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Hydrocortisone administration in preterm infants is not associated with adverse cardiovascular outcomes in childhood

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BACKGROUND: To assess whether administering hydrocortisone in the perinatal period is associated with subsequent adverse cardiovascular outcomes.
METHODS: The children/adolescents enrolled in the PREMILOC trial underwent resting blood pressure (BP) measurement, tonometry evaluation (pulse wave velocity (PWV), aortic systolic BP), continuous BP and ECG measurements (supine and standing), and ambulatory BP monitoring. Heart rate variability (HRV) indices, baroreflex sensitivity (BRS), and orthostatic systolic BP (SBP) response were calculated.
RESULTS: Fifty-two subjects (median [25th; 75th percentile] birth weight: 892 g [750; 982]; gestational age: 26^{+3} [25^{+1}; 27^{+4}]; age at assessment: 11.7 years [10.5; 12.7]; z-score of body mass index: 0.23 [−0.65; 1.27]; 27 girls) who received hydrocortisone ($n = 28$) or placebo ($n = 24$) were enrolled. The PWV was not different (hydrocortisone: 4.84 m/s [4.40; 5.48] vs. placebo: 5.00 m/s [4.48; 5.34], $p = 0.969$), and similar results were observed for HRV and BP measurements. Overweight/obese children ($n = 17$) vs. other children ($n = 35$) were characterized by higher office SBP, lower supine descending BRS, and higher orthostatic SBP response.
CONCLUSION: Early hydrocortisone administration after extremely preterm birth in a randomized trial is not associated with detrimental cardiovascular indices in children/adolescents, while overweight/obesity is already associated with cardiovascular morbidity.
The study has been registered, ClinicalTrials.gov ID NCT05451264: https://clinicaltrials.gov/study/NCT05451264?cond=NCT05451264&rank=1.

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IMPACT:

- A meta-analysis on the effects of early postnatal administration of corticosteroids concluded that the hypertensive risk was increased in infants, but that long-term studies should be carried out.
- We show that early hydrocortisone administration after extremely preterm birth in a randomized trial is not associated with detrimental cardiovascular indices in children/adolescents, at least in one center of the trial
- Thus, our study suggests that early markers of the risk of hypertension are not altered by hydrocortisone.

INTRODUCTION

Preterm births account for more than 10% of births worldwide and are associated with a long-term increase in cardiovascular disease risk. The period around preterm birth is a rapid and critical phase of cardiovascular development, which might explain why changes in multiple components of the cardiovascular system have been observed in individuals born preterm.[1] These alterations include reduced microvascular density, increased macrovascular stiffness, and higher systolic and diastolic blood pressure.[1] A meta-analysis showed that infants who were born preterm or with very low birth weight had modestly higher systolic blood pressure (BP) later in life (an increase in systolic BP of 3.8 mmHg on average at an average age of 18 years) and may be at increased risk of developing hypertension.[2] Along this line, a study found a prevalence rate of hypertension in adolescence of 15%.[3] Antenatal glucocorticoid exposure in preterm infants has been associated with increased aortic arch stiffness,[4] which may increase the risk of hypertension. A meta-analysis on the effects of early postnatal administration of corticosteroids concluded that the hypertensive risk was increased in infants, but that long-term studies should be carried out.[5] One may hypothesize that resting BP is an insensitive marker in childhood. It would therefore be mandatory to study early markers of hypertensive risk such as carotid-femoral pulse wave velocity (cf-PWV, marker of arterial stiffness[6,7]), augmentation index (AIx, marker of arterial resistance[7]), baroreflex sensitivity (regulation of BP[8]), and heart rate variability indices (giving access to the cardiovascular sympathovagal balance[9]).

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The main objective of our prospective descriptive study was to evaluate whether the administration of hydrocortisone in the perinatal period in children born extremely preterm is associated with an increase in PWV at the age of 9–16 years compared to placebo. To this end, the children enrolled in the PREMILOC trial (prophylactic hydrocortisone treatment in extremely preterm infants)[10] at Robert Debré Hospital were evaluated. The secondary objectives were to evaluate whether the early administration of hydrocortisone is associated with modification of other early markers of risks of hypertension, such as heart rate variability indices and baroreflex sensitivity, compared to placebo, and to evaluate the prevalence of cardiovascular anomalies, including elevated blood pressure and hypertension, in the whole group of children/adolescents and the effects of overweight/obesity on cardiovascular outcomes since premature infants are more likely than full-term infants to be obese at the age of 6–16 years[11] and since obesity is a major risk factor of hypertension in childhood.[12] Finally, the effect of male sex on cardiovascular outcomes was also assessed in the whole population since a recent study showed that male sex enhanced the effect of preterm birth on blood pressure in adolescence.[13]

METHODS

Participants

We proposed to the families of the preterm children born in Robert Debré Hospital, included in the PREMILOC trial (the hydrocortisone group received 1 mg/kg of hydrocortisone hemisuccinate per day divided into two doses per day for 7 days, followed by one dose of 0.5 mg/kg per day for 3 days, between May 25, 2008, and January 31, 2014), and followed up by the neonatologist team to have a single-day hospitalization for cardiovascular disease prevention. The PREMILOC trial has previously been described in detail and was designed to assess whether low-dose hydrocortisone improved survival without bronchopulmonary dysplasia in extremely preterm infants.[10] The present trial was sponsored by the Assistance Publique – Hôpitaux de Paris (APHP211326) and declared in ClinicalTrials.gov (NCT05451264). The reporting of the results complied with the STROBE guideline checklist for observational studies.

BP was measured in the seated position after 5 min of rest from both right and left arms with an oscillometric device (Datascope Accutorr Plus™, Paramus, NJ) with appropriate pediatric cuff sizes. The mean of the systolic and diastolic BP was reported. Since normal BP varies during childhood with sex, age, and height, all BP measurements were expressed as percentiles. Percentiles for each BP measurement were extrapolated from Ln relationships that were established between BP norms and percentiles (50th, 90th, and 95th percentiles) available from guidelines,[14] as previously described.[15]

Pulse wave velocity (PWV) and tonometry

Arterial stiffness was assessed using a carotid-femoral (cf) PWV measurement (SphygmoCor, AtCor Medical, Sydney, Australia), as previously described.[16] The measurement was performed with the patient in a supine position after 10 min of rest. The tonometer was applied to the right common carotid and right femoral artery to measure the travel time of the pulse wave (*t*). The direct straight distance between the two measurement sites was measured using a tape measure (d), and cf-PWV was then calculated using PWV = 0.8 d/t (m/s), as proposed.[17] All measurements were made in at least triplicate, and the measurement with the lowest coefficient of variation was recorded. The % predicted value of cf-PWV was also calculated.[18]

The aortic pulse pressure waveform was derived from the recorded peripheral waveform using the generalized transfer function in the device's built-in software. The augmentation index (AIx) was determined as augmented pressure (AP) over pressure height, with pressure height being the difference between aortic systolic BP and diastolic BP. AIx was normalized to a heart rate of 75 bpm (AIx_{75}). All measurements were made in at least triplicate, and the recording with the highest quality (defined and calculated by the SphygmoCor software as '*operator index*') was chosen. Measurements with insufficient quality ('*operator index*' ≤ 70) were excluded according to the manufacturer's instructions. The subendocardial viability ratio (SEVR: diastolic time index over tension time index) was calculated by the SphygmoCor software. The SEVR, also known as the Buckberg index, is an estimate of myocardial perfusion to myocardial contraction and assesses the heart's workload.

HRV and baroreflex sensitivity (BRS) measurements

We continuously monitored ECG, noninvasive arterial pressure (using the vascular unloading technique and a CNAP® Monitor from CNSystems, Austria), and respiratory activity (using a piezoelectric belt from BIOPAC Systems, Paris, France) and digitized signals with the MP-160 system (BIOPAC Systems) as previously described.[16] A beat-by-beat data series taken during 5-min rests in the supine position was selected offline. Baroreflex was analyzed with AcqKnowledge's Baroreflex Sensitivity Analysis (BIOPAC Systems, Paris, France) software package using the sequence method with a minimal requirement of three cardiac cycles, a heart rate threshold of 5 ms, a systolic BP threshold of 1 mmHg, and a correlation coefficient greater than 0.85. HRV was analyzed with HRVanalysis software 1.1 downloaded from https://anslabtools.univ-st-etienne.fr and validated by Pichot et al.'s[19] method, as previously described.[15] The advantages of the sequence method of baroreflex assessment are that intra-subject measurement variability is reduced and distinct measurements are obtained for increasing and decreasing arterial pressure values, thus allowing the well-known asymmetry of the baroreceptor response to be taken into account. After supine measurements, measurements were taken while the patient was breathing deeply (six breaths per minute, allowing us to study respiratory sinus arrhythmia, mainly related to parasympathetic modulation) for 3 min (tidal breathing was then obtained for 1 min) and while standing (mainly related to sympathetic modulation) for a subsequent 5 min. Thus, the minimum duration of the recording was 14 min.

The standing measurements allowed the mean BP and HR to be calculated. An exaggerated orthostatic pressor response was defined as a sustained increase in systolic BP ≥ 20 mmHg when changing from the supine to the standing position regardless of absolute BP while standing.[20] The mean values of systolic BP (SBP) and diastolic BP (DBP) were obtained from the 3rd to the 5th min in the standing position, as previously described.[16]

HRV indices in the supine and standing positions and during deep breathing. Frequency-domain HRV variables were calculated. After the fast Fourier transform, the power spectrum indices were calculated as recommended.[21] The spectrum was calculated using Welch's periodogram algorithm with a Hamming window of 256 points, an overlap of 50%, and a precision of 256 points/Hz. The very low frequencies (VLF: 0–0.04 Hz), low frequencies (LF: 0.04–0.15 Hz), and high frequencies (HF: 0.15–0.40 Hz) were calculated. LF and HF were also expressed as normalized values, and the LF/HF ratio was calculated. According to Billman,[22] LF/HF = (0.50 parasympathetic + 0.25 sympathetic nerve activity)/(0.90 parasympathetic + 0.10 sympathetic nerve activity).

Baroreflex. We calculated the ascendant and descendant baroreflex in the supine and standing positions. In some subjects, ascendant or descendant BRS could not be computed due to either failure to obtain the required criteria for computation or the device slipping out of position while the subject was standing.

Ambulatory blood pressure monitoring (ABPM)

Each subject underwent 24-h ABPM using an oscillometric device (SpaceLabs 90207, SpaceLabs Medical, Redmond, WA), as previously described.[15] The cuff was chosen to match the subject's arm size and placed around the nondominant arm, as recommended.[23] The monitor was programmed to read the patient's BP every 20 min during the daytime (7 a.m. to 10 p.m.) and every 30 min during the nighttime (10 p.m. to 7 a.m.). The patients' bedtimes and wake-up times were recorded. BP measurements were compared to the normative ABPM values of healthy children,[23] and elevated BP (≥90th percentile and <95th percentile) and hypertension (≥95th percentile) were defined according to the current recommendations for children.[14] Dipping status during nighttime was also recorded. Percentiles for each BP measurement were extrapolated from logarithmic relationships that were established between BP norms and percentiles (50th, 75th, 90th, and 95th percentiles) available from the literature,[23] as previously done.[15]

Questionnaire

Evaluating the patient's fitness is important when assessing cardiovascular endpoints. We systematically recorded each patient's hours per week of sports

Table 1. Comparison of the included versus non-included infants.

Characteristics median [interquartile] or *n* (subjects)	Non-included infants *N* = 57	Included infants *N* = 52	*P* value
Gestational age, weeks^{+days}	27^{+0} [26^{+0}; 27^{+3}]	26^{+3} [25^{+6}; 27^{+3}]	0.09
Birthweight, g	910 [830; 1010])	893 [750; 983])	0.14
Very low/extremely low birth weight, *n* (%)	20 (34)/39 (66)	12 (23)/40 (77)	0.21
Multiple birth, *n* (%)	23 (39)	21 (40)	0.88
Chorioamnionitis, *n* (%), missing data, *n*	38 (64), *1*	32 (62), *1*	0.92
Bronchopulmonary dysplasia, *n* (%)	10 (17)	14 (27)	0.20

practice and evaluated them with the Pediatric Quality of Life (PedsQL) questionnaire, which assesses both physical and psychosocial health.[24]

Statistical analyses

Sample size calculation. The child-adolescent PWV norms established by Reusz and colleagues show that there is a difference of ~1 m/s between the 50th and 95th percentiles,[25] representing 1.64 standard deviations. With an alpha risk of 5% and a beta risk of 20%, 50 children (25 per group) were necessary to show a difference of 0.5 m/s in average PWV with a standard deviation of 0.61 m/s. This sample size is in accordance with the number of children included in Rossi et al.'s study that demonstrated an increase in PWV in adolescents born with low birth weight as a result of preterm birth ($n = 25$).[26]

Results were expressed as median [25th; 75th percentile]. The 95% confidence intervals (CIs) of the main proportions were calculated using the binomial "exact" calculation. Dichotomous variables were compared with the χ^2 test (or Fisher's exact test, as appropriate). Continuous variables were compared with the Mann–Whitney U test. Correlations were evaluated using the Spearman rank test. We tested whether there was an interaction between corpulence and treatment having an effect on SBP, using a one way ANCOVA analysis with participants' BMI as a covariate. Additionally, postnatal steroid treatment outside study intervention was included as a second covariate in the model to account for its potential confounding effect. A p value < 0.05 was deemed statistically significant. All statistical analyses were performed with R software version 4.1.0.

RESULTS

Among 109 surviving children recruited at Robert Debré Children's Hospital in the PREMILOC trial, 52 children were enrolled in this study and evaluated between January 2023 and July 2024. The comparison of this included group ($n = 52$) vs. the non-included group ($n = 57$) is provided in Table 1, showing the absence of significant difference for the neonatal characteristics.

Analyses according to the administration of hydrocortisone or placebo in the early postnatal period: main objective

Tables 2 and 3 show the participants' characteristics according to the randomization group. The median PWVs of both groups were not significantly different, and a similar result was observed for the other cardiovascular outcomes. The only significant difference was the lower physical quality of life in children who received hydrocortisone. Overall, compared with 0/24 children in the placebo group, 4/28 children in the hydrocortisone group were considered to have abnormal neurological findings at the time of the study ($p = 0.115$).

Analyses of the whole population: secondary objectives

Due to the absence of deleterious effects of hydrocortisone on cardiovascular outcomes, secondary objectives were analyzed in the whole population: $n = 52$, median age: 11.7 years.

The prevalences of office elevated BP and hypertension were 5/52 (9.6%, 95% CI: 3.2–21.0) and 4/52 (7.7%, 95% CI: 2.1–18.5), respectively, while these prevalences using ABPM were 4/52 (7.7%, 95% CI: 2.1–18.5) and 3/52 (5.8%, 95% CI: 1.2–15.9), respectively. Abnormal BP obtained in the office and from ABPM were associated ($p = 0.002$); nevertheless, two children had white coat hypertension, while two other children had masked nighttime hypertension.

In the 52 participants, the PWV correlated with age (Rho = 0.41, $p = 0.004$), office SBP (Rho = 0.30, $p = 0.033$), and office DBP (Rho = 0.41, $p = 0.005$). The orthostatic pressure response correlated with age (Rho = 0.32; $p = 0.021$) and supine ascendant BRS (Rho = 0.35, $p = 0.028$).

Effect of overweight/obesity. When comparing underweight or normal-weight children (n = 35, median age 11.7 years [10.5; 12.4]) with overweight or obese children (n = 17; 32.7%, 95% CI: 20.3–47.1, median age 11.9 years [10.5; 13.2]), the latter group was characterized by a higher office SBP (111 mmHg [109; 119] vs. 104 [100; 110], $p < 0.001$ and 68th percentile [57; 87] vs. 51st [42; 64], $p = 0.009$), a higher central aortic pressure (102 mmHg [100; 115] vs. 96 [90; 100], $p = 0.005$), a lower supine descending BRS (13.1 ms/mmHg [8.3; 30.8] vs. 20.4 [14.6; 35.2], $p = 0.041$), a higher orthostatic BP response (+41 mmHg [+27; +58] vs. +25 [+16; +43], $p = 0.048$), and a not different daytime SBP during the ABPM (112 mmHg [109; 115] vs. 109 [104; 113], $p = 0.078$ and 42nd percentile [33; 54] vs. 36th [22; 49], $p = 0.238$). The use of postnatal steroid outside the study intervention was also not different: 17/35 versus 5/17, $p = 0.190$. These two groups of children had not different birth weight ($p = 0.339$) and age ($p = 0.740$) at the time of cardiovascular evaluation.

There were different values of AIx and not different values of the normalized AIx_{75} in overweight or obese children as compared to underweight or normal weight children (2% [−8; 14] vs. 14% [5; 28], $p = 0.007$ and 6% [−5; 14] vs. 14% [4; 27], $p = 0.060$; respectively). Overweight or obese children, as compared to underweight or normal weight children, had higher standing heart rates (101 beats/min [94; 107] vs. 95 [85; 100], $p = 0.038$).

In the full model, we observed no significant interaction between BMI (expressed as z-score) and treatment. In the ANCOVA model (adjusted reduced model), the effect of BMI did not differ between groups, nor did the use of postnatal steroid treatment outside study intervention. All other things being equal, BMI has a significant effect on SBP (β coefficient = 3.4, 95% CI: 1.3–5.4, $p = 0.002$).

The observed BMI's effect on SBP indicates that, in the context of this study/practice, BMI should be monitored as a potential confounding factor.

Effect of male sex on cardiovascular outcomes

When comparing boys ($n = 25$, median age 11.7 years [10.6; 12.8]) to girls ($n = 27$, median age 11.9 years [10.3; 12.4]), their cardiovascular outcomes were not different: PWV % predicted (102% [94; 108] versus 100% [89; 109], respectively, $p = 0.621$), daytime BP percentiles (systolic BP: 44th [26; 52] versus 39th [22; 49], respectively, $p = 0.412$; diastolic BP: (35th [18; 51] versus 29th [14; 56], respectively, $p = 0.858$) (data not shown for the other outcomes).

Table 2. Clinical characteristics and main outcome of the 52 participants according to the randomization group.

Characteristics median [interquartile] or *n* (subjects)	Hydrocortisone *N* = 28	Placebo *N* = 24	*P* value
Gestational age, weeks^{+days}	26^{+3} [26^{+1}; 27^{+5}]	26^{+3} [25^{+1}; 27^{+3}]	0.124
Birthweight, g	897 [750; 975]	860 [745; 1010]	0.776
Very low/extremely low birth weight, *n* (%)	5 (18)/23 (82)	7 (29)/17 (71)	0.510
Multiple birth, *n* (%)	11 (39)	10 (42)	>0.999
Chorioamnionitis, *n* (%)	18 (64)	14 (58)	0.777
Bronchopulmonary dysplasia, *n* (%)	5 (18)	9 (37)	0.111
Insulin treatment, *n* (%)	10 (36)	7 (29)	0.768
Postnatal steroid treatment, *n* (%)[b]	12 (43)	10 (42)	0.931
Ethnicity, Af/As/C/M[a], *n* (%)	6 (21)/15 (54)/1 (4)/6 (21)	9 (37)/8 (33)/3 (12)/4 (17)	0.279
Sex, female/male, *n* (%)	17 (61) / 11 (39)	10 (42)/14 (58)	0.265
Age, years	11.5 [10.2; 12.2]	12.2 [10.9; 13.2]	0.069
Height, cm	149 [143; 156]	152 [146; 158]	0.183
Weight, kg	42.9 [33.0; 51.1]	42.4 [34.9; 58.7]	0.557
Body Mass Index z-score	0.14 [-0.33; 1.27]	0.33 [-1.03; 1.24]	0.673
underweight or normal/overweight/obesity, *n* (%)	19 (68) / 8 (29) / 1 (4)	16 (67) / 4 (17) / 4 (17)	0.212
Sport practice			
At school, hours per week	3 [3; 4]	3 [3; 3]	0.123
Extra-schoolar, hours per week	0 [0; 2]	1 [0; 2]	0.133
Peds-QL			
Physical health	84 [66; 94]	94 [86; 100]	0.029
Psychosocial health	77 [59; 92]	84 [76; 92]	0.151
Total score	80 [62; 92]	88 [78; 93]	0.052
Associated diseases, *n* patient affected (%)	5 (18)	1 (4)	0.199
Asthma, *n* (%)	2 (7)	1 (4)	
Attention-deficit/hyperactivity disorder, *n* (%)	2 (7)		
Autism spectrum disorder, *n* (%)	1 (4)		
Epilepsy, *n* (%)	1 (4)		
Treatments			
Long acting beta-agonist and inhaled corticosteroid, *n* (%)	2 (7)	1 (4)	
Methylphenidate, *n* (%)	1 (4)		
cf-PWV, m/s	4.84 [4.40; 5.48]	5.00 [4.48; 5.34]	0.969
cf-PWV, % predicted	101 [94; 110]	103 [92; 106]	0.704
Aortic SBP, mmHg	98 [92; 100]	100 [95; 109]	0.097
Augmented Pressure, mmHg	10 [4; 16]	8 [2; 12]	0.252
AIx, %	9 [3; 24]	12 [-2; 23]	0.551
AIx_{75}, %	11 [5; 27]	9 [-1; 23]	0.225
SEVR, %	117 [107; 144]	137 [113; 161]	0.132

[a]African/Asian/Caucasian /Mixed ethnicity.
[b]Postnatal steroid treatment outside study intervention (corticosteroids were allowed after the end of the treatment period[1]): systemic hydrocortisone, systemic betamethasone, inhaled corticosteroid.
Very low birth weight: 1000–1500 g and extremely low birth weight < 1000 g.
The CDC cut-offs are the 85th (overweight: z-score 1.036) and 95th (obesity: z-score 1.645) centiles of the Body Mass Index distribution, for age 2–20 in both sexes.

DISCUSSION

The main results of our cross-sectional descriptive study of children/adolescents with extremely preterm birth are that early hydrocortisone administration did not affect cardiovascular indices known to be associated with subsequent hypertension, while overweight/obesity was already associated with markers of cardiovascular morbidity.

Early hydrocortisone exposure as a risk factor for cardiovascular morbidity

Earlier studies indicated increased arterial stiffness after either preterm birth or low birth weight[26,27] while more recent studies did not.[13,28] This could partly be related to the evolving standard of care in preterm birth, such as the early postnatal administration of corticosteroids. Along this line, a meta-analysis concluded that there is a compelling need for long-term follow-up and reporting of late outcomes among surviving infants who participated in all randomized trials of early postnatal corticosteroid treatment,[5] justifying our study. Overall, our study shows that all the cardiovascular parameters studied (sympathovagal cardiac balance, baroreflex, aortic stiffness, and blood pressure) were not significantly affected by early corticosteroid exposure in a randomized trial, which confirms the results of de Vries et al.[29] using a better control group (placebo group in our study).

Table 3. HRV and blood pressure characteristics according to the two groups of randomization.

Characteristics median [interquartile], *n* (missing data or %)	Hydrocortisone $N = 28$	Placebo $N = 24$	*P* value
Supine measurements			
Heart rate /min	76 [70; 88]	70 [66; 78]	0.091
VLF, ms^2	1354 [666; 2199]	2336 [878; 3821]	0.128
LF, ms^2	1339 [514; 2131]	1746 [1036; 2237]	0.295
LFnu, %	47 [38; 60]	47 [39; 53]	0.790
HF, ms^2	976 [628; 1707]	1332 [884; 2249]	0.295
HFnu, %	43 [30; 49]	40 [28; 46]	0.588
LF/HF ratio	1.10 [0.72; 1.96]	1.14 [0.86; 1.62]	0.769
Ascendant BRS, ms/mmHg (missing)	18.5 [8.4; 34.4] (6)	22.4 [17.5; 39.5] (6)	0.289
Descendant BRS, ms/mmHg (missing)	17.3 [10.0; 32.4] (2)	29.4 [14.7; 33.2] (5)	0.175
Deep breathing measures			
Heart rate /min	81 [70; 93]	74 [66; 79]	0.065
VLF, ms^2	1360 [699; 3794]	1303 [547; 2516]	0.779
LF, ms^2	3123 [1775; 4200]	3788 [2534; 6508]	0.065
LFnu, %	64 [52; 78]	70 [59; 81]	0.203
HF, ms^2	1201 [759; 1881]	1526 [831; 2476]	0.367
HFnu, %	27 [19; 38]	23 [15; 31]	0.293
LF/HF ratio	2.29 [1.47; 4.00]	3.16 [1.80; 5.59]	0.307
Standing measurements			
Heart rate/min	96 [89; 106]	95 [86; 101]	0.408
VLF, ms^2	753 [369; 1235]	650 [281; 1496]	0.727
LF, ms^2	1019 [801; 1952]	1004 [718; 1962]	0.713
LFnu, %	58 [48; 70]	63 [53; 71]	0.557
HF, ms^2	515 [320; 921]	388 [227; 1001]	0.295
HFnu, %	28 [20; 38]	25 [19; 36]	0.503
LF/HF ratio	2.01 [1.22; 3.42]	2.25 [1.51; 3.64]	0.497
Ascendant BRS, ms/mmHg (missing)	6.0 [4.3; 9.3] (6)	7.8 [6.5; 10.7] (6)	0.128
Descendant BRS, ms/mmHg (missing)	5.6 [4.5; 9.6] (4)	7.3 [4.1; 11.3] (2)	0.809
ΔSBP (standing minus supine BP), mmHg (missing)	+28 [+21; +47] (2)	+28 [+11; +49] (1)	0.707
ΔDBP (standing minus supine BP), mmHg (missing)	+32 [+16; +54] (2)	+38 [+12; +62] (1)	0.804
Exaggerated orthostatic pressure response, *n* (%)	22 (79)	15 (62)	0.234
Office blood pressure (BP)			
Systolic BP, mmHg	106 [101; 112]	108 [103; 114]	0.344
Systolic BP percentile	59 [44; 69]	57 [46; 83]	0.594
Diastolic BP, mmHg	63 [59; 67]	63 [60; 65]	0.861
Diastolic BP percentile	51 [39; 65]	51 [36; 60]	0.840
Elevated BP/hypertension, *n* (%)	3 (11) / 1 (4)	2 (8) / 3 (12)	0.476
ABPM			
Daytime SBP, mmHg	109 [105; 113]	111 [104; 114]	0.643
Daytime SBP, percentile	39 [23; 52]	40 [24; 48]	0.887
Daytime DBP, mmHg	68 [63; 72]	68 [64; 72]	0.850
Daytime DBP, percentile	35 [14; 54]	34 [17; 56]	0.977
Nighttime SBP, mmHg	99 [95; 105]	100 [96; 105]	0.428
Nighttime SBP, percentile	56 [45; 68]	54 [47; 67]	0.771
Nighttime DBP, mmHg	55 [51; 60]	56 [51; 58]	0.944
Nighttime DBP, percentile	55 [43; 73]	55 [43; 66]	0.904
Nighttime systolic dipping, %	10 [5; 14]	7 [5; 10]	0.193
Nighttime diastolic dipping, %	17 [13; 21]	17 [12; 22]	0.992
Elevated BP/hypertension, *n* (%)	2 (7)/2 (7)	2 (8)/1 (4)	0.893

Early initiation (<seven days after birth) of systemic hydrocortisone is considered an ineffective intervention in a recent overview of systematic reviews because of an unfavorable balance between benefits and harms.[30] This early administration was associated with significant short- and long-term adverse effects, such as an increased risk of gastrointestinal bleeding, intestinal perforation, hyperglycemia, and hypertension, as well as abnormal neurological examination and cerebral palsy. Interrupted vascular tree development is a key component of several major prematurity-related complications, including bronchopulmonary dysplasia and retinopathy of prematurity.[31] Interestingly, a systematic review of early systemic postnatal corticosteroids for the prevention of bronchopulmonary dysplasia in preterm infants concluded that early systemic corticosteroids reduced any retinopathy of prematurity.[32] Thus, the absence of a deleterious effect of early hydrocortisone administration on systemic vascular indices may seem consistent with the effect on retinopathy.

The only significant difference between the two groups was a better physical quality of life in the placebo group, which may be related to a trend for more extracurricular sport practice and less associated diseases in this group.

Results of the whole cohort

Overall, our children had a normal quality of life, which is in agreement with the findings of a meta-analysis showing that teenagers noted normal performance in their global health, behavior, and physical functioning.[33] The prevalence rates of both elevated BP and hypertension were not clearly increased due to our population's restricted sample size (see confidence intervals) as compared to those expected in a healthy population, given the statistical definition of these abnormalities (5% for both).

A recent meta-analysis showed that premature infants were more likely than full-term infants to be obese at the age of 6–16 years. Birth weight had no effect on the incidence of obesity.[11] Our results are in line with these findings. In our study, office peripheral and central BP were elevated in children with overweight or obese, which was associated with decreased BRS sensitivity and an increased orthostatic BP response. Overall, an exaggerated orthostatic BP response was very prevalent in these formerly preterm children/adolescents, which was associated with BRS sensitivity in our whole population. Orthostatic hypertension has recently been defined on a consensus basis,[20] which is important due to its prognostic value for subsequent hypertension.[20] The tracking of blood pressure levels from childhood to adulthood is well demonstrated, and higher BMI resulted in increasing blood pressure across trajectories, particularly for the higher blood pressure groups.[34] The association between systolic blood pressure trajectories derived from childhood and subclinical cardiovascular risk in young adulthood has also been demonstrated.[12] Thus, our results have clinical implications: children born extremely preterm with overweight or obesity should be followed up using systematic ABPM, as recommended.[23]

Finally, we did not observe a significant effect of male sex on cardiovascular outcomes.

Limitations of the study

The first limitation is its cross-sectional design in children/adolescents in whom puberty stage was not evaluated, which may have affected our results. In a population of 7–12-year-old children, Li et al. showed that puberty advancement is significantly more associated with BP value than chronological age.[35] Nevertheless, it has not been determined how to interpret BP values depending on the stage of puberty so far.[36] Second, not all the surviving children included in the PREMILOC trial in our hospital were assessed, since many families had moved away, and the 52 subjects who were evaluated constitute a small fraction of the infants included in the trial (406 survived to 2 years of age). This small sample size is a limitation for some of our outcome measures. Third, the absence of a significant difference in PWV between the two groups may be related to our population's small sample size. Nevertheless, no trend was evident, and the other cardiovascular indices were not different, while some differences were evident in overweight/obese participants, arguing for the adequacy of the sample size. Due to the pathophysiological proof-of-concept design of our study, statistical analyses were not corrected for multiplicity, as proposed[37], and consequently, some results could be related to type 1 error. Finally, we did not include a healthy group of children, which was beyond our study's scope.

In conclusion, early hydrocortisone administration in infants with extremely preterm birth included in a randomized trial is not associated with detrimental cardiovascular indices in children/adolescents, while overweight/obesity was already associated with markers of cardiovascular morbidity.

DATA AVAILABILITY

The data that support the findings of this study are available from Aguettant France, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Aguettant France https://www.aguettant.fr/.

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AUTHOR CONTRIBUTIONS

Conceptualization: C.D.; Data curation: C.B., K.D., P.C., and S.G.C.; Formal analysis: S.A., P.C., S.G.C., and C.D.; Funding acquisition: C.B. and C.D.; Investigation: C.B., K.D., P.B., and C.D.; Methodology: P.B., S.G.P., V.B., O.B., and C.D.; Project administration: S.A., K.D., S.G.C., and C.D.; Supervision: S.G.C., V.B., O.B., and C.D.; Validation: P.C., S.A., S.G.C., and C.D.; Visualization: P.B., P.C., S.A., and S.G.C.; Roles/Writing—original draft: C.D.; and Writing—review and editing: C.B., P.B., P.C., S.A., K.D., S.G.C., O.B., and V.B.

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COMPETING INTERESTS

The authors declare no competing interests.

CONSENT STATEMENT

The study was approved by an ethics committee (Comité de Protection des Personnes Sud-Méditerranée III, N° 2022.04.07_ 22.01163.000091), and the parents and children/adolescents gave their informed written consent.

ADDITIONAL INFORMATION

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