Kidney growth in twin children born small for gestational age

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Abstract

Background. Low birth weight (LBW) is associated with adult-onset diseases, including hypertension and renal disease; altered renal development after intrauterine growth restriction (IUGR) may underlie related prenatal programming. No data are available on longitudinal renal growth in twin infants born small for gestational age (SGA). The aim of this prospective longitudinal study was to estimate the renal size during the first 2 years of life in SGA twin infants.

Methods. The study included 613 children, of which 145 were SGA twins, 141 twins appropriate for gestational age (AGA), 148 matched AGA singletons and 179 matched SGA singletons, classified according to GA into two groups (28–36 and >36 weeks). The SGA children were also classified according to the degree of IUGR: birth weight (BW) <3rd percentile and BW 3rd–10th percentiles. Serial renal ultrasonography (US) for kidney length (KL) measurement was performed at the ages of 36 and 40 weeks corrected age (CA) and 3, 6, 12 and 24 months of age, and KL was related to other anthropometric indices. Twin data were examined both as individuals and as members of twin pairs.

Results. A total of 2317 measurements were performed. KL was lower at 40 weeks CA in all the SGA twin subgroups. In the SGA twins with GA >36 weeks, KL increased thereafter and became similar to AGA twins and single AGA control subjects. Among pre-term infants of GA <36 weeks, only those with BW 3rd–10th percentile experienced catch-up in KL, while in those with BW <3rd percentile, KL remained lower than in AGA infants throughout the study period, both in absolute terms and relative to other anthropometric indices. No differences in KL were found between twin SGA and singleton SGA or between twin AGA and singleton AGA infants. Intrapair BW differences were correlated with the intrapair differences in KL.

Conclusions. Twin SGA infants born prematurely with BW <3rd percentile are unable to achieve catch-up in KL in the first 24 months of life, and long-term follow-up is recommended.

Keywords: compensatory kidney growth; kidney size; neonate; small for gestational age; twins

Introduction

Studies show that fetal growth restriction (GR) is associated with reduced nephron numbers and greater glomerular volume in human neonates [1,2], and experimental studies in animal models have also demonstrated this association [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 [5]. Glomerular hypertrophy is regarded as an initial step in this process. Histomorphometric studies in adults have confirmed the relationship between reduced nephron numbers and primary hypertension [6].

Renal size, as estimated by ultrasonography (US), may be used as a surrogate measure for nephron numbers and an indirect index of renal growth under a variety of clinical conditions [7–9]. Two recent studies examined renal size by US in pre-term and full-term children born small for gestational age (SGA) [10,11]. Both studies demonstrated that SGA infants had smaller kidneys at birth than appropriate for gestational age (AGA) controls [10,11]. The degree of compensatory kidney growth was related to the gestational age (GA) and to the degree of in utero growth restriction [11].

To our knowledge, no studies have been reported on kidney growth in twin children born either SGA or AGA. Twin pregnancies have increased by >60–80% in recent years because of the increased rate of in vitro fertilization, and twins now comprise ~3–4% of all newborn infants [12,13]. Twins are thought to represent a special category of stunted fetal growth, which usually affects one of the twins only, and may be produced by mechanisms different from those causing in utero growth restriction in singletons. This appears to be an adaptation to prolong the pregnancy by reducing total fetal mass [12]. About 50% of twins are below the 10th percentile in birth
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weight when singleton charts are used [12]. Taking into consideration the increased numbers of twin pregnancies, SGA twins comprise a large SGA group. It is not known if this in utero restriction pattern affects kidney size postnatally. One experimental study in sheep showed that twin animals had 40% lower nephron number than singleton controls and were at risk for subsequent development of hypertension [3].

The present study was designed to examine kidney size in the first 2 years of life in twin SGA children, in comparison with that of twin and singleton AGA children and singleton SGA children.

Materials and methods

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 twin neonates born at 28–40 weeks of GA during a 4-year period (January 2004–January 2008) were eligible for the study. Infants with documented hydronephrosis or urinary tract infection were excluded. The twin infants were classified as SGA [birth weight (BW) <10th percentile for GA] or AGA (BW 10th–90th percentile for GA) using the relevant age–gender-specific percentiles in the growth curves specific for Greek children. The SGA twin neonates of the study were further classified into two groups according to the degree of intrauterine growth restriction (IUGR). The first group included those with BW <3rd percentile and the second group those with BW between the 3rd and 10th percentiles.

The twin children were considered both as individuals and as pairs. The SGA and AGA twin groups were compared as individuals with a control group of singleton AGAs, while the SGA twin group was also compared with a control group of SGA singletons. The control groups were born in the same hospital during the same time period and were matched for GA, gender and occupational status with the SGA twins. The SGA and AGA groups were divided into subgroups according to GA, based on the timing of renal nephron formation: those of GA >36 weeks, at which time nephrogenesis is regarded complete, and those of GA 28–36 weeks, when nephrogenesis is still incomplete [14]. GA at birth was measured according to an early US scan and confirmed by assessment by neonatologists of each infant's maturity within 24 h of delivery. To determine the zygosity of the twin children of the same gender, the mothers of twins completed a zygosity questionnaire for mothers of young twins [15,16]. The early US scan findings on chorionicity were used [11].

The study protocol was approved by the Hospital Ethics Committee, and informed parental consent was obtained for participation of the infants in the study. The files of all the study babies were examined, and information was extracted about administered drugs potentially affecting kidney, such as aminoglycosides, vancomycin, furosemide and corticosteroids. For babies who received aminoglycosides, information on the drug levels was recorded.

For infants of GA >36 weeks, US kidney measurement was performed at the corrected age (CA) of 40 weeks [CA (in weeks) = GA (in weeks) plus age after birth (in weeks)], and at the chronological ages of 3, 6, 12 and 24 months (five measurements in total). Pre-term infants of GA 28–36 weeks had an additional measurement at the CA age of 36 weeks (six measurements in total). The US examinations were performed blindly and independently by two of the authors (M.A. and F.P.), who are senior paediatric radiologists. Measurements in total). 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 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 [17–20]. The inter-observer variability and the limits of agreement were estimated in a sample of 35 KL measurements in infants based on the method of Bland and Altman [21] by the same radiologists in a previous study of similar design [11].

The 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 ± (1.96 × SDD)] expressed as a percentage (% of KL varied from −0.64% to +5.1%.

BoW and crown-to-heel length (CHL) were measured using methods already described [11]. BW Z-scores were estimated in all study groups, based on local GA- and gender-specific growth charts. Gender- and age-specific Z-scores were derived for KL, CHL, BoW and body surface area (BSA). The values of the singleton AGA children were used as the reference group to derive Z-scores for the other groups. Side-specific KL Z-scores were also derived. BSA was calculated using Boyd’s equation [BSA (square metre) = 0.0003207 × height (centimetre) 0.3 × weight (gram)] [22]. Venous blood samples were taken for measurement of serum creatinine (SeCr) at the 12th month of examination, and the estimated GFR (eGFR) was calculated using the Schwartz formula: GFR (millilitre per minute per 1.73 m²) = 0.45 (height) / SeCr.

Statistical analysis

Overall statistical analysis was performed by analysis of variance using the StatView software of SAS Institute, Inc. Differences between the two SGA twin subgroups (BW <3rd and 3rd–10th percentile), the two SGA singleton subgroups (BW <3rd and 3–10th percentile) and the two AGA groups (twins and singletons) for each parameter and each time period were evaluated using the one-way ANOVA test followed by the Fisher’s PLSD test. Simple and multiple regression analyses were performed to relate BW Z-scores, BoW and KL at the various study periods. Differences were considered significant at $P < 0.05$. The number of infants included in the study was selected to allow a minimum of 40–50 measurements for each comparison in any study period, after taking into account the drop-off trends from a previous study of similar design [11,23]. 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 0.05. In sample size calculation, data of the mean values (MV ± 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 ± (1.96 × SDD)] expressed as a percentage (% of KL varied from −0.64% to +5.1%.

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Results

Of the babies born during the 4-year period, 350 twin neonates were eligible for the study, while 10 twins were excluded because they diagnosed with urinary tract infection or hydronephrosis. The parents of 316 (90%) agreed for their infants to participate in the study. Among 316 participants enrolled initially, 286 twins (90.5%) finished the study, specifically both babies of 135 pairs of twins and only one of the two babies of 16 pairs of twins. The non-participant baby of these 16 twin pairs either did not survive (n = 6), or missed scans (n = 7) or did not meet the last appointments due to the parents' decision to discontinue follow-up (n = 3). A further seven pairs of twins discontinued follow-up. The non-participants did not differ significantly from the participant twins with respect to anthropometric indices, GA, gender and socioeconomic status. In the final SGA twin study group, there were 145 neonates, 63 <3rd percentile and 82 3rd–10th percentile, and in the AGA twin group 141 neonates. Among the 135 pairs of twins, 123 (91%) pairs were dizygotic, and 12 pairs were monozygotic. The AGA twins did not differ from the SGA twins with respect to the GA, gender and socioeconomic status. Control groups of singleton AGA and SGA neonates, matched for GA, gender and socioeconomic status with the SGA twin participants, numbered 148 and 179, respectively. No significant differences were
registered in GA and gender between the two SGA twin subgroups, the two SGA singleton groups and the AGA groups at any study period. A total of 2317 measurements were performed in the study children, with a mean number of 3.8 measurements of KL on each child. No differences were observed between the length of the right kidney and the left kidney, a finding observed previously in some [17,18] but not all studies [24]. Despite the absence of differences between the right and left kidney measurements, renal side was taken into consideration in the analysis. No differences were observed in the frequency and duration of treatment and serum levels of administered aminoglycosides or vancomycin. No study infant received furosemide or corticosteroids systematically. Risk factors for fetal growth restriction other than twin pregnancy were identified in 22 (15%) of the SGA twin infants of the study (14 of the <3rd percentile and 8 of the 3rd–10th percentile SGA infants). These were pregnancy-induced hypertension in 8, placental insufficiency in 4, previous SGA born child in 2, chronic maternal disease in 2, low weight gain during pregnancy in 4 and cigarette smoking in 2.

Comparisons with AGA singletons

Figures 1 and 2 depict the KL Z-scores, and Table 1 shows the values of the CHL and BoW Z-scores, throughout the study period, in twin SGA, twin AGA and singleton AGA infants. As renal side evaluation showed no differences between right and left kidneys, the mean Z-scores of both kidneys are presented.

i. Twins of <36 weeks GA: In the SGA twins with BW 3rd–10th percentile, KL was lower at 36 weeks but did not differ from that of the AGA infants thereafter (Figure 1). Conversely, in the SGA twins with BW <3rd percentile, KL remained lower up to the second year of life, compared with both the AGA twins and the AGA singletons (Figure 1).

The SGA twins with BW 3rd–10th percentiles showed catch-up in CHL and BoW, and did not differ from the two AGA groups after the measurement at 6 months (Table 1). The SGA twins with BW <3rd percentile remained shorter and lighter up until the end of the study.

ii. Twins of >36 weeks GA: After the third month and up to 2 years, KL did not differ among the two subgroups of SGA twins and AGA groups (Figure 2). Conversely, BoW was lower in both subgroups of SGA twins up to 2 years of life, compared with both AGA twins and AGA singletons (Figure 2).

Comparisons with SGA singletons

Table 1A and B (addendum) depicts the comparisons of KL and anthropometric indices between SGA twins and SGA singletons with GA <36 (Table 1A) and >36 weeks (Table 1B), respectively. No consistent differences were found in anthropometric indices and KL between twin and singleton SGA children throughout the study period, even on comparing the specific for gender and renal side Z-scores.

Relative kidney length

Figures 3 and 4 depict the Z-score values of the relative KL (the ratio KL to CHL and KL to BSA) in the two subgroups of SGA twins and in the AGA twins.

i. Twins of <36 weeks GA: In the SGA twins with BW <3rd percentile, the KL/CHL Z-score was lower at 6, 12 and 24 months than in AGA twins and singletons (Figure 3). Conversely, the KL/BSA Z-score was higher than in AGA singletons up to 3 months of life but became lower at 12 months reflecting an increase with lower velocity in KL, comparing to the other auxological parameters after this time point. In the SGA twins with BW 3rd–10th percentiles and in the AGA twins, the relative KL parameters did not differ from those of the AGA groups (Figure 3).
ii. Twins of >36 weeks GA: In the SGA twins with BW <3rd percentile, the KL/CHL Z-scores did not differ from that of AGA twins and singletons (Figure 4). In the SGA twins with BW 3rd–10th percentiles, the KL/CHL Z-score was lower at 6 months and higher at 24 months (Figure 4). In both SGA subgroups, the KL/BSA was similar to or higher than that of the control subjects (Figure 4). In the AGA twins, KL/CHL Z-score was lower than that of AGA singletons at 3 and 6 months, while KL/BSA Z-scores did not differ at any study period (Figure 4).

The KL/BoW Z-scores showed the same patterns as KL/BSA in both GA groups (data not shown).

Regression analysis

A regression analysis was made correlating the specific for gestational age and gender Z-scores for BW with KL Z-scores (right and left kidneys) at the various study periods in the total cohort of children (Table 2). A positive relationship was found mainly in the children with GA <36 weeks, which disappeared when current BoW was added to the regression model. As kidney side did not modify the results, the mean values of KL are presented in Table 2.

The results were the same after exclusion from the analysis of the 22 children with an additional risk factor, other than twin pregnancy, for SGA, and also when, the 12 pairs of monozygotic twins were excluded from the overall analysis.

Intrapair comparisons

Among the 135 twin pairs, 107 had a difference in BW of at least 10%. In this subgroup, a simple regression analysis was made, comparing the difference in BW (δBW) with the difference in KL (δKL) in each kidney at each time point in the study. A positive relationship was found at most time points (Table 3). After adjusting for the difference in current BoW (δBoW), it was shown that δBW continued to be positively related with δKL at the following time points: at 6 and 12 months in the <36 weeks group (t = 1.9 and 2.2; beta = 0.21 and 0.23, respectively, P < 0.05), at 3 and 6 months in the >36 weeks group (t = 2.4 and 2.2; beta = 0.23 and 0.19; P < 0.01 and P < 0.05, respectively) and at 6, 12 and 24 months in the pooled group (t = 2.1, 2.2 and 1.9; beta = 0.22, 0.22 and 0.20, respectively, P < 0.05). The analysis of δKL of right or left kidney yielded similar results, and the mean δKL is presented. The results were the same after excluding monozygotic twins (12 pairs) from the analysis.

Estimated GFR

SeCr was measured at the 12th month of examination in all twin children and all single SGA children, and in
45/50 and 35/40 singleton AGA children, in the <36 weeks and >36 weeks groups, respectively, and eGFR was derived. The mean values of eGFR (mL/min/1.73 m²) were 77 ± 12, 80 ± 13, 79 ± 11, 81 ± 13 and 81 ± 13 in those with GA <36 weeks, and 80 ± 14, 80 ± 14, 78 ± 12, 76 ± 10, 77 ± 10 and 81 ± 15 in those with GA >36 weeks for the groups twin SGA <3, twin SGA 3–10, single SGA <3, single SGA 3–10, twin AGA and single AGA, respectively. There were no statistically significant differences among the study groups. The eGFR was not related with BW Z-scores in any of the SGA and AGA groups examined either as individuals or with δW in the intrapair comparisons.

**Discussion**

The results of this study showed that SGA twins with GA >36 weeks exhibited rapid increase in KL, which at the end of second year of life was no different from that of AGA twins and singletons, although their BoW and CHL remained lower. In SGA twins with GA <36 weeks, catch-up in KL was observed only in those with milder growth restriction at birth (BW 3rd–10th percentiles). Conversely, in those with BW <3rd percentile, KL remained lower throughout the study period, both in absolute terms and relative to CHL. It was also found that, in SGA twins, KL did not differ from that in SGA singletons, despite the fact that the mechanism of growth restriction may differ between the two groups.
To our knowledge, there have been no reports of previous human studies on kidney growth in twin SGA or AGA infants with which to compare these findings. An animal study investigated nephron endowment and renal filtration surface area in fetal sheep in which IUGR resulted from either late gestational umbilico-placental embolization or natural twinning [3]. Growth restriction due to twinning lead to reduced nephron endowment, whereas late gestational growth restriction did not. Nephron endowment was 40% lower in twin fetuses compared with controls [3]. Two recent studies in singleton SGA infants showed in full-term infants the presence either of moderate or rapid catch-up kidney growth, while in pre-term infants the absence of catch-up kidney growth [11]. These findings are in agreement with the findings of the present study in SGA twins. Small kidney size may imply lower nephron numbers, while early catch-up in kidney growth may imply early compensatory hypertrophy. Both conditions can cause later kidney dysfunction. Gielen et al. studied Cr clearance in 25-year-old twin adults [25]. When the twins were examined as individuals, those with BW <2500 g had 4 mL/min lower Cr clearance, unadjusted to BSA, than those with BW >2500 g. Intrapair BW difference correlated positively with the intrapair difference in Cr clearance to an equal degree in monozygotic and dizygotic twins, suggesting that fetoplacental than genetic factors were possibly related to renal function in this group. In a large epidemiological study in twins, it was found that the risk of hypertension increased with reduced BW both in the total cohort of twins and after pairwise analysis [26]. No differences were found between groups in eGFR in the present study at 12 months of life. More sensitive renal function indices (i.e. microalbumin) and long-term follow-up could possibly delineate subtle differences in renal function among the several groups.

The aetiology of the observed differences in KL catch-up between the SGA subgroups and the AGA infants can only be speculated upon. The GA of 36 weeks is the time point by which the number of nephrons in the human is completed. Infants born earlier than 36 weeks may be unable to continue nephrogenesis after birth because, as was shown recently, nephrogenesis in pre-term infants is impaired after birth, and only few new nephrons are formed [27]. All the SGA twins in this study may have a lower nephron endowment due to in utero GR, but those with GA <36 weeks may have even lower nephron numbers because of incomplete nephrogenesis after birth. The above speculations could explain the differences observed in KL between full-term and pre-term children. Among the four SGA twin subgroups, only in the subgroup combining severe growth restriction (BW <3rd percentile) and prematurity (GA <36 weeks) did the kidneys remain smaller at 2 years, possibly because their development was affected both prenatally and postnataally. Conversely, the other three twin SGA subgroups had milder in utero growth restriction (BW 3rd–10th percentiles) or/and greater GA (>36 weeks), and their kidneys exhibited catch-up. This catch-up in KL may imply either accelerated maturation or compensatory kidney growth [28]. The latter if accompanied by hyperfiltration may be disadvantageous in the long-term.

The in utero growth pattern in twins is different from that of singletons [12,13]. It is believed that the uterine environment limits the growth potential of the individual fetus in a multiple pregnancy, although the mechanisms involved are not known. In the vast majority of twin pregnancies, a deceleration of fetal growth takes place, especially at between 28 and 32 weeks GA [12]. This deceleration usually affects one of the two twins to a greater degree [12,13]. After this period and up until birth, their growth continues without any further restriction. This type of growth restriction, which arises from the need for the gestation to be continued by limiting total fetal size, has been regarded as ‘more physiological’, in contrast to other causes of GR [12], but nevertheless, it appears to affect KL during infancy. As between 28 and 32 weeks of gestation the nephron formation process is very active, it could be speculated that it may be affected in twin pregnancy, especially in severely growth restricted twins (i.e., BW <3rd percentile) as was observed in the present study. The rapid catch-up in KL observed in the other three twin SGA groups may be the cause of the absence of a relationship between BW Z-scores (adjusted for GA, sex, renal side and current BW) and KL at any of the study period.

In this study, not only AGA twins but also matched AGA singleton infants were examined as control groups. As a result, it was possible to compare KL not only between SGA twins and AGA twins, but also between AGA twins and AGA singletons, which was a useful distinction, as AGA twins could have had KL growth patterns different from those of AGA singletons, as twins and single individuals may differ in many aspects. This study documented a similar kidney growth pattern in twin and singleton AGA infants, at least up to the end of the second year of life. SGA twins were also compared with SGA singletons to examine whether KL was different in the two groups with different aetiologies of growth restriction (twinning vs. IUGR caused by several different factors). One could speculate that, despite the different aetiology of growth restriction in the two groups, its effect on KL was similar up to the second year of life.

In studying twins as pairs, a positive relationship was observed between BW difference and KL difference in the twin pairs with discordant BW. This relationship suggests that KL in twin pairs with discordant BW may be affected by BW at least up to the second year of life. As the vast majority of studied pairs were dizygotic, it could be speculated that the genetic differences between siblings could account for both intrauterine growth rates and postnatal KL. However, the number of monozygotic pairs in this study was too small to allow a comparative study.

Conclusion

It is concluded that KL remains small in the pre-term, severely growth restricted SGA twins. In the less severely growth restricted pre-term twins and in the full-term SGA twins, the KL patterns show compensatory growth.

Conflict of interest statement. None declared.
Aortic abnormalities in males with Alport syndrome

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