	31.02 ± 2.27	30.57 ± 2.14
Estimated weight (g)	1 566 ± 342	1 566 ± 338
Contractions present	17 (20%)	14 (16%)
Cervical dilation (cm)		
0	54	54
1	15	18
2	8	8
3	7	4
Unknown	18	18

The neonatal data are given in Table III. There was a trend toward fewer perinatal deaths in the dexamethasone group (OR 0.37, 95% CIs 0.09 - 1.34). There was no difference between the groups with regard to RDS and the need for mechanical ventilation. A clear diagnosis of HMD was made in only 16 (7.9%) of the total number of neonates included in the study. Surprisingly few neonates required ventilation, namely 15% and 16% in the dexamethasone and saline groups respectively. No case of intraventricular haemorrhage was diagnosed in either group. The causes of perinatal death are shown in Table IV. The major factor in the death of the infant with Dandy-Walker syndrome was thought to be respiratory complications.

Twenty-eight women (27.5%) in the dexamethasone group delivered within 24 hours of entry into the trial compared with 18 women (17.6%) in the saline group ($P = 0.13$, OR 1.76, 95% CIs 0.86 - 3.64). A sub-group analysis of women who delivered after 24 hours was undertaken because it is well known that the greatest benefit of corticosteroids occurs after 24 hours.[4] The groups were again clinically well balanced and very similar to the whole group (Table I). A comparison of the maternal and neonatal outcomes between the dexamethasone and saline groups is shown in Table V. Significantly fewer perinatal deaths occurred in the dexamethasone group (1 versus 7, $P = 0.047$), and there was a trend towards fewer infants developing respiratory distress and NEC and needing mechanical ventilation. The prevalence of neonatal infections was the same in the two groups (11%).

DISCUSSION

This is the first randomised trial in women with PPROM to compare the effects of the use of corticosteroids with placebo, where all women received prophylactic antibiotics concomitantly with the corticosteroids. In this trial there was a significantly improved survival in the infants whose mothers received dexamethasone and who delivered more than 24 hours after trial entry. There was no difference in infectious complications in the mothers or their infants. These findings are in agreement with the findings of the systematic review of Crowley[6] with regard to the use of corticosteroids in PPROM.

Increased survival was most marked in the sub-group where women delivered their infants more than 24 hours after admission to the trial. This difference can be explained by the trend for fewer complications to occur in the neonates with regard to RDS and NEC.

The Dexiprom Study Group decided to discontinue the study before the target sample size was reached because an increasing body of evidence became available indicating that

Table II. Comparison between outcomes of mothers in the dexamethasone and saline groups

	Dexamethasone (*N* = 102)	Saline (*N* = 102)	*P*	OR (95% CI)
Method of delivery				
Vaginal	86 (84%)	82 (80%)		
Caesarean section	15 (15%)	20 (20%)	0.477	1.39 (0.63 - 3.11)
Unknown	1 (1%)	—	—	
Reason for delivery				
Suspicion of clinical chorio-amnionitis	11 (11%)	8 (8%)	0.61	1.44 (0.51 - 4.12)
Antepartum-haemorrhage	2 (2%)	2 (2%)		
Fetal distress	2 (2%)	7 (7%)		
Spontaneous labour	78 (76%)	73 (71%)		
> 34 wks	6 (6%)	12 (12%)		
Other	2 (2%)		—	
Unknown	1 (1%)		—	
Maternal complications postpartum				
Temp. > 38°C	7 (7.2%)	7 (7%)	0.83	1.03 (0.31 - 3.44)
Postpartum sepsis				
Endometritis	4 (4%)	7 (7%)	0.53	0.55 (0.13 - 2.19)
Urinary tract infection	2 (2%)	2 (2%)		
Wound	1 (1%)	1 (1%)		
Pneumonia	1 (1%)	—	All	0.73 (0.27 - 1.96)
Pharyngitis	1 (1%)	1 (1%)	0.64	
Sinusitis	-	1 (1%)		
No sepsis	93 (91%)	90 (88%)		

Table III. Comparison between neonatal outcomes in the dexamethasone and saline groups

	Dexamethasone (*N* = 105)	Saline (*N* =103)	*P*	OR (95% CI)
Birthweight (g)	1 795 ± 437	1 791 ± 542	NS	
Perinatal deaths				
IUD	—	2		
ENND	1	3		
LNND	1	3		
PRID	2	2		
Total	4 (3.8%)	10 (9.7%)	0.16	0.37 (0.09 - 1.34)
Respiratory distress				
Unknown/IUD	3	3		
RDS (total)	32 (31%)	27 (27%)	0.59	1.24 (0.64 - 2.38)
Mechanical ventilation	15 (15%)	16 (16%)	0.95	0.9 (0.39 - 2.08)
NEC	6 (6%)	8 (9%)	0.75	0.72 (0.21 - 2.4)
Neonatal infection				
< 72 hrs	11 (11%)	11 (11%)	0.88	0.98 (0.36 - 2.54)

IUD = intra-uterine death; ENND = early neonatal death; LNND = late neonatal death; PRID = perinatally related infant death; RDS = respiratory distress syndrome; NEC = necrotising enterocolitis; NS = not significant.

Table IV. Causes of perinatal death in the dexamethasone and saline groups

Group	Time	Admission delivery time (h)	Birthweight (g)	Cause
Dexamethasone	ENND	< 24	1 334	Septicaemia
	LNND	< 24	1 526	NEC and perforation of bowel
	PRID	< 24	774	NEC and *Candida* septicaemia
	PRID	> 24	1 200	Nosocomial infection
Saline	Stillbirth	< 24	1 776	Unknown
	Stillbirth	> 24	2 300	Sepsis
	ENND	< 24	1 160	HMD, no ventilation facilities
	ENND	> 24	1 560	Possible sepsis
	ENND	> 24	1 900	*Escherichia coli* septicaemia
	LNND	> 24	1 000	RDS, Dandy-Walker syndrome
	LNND	> 24	1 495	Fulminating NEC
	LNND	> 24	1 000	Fulminating NEC, DIC, pulmonary haemorrhage
	PRID	< 24	1 300	Unknown
	PRID	> 24	1 000	NEC

ENND = early neonatal death; LNND = late neonatal death; PRID = perinatally related infant death; NEC = necrotising enterocolitis; HMD = hyaline membrane disease; DIC = disseminated intravascular coagulation; RDS = respiratory distress syndrome.

Table V. Comparison between outcomes of mothers and infants in the dexamethasone and saline groups where the delivery occurred more than 24 hours after admission into the trial

	Dexamethasone	Saline	OR (95% CI)
Number of deliveries > 24 hours	74 women 75 infants	84 women 84 infants	
Maternal outcomes			
Clinical chorio-amnionitis	10 (13%)	8 (10%)	1.51 (0.51 - 4.5)
Endometritis	4 (5%)	6 (8%)	0.75 (0.17 - 3.18)
Neonatal outcomes			
Perinatal deaths	1 (1.3%)	7 (8.3%)	$P = 0.047$ (Fisher's exact test)
Respiratory distress	19 (26%)	24 (29%)	0.82 (0.4 - 1.86)
Mechanical ventilation	8 (11%)	13 (15%)	0.66 (0.23 - 1.86)
Necrotising enterocolitis	4 (5%)	8 (10%)	0.54 (0.13 - 2.11)
Neonatal infection < 72	8 (11%)	9 (11%)	1.01 (0.33 - 3.1)

the use of corticosteroids in women with PPROM was clearly advantageous to the infant.[6,7] It was stated that it was unnecessary to perform any more studies comparing corticosteroids with placebo[6] in women with PPROM. Furthermore, the disadvantages of a possible increased incidence of infection in mothers and infants were fewer than anticipated. The original calculation of the sample size, based on the prevalence of HMD at 30%, led to an underestimate of the sample size required since HMD in the South African black population is less frequent than in the white population.[8] If the data of Cooper *et al.*[8] had been used the baseline prevalence of HMD for the applicable weight category would have been approximately 15%. In this study the actual prevalence of HMD was 7.9%. This lower than expected prevalence may be the result of the use of prophylactic antibiotics, as their use has been associated with a decreased prevalence of RDS.[9,10] Another problem with calculating the sample size was that the end points of maternal sepsis or neonatal sepsis could not be calculated from the local data or the literature because antibiotics were used routinely in both groups in this study, contrary to almost all previous studies.[11]

In all the earlier studies[11] prophylactic antibiotics were not used as part of the management protocol of PPROM. In some of these studies[12,13] a significant increase in maternal infection and a trend towards an increase in neonatal infection was observed in the corticosteroid groups. The lack of evidence of infectious complications in this study may be ascribed to the use of prophylactic antibiotics. There was not one case of severe maternal sepsis. However this does not mean that this complication will not occur in the future.[14] In a study of this

sample size the maximum risk (upper 95% CI) that a woman has of developing severe sepsis after the administration of corticosteroids is 3%. If all cases reported in randomised trials where corticosteroids were used in women with PPROM are combined, the maximum risk of developing severe sepsis is approximately 1%.[8] These findings are supported by the study of Pattinson *et al.*[15] which found that no biochemical effect, with possibly only a slight depression of cell-mediated immunity could be detected in women with PPROM who were given dexamethasone.

The results of this multicentre study, in which participants were almost exclusively indigent women, showed that there was no increased risk of maternal or infant sepsis and that there was improved survival for infants when dexamethasone was given to women with PPROM. This indicates that in developing countries the use of corticosteroids has more advantages than disadvantages. We agree with Crowley[6] that: 'Every effort should be made to treat women with corticosteroids prior to preterm delivery as a result of either preterm labour or elective preterm delivery', and that this is also applicable to developing communities with a higher prevalence of underlying infections. We suggest that prophylactic antibiotics be seriously considered when women with PPROM are given corticosteroids.

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