Blood Pressure at 6 Years of Age After Prenatal Exposure to Betamethasone: Follow-up Results of a Randomized, Controlled Trial

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ABSTRACT. *Objective.* To determine whether prenatal exposure to betamethasone for the prevention of neonatal respiratory distress syndrome (RDS) alters blood pressure in childhood.

Design. Prospective follow-up study of a randomized, double-blind, placebo-controlled trial.

Setting. National Women's Hospital (Auckland, New Zealand).

Participants. Two hundred twenty-three 6-year-old children of mothers who presented with unplanned premature labor and took part in a randomized, controlled trial of prenatal betamethasone therapy for the prevention of neonatal RDS.

Intervention. Mothers received 2 doses of betamethasone (12 mg) or placebo, administered through intramuscular injection, 24 hours apart.

Main Outcome Measures. Systolic and diastolic blood pressure at 6 years of age.

Results. Children exposed prenatally to betamethasone ($n = 121$) did not differ in systolic or diastolic blood pressure from children exposed to placebo ($n = 102$) (mean difference: systolic: −1.6 mm Hg; 95% confidence interval: −4.1 to 0.8 mm Hg; diastolic: −0.3 mm Hg; 95% confidence interval: −2.5 to 1.8 mm Hg).

Conclusion. Prenatal exposure to betamethasone for prevention of neonatal RDS does not alter blood pressure at 6 years of age. *Pediatrics* 2004;114:e373–e377. URL: http://www.pediatrics.org/cgi/content/full/114/3/e373; *prenatal glucocorticoids, respiratory distress syndrome, blood pressure, long-term follow-up.*

ABBREVIATIONS. RDS, respiratory distress syndrome; CI, confidence interval; RCT, randomized, controlled trial.

Neonatal respiratory distress syndrome (RDS) is a major cause of early morbidity and death among the 10% of neonates who are born prematurely. Prenatal glucocorticoid therapy is recommended in the management of preterm labor, for the prevention of RDS, and is very widely used. Such prenatal use of glucocorticoids results in substantial decreases in the rates of neonatal morbidity and death, as well as considerable cost savings. However,

the long-term physical effects remain poorly described.[1,2] Furthermore, fetal exposure to excess glucocorticoids has been proposed as one of the core mechanisms explaining the epidemiologic association between low birth weight and subsequent increased blood pressure (the fetal origins of adult disease hypothesis).[3] In a number of animal models, exposure to glucocorticoids before birth results in increased blood pressure in the offspring.[3,4] To date, the data on subsequent blood pressure among human subjects exposed prenatally to glucocorticoids for prevention of RDS have been contradictory. One nonrandomized cohort study found that extremely premature neonates exposed prenatally to glucocorticoids had higher blood pressure in the first 48 hours after birth.[5] Another nonrandomized cohort study of 177 fourteen-year-old children born preterm found that those exposed to glucocorticoids had higher mean systolic and diastolic blood pressures (mean difference: systolic: 4.1 mm Hg; 95% confidence interval [CI]: 0.1 to 8.0 mm Hg; diastolic: 2.8 mm Hg; 95% CI: 0.05 to 5.6 mm Hg).[6] In contrast, a small follow-up study of 81 twenty-year-old subjects from a randomized, controlled trial (RCT) found lower mean systolic blood pressure among those exposed prenatally to glucocorticoids (mean systolic blood pressure: male: 116 vs 119 mm Hg; female: 112 vs 116 mm Hg; $P = .05$).[7] There have been no reports of blood pressure in prepubescent children after prenatal glucocorticoid exposure. We analyzed prospective follow-up data on children from the first and largest RCT of prenatal glucocorticoid therapy (the Auckland Steroid Trial),[8,9] to assess the long-term effects of prenatal glucocorticoid exposure on later blood pressure.

METHODS

Protocol

The Auckland Steroid Trial and follow-up have been described previously.[8–11] Briefly, all women who were expected to deliver between 24 and 36 weeks at National Women's Hospital (Auckland, New Zealand), between December 1969 and February 1974, were eligible for enrollment unless immediate delivery was indicated. Women were randomized to receive an intramuscular injection of 6 mg of short-acting betamethasone phosphate and 6 mg of long-acting betamethasone acetate or an identical-appearing placebo injection of 6 mg of cortisone acetate (with 1/70th of the glucocorticoid potency). The allocated treatment was repeated 24 hours later if delivery had not occurred. If possible, labor was arrested with tocolytic agents for 48 hours. Primary endpoints were RDS and perinatal death.

A total of 1142 women were enrolled and delivered 1218 infants. The first 318 neonatal survivors (born between December

1969 and April 1972) delivered by women who presented with unplanned premature labor were followed-up at 4 years[10] and 6 years[11] of age. Verbal or written consent was obtained at the time of follow-up evaluation. This follow-up excluded infants born following planned premature delivery, in the presence of severe maternal hypertension-edema-proteinuria syndrome, or with major fetal abnormalities. Children were assessed by psychologists with respect to neurodevelopmental outcomes and by a pediatrician (A.L.) with respect to physical outcomes. No difference was found in neurodevelopmental outcomes at 4 years and 6 years of age.[10,11] We retrieved the follow-up trial data sheets and undertook analysis of the previously unpublished blood pressure data.

Blood pressure was measured by a pediatrician (A.L.), using an appropriately sized cuff and a standard mercury sphygmomanometer. The measurements were recorded from the dominant arm, after a 5-minute rest, with the child calmly seated. Diastolic blood pressure was recorded as the fourth Korotkoff sound. Ethical approval for the Auckland Steroid Trial and follow-up study was obtained from the National Women's Hospital Medical Committee.

Assignment and Masking

Randomization was generated, via random number tables, by the chief pharmacist, who held the randomization key. The study drug was supplied in identical numbered ampoules. Women were enrolled in the trial by obstetric staff members. Staff members who cared for the women and the infants were blinded with respect to the study allocation. Pediatricians and psychologists who assessed the children in the neonatal period and in childhood were also blinded with respect to the study allocation.

Participant Flow and Follow-up

By April 1972, 465 women had delivered 499 infants: 263 exposed to betamethasone and 236 exposed to placebo. Fifty-one betamethasone-exposed and 50 placebo-exposed children died in the neonatal period. Thirty-five betamethasone-exposed and 45 placebo-exposed children were excluded from the follow-up study because their births were not considered to be the result of simple, unplanned, premature labor. Follow-up evaluation was attempted for 318 children. By 6 years of age, 7 betamethasone-exposed and 7 placebo-exposed children had died. Of the remaining 304 children, 54 were lost to follow-up, 14 had lost follow-up records, and 5 did not undergo blood pressure recording (Fig 1). The 8 children who had been randomized more than once during the same pregnancy were excluded from analyses.

Statistical Analyses

Analyses were performed with SAS version 8.02 software.[12] Continuous variables were compared with unpaired t tests or Mann-Whitney tests for parametric and nonparametric data, respectively. Categorical data were compared with χ^2 tests as appropriate. Point estimates are given as means, medians, or relative risks with 95% CIs.[13] Possible confounders were analyzed with multiple linear regression analyses, using the change-in-estimates technique at the 10% level.[14] Age at follow-up evaluation, gender,
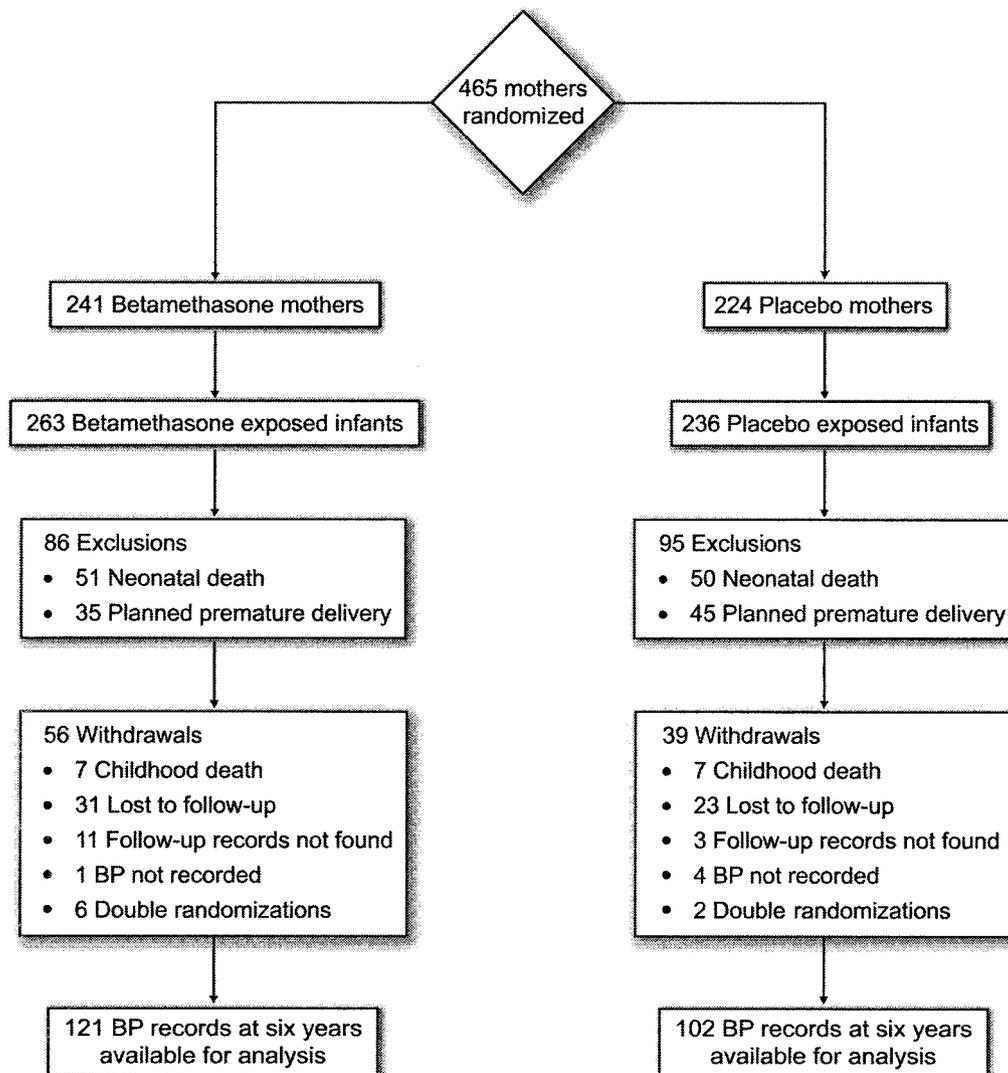

Fig 1. Participant flow to follow-up evaluation at 6 years. BP indicates blood pressure.

TABLE 1. Neonatal Characteristics of Children With and Without Blood Pressure Follow-up Data at 6 Years of Age Available for Analysis

Neonatal Variables	BP Records (n = 223)*	No BP Records or Follow-Up Data (n = 95)*	Difference (95% CI)†	P
Birth weight, g	2190 (1860 to 2650)	2060 (1760 to 2710)	80 (−70 to 250)	.24
Birth weight z score‡	−0.35 (−0.82 to 0.18)	−0.34 (−0.76 to 0.18)	−0.02 (−0.19 to 0.16)	.74
Gestational age, d	244 (231 to 259)	239 (224 to 259)	4 (−2 to 9)	.12
Entry/delivery interval, d	2.6 (1 to 29)	3.6 (1–31)	−0.3 (−1.5 to 0.5)	.67
Term delivery	59 (26.5%)	24 (25.3%)	0.95 (0.63 to 1.44)	.82
Male	128 (57.4%)	55 (57.9%)	1.01 (0.82 to 1.24)	.93
Betamethasone	121 (54.3%)	56 (58.9%)	1.09 (0.88 to 1.34)	.44
RDS	21 (9.4%)	11 (11.6%)	1.23 (0.62 to 2.45)	.56
RDS (moderate or severe)	18 (8.1%)	7 (7.4%)	0.91 (0.39 to 2.11)	.83
5-min Apgar score of >7	172 (77.1%)	72 (75.8%)	0.98 (0.86 to 1.12)	.80
Multiple pregnancy	28 (12.6%)	20 (21.1%)	1.68 (1.00 to 2.82)	.05
Instrumental delivery	114 (51.1%)	50 (52.6%)	1.03 (0.82 to 1.30)	.81

BP indicates blood pressure.
* Data are either median (interquartile range) or count (percentage).
† Data are either difference between medians (95% CI) or relative risk (95% CI).
‡ Based on all live births in New Zealand, 1991/1992.[15]

birth weight z score, and body mass index were included in the final model a priori.

RESULTS

Blood pressure was analyzed for 223 children of the 318 for whom follow-up evaluations were attempted (70%). For those analyzed, delivery occurred at a median gestation time of 34 weeks 6 days. The neonatal characteristics of the children whose blood pressure recordings were analyzed did not differ from those of the children whose recordings were not analyzed (Table 1).

Blood pressure records were available for analysis for 121 betamethasone-exposed children (median

age: 6 years 3 months) and 102 placebo-exposed children (median age: 6 years 2 months). The neonatal characteristics and possible confounders at follow-up evaluation did not differ between the 2 treatment groups (Table 2).

Neither systolic blood pressure nor diastolic blood pressure differed significantly between the 2 treatment groups (mean difference: systolic: −1.6 mm Hg; 95% CI: −4.1 to 0.8 mm Hg; P = .19; diastolic: −0.3 mm Hg; 95% CI: −2.5 to 1.8 mm Hg; P = .74) (Fig 2). Adjustment for age, gender, birth weight z score, body mass index, and age at the introduction of solid foods did not alter the result (Fig 2).

TABLE 2. Neonatal and 6-Year Follow-up Characteristics of Children With Blood Pressure Follow-up Data at 6 Years of Age Available for Analysis Who Were Exposed Prenatally to Betamethasone or Placebo

	Betamethasone*		Placebo*		Difference (95% CI)†	P
	n	Parameter	n	Parameter		
Neonatal variables						
Birth weight, g	121	2110 (1820 to 2620)	102	2295 (1950 to 2700)	−170 (−320 to 0)	.05
Birth weight z score‡	121	−0.36 (−0.92 to 0.1)	102	−0.35 (−0.78 to 0.23)	−0.08 (−0.29 to 0.13)	.50
Gestational age, d	121	241 (230 to 259)	102	245 (238 to 259)	−6 (−11 to 0)	.08
Entry/delivery interval, d	121	3.1 (1.1 to 27)	102	2.4 (1 to 31)	0 (−0.7 to 0.5)	.99
Term delivery	121	31 (25.6%)	102	28 (27.5%)	0.93 (0.60 to 1.45)	.76
Male	121	72 (59.5%)	102	56 (54.9%)	1.08 (0.86 to 1.36)	.49
RDS	121	10 (8.0%)	102	11 (10.8%)	0.77 (0.34 to 1.73)	.52
RDS (moderate or severe)	121	9 (7.4%)	102	9 (8.8%)	0.84 (0.35 to 2.04)	.71
5-min Apgar score of >7	121	95 (78.5%)	102	77 (75.5%)	1.04 (0.90 to 1.20)	.59
Multiple pregnancy	121	16 (13.2%)	102	12 (11.8%)	1.12 (0.56 to 2.26)	.74
Instrumental delivery	121	59 (48.8%)	102	55 (53.9%)	0.90 (0.70 to 1.17)	.44
6-year follow-up variables						
Age at follow-up, mo	121	75 (74 to 76)	102	74 (74 to 75)	0 (0–1)	.34
Height, cm	119	116.1 (112.5 to 120.1)	102	116.4 (112.7 to 120.0)	−0.1 (−1.4 to 1.2)	.81
Weight, kg	118	21.3 (19.5 to 23.4)	101	21 (19.6 to 23.3)	0 (−0.7 to 0.7)	.78
Head circumference, cm	121	52.1 (51.1 to 53)	102	51.9 (51 to 53)	0.2 (−0.2 to 0.6)	.32
Body mass index, kg/m²	118	15.8 (15.0 to 16.7)	101	15.7 (14.9 to 16.6)	0.1 (−0.2 to 0.4)	.73
Low income§	119	19 (16.0%)	102	19 (18.6%)	0.86 (0.48 to 1.53)	.11
Maternal smoking	119	62 (52.1%)	102	51 (50.0%)	1.04 (0.80 to 1.35)	.42
Paternal smoking	119	65 (54.6%)	102	57 (55.9%)	0.98 (0.77 to 1.24)	.60
Age solids introduced (wk)	99	12 (8 to 16)	90	12 (8 to 16)	2 (0 to 4)	.76
Breastfed	101	25 (24.8%)	90	27 (30.0%)	0.83 (0.52 to 1.31)	.85

* Data are either median (interquartile range) or count (percentage).
† Data are either difference between medians (95% CI) or relative risk (95% CI).
‡ Based on all live births in New Zealand, 1991/1992.[15]
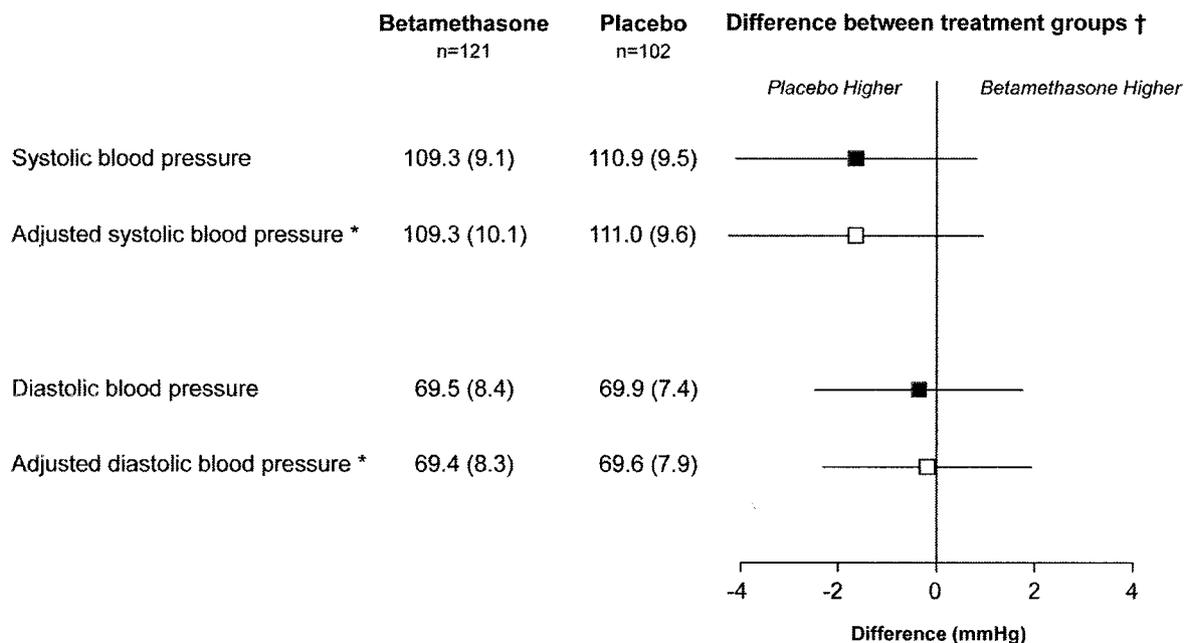§ Household income of <$5000 (1976–1978 New Zealand dollars) or receiving state social welfare benefit.

	Betamethasone n=121	Placebo n=102	Difference between treatment groups †
			Placebo Higher | Betamethasone Higher
Systolic blood pressure	109.3 (9.1)	110.9 (9.5)	
Adjusted systolic blood pressure *	109.3 (10.1)	111.0 (9.6)	
Diastolic blood pressure	69.5 (8.4)	69.9 (7.4)	
Adjusted diastolic blood pressure *	69.4 (8.3)	69.6 (7.9)	

Difference (mmHg) [-4, -2, 0, 2, 4]

Fig 2. Systolic and diastolic blood pressure at 6 years. Data are mean (SD) mm Hg. *Adjusted for age at follow-up evaluation, gender, birth weight z score, body mass index, and age at the introduction of solids. †Difference between means and 95% CI.

DISCUSSION

Our study showed that prenatal exposure to a single course of betamethasone for the prevention of RDS did not alter blood pressure at 6 years of age. This result adds to the body of evidence indicating that a single course of prenatal betamethasone treatment does not cause long-term adverse outcomes.[1,2]

Our study is the first to report blood pressure among prepubescent children after prenatal exposure to betamethasone and comes from the first and largest RCT in the field. The only other report of blood pressure from a RCT of prenatal betamethasone exposure was from a smaller study, at a mean age of 20 years.[7] The authors found that systolic blood pressure was significantly lower among the betamethasone-exposed offspring. This finding is potentially consistent with the trend toward lower systolic blood pressure among the betamethasone-exposed children in our study. We are currently undertaking additional follow-up of this cohort (now ~30 years of age), which should clarify whether this trend becomes more apparent with age.

Our findings differ from those for a previous, non-randomized, preterm cohort studied in adolescence.[6] It is possible that the reasons why mothers did or did not receive glucocorticoids in that cohort might have introduced unidentified biases, which might account for the higher blood pressure in the exposed offspring. It is also possible that the effects of glucocorticoid exposure vary with birth weight or gestation. The adolescents studied all had birth weights of <1500 g, whereas our study included only 20 children with birth weights of <1500 g (9%). Although adjustment for prematurity did not alter our results, the small numbers of very preterm children might have limited our ability to detect such an effect, if present.

The exclusion from follow-up study of 80 children might be viewed with concern, in light of the current preference for intention-to-treat analyses. Thirty years ago, however, infants classified as having major fetal abnormalities experienced much higher morbidity and mortality rates than those seen in current clinical practice. Furthermore, obstetric management of the conditions representing the other exclusion criteria has changed dramatically. Therefore, the children born after unplanned premature labor who were the subject of this study perhaps represent the group most directly comparable to similar children who are currently exposed prenatally to glucocorticoids. Within this group, the follow-up rate was 70%. The losses to follow-up should be of concern only if they were different for the treated and placebo groups; there was no evidence that this was the case.

In fact, this cohort was particularly suitable for assessment of the long-term effects of prenatal glucocorticoid exposure, because there was little evidence of differences in neonatal morbidity rates between the 2 groups, which might have affected later blood pressure. In the Auckland Steroid Trial as a whole, rates of the primary endpoints of RDS and perinatal death were significantly reduced among the glucocorticoid-exposed infants. In this subgroup of survivors, however, the incidences of RDS, low Apgar scores, and neonatal infection were all similar in the betamethasone-exposed and placebo-exposed groups. Therefore, it seems unlikely that differences in neonatal illness severity or treatments could explain our findings.

An additional concern might be that this study included only 8 children born at <30 weeks of gestation. However, the expected neonatal outcomes for these very immature infants today are similar to those for our more mature cohort 30 years ago.

Although our study does not provide direct support for the glucocorticoid hypothesis for fetal ori-

gins of adult disease,[16] it does not refute it. Our results showed that exposure of a human fetus in late gestation to a single course of maternal betamethasone treatment for prevention of RDS did not program blood pressure in childhood. However, that exposure resulted in fetal glucocorticoid levels that were similar to those induced by the stress of premature delivery and RDS and were much lower than those resulting from the administration of glucocorticoids to prevent or treat neonatal chronic lung disease.[1] In contrast, the many animal studies that demonstrated that prenatal glucocorticoid exposure programmed postnatal blood pressure involved exposure either very early in gestation[4] or in high doses for long periods.[3] Unfortunately, there are no studies on animals of short-term, lower-dose exposure, comparable to that used in clinical practice. It remains possible that earlier and/or longer glucocorticoid exposure could program postnatal blood pressure in human populations, although the critical exposure period and size of the effect among human subjects remain unclear. Because current obstetric practice often involves glucocorticoid administration beginning much earlier in gestation than in this trial, with repeated courses,[17] long-term follow-up monitoring of more recent RCT participants will be essential for clarification of this issue.

Our study suggests that obstetricians can continue to use a single course of prenatal glucocorticoid treatment for the prevention of neonatal RDS with the confidence that such exposure does not alter blood pressure at 6 years of age. The long-term effects among human subjects of repeated courses of prenatal glucocorticoid treatment and of exposure in early gestation remain unknown.

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