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Long-term renal disease after prematurity or fetal growth restriction: who is at risk?

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INTRODUCTION

Low birthweight (LBW) has been associated with increased risk of developing cardiorenal diseases later in life [1]. LBW can be considered as a clinical surrogate for multiple pathologies, such as prematurity or fetal growth restriction (FGR). Surprisingly, these subcategories have barely been studied within the field of Developmental Origins of Health and Disease (DOHaD). Considering the diverse influence of perinatal complications on kidney development, this can limit early identification of patients at risk of developing renal disorders. In addition, while preclinical DOHaD studies mostly focused on LBW as a result of FGR, as yet, no clearly defined FGR human population has been used to study long-term risk of developing chronic kidney disease [2, 3]. Therefore, although LBW served as a good starting point, the time has come to dig deeper.

DEFINITION OF LBW, FGR, PREMATURITY AND SGA

LBW is most commonly defined as an absolute birthweight <2500 g [4]. LBW results mainly from prematurity or FGR.

Prematurity is defined as being born before the 37th week of gestation [4]. FGR is prenatally detected by ultrasound showing impaired biometry (estimated fetal weight and/or abdominal circumference below the 10th percentile) or deflecting growth. These parameters of impaired fetal growth in combination with abnormal blood flow patterns in the uterine artery, umbilical cord or fetal middle cerebral artery indicate placental insufficiency induced FGR [5]. Placental insufficiency is the major cause of FGR, in which a reduced utero-placental blood flow hampers nutrients and oxygen transfer towards the fetus throughout pregnancy. Small for gestational age (SGA) is another category in which 'small' babies are detected postnatally when birthweight is under the 10th percentile for their gestational age and gender [4]. SGA also includes causes other than FGR induced by placental insufficiency, such as being small as a genetic trait ('genetically small'), congenital malformations, chromosomal abnormalities or infections. Note that while prematurity, FGR and SGA can overlap, none of them is interchangeable (Figure 1). The term FGR is often confused with SGA as it seems logical that FGR results in birthweight under
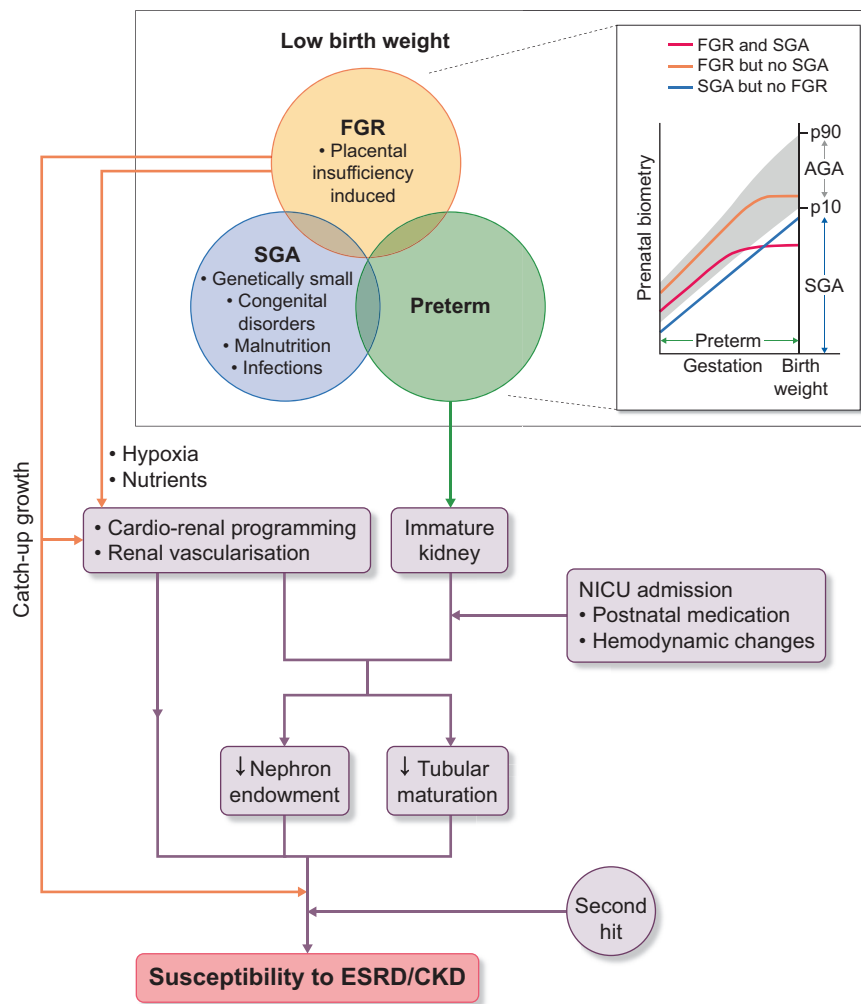
FIGURE 1: Potential mechanisms of how the different subcategories of LBW result in increased susceptibility for ESRD or CKD. AGA, appropriate for gestational age; CKD, chronic kidney disease; ESRD, end-stage renal disease; FGR, fetal growth restriction; LBW, low birth weight; NICU, neonatal intensive care unit; SGA, small for gestational age.

the 10th percentile. However, fetuses showing deflecting growth but born with a birthweight between p10 and p90 are still considered FGR. Likewise, SGA includes more than placental insufficiency induced FGR. Incorrect interchangeable use of FGR and SGA is also illustrated in our recently published integrated animal and human meta-analysis; we observed a clearly increased risk of hypertension in FGR offspring in rats, where clear models of placental insufficiency induced FGR were used, but this difference was not observed in human studies, where FGR was often poorly defined using SGA criteria [2].

POTENTIAL MECHANISM OF IMPAIRED KIDNEY DEVELOPMENT AFTER ADVERSE EARLY-LIFE EVENTS

Human nephrogenesis is complete around 34–37 weeks of gestation and thereafter no new nephrons are formed.

Therefore, pregnancy forms a vulnerable period in which early-life events might impair kidney development. Adverse *in utero* environments are believed to negatively influence (epi)genetic programming of cardiovascular and renal pathways (Barker hypothesis) [6]. The earlier these adverse events occur during pregnancy, the longer they could impact nephrogenesis. Premature delivery entails that neonates are born with immaturely developed kidneys and incomplete nephron formation. Impaired nephron endowment could lead to hypertension and compensatory hyperfiltration in the remaining nephrons, causing accelerated wear and subsequent loss of them (Brenner hypothesis) [7]. In addition, tubular maturation might also be impaired, but little research has been performed on this potential causal relation. Each of these potential mechanisms results in increased susceptibility to develop kidney disease in later life (Figure 1). Interestingly, while these theories and hypotheses were

formed decades ago, the causal link has never been proven and the field did not progress much after the few initial studies showing an association between LBW and chronic kidney disorders [1, 3].

THE IMPORTANCE OF DISTINGUISHING BETWEEN SUBCATEGORIES UNDER THE UMBRELLA TERM LBW

Currently, studies are still barely making the distinction between the different LBW entities described above. Therefore, we applaud the article published by Gjerde et al. as they are, to our knowledge, the first to make the distinction between LBW, SGA and prematurity in relation to risk of end-stage renal disease (ESRD) [8]. They found within their Norwegian population that within these categories, a single factor did not increase the risk of ESRD, while a combination did. This study underscores the importance of making the distinction between different subcategories instead of using LBW as an umbrella term. Avoiding the LBW umbrella allows identification of who is actually hit by the rain. This would permit specific monitoring programmes restricted to risk patients specifically instead of follow-up of large groups.

THE NEED OF INVOLVING FGR INDUCED BY PLACENTAL INSUFFICIENCY AS A SUBCATEGORY

While this study of Gjerde et al. is very useful and a step in the right direction, we would like to emphasize that the true FGR induced by placental insufficiency was still not specifically assessed. This population is especially of interest since the early-onset chronic *in utero* exposure of hypoxia and malnutrition could have a more negative influence on kidney development than either prematurity or SGA [3]. Most preterm neonates are born between 34 and 37 weeks of gestation when nephrogenesis is almost complete [4]. Our meta-analysis in human studies failed to show a blood pressure difference between SGA offspring compared with normal growth peers [2]. Interestingly, we noted that the only remarkable blood pressure difference (19 mmHg) was observed in the single study that investigated a population with FGR induced by placental insufficiency [9]. This highlights the need to include a clearly defined FGR population as a separate subcategory in future studies.

ONE GLOBALLY USED DEFINITION TO DIAGNOSE PLACENTAL INSUFFICIENCY INDUCED FGR

The lack of a globally used definition of FGR makes it very difficult to compare results in the growing body of literature. As Gjerde et al. mention in their discussion, their results might only apply to the Norwegian population and it may not be possible to extrapolate them to other countries merely because of discrepant definitions of LBW, SGA and prematurity [8]. Gordijn et al. proposed an international consensus-based definition for FGR that includes signs of placental insufficiency [5]. We recommend using this definition when setting up research, since it helps to identify the small babies with a truly unfavourable antenatal environment.

HIGHER RISK OF ESRD: COMBINATION OF PREMATURITY AND SGA OR SEVERE CASES OF FGR?

The more severe phenotype of FGR might be more at risk of developing chronic cardiorenal diseases. Indeed, in our meta-analysis, we found that the most severe and early-onset induced animal models of FGR resulted in the largest blood pressure differences compared with control offspring [2]. Although not in FGR specifically, this pattern was supported by Gjerde and colleagues as their study reported that more severe SGA increases the risk of developing ESRD [8]. They also showed that when only one factor (LBW, SGA and prematurity) was present, this did not increase the risk of developing ESRD but that the presence of multiple factors did increase this risk. FGR and (iatrogenic) prematurity often co-occur, especially in the severe cases of FGR when premature delivery is required to prevent stillbirth. Hence, this raises the question of whether we are looking at an increased hazard ratio by multiple factors or we are actually looking at the severe FGR cases that are at risk because of prematurity with FGR. This question remains unanswered as FGR was not included as a separate factor.

DIFFERENT UNDERLYING MECHANISMS

To reach a better understanding of the underlying mechanisms involved in the relation with kidney diseases, it is advisable to study each subgroup separately as they each have their own pathogenesis. This contributes to the search for therapeutic or prophylactic agents. In addition, sex hormones could play a protective role in one subcategory but not in the other, so that gender-specific effects could be missed in the overall SGA or LBW groups. Indeed, Gjerde et al. found a relation between preterm birth and ESRD in males but not in females; this gender difference was not revealed in the LBW or SGA group [8]. Potentially, preterm infants might have enough renal reserve, but postnatal (nephrotoxic) medication during their admission at the neonatal intensive care unit is what might put them at risk [10].

FUTURE PERSPECTIVES

Future research within the DOHaD field should stop merely using the clinical surrogate LBW and start studying the effects of its subcategories on long-term risk of cardiorenal diseases. Since these entities each have their own pathophysiology, they also will have their own (gender-specific) risk of association with developing kidney disease later in life. We would like to emphasize the need to include the category of FGR induced by placental insufficiency, this being the most important category that could negatively influence nephrogenesis throughout pregnancy. Considering that long-term follow-up studies in humans are challenging to perform, we will need high-quality birth registries that include (prenatal) data on FGR. Such a study design will contribute to a better understanding of the underlying mechanisms allowing identification of new therapeutic targets,

and help us pinpoint who is at risk of developing renal disease later in life. Ultimately, we must identify those young patients who are truly at risk for long-term cardiorenal disease to prevent or delay the onset of such disease by timely initiation of preventive measures such as blood pressuring lowering.

AUTHORS' CONTRIBUTIONS

Conceptualization, visualization and writing: the original draft preparation was done by F.T. Supervision and writing: reviewing and editing were done by A.T.L.

CONFLICT OF INTEREST STATEMENT

The authors declare that they do not have any conflict of interest.

(See related article by Gjerde et al. Intrauterine growth restriction, preterm birth and risk of end-stage renal disease during the first 50 years of life. Nephrol Dial Transplant 2020; 35: 1157–1163)

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The Gordian knot of the long-term safety of dialysate citrate: is there really a concern about patient hard outcomes?

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The bicarbonate-based dialysate contains a few millimoles of acetic acid to stabilize the pH. Due to the favourable dialysate–plasma gradient, the plasma acetate levels at the end of the haemodialysis (HD) session are several times higher than pre-treatment, such as to induce the well-known acetate adverse effects [1]. Citric acid is an alternative dialysate buffer that is converted to its anion citrate into the body. Compared with controls with normal renal function, citrate clearance by the Krebs cycle is not impaired in long-term HD patients [2]. As for acetate, the metabolism of citrate is not completed during the dialysis session since the hepatic and muscular metabolism occurs partly after the end of the treatment. In addition, there are fast and slow metabolizing patients, depending on liver function and muscle mass. For instance, in patients with liver insufficiency, citrate clearance is reduced by 50% [3]. Indeed, citric acid not only may substitute acetic acid as a pH stabilizer, but also is an effective anticoagulant on dialysis membranes [4]. Ahmad et al. [5] were the first to demonstrate almost two decades ago that citric acid-based dialysate increases the delivered dialysis dose. These results were confirmed in a large prospective controlled study in 2009 [6]. Moreover, Sands et al. [7] could reduce the heparin dose by up to one-third without any detrimental effect on K_t/V, shifting a large cohort of patients from standard bicarbonate-based dialysate to citric acid-based dialysate. Small, acute studies have challenged the feasibility of heparin-free citric acid-based dialysate in HD [8] and postdilution on-line haemodiafiltration (HDF) [9], respectively. However, the follow-up periods were short.