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Impaired kidney growth in low-birth-weight children: Distinct effects of maturity and weight for gestational age

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Impaired kidney growth in low-birth-weight children: Distinct effects of maturity and weight for gestational age.

Background. Low birth weight is an important risk factor for hypertension and unfavorable prognoses of a number of renal diseases. It is also associated with reduced kidney size and nephron number. A differentiation between the effects of low birth weight versus being born premature or small for gestational age has, however, not been addressed.

Methods. The influence of weight for gestational age (percentage deviation from expected mean), gestational age, birth weight, and early diet on kidney growth was studied in 178 children born pre- or postmature and/or small or large for gestational age, comparing them to 717 mature children, birth weight appropriate for gestational age. Kidney size was determined by bilateral ultrasonography measuring length, width and depth, using the equation of an ellipsoid for volume calculation. The examinations were performed at 0, 3, and 18 months of age together with measurements of body weight, height, and skinfold thickness.

Results. Weight for gestational age had a significant, positive effect on combined kidney volume at all three ages (0 months, $P < 0.001$; 3 months, $P < 0.001$; and 18 months, $P < 0.001$). A slight catch-up growth in kidney size was seen in the most growth-retarded infants (<10th percentile) between 0 and 18 months of age (mean Δz score$_{0-18mo} = +0.22$ SD) ($P = 0.037$). Premature children had smaller kidneys compared to mature at all ages (0 months, $P = 0.001$; 3 months, $P = 0.007$; and 18 months, $P = 0.042$), without any significant catch-up with age. Relative kidney volume was inversely correlated with weight for gestational age at birth ($P = 0.007$) but positively at 18 months ($P = 0.008$). Relative kidney growth 0 to 18 months was positively correlated to weight for gestational age ($P = 0.013$). Low birth weight was associated with impaired relative kidney growth in response to formula feeding.

Conclusion. Being small for gestational age is associated with small kidneys at birth and impaired kidney growth in early childhood. The present data suggest that intrauterine growth has a regulatory influence on nephron formation and renal function in humans reaching beyond the neonatal period.

Key words: nephrogenesis, infant, kidney size, intrauterine growth retardation, birth weight, gestational age.

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Low birth weight has been identified as an important risk factor for unfavorable course or progression of a number of renal diseases [1–6]. Likewise, an inverse association between birth weight and blood pressure in childhood and adult life is well-documented [7]. Possible underlying pathophysiologic mechanisms include renal, metabolic, and vascular changes [8]. One hypothesis is that intrauterine growth retardation may cause a reduced number of congenital nephrons [9], leading to increased single nephron glomerular filtration rate (GFR), thereby augmenting the risk of glomerulosclerosis and subsequently elevated blood pressure [10]. This hypothesis has been substantiated by several animal studies [11–14] and questioned by some [15]. In humans, low birth weight has been associated with reduced nephron number or density in autopsy studies [16–19], whereas others did not find any association between birth weight and glomerular number or the progression of diabetic nephropathy [20, 21].

As age-adjusted kidney weight is strongly positively correlated to the total number of glomeruli, kidney volume can be regarded as a proxy for nephron number [22]. Low birth weight, both pathologically low (<2.5 kg) and relatively within the normal range, has been associated with reduced kidney size in infants and adults [16, 23, 24]. However, due to lack of accurate information on gestational age distinctions between an effect of low birth weight per se versus being small for gestational age or premature could not be made. In a recent autopsy study of premature infants (gestational age <28 weeks) of extremely low birth weight (≤1000 g) radial glomerular counts were markedly decreased compared to mature infants [25]. Glomerulogenesis continued until 40 days of age but did never reach the level of mature infants. Likewise, in vivo studies of kidney size in human fetuses of known gestational age have shown that intrauterine growth retardation is accompanied by decreased fetal kidney volume compared to fetuses of appropriate weight for gestational age [26–28]. How kidney growth further evolves during infancy in small for gestational age or preterm children has not been described.

Formula feeding induces increased kidney size compared to breast feeding in 3-month-old healthy infants born at term with birth weight appropriate for gestational age [29]. Many preterm or small for gestational age infants are prone to receive infant formula. Whether they respond equally by increasing kidney size has not yet been investigated.

To investigate the influence of intrauterine growth, maturity, birth weight, and early diet on kidney growth and shape, we have followed 189 children born pre- or postmature as well as small or large for gestational age for the first 18 months of life, comparing them to a normal reference material of 717 mature, healthy singletons with birth weight appropriate for gestational age [30].

METHODS

Study design

A prospective longitudinal cohort study was performed from 1997 to 2002 at Rigshospitalet and Hvidovre Hospital, University of Copenhagen. All pregnant women of Danish origin, geographically belonging to the hospital referral area, and not referred because of expected complications in pregnancy, were consecutively asked to join the study in their first trimester of pregnancy. The children were part of an ongoing cohort study establishing reference materials for kidney size and prevalence of renal malformations, genital development and malformations, and body growth [29–33].

The children were examined within the first 5 days of life (0 months) and again at 3 and 18 months of age. In case of preterm birth, examination took place around the expected date of delivery and again 3 and 18 months later. In case of postterm birth the child was examined shortly after birth and again 3 and 18 months after the expected date of delivery. At all examinations bilateral kidney ultrasonography and anthropometric measurements were performed. At each visit the child was examined by one out of a team of eight doctors. All methods of measuring were standardized at workshops.

Inclusion and exclusion criteria

Children were included if they were born pre- or postmature and/or small or large for gestational age. Children with major congenital malformations or severe chronic diseases were excluded; however, mild hydronephrosis (pelvic anteroposterior diameter 5 to 10 mm) at one examination or coexistence of cryptorchidism or hypospadias was allowed. The normal reference ranges for kidney size, shape, and growth in mature healthy children with birth weight appropriate for gestational age have previously been published [30]. Data from these children were included as reference material in the present analysis.

Gestational age and anthropometry

Gestational age (days) was determined by routine ultrasonography in pregnancy week 18 to 20. In 2.8% gestational age was determined by last menstrual period. Prematurity was defined as gestational age below 259 days (<37 weeks), and postmaturity as gestational age above 294 days (>42 weeks). Birth weight (kg) was obtained from birth records. Weight for gestational age was expressed as the percentage deviation from the expected mean weight for gestational age. For this calculation a gender-specific fourth-degree polynomial equation was used [34]. Small or large for gestational age was defined as weight for gestational age below −22% or above +22% of expected weight for gestational age approximate to −2 SD and +2 SD. Weight for gestational age was additionally stratified into six classes according to percentiles: 0 to 9.9, 10 to 24.9, 25 to 49.9, 50 to 74.9, 75 to 89.9, and 90 to100 percentiles.

Body weight was measured on a digital scale (Baby-Scale Model) (Solotop Oy, Helsinki, Finland) to the nearest 0.005 kg. Body length was measured supine with a Kiddimeter (Raven Equipment LTD, Essex, UK) to the nearest 0.1 cm. Body fatness was estimated measuring subscapular skinfold thickness to the nearest 0.1 mm using a skinfold calliper (Harpenden, British Indicators LTD, London, UK). All anthropometric measurements were registered as the mean of three measurements.

Ultrasonography

Kidney size was determined by ultrasonography using a 5 MHz sector probe with an accuracy of 0.1 mm (Aloka SSD 500) (Aloka Co., Ltd. Tokyo, Japan). The probe was placed on the back of the child, at the neonatal examination with the child lying on the contralateral side in a ventrally curved position, and at 3 and 18 months of age in a supported sitting position. The kidney was identified in the sagittal plane along its longitudinal axis. In this position three longitudinal anteroposterior measurements of the largest length and width were performed. The probe was then rotated 90 degrees and three cross-sectional anteroposterior measurements of the width and depth at the hilar level were performed. All dimensions were measured to nearest 0.1 cm in both kidneys.

Mean length and depth were calculated as the average of three measurements and mean width as the average of six. Maximum pelvic anteroposterior diameter was measured to nearest 0.1 mm and renal malformations classified. Kidney volume was calculated in cubic centimeters using the equation of an ellipsoid: volume = mean length ∗ mean width ∗ mean depth ∗ 0.523 [35]. Left and right kidney volumes were added for the combined