Cardiovascular Follow-up at School Age After Perinatal Glucocorticoid Exposure in Prematurely Born Children

Perinatal Glucocorticoid Therapy and Cardiovascular Follow-up

Willem B. de Vries, MD, PhD; Rosa Karemaker, MD, PhD; Nicole F. Mooy; Jan L. M. Strengers, MD, PhD; Hans Kemperman, MD, PhD; Wim Baerts, MD, PhD; Sylvia Veen, MD, PhD; Gerard H. A. Visser, MD, PhD; Cobi J. Heijnen, PhD; Frank van Bel, MD, PhD

Objective: To study whether antenatal or neonatal glucocorticoid therapy to reduce the incidence and severity of chronic lung disease in preterm infants is associated with long-term adverse cardiac effects and hypertension.

Design: Retrospective matched-cohort study.

Setting: Outpatient clinic of a tertiary care hospital.

Participants: One hundred ninety-three children aged 7 to 10 years who had been born prematurely between December 2, 1993, and September 15, 1997.

Main Exposure: Neonatal treatment with dexamethasone disodium phosphate (n=48) or the clinically equally effective glucocorticoid hydrocortisone (n=51), or only antenatal treatment with betamethasone disodium phosphate and betamethasone acetate (n=51). These 3 groups were compared with a reference group of prematurely born children who had not been exposed to perinatal glucocorticoid therapy (n=43).

Main Outcome Measures: General hemodynamic data (heart rate and blood pressure), cardiovascular function as assessed at echocardiography, intima-media thickness of the carotid arteries, and cardiac biochemical features as early markers of expansion and volume overload of the cardiac left ventricle (B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide).

Results: No significant group differences were found for heart rate, blood pressure, biochemical features, intima-media thickness, or systolic or diastolic left ventricular function.

Conclusions: Although no differences were found in blood pressure and cardiovascular function at school age in children antenatally or neonatally treated with glucocorticoids, further cardiovascular follow-up may be advisable because cardiovascular dysfunction may become apparent only later in life.

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Author Affiliations:
Departments of Neonatology (Drs de Vries, Karemaker, and van Bel), Pediatric Cardiology (Ms Mooy and Dr Strengers), Clinical Chemistry and Haematology (Dr Kemperman), and Obstetrics (Dr Visser), and Laboratory for Psychoneuroimmunology (Drs Karemaker and Heijnen), University Medical Center Utrecht, Utrecht; Department of Neonatology, Isala Clinics, Zwolle (Dr Baerts); and Department of Neonatology, University Medical Center Leiden, Leiden (Dr Veen); the Netherlands.
et al\(^\text{17}\) reported no abnormalities in global cardiac function at age 8 years. Animal studies, however, showed untimely degeneration of cardiomyocytes after neonatal dexamethasone therapy as a result of temporary arrest of proliferation of cardiomyocytes\(^\text{17}\) and hypertension during adulthood.\(^\text{18}\)

In the present study, we investigated blood pressure and cardiovascular function by assessing systolic and diastolic function of the left ventricle (LV), intima-media thickness of the carotid arteries, and early biochemical markers of ventricular expansion and volume overload at school age (age 7-10 years) in 3 retrospective matched cohorts of prematurely born children who had been treated neonatally with either dexamethasone or hydrocortisone or treated only antenatally with betamethasone. These groups were compared with a reference group of prematurely born infants not treated with antenatal or neonatal glucocorticoids. We hypothesized that, in comparison with the reference group, neonatal dexamethasone treatment but not hydrocortisone treatment or antenatal betamethasone treatment will lead to higher blood pressure and altered cardiovascular function.

The study population in this retrospective matched-cohort study consisted of prematurely born infants admitted to the neonatal intensive care units (NICUs) of University Medical Center Utrecht/ Wilhelmina Children’s Hospital, Leiden University Medical Center, Free University Medical Center Amsterdam, and Isala Clinics Zwolle, all in the Netherlands, between December 2, 1993, and September 15, 1997. The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht and by the scientific boards of the 4 participating hospitals. Written parental consent was obtained for all study participants. The NICU of the University Medical Center Utrecht/Wilhelmina Children’s Hospital used neonatal hydrocortisone therapy exclusively to prevent or to reduce the incidence and severity of “chronic lung disease,” defined as the need for additional oxygen at 36 weeks’ postmenstrual age because of severe respiratory distress syndrome, with a course starting at 5 mg/kg/d and tapering to 1 mg/kg/d over 22 days. The other NICUs used dexamethasone for this purpose, with a course starting at 0.5 mg/kg/d and tapering to 0.1 mg/kg/d over 21 days. At all centers, glucocorticoid therapy was occasionally extended depending on patient response. Treatment indication was in all instances used as a rescue method, that is, the inability to wean the infant from ventilation therapy in addition to prolonged dependency on supplemental oxygen (fractional concentration of oxygen in inspired gas >0.30), always based on the initial phase of chronic lung disease. In addition to these 2 groups treated neonatally with glucocorticoids, a group of prematurely born infants treated antenatally with betamethasone (two 12-mg intramuscular injections in the mother, with an interval of 24 hours between injections) who had not been treated neonatally with glucocorticoids and a reference group of preterm infants who had not received antenatal or neonatal glucocorticoid therapy were included. Moreover, the latter 2 groups did not receive postnatal glucocorticoid therapy at any time in their first year of life.

**STUDY GROUPS**

Criteria for inclusion in one of the study groups were as follows: (1) availability to participate in the study protocol; (2) no or grade 1 or 2 periventricular or intraventricular hemorrhage as classified according to Papile et al\(^\text{19}\); and (3) absence of major congenital anomalies. Infants with periventricular leukomalacia were also excluded. With 52 children in each group, it should be possible to detect clinically significant group differences in the examined cardiac measures, assuming an α value of 0.05 and power of 0.80. The hydrocortisone group was composed of infants from the NICU of Wilhelmina Children’s Hospital born before 32 completed weeks of gestation who were treated with hydrocortisone during the defined period, and the dexamethasone-treated group was recruited similarly from the other 3 NICUs, which used only dexamethasone for reduction of incidence and severity of chronic lung disease. Infants who fulfilled the inclusion criteria were matched for birth year, birth weight, gestational age, period of admission, severity of respiratory distress syndrome (classified as no, moderate, or severe according to clinical symptoms and the classification of Giedion et al\(^\text{20}\)), and presence or absence of a minor periventricular or intraventricular hemorrhage (grade 1 or 2). To ensure that possible differences in outcome between hydrocortisone and dexamethasone therapy were related to use of a different choice of glucocorticoids and not to differences in clinical management, we also evaluated the ratio of inborn to outborn, postnatal age at the start of glucocorticoid therapy (Table 1), and incidences of neonatal sepsis and necrotizing enterocolitis in the hydrocortisone and dexamethasone groups. No difference was found for any of these variables. In the Netherlands, neonatal intensive care is highly organized with structural deliberation between the 10 Dutch NICUs with respect to patient care strategies.

Participants in the antenatal betamethasone treatment group and those in the reference group were also recruited from the 4 participating NICUs. The betamethasone and reference groups consisted of children who had been born prematurely who were not treated postnatally with glucocorticoids. Although we tried to match these latter groups for gestational age and birth weight with a dexamethasone- and hydrocortisone-treated couple, this was not always possible.

**STUDY PROTOCOL**

The follow-up team consisted of a neonatologist (W.dV.), a doctoral student (R.K.), and a research nurse trained to perform a medical evaluation including weight, height, and general hemodynamic data. Cardiac function was analyzed using 2-dimensional echocardiography. Intima-media thickness of both carotid arteries was measured (see “Intima-Media Thickness Measurements” subsection), and cardiac biochemical features were obtained. The follow-up team was unaware of the treatment that the child had received. All participating children were studied in the outpatient clinic of Wilhelmina Children’s Hospital.

**GENERAL HEMODYNAMIC DATA**

Heart rate and systolic and diastolic blood pressure were obtained at the beginning of the medical evaluation for each individual in the morning, while the child was sitting.

**CARDIAC FUNCTION**

Echocardiography was performed following a standardized protocol using an ultrasound system (Vivid 7; GE Medical Systems, Milwaukee, Wisconsin). Measurements were performed off-line using software provided by the manufacturer.

Systolic LV function was assessed by determining cardiac output and cardiac index (cardiac output/body surface area),
stroke volume, fractional shortening, and ejection fraction.\textsuperscript{21} Diastolic LV function was assessed by determining mitral valve (MV) early diastolic peak velocity, MV deceleration time, ratio of MV early diastolic peak velocity to late (atrial) diastolic peak velocity, and LV internal dimension in diastole.\textsuperscript{21} Possible myocardial hypertrophy was assessed by determination of LV mass in diastole and LV mass index (LV mass/body surface area).\textsuperscript{21}

### BIOCHEMICAL FACTORS

B-type natriuretic peptide (BNP) and N-terminal pro-BNP were used as early markers of ventricular expansion and volume overload.\textsuperscript{22-24} Immunochemistry was used to analyze BNP (ADVIA Centaur immunoassay system; Bayer Healthcare Diagnostics Division, Tarrytown, New York) and N-terminal pro-BNP (Elecys immunochemistry system; Roche Diagnostics, Indianapolis, Indiana).

### INTIMA-MEDIA THICKNESS MEASUREMENTS

Both left and right common carotid arteries were recorded in B-mode ultrasonography (HDI 5000 ultrasound system; ATL Ultrasound/Philips Medical Systems International BV, Best, the Netherlands). Longitudinal images of the far wall of the carotid artery were obtained approximately 1 cm proximal to the bifurcation. The intima-media thickness measurements were performed off-line. A total of 6 measurements were obtained. The median of the multiple measurements of left and right intima media thickness per individual was computed and used for analysis.

### STATISTICAL ANALYSIS

Data are presented as mean (SD), median (range), or as percentage where appropriate. Continuous data were analyzed using analysis of variance followed by the Bonferroni post hoc test procedure if a significant difference was detected. Categorical data were compared using the \(\chi^2\) test. Given the patient characteristics (Table 1), we corrected for sex, gestational age, age at day of testing, antenatal glucocorticoid treatment, and hospital where neonatal treatment was administered. All statistical analyses were performed using commercially available software (SPSS version 12.0.1; SPSS Inc, Chicago, Illinois). \(P < .05\) was considered statistically significant.

### RESULTS

Two hundred eight children who had been born prematurely at less than 32 weeks of gestation were initially included in the study, with 52 children in each group. Fifteen patients were excluded from the study (Figure). One hundred ninety-three children composed the final population. The Figure shows subject flow from enrollment to follow-up.

### IMPORTANT CLINICAL PERINATAL AND FOLLOW-UP DATA

Perinatal and neonatal characteristics are given in Table 1. Although we tried to match the reference and betamethasone-
treated groups with the hydrocortisone- and dexamethasone-treated groups, the first 2 groups had significantly higher birth weight, gestational age, and head circumference at birth and less severe respiratory distress syndrome with fewer days of mechanical ventilation. In addition, the sex ratio was different, favoring boys in the hydrocortisone- and dexamethasone-treated groups compared with the reference and betamethasone-treated groups. To have an indication for illness severity with respect to chronic lung disease and its potential effect on the cardiovascular features studied, we determined the number of children who had chronic lung disease at 36 weeks' postmenstrual age (ie, the need for supplemental oxygen; see “Methods” section). No differences were noted between the dexamethasone- (n=10) and hydrocortisone-treated (n=9) groups.

The general characteristics of the children at follow-up are given in Table 1. A slight difference in age was noted between the dexamethasone-treated group and both the reference and hydrocortisone-treated groups. We considered this small difference in age of no clinical relevance.

**GENERAL HEMODYNAMIC DATA**

Heart rate and blood pressure were within the normal range (Table 2). No group differences were detected.

**CARDIAC FUNCTION**

Our primary focus was on cardiac (systolic and diastolic) function and possible LV myocardial hypertrophy. For systolic function, values were within the normal range in all children, and no differences in cardiac output, stroke volume, cardiac index, shortening fraction, or ejection fraction were noted between the groups (Table 2). Similar observations were made for all diastolic measures (MV early diastolic peak velocity, MV deceleration time, LV internal dimension in diastole, and ratio of MV early diastolic peak velocity to late [atrial] diastolic peak velocity) (Table 2). None of the groups exhibited signs of myocardial hypertrophy (LVd Mass internal dimension in diastole), and we did not observe differences between groups for this outcome measure (Table 2).

**BIOCHEMICAL FACTORS**

Values for BNP and N-terminal pro-BNP were all within the normal range, and no group differences were observed (Table 3).

**INTIMA-MEDIA THICKNESS MEASUREMENTS**

Values for intima-media thickness of the carotid arteries were within the normal range, and no group differences were observed (Table 3).

In the present study, in children aged 7 to 10 years, no differences were noted between those who had been born...
prematurely and treated neonatally with dexamethasone or hydrocortisone or antenatally with betamethasone compared with the reference group of children who had been born prematurely with respect to long-term changes in blood pressure or cardiac function, even though children in the betamethasone-treated and reference groups were more mature, had higher birth weights, and had less severe chronic lung disease. Carotid artery intima-media thickness or early markers of ventricular expansion and volume overload (BNP and N-terminal pro-BNP) were also not different compared with the reference group. This led us to reject our hypothesis that dexamethasone-treated children had less optimal cardiac function than hydrocortisone-treated children at the age of 7 to 10 years compared with the reference group.

These results are in line with those of earlier (scarce) studies that investigated possible prolonged effects of neonatal dexamethasone treatment on cardiovascular function. A small study by Mieskonen et al16 investigated the cardiovascular status in eight 8-year-old children treated neonatally with dexamethasone, which did not differ from 8 children who did not receive neonatal dexamethasone treatment. Furthermore, a recent study by Jones20 reported on blood pressure in a group of 187 children aged 13 to 17 years who had participated in a randomized controlled trial of neonatal dexamethasone therapy because of chronic lung disease. These authors also found no differences in blood pressure between children who received dexamethasone and those who received placebo. With respect to the relation between exposure to antenatal glucocorticoid treatment for reduction of the incidence of respiratory distress syndrome and cardiovascular function, Dessens et al27 found no difference in blood pressure in 48 young adults aged 20 to 22 years who had been treated antenatally with betamethasone compared with a control group.27 Dalziel et al28 reported no clinical effect on cardiovascular risk factors at age 30 years in 534 individuals whose mothers participated in a double-blind, placebo-controlled, randomized trial of antenatal betamethasone therapy for the prevention of respiratory distress syndrome. A recent study by Mildenhall et al29 in neonates (birth to 4 weeks of age) treated

| Table 2. Blood Pressure, Heart Rate, and Myocardial Performance Indices |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Variable                    | Reference Group (n = 43)    | Antenatal Betamethasone-Treated Group (n = 51) | Postnatal Hydrocortisone-Treated Group (n = 51) | Postnatal Dexamethasone-Treated Group (n = 48) |
| Blood pressure, mean (SD), mm Hg | 102 (14)                   | 104 (11)                   | 103 (13)                   | 99 (12)                     |
| Systolic                    | 65 (11)                    | 67 (11)                    | 66 (10)                    | 64 (11)                     |
| Heart rate, mean (SD), bpm  | 82 (12)                    | 83 (14)                    | 83 (11)                    | 84 (13)                     |
| Systolic function           | Cardiac output, mean (SD), L/min | 2.87 (0.86)               | 2.93 (0.71)               | 2.80 (0.66)               | 2.78 (0.81)               |
| Cardiac index, mean (SD), L/min/m² | 2.75 (0.68)               | 2.84 (0.65)               | 2.76 (0.62)               | 2.88 (0.64)               |
| Stroke volume, mean (SD), mL | 49.1 (10.3)                | 49.3 (9.1)                | 48.1 (8.9)                | 46.7 (11.5)                |
| Fractional shortening, %    | 38.8 (5.3)                 | 39.3 (4.3)                | 39.1 (5.5)                | 40.7 (4.7)                |
| Ejection fraction, %         | 69.3 (8.5)                 | 70.2 (5.2)                | 69.8 (6.9)                | 71.9 (5.4)                |
| Diastolic function          | Mitral valve early diastolic peak velocity, mean (SD), m/s | 1.07 (0.16)               | 1.06 (0.13)               | 1.06 (0.18)               | 1.09 (0.15)               |
| Mitral valve deceleration time, mean (SD), ms | 201.2 (48.8)              | 209.7 (69.9)              | 197.2 (42.8)              | 197.6 (57.4)              |
| Ratio of mitral valve early diastolic peak velocity and late (atrial) diastolic peak velocity | 1.96 (0.55)               | 1.82 (0.41)               | 1.91 (0.53)               | 1.85 (0.42)               |
| LVID, mean (SD), cm         | 4.01 (0.32)                | 3.97 (0.35)               | 3.96 (0.27)               | 3.85 (0.36)               |
| Wall thickness              | LVID mass, mean (SD), g    | 75.8 (18.1)                | 74.8 (19.0)                | 77.4 (18.9)                | 69.8 (21.4)                |
| LVID index,a mean (SD), g/m² | 73.2 (16.3)                | 72.0 (16.4)               | 75.5 (15.4)               | 71.2 (18.9)               |

Abbreviations: bpm, beats per minute; LVID mass, left ventricular mass in diastole; LVID, left ventricular internal dimension in diastole.

Table 3. Biochemical Markers and Intima-Media Thickness

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Group (n = 43)</th>
<th>Antenatal Betamethasone-Treated Group (n = 51)</th>
<th>Postnatal Hydrocortisone-Treated Group (n = 51)</th>
<th>Postnatal Dexamethasone-Treated Group (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP, mean (SD), pmol/L</td>
<td>2.9 (1.7)</td>
<td>3.1 (1.8)</td>
<td>2.5 (1.7)</td>
<td>2.7 (1.8)</td>
</tr>
<tr>
<td>N-terminal pro-BNP, mean (SD), pmol/L</td>
<td>5.39 (3.77)</td>
<td>5.58 (2.97)</td>
<td>5.26 (3.81)</td>
<td>5.52 (3.55)</td>
</tr>
<tr>
<td>Intima-media thickness, mean (SD), mm</td>
<td>0.38 (0.05)</td>
<td>0.39 (0.05)</td>
<td>0.39 (0.03)</td>
<td>0.38 (0.04)</td>
</tr>
</tbody>
</table>

Abbreviation: BNP, B-type natriuretic peptide.
tally with either a single course or repeated courses of glucocorticoid therapy to reduce the incidence and severity of respiratory distress syndrome found no differences in blood pressure or echocardiographically determined myocardial performance compared with a comparable group of infants whose mothers had refused to enter the initial trial.

Neither antenatal nor neonatal glucocorticoid therapy in prematurely born infants induced cardiovascular changes in the long run. Does this mean that glucocorticoid therapy can be safely administered in the preterm infant or fetus? We are not fully convinced, at least with respect to neonatal dexamethasone treatment. This hesitation is based on results of earlier animal studies conducted by our group. Newborn rat pups who were treated on days 1, 2, and 3 with dosages of dexamethasone comparable to dosages used in preterm human neonates showed suppression of normal cardiomyocyte proliferation during dexamethasone treatment and a reduced number of cardiomyocytes during adulthood that may directly result from the inhibition of proliferation. In a simultaneously performed survival study of neonatal rats treated with dexamethasone, however, it seemed that dexamethasone-treated rats developed hypertension during early adulthood and cardiovascular and renal disease later in life, resulting in early death in both male and female rats. Although a histopathologic study of these rats treated neonatally with dexamethasone at 45 weeks of age (normal life span, 2½-3 years) showed cardiomyocyte hypertrophy and signs of early degeneration, only relatively late in adulthood (80 weeks) did abnormal cardiac function become clearly manifested, with significantly decreased systolic function, compared with rats not treated with dexamethasone (M. P. Bal, MD, PhD, and P. Steendijk, PhD; unpublished data; April 2007). This suggests that cardiomyocyte hypertrophy may initially compensate for the loss of cardiomyocytes during neonatal dexamethasone treatment but that cardiac function in these rats deteriorated relatively late during adulthood, ultimately resulting in a shortened life span.

We are aware that we cannot simply extrapolate the reported data in our animal studies to the human preterm infant and adult because the rat myocardium may have a different affinity for dexamethasone and, despite similarities reported, the development of the rat myocardium differs from the myocardium in a prematurely born human baby. Nevertheless, we suggest that the present clinical study was performed too early, between 7 and 10 years of age, to reveal glucocorticoid-related adverse effects on cardiovascular function, which may be detected only at an older age. If this is also true for the children treated antenatally with betamethasone, the question remains because follow-up studies were performed during early adulthood. However, a study in fetal sheep treated with cortisol showed inhibition of cardiomyocyte replication and altered myocardial growth, thereby also raising concerns about antenatal administration of glucocorticoids.

A limitation of the present study is that the cardiovascular factors were determined in a nonstrained condition and that our echocardiographic investigations possibly were not sensitive enough to diagnose cardiomyopathy early in life. Further follow-up studies in the same cohort of children at an older age, with challenge tests and using more sophisticated echocardiographic methods such as tissue Doppler imaging and strain echocardiography, are, therefore, recommended.

Our hypothesis that neonatally administered hydrocortisone, a glucocorticoid clinically equally effective as dexamethasone but without adverse effects on neurodevelopmental outcome, may have a different effect on the cardiovascular system after neonatal treatment compared with dexamethasone could not be confirmed in this study. Also, one should be aware that our study included children who were born in the mid-1990s. Today, neonatologists are much more reluctant to start glucocorticoid (eg, dexamethasone) therapy and treatment courses are much shorter. Moreover, newer mechanical ventilation strategies are probably less damaging to the lungs. This has profoundly altered the need for neonatal glucocorticoid therapy.

In summary, neonatal treatment with dexamethasone or hydrocortisone and antenatal treatment with betamethasone in children who had been born prematurely did not have adverse effects on heart rate and blood pressure, cardiovascular function, intima-media thickness of the carotid arteries, or cardiac biochemical markers for left ventricular function at age 7 to 10 years. However, prolonged cardiac follow-up is recommended in children who were neonatally treated with glucocorticoids because animal studies show that the functional consequences of the structural myocardial abnormalities established during neonatal glucocorticoid therapy may become manifest only in adulthood.

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Correspondence: Willem B. de Vries, MD, PhD, Department of Neonatology, Room KE.04.123.1, Wilhelmina Children’s Hospital, University Medical Center Utrecht, PO Box 85090, 3508 AB Utrecht, the Netherlands (w.b.devries-3@umcutrecht.nl).

Author Contributions: Dr van Bel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: de Vries, Karemaker, Visser, Heijnen, and van Bel. Acquisition of data: de Vries, Karemaker, Mooy, Kemperman, Baerts, and Veen. Analysis and interpretation of data: de Vries, Strengers, Kemperman, Heijnen, and van Bel. Drafting of the manuscript: de Vries, Strengers, Heijnen, and van Bel. Critical revision of the manuscript for important intellectual content: Karemaker, Mooy, Kemperman, Baerts, and Veen. Study supervision: Strengers, Heijnen, and van Bel. Statistical analysis: de Vries and van Bel. Obtained funding: Heijnen and van Bel. Administrative, technical, and material support: Karemaker, Mooy, Kemperman, Baerts, Veen, and Visser. Study supervision: Strengers, Heijnen, and van Bel.

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