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Preamble:
In this month's Karger Blogs I comment on two papers, both published in the *American Journal of Nephrology* and both constructing a novel concept about kidney disease. One builds on strong, scientifically-based experimental observations that the intestinal barrier function is somehow altered in the course of chronic kidney disease, while the other postulates (indirectly) from clinical studies that nephron endowment at birth can have a material impact on the nature of predisposition to develop a specific kidney lesion; namely, focal and segmental glomerulosclerosis. While both papers represent an early stage of experimental or clinical investigation, they are tantalizingly attractive as they may evoke new strategies for prevention and treatment of kidney diseases.

Low Birth Weight and Premature Birth Are Risk Factors for Podocytopenia and Focal Segmental Glomerulosclerosis

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Commentary

By Professor Richard Glassock

It is abundantly clear that fetal and child health has a profound impact on kidney development and the later occurrence of kidney disease and hypertension (see V.A. Luyckx et al. Lancet 2013;382:273–283). Prematurity and low birth weight (LBW) for gestational age are both common and strongly associated with a deficiency in nephron endowment. It has been estimated that for each kg increase in birthweight, each kidney is endowed with about 250,000 more glomeruli at birth. As experimental nephron reduction studies have shown, a deficiency in nephron number can evoke maladaptive circulatory changes promoting the development of a lesion podocyte injury, apoptosis and focal and segmental glomerulosclerosis (FSGS) accompanied by proteinuria and progressive renal failure. Human nephrogenesis is complete at about 36 weeks, so LBW due to prematurity (delivery prior to 36 weeks) is not necessarily synonymous with nephron under-endowment, although the glomeruli of premature infants are larger and abnormal. Infants born at 36–40 weeks who are underweight for gestational age (<2.5 kg) almost invariably have nephron deficiency that does not improve with further postnatal development. The 'normal' adult has from 210,000 to 2.7 million nephrons per kidney; this extraordinary variability is largely conditioned by maternal and genetic factors present in the early stages of fetal development. Ikezumi and colleagues conducted an observational study of 16 subjects with a biopsy-proven lesion of FSGS, 10 of whom had normal birth weight (NBW) and 6 of whom had LBW (<2.5 kg). These were compared to subjects with biopsy-proven minimal change disease (MCD) with NBW. Of the LBW infants with FSGS, 5 out of 6 were premature (gestational age ≤36 weeks), and only one was truly LBW with normal gestational age. The frequency of LBW (or prematurity) was 37.5% in those with FSGS. 12.5% in those with MCD and <10% (range 0–9.1%) in another 186 subjects with a variety of other glomerular lesions. Podocytopenia was documented in the LBW subjects with FSGS. Striking glomerulomegaly was found in those with LBW and FSGS, but not in FSGS associated with NBW. The Fogo-D'Agati variant of Peri-Hilar FSGS was common (50%) in the FSGS subjects with LBW but was not observed in those with FSGS and NBW. The MCD patients were biopsied during a steroid-induced remission, and the FSGS patients were non-nephrotic at the time of biopsy (urine protein excretion 0.43–1.91g/day). Surprisingly, 3 of the 16 patients (19%) with FSGS had the Peri-Hilar lesion. These characteristics may indicate a subtle bias in the selection of cases for study, and may have influenced the results.

These novel findings raise some interesting questions. Was it the prematurity per se or some other process, such as an underlying genetic abnormality (RET polymorphism, PAX2 haplotype, I/D ACE polymorphism, etc.) that led to the high association of LBW with Peri-Hilar FSGS lesion? Do these findings have therapeutic or prognostic implications? For now, it would be highly advisable if birth weight and gestational age were recorded for all patients with biopsy-proven glomerular disease (especially FSGS).

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