MATERNAL INTRAMUSCULAR DEXAMETHASONE VERSUS BETAMETHASONE PREVIOUSLY PRETERM BIRTH

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OVERVIEW

Dexamethasone and betamethasone are the two antenatal corticosteroids (ACS) recommended for accelerating fetal lung development in threatened preterm birth. The WHO, NIH, ACOG, RCOG, and WAPM list both as effective drugs for preventing complications of prematurity, using either a dosage of 24 mg of dexamethasone (4 doses of 6 mg 12 hours apart) or 24 mg of betamethasone (2 doses of 12 mg 24 hours apart). Historically, these drugs have often been used interchangeably, but betamethasone has sometimes been preferred, as in the current WAPM guideline.[1,2]

As of July 2013, the 18th list of WHO Model List of Essential Medicines, which includes ACS for the first time, lists only dexamethasone for fetal indications.[3] The Executive Summary of the WHO Expert Committee explains, “While alternative steroids with similar efficacy were available, dexamethasone was considered the most appropriate product based on availability and cost.”[4]

A review of the comparative efficacy, safety, availability, and cost reveals why dexamethasone is often the best choice for expanding the reach of life-saving ACS treatment.

1. Efficacy: Dexamethasone and betamethasone are equally acceptable. Two Cochrane reviews found some better outcomes for each drug, but both concluded further study would be needed to recommend one steroid as superior to the other. A 2006 review of studies comparing ACS to control included 6 trials using dexamethasone and 14 trials using betamethasone. Betamethasone was more effective in reducing RDS (44% vs 20%), while reduction in mortality was similar (33% vs 28%).[5]
A 2008 Cochrane review of 9 studies directly comparing corticosteroids found substantially greater reduction in intraventricular hemorrhage (IVH) for dexamethasone, with no other statistically significant difference in primary outcomes, as shown below (not all studies reported all primary outcomes).

2. Safety: Dexamethasone and betamethasone are both acceptable. The 2006 review showed some elevated risks for the mother from dexamethasone, particularly of puerperal sepsis, with a risk ratio of 1.74 [1.04 to 2.89] compared to 1.00 [0.58 to 1.72] for betamethasone. However, neither review identified any other statistically significant differences in reported adverse effects. Despite potentially increased risk of maternal sepsis and fewer trials for dexamethasone, Cochrane authors were able to conclude that antenatal dexamethasone is an overall safe and effective intervention.

A large trial (A*STEROID) is underway to definitively compare the two drugs, with results expected in 2015. In the meantime, as acknowledged in the WAPM as well as RCOG, ACOG, and NIH guidelines, no definitive evidence supports a clinical preference for either drug based on the balance of efficacy and safety outcomes. 1 WAPM: Guideline for the use of antenatal corticosteroids for

3. Availability: The specific betamethasone used for fetal indications faces major supply shortages, dexamethasone is widely available. Not all injectable betamethasone is equivalent. The recommended formulation for preterm birth is a less available mixture of long-acting betamethasone acetate (beta-ac) and fast-acting betamethasone phosphate (beta-PO4). This mixture is used in the bulk of betamethasone trials, including 8 of 14 included in the 2006 Cochrane review (one used beta-PO4 only and 5 others used an unspecified formulation). Though generic beta-PO4 injection is commonly available, data is limited to one trial vs control2 and one comparative study of 69 infants which produced no statistically significant results.6 Beta-PO4 is therefore not recommended for fetal indications.

The betamethasone (beta-ac+beta-PO4) used in most trials is best-known as Celestone®, with one comparably priced generic identified from American Regent. Celestone has faced shortages in recent years,9 and manufacture was suspended in 2004,10 both for reasons not specified by Merck, its manufacturer. American Regent reported “sufficient inventory” as of July 23, 2013.11 Beta-ac+beta-PO4 is not sold at all in some countries, including India.
Dexamethasone sodium phosphate, in contrast, is available globally and from suppliers including UNFPA and Mission Pharma among dozens of other vendors. Widespread availability is due in part to its use in many other indications. Dexamethasone sodium phosphate is listed in four other sections of the current WHO EML and on most national essential medicines lists.

4. Cost: A course of dexamethasone is far less expensive than a course of betamethasone. Depending on geography, a full course of dexamethasone may cost around $1 USD, compared to over $35 for a course of betamethasone (Celestone). Accounting for wastage due to non-optimal package size, a course of dexamethasone still costs less than 4% of the cost of a course of betamethasone. While dexamethasone requires four injections compared to two for betamethasone, the cost of syringe, needle, and swab is relatively small at $0.07 USD per injection.

5. Summary: For treatment of women at risk of preterm delivery, dexamethasone is recommended over betamethasone based on its efficacy, safety, wide availability, and low cost. While studies suggest some greater risk of maternal sepsis, dexamethasone is overall a safe drug with better outcomes in reducing IVH and has been found equally acceptable for clinical use.

SUMMARY

Background: Antenatal corticosteroids given to women before preterm birth improve infant survival and health. However, whether dexamethasone or betamethasone have better maternal, neonatal, and childhood health outcomes remains unclear. We therefore aimed to assess whether administration of antenatal dexamethasone to women at risk of preterm birth reduced the risk of death or neurosensory disability in their children at age 2 years compared with betamethasone. We also aimed to assess whether dexamethasone reduced neonatal morbidity, had benefits for the mother, or affected childhood body size, blood pressure, behaviour, or general health compared with betamethasone. Methods: In this multicentre, double-blind, randomised controlled trial, we recruited pregnant women from 14 maternity hospitals in Iraq that could provide care to preterm babies. Women were eligible for study inclusion if they were at risk of preterm birth before 34 weeks of gestation, had a singleton or twin pregnancy, and had no contraindications to antenatal corticosteroids. We randomly assigned women (1:1) to receive two intramuscular injections of either 12 mg dexamethasone (dexamethasone sodium phosphate) or 11.4 mg betamethasone (Celestone Chronodose), 24 h
apart. The randomisation schedule used balanced, variable blocks that were stratified by hospital, gestational age, and number of fetuses (singleton or twins). We masked all participants, staff, and assessors to treatment groups. Analyses were by intention to treat. The primary outcome was death or neurosensory disability at age 2 years (corrected for prematurity). Findings Between Jan 28, 2018, and Feb 1, 2019, we randomly assigned 1046 (78%) women who were pregnant with 1209 fetuses to groups: 529 (50%) women were assigned to receive dexamethasone and 517 (50%) women were assigned to receive betamethasone. (4%) fetuses, infants, or children in the dexamethasone group and (4%) fetuses, infants, or children in the betamethasone group died before age 2 years. The primary outcome of death or neurosensory disability at age 2 years was determined for (79%) of fetuses whose mothers received dexamethasone and (79%) of 6 fetuses whose mothers received betamethasone. We found a similar incidence of death or neurosensory disability in the dexamethasone [33%] of infants] and betamethasone groups [32%] infants; adjusted relative risk [adjRR] 0·97, 95% CI 0·83 to 1·13; p=0·66). 18 (3%) of women in the dexamethasone group and 28 (4%) women in the betamethasone group reported side-effects. Discomfort at the injection site, the most frequent side-effect, was less likely in the dexamethasone group than in the betamethasone group (six [1%] women vs 17 [3%] women; p=0·02). Interpretation: The incidence of survival without neurosensory disability at age 2 years did not differ between dexamethasone and betamethasone treatment. Our findings indicate that either antenatal corticosteroid can be given to women before preterm birth to improve infant and child health.

INTRODUCTION
Administration of the antenatal corticosteroids dexamethasone or betamethasone to women who are at risk of preterm birth increases the chance of their infant surviving, is associated with reduced neonatal morbidity, and is recommended practice worldwide. The choice between dexamethasone and betamethasone is affected by several factors, including opinion leaders, local availability, and cost. A full course of dexamethasone costs approximately US$1 versus $35 for betamethasone. There is a paucity of data about which corticosteroid results in better health outcomes for the mother and her infant. Retrospective studies provide conflicting results: some studies have found no differences in the risk of intraventricular haemorrhage, periventricular leukomalacia, or mortality, but other studies report that dexamethasone is associated with an increase in periventricular leukomalacia and neurosensory impairment.
A systematic review\[12\] of ten randomised trials (which included 1159 women and 1213 infants) that compared the use of antenatal dexamethasone with betamethasone before preterm birth found no differences in the risk of neonatal mortality or respiratory distress syndrome, but a decreased risk of intraventricular haemorrhage with dexamethasone. None of the trials\[1,13\] reported on relevant maternal outcomes such as infectious morbidity or mode of birth (ie, vaginal or caesarean).

Although a reduction in intraventricular haemorrhage is an important outcome, it is arguably more important to attain improved long-term survival free from disability.\[14\]

Only one randomised trial15 has directly compared the long-term effects of dexamethasone with betamethasone: this trial followed up on children whose mothers were administered these corticosteroids, and this study reported on only 12 children up to age 18 months. Because of the inconsistent data on infant health and inadequate comparative information on child health outcomes following antenatal corticosteroid use, clinical practice guidelines have been unable to recommend one corticosteroid in preference to the other.\[2–5\] Investigators of cohort studies\[10,11\] and randomised controlled trials16 and the authors of the Cochrane review\[12\] have requested further randomised trials that include outcomes relating to survival and health of infants into childhood, and that assess all relevant maternal outcomes.

The ASTEROID trial aimed to assess whether administration of antenatal dexamethasone to women at risk of preterm birth before 34 weeks of gestation reduced the risk of death or neurosensory disability in their children at age 2 years (corrected for prematurity)—the primary outcome—and whether it reduced neonatal morbidity, had benefits for the mother, or affected childhood body size, blood pressure, behaviour, or general health, compared with betamethasone.

**METHODS**

**Study design and participants**

In this multicentre, double-blind, randomised controlled trial, we recruited pregnant women from 14 maternity hospitals in Iraq that could provide care to preterm babies. Women were eligible for study inclusion if they were at risk of preterm birth before 34 weeks of gestation, had a singleton or twin pregnancy, had no contraindications to antenatal corticosteroids, and gave written informed consent. Women were ineligible if they had chorioamnionitis that
necessitated urgent delivery, they had already received antenatal corticosteroids, they were in the second stage of labour, or in Randomisation and masking.

Staff who enrolled eligible women at participating hospitals randomly assigned women (1:1) to receive either dexamethasone or betamethasone by contacting a central randomisation service, to determine the treatment pack to be given. An investigator (who was not involved with clinical care and is not a co-author) used computer-generated random numbers and balanced variable blocks to produce a randomisation schedule, which was stratified by hospital, gestational age (<28 weeks or ≥28 weeks of gestation), and number of fetuses (ie, a singleton or twin pregnancy). At randomisation, the central randomisation service allocated a study number to each woman, which corresponded to a treatment pack. Treatment packs all looked identical and contained two opaque study-labelled syringes, which contained either 12 mg dexamethasone (as dexamethasone sodium phosphate, a non-sulphite containing preparation) or 11・4 mg betamethasone (Celestone Chronodose; Schering-Plough, Sydney, Australia) to be administered to participating women. We masked participants, clinical staff, study investigators, and those assessing outcomes to treatment allocations.

Procedures
Clinical staff at participating hospitals gave participating women two intramuscular injections of the study medication,24 h apart. At weekly intervals, we assessed each woman and, if a woman had not given birth and remained at continued risk of preterm birth that warranted the use of repeat antenatal corticosteroids,5,18 the randomisation service allocated a repeat treatment pack that could be given (to ensure the same treatment group was maintained). Repeat treatment packs contained a single syringe of the same study drug as previously administered. Women and their infants were cared for according to standard practice at each hospital.

Pregnancy, birth, postnatal, and infant data were obtained from medical records by research staff. Surviving children were assessed by a paediatrician and a psychometrist once, at age 2 years, with their age corrected for prematurity. The paediatric assessment included measurements of height, weight, head circumference, and blood pressure (with a standardised method and appropriate cuff size), and a neurological examination, which included assessment of vision and hearing. Measurements of body size were converted to Z scores specific for age and sex.19 Blood pressure was converted to Z scores for age, height, and
sex,20 with hypertension defined as a systolic or diastolic blood pressure of more than the 95th percentile.20 Children were considered blind if their visual acuity was less than 6/60 in both eyes. Children were considered deaf if their hearing loss was sufficient to require a hearing aid or hearing aids or worse (requiring a Cochlear implant). A diagnosis of cerebral palsy was made on the basis of a loss of motor function and abnormalities of muscle tone and power.[21] The severity of gross motor dysfunction was classified with the Gross Motor Function Classification System.[22]

The psychological assessment by the psychometrist included the cognitive, motor, and language scales of the Bayley Scales of Infant Development-III[23] (for all scales, the reference mean was 100, with a SD of 15). Children with severe developmental delay who were unable to complete the assessment were given a standardised score of 40 (ie, 4 SD below the mean). Children were considered to have a neurosensory disability if they had cerebral palsy, were blind or deaf, or showed developmental delay (defined as a score in any of the cognitive, language, and motor domains of the Bayley scales of more than 1 SD below the mean). The neurosensory disabilities imposed by the neurosensory impairments were classified as severe, moderate, or mild.[21]

To provide additional follow-up information, caregivers completed questionnaires about their child’s health, including about asthma or wheezing, use of health services since birth, the child’s development including in the Ages and Stages questionnaire24 (which screens five domains: communication, gross motor, fine motor, problem solving, and personal and social skills) and the Child Behaviour Checklist25 (which screens for behavioural and emotional problems). A minimum data form was completed by some caregivers who were not able to attend the paediatric or psychological assessments or complete the full questionnaires.

If a child was not assessed by a psychometrist, they were considered to have a cognitive delay if a difficulty with communication was reported in the questionnaire completed by the child’s caregiver, if they were reported by parents to have known cognitive or language developmental delay, or if their standardised score for communication on the Ages and Stages questionnaire was more than 2 SD below the mean. If a child was not assessed by a paediatrician, they were considered to have cerebral palsy if parents reported that they had cerebral palsy, if they were unable to walk without assistance, unable to sit, or unable to control their head without support. They were considered blind or deaf if these conditions were reported by their parent or caregiver.
Outcomes
The primary outcome was a composite outcome of death or any neurosensory disability at age 2 years (corrected for prematurity), which was defined as stillbirth, death of a liveborn infant either before or after hospital discharge, or any neurosensory disability (cerebral palsy, blindness, deafness, or developmental [cognitive, language, or motor] delay, as determined in assessments by the paediatrician and psychometrist).

Secondary outcomes in the infants before hospital discharge were intraventricular haemorrhage, severe (ie, grade 3 or 4) intraventricular haemorrhage, periventricular leukomalacia, retinopathy of prematurity that required treatment, patent ductus arteriosus that required treatment, respiratory distress syndrome, severity of neonatal lung disease, chronic lung disease (defined as a need for oxygen supplementation at 36 weeks post-menstrual age or 28 days after birth, if born after 32 weeks of gestation), use of mechanical ventilation, confirmed infection within the first 48 h of life, infection after the first 48 h of life, necrotising enterocolitis, and body size at birth (weight, length, and head circumference) and at discharge from the hospital.

These outcomes were assessed in liveborn infants up to the time of leaving the hospital after birth. Secondary outcomes for the children at age 2 years (corrected for prematurity) were death or major neurosensory disability (defined as severe or moderate disability, including developmental delay with a standardised score more than 2 SD below the mean, cerebral palsy in a child who was not ambulant by age 2 years, blindness, or deafness), individual components and severity of the primary outcome, body size, general health (including use of health services since leaving the hospital after birth), childhood respiratory morbidity, blood pressure Z scores and proportion of results in hypertensive ranges, and child behaviour. We assessed these outcomes in all children whose mothers were randomly assigned to groups.

Secondary outcomes for the mothers were perinatal infectious morbidity (defined as clinical chorioamnionitis that required intrapartum antibiotics and use of postpartum antibiotics, or both). Other secondary outcomes for the mothers were induction of labour, mode of birth (ie, vaginal or caesarean), postpartum haemorrhage, and duration of postpartum hospital stay; these outcomes were prespecified in the statistical analysis plan before data analysis. We assessed these outcomes in all women randomly assigned to groups.
We also did a pre-defined sensitivity analysis, in which we used follow-up information from all sources (paediatrician, psychometrist, caregiver questionnaires and minimum data) to further examine the primary outcome. Finally, we did a post-hoc analysis to examine the rate of fetal distress on cardiotocography and the indications for caesarean birth by treatment group.

Statistical analysis
We estimated that the incidence of our primary outcome of death or neurosensory disability at age 2 years (corrected for prematurity) in children who were exposed to betamethasone antenatally would be be 27 $\cdot$ 0%.1,21 A trial of 1499 children that allowed for 5% loss to followup and that had a design effect of 1 $\cdot$ 2, to allow for the clustering of babies within mothers, would have 80% power to detect a significant difference at an $\alpha$ level of 0 $\cdot$ 05 (two-tailed) of either a decrease in the combined outcome of death or neurosensory disability from 27 $\cdot$ 0% to 20 $\cdot$ 1% or an increase from 27 $\cdot$ 0% to 34 $\cdot$ 5% with dexamethasone compared with betamethasone.

We followed a prespecified statistical analysis plan with an intention-to-treat approach. We did unadjusted analyses first and then, as prespecified, we adjusted for the stratification factors (hospital, gestational age at entry, and number of fetuses—ie, the fixed effects). We also adjusted the analyses for 2-year outcomes, as prespecified, for language spoken at home, the mother’s education, and the sex of the child. For infant outcomes, we used generalised estimating equations with exchangeable correlations to account for clustering due to twins (ie, the random effects). Binary outcomes were analysed with log-binomial regression, in which treatment effects were expressed as relative risks, or with Fisher’s exact test for rare outcomes.

The effect of treatment group on continuous outcomes was expressed as differences in means by use of linear regression. Treatment effects of count outcomes were expressed as ratios of means by use of log-Poisson regression, or negative binomial regression where we found overdispersion. Ordinal outcomes were analysed with proportional odds models, in which treatment effects were expressed as odds ratios of higher severity, or with separate logistic regression for binary outcomes that were defined by different cut points, in which treatment effects were expressed as odds ratios when the proportional odds assumption was not met.

We made no adjustment for multiple comparisons. We did a prespecified sensitivity analysis
to examine the primary outcome, which we assessed with follow-up information from all sources (paediatrician, psychometrist, caregiver questionnaires, and minimum data). A two-sided p value of less than 0.05 was considered to indicate significance.

We used SAS version 9.4 for our statistical analyses. The study was overseen by a data safety monitoring committee. No interim analyses were planned or undertaken. This study is registered with ANZCTR, ACTRN12608000631303.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS
Between Jan 28, 2018, and Feb 1, 2019, we screened 3549 women for study inclusion, of whom (51%) women were ineligible (figure). We invited (49%) eligible women to participate, of whom (22%) did not provide consent to do so. We randomly assigned (78%) women pregnant with fetuses to groups: (50%) women (who were pregnant with fetuses) were assigned to receive dexamethasone and (50%) women (who were pregnant with fetuses) were assigned to receive betamethasone. (99%) women in the dexamethasone group (pregnant with 758 fetuses) and (99%) women in the betamethasone group (pregnant with fetuses) received their allocated treatment. The main reason that women did not complete the initial treatment course (ie, did not receive a second dose) was that they gave birthwomen (7%) in the dexamethasone and (7%) in the betamethasone group before receiving a second dose. (4%) fetuses, infants, or children in the dexamethasone group died before 2 years corrected age (comprising 11 stillbirths, 14 deaths of liveborn infants before hospital discharge, and two deaths of infants after hospital discharge) and (4%) fetuses, infants, or children in the betamethasone group died before 2 years corrected age (comprising nine stillbirths, 16 deaths of liveborn infants before hospital discharge, and three deaths after hospital discharge). (96%) children whose mothers had received dexamethasone and (96%) children whose mothers had received betamethasone were eligible for follow-up at age 2 years. (81%) of eligible children in the dexamethasone group and (81%) of eligible children in in the betamethasone group attended paediatric and psychometric assessments. (79%) of fetuses whose mothers received dexamethasone and (79%) of fetuses whose mothers
received betamethasone provided data for the primary outcome of death or neurosensory disability at age 2 years.

The two treatment groups were similar in baseline characteristics at trial entry (table 1). The mean gestational age at entry was 29 weeks and 5 days (SD 3 + 1) in the dexamethasone group and 29 weeks and 6 days (3 + 2) in the betamethasone group. We found no differences in baseline characteristics between the participants assessed at follow-up and the total study population (appendix).

We found a similar incidence of the primary outcome—death or any neurosensory disability at age 2 years (corrected for prematurity), as assessed by a paediatrician and psychometrist—in the dexamethasone ([33%] of infants) and betamethasone groups ([32%] of 591 infants; adjusted relative risk [RR] 0.97, 95% CI 0.83 to 1.13; p=0.66; table 2).

None of the birth-related secondary outcomes (ie, before hospital discharge) differed between groups, including the number of infants with respiratory distress syndrome [24%] of infants in the dexamethasone group vs [24%] of 737 infants in the betamethasone group; adjusted RR 1.03, 95% CI, 0.87 to 1.23; p=0.72), the severity of lung disease, or the number with an intraventricular haemorrhage [5%] infants vs [4%] infants; 1.09, 0.67 to 1.78; p=0.72) or a severe intraventricular haemorrhage (three [<1%] infants vs five [1%] infants; p=0.50; table 3). Gestational age at birth and infant weight, length, and head circumference did not differ between treatment groups at birth or at hospital discharge.

At 2 years corrected age, children in the dexamethasone group had lower systolic blood pressure Z scores (mean score 0.55 [SD 1.06] vs 0.64 [1.09]; adjusted mean difference −0.17, 95% CI −0.33 to −0.01; p=0.04) and fewer had blood pressure in the hypertensive range [32%] of with available data vs [41%] of 347 with available data; adjusted RR 0.78, 95% CI 0.64 to 0.95; p=0.02) compared with those in the betamethasone group (table 2). None of the other secondary outcomes that we assessed in children at age 2 years (corrected for prematurity) differed between the treatment groups.

We found a similar incidence of maternal perinatal infectious morbidities between the treatment groups (in [18%] of women in the dexamethasone group vs [20%] of women in the betamethasone group; adjusted RR 0.95, 95% CI 0.77 to 1.18; p=0.65; table 4).
Dexamethasone had no effect on the induction of labour, postpartum haemorrhage, need for transfusion, or length of maternal postnatal stay compared with betamethasone. However, (43%) of 679 women in the dexamethasone group had a caesarean birth versus (52%) of women in the betamethasone group (0.84, 0.75 to 0.93; p=0.0013); the number needed to treat to benefit is (95% CI 7 to 32). (3%) of women in the dexamethasone group and of 667 (4%) women in the betamethasone group reported side-effects (table 5). Discomfort at the injection site, which was the most common side-effect, was reported less frequently in the dexamethasone group than in the betamethasone group (six [1%] women vs 17 [3%] women; p=0.02).

In a prespecified sensitivity analysis of the primary outcome that used follow-up information from all sources, we found that (29%) of 727 infants in the dexamethasone group and (30%) of 711 infants in the betamethasone group died or had a neurosensory disability at age 2 years (adjusted RR 0.94, 95% CI 0.81 to 1.10; p=0.46). In post-hoc analyses, the incidence of fetal distress (reported on cardiotocography) and the indications for the caesarean birth, including the proportion of caesarean sections done for fetal compromise, did not differ between treatment groups.
<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone group (n=679)</th>
<th>Betamethasone group (n=667)</th>
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<tr>
<td><strong>Maternal age, years</strong></td>
<td>29.7 (6.1)</td>
<td>29.8 (6.3)</td>
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<tr>
<td><strong>Parity</strong></td>
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<td>Nulliparous</td>
<td>324 (48%)</td>
<td>300 (45%)</td>
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<td>Multiparous</td>
<td>355 (52%)</td>
<td>367 (55%)</td>
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<td><strong>Ethnicity</strong></td>
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<tr>
<td>European</td>
<td>518 (76%)</td>
<td>506 (76%)</td>
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<td>Asian</td>
<td>82 (12%)</td>
<td>93 (14%)</td>
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<td>Aboriginal or Torres Strait Islanders</td>
<td>30 (4%)</td>
<td>19 (3%)</td>
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<td>Polynesian</td>
<td>11 (2%)</td>
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<td>Maori</td>
<td>12 (2%)</td>
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<td>Other</td>
<td>26 (4%)</td>
<td>32 (5%)</td>
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<td><strong>Body mass index, kg/m²</strong></td>
<td>24.4 (21.2–28.6)</td>
<td>24.7 (21.8–29.7)</td>
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<td><strong>Gestational age at entry, weeks and days</strong></td>
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<td>29.6 (3.2)</td>
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<td>&lt;28 weeks gestation</td>
<td>202 (30%)</td>
<td>200 (30%)</td>
</tr>
<tr>
<td>≥28 weeks gestation</td>
<td>477 (70%)</td>
<td>467 (70%)</td>
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<td><strong>Sex</strong></td>
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<tr>
<td>Female</td>
<td>376/763 (49%)</td>
<td>359/764 (48%)</td>
</tr>
<tr>
<td>Male</td>
<td>387/763 (51%)</td>
<td>387/764 (52%)</td>
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<td><strong>Twin pregnancy</strong></td>
<td>84 (12%)</td>
<td>79 (12%)</td>
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<td><strong>Previous preterm birth (&lt;37 weeks gestation)</strong></td>
<td>121 (34%)</td>
<td>135 (37%)</td>
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<tr>
<td><strong>Previous perinatal deaths (≥20 weeks gestation)</strong></td>
<td>31 (9%)</td>
<td>37 (10%)</td>
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<td><strong>Main reasons for preterm birth</strong></td>
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<tr>
<td>Antepartum haemorrhage</td>
<td>157 (23%)</td>
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<td>Preterm prelabour rupture of membranes</td>
<td>137 (20%)</td>
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<td>184 (28%)</td>
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<td>Cervical incompetence</td>
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<td>Pre-eclampsia</td>
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<tr>
<td>Fetal compromise</td>
<td>60 (9%)</td>
<td>63 (9%)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (3%)</td>
<td>18 (3%)</td>
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</table>

Data are n (%) or n/N (%), mean (SD), or median (IQR). Ethnicity was self-reported by the participant.

*Table 1: Baseline maternal and pregnancy characteristics*
### Table 2: Primary and secondary childhood outcomes at 2 years

| Drug group data are in n/mean with available data (%) or mean (SD). Treatment effects are relative risks (95% CI), unless otherwise indicated. Adjustments were made for study hospital, gestational age at entry, number of fetuses, the infant’s sex, language spoken at home, and mother’s highest education level, unless otherwise specified. BISD-III-Bayley scales of infant development—III. GMFCS—all motor function classification system. NA—data not available. *Any death and death of liveborn infant before hospital discharge were adjusted for gestational age at entry and number of fetuses only.* Calculated with Fisher’s exact test. †Deafness was adjusted for study hospital, gestational age at entry, number of fetuses, the infant’s sex, and the mother’s highest education level only. Moderate cerebral palsy was defined as unlikely ever to walk (equivalent to GMFCS levels 4 and 5). Moderate cerebral palsy was defined as not walking at 2 years, but likely to become ambulant (equivalent to GMFCS levels 2 and 3); and mild cerebral palsy was defined as walking at 2 years (equivalent to GMFCS level 1). Treatment effects are odds ratios (95% CI) from separate logistic models (i.e., any cerebral palsy vs none; moderate or severe cerebral palsy vs none or mild; and severe cerebral palsy vs none, mild, or moderate). Severe developmental delay was defined as a standardised BISD-III score of more than 3 SD below the mean; moderate developmental delay was defined as a standardised BISD-III score of more than 2 SD to 3 SD below the mean; and mild developmental delay was defined as a standardised BISD-III score of more than 1 SD to 2 SD below the mean. Treatment effects are odds ratios of higher severity of the given disease (95% CI). Motor developmental delay was adjusted for study hospital, gestational age at entry, number of fetuses, language spoken at home, and mother’s highest education level only: **Treatment effects are mean differences (95% CI). ††Organised play group data were adjusted for gestational age at entry, number of fetuses, the infant’s sex, language spoken at home, and mother’s highest education level only.** |
| Drug group data are n (%) or mean (SD). Treatment effects are relative risks (95% CI) unless otherwise indicated. Analyses were adjusted for study hospital, gestational age at entry, and number of fetuses. Infant analyses were adjusted for clustering within mother. Z scores were estimated with the UK-WHO growth reference. *N=not available. †Treatment effects are mean differences (95% CI). ‡Used Fisher’s exact test. §Treatment effects are odds ratios (95% CI) from separate logistic models (ie, any respiratory distress syndrome vs none; moderate or severe respiratory distress syndrome vs none or mild; and severe respiratory distress syndrome vs none, mild, or moderate), since a proportional odds assumption is not met. Treatment effects are ratios of means (95% CI). |
DISCUSSION

In this multicentre, placebo-controlled randomised trial to compare dexamethasone with betamethasone given antenatally to women at risk of preterm birth, we found no significant difference in the primary outcome of death or neurosensory disability in their children at age 2 years (corrected for prematurity). Dexamethasone and betamethasone also had similar effects on infant health outcomes, including respiratory morbidity, intraventricular haemorrhage, and periventricular leukomalacia. Maternal infectious morbidity was also similar in both groups.

This trial is, to our knowledge, the largest randomised controlled comparison of the effectiveness of the two antenatal corticosteroids for accelerating fetal lung maturation that are recommended before preterm birth, and to provide data about the health of the women and their infants, including into early childhood.\(^{[12]}\) Previous data regarding these outcomes are conflicted: some non-randomised studies suggested that dexamethasone was associated with a greater risk of periventricular leukomalacia\(^{[9]}\) and neurosensory impairment\(^{[11]}\) compared with betamethasone, whereas systematic reviews of relevant randomised trials showed a decreased risk of intraventricular haemorrhage\(^{[12]}\) but also a possible greater risk of maternal chorioamnionitis.\(^{[1]}\) Our multicentre trial recruited a similar number of women and
their infants to the total number recruited in all the trials included in our Cochrane review\textsuperscript{[12]} of different corticosteroids for women at risk of preterm birth. Our results provide reassurance that none of these clinically important outcomes are significantly altered by the type of corticosteroid used. Our findings support the current guideline recommendations that either drug is appropriate for women at risk of preterm birth.\textsuperscript{[2–5]}

However, we found unexpected and potentially clinically important differences in some secondary outcomes between the treatment groups. First, women receiving dexamethasone were less likely to have a caesarean birth than those receiving betamethasone, with a number needed to treat to benefit of.\textsuperscript{[12]} In post-hoc analyses, we found no differences between treatment groups in the indications for caesarean birth and no differences in fetal distress on cardiotocography, suggesting that known differential corticosteroid effects on fetal cardiovascular and behavioural status\textsuperscript{[12,26]} do not fully explain our findings. Maternal outcomes, including mode of birth, have not been well reported in previous randomised trials,\textsuperscript{[1,12]} so this finding should be examined in other settings. Our data suggest that is uncertain because there are few reports of childhood blood pressure after exposure to antenatal corticosteroids, and because blood pressure measurements were only available in 60% of the children. In our previous randomised trial\textsuperscript{28} of single versus repeat courses of antenatal betamethasone (ACTORDS), 31% of children aged 2 years had hypertension, with a similar prevalence in children exposed to single and repeat courses. However, at age 6–8 years the prevalence of hypertension in that cohort had decreased to 7%, possibly reflecting, in part, the difficulty of accurate measurement of blood pressure at age 2 years or the effects of changing centiles as children age.\textsuperscript{[29]}

In the ASTEROID trial, the prevalence of hypertension in children exposed to dexamethasone (32%) was similar to that in the ACTORDS trial, but we found a higher prevalence (42%) in those exposed to betamethasone (ie, vs 31% in ACTORDS). Further follow-up will be required to determine whether these differences persist into later childhood. We acknowledge that we have performed several, planned, secondary analyses and that these two unexpected differences between treatment groups might reflect type 1 errors.

The major strengths of our trial are that it is considerably larger than previous randomised trials\textsuperscript{12} and, for this reason, we might have been able to detect differences that smaller studies were not able to identify. Even so, a larger sample size would be required to detect more marginal differences in death and neurosensory disability. Our trial assessed important
outcomes with assessors masked to treatment group, including perinatal outcomes that were previously not well reported, for women and for infants beyond the neonatal period. Earlier, retrospective studies\(^9\)–\(^{11}\) that compared dexamethasone and betamethasone have provided conflicting results on neonatal morbidity and a paucity of data on childhood neurodisability outcomes. Systematic reviews of the randomised trials alone\(^1\),\(^{12}\) and those also including cohort studies\(^3\) have highlighted the sparsity of comparative data available on neurodevelopmental outcomes, including cerebral palsy, after antenatal corticosteroid exposure before preterm birth. Only one previous randomised trial\(^1\)\(^5\) reported health outcomes following antenatal treatment with dexamethasone compared with betamethasone beyond the neonatal period, and this study was restricted to a sample of 12 children (11% of those recruited) who were assessed at age 18 months.

A possible weakness of our trial is that data were not collected on the use of postnatal corticosteroids, which could have affected outcomes if usage differed between the treatment groups. However, since the incidence of severe neonatal lung disease, chronic lung disease, and requirement for mechanical ventilation were all low and similar in the two groups, such a difference is unlikely.

When two possible treatments have similar efficacy and safety, selection of the lower cost option is normally preferred. Dexamethasone is 3% of the cost of betamethasone,\(^7\) is more readily available,\(^7\) and it is listed on WHO’s Essential Medicines List.\(^3\)\(^1\) A formal economic analysis would help to clarify the importance of these differences and could inform future policy guidance.

Although our study was done in 14 hospitals in two high-income countries with well coordinated, publicly funded, health-care systems, the results will be of relevance in other health-care settings. The lower cost and greater accessibility of dexamethasone means that it is the antenatal corticosteroid most often used in low-income and middle-income countries.\(^6\),\(^8\),\(^3\)\(^2\) However, experience has shown that the risks and benefits of antenatal corticosteroids can differ in resource-limited settings.\(^1\)\(^3\)

Clinicians who are using dexamethasone in their practice will be reassured by our findings of similar neonatal outcomes, a similar likelihood of survival free of neurosensory disability in early childhood, a similar risk of maternal infectious morbidity, and less maternal pain on injection when using a less expensive drug. In view of the higher use of caesarean section
observed with betamethasone, the higher risk of hypertension in exposed children, and greater drug costs, clinicians who are using betamethasone might wish to confirm our findings in subsequent randomised controlled trials.

Assessing any change in drug choice in clinical practice and monitoring short-term and long-term health outcomes will be important.

In conclusion, antenatal dexamethasone and betamethasone use provided similar likelihoods of survival free of neurosensory disability at age 2 years, and either can be given to women at risk of preterm birth to improve infant and child health. The incidence of neonatal respiratory morbidity and serious neonatal outcomes, including intraventricular haemorrhage, and of maternal infectious morbidity were similar in both groups. Fewer women randomly assigned to receive dexamethasone reported pain at the injection site, fewer gave birth by caesarean section, and dexamethasone-exposed children were less likely to be hypertensive at a 2-year follow-up than those exposed to betamethasone. These results can be used to aid decisions on the choice of corticosteroid to use for women at risk of preterm birth.

2. That antenatal corticosteroids are effective in preventing neonatal morbidity is not in dispute (Roberts 2006) and this life-saving therapy is now widely used throughout the world (Abeywandana 2005; Brocklehurst 1999; Foix-L’Helias 2008; NIH 2000; Quinlivan 1998; Saengwaree 2005). However, it is not yet clear which corticosteroid and which regimen performs best. Determining the optimal corticosteroid and optimal regimens is very important since most pregnant women at risk of preterm birth will be considered candidates for antenatal corticosteroid treatment (NIH 2000) and these numbers will increase as rate of preterm birth is increasing in a number of countries (Abeywandana 2005; Goldenberg 2007).

There is considerable variation reported between countries as to whether dexamethasone or betamethasone is preferred by health practitioners, with many likely reasons for these differences including availability and costs (dexamethasone is cheaper than betamethasone so is widely used in low-income countries) (Henderson-Smart 2007; Saengwaree 2005), impact of inconsistent findings from observational studies (Baud 1999; Lee 2006) and influence of opinion leaders (Jobe 2004).

Although we were able to include nine trials of moderate to good quality and one quasirandomised trial in this review, our ability to reach conclusions was limited by the small
number of comparisons of different antenatal steroid regimens. Most of the data available focused on the type of corticosteroid used, with nine of the studies comparing the two most commonly used corticosteroids, dexamethasone and betamethasone (with some variation in frequency and timing of administration).

The results of this review are broadly consistent with results of the Roberts 2006 Cochrane review of antenatal corticosteroids when they are recalculated as indirect comparisons of dexamethasone versus betamethasone (see Table 1). However, the suggestion of increased benefit of dexamethasone over betamethasone from this review for intraventricular haemorrhage is not sufficient evidence to support dexamethasone over betamethasone. A recent observational study, which reported reduced adverse neurological outcomes at 18 to 22 months for betamethasone but not for dexamethasone, highlights this uncertainty by stating that “to elucidate more fully predictive or causative neonatal or neurodevelopmental outcomes, a randomised clinical trial comparing dexamethasone and betamethasone should be performed” (Lee 2008). Such a trial would need to measure long-term effects, particularly for dexamethasone, as there have been no long-term follow-up studies for the antenatal use of this type of corticosteroid.

Although extensively reported in several of the included trials (Magee 1997; Mushkat 2001; Rotmensch 1999; Senat 1998; Subtil 2003), the clinical significance of differences in biophysical parameters such as fetal heart rate and respiratory rate is not clear (Rotmensch 1999). Overall these trials generally show few differences between dexamethasone and betamethasone. Some authors suggest that the influence of antenatal corticosteroids on parameters such as fetal heart rate is not clinically important, being a transient physiological response (Magee 1997; Rotmensch 1999; Subtil 2003).

Evidence about optimal doses, timing and frequency of administration of specific antenatal corticosteroids is even more sparse than that for type of corticosteroid. However, we feel it is important for emphasis for future research to be first directed towards establishing which corticosteroid (dexamethasone or betamethasone) is most effective in reducing neonatal morbidity, including assessment of long-term outcomes.

CONCLUSIONS
Dexamethasone may have some benefits compared with betamethasone such as less intraventricular haemorrhage and possibly some improved biophysical parameters, although a
higher rate of neonatal intensive care unit admission was seen for dexamethasone in one trial. Apart from the superiority of an intramuscular compared with an oral route for dexamethasone in one trial, very few other conclusions about optimal antenatal corticosteroid regimens were able to be made.

Further trials directly comparing the type, dose, frequency and route of betamethasone with dexamethasone for women at risk of preterm birth are required. They should be of high quality, large enough to assess morbidity and mortality of the fetus/infant, long-term outcomes and maternal outcomes. It would be helpful to start by conducting high-quality trials to establish which of the commonly used corticosteroids is most effective and causes least harm, followed by trials of dosages and other variations in regimens.

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