The Effect of Abnormal Birth History on Ambulatory Blood Pressure and Disease Progression in Children with Chronic Kidney Disease

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Objective To examine the associations between abnormal birth history (birth weight <2500 g, gestational age <36 weeks, or small for gestational age), blood pressure (BP), and renal function among 332 participants (97 with abnormal and 235 with normal birth history) in the Chronic Kidney Disease in Children Study, a cohort of children with chronic kidney disease (CKD).

Study design Casual and 24-hour ambulatory BP were obtained. Glomerular filtration rate (GFR) was determined by iohexol disappearance. Confounders (birth and maternal characteristics, socioeconomic status) were used to generate predicted probabilities of abnormal birth history for propensity score matching. Weighted linear and logistic regression models with adjustment for quintiles of propensity scores and CKD diagnosis were used to assess the impact of birth history on BP and GFR.

Results Age at enrollment, percent with glomerular disease, and baseline GFR were similar between the groups. Those with abnormal birth history were more likely to be female, of Black race or Hispanic ethnicity, to have low household income, or part of a multiple birth. Unadjusted BP measurements, baseline GFR, and change in GFR did not differ significantly between the groups; no differences were seen after adjusting for confounders by propensity score matching.

Conclusions Abnormal birth history does not appear to have exerted a significant influence on BP or GFR in this cohort of children with CKD. The absence of an observed association is likely secondary to the dominant effects of underlying CKD and its treatment. *(J Pediatr 2014;165:154-62)*.

There is growing evidence that adverse events early in life, particularly in utero, increase the risk of chronic diseases. Children with chronic kidney disease (CKD) are more likely to have been premature, low birth weight (LBW), or small for gestational age (SGA) compared with children without CKD.[1,2] Abnormal birth history (defined as premature, LBW, or SGA) may be an indicator of impaired nephrogenesis,[3-6] which in turn may increase the risk for hypertension and CKD.[3,7]

In the general population, abnormal birth history is known to be associated with a higher incidence of adult cardiovascular disease.[8,9] The effect on adult blood pressure (BP) is reasonably well established.[10-13] Recent studies have found inverse associations between birth weight and several BP measures, even in the pediatric age range.[10,14-21]

Among children with CKD, the effect of abnormal birth history on BP and renal function has not yet been studied. If abnormal birth history is associated with increased BPs or worsening renal function in the presence of CKD, such children may require more intensive monitoring and therapy early in life. The purpose of the present analysis is to investigate the effect of abnormal birth history on casual and ambulatory BP (ABP) and renal function among children with CKD.

Methods

The Chronic Kidney Disease in Children (CKiD) Study is a prospective observational cohort study initiated in 2005 to investigate the natural history of CKD at 51 pediatric nephrology centers in North America.[22] The study protocol was approved by the Institutional Review Boards of each participating center and

ABP	Ambulatory BP	HR	Heart rate
ABPM	ABP monitoring	ieGFR	Combination of iohexol GFR and estimated GFR
BP	Blood pressure		
CKD	Chronic kidney disease	LBW	Low birth weight
CKiD	Chronic Kidney Disease in Children	SBP	Systolic BP
DBP	Diastolic BP	SGA	Small for gestational age
GFR	Glomerular filtration rate		

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*List of members of the CKiD Study is available at www.jpeds.com (**Appendix**).

Funded by the National Institute of Diabetes and Digestive and Kidney Diseases, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute (U01-DK-66143, U01-DK-66174, U01DK-082194, U01-DK-66116). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.02.051

informed consent and assent were obtained from all participants according to local requirements.

Children were eligible for enrollment in CKiD based on age (1-16 years) and estimated Schwartz formula glomerular filtration rate (GFR) (30-90 mL/min/1.73 m^2).[23] Clinical and demographic data were collected at baseline, including CKD diagnosis. The primary diagnosis of CKD was self-reported at baseline for each participant and categorized as either nonglomerular or glomerular. Full descriptions of the CKD diagnoses and their associated categories used in the CKiD Study have been previously reported.[2,22]

Abnormal Birth History

LBW, premature birth, and SGA were parent-reported at study entry with the following definitions: LBW was birth weight <2500 g, prematurity was gestational age <36 weeks, and SGA was birth weight <10th percentile for gestational age as previously reported.[2] Abnormal birth history for purposes of this analysis was defined as the presence of any one of these abnormalities (LBW, premature, or SGA).

Outcomes

The primary outcomes of interest were BP levels and variability (casual and ambulatory), ambulatory heart rate (HR) variability, and change in GFR. Casual BP measurements were obtained at each CKiD Study visit using an aneroid sphygmomanometer. At each study visit, 3 BP measurements at 30-second intervals were obtained by auscultation of the brachial artery using the first Korotkoff sound for systolic BP (SBP) and the fifth Korotkoff sound for diastolic BP (DBP). The average of the 3 BP measurements was recorded as the participant's casual BP for that visit. The CKiD Clinical Coordinating Centers provided all participating sites the same aneroid sphygmomanometer (Mabis MedicKit 5; Mabis Healthcare, Waukegan, Illinois). CKiD clinical staff were trained and certified yearly in the auscultatory BP measurement technique, and annual calibration of each center's aneroid device was performed. Details of the standardized casual BP measurement technique have been previously published.[24]

ABP monitoring (ABPM) was performed 1 year after study entry, and every other year thereafter using a SpaceLabs 90217 oscillometric device (SpaceLabs Healthcare, Issaquah, Washington). Monitors are programmed centrally at the ABPM Center (University of Texas at Houston), shipped to the clinical sites, and placed on the subject's nondominant arm. BP readings were obtained every 20 minutes throughout the monitoring period. All participating clinical sites received annual training in monitor placement from the ABPM Center. Details of the ABPM procedure have been previously described.[25] Because we were interested in the putative effect of abnormal birth history on ABP, the analysis was restricted to participants with available ABPM data.

Casual BP levels were summarized by age-, sex-, and height-adjusted z-scores[26] and were interpreted as SD units from the mean of the normal population (z-score = 0). Summarized ABP levels are reported BP index, calculated as the mean ABP, by wake or sleep state, divided by the corresponding 95th percentile for age, sex, and height for the normal population as previously reported.[25] ABP load represents the proportion of readings greater than the 95th percentile, by wake and sleep states. Mean SBP or DBP levels above the 95th percentile or SBP or DBP loads greater than 25%, for each wake and sleep states were classified as having abnormal ABP.[25]

GFR was determined at each annual CKiD Study visit. Directly measured GFR by iohexol plasma clearance occurred at study entry, 1 year later, and then biennially. When iohexol GFR was not measured, estimated GFR was used in its place,[23] a validated approach used previously with CKiD data.[27,28] This combination of iohexol GFR and estimated GFR is hereafter referred to as ieGFR.[27] Individual regressions of ieGFR in the log scale (dependent variable) on time in years (independent variable) provided subject-specific intercepts and slopes,[27] which are interpreted as GFR at study entry and the average change in GFR over time, respectively. The 332 subjects included in the analysis contributed 1736 ieGFR measurements and 50% of these subjects contributed 5 observations (approximately 4 years of follow-up). Urine protein:creatinine (mg/mg of creatinine) was measured at each annual CKiD Study visit.[22]

Propensity Scores

In order to determine the effect of abnormal birth history on BP and GFR measurements, independent of confounders such as maternal factors and socioeconomic status, propensity score matching and weighting methods[29,30] were used to create comparable groups of exposed subjects (children with abnormal birth history) and unexposed subjects (children without abnormal birth history) who were similar with respect to baseline characteristics. Matching of propensity scores, which reflect each child's predicted probability of having an abnormal birth history, was used to achieve balance in confounding variables between the exposed (abnormal birth history) and unexposed (normal birth history) children. The propensity scores were derived from a logistic regression model with the odds of abnormal birth history as a function of observed baseline demographic, clinical, and maternal characteristics. Demographic variables included sex, race (black vs non-black), ethnicity (Hispanic vs non-Hispanic), and age of the child at time of study entry. Clinical variables included primary CKD diagnosis (glomerular vs nonglomerular), percent of life with CKD (>90%, 50%-90%, <50%), and history of twin/multiple birth. Maternal variables were age at birth (< or ≥24 years), highest level of education attained, height, weight, and body mass index at time of study entry; and household socioeconomic status: household income (<$36 000/y), birth parents living separately, a family size of less than 3, adult smoker in the household, and no employer health insurance at the time of study entry.

Variables that were in the causal pathway from abnormal birth history and disease severity were excluded from matching because these would mediate the putative detrimental