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Increased blood pressure but normal renal function in adult women born preterm

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Abstract It has been suggested that children born small for gestational age may develop hypertension and renal dysfunction in adulthood due to impaired fetal kidney development. Very little information on this issue is available on children born preterm. The objective of this study was to investigate the relationship between birth weight, blood pressure, and kidney function in adult subjects who were born preterm or born small for gestational age (SGA). *Study design:* Subjects (*n*=50), all women born between 1966 and 1974, were evaluated at a mean age of 26±1.9 years. They were allocated to three groups: (1) born before gestational week 32 (*n*=15), (2) born full term with birth weight <2600 g (*n*=18) (SGA), and (3) controls, born full term with appropriate birth weight (*n*=17). Casual blood pressure, ambulatory 24-h blood pressure (ABPM), glomerular filtration rate (GFR), renal plasma flow (ERPF) and urinary albumin excretion were determined. *Results:* Preterms had significantly higher casual systolic and mean arterial blood pressure levels compared to controls (123±13 vs 110±7 mmHg, $P<0.01$, and 87±9 vs 79±6 mmHg, $P<0.005$, respectively). ABPM was not significantly different between the groups. When the number of systolic recordings >130 mmHg/subject during ABPM was calculated, the preterms had significantly more recordings above this value ($P<0.05$) as well as a significantly increased area under the curve >130 mmHg and >140 mmHg systolic ($P<0.05$) compared to the controls. SGA subjects were not significantly different from controls. There were no significant differences in GFR, ERPF or urinary albumin excretion between the three groups. *Conclusion:* Women born preterm seem to have a disturbance in blood pressure regulation in adulthood, a finding that is not observed for those born small for gestational age. Kidney function in early adulthood seems to be normal in subjects born preterm or small for gestational age.

Key words Fetal growth retardation · Preterm birth · Glomerular filtration rate · Ambulatory blood pressure

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Introduction

Several studies have suggested that poor intrauterine growth has subsequent effects on adult health due to increased risk of death for cardiovascular disease [1, 2]. Many epidemiological retrospective studies have provided support for this theory by demonstrating a higher incidence of cardiovascular disease [3] or high blood pressure [4] in adult subjects born with a low birth weight due to intrauterine growth retardation compared to subjects born with normal birth weight. The mechanisms responsible for this relationship are still under debate. One suggestion is that renal dysfunction will lead to hypertension and that this is the cause of the cardiovascular disease [5]. According to this hypothesis, fetal growth retardation will lead to impaired nephron formation. Fewer nephrons are thought to predispose to progressive renal failure, glomerular sclerosis, essential hypertension, and macrovascular disease [6]. Two different experimental models have shown that animals born with fetal growth retardation have smaller kidneys and a decrease in the total number of nephrons and that they are prone to develop hypertension as adults [7, 8].

Preterm birth may be wrongly associated with fetal growth retardation if only the birth weight, and not the gestational age, is accounted for. Preterm infants initially have a stressful life, which affects their nutritional balance and postnatal growth. A decrease in glomerular filtration rate at 9 months corrected age has been found in preterm infants born less than 30 weeks of gestation, compared to infants born full term [9]. Moreover, there have been findings suggesting smaller kidneys and renal

dysfunction in early childhood in preterm infants [10]. Blood pressure levels in subjects born preterm have been studied mostly in the immediate neonatal period [11] or during their 1st year of life [12, 13]. There are, to our knowledge, no long-term follow-up studies investigating whether this moderate renal impairment is permanent and whether it will lead to an increase in blood pressure in adulthood.

In the present study, casual and 24-h ambulatory blood pressures, glomerular filtration rate (GFR) and renal plasma flow (ERPF) were determined in adult subjects with low birth weight of different origins, i.e., preterm infants, born with a low birth weight due to an early delivery and full-term infants born small for gestational age. Studies on adult men concerning birth size, gestational age and 24-h ambulatory blood pressures have been performed previously [14] but our study is the first to investigate this relation in women.

Materials and methods

Selection of participants

Fifty women, with a mean age of 26±1.9 years (range 23–30 years), were included in the present study and they were allocated to three groups: (1) preterms, born before gestational week 32 (n=15), (2) born full term (between gestational weeks 37 and 42) with birth weights <2600 g (n=18) and defined as having birth weights below the 25th percentile for gestational age (SGA), and (3) controls, born full term with appropriate birth weight for gestational age (n=17). None of the participants suffered from a chronic disease or was taking medications that might affect the blood pressure.

The preterm subjects, born in Stockholm, Sweden, between the years 1970 and 1974, were randomly selected from neonatal clinical records at the St. Goran Children's Hospital (n=12) and from the National Medical Birth Register (n=3). In total, 25 women were contacted by letter, of whom 15 agreed to participate in the study.

Growth retarded subjects born in Stockholm between 1966 and 1974 were randomly selected from medical reports from Sabbatsbergs Hospital or from the National Medical Birth Register. Subjects fulfilling the criteria for the study and who could be traced in the local area were contacted by letter. Twenty-nine women were contacted; 18 of them agreed to take part in the study.

Control age-matched women born in the Stockholm area were randomly selected from the National Medical Birth Register (n=11), from healthy volunteers (n=4) and from neonatal records taken on the same day and in the same hospital as subjects in the other two groups (n=5).

Anthropometric data

The gestational age and birth weight were obtained from medical records. Present clinical history was evaluated and a clinical investigation was performed by a doctor (A.K.) at the outpatient clinic. Adult height and weight were measured on a portable scale to the nearest 0.1 kg. Adult body mass index [weight (kg)/(height)^2 (m)] and neonatal ponderal index [birth weight (kg)/(birth length)^3 (m)] were then calculated.

Casual blood pressure measurements

The blood pressure of each participant was measured by an automatic blood pressure recorder, 3 times in the horizontal position, after a rest of at least 15 min. The mean of the three measurements was designated as casual blood pressure. Mean arterial blood pressure was calculated according to the following formula: diastolic + (systolic–diastolic/3). The participants were then asked to rise and two measurements were obtained in the standing position. The mean value of the two measurements was recorded as standing casual blood pressure.

Ambulatory blood pressure measurements

A SpaceLabs model 90207 monitor (Spacelabs Inc., Redmond, WA) was used. This device employs an oscillometric method with a deflation rate of 8 mmHg/s. The cuff was placed on the non-dominant arm and extended completely around the arm. The accuracy of the monitor was tested in each subject under resting conditions at the beginning of the monitoring period against an "ordinary" mercury manometer to verify that the blood pressure recorder and the mercury device gave similar values. Ambulatory blood pressure measurements were performed during a regular day during the week with normal activities, although the subjects were instructed not to engage in hard physical exercise. The recordings began between 9:00 a.m. and 3:00 p.m. Blood pressure was recorded every 20 min over 24 h. The participants were asked to record their activities during the day and when they went to bed. During the day an acoustic signal was programmed to remind the subject to relax the arm before the measurements.

The device estimated mean diastolic and systolic blood pressure levels for the 24-h period with all the valid recordings noted during the period. Mean diastolic and systolic blood pressure levels during day- (06:00–24:00) and nighttime (24:00–06:00) were also calculated. The total number of systolic recordings >130 mmHg and >140 mmHg in each individual subject, as well as the total number of diastolic recordings >80 mmHg and >90 mmHg, were counted. Systolic and diastolic blood pressure loads were assessed as the percentage of readings in each subject that were >140 mmHg and >90 mmHg, respectively, during the 24-h period and during day- (06:00–24:00) and nighttime (24:00–00:00) [15]. The integrated area under the BP curve in each individual was calculated during the whole ABP measurement (24 h) as well as the area above a certain variable blood pressure level (130 and 140 mmHg systolic and 80 and 90 mmHg diastolic, respectively) [16]. All measurable points were assessed as bars with a width corresponding to the time interval between the recordings (20 min) and a height corresponding to the measured recording. The area was calculated as the total sum of the recordings and as the sum of the recordings above a certain blood pressure (130 and 140 mmHg systolic blood pressure and 80 and 90 mmHg diastolic, respectively).

Renal function

GFR was determined by the clearance of iohexol and ERPF as *p*-aminohippurate clearance (PAH). The clearance measurements were performed between 8:00 and 12:00 a.m. To measure GFR, 5 ml omnipaque (Omnipaque 300 mg I/ml, Nycomed, Sweden) was given in a single bolus dose. PAH was given as a continuous infusion after a bolus dose of 0.05 ml/kg, given during 3 min. A solution of 20% PAH (2 g/10 ml sodium aminohippurate, MSD, Merck Sharp & Dohme) was used, and 14 ml of the 20% solution was dissolved in 86 ml NaCl. The speed of the infusion was 25 ml/h. A plastic cannula was inserted into a cubital vein in each arm. Blood samples were collected before the injection and for PAH after 140, 160 and 180 min. Blood samples for iohexol were taken before the injection and after 180, 200, 220 and 240 min. The filtration fraction for each subject was calculated by dividing the obtained ERPF value with the GFR value.

Urine albumin

Eight-hour night urine was collected from each participant. Urine albumin (µg/min) was determined by dry chemistry (Vitros, Orthoclinical Diagnostics, Johnson & Johnson, Strasbourg).

Table 1 Weight, length and BMI at birth and at follow-up

	Small for gestational age (*n*=18)	Preterm (*n*=15)	Controls (*n*=17)	*P**
Birth weight (g)	2175±278	1293±283	3720±313	<0.001
Length (cm)	45.5±1.9	39.5±2.1	51.0±1.8	<0.001
Ponderal index (kg/m^3)	23.0±2.4	20.8±2.8	28.1±2.0	<0.001
Adult weight (kg)	57.1±9.2*	63.9±9.3	67.9±9.2	<0.01
Length (cm)	160.4±5.8*	165.3±7.8	168.5±5.6	<0.01
Body Mass Index (kg/m^3)	22.2±4.0	23.4±2.9	23.9±3.1	NS

*Analysis of variance $P<0.01$ vs control

Table 2 Blood pressure control at follow-up

	Small for gestational age	Preterm	Controls	*P**
At first examination (mean)				
Systolic	111±10	123±13[a]	110±7	<0.001
Diastolic	67±9	69±8	64±7	0.155
Mean arterial	82±9	87±9[b]	79±6	0.018
Systolic standing	121±8	128±13[c]	120±10	0.093
Diastolic standing	75±8	75±8	75±7	0.945
24 h ambulatory (mean)				
Systolic mean day	119±7	124±9	119±7	0.124
Systolic mean night	105±8	106±9	105±8	0.920
Systolic mean (24 h)	116±7	120±7	116±7	0.231
Diastolic mean day	75±5	76±7	73±4	0.258
Diastolic mean night	60±6	59±6	57±3	0.314
Diastolic mean (24 h)	71±5	72±7	69±4	0.263
Heart rate mean (24 h)	73±8	72±8	72±9	0.924
No. of registrations [median (range)]				
Systolic >130 mmHg	4.5 (0–34)	18.5 (3–46)[d]	5 (0–40)	0.029**
Systolic >140 mmHg	0 (0–19)	2 (0–24)	1 (0–12)	0.077**
Diastolic >80 mmHg	19.5 (2–38)	13.5 (4–49)	10 (1–28)	0.109**
Diastolic >90 mmHg	2 (0–17)	1.5 (0–28)	1.5 (0–7)	0.603**
Area under the curve [median (range)]				
Systolic >130 mmHg	400 (0–10,240)	2150 (320–11,680)[e]	460 (0–6940)	0.037**
Systolic >140 mmHg	0 (0–4800)	340 (0–4260)[c]	60 (0–1520)	0.044**
Diastolic >80 mmHg	2090 (100–7880)	1700 (300–12,400)	1260 (80–4140)	0.326**
Diastolic >90 mmHg	150 (0–1840)	180 (0–4360)	160 (0–1020)	0.685**

* Analysis of variance; **Kruskall-Wallis test: [a] $P<0.01$ vs control, [b] $P<0.005$ vs control, [c] $P=0.06$ vs control, [d] $P=0.03$ vs control, [e] $P<0.05$ vs control

Statistical analysis

Results are presented as means ± SD, median and range. For statistical comparisons, analysis of variance (ANOVA), regression analysis, the non-parametric Kruskall-Wallis test and Fisher's exact test were used. Power calculations were made in order to secure the minimal number of individuals to detect a difference in renal function, albuminuria and blood pressure control between the groups. The alternative hypothesis could be rejected when no significant differences in recordings were found between the groups studied.

Results

A total of 50 women were studied. Fifteen were born with a mean gestational age of 30±1 weeks (range 28–32 weeks) (preterms), 18 were born full term, mean gestational age 40±1 weeks (37.5–41.5 weeks) with birth weight <2600 g (small for gestational age), and 17 controls were born full term, mean gestational age 41±1 weeks (39–42 weeks) with appropriate birth weight. Blood pressure control, renal function and urinary albumin excretion were determined at ages (range) 24.7±0.9 (23–26) years, 26.8±2.0 (25–30) years and 25.8±1.8 (24–30) years, respectively. The differences in age were not statistically significant.

Table 1 shows weight and length at birth and at follow-up. Significant differences in weight and length persisted into adulthood in the small for gestational age group compared to the control group. There were no significant differences between the three groups concerning the use of contraceptive pills, smoking or drinking habits (data not shown).

Blood pressure control

There was a significant difference in casual systolic and mean arterial blood pressures recorded after 15 min of rest at the first visit and examination at the outpatient clinic between the three groups ($P<0.001$ and $P<0.02$, respectively, Table 2). The preterm group showed sig-

Table 3 Renal function and urinary albumin excretion (µg/min) at follow-up

	Small for gestational age (*n*=18)	Preterm (*n*=15)	Controls (*n*=17)	*P*[a]
GFR (ml/min×1.73 m^2)	100±14	103±11	107±14	NS
No (%) of individuals with GFR <90 ml/min×1.73 m^2	4 (22)	1 (7)	1 (6)	NS[b]
ERPF (ml/min×1.73 m^2)	659±103	643±91	676±109	NS
FF (%)	15±2	16±2	16±2	NS
U-albumin (µg/min)	3.9±0.8	4.3±0.9	2.8±0.8	NS
No. (%) individuals with U-alb. >20 mg/l	2 (12)	1 (7)	0	NS[b]

[a] Analysis of variance
[b] Fisher's exact test

nificantly increased casual systolic and mean arterial blood pressures recorded after 15 min of rest compared to the control group ($P<0.01$ and $P<0.005$, respectively, Table 2). No differences were observed for diastolic blood pressures and blood pressures recorded in the standing position.

At ABPM, no significant differences in systolic or diastolic blood pressures during day- or nighttime were observed (Table 2). There was, however, a significant difference between the three groups with regard to the number of systolic blood pressure registrations >130 mmHg during 24-h ambulatory blood pressure ($P<0.05$, Table 2); the preterms showed a significantly increased number of systolic blood pressure recordings >130 mmHg during 24-h ambulatory blood pressure compared to the controls [median (range): preterms=18.5 (3–46), controls=5 (0–40), $P=0.03$, Table 2]. The systolic and diastolic blood pressure loads showed no significant differences between the groups during the 24-h period [systolic load: median (range): preterms=3% (0–34), SGA=0% (0–26), controls=1% (0–16), $P=0.09$; and diastolic load: median (range): preterms=2% (0–41), SGA=3% (0–23), controls=1% (0–9), $P=0.57$] or during day- and nighttime (data not shown). There were no differences between the three groups when the systolic and diastolic integrated area under the curve was calculated [systolic: median (range): preterms=176,000 mmHg min (151,000–196,000), SGA=170,000 mmHg·min (153,000–193,000), controls=173,000 mmHg min (154,000–197,000), $P=0.62$; and diastolic: median (range): preterms=107,000 mmHg·min (90,000–123,000), SGA= 106,000 mmHg·min (88,000–123,000), controls=104,000 mmHg·min (85,000–113,000), $P=0.39$]. However, we found a significant difference between the groups when the integrated area under the curve >130 mmHg systolic was calculated [median (range): preterms= 2150 mmHg·min (320–11,680), SGA=400 mmHg·min (0–10,240), controls=460 mmHg·min (0–6940), $P<0.05$, Table 2].

Renal function and urinary albumin excretion

There were no significant differences in GFR between the three groups (Table 3). The number of individuals with a GFR <90 ml/min×1.73 m^2 was 22% in the SGA group, 7% in the preterm group and 6% among controls (NS). Furthermore, there were no significant differences in ERPF and Filtration Fraction (FF) between the three groups. The mean excretion of albumin in the urine (µg/min) was low and within the normal range (0–17 µg/min) in all subjects in the three groups.

Correlation between renal function, urinary albumin excretion and blood pressure control

In the group of women born small for gestational age there was a significant negative correlation between GFR and the mean systolic blood pressure recorded during 24-h ambulatory blood pressure registrations and the mean systolic blood pressure during daytime ($r=0.53$, $P<0.05$, for both regression analyses). In the same group of patients there was a significant positive correlation between urinary albumin excretion and the systolic and diastolic blood pressure registrations in the standing position at the first examination at the outpatient clinic ($r=0.55$, $P<0.05$, and $r=0.60$, $P<0.01$, respectively).

No other significant correlations between renal function, urinary albumin excretion and blood pressure were observed when the three groups were studied separately or when all subjects were evaluated together.

Discussion

Women born preterm and women born small for date, aged from 23 to 30 years, were investigated in the present study. We evaluated casual and ambulatory blood pressures in adults born preterm or born SGA. The subjects born preterm examined in the present study seem to have minor alterations in their blood pressure control. The mean casual systolic and mean arterial blood pressure measurements in the horizontal position showed significantly higher values in the preterms compared to controls. In the standing position, their systolic blood pressure showed a tendency to increased levels. Their ambulatory blood pressure profiles showed no significant differences in mean systolic and diastolic blood pressure during the 24-h recording compared to controls.

Adult subjects born preterm had more maximum to mean variation in their systolic blood pressure profiles, with significantly more systolic recordings >130 mmHg during the 24-h ambulatory blood pressure recording and significantly increased area under the curve >130 mmHg systolic, compared to controls.

By contrast, the casual blood pressure measurements in the horizontal and standing position in the SGAs and the ambulatory systolic blood pressure level in the SGAs did not differ significantly from the controls.

There is very little information in the literature on blood pressure measurements in adult subjects born preterm since most studies have been performed on subjects born full term with low birth weight due to intrauterine growth retardation. There is, however, epidemiological evidence of a relationship between increased systolic and diastolic blood pressure levels in adulthood and being born preterm, although this study was performed on men [14]. Our results, in women, partially support these findings. We found a slight increase in casual blood pressure but no statistical differences in systolic or diastolic ambulatory blood pressure. The discrepancy between the casual blood pressure measurements and the ambulatory blood pressure could be attributed to the so-called white-coat syndrome. The standard definition of white-coat hypertension (WCH) is an elevation in casual blood pressure measurement(s) but normal ABP monitoring [17]. There is a continuing discussion today as to whether WCH simply represents a benign manifestation of a reactive sympathetic nervous system or a true pathological condition, with associated morbidity. Recent studies seem to conclude that WCH is not an entirely benign condition. Left ventricular mass and carotid atherosclerosis have both been shown to be increased in white coat hypertensives compared to normal controls [18–20]. The literature is, however, at variance on the subject, with some reports suggesting a relatively benign outcome of the phenomenon [21, 22]. The risk for subjects with WCH of developing sustained hypertension is not clear although one small prospective study indicated that persistent daytime hypertension occurred in as many as 75% of patients with WCH over a 5-year period of time [23]. Trenkwalder and collaborators have shown that white-coat hypertension is probably a variant of a rise in blood pressure during stress [24]. It seem likely that in our study women born preterm are more sensitive to stress, also indicated by an increased area under the curve above a certain level (>130 mmHg systolic) and more single recordings above 130 and 140 mmHg.

Values recorded from a 24-h ambulatory blood pressure measurement are argued to be a stronger predictor of cardiovascular risk than those obtained from casual blood pressure measurements [25]. There are, however, very few ambulatory blood pressure measurement studies made on adult subjects born small for dates or preterm. Lurbe and colleagues measured ambulatory blood pressure in individuals aged between 6 and 16 years in the absence of intrauterine growth retardation [26]. They found that children who had lower birth weights tended to have higher systolic daytime blood pressures and higher systolic load, an association that became stronger with increasing age. An increase in diastolic blood pressure during young adulthood in SGA subjects has also been reported by Uiterwal and colleagues [27]. In our study, we found no such differences in systolic blood pressure in adulthood in women born small for dates compared to controls. The discrepancy between these two studies may also be due to difference in gender. Recently, it has been reported that protein deprivation during pregnancy has a more harmful effect in male than in female rats [28].

We also investigated kidney function and albuminuria in preterm subjects and in subjects born small for gestational age. We observed that the adults born preterm have equivalent normal kidney function compared to the controls. It is believed that nephrogenesis, i.e., nephron formation, is completed by 34–36 weeks of gestation [29]. GFR increases after birth and is normally considered to reach adult levels in humans by the age of 2 years [30]. A follow-up study by Jones and coworkers in children born preterm at the age of 4–5 years showed signs of renal impairment in preterm subjects [10]. However, there are also indications of a normal kidney function in preterm infants studied at the age of 8 years [9]. Our result are in accordance with these findings. Preterm subjects may have a delayed kidney maturation after birth, but in adulthood they achieve normal renal function.

In our study, we did not find evidence of glomerular damage in SGA women studied at 30 years of age. In Australian aborigines higher rates of progressive albuminuria and renal failure have been found in low birth weight adults compared to adults with normal birth weights [31, 32]. We found, however, no significant differences in renal function or albuminuria in our SGAs compared to controls. Studies in young adults unilaterally nephrectomised because of Wilms tumor in infancy support our findings [33–35]. GFR showed no reduction, and only a slight deviation in urinary albumin excretion rate was found 11–28 years after the operation [34]. Autopsy studies have shown a possible reduction in nephron number in humans born with intrauterine growth retardation [36]. It is therefore possible to speculate that even if SGAs are born with fewer nephrons the progression to glomerular sclerosis is very slow or undetectable at least during their first 30 years of life. It is reasonable to assume that the postpartum neonatal care (particularly with regard to nutrition) was of a higher quality in our population as compared to Australian aborigines born in the beginning of the 1960s and 1970s, which may have contributed to better renal development. Many different factors can contribute and lead to increased blood pressure levels. We cannot exclude that, in our subjects, renal function may start to deteriorate later in life. Further studies are required in older age to exclude that a moderate alteration in kidney function together with alterations in blood pressure will not occur in adults born SGA.

In conclusion, young women born preterm seem to have a slight disturbance in blood pressure regulation in adulthood, a finding that was not observed for those born small for gestational age. The pathogenesis for this finding is unknown but may be explained by a reduced capacity to adapt to stress-related situations.

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