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The fetal environment: a critical phase that determines future renal outcomes in autosomal dominant polycystic kidney disease

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Abstract

Orskov and colleagues demonstrate the impact of birth weight on the mean age of end-stage renal disease (ESRD) in a large Danish ADPKD cohort. Each kilogram of birth weight extended the mean age of ESRD onset by 1.7 years. Placental insufficiency, activation of the renin-angiotensin-aldosterone system, increased fetal vasopressin levels, compensatory increases in insulin like growth factor-I, and a reduction in total nephron number may all contribute to this observation. Collectively, these changes result in an accelerated pace of cyst formation and expansion, and an inability to maintain glomerular hyperfiltration during kidney expansion which results in a more rapid progression to ESRD. Therefore the intrauterine environment may play a critical role in disease severity in ADPKD.

Orskov and colleagues[1] (this issue) and the Danish government are commended for increasing our understanding of the factors associated with risk for progression of renal disease in autosomal dominant polycystic kidney disease (ADPKD). The carefully performed analyses of Orskov *et al.*[1] provide the key observation that lower birth weight associates with an earlier age of onset of end-stage renal disease (ESRD) in ADPKD. Diligent investigative work and the availability of accurate, complete, and validated medical archival data from the Danish State Archives, the Danish National Registry of Dialysis and Transplantation, the Danish Data Protection Agency, and the Danish Nephrology Practice Groups were able to provide two decades of longitudinal information from more than 95% of diagnosed ADPKD patients in Denmark.

The association between a kilogram increase in birth weight and an increase in age of onset of ESRD of 1.7 years is further support for the hypothesis put forward by Barker more than 50 years ago, indicating that the fetal environment contributes to the development of a variety of chronic adult diseases.[2] Previous investigators have demonstrated an association between birth weight and the development of the metabolic syndrome, and age of onset of ESRD in type 2 diabetes, IgA nephropathy, and minimal-change disease. [1] Brenner and colleagues have carried the Barker paradigm forward and established the importance of the placental or intrauterine environment with regard to the determination of terminal nephron number, glomerular size, and salt sensitivity in humans. [3]

ADPKD is a hereditary renal disorder in which renal failure typically does not occur until the fifth or sixth decade of life. Post-natal epigenetic and environmental factors play a

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ABC is a consultant for Pfizer and for Otsuka Pharmaceuticals.

significant role in the progression to renal failure in this disease.[4] As Orskov *et al.*[1] now show, the intrauterine environment significantly impacts the severity of ADPKD through determination of birth weight. Adequate polycystin levels are critical for normal fetal kidney development. Under normal conditions, polycystin activity is upregulated during embryogenesis at specific phases of renal development. Also, under normal conditions, polycystin activity increases in response to ischemia reperfusion injury. If polycystin concentrations are low, as occurs in ADPKD, cyst formation rather than normal renal tubule development takes place. If ischemia or reduced placental blood flow is also present, activation of the renin-angiotensin-aldosterone system and increases in vasopressin levels occur, potentially augmenting cyst formation and growth.

Intracellular cyclic adenosine mono-phosphate (ic cAMP) levels are increased in cystic epithelial cells and impact both proliferative and secretory aspects of cyst formation and growth in ADPKD. Vasopressin availability and action augments ic cAMP levels and cyst growth in ADPKD. Reduced vasopressin action is associated with reduced disease severity in a variety of different renal cystic disease models of ADPKD. When intrauterine growth retardation occurs and during the obligate process of birth through labor and delivery, vasopressin levels increase significantly in both amniotic fluid and the fetal circulation. Whether these increases in fetal vasopressin levels translate to increases in fetal renal tubular epithelial ic cAMP levels and more robust and earlier renal cyst development in ADPKD is not yet known.[5]

Important to consider in current day conditions, infants “behind” in growth at the time of birth, have an accelerated growth rate post-natally. Post-natal growth may be important for programming predisposing to adult diseases as well. Relevant to ADPKD, the insulin like growth factor-I system is important in post-natal growth and mediates epithelial cell proliferation in polycystic kidney disease.

As described by other investigators, reduced birth weight at a threshold of less than 2500 g associates with a reduced number of nephrons at birth, an increase in glomerular size, and glomerular hyperfiltration. Recently, available evidence from a number of observational cohorts suggests why reduced nephron number and glomerular hyper filtration may be particularly devastating to patients with ADPKD with regard to risk for progression to ESRD. Data from observational registries indicate that cyst formation and expansion forecasts future renal failure in ADPKD.[6] Through standardized and validated magnetic resonance image acquisitions, the Consortium for Radiologic Imaging in Polycystic Kidney Disease (CRISP), the SUISSE cohort and the pediatric ADPKD cohort at the University of Colorado show that growth and expansion renal cysts result in an increase in total kidney volume (TKV) in the vast majority of ADPKD individuals, detectable within a relatively short period or time (six months), over decades prior to loss of kidney function. [7–9] Importantly, in both animal and human microdissection studies, renal cyst growth in ADPKD is focal, affecting fewer than 5% of all nephrons. Therefore, the significant focal cyst expansion that takes place in ADPKD is sufficient to result in massive kidney enlargement, with most end-stage kidneys weighing more than 8 kg. The ability to maintain normal renal function through incompletely understood mechanisms of glomerular hyperfiltration is required in ADPKD patients during the decades of continuous cyst and renal growth. If one were to have fewer nephrons overall, due to low birth weight, the adaptive glomerular hyperfiltration needed to maintain normal kidney function during the periods of significant cyst growth and expansion in the first four decades of life would be lost.

Finally, evidence suggests that there are specified periods of accelerated cyst growth in ADPKD that may include the pre-natal period.[1,3] Children with ADPKD demonstrate a

greater rate of increase in TKV than adults (9.0 vs. 5.7% per year).[10,11] Mathematical modeling of the TKV growth curves measured in adult CRISP participants predict rate of cyst growth and expansion prior to enrollment in the CRISP study at least fourfold greater than measured during CRISP. [12] In addition, these modeling experiments indicate that the majority of cysts responsible for the TKV measured in CRISP occur extremely early, close to the time of birth. [12] These observations show that there are critical times of accelerated cyst growth that link to disease severity in ADPKD. Therefore, in this context it is not surprising that the intrauterine environment manifested as birth weight is important in determining renal outcomes in this disorder.

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