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Original Article

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The effects of gestational age and growth restriction on compensatory kidney growth

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Abstract

Background. Low birth weight is associated with altered renal development, adult onset hypertension and renal disease. The aim of this prospective longitudinal study was to estimate the renal growth during the first 2 years of life in small-for-gestational age (SGA) infants of varied gestational age (GA) and with differing degrees of growth retardation (GR) at birth.

Material and methods. The study included 466 children: SGA, $n = 243$, and appropriate-for-gestational age (AGA), $n = 223$, classified according to GA into three groups (28–34, 34–36 and >36 weeks, respectively). The SGA children were also classified according to the degree of GR: birth weight <3rd percentile, and birth weight 3–10th percentiles. Serial renal ultrasonography (US) for kidney length (KL) measurement was performed at the ages of 36 and 40 weeks corrected age and 3, 6, 12 and 24 months of chronological age. The ratios of KL^3 to crown to heel length (CHL), body weight (BW) and body surface area (BSA) were used as estimators of relative kidney length (RKL).

Results. A total of 1898 measurements were performed. In the full-term and near-term SGA infants (GA >36 weeks), RKL was similar to or even higher than that in AGA controls ($P < 0.05$ at 12 and 24 months). In two groups of preterm infants (GA 34–36, 28–34 weeks), RKL was lower than in AGA controls either after the first 6 months (GA 34–36 group, $P < 0.05$) or throughout the study period (GA 28–34 group, $P < 0.05$). The absolute KL was more severely affected in the preterm babies (GA <36 weeks) with BW <3rd percentile than in those of GA 3rd–10th percentile.

Conclusion. While in full-term and near-term SGA infants RKL is similar to or even higher than that of AGA infants, in smaller preterm babies (<36 weeks of GA) the RKL is impaired up to the second year of life.

Keywords: compensatory renal growth; growth restriction; kidney length; neonate; small-for-gestational age

Introduction

Several studies have shown that factors affecting intrauterine growth and development may pre-programme the organism for subsequent hypertension and cardiovascular and renal disease [1,2]. It has been proposed that fetal growth retardation (GR) may be associated with impaired nephronogenesis [3,4]. Glomerular hyperfiltration resulting from reduced nephron numbers could stimulate physical and cellular factors leading to systemic hypertension, glomerular sclerosis and progressive deterioration of renal function [3]. Glomerular hypertrophy is regarded as an initial step in this hypothesis.

Clinical observations have demonstrated that fetal GR is associated with reduced nephron numbers at birth. Studies in the human neonate have shown that fetal GR is associated with reduced nephron numbers and greater glomerular volumes in human neonates [5,6], and experimental studies in animal models have also demonstrated this association [7,8]. Recent histomorphometric studies have shown reduced nephron numbers in adults with primary hypertension [9].

Renal size, as estimated by ultrasonography (US), may be a used as a surrogate measure for nephron numbers and an indirect index of renal growth under a variety of clinical conditions [10–12].

Data on postnatal kidney growth in infants born small-for-gestational age (SGA) are very limited [13–15]. The kidney size measured by US in this group appears to be small at birth compared with babies born appropriate-for-gestational age (AGA) [13–15]. To the knowledge of the authors, no previous study has examined kidney growth in SGA infants taking into consideration both the gestational age (GA) and the severity of GR at birth. It is known that nephron formation is dependent on GA and babies have acquired their final number of nephrons only after 34–36 weeks of GA [16].

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This study was designed to estimate the renal growth during the first 2 years of life in SGA infants of varied GA and with differing degrees of GR at birth.

Patient and methods

This prospective, longitudinal study included infants born between 28 and 41 weeks of GA with low birth weight for GA. The infants enrolled in the study were born at the University Hospital of Ioannina, which is the regional hospital hosting the majority of the deliveries (>85%) in the area of Northwest Greece. Following discharge, the children were followed up at the outpatient clinic for monitoring of growth and development. All neonates of 28–41 weeks of GA born SGA during a 2-year period (January 2003 to January 2005) were eligible for the study. Infants with documented hydronephrosis or urinary tract infection were excluded. The control group comprised infants born AGA in the hospital during the same time period, matched for GA, gender and socioeconomic status. The study protocol was approved by the Hospital Ethics Committee, and informed parental consent was obtained. GA at birth was assessed according to an early US scan at 12–18 weeks of GA, and confirmed by assessment by neonatologists of the infants' maturity within 24 h of delivery [17].

Infants were classified as SGA (birth weight <10th percentile for GA) or AGA (birth weight 10th–90th percentile for GA) using the relevant age–gender-specific percentiles in the growth curves specific for Greek children. SGA neonates comprise a heterogeneous group in terms of cause, timing and severity of GR [18]. The SGA neonates of the study were further classified into two groups according to the degree of GR. The first group included those with birth weight < 3rd percentile and the second group those with birth weight between the 3rd and 10th percentiles. SGA and matched AGA controls were divided into three GA groups after taking into consideration the timing of renal nephron formation: those of GA >36 weeks, where nephrogenesis is regarded complete, those of GA 34–36, where nephrogenesis may be not be fully completed, and those of GA 28–34 weeks, where nephrogenesis is still incomplete [16].

The files of all the study babies were examined and information extracted about administered drugs potentially affecting kidney, such as aminoglycosides, vancomycin, furusemide and corticosteroids. For babies who received aminoglycosides, information about drug levels was recorded.

For infants of GA >36 weeks, US kidney measurement was performed at the corrected age of 40 weeks [corrected age (in weeks) = GA (in weeks) plus age after birth (in weeks)], and at the chronological ages of 3, 6, 12 and 24 months (total 5 measurements). Preterm infants of GA 28–36 weeks had an additional measurement at the corrected age of 36 weeks (total 6 measurements). The US examinations were performed blindly and independently by two of the authors (M.A. and F.P.), who are senior paediatric radiologists. Measurements of kidney length (KL) were made using 5–8 MHz linear or curved array transducers (7 MHz) (HDI Philips 5000). A single maximal longitudinal measurement of each kidney was obtained sonographically in the supine position [19–21]. The interobserver variability and the limits of agreement for this study were estimated in a sample of 35 KL measurements in infants based on the method of Bland and Altman [23]. The mean value of the difference (MV) and the standard deviation of the difference (SDD) were 1.10 and 0.71 mm, respectively. The SDD is a measurement of the inter-observer variability. The respective 95% limits of agreement [MV± (1.98 × SDD)] expressed as a percentage (%) of KL varied from −0.64% to +5.1%.

Body weight (BW) was determined at each visit to the nearest 0.1 kg with the child dressed only in underwear and wearing no shoes, using a digital electronic scale (SECA, Hamburg, Germany). Crown to heel length (CHL) was measured to the nearest 0.1 cm by a Harpenden stadiometer. BW and CHL were converted into age and gender specific SDS scores (*z*-scores) using the formula (SDS_y – SDS_{mean})/SD where SDS_y represents the value of the individual infant. SDS_{mean} represents the specific mean value in the AGA children of the same age and gender and SD the standard deviation of the specific mean value. As renal length relates to renal weight via a cubic relationship, the cubed factor of KL was calculated (KL^3) and the ratios KL^3/CHL, KL^3/BW, KL^3/body surface area (BSA) were calculated for the estimation of the relative kidney length (RKL). BSA was calculated using Boyd's equation [BSA (m^2) = 0.0003207 × Height (cm)$^{0.3}$ × Weight (grams)$^{(0.7285 - (0.0188 \times \text{LOG BW(grams)}))}$] [22].

Sample size

The number of infants was selected to allow a minimum of 50 measurements for each comparison in any study period. This number of infants was considered to be sufficient to document a 10% difference in KL between groups with a power of >0.85 at a significance level of 0.05. In sample size calculation, data of the mean values of KL (±SD) of an earlier study in SGA infants was used [14,24].

Statistical analysis

Statistical analysis was performed by repeated measures analysis of variance (ANOVA) using the StatView software of S.A.S. Institute Inc. Differences between the three subgroups (SGA <3rd percentile, SGA 3–10th percentile, AGA control) for each parameter, and for every time period, were evaluated by using the one-way ANOVA test followed by Fisher's PLSD test. Differences were considered significant at a P level <0.05.

Results

Of 378 SGA neonates eligible for the study, the parents of 293 (78%) agreed for them to participate in the study. As the measurements of 89 infants were excluded from the analysis because of inconsistent follow-up (less than three US examinations), the measurements of 466 infants (SGA: 243, AGA: 223) were included in the final analysis. The non-participants did not differ significantly from the

Table 1. Number of kidney length (KL) measurements in the three study groups of infants of different gestational age (GA) and number of infants treated with aminoglycosides (AG) or vancomycin (VM)

Groups	Subgroups	Mean GA	KL measurements	AG Rx (number/days of Rx)	VM Rx (number/days of Rx)
GA >36 weeks	SGA < 3 $n = 36$	37.4 ± 1.2	167	14/3.1	2/5
$N = 171$	SGA 3–10 $n = 45$	37.5 ± 0.8	189	17/3.5	3/5.3
	AGA $n = 90$	37.7 ± 1.4	424	29/3.1	2/6
GA 34–36 weeks	SGA < 3 $n = 35$	34.8 ± 0.5	145	14/3.7	3/6.3
$N = 141$	SGA 3–10 $n = 45$	34.9 ± 0.6	189	15/3.5	3/6.3
	AGA $n = 61$	34.7 ± 0.7	226	22/3.6	4/6
GA 28–34 weeks	SGA < 3 $n = 50$	31.3 ± 2.1	168	28/4.1	5/5.7
$N = 154$	SGA 3–10 $n = 50$	31.5 ± 1.6	190	29/4.2	4/5
	AGA $n = 54$	31.2 ± 2.1	200	26/3.9	4/6.1

SGA = small-for-gestational age, AGA = appropriate-for-gestational age.

Table 2. Birth weight (BW) and crown to heel length (CHL) *z*-scores in the two groups of the SGA infants of the study (birth weight < 3rd and 3rd–10th percentile). Values of reference (*z*-score = 0) are from the control infants of the study

SGA groups	>36 weeks		34–36 weeks		28–34 weeks	
Birth	BW *z*-score	CHL *z*-score	BW *z*-score	CHL *z*-score	BW *z*-score	CHL *z*-score
<3rd	a −2 ± 0.6***	a −1.5 ± 1.1***	a −3.3 ± 1.8***	a −1.8 ± 0.9***	a −1.7 ± 0.7***	a −1.1 ± 0.9***
3–10th	−1.4 ± 0.3***	−0.8 ± 0.6***	−1.4 ± 1***	−0.6 ± 1***	−0.7 ± 0.6***	−0.3 ± 0.7*
36 weeks						
<3rd	–	–	a −1.7 ± 0.8***	a −1.4 ± 0.7***	a −1.3 ± 0.6***	a −1.3 ± 0.9***
3–10th	–	–	−0.7 ± 1**	−0.5 ± 1**	−0.5 ± 0.7***	−0.5 ± 0.9**
40 weeks						
<3rd	−1.5 ± 1***	−1.3 ± 0.8***	a −1.7 ± 1.3***	b −1.3 ± 0.8***	a −1.5 ± 0.9***	b −1.4 ± 0.9***
3–10th	−1.2 ± 0.7***	−0.9 ± 0.6***	−0.8 ± 0.8***	−0.7 ± 0.7***	−0.5 ± 0.9**	−0.5 ± 0.9**
3 months						
<3rd	−1.1 ± 1.1***	−1 ± 1.2**	a −1.6 ± 0.8***	a −1.4 ± 1.9***	a −1.1 ± 0.9***	a −1.5 ± 1.3***
3–10th	−0.8 ± 0.6**	−0.9 ± 1.2**	−0.6 ± 1.1**	−0.5 ± 1**	−0.3 ± 0.8*	−0.4 ± 1*
6 months						
<3rd	−0.7 ± 1.2*	−0.7 ± 0.9*	a −1.2 ± 1.3***	a −1.4 ± 0.9***	b −0.9 ± 0.9**	b −1 ± 0.9***
3–10th	−0.7 ± 1.3*	−0.6 ± 1.0*	−0.4 ± 0.7*	−0.6 ± 0.8 **	−0.4 ± 1*	− 0.3 ± 0.8*
12 months						
<3rd	−1.1 ± 1.5*	−1.1 ± 1.3*	−1.5 ± 1.1***	b −1.3 ± 1.3***	b −0.7 ± 1.4**	b −0.7 ± 0.9**
3–10th	−1 ± 1.1*	−0.9 ± 1	−1 ± 1.8**	−0.5 ± 1.4 *	−0.3 ± 0.95	−0.2 ± 1.1
24 months						
<3rd	−0.6 ± 0.4*	−1.1 ± 0.7 **	−0.9 ± 0.9**	b −0.8 ± 0.8*	b –0.6 ± 0.7**	b −1.2 ± 1**
3–10th	−0.3 ± 0.5	−0.4 ± 0.7	−0.7 ± 0.8*	−0.1 ± 0.6	−0.2 ± 0.5	−0.5 ± 1.1*

***$P < 0.001$, **$P < 0.01$, *$P < 0.05$, denotes the significant difference in BW and KL *z*-scores between each SGA group (<3rd or 3rd–10th percentile) and the respective controls (*z*-score = 0).
$a = P < 0.01$ and $b = P < 0.05$, denotes the significant difference in BW and KL *z*-scores between the two SGA groups (<3rd versus 3rd–10th percentile).

participant group with respect to the anthropometric indices, GA, gender and socioeconomic status. The AGA controls were matched for GA, gender and socioeconomic status with the SGA participants.

The mean GA and the number of KL measurements in each GA subgroup are depicted in Table 1. There were no significant differences in GA and gender between the two SGA groups and the AGA group at any study period. The study children had a mean of 4.1 measurements of KL, 13% had 6 KL measurements, and 19.7%, 30% and 37.5% had 5, 4 and 3 measurements, respectively. Babies who missed appointments for US renal scans did not differ from the rest of the group with respect to anthropometric indices, GA, gender and socioeconomic status at each study period. The reason for missing scans was inability of the parents to meet the appointment because of illness or other commitments. No differences were observed between the length of the right kidney and the left kidney, a finding observed previously [19,20]; therefore, the mean value of the two kidneys (KL) was used in the analysis.

No differences were observed in the frequency and duration of treatment and serum levels of administered aminoglycosides or vancomycin (Table 1). No study infant received furosemide or corticosteroids systematically.

Catch-up growth in BW and CHL

SGA with birth weight less than third percentile

In the two groups of preterm SGA infants (GA 28–34, 34–36 weeks), the subgroup with birth weight <3rd percentile had CHL and BW *z*-scores lower than either the SGA infants with birth weight between the 3rd and 10th percentiles or AGA infants, up to the 24th month of life ($P < 0.05$, 0.01, respectively; Table 2). In the group of near-term and term

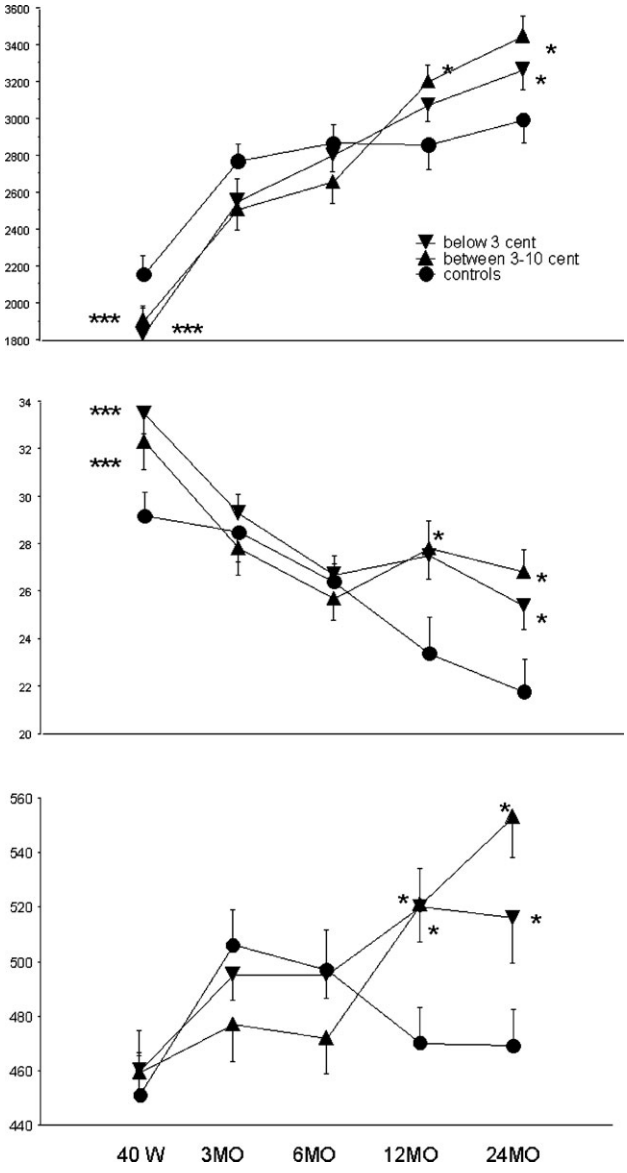

Fig. 1. Ratios between cubed kidney length (KL^3) and crown to heel length (CHL), body weight (BW), body surface area (BSA) (top to the bottom) in the three subgroups of studied infants (SGA <3rd percentile, SGA 3rd–10th percentile, AGA controls) with gestational age (GA) >36 weeks. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. SGA = small-for-gestational age, AGA = appropriate-for-gestational age.

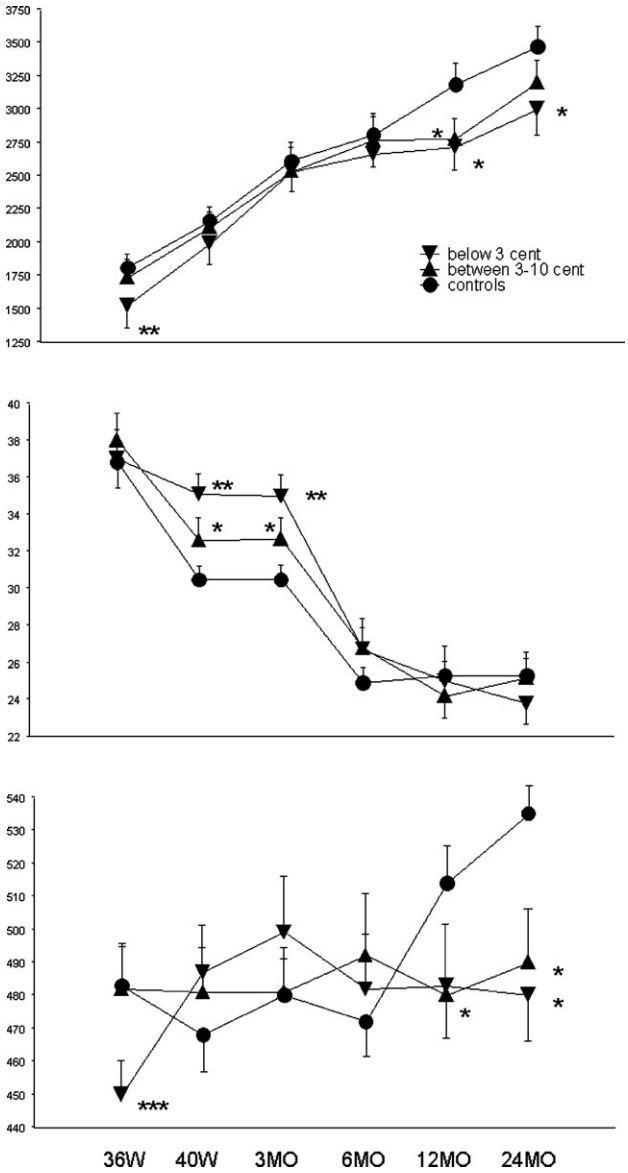

Fig. 2. Ratios between cubed kidney length (KL^3) and crown to heel length (CHL), body weight (BW), body surface area (BSA) (top to the bottom) in the three subgroups of studied infants (SGA <3rd percentile, SGA 3rd–10th percentile, AGA controls) with gestational age (GA) 34–36 weeks. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. SGA = small-for-gestational age, AGA = appropriate-for-gestational age.

infants (GA >36 weeks), there was no significant difference in BW and CHL between the two SGA subgroups.

SGA with birth weight 3rd–10th percentile

In the SGA infants with birth weight between the 3rd and 10th percentiles the CHL and BW *z*-scores were lower than those of the respective AGA controls at the following time periods: in the group with GA >36 weeks, up to the 12th month of life ($P < 0.05$); in the group with GA 34–36 weeks, up to 12 and 24 months, respectively ($P < 0.05$); in the group with GA 28–34 weeks, up to the 24th and 6th months, respectively ($P < 0.05$) (Table 2).

Relative kidney growth

In Figures 1–3, we depict the ratios of KL^3 with CHL, BW and estimated BSA in the three study groups.

Children with GA >36 weeks (Figure 1)

The KL^3/CHL ratio, although lower in both SGA groups at 40 weeks, became higher than that of the AGA group at 24 months. Conversely the KL^3/BW ratio was higher in both SGA groups at 40 weeks and remained higher than that of the AGA group after 12 months. The KL^3/BSA ratio was also higher in both SGA groups after the 12th month of life.

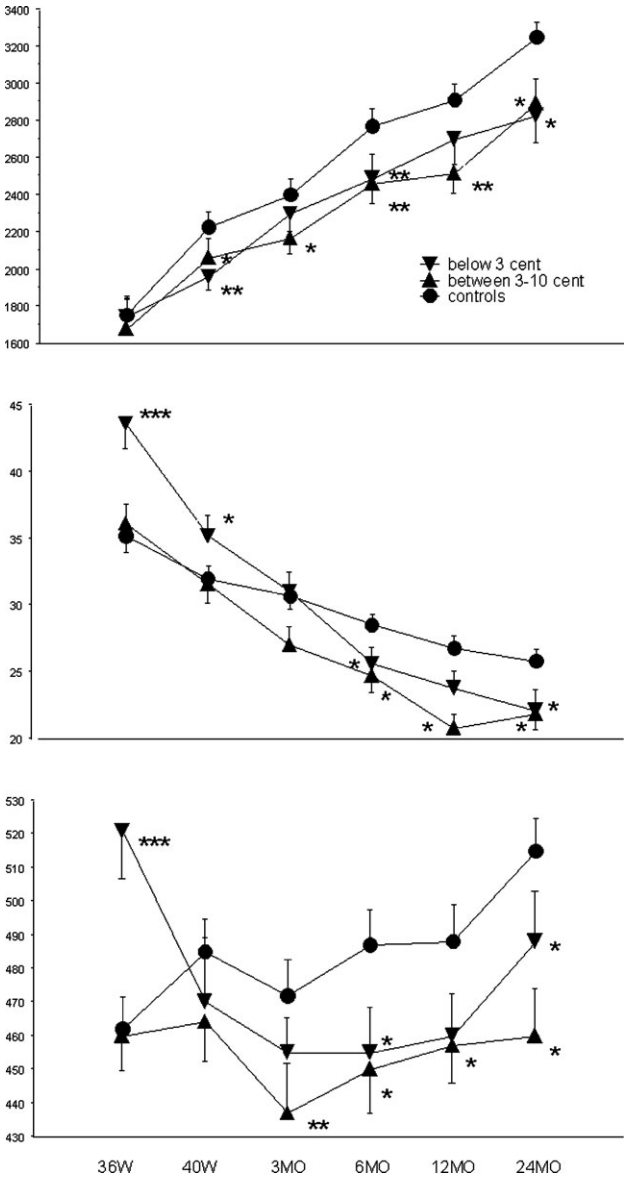

Fig. 3. Ratios between cubed kidney length (KL^3) and crown to heel length (CHL), body weight (BW), body surface area (BSA) (top to the bottom) in the three subgroups of studied infants (SGA <3rd percentile, SGA 3rd–10th percentile, AGA controls) with gestational age (GA) 28–34 weeks. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. SGA = small-for-gestational age, AGA= appropriate-for-gestational age.

No differences in any KL ratio were found between SGA infants with birth weight <3rd percentile and those with birth weight between the 3rd and 10th percentiles.

Children with GA 34–36 weeks (Figure 2)

KL^3/CHL and KL^3/BSA were similar in the SGA and AGA groups between 40 weeks and 6 months and lower in both SGA groups than in the AGA group after the 6th month. KL^3/BW was higher in the SGA groups at the 40-week and 3-month periods and similar thereafter. No difference in any parameter was found between SGA infants with birth weight <3rd percentile and those with birth weight between the 3rd and 10th percentiles, except for KL^3/CHL and KL^3/BSA at 36 weeks which were lower in the <3rd percentile group, $P < 0.05$).

Children with GA 28–34 weeks (Figure 3)

KL^3/CHL was lower in both SGA groups after the 40-week period compared with the AGA group. KL^3/BW was lower in both SGA groups after the 6th month and up to the 24th month of life. KL/BSA was lower in both SGA groups after the third month of life. No difference was found in any parameter between SGA infants with GA <3rd percentile and those with BW between the 3rd and 10th percentiles, with the exception of KL^3/BW and KL^3/BSA at the 40-week measurement, which was higher in the SGAs with BW <3rd percentile, $P < 0.01$).

Discussion

The results of this study suggest that postnatal kidney growth in SGA infants is mainly dependent on GA. In the full-term and near-term SGA infants (GA >36 weeks), RKL was similar to or even higher than that of AGA controls ($P < 0.05$ at 12 and 24 months) while in the two groups of preterm infants RKL was lower than that of AGA controls. In the GA 34–36 weeks group, RKL was lower than that of controls after the first 6 months (relative to KL and BSA) while in the GA 28–34 weeks group RKL was lower than that of controls throughout the study period for all three parameters. This implies that in preterm SGA infants, the kidneys remain shorter up to the second year of life not only because babies remain shorter and lighter but also possibly as an effect of *in utero* restriction.

The timing of nephron formation may play a role in the interpretation of the observed differences among the three GA groups. It is known that nephrogenesis continues up until 34–36 weeks of intrauterine life [16]; therefore, infants born after 36 weeks of GA should have completed their nephron formation in contrast with the less-matured preterm infants. Recent data on preterm infants (of mean GA 31 weeks) showed that nephron formation might be compromised postnatally, while nephrogenesis in some neonates is reported to stop after the 10th day of life [25]. In this study, the SGA infants with GA 28–34 weeks may have two reasons for their reduced KL, namely, fewer nephrons at birth because of their GR and impaired nephrogenesis after birth due to their prematurity. The infants of GA 34–36 weeks showed only transient catch-up kidney growth up to the sixth month of life, which could be due to a lower nephron endowment compared with the infants of GA >36 weeks, in whom nephrogenesis may have been completed before birth.

Recent experimental studies showed that kidneys of full-term SGA newborn lambs have not only lower nephron numbers but also a more immature structure compared with kidneys of AGA newborns lambs of similar GA [7]. The glomeruli appeared to be less mature, the tubules were not as well defined and fewer glomeruli had a visible Bowman's

space. These findings support the concept of nephropathy caused by GR [7]. Such structural deficits in the kidneys of human babies born with GR could be an additional adverse factor for postnatal kidney growth in premature neonates [25,26]. Alterations in intra-renal hormones due to growth restriction may also play a role [27,28].

SGA infants, such as those studied, can overcome their nephron deficit by accelerating the functional and structural maturation of the existing nephrons [29]. Compensatory hypertrophy could also contribute to this adaptation process and, as a consequence, a prolonged hyperfiltration period may begin soon after birth.

BW and CHL *z*-scores of SGA infants remained lower than those of the AGA control infants, an observation which is in agreement with the findings of previous studies [30]. The groups of preterm infants with GA <36 weeks with more severe GR (BW less than third percentile) also had the lowest catch-up growth. The severity of GR did not appear to affect the RKL, and the GA subgroups had similar RKL throughout the study period. In absolute terms, kidney growth was more severely affected in the preterm babies with BW less than third percentile as were the BW and CHL in this group.

Previous studies have examined kidney development in SGA neonates with asymmetrical and symmetrical GR [14,15]. In a study of preterm SGA infants (GA 31–36 weeks), limited to the first year of life, it was shown that kidney growth followed the other auxological parameters closely [14], and that SGA infants with a symmetrical type of GR had poorer catch-up kidney growth than those with an asymmetrical type of GR during the first year of life. When full-term and near-term infants were studied it was shown that kidney growth was independent of the type of growth restriction (symmetrical or asymmetrical) [15]. Schmidt *et al*. [13] observed in a group of 80 SGA full-term infants with birth weight <10th percentile (27 <3rd percentile) slight but statistically significant catch-up kidney growth from birth to 18 months, which they interpreted as limited catch-up kidney growth [13]. In the present study, rapid catch-up growth in RKL was observed in full-term infants but not in preterm SGA infants of GA <36 weeks. Differences in the distribution of the BW and in the severity of GR between the two studied populations of SGA infants may account for the slightly different findings between the two studies.

Low birth weight has been associated with reduced kidney size in infants and adults [6,31,32]. In these studies, AGA preterm infants and SGA infants are examined together, so the effect of each parameter individually (prematurity and GR) on the findings is not obvious. Prematurity *per se* may have an adverse effect on renal growth from the immediate postnatal period [33], while recent studies which examined low birth weight and renal function in adulthood have shown that the results are different when the effects of prematurity and GR are examined separately [34]. The SGA infants in the present study were classified according to GA, taking into account the timing of nephrogenesis, and the degree of GR, and compared with AGA infants of matched GA, so that the impact of SGA status on kidney growth at any given GA was separated from the impact of low birth weight due to prematurity.

Conclusions

This study suggests that kidney growth in SGA infants is affected by the GA. While near-term (>36 weeks of GA) and full-term SGA infants have RKL similar to or even higher than that of AGA control infants; this is not the case for the smaller preterm babies (<36 weeks of GA), in which RKL is lower up to the second year of life and for which long-term follow-up is needed. The severity of GR appears to affect kidney growth to a similar degree as it affects the other growth parameters.

Conflict of interest statement. None declared.

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