

Maternal and environmental risk factors for neonatal AKI and its long-term consequences

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Abstract | Acute kidney injury (AKI) is a common and life-threatening complication in critically ill neonates. Gestational risk factors for AKI include premature birth, intrauterine growth restriction and low birthweight, which are associated with poor nephron development and are often the consequence of pre-gestational and gestational factors, such as poor nutritional status. Our understanding of how to best optimize renal development and prevent AKI in its infancy; however, the identification of pre-gestational and gestational factors that increase the risk of adverse neonatal outcomes and the implementation of interventions, such as improving nutritional status early in pregnancy, have the potential to optimize fetal growth and reduce the risk of preterm birth, thereby improving kidney health. The overall risk of AKI among critically ill and premature neonates is exacerbated postnatally as these infants are often exposed to dehydration, septic shock and potentially nephrotoxic medications. Strategies to improve outcomes — for example, through careful evaluation of nephrotoxic drugs — may reduce the incidence of AKI and its consequences among this population. Management strategies and updated technology that will support neonates with AKI are greatly needed. Extremely premature infants and those who survive an episode of AKI should be screened for chronic kidney disease until early adulthood. Here, we provide an overview of our current understanding of neonatal AKI, focusing on its relationship to preterm birth and growth restriction. We describe factors that prevent optimal nephrogenesis during pregnancy and provide a framework for future explorations designed to maximize outcomes in this vulnerable population.

Acute kidney injury (AKI) is a life-threatening condition that affects approximately 13 million individuals per year, of whom 85% live in low-to-middle-income countries¹. In patients who survive the acute insult, tissue injury is often considered reversible on the basis of the assumption that the surviving tubular epithelial cells will dedifferentiate and proliferate to replace lost cells^{2–4} and/or that tubular progenitor cells will undergo expansion to regenerate necrotic tubule segments⁵. However, the extent of this regenerative process remains ill-defined⁴, and a growing body of evidence indicates that even a mild episode of AKI can substantially increase the risk of developing chronic kidney disease (CKD)⁶, suggesting that kidney regeneration following AKI is limited. The relationship of AKI with CKD is important given the global burden of CKD — a disease that affects approximately 10% of the general population⁷ and has a risk-multiplier effect on cardiovascular morbidity and mortality^{8–11}.

The contribution of fetal events to the development of chronic diseases — such as cardiovascular disease,

obesity, hypertension and CKD — is increasingly recognized^{12–14}. We now understand that stressful events experienced in utero and during early postnatal life can affect organ development and shape susceptibility to disease through a process known as developmental programming¹⁵. One of the first observations of developmental programming was made by David Barker, a British physician, who reported high rates of cardiovascular disease among the poorest regions of England and Wales¹⁶ despite heart disease being considered a condition of affluence. In a study of >15,000 adult individuals, he found an unexpected association between low birthweight (LBW) and cardiovascular disease in adults^{16,17}. We now understand that LBW (defined as birthweight <2,500 g) and preterm birth (defined as birth before 37 weeks of gestation) are associated with fetal malnourishment, abnormal programming of organs including the kidneys and surrogate markers of low nephron number^{18,19}. In humans, nephrogenesis occurs only before birth at term. In infants born at term, nearly

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Key points

- Even after controlling for multiple potential confounders, acute kidney injury (AKI) is an important determinant of morbidity and mortality in critically ill neonates.
- Prematurity and low birthweight (LBW), which are surrogate indices of reduced nephron endowment, might predispose neonates to AKI.
- Prematurity and LBW are associated with several comorbidities that are themselves risk factors for AKI in neonates.
- Neonates with critical illness, especially those born prematurely, often receive medications that might increase susceptibility to toxic renal injury and risk of AKI.
- The identification of pre-gestational risk factors and early intervention during pregnancy, especially in the context of maternal nutrition, as well as careful evaluation of infant exposure to nephrotoxic medications, might limit neonatal AKI, although further research is required to optimize renal development in premature infants and support neonates with AKI.
- Neonates who survive AKI might experience long-term renal dysfunction and should be monitored and screened periodically for chronic kidney disease throughout childhood and young-adult life.

60% of nephrons develop in the third trimester of pregnancy²⁰. Although nephrogenesis might continue in kidneys of preterm infants for up to 40 days after birth, evidence suggests this process is aberrant, leading to abnormal nephron morphology^{20,21}. Observations from autopsy studies have documented lower than average nephron numbers among infants born prematurely or with LBW^{18–20,22} (TABLE 1). These findings support Brenner's hypothesis that disrupted developmental programming in the kidney occurring as a result of maternal stresses experienced during gestation and shortened time to develop a full complement of nephrons ultimately lead to a reduction in nephron number. In turn, this reduced nephron number increases the risk of neonatal AKI and sets up the individual to be at risk of CKD later in life²³. This increased risk of AKI and CKD among individuals born prematurely or with LBW therefore represents an unmet target for preventive interventions.

In this Review, we explore the evidence that intrauterine growth restriction (IUGR), premature birth and LBW contribute to neonatal AKI and the genetic and maternal factors that might influence these fetal outcomes. We also analyse perinatal and postnatal risk factors that might synergize with low nephron endowment and increase the risk of AKI among neonates, and we address approaches to prevent and treat neonatal AKI. Finally, we briefly discuss the long-term sequelae of neonates who survive episodes of AKI.

Epidemiology of neonatal AKI

Our understanding of AKI in critically ill neonates lags behind that of AKI in paediatric and adult populations; however, the past 5 years have seen an intensification of research in this area. Small, single-centre studies in select neonatal groups such as those with very low birthweight (VLBW)^{24–30}, IUGR and preterm birth^{27,31}, congenital heart disease^{32–35}, sepsis³⁶, hypoxic injury^{37–40} and infants who receive extracorporeal membrane oxygenation (ECMO)^{41–43} suggest that AKI is common in critically ill neonates. Infants who develop AKI have worse clinical outcomes than those who do not develop AKI. For example, in a cohort of 229 infants with VLBW (defined as <1,500 g), 18% experienced AKI during their stay

in the neonatal intensive care unit (NICU), and mortality among these neonates was higher than in those without AKI, even adjusting for potential confounders (42% versus 5%)²⁵. Other estimates suggest that 4–40% of extremely low birthweight (ELBW) infants develop AKI. The wide range in the incidence of AKI probably stems from differences in the definition of AKI and the frequency of ascertainment of serum creatinine (SCr) and urine output to define AKI (discussed below)^{27,44,45}. In one cohort, the mortality of ELBW neonates with AKI was 54%, more than double that of ELBW infants without AKI⁴⁴.

These studies and others^{27,31,46} have consistently shown that mortality is higher in infants with AKI than in those without; however, our ability to determine whether AKI is an independent risk factor for mortality after controlling for confounders is limited by sample sizes and study design. In the largest study to date of AKI in neonates, investigators of the Assessment of Worldwide Acute Kidney Epidemiology in Neonate (AWAKEN) study⁴⁷ retrospectively assessed the prevalence of AKI according to gestational age among 2,022 infants admitted to NICUs across 24 sites in 4 countries. Using the modified Kidney Disease: Improving Global Outcomes (KDIGO) definition of AKI for neonates (discussed further below), they identified AKI in 30% of the cohort but reported differences in the incidence of AKI according to gestational age, with AKI occurring in 45% of infants born at ≤29 weeks gestation, in 14% of infants born at 29–36 weeks gestation and in 41% of infants born at >36 weeks gestation. A possible explanation of these findings is that the most premature infants have the highest prevalence of AKI owing to a lack of renal reserve and because they are in the NICU for a long time, where they are exposed to many risk factors for AKI (such as sepsis and nephrotoxic medications). The high prevalence of AKI in the near-term cohort compared with that of neonates born at 29–36 weeks gestation is probably because these infants are very sick. Even after adjusting for multiple confounders, the risk of death among neonates with AKI was more than four times that of neonates without AKI (adjusted OR 4.6, 95% CI 2.5–8.3; $P < 0.0001$); AKI was also associated with more days in the NICU (adjusted days 8.8, 95% CI = 6.9–11.5; $P < 0.001$). These data mirror findings from multicentre studies in other critically ill populations. AKI in neonates is strongly associated with poor outcomes and supports the notion that critically ill patients die 'from' AKI and not simply 'with' AKI.

Challenges with the diagnosis of neonatal AKI

A limitation to epidemiologic studies and those evaluating risk factors for neonatal AKI is the potential for misclassification of AKI, leading to underestimations of AKI incidence. Part of the reason for this misclassification is that no accepted guidelines exist for when measurements of SCr level and urinary output should be obtained. Most studies that have assessed the incidence of AKI in neonates are retrospective, limiting researchers to SCr values available in medical records. Wide differences also exist in the rate of SCr monitoring. For example, the AWAKEN retrospective study⁴⁷ relied on clinical

record data, which varied widely in measurement frequency. The median number of SCr measurements per baby ranged from 1 to 12 per institution, which correlated with the wide range of AKI rates reported by the centres (3–56% among institutions). Not surprisingly, there was a significant correlation between the frequency of SCr monitoring and rates of AKI between institutions.

In addition to variations in SCr and urine output measurement, the methods used to define AKI in neonates are not uniform. SCr level is the most widely used method to define AKI in this population; however, the use of SCr to define AKI in neonates is particularly challenging owing to the obligate cardiovascular and renal adaptations that occur during the transition into the extrauterine environment. Neonatal SCr at birth reflects maternal SCr, but over the following days the neonate establishes its own steady-state SCr level, which is primarily determined by innate kidney function. Kidney function varies greatly by gestational age, as do SCr trajectories and steady-state SCr levels⁴⁸ (FIG. 1). For example, the SCr of a normal-term neonate will initially reflect maternal SCr and improve over the coming days such that by day 5–7 of life, their SCr has reached a nadir. In very premature infants, however, SCr will stay high (or perhaps rise to a degree) for weeks, before decreasing, such that their SCr reaches a nadir at 2–4 weeks of age. In this context, it may be normal for an extremely premature infant without AKI to experience a slight rise in SCr level after birth concomitant with the establishment of stable innate kidney function. A study of ELBW infants showed that 89% of infants born <26 weeks gestational age had a rise in SCr ≥ 0.3 mg/dl (26.52 μ mol/l) over 48 h during the first week of life²⁷. As mentioned

above, a healthy neonate with normal kidney function should experience a steady decline in SCr level after birth. The absence of this normal trajectory could signify a substantial injury, as shown in a study of full-term neonates with asphyxia. In this study, infants whose SCr trajectories did not drop as expected (but did not meet the AKI criteria) were compared with those who had a normal SCr trajectory and those with AKI (defined by an increase in SCr ≥ 0.3 mg/dl (26.52 μ mol/l)). Infants whose SCr trajectories did not drop as expected were much more similar to those with AKI than to those with normal SCr trajectories with regard to multiple clinical outcomes (such as ventilator time, vasopressin use and length of hospital stay) and biological outcomes (as determined by urine biomarkers of kidney injury). This finding suggests that, among full-term infants, an abnormal decline in SCr level or any incline in SCr level during the first postnatal week could be indicative of notable kidney injury⁴⁹. As a consequence, diagnosing AKI in neonates on the basis of a small rise in SCr remains challenging, and thus far this issue is unresolved.

Despite these limitations, the most common definitions of neonatal AKI are based on a modification of the KDIGO definition for children and adults, termed the neonatal modified KDIGO criteria^{31,50}. This definition relies on an absolute increase in SCr level from a previous trough or a decrease in urine output and defines three levels of AKI. The difference between the neonatal modified AKI KDIGO criteria and the KDIGO criteria for AKI in children and adults mainly resides in the definition of the reference SCr level as the lowest previous SCr value (TABLE 2). The neonatal modified KDIGO criteria seem to be able to predict clinical outcomes

Table 1 | Analyses of nephron number in newborn babies with low birthweight or born preterm

Study	Population (n)	Gestational age (weeks)	Birthweight	Glomerular number or radial glomerular counts ^a
Manalich et al. (2000) ¹⁸	Neonates (18)	37.0 \pm 1.05	Low birthweight	Glomerular number: 92.9 \pm 4.85 \times 0.6 mm ² of renal cortex ^b
	Neonates (17)	38.9 \pm 1.29	Normal birthweight	Glomerular number: 105.8 \pm 3.91 \times 0.6 mm ² of renal cortex
Rodriguez et al. (2004) ²⁰	Preterm infants surviving <40 days (17)	24 \pm 2	Extremely low birthweight: 607 \pm 148 g	Radial glomerular counts: 5.6 \pm 0.5
	Preterm infants surviving \geq 40 days (12)	27 \pm 3	Extremely low birthweight: 735 \pm 167 g	Radial glomerular counts: 8.0 \pm 1.2 ^c
	Newborn babies at term (10)	40 \pm 1 ^d	3,216 \pm 643 g ^d	Radial glomerular counts: 10.4 \pm 0.8 ^e
Faa et al. (2010) ²⁴⁹	Preterm infants (12)	25–38	<ul style="list-style-type: none"> • 2 of 12 preterm infants showed a low birthweight • 8 of 12 preterm infants showed an extremely low birthweight, ranging from 665 g to 840 g 	Radial glomerular counts: 5–7
	Newborn babies at term (3)	38–41	Normal birthweight	Radial glomerular counts: 7–9

Studies were performed using tissue samples obtained at autopsy. ^aRadial glomerular counts were obtained by counting the layers of glomeruli, following a straight line beginning in the deepest zone of the cortex and progressing systematically to the renal capsule, in well-oriented areas. Radial glomerular counts were standardized by counting, in every patient, one renal section in four different locations and averaging them. ^b $P < 0.0001$ versus normal birthweight. ^c $P < 0.001$ versus preterm babies surviving <40 days. ^d $P < 0.05$ versus preterm babies surviving <40 days and preterm babies surviving \geq 40 days. ^e $P < 0.001$ versus preterm babies surviving <40 days and preterm babies surviving \geq 40 days.

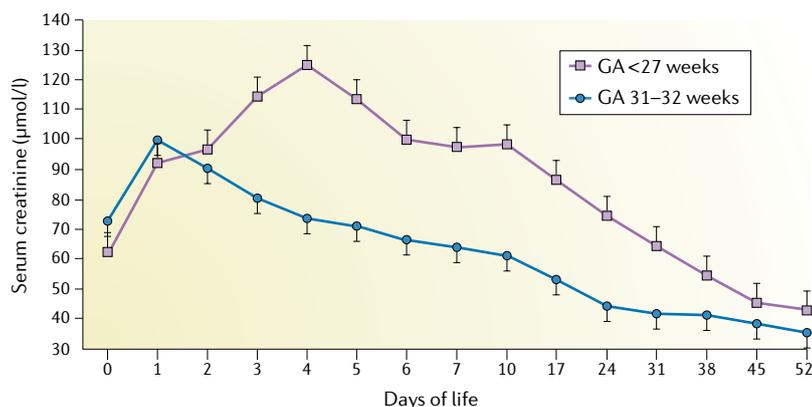


Fig. 1 | Changes in serum creatinine concentrations over the first 52 days of life in preterm neonates (gestational age (GA) <27 weeks and 31–32 weeks). Figure adapted from REF.⁶⁵, Springer Nature Limited.

independently of potential confounders. In 2013, an expert working group from the US National Institutes of Health (NIH)-sponsored Neonatal AKI Workshop recommended that researchers use the KDIGO definition to define neonatal AKI to enable comparison between studies⁵¹. However, despite increased use of the modified neonatal KDIGO criteria over the past few years, it must be noted that this definition was adapted from the adult literature⁵² and has not been validated in neonates. The NIH working group emphasized that these modified criteria or any new definition of neonatal AKI need to be tested against hard end points such as mortality and the development of CKD.

In the absence of this critical step, the field risks using inappropriate definitions to describe the natural history of kidney disease in neonates, which could lead to the failure of intervention studies⁵¹. Beyond the need to test these criteria in an appropriate population, we suggest that consideration should be given to three important components of the criteria. First, we propose that the use of both percentage SCr rise and absolute SCr rise might add complexity to the neonatal AKI definition without benefit. Perhaps an absolute rise in SCr would be more informative. Second, we note that the use of urinary output as a criterion for neonatal AKI has not been rigorously tested and suggest that studies specifically address the utility of urinary output as a marker of AKI in neonates. Third, our increasing understanding of the impact of fluid overload on outcomes suggests that incorporation of fluid overload into the definition of neonatal AKI could optimize the ability to predict outcomes.

Last, as in adults, kidney injury in neonates will not necessarily lead to an immediate increase in SCr level, with SCr level increasing only once 25–50% of renal function is lost⁴⁸. SCr level is therefore not an ideal biomarker for the early detection of AKI in infants, further complicating the diagnosis of AKI in this population. Novel biomarkers to enable earlier identification of AKI include urine neutrophil gelatinase-associated lipocalin (NGAL), cystatin-C, and kidney injury molecule 1 (KIM1; also known as HAVCR1)^{53–59}. However, although promising, the diagnosis of AKI in neonates remains based on a rise in SCr level or changes in urine output.

Chorioamnionitis

Also known as intra-amniotic infection, it is an inflammation of the fetal membranes (amnion and chorion) due to a bacterial infection.

Risk factors for neonatal AKI

Preterm birth and LBW are associated with an increased risk of AKI in newborn babies⁴⁷. AKI is particularly common among critically ill neonates in intensive care units (ICUs) and is an important determinant of morbidity and mortality in these infants, many of whom were born with LBW or prematurely³¹. Such infants are more likely than full-term or normal-birthweight infants to have been exposed during intrauterine life to factors that can induce fetal distress, including IUGR, infection, placental insufficiency or maternal medications^{26,31,60–62}.

Prematurity and LBW increase the risk of neonatal AKI because impaired nephrogenesis and low nephron endowment^{26,27,31,60,62,63} can result in impaired renal tubular function and low glomerular filtration rate (GFR) and can disrupt renal vasoregulatory processes through ischaemia–reperfusion injury, leading to high renal vascular resistance^{27,61,64}. Together, these outcomes increase the vulnerability of the kidney to renal injury after birth^{65,66}.

Interestingly, compared with premature infants born to mothers without pre-eclampsia, premature infants born to mothers with pre-eclampsia are protected against AKI⁶⁷. The mechanism for this protective effect of pre-eclampsia is unclear but might involve changes in the renal physiology of the neonates (potentially as a result of intermittent renal ischaemia–reperfusion in utero). Alternatively, this observation could reflect the fact that infants born to pre-eclamptic mothers are ‘healthy’ but delivered early to prevent maternal morbidity, in contrast to infants that are born prematurely because of fetal distress such as chorioamnionitis. Because premature and LBW infants are at increased risk of developing AKI, it is important to understand how pre-gestational and gestational maternal factors affect intrauterine kidney development as well as postnatal risk factors in order to identify preventive and therapeutic interventions.

Pre-gestational risk factors

Socio-economic factors. Socio-economic disadvantage, whether defined by income, education or occupational status, is associated with an increased risk of giving birth to a preterm^{68–70} or LBW⁷¹ baby. Several pathways linking maternal social deprivation and neonatal outcomes have been proposed. For instance, chronic exposure to psychological stress as a consequence of social deprivation might contribute to the use of behavioural coping mechanisms such as alcohol abuse or tobacco consumption, which are known to influence gestational age at birth as well as birthweight⁷². Chronic stress and lack of social support might also affect birth outcomes through neuroendocrine mechanisms, for example, through the release of noradrenaline and cortisol, which have been linked to preterm labour and delivery⁷².

Age. Both young and advanced maternal age are associated with less favourable birth outcomes. A study that pooled data from five low-to-middle-income countries found that, compared with women aged 20–24 years, young mothers (≤ 19 years) had an increased risk of giving birth to an LBW (adjusted OR 1.18, 95% CI 1.02–1.36) or preterm (adjusted OR 1.26, 95% CI 1.03–1.53) infant, whereas mothers aged ≥ 35 years had an increased risk

Table 2 | Proposed neonatal modified AKI KDIGO classification

Stage	Serum creatinine	Urine output
0	No change in serum creatinine or rise <0.3 mg/dl	≥0.5 ml/kg per h
1	Serum creatinine rise ≥0.3 mg/dl within 48 h or serum creatinine rise ≥1.5–1.9 × reference serum creatinine ^a within 7 days	<0.5 ml/kg per h for 6–12 h
2	Serum creatinine rise ≥2.0–2.9 × reference serum creatinine ^a	<0.5 ml/kg per h for ≥12 h
3	Serum creatinine rise ≥3.0 × reference serum creatinine ^a or serum creatinine ≥2.5 mg/dl (221 μmol/l) ^b or receipt of dialysis	<0.3 ml/kg per h for ≥24 h or anuria for ≥12 h

Differences between the proposed neonatal modified acute kidney injury (AKI) Kidney Disease: Improving Global Outcomes (KDIGO) criteria and KDIGO criteria for AKI in children and adults include the following: ^areference serum creatinine is defined as the lowest previous serum creatinine value, and ^ba serum creatinine value of 2.5 mg/dl (221 μmol/l) represents a glomerular filtration rate of <10 ml/min/1.73 m². Reproduced with permission from REF.³¹, AAP News and Journals Gateway.

of having a preterm child (adjusted OR 1.33, 95% CI 1.05–1.67)⁷³.

Body weight. The effect of pre-pregnancy body mass index (BMI) on neonatal outcomes has also been studied⁷⁴. A meta-analysis of >1 million pregnancies found that singletons born to underweight women (as defined by the original study) were at higher risk of being preterm (adjusted relative risk (RR) 1.29, 95% CI 1.15–1.46) and LBW (adjusted RR 1.64, 95% CI 1.38–1.94) than singletons born to healthy-weight mothers⁷⁵. This relationship between low maternal weight, LBW and prematurity might be explained by the direct effects of nutrient insufficiency on fetal growth and the duration of gestation or by indirect effects of risk factors associated with low maternal weight, such as smoking or the existence of medical conditions⁷⁵. At the other end of the spectrum, an accumulating body of evidence indicates that women who are obese or overweight before pregnancy have an increased risk of adverse neonatal outcomes, including high birthweight and being large for gestational age^{76,77}. Although the pathophysiological mechanism or mechanisms by which maternal high body weight adversely affects perinatal outcomes are not clear, insulin resistance associated with obesity is likely to have an important role⁷⁸.

Kidney dysfunction and diseases. The prevalence of CKD is around 3% among women of childbearing age⁷⁹. Data from population-based studies⁸⁰, large prospective cohort studies⁸¹ and a meta-analysis⁸² indicate that infants born to women with CKD have worse neonatal outcomes than infants of women without CKD, including preterm birth^{80–82}, LBW^{80,82} and being small for gestational age^{81,82}. The rates of these complications increased with severity of CKD⁸¹. Adverse neonatal outcomes have also been reported for specific CKD aetiologies. For example, women with diabetic nephropathy and an SCr level >1.5 mg/dl (132.6 μmol/l) in the first trimester of pregnancy have a higher risk of having a VLBW baby (44.4% versus 5.1%; *P* = 0.004) and delivering before 32 weeks gestation (44.4% versus 7.7%; *P* = 0.020) than women with an SCr level ≤1.0 mg/dl (88.4 μmol/l)⁸³. A retrospective analysis of 43 women with diabetic

nephropathy and median SCr levels of 0.77 mg/dl (68 μmol/l) before pregnancy reported much higher rates of poor pregnancy outcomes than anticipated on the basis of the degree of renal dysfunction, including pre-eclampsia in 42% of patients and preterm birth in 77% of infants, suggesting that aetiology-specific factors, such as hyperglycaemia, also drive adverse neonatal outcomes⁸⁴.

Two studies published in 2018 reported higher rates of preterm birth (RR 3.2, 95% CI 2.5–4.1) and LBW (RR 4.2, 95% CI 3.4–5.3) among offspring of patients with systemic lupus erythematosus than among offspring of population controls^{85,86}, although available evidence suggests that the risk of pregnancy complications for women with inflammatory connective tissue diseases has decreased over the past few decades⁸⁷. Notably, the effect of lupus nephritis on neonatal outcomes depends on the activity of renal disease. Active lupus nephritis during pregnancy is associated with a higher incidence of maternal⁸⁸ and neonatal complications^{86,88,89} than is seen in those with inactive disease. Hypocomplementaemia or positivity for antibodies to double-stranded DNA consistently correlate with increased rates of miscarriage and preterm birth⁹⁰. Women with a combination of high clinical disease activity and serological markers of systemic lupus erythematosus face the highest risk of adverse pregnancy outcomes⁹⁰.

Chronic hypertension complicates about 1–4% of pregnancies⁹¹. A meta-analysis involving >750,000 women from studies in the USA found that the incidence of superimposed pre-eclampsia (RR 7.7, 95% CI 5.7–10.1), preterm delivery (RR 2.7, 95% CI 1.9–3.6), LBW (RR 2.7, 95% CI 1.9–3.8), NICU admission (RR 3.2, 95% CI 2.2–4.4) and perinatal death (RR 4.2, 95% CI 2.7–6.5) was higher in pregnant women with chronic hypertension than in those from the US national population data set⁹².

Interval between pregnancies. In addition to the aforementioned pre-gestational conditions, both short and long intervals between pregnancies are associated with unfavourable neonatal outcomes, including preterm birth, LBW and neonates small for gestational age^{93,94}. By analysing two interpregnancy intervals per mother in a sample of 40,441 mothers, Ball et al. showed that an interpregnancy interval <6 months was associated with a very small increase in the risk of having a preterm (adjusted OR 1.07, 95% CI 0.86–1.34), LBW (adjusted OR 1.03, 95% CI 0.79–1.34) or small for gestational age (adjusted OR 1.08, 95% CI 0.87–1.34) child compared with the reference interpregnancy interval of 18–23 months. This study enabled each mother to act as her own control for risk factors that vary greatly among women but tend to persist between pregnancies, such as genetic predisposition, lifestyle or social conditions⁹⁵.

Gestational risk factors

Assisted reproductive technologies. Worldwide, >5 million babies have been born as a result of assisted reproductive technologies (ART), including in vitro fertilization^{96,97}. Pregnancies conceived using ART are at increased risk of adverse perinatal outcomes, with

Hypocomplementaemia
A condition in which one of the components of complement is lacking or reduced in the blood.

Spontaneously conceived
Conception without the use of any medical interventions; also referred to as natural conception.

much of this risk being ascribed to multiple-gestation pregnancies. Indeed, twins resulting from ART pregnancies have a greater than tenfold increase in the odds of being premature (OR 11.84, 95% CI 10.56–13.27) or LBW (OR 10.68, 95% CI 9.45–12.08) than singletons from ART pregnancies⁹⁸. Of note, however, even singleton ART pregnancies are subject to higher rates of preterm birth than spontaneously conceived singletons (RR 2.13, 95% CI 1.26–3.61)⁹⁹. Subfertility and/or its causes, the controlled ovarian hyperstimulation before ART or the ART procedure itself have been suggested to influence the neonatal outcomes of singleton pregnancies resulting from in vitro fertilization^{100,101}.

Genetic susceptibility. A substantial body of evidence supports a role for genetic factors — mainly from the maternal genome — in the regulation of fetal development^{63,102–106}. A large genome-wide association study (GWAS) of samples from >43,000 women of European ancestry, replicated in samples from an additional 8,643 women from three Nordic Birth studies^{107,108}, identified six loci — *EBF1*, *EEFSEC*, *AGTR2*, *WNT4*, *ADCY5* and *RAP2C*, which encode proteins with functions consistent with the timing of birth, such as maintaining redox status and antioxidant defences, and in modulating uteroplacental circulation — as being significantly associated with gestational duration¹⁰⁷. Notably, three of these loci (*EBF1*, *EEFSEC* and *AGTR2*) were associated with spontaneous preterm birth. The mechanisms by which these loci affect spontaneous birth remain speculative; it is unclear whether *EBF1* modulates pregnancy-specific pathways or general cardiovascular or metabolic signals that influence gestation. Variants at the *EEFSEC* locus might affect incorporation of the cysteine analogue, selenocysteine, into selenoproteins, which in turn might affect cellular homeostasis functions favouring spontaneous preterm birth¹⁰⁷. Variants within the *AGTR2* locus contribute to the risk of pre-eclampsia¹⁰⁹, which is a possible cause of premature delivery. However, these Nordic Birth studies excluded preterm births associated with pre-eclampsia, indicating a direct association between *AGTR2* variants and prematurity. IUGR is also in part genetically regulated, with various polymorphisms thought to have a role in different ethnic groups¹¹⁰. For example, polymorphisms in maternal and fetal genes that encode proteins involved in extracellular matrix metabolism affect the risk of being born small for gestational age¹¹¹, whereas in the placenta, polymorphism in the promoter of *SERPINA3* — a gene that encodes a protein involved in a wide range of biological processes, including coagulation, inflammation and wound healing — is associated with IUGR¹¹².

Epigenetic regulation of pregnancy outcomes. Gene expression can be modulated through epigenetic processes in response to environmental, nutritional and lifestyle factors¹¹³; available evidence suggests that epigenetic modifications at around the time of conception and during gestation contribute to IUGR by modulating gene expression through effects on histone modifications^{114,115}, DNA methylation^{116–119} and microRNA expression^{120,121}.

Maternal caloric restriction can affect the health not only of the direct offspring but also of future generations^{122,123}, although the role of epigenetic inheritance in this context remains unclear. In a mouse model of gestational undernutrition characterized by LBW, glucose intolerance and reduced pancreatic function for two subsequent generations, maternal caloric restriction resulted in hypomethylation of discrete loci in sperm and somatic tissues of first-generation male offspring. However, this differential methylation pattern did not persist in somatic tissues of the second-generation progeny, indicating that the LBW and metabolic phenotype observed in this generation did not result from long-term heritable memory of compromised male germ line development and DNA methylation reprogramming¹²⁴. These data suggest that epigenetic mechanisms other than DNA methylation, such as histone modifications or small non-coding RNAs, are responsible for the persistence of the altered metabolic phenotype in subsequent generations¹²⁵.

Nutrition. As mentioned in the previous section, neonatal outcomes also depend on maternal nutritional status. Adequate gestational weight gain is crucial for meeting maternal and fetal nutritional needs during pregnancy, and both insufficient and excessive gestational maternal weight gain adversely affect neonatal outcomes. A 2017 meta-analysis of >1,300,000 pregnancies reported that gestational weight gain below that recommended by the 2009 Institute of Medicine (IOM) guidelines¹²⁶ was associated with a higher risk of preterm birth infants (OR 1.70, 95% CI 1.32–2.20) and of the neonate being small for gestational age (OR 1.53, 95% CI 1.44–1.64)¹²⁷. Conversely, women who gained more weight than recommended by the IOM had an increased risk of Caesarean delivery (OR 1.30, 95% CI 1.25–1.35) and of the neonate being large for gestational age (OR 1.85, 95% CI 1.76–1.95)¹²⁷. The composition of maternal diet during gestation can also influence fetal growth and birth size. Similar to experimental studies, which have mostly shown that maternal protein restriction leads to reduced birthweight of offspring¹²⁸, some, but not all, human studies have shown an association between low protein intake during pregnancy and lower birthweight^{129–133}. Differences in baseline nutritional status between study populations, the gestational time at which diet was evaluated and methods for dietary ascertainment might account for inconsistent findings between studies.

Smoking and alcohol consumption. Maternal lifestyle, such as alcohol and tobacco consumption habits, also affects birth outcomes. It is now well established that heavy alcohol consumption during pregnancy increases the risk of giving birth to preterm, LBW and small for gestational age infants¹³⁴. However, lack of consensus exists regarding the effect of low to moderate maternal alcohol consumption, with studies and evidence reviews reporting a broad spectrum of effects associated with light alcohol consumption^{135–138}. Similar to heavy alcohol consumption, tobacco smoking during pregnancy is associated with an increased risk of having

Peripartum period

The peripartum period spans from the last month of gestation to 5 months after delivery.

Perinatal asphyxia

Also known as birth asphyxia, it is the failure to initiate and sustain respiration at birth.

Diaphragmatic hernia

The presence of a defect in the diaphragm that allows herniation of some abdominal viscera into the thoracic cavity, causing respiratory distress at birth with or without pulmonary hypoplasia and/or hypertension.

preterm, LBW and small for gestational age infants^{139–141}. Nicotine, the major tobacco alkaloid, has been posited to adversely affect gestational parameters, mainly by inducing vasoconstriction of uteroplacental blood vessels, which eventually reduces placental blood flow and the delivery of nutrients and oxygen to the fetus¹⁴². Intriguingly, mounting evidence suggests that derangements in epigenetic placental and fetal (re)programming are one mechanism involved in the association between prenatal tobacco exposure and fetal growth impairment^{143–145}.

Exposure to nephrotoxic medications. Maternal exposure to angiotensin-converting enzyme (ACE) inhibitors and angiotensin type 1 receptor antagonists can impair the development and function of the perinatal kidney¹⁴⁶, leading to varying degrees of renal papillary atrophy, impaired urinary concentrating ability¹⁴⁷ and renal failure¹⁴⁸ depending on the timing and duration of exposure. Similarly, nonsteroidal anti-inflammatory drugs, such as indomethacin, can cause renal vasoconstriction by inhibiting cyclooxygenases and prostaglandin synthase¹⁴⁹ and might adversely affect renal function in the developing fetus. Fetal urine output declines markedly within 5 h of indomethacin administration to pregnant women — an effect that has also been documented following antenatal exposure to ibuprofen and ketoprofen¹⁵⁰. Notably, women who are at risk of preterm delivery are sometimes administered indomethacin in the peripartum period, which can predispose neonates to transient or persistent oliguria and AKI^{150–152}.

Pregnancy-related complications. Pregnancy-related complications can also affect neonatal outcomes. In particular, pre-eclampsia affects about 3–5% of pregnancies¹⁵³ and is associated with an increased risk of premature birth (adjusted OR 2.86, 95% CI 2.68–3.06) and LBW in infants (adjusted OR 2.32, 95% CI 2.16–2.50)¹⁵⁴. Notably, both pre-eclampsia and LBW are independent risk factors for recurrence of pre-eclampsia and LBW in subsequent generations, providing evidence for the intergenerational impact of developmental programming¹⁵⁵.

Postnatal risk factors for AKI

As mentioned earlier, premature and LBW neonates are at increased risk of AKI at least in part owing to impaired nephrogenesis and low nephron endowment¹⁵⁶. Premature and LBW infants are also often affected by comorbidities such as sepsis, necrotizing enterocolitis, use of nephrotoxic medications and dehydration due to excessive urine output¹⁵⁷ such that the comorbidities themselves are risk factors for AKI. Moreover, despite being born with a full complement of nephrons, critically ill near-term and term neonates are at increased risk of developing AKI and its sequelae. Most cases of AKI in neonates are multifactorial, resulting from a combination of sepsis and reduced renal blood flow secondary to a decrease in intravascular volume (for example, from blood loss, excessive gastrointestinal losses and increased insensible fluid loss in premature neonates with immature skin)⁶⁰.

Cardiac and respiratory risk factors. Perinatal asphyxia resulting from deprivation of oxygen is one reason for ICU admission that is associated with an increased risk of neonatal AKI. In one single-centre study, AKI occurred in 38% of 96 asphyxiated neonates undergoing therapeutic hypothermia³⁹. The incidence of AKI was related to the extent of perinatal asphyxia, ranging from 9.1% to 56% among infants with moderate or severe asphyxia, respectively¹⁵⁸.

Cardiac and respiratory involvement in neonates, including complex congenital heart diseases that affect the systemic circulation, and the need for interventions, such as cardiopulmonary bypass surgery, medications to maintain blood pressure, high-frequency ventilation and ECMO, are also associated with neonatal AKI^{159–161}. A multicentre study reported that AKI occurred in 26% of neonates requiring ECMO for non-cardiac reasons. After adjustment, AKI in this population was associated with a 3.2-fold increase in mortality compared with neonates who did not develop AKI⁴¹. Similar findings were reported for neonates with congenital diaphragmatic hernia on ECMO, in whom AKI occurred in 71%, with 73% mortality in those with the highest stage of AKI, defined as a doubling of SCr (stage 2 or higher AKI by Acute Kidney Injury Network (AKIN) criteria)⁴².

Sepsis. Neonatal sepsis is a cause of substantial morbidity and mortality. A study from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) National Research Network estimated the overall rate of early-onset sepsis, defined as a positive blood or cerebrospinal culture <72 h following birth, to be 0.98 cases per 1,000 live births. Infection rates were inversely associated with gestational age and birthweight (affecting 10.96 per 1,000 live births for infants with birthweights of 401–1,500 g, 1.38 per 1,000 live births for infants with birthweights of 1,501–2,500 g and 0.57 per 1,000 live births for infants with birthweights >2,500 g)¹⁶². An immature immune system and need for invasive medical procedures (for example, prolonged intravenous access and endotracheal intubation) that impair barrier and clearance functions place preterm infants at increased risk of hospital-acquired infections¹⁶³. In addition, the humoral immune response is considerably reduced in preterm infants because transplacental passage of maternal IgG antibodies begins at about 13 weeks of gestation, with the largest amount being transferred during the third trimester¹⁶⁴.

Sepsis is a major cause of AKI in neonates, with some studies estimating that sepsis contributes to 78% of AKI cases^{28,165–167}. In a cohort of 200 full-term neonates with sepsis, 26% developed AKI. Infants that developed AKI had the lowest birthweights of the cohort and were more likely than infants who did not develop AKI to also develop septic shock in addition to other comorbidities such as meningitis and disseminated intravascular coagulation³⁶. The predisposition of septic neonates to AKI has been attributed to hypotension associated with systemic inflammation¹⁶⁸; however, the occurrence of AKI in septic neonates with normal systemic blood

Box 1 | Commonly used nephrotoxins

Various nephrotoxic agents are commonly administered to critically ill neonates. These agents and their renal effects are detailed below.

Antimicrobial and antimycotic medications**Aminoglycosides**

- Inhibition of lysosomal phospholipase and increased oxidative stress in the proximal tubule
- Intrarenal vasoconstriction
- Mesangial cell contraction in glomeruli

Amphotericin B

- Increased epithelial membrane permeability in the distal tubule
- Intrarenal vasoconstriction
- Inappropriate activation of tubuloglomerular feedback

Antiviral medications**Acyclovir**

- Intratubular crystal deposition
- Tubular obstruction

Nonsteroidal anti-inflammatory drugs**Indomethacin, ibuprofen and ketoprofen**

- Acute interstitial nephritis
- Inhibition of vasodilator prostaglandin production
- Glomerular filtration rate decline

Intravenous immunoglobulins

- Osmotic injury caused by the sucrose contents of the intravenous immunoglobulin formulations

Radiocontrast agents

- Increased oxidative stress in the tubules
- Intrarenal vasoconstriction

pressure and renal blood flow suggests a direct effect of sepsis on the kidney, possibly through dysregulation of the microcirculation^{168–171}.

Nephrotoxic agents. Nephrotoxic agents deserve particular consideration in terms of their role in increasing AKI risk. Critically ill neonates, who are already at increased risk of developing AKI, often receive medications that further increase susceptibility to AKI^{46,62,152}. Many of these medications (for example, ibuprofen and gentamicin) are predominantly cleared through renal filtration and secretory pathways. Impairments in these clearance pathways lead to progressive increases in drug concentrations in the tubular lumen and might promote nephrotoxicity^{46,152}. Interestingly, term neonates might be more susceptible than premature neonates to drug-induced nephrotoxicity because the unique mechanisms of the immature tubular transport system — which is unable to resorb the nephrotoxic medication into the cell — are thought to provide some protection against the nephrotoxic effects of agents that are cleared via renal tubular transport pathways¹⁷². However, studies in rats suggest that the administration of nephrotoxic medications to preterm progeny impairs any ongoing postnatal nephrogenesis¹⁷³. This observation is relevant given that most therapeutic agents used in the NICU have not been tested for safety, dosing and efficacy in infants and are not specifically labelled for use in neonates. Of interest, a study of paediatric labelling changes

to the US Food and Drug Administration (FDA) registry as a result of changes to federal legislation found that only 24 of >400 (6%) such changes made between 1997 and 2010 provided new information relating to the use of these drugs in neonates¹⁷⁴. The need for further information about the nephrotoxicity of medications given to neonates is highlighted by a 2014 epidemiologic study of 107 VLBW infants, which found that these neonates were frequently exposed to potentially nephrotoxic medications during their stay in the ICU, with 87% of neonates receiving at least one potentially nephrotoxic compound for an average treatment duration of 2 weeks⁴⁶. The greatest exposure occurred among the smallest and most immature neonates and in those who experienced AKI.

Available evidence suggests that a number of nephrotoxic agents are commonly used in the NICU (BOX 1). Aminoglycosides, which are the mainstay treatment for neonates with suspected sepsis or documented severe Gram-negative infections, accumulate in the proximal tubules, where they inhibit lysosomal phospholipase, disrupt mitochondrial ATP production and promote oxidative stress, leading to cell death^{175–177}. In addition to their toxic effects on the tubular epithelium, evidence also indicates that aminoglycosides cause intrarenal vasoconstriction and glomerular mesangial cell contraction, which eventually impairs glomerular haemodynamics¹⁷⁸. As a result, aminoglycoside nephrotoxicity leads to a number of electrolyte abnormalities and, in the most severe cases, acute tubular necrosis, oliguria and renal failure in LBW neonates or in those exposed concomitantly to other nephrotoxic drugs^{175,179}.

Amphotericin B is commonly used in critically ill neonates to prevent mycotic infections¹⁸⁰; antimycotic drugs exert nephrotoxic effects in the distal tubule and cause renal vasoconstriction^{181,182}. By inserting into cell membranes¹⁸², amphotericin B also increases the membrane permeability of macula densa cells to sodium chloride, leading to inappropriate tubuloglomerular feedback, afferent arteriolar vasoconstriction and GFR decline¹⁸³. Although incompletely understood, these mechanisms account for the electrolyte abnormalities and renal function impairment seen with administration of amphotericin B, which in neonates are usually transient but can be associated with considerable morbidity¹⁸⁴. Liposomal formulations of amphotericin B, developed to reduce toxicity, have been reported by some studies to be less nephrotoxic in premature neonates, with the incidence of nephrotoxicity ranging from 0% to 20%^{185–187}; however, the lower nephrotoxicity of the liposomal formulations than of conventional formulations is not widely accepted¹⁸⁶.

In addition to other antimicrobial and antiviral medications, as well as intravenous immunoglobulins, which can all cause nephrotoxicity (BOX 1), neonatologists and intensivists should consider the risk of AKI associated with the use of radiocontrast agents. Although the mechanisms of contrast-induced nephrotoxicity are incompletely understood, animal studies suggest that hypoxic medullary injury has a critical role¹⁸⁸.

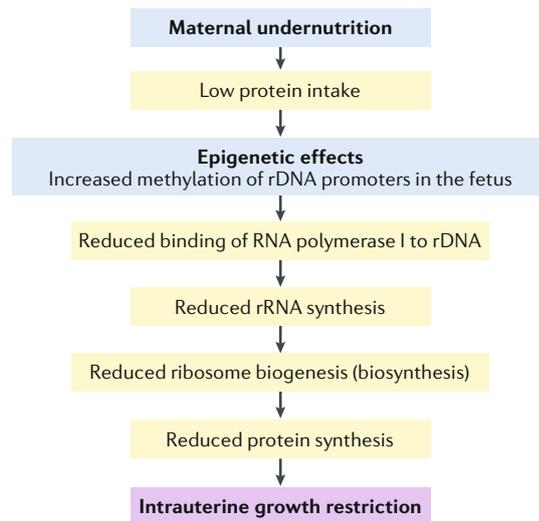


Fig. 2 | Maternal diet regulates epigenetic processes that influence fetal growth as demonstrated by studies in mice fed a low-protein diet during early gestation. Low protein intake in early pregnancy might increase the extent of methylation on the promoter of ribosomal DNA (rDNA) in the fetus. This increased methylation reduces the binding of the enzyme RNA polymerase I to rDNA, thereby reducing ribosomal synthesis and eventually ribosomal biogenesis. As a result, fetal protein synthesis is downregulated and intrauterine growth is impaired. rRNA, ribosomal RNA.

Management of maternal risk factors

The early identification of risk factors that increase the risk of preterm birth and LBW — including genetic pre-gestational and gestational risk factors — is essential to identify approaches to reduce the risk of these adverse pregnancy outcomes^{189–191}.

Macronutrients and micronutrients, including vitamins, calcium and zinc, influence fetal phenotypic adaptation by influencing the availability of methyl donors and mechanisms promoting DNA stability^{192–195} and could therefore be considered a nutritional intervention to promote intrauterine growth. This possibility is supported by findings from experimental animal studies that have highlighted the importance of maternal diet in regulating epigenetic processes that influence fetal growth^{196–198}. These processes are particularly relevant in the periconceptional period, as exemplified by the finding that a low-protein diet fed to mice specifically during the last few days of oocyte maturation¹⁹⁹ or during the short time of preimplantation embryo development^{200,201} induced responses in the placenta through epigenetic mechanisms that affected the rate of ribosome biogenesis, eventually affecting protein synthesis and intrauterine fetal growth^{202,203}. Indeed, administration of a low-protein diet downregulates expression of ribosomal RNA in mice — an effect that was reversed upon restoration of a normal diet²⁰⁴. Although the exact mechanisms by which protein insufficiency affects ribosome biogenesis are unclear, it has been suggested that the concentration of nutrients within the uterus regulates the extent of methylation on the promoter of ribosomal DNA, which thereby affects its ability to

interact with RNA polymerase I and modulates ribosome biogenesis²⁰⁴. Evidence also suggests that administration of a low-protein diet to pregnant mice modifies the trophoblast phenotype to regulate fetal growth by enhancing the transfer of nutrients to the fetus, although whether epigenetic processes are involved in this effect has not been investigated²⁰⁵ (FIG. 2). Notably, the presence of these epigenetic alterations has been documented in rural Gambians, who experience dramatic nutritional challenges during the rainy season. These seasonal variations affect the methyl-donor nutrient intake of mothers and can alter tissue DNA methylation at conception^{206,207}, but the effects of these epigenetic alterations on pregnancy outcomes have not been studied.

Evidence also suggests that administration of a protein-restricted diet to pregnant rats induces transcription of the genes encoding nuclear receptors glucocorticoid receptor and peroxisome proliferator-activated receptor- α (PPAR α) in the liver of the offspring by inducing hypomethylation of their respective promoters²⁰⁸, possibly by reducing DNA methyltransferase 1 expression²⁰⁹. Supplementation of the protein-restricted diet with folic acid prevented promoter hypomethylation and attenuated the increase in glucocorticoid receptor and PPAR α expression²⁰⁸. In addition, the impairment of placental growth in malnourished pregnant rats has been attributed to cell apoptosis secondary to reduced energy substrates for mitochondrial function¹⁹², but its relationship with epigenetic alterations remains unclear. Together, these observations suggest that nutritional changes affect epigenetic processes such as DNA methylation and histone deacetylation to regulate the expression of factors involved in stress and metabolic responses, such as the glucocorticoid receptor and PPAR α , and might be a target for therapeutic intervention¹⁹².

Indeed, improving nutritional status during pregnancy can positively affect birth outcomes. A 2015 analysis of 23 systematic reviews of randomized controlled trials of nutritional interventions given before and during pregnancy showed that oral supplementation with vitamin A, low-dose calcium, zinc and multiple micronutrients (defined as supplements that contain more than three micronutrients²¹⁰) was associated with a reduction in the risk of LBW²¹¹. Nutritional interventions containing multiple micronutrients and supplements with balanced protein–energy content also reduced the risk of neonates being born small for gestational age, whereas zinc or long-chain *n*-3 fatty acid supplementation significantly decreased the risk of preterm birth. Most evidence in support of these interventions, however, comes from a small number of trials, often with a limited number of participants, indicating the need for larger trials to reach more robust conclusions about the impact of nutritional interventions on pregnancy outcomes²¹¹. Of note, only few human studies to date have examined the contribution of epigenetic modifications to the relationship between maternal diet supplementation and birth outcomes. One study analysed the methylome of cord blood samples from 12 women, of whom 8 were given folic acid supplementation during pregnancy, and found a significant correlation between

the methylation status of 16 CpG loci with birthweight percentile, cord plasma homocysteine concentrations (an inverse measure of folate status) and global DNA methylation²¹². Although this study did not investigate the mechanism or mechanisms that link variations in DNA methylation to birthweight, the findings support an association between folic acid supply, changes in the epigenome and offspring phenotype.

Management of neonatal AKI

Despite the burden of AKI, no approved pharmacologic agents exist to treat neonates who develop AKI. Interventions are therefore confined to the management of sequelae associated with the acute renal insult, including the use of renal replacement therapy (RRT) in the form of dialysis to support the neonate while the kidney is unable to maintain proper fluid and electrolyte homeostasis.

Particular care should be taken to monitor fluid balance and the quantity of both fluid input and output documented. Neonates with AKI are usually non-oliguric, but in some cases infants develop oliguric or anuric renal failure that leads to fluid overload²¹³, which is an independent risk factor for morbidity and mortality independent of the severity of neonatal illness^{214,215}. In the setting of oliguric or anuric renal failure, diuretics are frequently used in an attempt to maintain urine output, despite the absence of specific guidelines for this treatment in infants with AKI. Patients who are not responsive to initial treatment with 1–1.5 mg/kg furosemide do not benefit from further diuretics and should be considered for early RRT^{216,217}. Limited evidence also suggests that in VLBW²¹⁸ and preterm infants

with AKI²¹⁹, the beneficial effect of the loop diuretic bumetanide on urine output occurs at the expense of worsening renal failure, indicated by an increase in SCr level, suggesting that diuretics should be used with caution in these patients. Serum electrolyte disturbances should also be adequately monitored and properly managed, in particular hyperkalaemia, a life-threatening complication of AKI.

The lack of any specific treatment for AKI has led to renewed interest in identifying interventions to prevent AKI in at-risk patients. The adenosine receptor antagonist theophylline has demonstrated renal benefits in randomized studies of neonates with perinatal asphyxia, possibly by inhibiting adenosine-induced vasoconstriction and improving renal blood flow^{220–223}. On the basis of available evidence, this methylxanthine is recommended by KDIGO for routine use in neonates with perinatal asphyxia who are at high risk of AKI⁵², but the potential neurologic adverse effects of the drug should be considered carefully²²⁴. Further studies on theophylline should be performed in the context of new clinical guidelines for systemic hypothermia in asphyxiated infants to determine whether the addition of this or other agents can reduce short-term or long-term morbidity and mortality.

Another methylxanthine, caffeine, a medication commonly used to assist in the extubation of premature infants²²⁵, might also protect against AKI. In the AWAKEN cohort, premature infants who received caffeine had much lower rates of AKI than those who did not receive caffeine (11.2% versus 31.6%; $P < 0.01$). Caffeine remained associated with reduced odds of developing AKI even after multivariable adjustment (adjusted OR 0.2, 95% CI 0.11–0.34), indicating that

Table 3 | Findings from long-term studies of CKD sequelae in term and preterm NICU graduates

Study	Aetiology (n)	Mean years at follow-up (range)	CKD rate	Method to assess CKD	Comparison of outcomes for survivors of AKI compared with those without AKI
Full-term infants					
Polito et al. (1998) ²⁵⁷	Asphyxia (6)	8.0 (6.5–19)	83%	eGFR <90 ml/min/1.73 m ² and BP >95th percentile	NA
Zwiers et al. (2014) ²⁵⁸	ECMO (169)	8.2 (5.2–12.1)	32%	eGFR <90 ml/min/1.73 m ² , BP >95th percentile and proteinuria	More CKD
Cooper et al. (2016) ²⁵⁹	CHD (51)	8.0 (6.9–9.6)	9%	eGFR <90 ml/min/1.73 m ²	Higher urinary IL-18 and liver-type fatty acid binding protein
Premature infants					
Abitbol et al. (2003) ²⁴²	ELBW (20)	7.5 (3.2–18.5)	45%	eGFR <75 ml/min/1.73 m ²	NA
Bruel et al. (2016) ²⁶⁰	<33 week GA (74)	6.6 (3.0–10.0)	30%	eGFR <90 ml/min/1.73 m ² , BP >95th percentile and albuminuria	Lower total kidney volume
Harer et al. (2017) ²⁵¹	VLBW (34)	5.0 (4.0–6.0)	44%	eGFR <90 ml/min/1.73 m ² , BP >95th percentile and albuminuria	More CKD

AKI, acute kidney injury; BP, blood pressure; CHD, congenital heart disease; CKD, chronic kidney disease; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; ELBW, extremely low birthweight (defined as <1,000 g); GA, gestational age; NA, not available; NICU, neonatal intensive care unit; VLBW, very low birthweight (defined as <1,500 g).

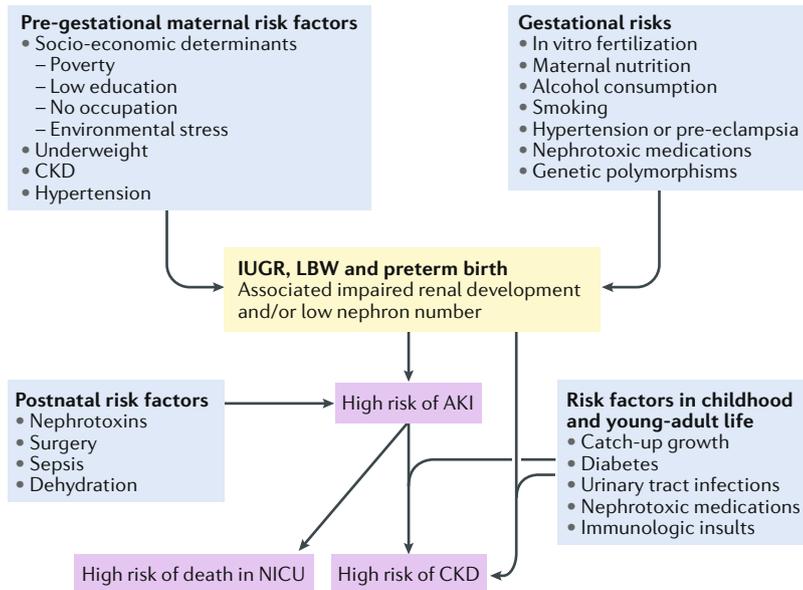


Fig. 3 | Pre-gestational and gestational risk factors for intrauterine growth restriction, low birthweight and preterm birth, which are associated with impaired renal development and low nephron number. In this framework, comorbidities and/or nephrotoxic medications in critically ill neonates might precipitate the already increased risk of acute kidney injury (AKI) associated with prematurity or low birthweight (LBW). Among AKI survivors, superimposed events in childhood and young-adult life might further increase the risk of developing chronic kidney disease (CKD). Infants born prematurely or with LBW might also be at risk of CKD independently of AKI development owing to their impaired renal development and low nephron endowment. IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit.

1 case of AKI was prevented for every 4.3 neonates exposed to caffeine²²⁶.

Mixed results have been reported with other vasodilators, such as the dopaminergic agonist fenoldopam. In small trials, even high-dose fenoldopam given to neonates failed to reduce the overall incidence of AKI following surgery for congenital heart disease, although one minor benefit was a reduced need for postoperative diuretics and vasodilators^{227,228}. At this time, firm recommendations cannot be made regarding the use of fenoldopam to prevent AKI in critically ill neonates⁵².

One key area for intervention in critically ill neonates that is often underappreciated is the careful evaluation of exposure to potentially nephrotoxic medications. Neonates should only receive nephrotoxic medications that they need and for only the duration required. Infants exposed to these medications should be closely screened for nephrotoxin-associated AKI, and evaluation of drugs required should be performed daily to limit the harm induced by the medications. As in children and adults, drugs given to infants with AKI can change their pharmacokinetics and pharmacodynamics owing to changes in the absorption, distribution, metabolism and excretion of medicines²²⁹. When alternative effective medications are available, clinicians should avoid nephrotoxic medicines. In the absence of alternative non-nephrotoxic medications, the minimal effective drug dose should be given to reduce the nephrotoxic burden; avoidance of harmful drug–drug interactions should be attempted. Although no clear guidelines are available

with regard to dosing or using concomitant medications in neonates with AKI, the stepwise clinical recommendations proposed by KDIGO in adults with AKI could be helpful in facilitating drug dosing in critically ill neonates and thereby limiting the risk of AKI²²⁹.

In order to mitigate nephrotoxin-associated AKI in children, researchers at Cincinnati Children’s Hospital have developed an automated screening system called Nephrotoxic Injury Negated by Just-in-time Action (NINJA), which extracts data from electronic medical records to identify children who are receiving at least three nephrotoxic medications or aminoglycosides for a duration of >3 days. Patients identified using this system received systematic surveillance with daily assessment of SCr levels. Over 3 years, use of this screening system resulted in a 38% decrease in the use of nephrotoxic medications in non-critically ill hospitalized children and a 64% decline in the rate of AKI²³⁰. Similar programmes have shown comparable reductions in AKI in critically ill newborn babies in the NICU (D.A., unpublished observations) and highlight the potential to reduce the burden of nephrotoxin exposure in neonates to limit the risk of AKI in vulnerable infants.

RRT is indicated when a risk of impending harm exists owing to an inability of the kidney to function properly. RRT should be considered for a number of complications, including refractory acidosis, electrolyte abnormalities, fluid overload and the inadequate nutrition despite conservative management. For example, and as described above, fluid overload, a potentially modifiable risk factor for mortality in critically ill children²³¹ and in sick late preterm neonates with AKI³⁸, can be prevented with careful fluid provision and early RRT initiation. Unfortunately, however, RRT is infrequently used in neonates owing to the challenges associated with its use in this population, including haemodynamic instability during initiation, coagulopathy, acidosis, hypocalcaemia, thrombocytopenia and decreased circuit survival.

Use of adult RRT machines in neonates increases the risk of complications owing in part to the size of the extracorporeal circuit compared with the blood volume of the neonate. Newer RRT machines designed for newborn babies (for example, continuous RRT machines with small extracorporeal volumes) should minimize these risks^{232–234}; however, further evaluation of these technologies in large multicentre studies is needed to determine their optimal timing and dose in order to minimize risk and optimize outcomes for neonates. Peritoneal dialysis is still the RRT modality of choice for critically ill neonates with AKI in most centres^{235–239}, provided the infant’s abdominal wall or cavity is preserved, there are no skin infections and there is no need for high ultrafiltration to manage fluid overload.

Long-term renal sequelae of neonatal AKI

Depending on the aetiology of AKI²⁴⁰, the degree of prematurity²⁴ and the severity of AKI, most critically ill neonates survive after AKI²⁴¹, as demonstrated in the AWAKEN study, in which approximately 90% of infants with AKI survived to NICU discharge⁴⁷. However, survivors of AKI are not without long-term renal problems²⁴², with studies in animal models²⁴³,

critically ill children^{244,245} and adults with AKI²⁴⁶ consistently documenting that an acute kidney insult can result in permanent kidney damage^{247,248} and promote the development of CKD. In a prospective cohort of 126 children who developed AKI in the paediatric ICU, 10% of patients had reduced GFR (<60 ml/min/1.73 m²) 3 years after the AKI episode, with a correlation between reduction in GFR and the severity of the acute insult during hospitalization²⁴⁵. Notably, 16.6% of neonates with AKI in this cohort developed CKD (over the same follow-up period). In a separate cohort, 70% of children demonstrated indices of residual renal damage (namely, reduced GFR, proteinuria or hypertension) 6 months after the development of nephrotoxin-associated AKI²⁴². The risk of developing adult CKD and end-stage renal disease (ESRD) following an episode of AKI was also highlighted by a 2012 meta-analysis²⁴⁶.

As mentioned above, evidence from small studies suggests that prematurity and IUGR are detrimental to nephrogenesis^{20,21,249,250}; given the association between prematurity and IUGR with AKI, we propose that the abnormal nephrogenesis contributes to the increased risk of CKD in AKI survivors. Available evidence from studies of term and preterm infants in the NICU suggests that 31% (range 9–83%) of neonatal AKI survivors will develop CKD (TABLE 3). Although these studies show that a considerable proportion of infants who develop AKI will also develop CKD, the attributable risk of AKI to CKD is unclear because AKI and CKD share many risk factors. Therefore, we do not yet know whether the development of CKD in a preterm infant who had AKI is simply due to impaired kidney development, the episode of AKI or a combination of the two²⁵¹. Although an adequately powered prospective cohort study is needed to evaluate the relationship between AKI in critically ill neonates and CKD development in later life, it is likely that the kidneys of premature infants and neonates with extreme growth restriction at birth are primed for the development of CKD in childhood or adulthood. In some individuals, CKD might fully manifest only when the compensatory response of the kidney to decreased nephron mass is lost through the effects of an immunologic or non-immunologic insult that further reduces the already limited capacity of the remaining renal tissue (FIG. 3). This hypothesis suggests that the renal function of individuals born prematurely or with LBW, or who experienced an episode of AKI as an infant, should be carefully monitored for CKD throughout childhood and adult life.

Of note, not only neonatal AKI but also any kidney disease experienced in childhood that is apparently resolved can increase the risk of developing CKD in adult life. A nationwide study in Israel involving >1.5 million

individuals found that a history of kidney disease in childhood, with no clinical or laboratory evidence of compromised GFR in adolescence, was associated with an increased risk of ESRD in later life compared with the risk of ESRD among those with no such history of kidney disease (HR 4.19, 95% CI 3.52–4.99)²⁵².

Conclusions

IUGR, preterm birth and LBW are increasingly recognized as key determinants of AKI in critically ill neonates and CKD sequelae in later life. Approaches to identify infants at risk of AKI and to establish measures to prevent the development of AKI are important given the association of AKI with prolonged length of hospital stay and increased mortality.

Although the true incidence of neonatal AKI remains ill-defined, the magnitude of preterm birth, with an approximate global incidence of 10%^{253,254}, and of LBW, which affects >22 million infants globally each year²⁵⁵, combined with the potential harmful effects of these entities on the immature kidney, calls for urgent research and interventional approaches to limit the development of AKI — a life-threatening condition. Because maternal health, nutrition and lifestyle are important determinants of fetal outcomes, studies should focus on exploring whether maternal education and simple nutritional interventions can reduce the rate of LBW and prematurity and whether these interventions can reduce the incidence of AKI in newborn babies^{253,254}. It also remains a priority to establish whether and to what extent AKI, severe prematurity and IUGR lead to CKD in childhood or young adulthood. Greater understanding of the relationships between these entities will aid in the development of cost-effective follow-up programmes over the life course of an individual with collaboration between neonatologists, paediatric nephrologists, paediatricians and adult nephrologists. Although validated guidelines are not available, recommendations for the follow-up of small for gestational age, preterm and LBW infants have recently been reported by the Low Birth and Nephron Number Working Group, a multidisciplinary working group that includes international expert obstetricians, neonatologists, paediatricians and nephrologists^{13,14}, and in 2017 guidelines from the UK's National Institute for Health and Care Excellence (NICE) on the developmental follow-up of children and young adults who were born preterm²⁵⁶. Adherence to these recommendations is needed, as are approaches to increase awareness of possible consequences of low nephron endowment associated with prematurity and LBW on the postnatal risk of AKI and CKD.

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Author contributions

N.P. and M.C. researched data for the article. N.P. and G.R. discussed how to organize the manuscript and which topics to cover. N.P. and M.C. wrote the first draft of the manuscript, which was reviewed, implemented and edited by D.A. and G.R. before submission.

Competing interests

The authors declare no competing interests.

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