Acute kidney injury in term neonates with perinatal asphyxia: a literature review

Shireen Adnan Bakhsh*

Abstract
It is well documented that in the first five days of birth, asphyxia is the main cause of Acute Kidney Injury (AKI) and transient kidney impairment with adverse effects. This literature review presents a comprehensive assessment of AKI among neonates caused by perinatal asphyxia. AKI has a range of clinical manifestations that may differ from a minimum kidney insult to conditions of total kidney failure. Prognosis depends on the seriousness of the triggering event, quickness and accuracy of the diagnosis, immediacy of treatment, and the attendance of potential severe iatrogenic problems. There are no unique and clear guidelines to diagnose AKI among neonates but currently the most accepted approach to diagnose is the rise in serum creatinine levels or changes in urine output. Management is primarily supportive and early diagnosis of AKI is vital in neonates with hypoxic ischemic encephalopathy to simplify suitable fluid and electrolyte management, because maintaining a stable biochemical milieu is essential in promoting the outcome in these infants. Ideal management involves close collaboration among different specialists such as primary care physicians, nephrologists, hospitalists, and other subspecialists contributing in the care of the patient. In conclusion, the diagnosis of AKI is still difficult and faces trouble by the lack of good markers. Most prevention and management activities currently focus on supportive care such as dialysis modalities, however, trials of interventions such as theophylline may suggest some advantage over it. To promote neonates’ health status, appropriate prevention with management strategies is needed for AKI.

Keywords: asphyxia, kidney injury, perinatal, infant, epidemiology.

Introduction
The World Health Organization (WHO) defines the perinatal asphyxia as “deficiency to initiate and sustain breathing at birth due to impaired gas exchange, hypoxia, hypercarbia, anaerobic glycolysis, and metabolic acidosis” [1]. It is well documented that there is a correlation between the presence of perinatal asphyxia, its severity and the growing incidence of Acute Kidney Injury (AKI) [2]. The incidence of AKI is about 1–10% per 1000 live births and some determinants such as the birth weight and gestational age of the baby including the local availability of medical resources can affect the incidence of AKI among neonates [3].

Kidneys are frequently engaged in ischemia with perinatal asphyxia playing a major role in the severity of neurological damage and damage caused by reperfusion [4, 5]. It is also well documented that in the first five days of birth, asphyxia is the main cause of AKI and transient kidney impairment with adverse effects [2, 6]. Renal insufficiency can happen within 24 hours of a hypoxic ischemic episode as a result of the high sensitivity of kidneys to oxygen deprivation, which if continues may even lead to irreversible cortical necrosis [7].

Kidney injury usually follows perinatal asphyxia, as blood is pushed toward vital organs [8]. In the first days of a neonate, hypoperfusion can seriously affect neonate’s kidneys. Therefore, newborn infants are susceptible to acute tubular necrosis or cortical necrosis [9]. AKI has a range of clinical manifestations that may differ from a minimum kidney insult to conditions of total kidney failure that need Renal Replacement Therapy (RRT).
literature review presents a comprehensive assessment of AKI among neonates caused by perinatal asphyxia.

**Definition and pathophysiology of perinatal asphyxia induced AKI**

AKI is traditionally defined as an unexpected decline in kidney function which causes imbalance in fluid balance, electrolytes, and waste products [10]. The primary causes of perinatal asphyxia induced AKI include ischemia, hypoxia and nephrotoxicity. It is usually associated with decreased renal blood flow which follows a rapid decline in the GFR [11]. Asphyxia can lead to multi-organ dysfunction while tends to maintain cerebral, cardiac and adrenal perfusion and potentially compromising renal, gastrointestinal and skin blood flow [12]. A complex coordination of vascular, tubular and inflammatory factors forms the baseline of pathophysiology of AKI, that is followed by a repair process that may restore function to normal or may result in chronic kidney disease [13]. Perinatal asphyxia induced AKI has a large impact on serum creatinine levels and causes oliguria [14]. Furthermore, as the infant adapts to extra-uterine life, there is substantial variability in neonatal GFR/ creatinine standards, which changes quickly in the immediate postnatal period [15, 16]. In addition to all this, there is the potential to underestimate SCr (Serum Creatinine) levels due to its interference with a commonly used assay (Jaffe) by hyperbilirubinemia, which is mainly challenging in the first week for neonates [17]. Henceforth, these reasons suggest that only considering SCr levels in the first few days of neonates as the criteria to define AKI should be treated with caution.

**Epidemiology of AKI**

Perinatal asphyxia is one of the main causes of neonatal mortality, and its incidence varies from 1–1.5% in developed countries [18, 19]. It is also notable that the incidence of AKI is strongly dependent on age, and newborns have the highest incidence [20]. Even among neonates, the incidence of AKI varies and is affected by factors including gestational age, birth weight, number and severity of problems, and the facilities of the Neonatal Intensive Care Unit (NICU) [21]. The risks of AKI are mostly apparent even in the first day of life, because of the low GFR, increased renal vascular resistance, high plasma renin function and reduced intercortical perfusion of the newborn [9].

As globally accepted, the renal failure in asphyxiated neonates is frequently non-oliguric, and many neonates can preserve a urine output of more than 1 mL/kg/h despite substantial renal dysfunction [5, 22]. Previous studies have demonstrated incidences of AKI, up to 72% among neonates with severe perinatal asphyxia [12, 23]. Neonates suffering from severe asphyxia which is also defined by clinical markers such as Apgar scores and the degree of Hypoxic Ischemic Encephalopathy (HIE), are more likely to experience renal failure when compared with those suffering from milder asphyxiation [24]. In a study conducted by Nouri, two thirds of newborns with AKI had grade II and one third with grade III [4]. Correlation between AKI and HIE has also been proved by a study that revealed that SCr level was significantly higher in asphyxiated and Hypoxic Ischemic Encephalopathy (HIE) neonates when compared to the control group (P<0.05) [7].

In a cohort study conducted by Alaro et al., (2014) to determine the prevalence of perinatal asphyxia-associated AKI among 60 full-term neonates in Nairobi with HIE, the results showed that there was a 15 fold increased risk of developing AKI in HIE III when compared to HIE I (p=0.03) [2].

**Mortality rate of Perinatal Asphyxia induced AKI and its influencing factors**

It is however important to know that AKI is normally not a direct cause of death [24]. It is also notable that the cause of death among AKI patients may not be the same as the original cause of AKI. The mortality rate is affected by other related conditions such as organ failures, particularly cardiac failure, birth asphyxia and other serious infections. In another study conducted in USA among 62 newborns with AKI, the results showed that congenital heart disease was the most common cause of AKI (27.4%) with 28 deaths(45.1%) [25]. Another study in Costa Rica showed the rate of AKI in newborns was 44% with a mortality rate of 42% [21]. Koralkar et al. (2011) also conducted a study which showed an incidence rate of AKI of 18% in Very Low Birth Weight (VLBW) infants [26].

AKI has been identified as the main complication in children who undergo cardiopulmonary bypass surgery. In another study the results showed that AKI occurred in 64% of the neonates with Congenital Heart Disease (CHD) who underwent cardiopulmonary bypass [27]. In another study, the prevalence of AKI among non-cardiac neonates on Extracorporeal Membrane Oxygenation (ECMO) was 26%, and AKI was observed with an adjusted mortality rate that was 3.2 times higher [28] and similar to those reported by Gadepalli et al. (2011) in which it was conducted amongst neonates with a congenital diaphragmatic hernia on ECMO where AKI occurred in 71% of cases, and those with the highest stage of AKI had a mortality rate of 73% [16]. Previous studies mentioning AKI in newborns with perinatal asphyxia showed mortality rates as high as 61% in those with AKI [23, 29].
For instance, Alaro et al., (2014) explained that mortality rates in perinatal asphyxia related AKI was 71.4 % with a 24 fold increase in the risk of death in neonates with AKI (p=0.001) [2]. A single-center study established that 38% of newborns undergoing therapeutic hypothermia had AKI. The results of this study showed that children with AKI on average were ventilated 4 days longer (P<0.001) and were hospitalized 3.4 days longer (P=0.02) [23]. Tanigasalam et al., (2016) conducted a study which showed that the incidence of AKI among term neonates perinatal asphyxia was less in therapeutic hypothermia group (32%) than the control group (60%) (p<0.05). With a significant difference, the results showed that the mortality rate was less in therapeutic hypothermia group (26%) compared with the control group (50%), (p<0.05) [8].

Previous studies have shown a significant association between low Apgar score at the 5th min and AKI, with a level of significance as low as p = 0.0013 by Nouri [4]. In another study, the prevalence of AKI was 14% among neonates with severe Apgar score while it was 86% among those with moderate asphyxia [2].

The mortality rate of AKI caused by asphyxia is affected by the grade of asphyxia as shown in a study by Matata et al., (2015) which described the mortality rate that was higher among neonates with severe perinatal asphyxia (57.9%) when compared with moderate perinatal asphyxia (36.4%) [30].

**Diagnosis of asphyxiated neonates with AKI**

As previously mentioned, there is no unique and clear guidelines to diagnose AKI among neonates but currently the most accepted approach to diagnose AKI in neonates is the rise in Serum Creatinine (SCr) levels or changes in urine output [31]. This approach has been used in different studies with significantly different results. For instance, Gopal et al., (2014) conducted a study among 50 asphyxiated and 25 healthy neonates whose levels of blood urea and SCr were significantly higher in asphyxiated neonates than the healthy controls (p<0.001), although serum sodium and creatinine clearance had significantly different values in asphyxiated neonates than the controls [32]. In another study conducted by Gupta (2005), asphyxiated neonates had significantly lower levels of serum sodium when compared with the healthy neonates. This can be explained by the underlying pathophysiology of neonates’ kidneys. During birth, their tubular function is immature so that the capacity of sodium re-absorption is restricted and if the load of sodium reaching the distal convoluted tubule increases considerably, this re-absorption will not happen appropriately and the extra sodium load will be excreted in urine [7]. On the basis of above discussed studies diagnosis can be considered on the basis of serum creatinine, serum sodium and blood urea of asphyxiated neonates having AKI.

If only SCr is considered as the main approach to diagnose AKI in neonates, the SCr levels should be above 133 μmol/l [33, 34]. Based on the Acute Kidney Injury Network (AKIN), AKI is defined as an absolute rise in serum creatinine of ≥ 26.4μmol/l (or 50% increase in SCr) over two consecutive days [33]. Schwartz mentions that among normal newborns, the creatinine is 79 μmol/l at day 1 and drops to 44 μmol/l on day 5 [35]. Many other researchers considered a criterion to diagnose AKI based on the SCr threshold of 133 μmol/l at 48 hours [5, 17]. Along with the level of SCr other biomarkers of AKI also need to be considered in the first 48 hours that are useful in the diagnosis and also help with prognostic predictions. These biomarkers include; urinary beta 2- microglobulin (B2M) and N-acetyl-beta-D-glucosaminidase (NAG), which are specific urinary indicators of renal tubular injury and can diagnose renal damage from asphyxia at the first 48 hours of the insult [36]. Using non-specific methods like radiological imaging and renal ultrasonography will usually identify normal-sized hyperechoic kidneys with reduced corticomedullary differentiation [12].

**The process of neonatal Renal Function**

As a part of the growth of body organs, by 34 weeks of gestation, nephrogenesis is complete and will be continued and the term neonate is developed with their full complement of nephrons [12]. If a neonate has an issue in kidneys, in the first weeks after birth there will be numerous changes to both the GFR and tubular function. In term neonates GFR varies considerably and is stated as an average value of 20 mL/min/1.73m² [37]. There is an adoption in the extraterine life which includes a decrease in the extracellular fluid content. Thereby, in the first few days after birth, the fractional excretion of sodium will rapidly decline as the newborn begins to conserve sodium efficiently. Following this change, the tubular function will be developed so that there is a reduced renal bicarbonate threshold and a reduced capability to concentrate the urine (not>700 mOsm), the latter being secondary to a reduced generation and concentration of urea in the medulla. Based on these continues changes there still remains the clinical challenge of measuring renal function in the neonates [12].

It is important to note that similar to changes in different functions, there are also substantial changes occurring in neonatal renal blood flow after birth which also constitutes for diagnostic symptoms of AKI occurring in neonates. For example, in comparison with the adults’ kidney function
which includes 20% to 25% of cardiac output, for infants and at birth, the kidneys receive only 2.5% to 4% of the cardiac output. Over time, this volume will be increased to 6% to 24 hours after birth, then to 10% a week, and 15% to 18% at 6 weeks of age [38-40]. This continuous increase in infant’s renal blood flow after birth is due to the improved renal perfusion pressure, better systemic arteriolar resistance, and reduced renal vascular resistance which are in-turn due to the neuro-humoral changes with angiotensin II and prostaglandins playing an important role [41].

Risk factors

It is well documented now that the cause of AKI in neonates is of multifaceted etiology and, usually, there is at least one associated contributing factor to it. In has been highlighted by numerous studies that peri-natal asphyxia and sepsis are the most commonly related conditions for AKI in neonates [42]. There are different other associated risk factors for development of AKI in the newborns such as respiratory distress syndrome, dehydration, congestive heart failure and nephrotoxic drugs [43]. Amongst these factors, perinatal asphyxia has been recognized to be the most common cause of AKI (40–56%) [22, 34].

Several factors can also contribute to perinatal asphyxia, and the insult can happen prenatally, during delivery, or after birth. Such insults comprise cord compression, abrupted placenta, meconium aspiration, fetal-maternal transfusion, birth trauma, congenital abnormalities, airway obstruction, and maternal opiates with resulting respiratory depression. By considering the fact that renal failure in the neonates usually happen because of oliguria, a high index of suspicion is warranted. Moreover, due to the complications of interpreting a single SCr value in the neonates, serial tests are vital to evaluate the increasing trends, regardless of the absolute value [12].

Treatment

There is no definitive treatment of AKI in most cases, the focus is on symptomatic treatment. Generally, AKI is treated through maintaining fluid and electrolyte balances until recovery [5, 44]. It is henceforth, vital for early diagnosis of AKI and to apply therapies aimed at preventing or treating predicable complications, which may obviate the need for dialysis and/or allow for planned rather than emergent use of RRT [12]. Based on the treatment protocols, primary goal of the treatment is to evaluate criteria such as the modification of fluid overload with furosemide, adjustment of severe acidosis with bicarbonate administration, which can be significant as a bridge to dialysis, correction of hyperkalemia, amendment of hematologic abnormalities (e.g., anemia, uremic platelet dysfunction) with methods such as transfusions and administration of desmopressin [45].

Through the fluid management and maintenance of volume homeostasis, it is easier to treat non-oliguric renal failure. It is essential to consider the possible risks of nephrotoxicity (furosemide) and neurotoxicity (mannitol) as side effects of medication when trying to maintain urine output in the asphyxiated neonate with decreasing urine flow [21]. Knowing that AKI related with asphyxia is predominantly non-oliguric, the SCr level should be monitored on a daily basis in severely asphyxiated neonates [46]. A major supportive treatment such as RRT is essential in less than one-fourth of all cases [22, 47]. In the cases with RRT, conducting peritoneal dialysis is the favored choice for newborns [48, 49].

Different protocols of treatment have been examined among neonates to measure the efficiency of treatment on AKI. Two studies proved that a small dose of theophylline given within the first hour after birth considerably reduced SCr and urinary B2M excretion and increased GFR [50, 51]. In another study, Bhat et al (2006) conducted a randomized placebo controlled trial among 70 term neonates by providing a higher dose of theophylline (8 mg/kg) within the first hour of delivery. The participants with renal dysfunction were followed up for at least a year and the results showed that the treatment reduced the incidence of severe renal failure, defined with a rising serum creatinine>1.5 mg/mL on two consecutive days, increased creatinine clearance and reduced urinary excretion of B2M [52]. After one year of follow up and comparing two groups, the results revealed that there was no difference in the serum creatinine or creatinine clearance between the two groups at 1 year of age [12].

Prevention and management

Other health conditions, early detection of AKI and appropriate management of these neonates can prevent the progression to severe AKI. Through improving the newborn care with perinatal asphyxia, a substantial reduction in overall mortality will be inevitable [53]. Previous studies confirm the effectiveness of using AKI management on the neonates’ health status. The result of the study done by Pauliah et al. (2013) is useful to recognize potential factors which can affect the quality of treatment and management strategies for neonates suffering with AKI. Potential factors such as the heterogeneity and low quality of the included studies, using low quality technologies and devices in treatment, absence of best neonatal intensive care, lack of sedation and ventilator support, and overuse of oxygen can affect the treatment outcome. Other factors such as fundamental differences in population, for example, higher rates of
perinatal infection, intrauterine growth retardation, obstructed labor, and maternal malnutrition can be effective in the difference of the outcome of AKI in developed and developing countries [54].

The renal parameters are needed to be monitored continuously as mistakes are committed in renal dysfunction and AKI. Therefore, among neonates with perinatal asphyxia, the main concern is to preserve renal function along with cerebral protective strategies. The evaluation of a neonate with AKI is based on a systematic method, which commonly comprise evaluating pre-renal, intrinsic, and post-renal causes. Patient’s clinical history including assessment of their gestational age, antenatal, maternal, birth, and postnatal events need to be fully assessed.

The physical examination should emphasize on volume status and vital signs; volume status such as assessment of serum electrolytes, fluid balance, and body weight. These essential measurements and evaluations can contribute in determining both hypovolemia and hypervolemia. As a useful process, evaluation of fractional excretion of sodium can lead to distinguishing the prerenal (hypovolemia) from intrinsic (acute tubular necrosis) causes of AKI, however it is not usually an effective parameter among premature infants. Ultrasound should be acquired to assess potential post renal (obstruction) causes of AKI [45]. One of the main aspects need to be considered especially after the diagnosis of AKI is to prevent the progress of sequelae. Monitoring of drug levels, avoiding of nephrotoxic through daily evaluation of medications and the participation of a pharmacist formulate can be an essential strategy in the management of the neonates suffering with severe AKI. All fluid input and output, serum electrolytes, and weight measurements need to be documented to improve fluid status [14].

It is necessary to reduce all medications that may possibly affect renal function through direct toxicity or by hemodynamic mechanisms. In order to do that, the amounts of necessary medications need to be adjusted for the lower level of kidney function. Supportive treatments such as antibiotics, upkeep of suitable nutrition, mechanical ventilation, glycemic control, and anemia assessment should be tracked based on standard management strategies. For neonates who experience rapidly progressive glomerulonephritis, certain treatments can be implemented after approval of the diagnosis through a kidney biopsy. These include treatment with pulse steroids, cytotoxic therapy, or by combining both together [55]. With such other health conditions, RRT is needed in some cases when the metabolic consequences of AKI cannot be sufficiently controlled through conservative management. Some indications such as refractory hyperkalemia, volume overload refractory to medical management, uremia, refractory acidosis, failure to provide adequate nutrition, and specific poisonings and intoxications offer RRT among neonates [56].

To uphold urine output, diuretics are regularly used in neonates with AKI. It is notable that using diuretics for neonates with severe AKI doesn’t have any beneficial outcome and can also make worse outcomes in patients with AKI. For instance, in a randomized control study, using bumetanide among infants with AKI further developed the urine output of ELBW at the expense of increasing their SCr [57]. In another study, with using bumetanide among premature infants with oliguric, AKI significantly increased the urine output but at the expense of a transient increase in SCr [58].

Despite the absence of evidence in neonates, a trial is necessary for using diuretics among oliguric neonates with AKI, given the difficulty of RRT. The relationship between fluid overload and mortality among neonates suffering with serious AKI is a challenging issue for researchers who are still trying to recognize the relationship [59]. There is a paucity of data regarding fluid overload in neonates. Askenazi et al (2013) conducted a study among preterm neonates with AKI and found that they had higher median fluid overload at day 3 after birth when compared with those without AKI (+8.2% vs –4%, P=0.001) [60]. As a result of this potentially modifiable risk factor for mortality, it is now essential to understand about fluid provision and the timing of renal RRT. Applying RRT among neonates is a challenge with peritoneal dialysis (PD) being the modality of choice in infants as there is no need for vascular access or an extracorporeal blood circuit. The effectiveness of PD has been proved with several different techniques especially among critically ill neonates as small as 830 gms [61-63].

Conclusion
Increase in AKI has been consistently established as an independent risk factor for mortality among children, from neonates to adolescents. Perinatal asphyxia is the main cause of AKI in neonatal. AKI is known as a common manifestation of asphyxia among the term neonate. However, even after substantial improvements in neonatal care, the morbidity and mortality rates of AKI induced by perinatal hypoxia still remain high. To prevent the burden of mortality and morbidity of this disease, the key point lies in considering prevention strategies for AKI, and this will only be achieved through growing knowledge of the true incidence and clinical influence of AKI amongst the community, general and family physicians, and other
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health-care specialists. Most etiologies of AKI can be prevented by interventions at the individual, community, regional, and in-hospital levels.

List of Abbreviations

- (AKI) acute kidney injury
- (B2M) beta 2-microglobulin
- (CHD) congenital heart disease
- (CI) confidence intervals
- (ECMO) extracorporeal membrane oxygenation
- (ELBW) extremely low birth weight
- (GFR) glomerular filtration rate
- (HIE) hypoxic ischemic encephalopathy
- (NAG) N-acetyl-beta-D-glucosaminidase
- (NGAL) neutrophil gelatinase-associated lipocalin
- (NICU) neonatal intensive care unit
- (PD) peritoneal dialysis
- (RRT) renal replacement therapy
- (SCr) serum creatinine
- (VLBW) very low birth weight
- (WHO) World Health Organization

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Author details

Shireen Adnan Bakhsh

1. Department of Pediatrics, Security Forces Hospital, Riyadh, Saudi Arabia.

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