Oligonephropathy of Prematurity

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Abstract

Objectives: With improved health care, the number of premature babies who survive to adulthood is expected to increase. The objective of this review is to determine whether premature infants have an increased risk of chronic kidney disease (CKD).

Study design: A literature review was performed by searching PubMed (US National Library of Medicine) and the Cochrane Library, using the keywords prematurity, kidney, nephrogenesis, oligonephropathy, and kidney impairment. Articles published in English since 1990 were reviewed.

Results: Increasing evidence suggests that prematurity causes oligonephropathy independently of, and coexisting with, intrauterine growth restriction. Animal studies show that nephrogenesis continues for up to 3 weeks in extrauterine life, but with up to 18% abnormal glomeruli. Nephrogenesis is further impaired in preterm infants who develop renal impairment in the early postnatal period, which is estimated to be 8% to 24%.

Conclusion: Premature infants are at risk for CKD. A larger longitudinal study is needed that follows up premature infants to determine the exact incidence of CKD. Until then, renal assessment in ex-premature infants should be incorporated into follow-up guidelines, in addition to the current assessment of growth and neurodevelopmental outcomes. The cost implications to a comprehensive program, impact of early identification and strategies to improve outcomes in this population are needed.

Keywords: oligonephropathy, preterm, nephrogenesis, chronic kidney disease

The World Health Organization estimates that approximately 12 million premature babies are born per year and the numbers are increasing.[1] Current knowledge suggests that low birth weight (LBW; < 2500 g)[2] constitutes a risk factor for adult renal disease.[3-6] LBW is associated with a lower nephron number, and individuals with LBW are at greater risk of developing chronic kidney disease (CKD) in adult life than are individuals with normal birth weight.[5-9] LBW infants constitute a heterogeneous group of babies who can be premature, growth restricted (birth weight below the 10$^{th}$ centile), or both. This literature review presents data to support the association of prematurity and the development of CKD.[10-12]

## Embryology

Kidney development starts early in gestation, with the pronephros appearing at approximately 3 weeks of gestation, followed by involution by 5 weeks, as the mesonephros and metanephros develop.[13] Although the mesonephros degenerates by approximately the 11$^{th}$ week, the metanephros continues to develop until weeks 34 to 36, when nephrogenesis is complete.[14,15] Nephron maturation begins in the juxtamedullary region and then progresses outward to the capsule.[16] The critical window of the final stages of kidney development thus spans 32 to 35 weeks of gestational age (GA), and no new nephrons are formed after 36 weeks GA. Nephron endowment is, at that point, fixed for life.[4,15] Premature infants are born prior to these final stages and so risk incomplete nephrogenesis. Occasionally, a rare genetic condition such as renal coloboma syndrome, an autosomal dominant disorder caused by PAX2 gene mutations, interrupts normal kidney development and causes renal hypoplasia.[17]

## Animal studies

Animal studies have shown that insults during the development of the fetus could have a deleterious effect on the growing kidneys. Because of the complexity of the postnatal care of the premature human infant and the possible confounding factors associated with human autopsy studies, it is essential to undertake controlled animal studies in an appropriate model to examine the effects of preterm birth on nephrogenesis.[18] The kidney in a baboon matures just before birth, similar to that of the human fetus, making the baboon fetus the most suitable animal experimental model to investigate the impact of in utero insult on kidney growth.[18] Gubhaju et al.[12] showed that in prematurely born fetal baboons, glomerular and nephron numbers increased in the first 3 weeks of extrauterine life during which period the fetuses continue to receive respiratory support in the neonatal intensive care. Similar to findings in preterm human neonates,[19] kidney weight and volume relative to body weight were higher in the premature baboon neonates compared with GA-matched controls, suggesting an increased demand on the neonatal kidney following the transition from the intrauterine to the extrauterine environment. Although nephrogenesis was found to continue in the extrauterine environment following preterm birth, there was a high percentage (up to 18%) of abnormal glomeruli.[12,20] It is, however, impossible to determine whether these changes are reversible, as the animals were euthanized after the renal biopsy was completed. Human preterm babies very often remain longer in a neonatal intensive care unit, undergoing various forms of treatment and intervention.

Animal studies involving other species have also shown adverse effects of commonly used medications such as aminoglycosides and steroids on fetal kidney

growth.[21,22] Antenatal exposure of gentamicin has been associated with reduction in nephron number.[23] The use of antenatal steroids has a huge impact on the outcome of premature babies.[24] In addition, animal studies have shown that fetuses exposed to antenatal steroids have a reduced number of nephrons.[22]

Histopathological findings in humans

Rodriguez et al.[25] looked for evidence of abnormal postnatal glomerulogenesis in extremely LBW preterm infants. Renal autopsy tissues from 56 extremely premature and 10 full-term infants were studied. All preterm infants weighed less than 1000 g at birth and 42 (75%) of them were appropriate for gestational age (AGA). The GA ranged from 23 to 30 weeks. Preterm infants were divided into two groups (short survival of < 40 days and long survival of ≥ 40 days). Each group was subdivided into those with acute kidney injury (AKI) and those with normal renal function. Using computer-assisted glomerular morphometry and radial glomerular counts (RGCs), the investigators showed that glomerulogenesis was markedly decreased in all preterm infants compared with term controls, the degree of which correlated significantly with GA. RGC is a technique in which layers of glomeruli are counted following a straight line beginning in the deepest zone of the cortex, progressing systematically to the renal capsule. Although nephrogenesis continued after birth in the preterm infants, fewer glomeruli were produced. Preterm infants who developed AKI had significantly lower RGCs, suggesting that an insult in the early postnatal period further impaired nephrogenesis. The investigators concluded that prematurity in of itself could cause oligonephropathy.

A similar recent study investigated postnatal nephrogenesis in a cohort of preterm infants and fetuses.[26] Kidney samples were obtained at autopsy from eight

human fetuses (15 to 22 weeks), 12 premature infants (GA ranging from 25 to 38 weeks), and three term newborns. None of the deaths were related to renal conditions. Eight of the 12 premature infants weighed less than 1000 g and two were less than 2500 g. In each kidney, RGCs were determined similarly to the earlier study[25], and the investigators found that in those infants who were born alive, nephrogenesis continued for only a short period after birth (up to 3 weeks). The renal autopsy from a preterm infant who survived the longest in this cohort (3 months) showed retardation in glomerulogenesis despite an increase in body weight.

Both of these studies provide histopathological evidence that premature babies could have impaired postnatal nephrogenesis. Babies who are born prematurely end up with a nephron deficit from infancy. Lower nephron endowment is believed to increase the risk of hypertension and chronic renal diseases in later life.[9,27] Glomerular filtration rate (GFR) is determined by the filtration rate of a single nephron and by the total number of nephrons. When the number of nephrons is diminished, the kidney compensates by increasing the single-nephron GFR.[28] According to the Brenner's hypothesis, this compensatory mechanism of single-nephron hyperfiltration leads to proteinuria, hypertension, glomerulosclerosis and ultimately CKD. [29]

Clinical studies

With improved standards of clinical care and technology, more and more premature infants are being saved. A premature baby born at 24 weeks gestation can be expected to stay in the neonatal intensive care unit for 16 to 18 weeks or longer.[30] During this period, the infant will be subjected to various forms of invasive procedures and treated with various medications, some of which have been recognized to cause renal

impairment.[28] The incidence of premature infants developing AKI during this period is high.[31] AKI is a complex clinical condition of the kidney ranging from mild dysfunction to complete renal shutdown with anuria.[28] Due to the shortcomings of using serum creatinine based formulas to describe AKI, the exact incidence of AKI in neonates is unknown. Nonetheless, reported estimates are between 8 and 24%.[31]

Studies in very low birth weight (VLBW) infants have shown that the presence of AKI and elevated serum creatinine are independent risk factors for mortality.[32] Neonates with AKI are believed to be at higher risk of developing CKD.[28] Longitudinal follow-up data of pediatric patients after AKI irrespective of cause showed that this cohort of children has a high risk of ongoing residual renal injury and death in the long run.

Huang et al.[19] investigated early postnatal kidney growth in premature infants, comparing intrauterine and extrauterine renal growth. One hundred neonates were enrolled in the study and renal volumes were measured by ultrasound. Extrauterine renal growth in a group of premature infants who were less than 34 weeks was compared with intrauterine renal growth for a group of term infants. Left kidney volume, body weight, height, and age were used in the correlation analysis. Premature babies had smaller kidney volumes compared with their term counterparts at a similar GA. The authors concluded that kidney growth in premature babies was reduced compared with intrauterine renal growth at an equivalent GA.

Renal size has been measured in a cohort of young adults who were born prematurely. The patients recruited in this study were part of the Project on Premature and Small for Gestational Age Infants (POPS) cohort.[33] Subjects who were born prematurely (<32 weeks GA) were divided into two groups (AGA and SGA). Babies born full term and AGA were recruited as controls. Kidney length and volume

measurements were taken and then compared between each group and the controls. Renal size did not differ between SGA and AGA individuals. Left kidney length and volume were significantly lower than right in both SGA and AGA individuals, notably more so in women. The left kidney was larger than the right one in 70% of controls compared with 40.9% of the SGA group and 48.3% of the AGA group. Renal structural anomalies were present in only eight prematurely born participants. The investigators concluded that kidney growth is stunted after preterm birth, especially on the left side, and more so in females. The long-term consequences of this association, however, have not been determined.

Others have evaluated large cohorts of children with CKD to determine perinatal demographics (such as SGA, LBW) with CKD. Franke et al.[3] reviewed perinatal parameters of 435 children with CKD. Kidney disease was classified as either congenital with onset of renal disease during fetal life (*n* = 260; 60%), hereditary as genetically determined with onset after 3 months of life (*n* = 93; 21%), or acquired (*n* = 82; 19%). The investigators found that the rate of prematurity was elevated in children with congenital (39.3%), hereditary (24.7%), and acquired CKD (15.5%) compared with the rate of prematurity in children with normal renal function (8%); similarly, the rate of small for gestational age (SGA) babies was elevated in children with congenital (29.2%), hereditary (22.6%) and acquired CKD (29.3%). The investigators concluded that both SGA and prematurity predispose a child to CKD. Greenbaum et al.[34] investigated the association between abnormal birth history and growth in children with CKD. In this study, growth outcomes from 426 participants were assessed. This cohort had a high prevalence of LBW, SGA, and premature infants. In this study, growth outcomes were quantified by age-sex-specific height and weight z-scores during clinical visits. This study showed that patients who were born

with LBW and SGA had poorer growth and weight gain. Incomplete nephrogenesis could lead to persistent oligonephropathy, which therefore may represent a major risk factor for progressive renal disease in adulthood.

Is there any evidence that oligonephropathy can be seen in adults born prematurely? Focal segmental glomerulosclerosis (FSGS) is recognized as a pattern of injury mediated by elevated glomerular capillary pressures and flow rates. These changes can occur as an adaptive response in conditions in which the number of functioning nephrons is reduced.[35] Hodgin et al.[36] reviewed histopathological data from six adults who were born at 22 to 30 weeks gestation with a mean birth weight of 1054 g (range 450 to 1420 g). These patients all had clinically significant proteinuria and no other potential risk factors for secondary FSGS. A review of the renal biopsy results showed that these patients had histopathological changes typical of postadaptive FSGS (glomerulosclerosis, glomerulomegaly, and mild foot process effacements). The investigators concluded that prematurity promotes the development of secondary FSGS and, because birth history is often omitted by physicians who treat adults, this risk factor is likely to be underrecognized. This study is limited by the number of patients reviewed and by the fact that neonatal care has changed tremendously in the last 20 years.

Follow-up of ex-premature infants

Should infants who were born prematurely thus be screened regularly for evidence of renal impairment? The currently available guidelines in the United Kingdom

recommend that the assessment of health status at two years of age, corrected for prematurity, be carried out for all births of less than 31 weeks gestation or less than a birth weight of 1000 g.[37] The focus of this guideline is on assessment of growth, neurodevelopmental outcome, and cognitive function. No specific recommendations exist regarding assessment of renal status (blood pressure, renal function, or urine analysis) when the child is seen at two years of age. Similarly, long-term follow-up plans from other countries focus on developmental outcomes and the incidence of chronic lung disease.[38,39] There is no consensus about how renal assessment should be done on premature infants upon discharge. It has been proposed that blood pressure measurements should initially be monitored yearly and, later, every two to three years for at least two or three decades in all people born prematurely.[40] This suggestion appears to be very practical, considering the earlier information. Evidence shows that young adults who were born prematurely have elevated blood pressure.[41] Blood pressure in a cohort of 50 young adults who were born prematurely (< 32 weeks gestation; 23 SGA and 29 AGA) was compared with that from a group born at term. Twenty-four-hour ambulatory blood pressures and renin concentrations were determined in all subjects. Systolic blood pressure in both AGA and SGA premature infants was higher than in control infants. No significant difference was observed in the blood pressure of AGA and SGA infants. The renin level in the AGA group was found to be higher, although the clinical significance of this finding is unclear. The authors concluded that very preterm individuals have higher systolic blood pressures as well as a higher risk of hypertension at a young adult age.

Bacchetta et al.[10] performed an assessment of renal function on a group of 50 children who were born preterm (GA < 30 weeks). A group of babies born at term were recruited as the control group. The mean age in this cohort was 7.6 years. Blood

pressure, kidney size, and GFR using inulin clearance were measured in both groups. Children who were born preterm had smaller kidneys, elevated mean diastolic blood pressures, and impaired GFR. As a result, the authors recommended that long-term renal follow-up (blood pressure, serum creatinine, urine albumin-to-creatinine ratio) be performed on all children who are born preterm. This study, however, did not provide any data on neonatal management (such as umbilical artery catheterization) and its possible influence on blood pressure.

The role of routine urine analysis in the detection and prevention of CKD in not well defined. Ambiguity about screening children exists because of the uncertainty as to whether early detection of renal disorders in childhood will lead to effective interventions and a reduction in the number of individuals who subsequently progress to CKD. A related concern is whether the adoption of urinary screening programs is cost-effective. The most common method used for screening children for CKD involves the measurement of spot samples of urine for hematuria and/or proteinuria.[42] A subtle increase in urinary albumin excretion, known as microalbuminuria, has been identified as a prognostic marker for cardiovascular and/or renal disease in diabetic and nondiabetic adults.[43] Microalbuminuria is defined as urinary albumin excretion from 30 to 300 mg/24 h or equivalent amounts (3 mg/mmol creatinine or 30 mg/g creatinine) when spot urine samples are used. For clinical purposes, immunologic techniques are most frequently used, as they are easy to use at relatively low cost. In the absence of any inflammation in the urinary tract, intact albumin of glomerular origin is the major source of albumin in the urine.[43]
In a European study, spot urine tests from 109 young children who were in a cohort of VLBW (birth weight < 1000 g) were tested for microalbuminuria with the more sensitive technique of high-performance liquid chromatography (HPLC).[44] Results

obtained with the conventional immunoassay technique were compared with those obtained by using HPLC. The percentage of patients diagnosed with microalbuminuria was four times greater with HPLC than with the conventional technique (44.5% vs. 11%, P<0.001). The investigators concluded that microalbuminuria in a VLBW child was more marked when HPLC was used and the difference was significant. The high cost and expertise required for HPLC means that it can currently only be used as a research tool and may not be suitable for routine follow-ups of premature infants.

A follow-up study in children who survived AKI recommended that, in view of the incidence of renal insufficiency and death among this cohort, these children should be screened regularly for signs of renal disease.[45] However, there is no consensus on how this assessment should be done.

Future research

The limitation of some of these studies[33,36] is that they are unable to ascertain the number of patients with morphological changes (smaller kidneys) and histopathological changes who will develop symptomatic renal disease. Reduced kidney size has been proposed as a surrogate marker for reduced nephron mass, as the nephron number can only be determined by renal biopsy.[27] A lower nephron number has been associated with hypertension and renal diseases in adulthood.[46] Long-term studies are needed to determine the percentage of premature patients with hypertension, proteinuria, and abnormal renal function that develop CKD in later life. A cost-effectiveness study should also be conducted to determine the benefits of routine screening for renal conditions. These studies can also help determine the cost implications of these patients for the health care system, should they develop CKD. It

costs more than US$ 65,600 to treat an extremely premature infant (birth weight < 1000 g) and this figure is higher for the infants who develop other complications such as renal impairment.[47] CKD screening programs theoretically would allow for implementation of interventions in earlier stages, eventually decreasing costs because of less progression to CKD and improved health status at kidney replacement therapy initiation.[48] These follow-ups and assessments (blood pressure, urine for microalbuminuria, renal function, possibly using newer markers such as urinary neutrophil gelatinase-associated lipocalin) could be incorporated into the existing follow-up guideline.[37] In addition, the long-term impact of maternal perinatal condition and treatment on infant's health will need to be reviewed. Once the results from long-term studies are available, perhaps an intervention similar to those that have been successful in delaying CKD in adults can be considered from infancy.[49] A question that we can try to address after we have sufficient clinical data is, should nephron protection begin at birth?[4]

## Conclusion

The number of premature births continues to increase, and with improved health care and technology, more of them will survive to adulthood. Therefore, the increased number of children and adults with incomplete nephrogenesis will contribute to a rise in the number of CKD patients in the future. Most studies include both AGA and SGA cohorts, but a large longitudinal study that follows AGA premature infants to determine the incidence of kidney disease is needed. The final effect of oligonephropathy is likely to be a combination of inadequate nephrogenesis due to premature birth, complicated by abnormal glomerulogenesis and AKI in the neonatal period. Mechanisms and guidelines have already been established for the follow-up of

premature infants, which could be modified from their current focus on neurodevelopment outcome to also include routine renal assessment. Currently, it has not been well established whether renal assessment and treatment for ex-premature infants will prevent or delay the occurrence or presentation of renal disease. Future research should address all these aspects, including the incorporation of renal surveillance into the follow-up plans for preterm cohorts.

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