Twenty-Year Follow-Up of Antenatal Corticosteroid Treatment

Arianne B. Dessens, PhD; Hetty Smolders-de Haas, MD; and Janna G. Koppe, MD, PhD

ABSTRACT. *Objective.* To study late side effects of antenatal corticosteroid treatment on health and sexual development in subjects 20 to 22 years old.

Methods. A follow-up study among young adults whose mothers had, because of a threatening delivery, participated in a randomized, double-blind, placebo-controlled trial of betamethasone to prevent neonatal respiratory distress syndrome. Measurements were taken on general health, growth, development in puberty, reproductivity, genital or gynecological complaints, gender development, sexual orientation, sex-specific cognitive functioning, and psychoneuroticism. In addition, some measurements were performed on family diseases, socioeconomic status, and education.

Results. No differences were found between the corticosteroid-treated and placebo groups as to medical or psychological variables. In general, the subjects were healthy and had normal intellectual capacities. Groups did not differ on gender development, sexual orientation, sex-specific cognitive functioning, and psychoneuroticism. Systolic blood pressure was significantly lower in the corticosteroid group, but the groups did not differ as to diastolic blood pressure.

Conclusions. Our 20-year follow-up study indicates that 1 course of antenatally administered corticosteroid to prevent respiratory distress syndrome does not have adverse effects up to adulthood. *Pediatrics* 2000;105(6). URL: http://www.pediatrics.org/cgi/content/full/105/6/e77; *respiratory distress syndrome, corticosteroids, longterm follow-up, sexual development, cognitive development.*

ABBREVIATIONS. WAIS, Wechsler Adult Intelligence Scale; GIT, Groninger Intelligentie Test; GRAS, Gender Role Assessment Schedule; KSOG, Klein Sexual Orientation Grid; ANOVA, analysis of variance; GRB-child/adult, gender role behavior in childhood/adulthood; CGB-males/females, cross-gender behavior in males/females; SD, standard deviation.

The efficacy of antenatal administration of corticosteroids to prevent respiratory distress syndrome has been well demonstrated.[1] Follow-up studies in children up to 12 years old did not reveal negative side effects on either physical development or intellectual and neuropsychological capacities.[2–5] Long-term influences of antenatal corticosteroids on growth and on the onset of puberty, however, are not fully known. Marton[6] reported a retarded menarche in girls who had been antenatally

treated with corticosteroids (mean age: 13.5 years vs mean age: 12.4 years among Hungarian girls). Smolders-de Haas et al[5] observed that more 10- to 12-year-old boys who had antenatally been given placebos had entered puberty earlier than did boys who had received corticosteroids.

Animal research has shown that corticosteroid treatment during the neonatal period led to increased ano-genital distances in female pups.[7] In adulthood, no influence on cyclicity was found, but the females showed masculinized sexual behavior,[8] and the adult males showed feminized behavior.[7,9]

Investigations in individuals who had been prenatally exposed to atypical balances of gonadal hormones attributable to idiopathic condition (eg, females with congenital virilizing adrenal hyperplasia) or attributable to prenatal exposure to natural or synthetic progestins and diethylstilbestrol, opiates, or anticonvulsants revealed shifts in gender role behavior, sexual orientation, and sex-specific cognitive functioning.[10–13]

The aim of the present study was to investigate late side effects of antenatal corticosteroid treatment on sexual and psychosexual development. In addition, general health was assessed.

METHODS

Design

This is a follow-up of the study conducted by Schutte et al[14] that concerned a randomized, double-blind, placebo-controlled trial of betamethasone. In the present study, the subjects who had been antenatally treated with betamethasone were compared with the subjects who had received placebos on (psycho)sexual development, health, and sex-specific cognitive functioning. The study was approved by the Medical Ethics Committee of the Academic Medical Center.

Subjects

The original group of Schutte et al[14] consisted of 61 corticosteroid-treated and 58 placebo-treated subjects. All children were born between April 1974 and April 1977. The mothers had been referred to hospital because of a threatening delivery at weeks 26 to 32 of pregnancy. In addition to the intravenous betamimetic Orciprenaline, the mothers of the corticosteroid-treated infants had received twice, with a 24-hour interval, 12 mg of betamethasone (existing in 8 mg of betamethasone-sodium phosphate and 6 mg of betamethasone-acetate, a combination of rapid and slow release preparation). The mothers of the placebo-treated infants received Orciprenaline and 2 mL of saline. Three of the 61 corticosteroid-treated neonates died after birth; among the placebo group, this number was 14 of 58. Therefore, the surviving group consisted of 102 subjects.

In the corticosteroid group, the mean gestational age at birth was 32 weeks (range: 27–40 weeks); 5 children were born after 36 weeks of gestational age. The mean birth weight was 1821 g (range: 850-3820 g). Among the placebo subjects, the mean gestational age was also 32 weeks (range: 27–40 weeks). Also in this

group, 5 infants were born after 36 weeks of gestational age. The mean birth weight was 1875 g (range: 1070–3720 g).

Procedure

Current addresses of the subjects were obtained from the Dutch registry offices.

Participants were invited to the hospital for assessment or, in 2 cases, were visited at home. The subjects were informed about the purpose of the study and its design, but not about their corticosteroid/placebo condition. The researchers who examined the subjects (H.S.-dH. and A.B.D.) were also unaware of the corticosteroid/placebo condition of the subjects.

Methods

Socioeconomic Status

The professions of both the subjects and his or her parents were taken as indicators for socioeconomic status. This status was categorized according to a Dutch classification system.[15]

Medical Part of the Study

Growth was measured by height, weight, and head circumference. Subjects were carefully and systematically interviewed on diseases or complaints of all organ systems. Special attention was paid to genital and gynecological problems. To investigate fertility problems, males were asked to cooperate in a sperm analysis. Females who did not take hormonal contraception were asked to make a body temperature curve during the menstrual cycle to assess whether they had normal ovulation patterns. Furthermore, subjects were questioned on hereditary diseases. Diseases and consultations of different medical specialists over the previous 10 years were noted. Subjects were asked about onset of puberty and sexual development by means of semistructured interviews. Use of medication, tobacco, alcohol, and illegal drugs was recorded.

We did a general physical examination with special attention to the male or female habitus, and we measured blood pressure.

Psychological Part of the Study

Educational Level

The subject's education was measured by means of a semistructured interview with preset categories for answers, based on the system of Verhage.[16]

Cognitive Functioning

To estimate the present general level of intellectual functioning, some subtests from the Dutch version of the Wechsler Adult Intelligence Scale (WAIS) and Groninger Intelligentie Test (GIT) were chosen that are known to have the highest correlation with total verbal and performance scores of the WAIS and GIT.[17–19] From the WAIS, these were Similarities and Block Design, from the GIT, a Verbal Reasoning Test and a Picture Completion Test. Attention was measured by Digit Span, also a subtest of the WAIS. To test for sex-specific cognitive functioning, instruments were selected that are known to measure the largest sex differences: tests for mental rotation of pictorially presented objects and tests for fluent generation of words within a specified category or under particular constraints.[20–22] We selected Card Rotations and a Water Level Test to assess visuospatial construction.[23,24] Fluency in speech production was assessed by a Word Fluency test for naming animals and professions (from the GIT).[18] To measure functional asymmetry for auditory–verbal perception, a Dichotic Listening Test containing monosyllabic digits was selected, which was based on the procedures developed by Kimura.[25,26] Right- or left-handedness was assessed by questionnaire.[27]

Psychopathology

The Symptom Checklist-90 was used to assess psychoneuroticism.[28]

Psychosexual Development

Gender role behavior was assessed by the Gender Role Assessment Schedule (GRAS), a semistructured interview.[29] This interview contains questions on gender role behavior and cross-gender behavior during childhood and adulthood. Sexual orientation was measured by the Klein Sexual Orientation Grid (KSOG),[30] which is an extension of the classical scale on sexual orientation by Kinsey et al,[31] and includes items on several aspects of sexual orientation, such as behavior, fantasy, and self-identification. Furthermore, some questions were asked concerning ages at which several psychosexual milestones had been passed, such as first date, first petting, and first sexual intercourse.

Statistical Analyses

Socioeconomic Status

Data on socioeconomic status were analyzed by means of Mann-Whitney U test. This nonparametric test was chosen because these categorical data were not normally distributed in both study groups.

Medical Part of the Study

Measurements on interval level were analyzed by 2×2 (drug/nondrug group by sex) analysis of variance (ANOVA). The semistructured interviews contained normally distributed measures on nominal or ordinal levels. To analyze results on these measurements, χ^2 tests or Fisher's exact tests were applied.

Psychological Part of the Study

Data on education were categorical and did not follow a normal distribution and were, therefore, analyzed by Mann-Whitney U tests. The psychological tests and questionnaire measure on interval level. Differences between corticosteroid subjects on measurements for cognitive functioning and psychoneuropathology were tested by a 2×2 (drug/nondrug group by sex) ANOVA. Scores on the Dichotic Listening Test were analyzed in a $2 \times 2 \times 2$ (sex by drug/nondrug group by right/left ear) ANOVA. By applying classical item analysis techniques[32] on the GRAS, 4 scales could be constructed: gender role behavior in childhood (GRB-child; reliability: .60), gender role behavior in adulthood (GRB-adult; reliability: .75), cross-gender behavior in males (CGB-males; reliability: .72), and cross-gender behavior in females (CGB-females; reliability: .87). The CGB scales refer to behaviors and interests that are unusual for members of the other sex, such as frequent cross-dressing in boys.[12] Classical item analysis was also applied on the 7 items of the KSOG, reliability of the scale was .94. Differences between corticosteroid and placebo male and female subjects on the GRAS and KSOG scales were tested by a 1-way ANOVA. Differences between groups on attaining psychosexual milestones were also tested by 1-way ANOVA.

RESULTS

Response in Follow-Up

All 102 surviving subjects were asked to participate in this second follow-up study, 81 volunteered: 48 corticosteroid subjects (27 males and 21 females) and 33 placebo subjects (16 males and 17 females); the response rates were 83% and 75%, respectively.

Of these 102 subjects, 4 subjects had cerebral palsy (2 belonged to the corticosteroid group and 2 to the placebo group).[5] Two of these subjects participated in the present follow-up study: both had a mild form of cerebral palsy and 1 belonged to the corticosteroid group, the other to the placebo group. It was known that the 2 remaining subjects were more severely affected. One has severe motor and mental impairments, so he was unable to participate (H.S.-dH. interviewed his mother by telephone). The fourth subject with cerebral palsy refused to take part.

The 21 nonrespondents did not differ from respondents with respect to study group (10 subjects from the corticosteroid group and 11 subjects from the placebo group did not participate; $P = .34$), sex (there were 13 nonresponding males and 8 nonresponding females; $P = .47$), gestational age at birth (mean: 31.9 weeks; standard deviation [SD]: 3.4 in both the re-

spondent and nonrespondent groups; $P = .91$), or birth weight (nonrespondents, mean: 1763 g; SD: 670 and participants, mean: 1843 g; SD: 666; $P = .63$). The distance between the residence of the subjects and the hospital in which this study was conducted did not seem to be of importance; respondents and non-respondents came from all over the country.

Socioeconomic Status

The corticosteroid group and the placebo group did not differ with respect to socioeconomic status ($P = .64$) or parental socioeconomic status (father, $P = .27$; mother, $P = .98$).

Medical Part of the Study

Sexual Development

We did not find a difference in onset of puberty. For girls, the mean age for menarche in both groups was 12.8 years; the SD was 1.3 for corticosteroid females and 1.6 for control females ($P = .98$). The population mean age for menarche is 13.1 years of age.[33] The mean age of first ejaculation for the boys in the corticosteroid group was 14.1 years and 13.5 years for the boys in the placebo group ($P = .30$). The population mean age for first ejaculation is unknown.

Reproductivity

All subjects were interviewed on pregnancies or having initiated a pregnancy. Three corticosteroid and 2 placebo females had been pregnant; 1 of them had given birth. Spontaneous abortions and abortus provocatus were equally divided among the groups.

We had planned to assess ovulation patterns by means of body temperature curves but did not succeed; it turned out that a large majority of the females took hormonal contraception. We also asked about regularity of the menstrual cycle before they had started to take hormonal contraception. It seemed that 16% of the corticosteroid-treated females and 69% of the placebo females had an irregular cycle before starting hormonal contraception ($P = .005$). The population mean for irregular menstrual cycle for Dutch women 15 to 24 years of age is 11%; this percentage is based on women who consult their general practitioner and ask for help.[34]

Two males from the corticosteroid group had initiated a pregnancy. Unfortunately, most of the males refused to undergo sperm analysis; only 6 from each group took part. In each group of 6, 4 turned out to be normal and 2 abnormal. One corticosteroid male was infertile because of an azoospermia and 1 was subfertile because of an asthenozoospermia. Two placebo males were subfertile; 1 because of an oligoasthenozoospermia and 1 because of autoimmune antibodies. Although we tried to assess reproductivity among our subjects, we could not collect enough data for reliable analysis.

Gynecological Problems

We did not find a difference in gynecological treatments: 14% of the corticosteroid group and 18% of the placebo group had received some gynecological treatment (Fisher's exact test, $P = 1.00$). One of these girls suffered from polycystic ovarian syndrome that was detected during the study; the remaining girls did not have any serious problems (ie, minor vaginal infections and postcoital bleeding without serious cause).

Genital Problems

No differences between the 2 groups were found as to genital problems: 15% of the corticosteroid females and 24% of the placebo females ($P = .68$) and 12% of the corticosteroid males and 31% of the placebo males ($P = .22$) had some genital problem. One male in the placebo group had a morbus Peyroni (bend of the penis during erection), but there were no other serious problems (ie, cryptorchidism and phimosis). With respect to gynecological and genital problems, population means are not available.

Physical Health

In general, the subjects seemed to be healthy, well-functioning young people, and we did not find differences between the 2 groups. However, significantly more medication was used in the corticosteroid group ($P = .01$). Of the 14 corticosteroid subjects who took medication, 8 took medication against allergies or chronic obstructive pulmonary diseases. In the families of the corticosteroid group, significantly more allergic problems were found ($P = .03$). An elevation of chronic obstructive pulmonary diseases was found in the families of the corticosteroid group too, but the difference was not significant ($P = .11$). At the physical examination, 6 corticosteroid subjects had a palpable thyroid gland. Among these 6 subjects, 4 belonged to 2 dizygotic twins. None of the 6 subjects with palpable thyroid glands reported thyroid diseases in their families and none had any complaints related to thyroid functioning. Among the placebo group, no thyroid glands were palpable. The difference between the corticosteroid and placebo groups tended to significance ($P = .08$).

This study comprised 1 corticosteroid male who had a thrombosis once, probably attributable to a hyperhomocysteinemia. The 2 subjects with cerebral palsy who volunteered in this follow-up did not have any other disorders.

Growth

No effect of the antenatal corticosteroid treatment was found on the growth measures. With respect to height, the mean value for corticosteroid-treated males was 180 cm, and for placebo males, it was 177 cm (population mean: 184 cm; SD: 7.1 cm). For corticosteroid-treated females, the mean value was 169 cm and for placebo females, 170 cm (population mean: 170 cm; SD: 6.5 cm).[33] The P value for differences between corticosteroid and placebo groups on height was .52.

Mean values on weight for corticosteroid males was 71 kg, and for placebo males, 72 kg (the population mean weight by mean height on the 50th percentile is 72 kg).[33] For corticosteroid- and placebo-treated females, mean weight values were 61 kg and

67 kg, respectively (population mean weight by mean height on the 50th percentile: 62 kg).[33] The P value for differences between groups on weight was .28.

Also, on head circumference, no differences were found between groups. Mean values for corticosteroid- and placebo-treated males were 57.3 cm and 57.5 cm, respectively (50th percentile for head circumference for males is 57.8). For corticosteroid- and placebo-treated females, these were 55.7 cm (for females, the 50th percentile for head circumference is 55.3).[33] The P value for differences between groups was .84.

Blood Pressure

A slightly lower systolic blood pressure was found in the corticosteroid group (Table 1); no differences were found in diastolic blood pressure.

Psychological Part of the Study

Education

The corticosteroid- and placebo-treated groups did not differ with respect to the level of secondary education they had received ($P = .80$) or the level of professional training they (had) attended ($P = .68$).

Cognitive Functioning

On measurements for general level of intellectual functioning, no differences between groups, sex, or interaction effects of groups by sex were observed. The mean norm scores found on all WAIS and GIT subtests were ~6, which are the population means norm scores on these tests.[17,18] On WAIS-Similarities, the following P values were found: group, .84; sex, .44; and group by sex, .29. On WAIS-Block Design, P values were group, .42; sex, .30; and group by sex, .46. On GIT-Picture Completion, the P values were group, .86; sex, .65; and group by sex, .57. Compared with the control group, the corticosteroid subjects had slightly higher scores on the GIT-Verbal Reasoning Test (group, $P = .03$; sex, $P = .76$; and group by sex, $P = .94$). Although this difference between group is statistically significant, it is not clinically relevant as the mean norm scores of males and females in both groups were around 6. The 2 subjects with cerebral palsy had normal intellectual capacities.

Also, the test for attention, WAIS-Digit Span, revealed no differences between the corticosteroid and control groups (P values for group, .32; sex, .38; and group by sex, .43).

With respect to sex-specific cognitive functioning, we found the following results. On the tests for visuospatial construction, Card Rotations and the Water Level Test, the predicted differences between the sexes was demonstrated, but there were no differences between the corticosteroid and placebo groups and interaction effects were not found (Card Rotations: P values for group, .72; sex, .00; group by sex, .36; mean scores, between 92 and 116; Water Level Test: P values for group, .28; sex, .02; group by sex, .55; mean scores, between 54 and 147). Because both Card Rotations and the Water Level Test are primarily used in experimental research, Dutch population mean scores are not available.[23,24] However, we could compare the mean scores on Card Rotations and the Water Level Test in this study with those found in a study we previously conducted. In both studies, the ranges of the mean scores were nearly similar.[13] On GIT-Verbal Fluency, the expected sex difference was not observed. The performance of the groups did not differ significantly (P values for naming animals: group, .07; sex, .57; and group by sex, .68; P values for naming professions: group, .31; sex, .68; and group by sex, .49). The mean norm scores of males and females of both groups on naming animals and professions were around 6.

On left- or right-handedness, corticosteroid males and females did not differ from placebo subjects (P values: males, .48 and females, .72). Left-handedness, however, was more prevalent among our subjects, particularly among males, compared with that among Dutch inhabitants. Of the corticosteroid males, 16% were left-handed and among placebo males, 25% were left-handed. Of the corticosteroid and placebo females, 9% and 13% were left-handed, respectively. Eleven percent of the Dutch inhabitants are left-handed.[35] Right-handed subjects attained the following mean scores on the Dichotic Listening Test. On the right ear, corticosteroid males recalled 43 digits and placebo males recalled 42; corticosteroid and placebo females recalled 42 digits. On the left ear, corticosteroid males recalled 35 digits and placebo males recalled 34; corticosteroid and placebo females recalled 34 digits. The expected difference on ear was found ($P = .00$), whereas there was no difference for groups ($P = .60$) and sex ($P = .62$) and no interaction effect was found (group by sex, $P = .79$; ear by group, $P = 1.00$; ear by sex, $P = .94$; and ear by group by sex, $P = .72$. Because only 5 left-handed subjects had completed the Dichotic Listening Test, data on left-handed subjects are not described. Be-

TABLE 1. Blood Pressure

	Sex	n	Mean	Test	P Value	
Systolic blood pressure						
Corticosteroid	Males	27	116	ANOVA	Group	.05
Placebo	Males	15	119		Sex	.04
Corticosteroid	Females	21	112		Interaction	.83
Placebo	Females	17	116			
Diastolic blood pressure						
Corticosteroid	Males	27	69	ANOVA	Group	.45
Placebo	Males	15	69		Sex	.33
Corticosteroid	Females	73	73		Interaction	.27
Placebo	Females	69	69			

cause the Dichotic Listening Test is mostly used for research purposes, Dutch norm scores are not available.[25,26] This test too was used in our previous study.[13] Our subjects in this study attained similar scores compared with the subjects from the previous study.

Psychopathology

No difference was found between the corticosteroid and placebo groups on any of the 8 subscales or on the total score for psychoneuroticism (P values for differences between groups on anxiety, .30; agoraphobia, .44; depression, .20; psychosomatic complaints, .97; feelings of insufficience, .98; sensitivity, .62; hostility, .28; insomnia, .23; miscellaneous complaints, .17; and the total score for psychoneuroticism, .50). The mean norm values for all groups on all 8 subscales and on the total psychoneuroticism score were around 3, which are the population mean norm values for subjects who do not have psychiatric complaints (the comparable reference group).

Psychosexual Development

Corticosteroid-treated males and females did not score differently from placebo-treated males and females on the all scales of the GRAS. On the GRB-child scale, both corticosteroid and placebo males had mean scores of 13 and SDs of 2 (P = .86). On the GRB-adult scale, corticosteroid males had a mean score of 20 (SD: 3), whereas placebo males had a mean score of 21 (SD: 3; P = .69). On the CGB-males scale, corticosteroid males had a mean score of 8 (SD: 1), placebo males had a mean score of 9 (SD: 2; P = .25). For females, the following scores were found: mean scores on the CRB-child scale for corticosteroid and placebo females was 11 (the SD was 2 for corticosteroid females and 3 for placebo females; P = .49). Mean score on the CRB-adult scale for corticosteroid females was 13 (SD: 2), for placebo females, 14 (SD: 3; P = .20). Mean score on the CGB-females scale for corticosteroid females was 6 (SD: 2), for placebo females, 7 (SD: 2; P = .15). For the GRAS, population mean scores are not available; the interview has only been applied in research.

Again, no differences were found between the corticosteroid-treated group and the placebo-treated group as to sexual orientation. Attributable to the fact that some subjects believed they did not have enough experience to complete the whole questionnaire, the number of subjects on which these data are based is somewhat smaller than the number of subjects who filled out the questions on the other tests, questionnaires, and interviews. Twenty-six corticosteroid and 13 placebo males filled out this questionnaire. Corticosteroid males had a mean scrore of 7.5 (SD: 1.0), placebo males had a mean score of 7.0 (SD: 1.1; P = .20). Sixteen corticosteroid and 11 control females filled out the questionnaire: the mean score in the corticosteroid group was 7.4 (SD: 1.0), whereas the placebo females had a mean score of 7.2 (SD: 1.0; P = .54). Most subjects stated that they preferred heterosexual relationships, except for 1 male who was homosexual and 1 male who did not know whether he was a homosexual or a heterosexual. The

prevalence of homosexuality in The Netherlands is 5% for males and 2.5% for females.[36]

Also, on questions for attaining psychosexual milestones, groups did not differ. This questionnaire was also not filled out by all subjects for similar reason as described above. The question concerning their mean age at their first date was answered by 25 corticosteroid and 14 placebo subjects. The mean age for corticosteroid males was 13 (SD: 3), for placebo males it was 13.5 (SD: 3.4; P = .57). Mean ages at first petting was filled out by 26 corticosteroid and 15 placebo males: the mean age for corticosteroid males was 14.5 (SD: 2.5), for placebo males it was 13.6 (SD: 3.3; P = .35). Nineteen corticosteroid and 9 control males filled out their age at first intercourse: the mean age for corticosteroid males was 15.5 (SD: 2), the mean age for placebo males was 17 (SD: 1.8; P = .12). Fifteen corticosteroid and 14 placebo females answered the questions concerning first date and first petting. The mean age at the first date was 14.5 (SD: 1.2) for corticosteroid and 13.8 (SD: 3.6) for placebo females (P = .38). For first petting, mean ages were 14.5 (SD: 1.5) and 15.0 (SD: 2.0), respectively (P = .47). Mean ages at first intercourse was 16.5 (SD: 1.4) for 14 corticosteroid and 16.2 (SD: 2.1) for 13 placebo females (P = .70). Our findings on age at first intercourse were below the population mean, which is 18 for males and females.[36]

DISCUSSION

This follow-up study was conducted to investigate whether antenatal treatment with corticosteroids between 26 and 32 weeks of gestational age to prevent respiratory distress syndrome may affect general health and sexual and psychosexual development in the children later on. We found that the corticosteroid subjects did not differ from the placebo subjects on all medical and psychological measurements taken. The groups did not differ with respect to development during puberty and growth. The anamnesis only revealed a few serious diseases: 1 corticosteroid female had polycystic ovarian syndrome and 1 corticosteroid male had had thrombosis once. For both disorders, a relationship with antenatal corticosteroid treatment seems unlikely. A remarkably high percentage of placebo females indicated they had an irregular menstrual cycle before they started hormonal contraception. This might be explained by: 1) the small number of placebo females, and 2) the fact that some placebo females started hormonal contraception at an early age. In general, our subjects were healthy and they had normal intellectual capacities. As a group, they did not differ from other 20-year-old Dutch adults.

Despite the high response rate, the number of subjects on whom the data are based is restricted. Because of this, we should be careful interpreting the results. First, 17% of the corticosteroid-treated and 25% of the placebo-treated subjects had refused to participate in this follow-up. Of course, not much is known of these subjects. We have been able to test whether these nonrespondents differed from respondents on only a few variables but we did not find differences. Second, 1 of our aims was to study the

influence of corticosteroids on reproductivity, but the majority of our subjects had not planned to raise children yet. Third, to exclude hereditary influences, we also wanted to examine siblings. However, the number of same-sex siblings was low and some of them refused to take part. Spread out over the groups, the data of only a few siblings were available for statistical analysis. Therefore, we had to depend on the anamneses for information on hereditary diseases.

During a general, but unspecific, physical examination we found more palpable thyroid glands among corticosteroid subjects. Because no influences had been found in neonatal thyroid function,[37] we did not expect to find problems in thyroid functioning in adulthood. Therefore, at the start of this study, we had decided not to take blood samples for laboratory analysis. Smaller thyroid glands, however, had been observed in the offspring of mice who had been prenatally treated with dexamethasone.[38] Disturbances in the hypophyseal-thyroid axis, therefore, might be possible. Interpretation of our finding is difficult: there was a trend toward significance, but the subjects did not report any complaints that could be related to thyroid dysfunction. In addition, among them, there were 2 dizygotic twins. Contrary to findings in animal studies, we did not find an elevated diastolic blood pressure in corticosteroid-treated subjects.

With respect to variables on socioeconomic status and education, no differences were found between the 2 groups. It seems, therefore, unlikely that differences as to medical and psychological variables are influenced by differences in social status or education.

Although feminization has been observed in male rats and masculinization in female rats,[7–9] no indications for such changes in gender behavior, sexual orientation, or sex-specific cognitive functioning have been found in our subjects. The ages at which our subjects entered first dating and had their first sexual experiences were somewhat lower, compared with the population mean. However, this can be explained by the fact that these questions could not be answered by subjects who had not yet had these experiences. So the findings on sexual orientation and attaining psychosexual milestones are less stable, compared with those on other tests and questionnaires.

The 2 groups did not differ with respect to all cognitive measurements taken. In fact, despite the preterm birth of most of our subjects, both the corticosteroid- and placebo-treated subjects did not differ from other Dutch adults between 20 and 22 years of age with respect to intellectual capacities. They had mean scores on all psychological subtests. Recently, follow-up studies on prematurely born children showed that an elevated number of prematurely born children were not able to attend regular education because of cognitive or behavioral problems (at age 9, 19% among prematurely born infants, compared with 6% in the population).[39] These children need specialized education and, indeed, some of the subjects in our study group had attended special schools for children with learning problems.[4] Our subjects had probably profited from the extra training they had thus received, because they had all been able to attend regular secondary education. As adults, they were able to participate in regular jobs. This may indicate that some of the small cognitive deficits observed in prepubertal children may disappear during puberty. Soorani–Lunsing[40] observed disappearance of minor neurological dysfunction in prematurely born infants after the onset of puberty. Compared with the Dutch prevalence, left-handedness was more often seen among our subjects, particularly among males.

The subjects in our present study had only received 1 course of antenatal corticosteroid treatment at 27 to 32 weeks of gestational age. Therefore, the results cannot be extended to subjects who had undergone repeated treatment or to subjects who had been treated at a younger gestational age. Furthermore, during the period that the original study had been conducted (1974–1977),[14] surfactant was not administered to preterm infants. Follow-up studies in these children and adolescents are, thus, recommended. Because we observed a trend to palpable thryroid glands among subjects antenatally treated with corticosteroid, other follow-up studies should, in our opinion, focus on thyroid function and blood pressure.

ACKNOWLEDGMENTS

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