

Preterm Birth and/or Factors that Lead to Preterm Delivery: Effects on the Neonatal Kidney

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Abstract

Preterm birth (defined as birth prior to 37 completed weeks of gestation), occurs in approximately 10% of all births and is one of the leading causes of neonatal morbidity and mortality worldwide. Preterm infants are born at a time when kidney development is still ongoing, and consequently can lead to renal impairment (in both the short-term and long-term), as well as severe glomerular abnormalities in some preterm infants. Since the glomerular abnormalities are not present in all preterm kidneys, this suggests that it is not preterm birth per se that leads to the glomerular abnormalities but may relate to factors associated with the etiology of the premature delivery, or factors in neonatal care. In this review, we provide an overview of what is currently known of how prenatal and postnatal factors can potentially impact on the immature kidneys of infants born preterm.

Keywords: Preterm birth; Intrauterine growth restriction; Kidney, Nephrogenesis; Neonatal care

Introduction

Preterm birth occurs in approximately 10% of all births and is one of the leading causes of neonatal morbidity and mortality worldwide. Preterm infants are born at a time when their organ systems are immature and hence, being born early can lead to adverse effects on organ structure and function both in the short-term and in the long-term. Preterm birth can lead to renal impairment in the neonatal period and can lead to glomerular abnormalities in some preterm infants. Since the glomerular abnormalities are not present in all preterm kidneys, this suggests that it is not preterm birth per se that leads to the glomerular abnormalities but may relate to factors associated with the etiology of the premature delivery or factors in neonatal care. Indeed, the etiology of preterm birth is multifactorial and the neonatal care of preterm infants is different for all individuals, depending on their postnatal sequelae. In this review, we provide an overview of what is currently known of how prenatal and postnatal factors can potentially impact on the immature kidneys of infants born preterm.

Preterm birth

Preterm birth occurs in approximately 10% of all births and is one of the leading causes of neonatal morbidity and mortality worldwide [1]. Preterm birth is defined as birth prior to 37 completed weeks of gestation, with birth between 38-42 weeks of gestation considered as full term [2]. Preterm birth can be further sub-classified into moderately preterm, very preterm and extremely preterm. Moderately preterm infants are classified as those born between 32 to 36 weeks of gestation, very preterm births are those born between 28 and 31 weeks gestation, extremely preterm births are those born before 28 weeks gestation [3]. Babies born prior to 23 weeks usually do not survive. The majority (60-70%) of preterm newborns are born between 34 and 36 weeks of gestation. The incidence of preterm infants born at 32-33

weeks gestation is ~20% and ~15% are born at 28-31 weeks, preterm birth prior to 28 weeks is the least common [3].

The global number of preterm deliveries each year has been slowly increasing and at the present time it is around 10% of births worldwide [4]. In the USA the incidence of preterm birth is 12.3% [5], in Europe it is 5-7% [4], and in Australia it is 8.2% [6]. However, within these populations some ethnic groups have a higher incidence of preterm birth. For example in African Americans the incidence of preterm birth is high at 17.5% [7] and in Indigenous Australians 13.3% of all births are preterm [6]. Of concern, the prevalence of preterm birth in developing countries is very high; for example, up to 17.5% of the reported birth sin South Africa are preterm and this is likely to be even higher as many births are not recorded [4].

Survival following preterm birth (especially in those born very, extremely preterm) has improved dramatically since the first introduction of neonatal intensive care units (in the 1960s). With subsequent refinements in prenatal and neonatal care, newborns born as early as 25 weeks gestation now have a 80% chance of survival [8,9]. In particular, the use of antenatal/neonatal corticosteroids (which accelerate lung maturation in the newborn) and surfactant therapy (which reduces alveolar surface tension in the presence of respiratory distress syndrome) have facilitated the recent improvement in survival [10].

The cause of premature delivery is multifactorial and differs with each pregnancy. It can occur spontaneously or be the result of emergency induced delivery. The most common identified causes of spontaneous preterm delivery are onset of premature labour (45%), and premature pre-labour rupture of the membranes (25%) [3]. The main identified cause of emergency induced delivery is maternal and fetal infection (35%) [3]. To date, the etiological mechanisms leading to spontaneous preterm labour and premature pre-labour rupture of the membranes are not well defined. There are a number of risk factors associated with increased risk of preterm delivery [3]. Pregnancy complications that often lead to emergency induced preterm delivery include: Chorioamnionitis, placental insufficiency/abruption, pre-eclampsia, oligohydramnios (abnormal amniotic fluid levels) and

intrauterine growth restriction (IUGR); IUGR is often a co-morbidity of these other pregnancy complications.

Although there has been a marked improvement in the survival of preterm infants over recent decades, preterm birth still remains the leading cause of infant mortality and morbidity. Perinatal mortality is currently around 6 to 8.5 times higher in preterm infants than in term infants [11]. Preterm infants are vulnerable to many postnatal complications due to the increased functional demands in the extra-uterine environment, at a time when the immature organs are ill-equipped for the functional transition to life ex-utero.

The increasing awareness of the potential adverse effects of being born early to immature organ systems has led to many studies over recent years looking at the consequences of preterm birth on fetal organ development, such as in the lungs [12], brain [13,14], gastrointestinal tract [15], and the kidney [16-19]. The effects of preterm birth in the neonatal kidney form the focus of this review.

Preterm birth and its Effects on renal Function and Nephrogenesis

Renal Function: In the case of preterm infants, they are delivered at a time when nephrogenesis is often ongoing. In preterm neonates glomerular filtration rate (GFR) is very low at birth, and does not rise as rapidly as full term infants during the neonatal period [20,21]. As expected, glomerular filtration rate has shown to increase more rapidly after 34 weeks gestation [22,23] which coincides with the timing of the completion of nephrogenesis. Numerous studies have shown that preterm birth can lead to a high incidence of renal dysfunction in the neonate and under severe circumstances this can lead to renal failure [24,25]. The incidence of renal impairment in preterm infants is difficult to clearly define given that the kidneys are very immature at the time of birth. Hence, renal function is quite different in the preterm infant when compared to the term infant and many of these differences are due to immaturity rather than an underlying impairment. Certainly, both glomerular and tubular function are influenced by gestational age at birth and hence, it is difficult to establish whether the differences in renal function in preterm infants compared to term infants are solely due to underdevelopment of the nephrons or the result of injury in an immature kidney. During the first week after birth, glomerular filtration rate (GFR) is significantly lower in preterm infants compared to term infants [26-28] and it is positively correlated with gestational age at birth and postnatal age [29-31]. Likewise, creatinine clearance, one of the most commonly used markers of renal function, is positively correlated with both gestational age and postnatal age [20,21,29-39]. In addition, preterm neonates excrete high amounts of sodium in the early neonatal period compared to term neonates, with the fractional excretion of sodium inversely correlated with gestational age and postnatal age [29,39-43].

The presence of high levels of protein in the urine is indicative of pathological proteinuria (urine total protein ≥ 500 mg/l) and can be glomerular and/or tubular in origin. Specifically, the presence of proteins with a high molecular weight (albumin) in the urine, is indicative of a disruption in the integrity of the glomerular filtration barrier [44]. Alternatively, high levels of low molecular weight proteins (such as $\beta 2$ -microglobulin) are indicative of reduced reuptake by the proximal tubule cells [45,46]. The occurrence of proteinuria in neonates is strongly linked to gestational age at birth with studies in preterm infants reporting significantly greater albumin and $\beta 2$ -microglobulin concentrations over the first month of life in infants

born <32 weeks gestation, compared to neonates born >32 weeks gestation [39,47]. To date, it remains unclear whether the observed proteinuria in preterm infants is a result of their renal immaturity or due to postnatal renal injury.

Acute kidney injury (previously defined as acute renal failure) is reported to occur in 8% to 24% of preterm infants admitted to neonatal intensive care units [24,48]. The mortality amongst these infants that are born <32 weeks gestation has been reported to be as high as 30-60% [49]. Acute kidney injury is defined as a sustained extreme decline in creatinine clearance; the initial clinical symptoms are a marked increase in serum creatinine and/or a sustained very low urine output [50,51]. The major risk factors for acute kidney injury are very low gestational age and low birth weight [52]. Other factors that have been linked to acute kidney injury are: hypotension, hypoxia, sepsis, maternal and neonatal drug administration (NSAIDs, indomethacin, antibiotics and vasopressor), a low apgar score, intraventricular haemorrhage (grade III and IV), necrotising enterocolitis, patent ductus arteriosus, respiratory distress syndrome, clinical interventions (intubation at birth), catheterization, phototherapy, and mechanical ventilation [24,52,53]. Of concern, mortality rates were reported to be significantly higher in neonates with renal dysfunction/renal failure [52].

In addition, to the short-term effects in the kidney, preterm birth is reported to influence long-term renal function [54-56]. For example, Rodriguez et al. [57], found GFR to be significantly lower in children ranging in age between 6.1 and 12.4 years who were born preterm, with evidence of renal injury (defects in tubular transport of phosphate) [57]. Iacobelli et al [56], found that microalbuminuria was present in 8.3% of children examined that were born premature, ranging from 6-8 years of age. Similar findings were reported in a study of young adults; a lower GFR, higher serum creatinine and microalbuminuria was reported at 19 years of age in subjects born at <32 weeks gestation (and also small for gestational age) [54]. Furthermore, there is strong epidemiological evidence to link premature birth with the development of hypertension [58-63] and increased cardiovascular risk during adulthood [64,65]. This 'risk' may be further exacerbated in the presence of impaired renal function, possibly leading to hypertension, and the possible development of cardiovascular disease in later life [66].

Nephrogenesis: The nephrons are the functional units of the kidney and importantly, nephrogenesis (the formation of nephrons) is usually not completed until late in gestation (approximately 32 to 36 weeks gestation) [67]. Hence, the majority of preterm infants are born at a time when nephrogenesis is still ongoing. Over the past decade there have been a number of studies looking at the effect of preterm birth on nephrogenesis in the kidney. In the first of these studies, Rodriguez et al. [16] reported a reduced number of glomerular generations (thus implying reduced nephron endowment) in autopsied kidneys from babies that were born preterm compared to those born at term. However, in that study many of the preterm infants were also IUGR; hence, in that study interpretation of the findings is difficult, because it is well known that IUGR leads to reduced nephron endowment (see later section). Likewise, in another autopsy study the number of glomerular generations was significantly reduced in preterm kidneys compared to terms [68]. Concomitant with these studies, we have also conducted a number of studies looking at the effect of premature birth in immature preterm kidneys, both in a non-human primate model of preterm birth and in autopsied kidneys of preterm infants. Our studies have convincingly shown that when nephrogenesis is ongoing in

preterm infants at the time of birth, that nephrogenesis continues after birth; new nephrons are formed in the extra-uterine environment [17,19]. In our baboon studies, where the timing of nephrogenesis is similar to the human, we have shown that the kidneys are significantly larger in the preterm neonates, with a concomitant decrease in glomerular density, but nephron number was in the normal range (thus implying changes in tubular growth)[17]. Of concern, however, there was a high proportion of abnormal glomeruli (up to 18% in some kidneys) in the outer renal cortex in some of the preterm neonates. The abnormal glomeruli exhibited a shrunken immature glomerulus and an enlarged cystic Bowman's space. Similarly, in studies conducted in autopsied kidneys from infants born preterm[19], there was also an increase in kidney weight relative to body weight (probably due to the increased postnatal functional demands) and importantly new glomerular generations were formed after birth. However, there was a reduced nephrogenic zone width and a reduction in the proportion of glomeruli in the most immature stages (vesicle, comma-shaped, S-shaped and capillary loop stages), when compared to gestational age-matched controls, suggesting that cessation of nephrogenesis may be accelerated, and nephrogenic potential adversely impacted upon. To date, there have been no studies that have looked at exactly when nephrogenesis ceases in the preterm infant relative to gestational age-matched infants.

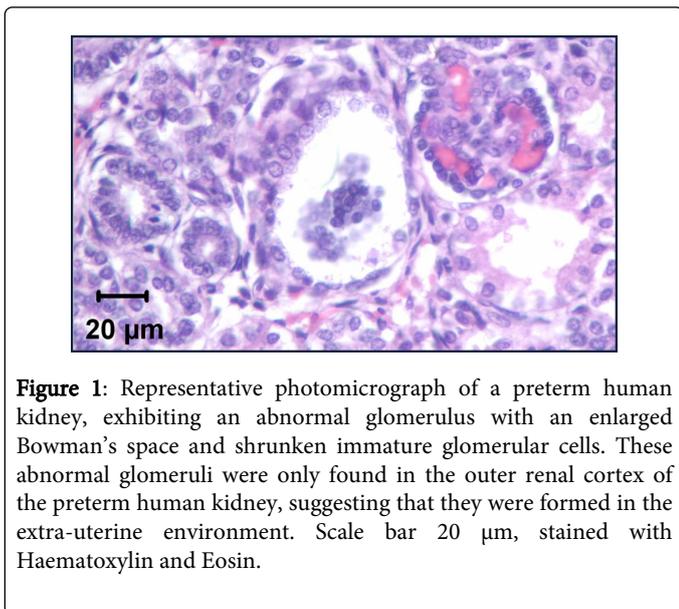


Figure 1: Representative photomicrograph of a preterm human kidney, exhibiting an abnormal glomerulus with an enlarged Bowman's space and shrunken immature glomerular cells. These abnormal glomeruli were only found in the outer renal cortex of the preterm human kidney, suggesting that they were formed in the extra-uterine environment. Scale bar 20 μ m, stained with Haematoxylin and Eosin.

Alarming, as seen in the preterm baboon kidneys, there was a high proportion of abnormal glomeruli (with shrunken glomerular tufts and an enlarged cystic Bowman's space) in the outer renal cortex (up to 13% of glomeruli) in some of the preterm human kidneys [19]. A representative example of an abnormal glomerulus in the preterm human kidney is shown in Figure 1. Given the severity of these glomerular abnormalities it is unlikely that these glomeruli will ever be functional. Hence, our findings suggest that in these preterm infants the endowment of functional nephrons is adversely impacted upon by preterm birth, thereby affecting renal function both in the early postnatal period and later in life. To date, the causes of the glomerular abnormalities in the preterm kidneys are unknown. Given that not all preterm kidneys exhibit abnormal glomeruli, it is likely that it may be factors in the intrauterine environment (that lead to preterm delivery) that have adversely impacted upon the developing glomeruli or alternatively, it may be factors in the extra-uterine environment

(haemodynamic and in the postnatal care) that have led to these glomerular abnormalities (Figure 2). In addition, there may be intrauterine factors and/or extra-uterine factors that adversely impact on nephrogenesis without inflicting glomerular pathologies. In the next sections, factors in the intrauterine environment (linked to the induction of preterm birth) and in the extra-uterine environment that could potentially adversely impact on the developing kidney are discussed.

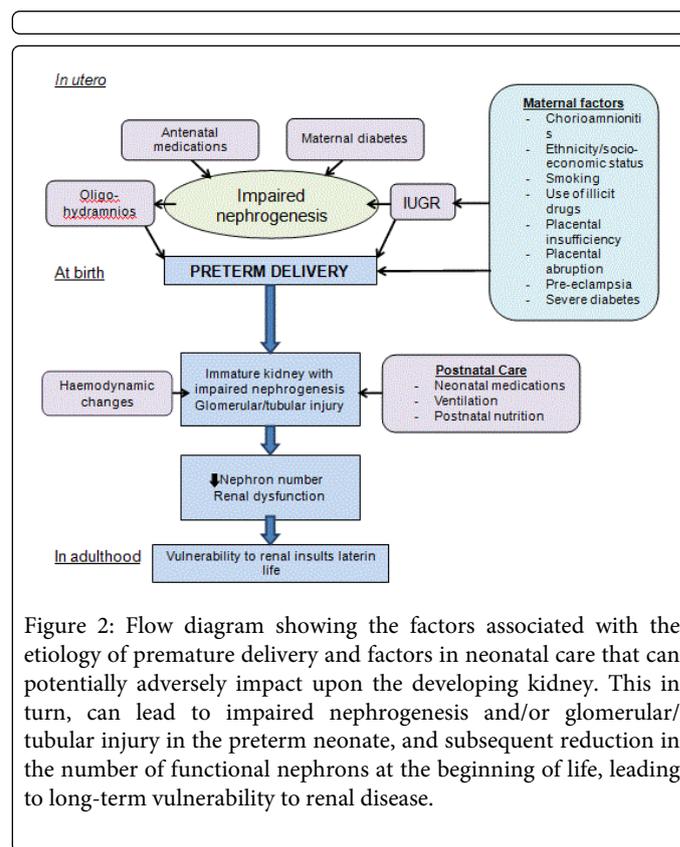


Figure 2: Flow diagram showing the factors associated with the etiology of premature delivery and factors in neonatal care that can potentially adversely impact upon the developing kidney. This in turn, can lead to impaired nephrogenesis and/or glomerular/tubular injury in the preterm neonate, and subsequent reduction in the number of functional nephrons at the beginning of life, leading to long-term vulnerability to renal disease.

Factors that can potentially impact on the development of the immature kidney

Intrauterine factors: It is now well recognised that the in utero environment can directly influence organ structure and development. Hence, it is likely that the factors that lead to the induction of preterm delivery (spontaneous or assisted) can potentially impact on nephrogenesis and/or render the kidneys vulnerable to premature delivery and subsequent pathology. In the next sections we describe some of the common factors/conditions associated with preterm birth and how these factors can adversely impact on the development of the fetal kidney.

Intrauterine Infection and Inflammation (chorioamnionitis): Intrauterine infection (in particular, chorioamnionitis) is widely acknowledged as a major contributor to premature delivery [13,69], especially in births prior to 32 weeks gestation [69,70]. A recent study by Ogge et al. [71], found that chronic chorioamnionitis was involved in 34% of the premature deliveries relating to preterm labour with intact membranes and 39% of preterm labour with membrane rupture. Chorioamnionitis is defined as inflammation of the chorion and amnion, caused by a bacterial infection which typically ascends from the vagina [3]. Importantly, chorioamnionitis can lead to fetal

inflammatory response syndrome (FIRS) [72], and this has been shown to adversely influence neonatal organ development. The effect of exposure to inflammation in utero on the fetal kidney has recently been examined in fetal sheep [73,74]. In the study by Galinsky et al. [73], there was a 20% reduction in nephron number, without any effect on body weight, when chorioamnionitis was induced in late gestation, using an acute intra-amniotic bolus dose of lipopolysaccharide (LPS, which initiates an inflammatory response similar to that observed with chorioamnionitis). Interestingly, however, when fetal lambs were exposed to a lower dose of LPS over a chronic period, during the period in gestation when nephrogenesis is rapidly ongoing, there were no observable detrimental effects on nephrogenesis [74]. Hence, it appears that with chronic low dose exposure that the kidney may be able to adapt, to prevent adverse effects on nephron formation. The contrasting findings from these two studies demonstrate that the timing, duration and extent of infection/inflammation are important factors when assessing the impact of chorioamnionitis on the developing kidney.

Maternal Diabetes: Exposure to intrauterine maternal diabetes can significantly influence fetal growth throughout gestation and lead to an early onset to preterm birth; this is of concern given the recent rise in Type 1 and type 2 and/or gestational diabetes [75,76]. A common consequence of intrauterine exposure to maternal diabetes is macrosomia, in particular asymmetric macrosomia [77]. Macrosomia often leads to exaggerated fetal growth, whereby the baby is born with a birth weight that is high for gestational age [78]. This increase in body weight is a result of excessive amounts of glucose and other nutrients crossing the placenta leading to an increase in fetal body growth. In contrast, when maternal diabetes (both Type 1 and Type 2) is severe, this can lead to IUGR in the infant [76,79]; the impacts of IUGR on the kidney are described later. With the increased prevalence of maternal diabetes there have been a number of recent studies looking at the effects on the fetal kidney. In a study conducted in preterm and term babies born to Pima Indian mother, exposure to maternal diabetes (Type 2 diabetes) during pregnancy led to a higher excretion of albumin (3.8 times higher) when compared to infants of pre-diabetic and non-diabetic mothers; thus indicative of renal injury in offspring exposed to diabetes in utero [80].

Animal studies, have reported an increased incidence of renal malformations in offspring born to diabetic mothers (Type 1 diabetes) [81,82]. In particular it has been shown that exposure to maternal diabetes can adversely impact nephrogenesis, with the offspring of diabetic mothers reported to have significantly smaller kidney and glomerular size, accompanied with a 40% reduction in nephron endowment [82]. The offspring of the diabetic mothers were significantly smaller in body weight, but there was no difference in kidney weight adjusted for body weight, compared to offspring of non-diabetic mothers [82]. Of concern, exposure to diabetes in utero led to greater glomerular and tubular apoptosis, compared to offspring not exposed to diabetes with the level of hyperglycaemia a strong determinant of the severity of the adverse effects observed in the kidneys [82].

It is important to note, that although many of the animal studies relate to induction of type 1 diabetes in the mothers, the findings in relation to fetal development are likely to be also relevant to maternal type 2 and gestational diabetes, where the developing infant in all cases of maternal diabetes is exposed to hyperglycemia.

Antenatal Medications: In general, administration of medications during pregnancy is avoided wherever possible, due to potential

adverse effects on the developing fetus. However, it is important to note that there are some medications which are specifically administered to women 'at risk' of delivering prematurely, and although these medications are considered safe, they have the potential to adversely impact on the developing fetal kidney. In this section, we describe what is currently known in relation to these routinely prescribed medications.

Glucocorticoids: When it is considered likely that a woman will deliver prematurely, she is routinely administered glucocorticoids, usually betamethasone or dexamethasone. These medications have been shown to accelerate the maturation of the fetal lungs and thus, enhance the survival of the infant at preterm delivery [83,84]. In addition to the effects in the newborn's lungs, the administration of glucocorticoids has also been observed to increase mean arterial blood pressure, renal blood flow and glomerular filtration rate [85-87] this in turn, has the potential to affect renal function.

The effect of glucocorticoids on the developing kidney has been studied in animal models including: the rat [88-90], sheep [91-93] and baboon [17,94]. The findings suggest that exposure to glucocorticoids can affect nephron endowment and renal maturation. In sheep studies, administration of glucocorticoids during pregnancy (over 26-28 days gestation) has been shown to significantly reduce nephron endowment in the exposed offspring [95] and in the neonatal rat, a reduction in glomerular density was observed when dexamethasone was administered at a time of ongoing postnatal nephrogenesis [96]. In our laboratory, we have looked at the effects of administration of antenatal glucocorticoids in a preterm baboon model [17]. Encouragingly, administration of antenatal glucocorticoids did not appear to have any direct adverse effects on the developing kidney and nephron endowment was within the normal range [17]. However, there was a 9% increase in developed glomeruli in the renal cortex in the betamethasone-exposed neonates, and a reduction in the width of the nephrogenic zone when compared to age-matched gestational controls. This suggests that there is accelerated renal maturation in response to glucocorticoid exposure and this is in accordance with other studies that show accelerated organ maturation as a result of glucocorticoid exposure [94,97].

Antibiotics: Infants that deliver preterm are often pre-exposed to antibiotics in utero, with antibiotics often prescribed to pregnant women with chorioamnionitis. Importantly, in this regard, antibiotics such as the aminoglycosides can readily cross the placenta [98] and there have been a number of experimental studies linking antibiotics with impairment of nephrogenesis [99-102]. For instance, it has been shown that incubation of metanephroi in culture with gentamicin leads to decreased branching morphogenesis of the ureteric tree and thus reduced nephron formation [99]. In addition, administration of antibiotics to guinea pig and rat dams has been shown to lead to oligonephronia in the offspring [103].

Indomethacin: Another routinely administered medication to women 'at risk' of preterm birth is indomethacin. Indomethacin is a tocolytic drug, which functions to reduce prostaglandin synthesis; it is thereby highly effective at prolonging pregnancy [104]. Of concern, however, in rodent studies in utero exposure to indomethacin has been reported to reduce nephron endowment and reduce glomerular filtration [105,106].

Oligohydramnios: Oligohydramnios is characterised by reduced levels of amniotic fluid during pregnancy. It can manifest as a result of fetal renal injury, such as decreased renal blood flow and/or reduced

renal perfusion, which ultimately leads to a reduction in the amount of fetal urine excretion and consequently, the amount of amniotic fluid [107]. Other renal causes that attribute to a reduction in amniotic fluid include congenital anomalies such as: renal agenesis, polycystic kidneys, multicystic dysplastic kidneys and uterine or urteral obstruction rupture of membranes [108]. It is also suggested that oligohydramnios can also result from bacterial infection within the amniotic cavity (such as chorioamnionitis), causing redistribution of blood flow within the developing fetus. A reduction in amniotic fluid at birth is often indicative of renal insufficiency in the neonate [109]. In utero detection of oligohydramnios often leads to the assisted induction of preterm labour as oligohydramnios has been linked to a number of inauspicious pregnancy outcomes such as perinatal death, fetal distress labour, low birth weight and poor infant health at birth [110].

Intrauterine Growth Restriction (IUGR): IUGR is defined as body growth below the 10th percentile for gestational age. IUGR is multifactorial in origin with maternal race, economic status, diet and lifestyle (which can be interlinked) and complications of pregnancy all associated with induction of IUGR (see Figure 2). IUGR is often a comorbidity of preterm birth and it is linked both to spontaneous and assisted premature deliveries. In many pregnancies, it is difficult to ascertain whether it is the underlying cause of the IUGR, or the poor in utero growth of the fetus that is the stimulus for spontaneous preterm delivery. Likewise, the developing kidney can be directly impacted upon by the factors leading to IUGR, or alternatively, it can be a direct corollary of the IUGR. Certainly, the general consensus of the findings from the literature would support the latter with IUGR (regardless of the underlying causes) linked to poor organ development in the fetus and concomitant impairment of kidney development [111,112]. In the next sections some of the common factors associated with IUGR are described, including their links with preterm delivery.

Maternal ethnicity / socio-economic status: Maternal race has been linked with premature delivery and IUGR [3,113,114]. For example in the USA, African and African American women have been shown to have a four times higher chance of delivering a premature newborn compared to other racial groups [3]. In addition, women from South Asia and the Indian subcontinent have very high rates of IUGR and low birth weight [3], whereas, women from East Asia and Hispanic regions have been shown to have lower rates of premature delivery. In Australia, Indigenous Australians have a much higher frequency of IUGR and preterm delivery (approximately twice that of non-Indigenous Australians) [6,115]. It is important to note, that in many of these populations (where there is a high incidence of IUGR) there is also a low socioeconomic status. Hence, the underlying cause of the IUGR may be due to poor maternal nutrition, lifestyle insults and poor maternal health (all described below), rather than their ethnicity per se.

Maternal diet: Malnutrition is a common cause of IUGR in underdeveloped countries [116]. It can result by under nutrition (inadequate food intake) and/or restriction of specific key nutrients in the diet. For example, data from the Dutch famine during World War 2 found that children born to mothers that had limited food available (less than 1000 calories per day) over the majority of their pregnancy gave birth to babies that were small for gestational age [117]. In another large study conducted in 538 women who delivered term, it was shown that a reduced protein diet during pregnancy leads to low birth weight in the neonate [118]. Similarly, in rat studies, IUGR is

consistently reported when rat dams are fed a low protein diet during pregnancy [119-122].

Maternal lifestyle: Maternal behaviours such as smoking, high alcohol consumption, and ingesting illicit drugs have all been recognised as contributors to the risk of IUGR and premature birth [123-127]. Cigarette smoking has been reported to increase the risk of premature rupture of the membranes, pregnancy bleeding and pre-term labour. In addition, maternal smoking has been identified as a major cause of IUGR in developed countries, contributing to as high as 40% of all cases of IUGR [116]. Smoking causes vascular changes in the mother that can lead to placental insufficiency and hypoxia in the fetus [128]. It has also been associated with the down-regulation of important miRNAs of the placenta, leading to newborns that are small for gestational age [128]. Furthermore, nicotine found in cigarettes has been shown to pass the placenta, thus exerting a direct negative effect on the growth of the fetus [128]. Importantly, Dejmek et al. [129] also showed that reduced birth weight in newborns of smoking mothers was dose-dependent (that is number of cigarettes smoked per day).

Consumption of alcohol and use of illicit drugs during pregnancy is also linked to increased risk of preterm birth. In a cohort of 3000 African American women, alcohol and cocaine use was found to be associated with extreme preterm birth [125]. Of particular concern, a study by O'Leary et al. [127], found that moderate ingestion of alcohol consumption (only during the first trimester of pregnancy) was associated with pre-term birth. In Australia, the high rate of preterm birth in the Indigenous community is thought to be attributed to high rates of tobacco, alcohol and drug use in pregnant women [130].

Placental Insufficiency/Abruption: The placenta is a vital organ that develops specifically during pregnancy to support the growth of the developing fetus. The role of the placenta is to supply the fetus with an adequate amount of nutrients and oxygen for normal fetal growth. In developed countries the most common cause of IUGR is placental insufficiency [131,132] and it is also strongly linked with preterm birth [133]. Placental insufficiency occurs when the placenta does not develop normally and thus it is unable to adequately support the developing baby. It is usually caused by reduced uterine artery blood flow (uteroplacental insufficiency) [131].

Placental abruption occurs in late gestation and is a serious condition where the placenta partially, or completely, separates from the lining of the uterus; the effects on the developing fetus depend on the severity [134]. The full separation of the placenta from the uterine lining can lead to in utero death and subsequent stillbirth, if the fetus is not delivered at the time of abruption. When there is partial placental separation the fetus is growth restricted and preterm birth will often ensue (spontaneous or assisted).

Pre-eclampsia: Pre-eclampsia is pregnancy-associated hypertension [135]; it is a multi-system disorder which affects approximately 8% of pregnancies [136]. It occurs when placentalation is abnormal, which can cause the mother to experience intravascular coagulation, bleeding and organ failure (hepatic and renal) following poor perfusion. These complications subside with the delivery of the fetus. Severe pre-eclampsia can lead to maternal death and thus, it is a major cause of assisted preterm birth [137]. In addition, pre-eclampsia during pregnancy is a major risk factor for IUGR [138,139] as it usually results in placental insufficiency. Higher rates of pre-eclampsia are seen amongst women with pre-existing hypertension, diabetes mellitus or previous history of pre-eclampsia [140]. Of concern, there has been

an increased incidence of pre-eclampsia in developing countries over recent years [141].

Multiple Births: Pregnancies with multiple fetuses exhibit a higher risk of placental dysfunction and placental insufficiency. This is associated with the slowed growth rate of twins during late gestation when compared to the singleton growth rate [142]. The incidence of multiple births is increasing and this is largely attributed to the increase in availability of infertility treatment, such as ovulation induction [143,144]. Monochorionic twins (identical twins that share one placenta) have a much greater chance of being born IUGR than dichorionic twins (twins that do not share the same placenta) [145,146]. Discordant growth, results from unequal distribution of uteroplacental blood flow to the fetuses [147].

IUGR adversely Impacts on Nephron Endowment at Birth

It is now well established that IUGR, regardless of the etiological origins (many of these described above), can adversely impact on the number of nephrons formed within the developing kidney. Indeed there are many experimental studies that have shown that when IUGR is induced by maternal dietary manipulations, or by induction of placental insufficiency, that nephron number is reduced in the offspring [148-152]. In general, nephron endowment at birth is directly proportional to kidney size [17,153,154], so in the case of the IUGR infant the reduction in body size at birth is accompanied by a decrease in kidney size and in the number of nephrons. In support of this concept, in autopsied human kidneys there was a linear relationship between the number of glomeruli (and therefore nephrons) and birth weight in full term neonates [155]; neonates below the 10th percentile of birth weight had 30% fewer glomeruli than the neonates with birth weights above the 10th percentile [155].

However, it is important to note that the timing of the growth insult during gestation is important. If the growth restriction occurs late in gestation, when nephrogenesis is already complete, or close to completion, the number of nephrons formed within the kidney will not be affected by the IUGR, yet birth weight will be significantly reduced. For example, in a study performed in our laboratory [151], placental insufficiency was experimentally induced in fetal lambs late in gestation (from 120-140 days gestation; term is 147 days) at a time when nephrogenesis was nearing completion. This study revealed a significant decrease in body weight and kidney weight in response to IUGR compared to appropriately grown lambs. However, nephron endowment in the IUGR lambs was not different to the control lambs. In contrast, IUGR caused by twinning led to a significant reduction in nephron endowment [151].

Extra-Uterine (Postnatal) Factors: There are a number of factors in the postnatal environment (haemodynamic and factors associated with postnatal care), that can potentially adversely impact on the immature kidneys of the preterm infant. Some of the major ones are described below.

Change in haemodynamics: There is a major hemodynamic transition at the time of birth, when the circulatory dependence on the placenta is terminated and the in utero configuration of circulation is changed to the ex utero configuration [156]. In the immediate period following birth the kidneys need to rapidly adapt to the extra-uterine environment whereby they are now required to independently control fluid and electrolyte levels [20]. Following birth, there is also a significant increase in mean arterial pressure and cardiac output and a reduced renal vascular resistance facilitates an increase in renal blood

flow [33]. Since resistance of the afferent and efferent arterioles is a determinant of glomerular capillary pressure the glomerular filtration rate also increases at birth and sodium reabsorption subsequently increases [157]. Hence, the immature kidneys of preterm infants are exposed to a marked increase in renal blood flow and blood pressure in the immediate neonatal period and this has the potential to lead to renal injury. To date, there is little information as to how changes in renal blood flow and pressure directly impact on nephrogenesis and on the recently formed immature nephrons in the preterm kidney. It is conceivable that increases in blood flow and blood pressure could lead to renal vascular injury and to the glomerular injury observed in preterm infants. In this regard, in future studies it will be important to look at the role of renal endothelial function in relation to prematurity. Certainly, endothelial dysfunction has been described in other organs following preterm birth and IUGR. Low birth weight and premature birth has been previously reported to cause endothelial dysfunction in the intestines, skin, retinal vessels and peripheral arteries [158]. Hence, it is plausible to suggest that preterm birth and low birth weight could also affect developing arteries and capillaries in the immature kidney. It is imperative in future studies to address this.

Hyperoxia and Ventilation: In utero, the fetus normally develops in a relatively hypoxic environment (5% oxygen) and this facilitates both vascular and tubular development in the kidney [159-161]. At birth, the neonate is exposed to an abrupt increase in oxygen from ~5% to 21% [161]. The blood oxygen saturation levels (SpO₂) rise from 45-55% in the fetus [162] to 80-90% in the first five minutes after birth [163]. Hence, when a baby is born preterm, the immature kidney is no longer growing in an hypoxic environment and hence, it is likely that this will lead to deleterious effects on the growth of the renal vasculature and the tubules. This is an important area for future research and to our knowledge this has not been investigated.

In addition, in the preterm neonate the lungs are very immature at the time of birth; therefore, the neonate requires resuscitation and ongoing ventilation [164]. Exposure to supplemental oxygen therapies, such as ventilation, can lead to exposure to very high concentrations of O₂ (up to 100%), in an attempt to normalise blood oxygen levels [165,166]. However, during this process the infant can experience high blood oxygen levels (often only transitory) until the blood oxygen levels become normalised. Of concern, hyperoxia can lead to oxidative stress of the neonate, which has been shown to subsequently cause cellular injury and cell death in response to accumulation of free radicals and thereby exhaustion of antioxidants [167,168]. Consequently, this can lead to a number of common morbidities of prematurity such as, retinopathy of prematurity, necrotizing enterocolitis and bronchopulmonary dysplasia [169]. In the kidney of the human neonate, oxidative stress has been reported to cause tubular injury [170] and it has been linked to impairment of nephrogenesis in animal studies [171]. In the rat model (where nephrogenesis is ongoing in the first two weeks after birth), a significant reduction of nephrons (25%) was reported in adulthood (25-35 weeks of age) [171] following exposure to 80% oxygen during the early postnatal period. In contrast, however, in a more recent study [172], exposure to 65% oxygen levels for seven days of postnatal life, did not appear to have any deleterious effects on nephrogenesis. However, in that study, the kidneys of the hyperoxia-exposed mice did exhibit glomerular hypertrophy in adulthood (postnatal day 56), suggestive of possible reduced renal functional capacity.

Neonatal Medications: Preterm infants are administered many medications in the immediate period following birth; the treatment

regime varies from infant to infant and is ultimately dependent on the clinical sequelae of each infant. Many of the medications administered to the infants are known to be toxic to the kidneys but their benefits to the infant outweigh the potential adverse effects on the kidneys. Some of the commonly administered drugs are: non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and ibuprofen and aminoglycoside antibiotics (such as gentamicin). There are a number of experimental studies which demonstrate that treatment with these medications can have adverse effects on renal function in the postnatal period and lead to renal injury [173-176]

NSAIDs: In the preterm neonate, exposure to indomethacin after birth has been shown to lead to a significant increase in the concentration of podocytes in the urine, as well as increased urine albumin excretion [177], suggestive of renal injury. Treatment with NSAIDs is also linked to impaired renal function. A recent study of renal function in preterm babies indicated that NSAIDs administered to the preterm infant significantly reduced neonatal renal drug clearance, likely associated with a reduced GFR [178]. In the rodent model, postnatal administration of NSAIDs and/or gentamicin during the period of postnatal nephrogenesis is associated with a number of structural changes in immature rodent kidneys [102]. These changes include proximal tubule vacuolization, interstitial oedema, and podocyte foot process effacement; the most severe effects were observed in animals that received combined NSAID and gentamicin treatment. In these studies early administration of indomethacin caused a significant reduction in nephron endowment at 14 days postnatal age in rats, however, these effects were not observed in the kidney when exposed to ibuprofen (Kent et al. 2014(personal communication)). In the mouse model, postnatal exposure to NSAIDs caused a significant reduction in glomerular density and glomerular and tubular volumes in the kidneys [179]. Importantly, in preterm baboons (born at a time, equivalent to ~27 week gestation in the human), administration of ibuprofen during the postnatal period caused a significant reduction in nephrogenic zone width [180]. This suggests that prostaglandin inhibition may result in the early cessation of nephrogenesis.

Antibiotics: It is known that antibiotics, such as the aminoglycosides, can be nephrotoxic in the newborn (with the preterm infant most vulnerable) [101] and they are also linked with impairment of nephrogenesis [103,173]. Administration of gentamicin in neonates has been shown to primarily result in renal tubular necrosis [100], which consequently leads to increased sodium excretion, proteinuria, and a significant reduction in GFR [101,181,182].

Preterm infants are often exposed to antibiotics in utero (see earlier section) and/or in the postnatal period when there is evidence of infection. In this regard, in a study of preterm human infants, using a multivariate logistic analysis, it was found that mothers of infants with acute renal failure received more drugs during pregnancy and delivery (mainly antibiotics and non-steroidal anti-inflammatory drugs) [183]. Moreover, in the first few days of life and before diagnosis of acute renal failure, the preterm infants that developed renal failure received more drugs (antibiotics, NSAIDs and diuretics) and for a longer period [183].

Postnatal Nutrition

Recent studies highlight the importance of postnatal nutrition on the growth and function of the kidney in IUGR and preterm infants. Certainly, when nephrogenesis is ongoing there are usually strong

linear correlations between nephron number and kidney size [155]. Impaired growth after birth (extra-uterine growth restriction; EUGR) often occurs during the postnatal period in preterm infants[184]; hence, it is likely that impaired body growth in the immediate period after birth will adversely affect kidney growth and nephron endowment in the preterm infant. Therefore, there is the potential for improved postnatal nutrition to positively impact on the number of nephrons formed. In support of this idea, in a recent study of preterm children (born <30 weeks gestation) [185] glomerular filtration rate was significantly decreased (suggestive of reduced nephron endowment) at 7 years of age, in those that were either intra or extra-uterine growth restricted. Importantly, the extra-uterine growth restricted children were found to have significantly lower protein-energy intake during their first week of life when compared to IUGR or appropriately grown children. In addition, Schmidt et al. [186] observed that consuming protein-rich formula, compared to just breast milk, during the early postnatal period caused a significant increase in kidney size.

Conclusion

This review highlights the many factors associated with the etiology of preterm birth and in the postnatal environment that can potentially impact on the immature kidney of the preterm infant. In order to improve long-term renal health in subjects born preterm, it is now important in future studies, to develop interventional strategies that mitigate the adverse impact of the intrauterine and extra-uterine environment on the immature kidney. At this stage, there is no clear indicator of the causes of the glomerular abnormalities associated with preterm birth. Carefully controlled animal studies can help to elucidate the causes of the glomerular abnormalities and this is an important area of future research. In regards to renal injury, this review highlights a number of medications, commonly used in the neonatal intensive care unit that can lead to renal impairment. Hence, it is the challenge for the neonatologist, when deciding to use these medications, to ascertain whether the benefits outweigh the risks.

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