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Renal disease in pregnancy: Fetal, neonatal and long-term outcomes

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A B S T R A C T

Renal disease in women of childbearing age is estimated to be approximately 3%; consequently, renal disease is not an uncommon comorbidity in pregnancy. There has been considerable evidence published over the last 20 years to suggest that renal disease in pregnancy is associated with higher maternal, fetal, and offspring morbidity. Studies published are largely heterogeneous; include unmatched cohort studies; and focus on early neonatal outcomes such as prematurity, small for gestational age, and neonatal unit admission. There appears to be an inverse relationship between maternal renal function and likelihood of neonatal morbidity using these outcome measures. Overall though, data regarding medium-to long-term outcomes for children born to mothers with renal disease are scarce. However, in view of emerging epidemiological evidence regarding cardiovascular programming in intrauterine life in those born premature or small for gestational age, it is likely that this population of children remain at high risk of cardiovascular disease as adults. The scope of this review is to amalgamate and summarize existing evidence regarding the outcomes of infants born to mothers with renal

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disease. Focus will be given to pregnancy-related acute kidney injury, chronic kidney disease, dialysis, and transplantation.

Introduction

Maternal and infant morbidity is high in pregnancies complicated by maternal renal disease. On a background of reduced fertility, pregnancy in this population can be both a physical and a psychological burden.

Over the past two decades, there has been a wealth of literature examining this challenging area, most of which consists of heterogeneous, small-scale, and unmatched cohort studies. Pregnancy in the latter stages of chronic kidney disease (CKD) is a relative rarity, thereby limiting the sample size and scope of most studies. In addition, there remains significant variation in the definitions and reported outcome measures. Finally, most studies focus on maternal and early fetal outcomes; relatively, little is known regarding neonatal and long-term pediatric outcomes. Together, these challenges have resulted in fragmented and often disparate data available to clinicians managing this group. However, the need to improve maternal and neonatal outcomes remains, while an emerging understanding of intrauterine factors affecting long-term health including cardiometabolic outcomes also makes understanding of this field essential.

The scope of this review is to amalgamate and summarize existing evidence regarding the outcomes of infants born to mothers with renal disease. Focus will be given to pregnancy-related acute kidney injury (AKI), CKD, dialysis, and transplantation.

Outcome measures

Maternal health is inextricably linked to infant development and outcomes. The fetus is nourished with oxygen and nutrients through a placental interface, and hence, the fetus develops and matures throughout pregnancy. Disease in pregnancy may result in disruption of this process. In severe cases, this may result in intrauterine death, small for gestational age (SGA), premature delivery, neonatal mortality, and adverse neurodevelopmental outcomes.

Renal disease during pregnancy results in an increased pathophysiological burden in affected mothers. Hemodynamic instability, pro-inflammatory uremic milieu, predisposition to cardiovascular disease, and potentially harmful medications may all coalesce to disrupt placental and fetal development. Therefore, there have been attempts to report the inter-relationship between maternal health in renal disease and fetal outcomes. In addition, mothers physically and psychologically affected by renal disease may be predisposed to difficulties in meeting the needs of their child. This may be compounded further if the child has increased medical or developmental needs.

There are limited long-term follow-up data examining the outcomes of infants born to mothers with renal disease. However, the fetal and neonatal outcome measures described in this review have been widely reported when evaluating therefore act as useful surrogates for the interplay between maternal renal disease and long-term infant outcomes.

Small for gestational age

SGA is defined as birth weight below the 10th centile for gestational age and gender of the reference population [1]. Premature infants born SGA are at higher risk of neonatal death, cerebral palsy, and future cognitive and behavioral difficulties than their appropriate-for-gestational age (AGA) counterparts [2,3]. Even SGA infants born at term have subtle cognitive deficits of up to 15 IQ points compared to AGA controls [4]. Adverse events, which impair fetal growth, result in "fetal programming" of adult diseases. This describes how genetic, epigenetic, and socioeconomic factors related to impaired in utero growth may predispose to disease in adulthood [5–7]. Epidemiological studies have shown that fetal growth restriction is a significant risk factor for developing cardiovascular, renal, respiratory, and metabolic disease [8,9].

Prematurity

Prematurity is defined as delivery before 37 completed weeks of gestation [1]. Premature birth exposes the infant to a host of risks in the short to medium term, including respiratory, neurological, gastrointestinal, and infectious diseases. Infants born prematurely are also prone to long-term sequelae including cerebral palsy, cognitive impairment, asthma, and adult-onset obstructive pulmonary disease [10,11].

Prematurity also increases the risk of cardiovascular disease in adult life [12–14]. The risk of death from cardiovascular disease is increased by 7% for each week of increased prematurity [15]. Both elevated blood pressure and metabolic syndrome in adulthood have also been associated with prematurity [16–18].

Breastfeeding

Breastfeeding is recommended for all babies as the nutritional standard until 6 months by the World Health Organization, American Academy of Pediatrics, and Royal College of Paediatrics and Child Health [19–21]. Feeding with human milk reduces childhood risk of infections (respiratory tract, otitis media, and gastroenteritis), allergic disease, autoimmune disease (type 1 diabetes, inflammatory bowel disease, and celiac disease), childhood leukemia, and obesity in adolescence and adulthood [20]. There are added benefits on rates of necrotizing enterocolitis, length of hospital stay, and neurodevelopmental outcomes in preterm and very low-birth-weight babies [20].

In the dialysis population, there is little evidence to direct healthcare professionals in their advice to mothers. There is evidence that sodium and chloride are significantly higher postdialysis than those predialysis but remains at safe levels comparable to those observed by formula feed [22].

National Transplantation Pregnancy Registry (NTPR) data show the prevalence of breastfeeding mothers who are on maintenance immunosuppression following renal transplant is increasing [23]. The safety of breastfeeding while on immunosuppression is therefore an important consideration for healthcare professionals and mothers alike. Breast milk transfer of prednisolone is 0.1% of total maternal dose. Maintenance prednisolone <20 mg/day leads to an infant dose <10% of endogenous corticosteroid production and is regarded to be safe [24]. The highest infant serum concentration of 6-mercaptopurine was found to be <1% of total maternal dose, far lower than that in the therapeutic window [25]. In addition, there have been no clinically observed adverse effects from maternal azathioprine use in breastfed infants with up to 3 years of follow-up [26]. The rate of cyclosporine ingestion from breast milk is < 0.1 mg/kg/day in comparison to a therapeutic dose of 2–10 mg/kg/day. Cyclosporine levels have also been measured as undetectable in these infants [27,28].

Early findings suggested that for breastfeeding mothers using tacrolimus, 50% of maternal serum concentration was detected in colostrum within the immediate postpartum period, which was associated with a 36% risk of transient hyperkalemia and mild renal impairment in the infants [29]. However subsequent studies demonstrated that total tacrolimus ingestion was <0.5% of total adult weight-adjusted dose, with no detectable tacrolimus level in infants' serum at 2–3 weeks postpartum [30,31]. Tacrolimus levels can be detected at birth due to in utero exposure. However, this becomes metabolized after birth, and in a further small study, no differences were reported between bottle and breastfed infants following serial testing. These data are limited and require further evaluation [32]. Mycophenolic acid treatment in the first trimester is associated with birth defects including microtia and facial abnormalities. It is avoided in women of childbearing age with strict advice to establish women on long-acting contraception before commencement. Therefore, there are limited data on the effects on breastfed infants of mothers taking mycophenolic acid. A limited series of 7 infants has suggested no discernible adverse effect in 7 infants from breastfeeding [23].

Acute kidney injury

An important cause of fetal and maternal morbidity and mortality is pregnancy-related AKI in mothers admitted for childbirth. The incidence of pregnancy-related AKI in the developed world has steadily reduced over recent decades. A large Canadian population study reported pregnancy-related AKI incidence of 2.68 per 10,000 births between 2009 and 2010 [33,34]. In contrast, the rates of pregnancy-related AKI in the developing world are profoundly high. In India, AKI complicates 178 per 10,000 births [35], and pregnancy-related AKI accounted for up to 10% of all AKI cases [36]. These observed differences can in part be attributed to differences in the rates of sepsis, as well as disparities in antenatal and perinatal care between the developed and developing world [37].

The etiologies of pregnancy-related AKI are wide-ranging as with the general population. Prerenal azotemia is the leading cause as a result of sepsis or hyperemesis gravidarum in the first trimester. In later trimesters, obstetric emergencies such as placental abruption or catastrophic hemorrhage become important causes and may result in irreversible acute cortical necrosis. Intrarenal causes such as pre-eclampsia or hemolysis, elevated liver function test, and low platelet (HELLP) syndrome; thrombotic microangiopathy; and lupus nephritis are also important causes of AKI in pregnancy [38].

There is significant morbidity and mortality to both mother and infant following pregnancy-related AKI. A large Canadian population-based cohort study showed that among 188 pregnancies complicated by AKI resulting in renal replacement therapy, 4.3% of women died and 3.9% remained dependent on chronic dialysis [39]. Furthermore, 35.6% of infants experienced adverse outcomes including prematurity (relative risk (RR) 2.5; 95% confidence interval (CI), 2.0 to 3.1), low birth weight (RR 4.7; 95% CI, 3.6 to 6.0), and SGA (RR 3.2; 95% CI, 1.9 to 5.3). The incidence of neonatal deaths was also higher than that in the general population (2.7%) [39].

In addition, a large systematic review analyzed 11 studies with a total of 845 pregnancies complicated by AKI of any stage [40]. This demonstrated that AKI results in more maternal deaths (odds ratio (OR) 4.5; 95% CI 2.7 to 7.4) and more stillbirth/perinatal deaths (OR 3.4; 95% CI 2.8 to 4.2). These pregnancies led to a lower mean gestational age at delivery (−0.70 week; 95% CI −1.2 to −0.2 week) and lower birth weight (−740 g; 95% CI −1180 to 310 g). Long-term outcomes showed that 2.4% of women in this cohort developed CKD requiring chronic dialysis [40]. There are no long-term outcome data through infancy and early childhood for offspring of pregnancies that were complicated with maternal AKI at present.

Chronic kidney disease

The overall prevalence of CKD can be estimated to be 3% in the population of women of childbearing age [41,42]. Maternal CKD is associated with an increased risk of pregnancy-related complications across the spectrum of CKD, with birth weight, SGA, prematurity, neonatal intensive care unit (NICU) admission, and stillbirth as the principal fetal and newborn adverse outcomes reported [9,11–22]. Estimated glomerular filtration rate (eGFR) correlates negatively in a stepwise fashion with fetal and newborn outcomes [43,45–51,54,55]. Studies published over the last decade investigating adverse maternal and fetal outcomes in pregnancies in mothers with CKD are summarized in Table 1. These data show a trend toward higher rates of SGA, prematurity, NICU admission, and pre-eclampsia with more severe stages of CKD. In general, the number of pregnancies studied declines with more severe stages of CKD, reflective of the lower incidence of pregnancy in these populations. In Table 1, studies are presented chronologically; however, there appears to be no clear trend toward changing outcomes with time despite changes in neonatal care.

A large meta-analysis examined the outcomes of pregnancy in CKD among 23 case–control/cohort studies with over 500,000 pregnancies and found an increased overall risk of preterm delivery (OR 5.7; 95% CI 3.3 to 10.0) and growth restriction (OR, 4.85; 95% CI 3.0 to 7.8) across all stages of CKD [56]. The risks of adverse maternal and fetal outcomes were found to be higher for women with CKD than pregnant women without CKD. In another systematic review of 9 studies, fetal outcomes were measured in 1760 pregnancies complicated by CKD [57]. There was a 13% incidence of preterm birth in the CKD population compared to 6% among healthy controls. There was also a trend toward increased morbidity over the other parameters studied, including SGA and stillbirth.

Hypertension, proteinuria, and systemic disease complicating maternal CKD have all been associated with less favorable pregnancy-related outcomes. One study including 176 pregnancies with stage 1 CKD observed that the presence of proteinuria independently increased the risk of neonatal admissions (OR 4.4; 95% CI 1.4 to 14.1) and maternal hypertension independently increased the risk of preterm delivery (OR 3.5; 95% CI 1.3 to 9.5) [47]. In one meta-analysis, pre-eclampsia and premature delivery have also been associated with macroproteinuria [56]. A further observational study reported

Table 1
Key findings from studies published in the last decade regarding pregnancy outcomes in women with CKD.

Author	Year	Study design	Population	Comparison groups	Total live births n (%)	SGA	Prematurity (%)	NICU admission (%)	Pre-eclampsia (%)
Munkhaugen et al. [41]	2009	Retrospective cohort	General (HUNT 2 cohort), Norway	Total	5655	9.5%	5.0%		3.6%
				eGFR > 90 ml/min/1.73 m^2	4656 (82.3%)	9.2%	4.8%		3.6%
				eGFR 75–89 ml/min/1.73 m^2	867 (15.3%)	10.8%	5.5%		3.9%
				eGFR 60–74 ml/min/1.73 m^2	126 (2.2%)	10.3%	10.3% OR 2.69[a] ($P < 0.004$)		2.4%
				eGFR <60 ml/min/1.73 m^2	6 (0.1%)	0	0		16.7%
Piccoli et al. [47]	2012	Retrospective cohort (single center)	CKD cohort compared with 267 healthy controls, Italy	Controls	267	10.5%	4.9%	1.1%	
				All CKD	176	17%	37.5%	21%	
				CKD stage 1	127 (72.2%)	14.2%	28.3% OR 8.50[a]	14.2% OR 16.1[a]	
				CKD stage 2	28 (16%)	14.3%	42.9% OR 2.84[a]	25% OR 2.59[b]	
				CKD stage 3	17 (9.7%)	29.4%	82.4%	47.1%	
				CKD stage 4	4 (2.3%)	75%	100%	100%	
Bharti et al. [49]	2016	Retrospective observational (single center)	Pregnant CKD cohort, India	Total	80	35%	57.5%		55%
				“early” CKD (stages 1–2)	46 (57.5%)	17.4%	No significant difference between groups		39.1%
				“late” CKD (stages 3–5)	34 (42.5%)	58.8% $P = 0.001$[b]		Rate of NICU admission increased for late vs. early ($P = 0.037$)	76.5% $P = 0.001$[b]
Bramham et al. [55]	2016	Longitudinal prospective cohort (dual center)	Pregnant women with CKD, healthy controls, U.K.	Controls	79	5.1%	3.8%	2.6%	
				All CKD	121				
				CKD stages 1–2	86 (71%)	16.3%	23.3%	13.8%	
				CKD stage 3	28 (23.1%)	39.3%	39.3%	32.1%	
				CKD stages 4–5	7 5.8%	57.1%	100% $P = 0.0001$[c]	57.1% $P = 0.009$[c]	

Piccoli et al. [43]	2015	Prospective cohort (dual center)	Pregnant women with CKD, healthy controls, (TOCOS cohort), Italy	Controls	836	4.5%	6.1%	1.8%	
				All CKD	504				
				CKD stage 1	370 (73.4%)	5.1% P < 0.001[d]	23.5% P < 0.001[d]	10.3% P < 0.001[d]	
				CKD stage 2	87 (17.3%)	6.0%	50.6% P < 0.001[e]	27.6% P < 0.001[e]	
				CKD stage 3	37 (7.3%)	5.4%	78.4% P = 0.007[%]	44.4% P = 0.05[e]	
				CKD stages 4–5	10 (2.0%)	25.0% P = 0.05[e]	88.9%	70.0%	
Imbasciati et al. [45]	2007	Longitudinal multicenter cohort	Pregnant Caucasian women with eGFR <60, Italy	All CKD	49	39%	63%		
				eGFR 40-59 Proteinuria <1 g/d	16 (32.7%)	38%	44%		
				eGFR 40-59 Proteinuria >1 g/d	6 (12.2%)	17%	66%		
				eGFR <40 Proteinuria <1 g/d	12 (24.5%)	33%	75%		
				eGFR <40 Proteinuria >1 g/d	15 (30.6%)	53%	73%		
Alsuwaida et al. [46]	2011	Not specified (? retrospective observational) (multicenter)	Pregnant women with CKD, Saudi Arabia, Bahrain, United Arab Emirates	All CKD	98	15.8%[f]	19.8%		20.8%
				CKD stage 1	67 (68%)	15%[f]	25.5%		12.9%
				CKD stage 2	21 (21.4%)	38.5%[f]	31.2% P = 0.02[g]		47.4%
				CKD stages 3–4	10 (10.2%)	42.9%[f]	75% P = 0.02[g]		44.4%
Piccoli et al. [54]	2010	Prospective cohort (single center)	Pregnant women with CKD, 267 healthy controls, Italy	Controls	267	10.5%	4.9%	1.1%	
				All CKD	91	16.5%	44%	26.7%	
				CKD stage 1	61 (67%)	13.1%	32.9% P < 0.0001[d]	18% P < 0.0001[d]	
				CKD stage 2	15 (16.5%)	6.7%	40%	20%	
				CKD stage 3	11 (12.1%)	27.3%	90.9%	54.5%	
				CKD stages 4–5	4 (4.5%)	75%	100%	100%	
Davidson et al. [48]	2015	Retrospective cohort (single center)	Pregnant women with CKD, healthy controls, Australia	Controls	62,032	7.2%	8.3%	19%	4.1%
				All CKD	55				
				CKD stages 1–2	27 (49%)	26%	56%	52%	63%
				CKD stages 3–5	28 (51%)	46%	86% P = 0.02[d]	68%	71%

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Study design	Population	Comparison groups	Total live births n (%)	SGA	Prematurity (%)	NICU admission (%)	Pre-eclampsia (%)
Singh et al. [44]	2015	Retrospective observational (single center)[g]	Pregnant women with CKD, India	All CKD	51	13.7%[f]	21.6%		17.6%
				CKD stages 1–2	32 (62.7%)	15.6%[f]	15.6%		6.3%
				CKD stages 3–4	19 (37.3%)	10.5%[f]	31.6%		36.8%
Chopra et al. [53]	2009	Retrospective observational (single center)	Pregnant women with CKD, India	All CKD	30	68%	85%		
Kendrick et al. [52]	2015	Retrospective cohort (multicenter)	Pregnant women with CKD, matched controls, USA	Controls	778	6.9%	13.6%	5.5%	8.5%
				All CKD	778	9.1%	19.4% ($P = 0.002$)[d]	9.6% ($P = 0.002$)	9.3%

CKD, Chronic Kidney Disease; eGFR, estimated Glomerular Filtration Rate; SGA, Small for Gestational Age; NICU, Neonatal Intensive Care Unit.

[a] OR shown compared to stage 1.

[b] P value shown compared to “early” stage.

[c] P value shown compared to stages 1–2.

[d] P value shown compared to controls.

[e] P value shown compared to stage above.

[f] Intrauterine Growth Restriction (IUGR) defined in this study as <2500 g.

[g] P value shown compared to stage 1 CKD.

that hypertension but not proteinuria was associated with SGA, fetal mortality, and neonatal admission [48]. More prospective data are needed to delineate the level of proteinuria associated with neonatal morbidity.

Stage 1 and 2 Chronic Kidney Disease

There is growing evidence that even the early stages of CKD are associated with adverse pregnancy and neonatal outcomes. The TOCOS cohort (Torino-Cagliari Observational Study) compared outcomes of 504 pregnancies of women with CKD with controls. In those with stage 1 CKD, patients without systemic disease, proteinuria, or hypertension had an increased risk of a composite of preterm delivery, SGA, neonatal intensive care admission, with odds ratio of 1.9 (95% CI 1.3 to 2.8) [43]. Another study that prospectively followed up 176 pregnancies in stage 1 CKD also found an increased risk of preterm delivery (OR 8.5; 95% CI 4.1 to 17.6) and neonatal admission (OR 16.1; 95% CI 4.4 to 58.7) [47].

A large Norwegian population-based cohort study also examined outcomes in CKD among 5655 pregnancies over an 11-year period [41]. A combination of hypertension and an eGFR 74–90 ml/min/1.73 m^2 resulted in increased risk of pre-eclampsia, SGA, or prematurity (OR 2.6; 95% CI 1.4 to 4.8). However, reduced eGFR (74–90 ml/min/1.73 m^2) alone did not increase the risk of adverse outcomes. In women with eGFR 60–74 ml/min/1.73 m^2, there was a significantly increased risk of preterm delivery (OR 2.7; 95% CI 1.4 to 5.2), and hypertension in this group compounded the risk of complications (composite OR 10.1; 95% CI 2.4 to 42.9). When comparing stage 2 CKD with stage 1 CKD, one retrospective study demonstrated increased fetal morbidity in subjects with stage 2 CKD. These patients had higher rates of preterm labor, SGA, fetal death, and low birth weight (OR 3.0; 95% CI 1.0 to 9.2) [46].

A limitation of all studies in this area is the risk of underestimating eGFR in pregnancy using Modified Diet in Renal Disease, Chronic Kidney Disease Epidemiology Collaboration, and Cockcroft-Gault equations. All these formulas have been shown to significantly underestimate GFR in pregnancy [58]. It is likely that bias toward classifying patients into higher stages of CKD stage results and consequently underestimates the impact of CKD on pregnancy outcomes.

Stage 3–5 Chronic Kidney Disease

As fertility becomes impaired with declining GFR, studies are limited by smaller sample sizes and mainly retrospective designs. Nevertheless, such studies still demonstrate an increased risk of adverse pregnancy-related outcomes in women with moderate-to-severe CKD. Offspring of mothers with stage 3–5 CKD have an increased risk of low birth weight, prematurity, and fetal death [44,45,48,49,59]. For stage 3–5 CKD, incidence of prematurity ranges from 31.6% to 100%. In studies evaluating stage 4–5 CKD, incidence of prematurity was above 75% (Table 1). This high rate of prematurity is likely explained by elective early delivery as a result of reduced growth, pre-eclampsia, or physiological burden on the mother. SGA incidence is quite variable at 5.4%–58.8% for stage 3–5 CKD. Studies comparing outcomes between different stages of CKD indicate that the severity of adverse outcomes correlates with severity of baseline CKD stage [48,49]. In addition, one study has also investigated the rate of renal malformations in fetuses, showing that moderate-to-severe CKD increases the risk of renal malformations [48].

In addition to pregnancy-related adverse effects, there are also small retrospective data that demonstrate pregnant women with moderate-to-severe CKD are at increased risk of an accelerated decline in GFR, especially during the third trimester. This decline persists in some women and hastens the onset of chronic renal replacement therapy [59]. A prospective observational cohort study reported women with GFR of <40 ml/min/1.73 m^2 and heavy proteinuria (>1 g/24 h) had an accelerated decline in renal function. This decline in renal function could potentially be ameliorated with improved blood pressure control [45]. There are currently no data describing the effects of declining GFR during pregnancy on the fetus; however, it is likely that overall stage of CKD will better indicate infant outcome.

There is a paucity of data analyzing treatments to protect long-term outcomes in infants. A small nonrandomized study compared fetal growth in pregnant women with stage 3–5 CKD to that in controls [n = 24 vs. 21 singleton pregnancies], who were maintained on low-protein diets as part of their medical management [60]. Although numbers were small, there was a significantly reduced prevalence of SGA in patients on the low-protein diet (44 vs 14%). This study also followed up children beyond the neonatal period. Growth and hospitalization rate at a mean follow-up of 2 years showed no difference between the two groups.

Dialysis

Pregnancy while on chronic dialysis has been rare due to the phenomenon of reduced fertility rate of up to 100-fold [61]. The first report of successful pregnancy to a woman on dialysis was in 1971 [62], and since then, significant progress has been made from a live birth rate of 23% in 1980 to 52% in 1993 and 70.9% in 2008 [63–65]. High blood urea nitrogen levels have been observed over decades to be particularly detrimental to fetal survival [66]. A retrospective cohort study showed that maternal urea level negatively correlated with both birth weight and gestational age at birth. There was also a higher incidence of fetal death in uremic patients [67]. Several studies have also shown improved live birth rates if conception occurred before starting chronic dialysis when compared to receiving dialysis from the start of pregnancy (91% vs. 63%) [67,68].

When comparing chronic hemodialysis (HD) with chronic peritoneal dialysis (PD), a recent systematic review examined 574 pregnancies on dialysis, including 51 pregnancies on PD and 523 on HD [69]. This analysis demonstrated that more intensive HD schedules were related to lower rates of prematurity and SGA. There was also a trend toward more SGA in patients with PD; however, more data are needed to support these conclusions. There are more data regarding HD in this population simply because HD remains more prevalent. Peritoneal dialysis has been associated with lower conception rates, potentially secondary to the effect of the peritoneal fluid on ovum survival and transport [70–72]. Other complications observed in pregnant women on dialysis include neonatal deaths (13%), respiratory distress (23%), and neonatal intensive care admissions (68%) out of an observational cohort of 23 live births to mothers on dialysis [61].

Over the past 15 years, there has been a shift toward intensive dialysis during pregnancy. In keeping with previous systematic review, improved outcomes with intensive HD regimes have been reported recently. The largest study demonstrating this compared pregnancy outcome data between the Canadian Toronto Pregnancy and Kidney disease (PreKid) cohort and US American Registry for Pregnancy in Dialysis (ARPD) cohort [73]. The 70 ARPD patients received significantly less time per week on dialysis than the 22 PreKid patients (mean 17 h vs. 43 h, respectively). Live birth rate was higher in the PreKid cohort (83.3%) than in the ARPD (52.6%) cohort. There were significant dose-dependent correlations observed between dialysis intensity and live birth rate, gestational age, and birth weight. More data, though, are needed to determine the optimal dialysis regime for improved maternal and fetal outcomes [40].

In terms of long-term neonatal and childhood outcomes, as with other renal diseases in pregnancy, there are few data. A small prospective study of 10 children born to mothers on dialysis examined neonatal and developmental outcomes, in addition to long-term measures of renal health. The authors reported normal developmental milestones, eGFR and blood pressure, were normal in all children; however, three of the ten children had persistent microalbuminuria [74]. Renal evaluation was performed at a median (range) age of 4.5 (0.8–25.2) years.

Renal transplant

At a population level, the live birth rate per 1000 women of childbearing age with a renal transplant is between fivefold and tenfold lower than that in the general population [61,75]. It is unclear whether fertility post-transplantation is impaired when compared to the general population or whether women are consciously choosing to delay pregnancy in view of immunosuppression regimes. However, once pregnant, the likelihood of completing a successful pregnancy is similar to or higher than that in the general population at approximately 75%–85% [76–79].

There is evidence from several studies that the rates of pregnancy and fetal complications in transplant recipients are higher than those in the general population but much improved when compared to those in dialysis patients [61,79,80]. When comparing transplant recipients to predialysis

CKD patients, there are few observable differences in overall maternal and fetal outcomes. A large multicenter observational study compared outcomes between infants born to mothers with stage 1–5 CKD (n = 610), transplant recipients stratified into stage 1, 2, and 3–5 CKD (n = 121), and healthy controls (n = 1418). Mean gestational age at birth was lower overall in the transplant group than in the CKD group (who had not received a kidney transplant), which was in turn lower than that in healthy controls. However, there were no significant differences in pregnancy outcomes between most of the stratified transplant and CKD groups (stages 2–5). Only in stage 1 CKD did the transplant group demonstrate a significantly higher rate of both preterm and SGA deliveries [81]. Prepregnancy serum creatinine >150 mol/L and proteinuria >300 mg in 24 h were associated with preterm delivery and lower birth weight [78]. Bramham et al. reported poorer neonatal outcomes with a prepregnancy creatinine >125 μmol/L or diastolic BP above 90 mmHg, especially during the second and third trimesters [82].

A large meta-analysis of 50 studies investigated the outcomes of 4706 pregnancies in 3750 transplant recipients [78]. The investigators found that rates of pregnancy-related complications were higher than those in the general population including gestational diabetes mellitus (8% vs. 3.9%), pre-eclampsia (27% vs. 3.8%), and preterm delivery (45.6% vs. 12.5%). The mean gestational age was 35.6 weeks and birth weight 2420 g compared to 38.7 weeks and 3298 g in the general US population, respectively. The mean time between transplant and pregnancy was 3.2 years. Studies were stratified on the basis on transplant-pregnancy interval (<2 years, 2–3 years, 3–4 years, and >4 years). More favorable pregnancy outcomes (live birth rate 80.1% and miscarriage rate 8.3%) were seen in studies with a mean interval of less than two years between transplant and pregnancy. However, this time interval was also associated with the highest rates of premature birth (65.4%) [78].

An interesting study analyzed immunophenotypic profile and immune function in 28 children born to transplanted women on immunosuppressive medication, who were compared with 40 healthy controls [83]. All women were on azathioprine (5–150 mg/day) and prednisolone (5 mg/day) and 70.4% were on tacrolimus (2–8 mg). The transplant group had a significantly lower mean birth weight and 29% of babies born to transplanted mothers were hospitalized for infections in the first year of life compared to 3.6% in matched controls. All children who were hospitalized were exposed to tacrolimus during pregnancy. Furthermore, 80% of infants born to transplanted mothers had low platelets, and leukocytes encompassing neutrophils, B-cells, CD8-and CD4-positive T cells, NK cells, and eosinophils [43]. Follow-up data on this cohort suggested that following birth, the observed weight discrepancies resolved. Of the affected infants, 28% had weight z-scores <-2. Despite this, 12 months later, all subjects were in the normal range for weight, and there was no difference in renal function between treatment and control groups [84].

Children born to mothers on immunosuppression are vaccinated as normal as per local vaccination schedules [85]. All vaccinations within the first 12 months of life are inactivated and therefore suitable for the potentially immunocompromised child [86]. Live vaccines, which are contraindicated in the immunocompromised child, are introduced after 12 months as routine.

Living kidney donors

A recent review estimated that approximately a half million living kidney donations have occurred since the mid-1950s when the first living transplants were performed [87]. Early noncontrolled cohort studies suggested that following donor nephrectomy, no impact on long-term outcomes including pregnancy morbidity for mother and child were observed in past kidney donors [88,89]. However, more recently, larger studies have suggested that pregnancy and fetal morbidity post donor nephrectomy are higher than those in the general population [90–92]. In one study, investigators conducted a retrospective questionnaire-based study of 3213 postdonation pregnancies and healthy controls. Significantly higher rates of pre-eclampsia (5.5% vs. 0.8% $p < 0.0001$) and gestational diabetes (2.7% vs. 0.7% $p < 0.0001$) were found in the postdonation group, with significantly higher rates of preterm delivery (26.3% vs. 15.4% $p < 0.0004$) and fetal loss (19.2% vs. 11.3% $p < 0.0001$) [90]. Another matched retrospective cohort study compared 131 donor pregnancies to 788 nondonor pregnancies using linked registries in Ontario, Canada; data from a registry of living kidney donors were linked to pregnancy-related data from a health insurance-based database. The authors found significantly higher rates of pre-eclampsia (11% vs. 5%, $p < 0.01$) in the donor cohort but no difference in gestational age or birth weight of offspring [91]. These contrasting data suggest a need for prospectively collected large studies to determine the true adverse pregnancy-related maternal and fetal outcomes in past kidney donors.

Specific conditions

Lupus nephritis

CKD patients with systemic lupus erythematosis (SLE) nephritis have higher rates of morbidity and poorer pregnancy outcomes than patients with CKD caused by other etiologies and SLE patients with no nephritis [93–98]. A large meta-analysis examining pregnancy outcomes of women with lupus nephritis showed the most common fetal complications included miscarriage (16%), premature birth (37%), intrauterine growth restriction (13%), stillbirth (4%), and neonatal death (2.5%) [94] Interpreting and extrapolating data from these studies are complicated by the heterogeneous outcomes across disparate populations across the world [58,64,99].

Similar to the general CKD population, the level of proteinuria in the SLE population is associated with adverse outcomes. A recent prospective cohort study followed up 71 pregnancies in women with SLE. The risk of premature delivery increased by 15% with each 1 g/day increase in proteinuria per trimester. In addition, this study also demonstrated that the risk of giving birth to an SGA baby was reduced by 85% in mothers who had been receiving hydroxychloroquine throughout the pregnancy [100].

Pregnancy itself is a risk factor for triggering a flare of lupus nephritis, with one meta-analysis suggesting an incidence of 25.6% [94]. Lupus anticoagulant positivity and non-white ethnicity increases this risk further up to 58% [101]. Finally, infants of mothers with SLE and circulating autoantibodies to anti-Ro/SSA or anti-La/SSB have a 1–2% risk of neonatal lupus [102]. This is secondary to transplacental passage of maternal autoantibodies and causes transient cutaneous, hepatologic, and hematological manifestations that are usually benign and self-limiting by 6 months of age. Cardiac complications include cardiomyopathy, complete heart block (CHB), and long-QT syndrome. CHB may be permanent and require pacemaker insertion for life, and neonatal lupus with cardiac involvement carries a 20–30% risk of mortality [102].

Diabetic nephropathy

Nephropathy secondary to diabetes mellitus (DM) is the most common cause of end-stage kidney disease and is estimated to complicate between 2% and 5% of pregnancies in diabetic women [103–105]. Birth weight and gestation are significantly lower and the incidence of pre-eclampsia significantly higher in women with diabetic nephropathy than in those with diabetes alone [106,107]. In one study, even early diabetic nephropathy manifesting only as microalbuminuria with normal eGFR was associated with an increased risk of pre-eclampsia (OR 4.0) [108]. There was no difference between nephropathy due to type 1 or type 2 DM [105]. Some studies also suggest an alarming rate of maternal mortality (35% within 16 years of giving birth) [109].

Infants born to mothers with prepregnancy diabetes are susceptible to a spectrum of complications at birth including respiratory distress syndrome, birth trauma secondary to macrosomia, and neonatal hypoglycemia secondary to hyperinsulinism. They are also at risk of a number of congenital anomalies including macrosomia, heart defects (hypertrophic cardiomyopathy, ventricular outflow obstruction, and ventricular septal defect), gastrointestinal problems, and congenital anomalies of the kidney and urinary tract (CAKUT) [110]. The rate of nonchromosomal congenital anomalies in infants born to mothers with diabetic nephropathy is higher than that in diabetic mothers with no underlying nephropathy (OR 2.5; 95% CI 1.1–5.3) [110]. In a retrospective cohort study of 108 pregnancies complicated by diabetic nephropathy, the incidence of SGA was 9.3%, preterm delivery 77%, and neonatal intensive care admission 49% [111]. With the exception of higher re-admission rate, fetal outcomes have not changed significantly over the 25-year follow-up time. This was echoed in a systematic review analyzing reports over the last three decades. Stillbirth incidence remains high at 5.5%–6% compared to that in the general population and has been largely static since the 1990s [112]. Mothers with diabetic nephropathy also is associated with a higher risk of preterm delivery than mothers with diabetes but without nephropathy [104].

Importantly, optimal blood pressure control has been shown to decrease the risk of preterm delivery in this group, and therapeutic intervention in this area can improve outcomes [113]. There are also limited data suggesting that there is a risk of developmental delay in this group; however, studies are small with limited follow-up [114].

Autosomal dominant polycystic kidney disease (ADPKD)

A case–control study found slightly higher maternal pregnancy risk including pre-eclampsia but no increased fetal morbidity in maternal ADPKD [115]. However, there is a 50% risk to the child of being affected by ADPKD if one parent is affected, which is reduced to 1%–2% if preimplantation genetic diagnosis is used [116]. Therefore, all women of childbearing age with ADPKD should have access to genetic counseling to discuss the option of preimplantation genetic diagnosis should they wish to start a family. If the baby is born without antenatal genetic investigation, screening postnatally is more controversial, as, currently, there is no specific treatment that will alter disease progression in childhood. All children should have regular (e.g., annual) blood pressure measurement and urinalysis for proteinuria. Diagnostic testing (genetic analysis for ADPKD mutations and renal ultrasound) should be discussed with the parents and child as age appropriate. The discussion should include an option of leaving the decision for diagnostic testing until adolescence when the young person can make an informed decision themselves [117].

Summary

While more data are needed, the evidence is clear from multiple studies that renal disease is associated with worsening maternal and neonatal outcomes. In the offspring, these adverse outcomes are evident in the fetal, neonatal, and early childhood period with an increased associated risk of prematurity, lower birthweight, and increased likelihood of admission to the neonatal unit. These risks additionally appear to be proportional to the decline in renal function. Long-term pediatric outcomes are scarce in this context. Hypertension and proteinuria in pregnant mothers with CKD are independent predictors of worse neonatal outcomes across all stages of CKD, highlighting the need for improved blood pressure control.

Immunosuppression for renal transplant recipient mothers may alter infant immune phenotype, resulting in increased risk of infection in infancy. Extensive data from the general population have demonstrated that prematurity and intrauterine growth restriction results in increased cardiovascular risk in adult life. The high rates of adverse neonatal outcomes make this population particularly susceptible to cardiovascular disease. With cardiovascular programming occurring at such an early stage in antenatal life, the effects of a uremic maternal environment may similarly compound this risk. Long-term follow-up studies are needed to evaluate and establish the long-term health consequences of maternal renal disease on the infant.

Conflicts of interest

None declared.

Practice points

- Renal disease is common in pregnancy and requires multidisciplinary input from obstetricians, nephrologists, and neonatologists for optimum outcomes for affected mothers and their babies.
- Pregnancy in the later stages of CKD has historically been rare but is now increasing in frequency; significant psychological and physical stress are involved for both mothers and children with mothers on renal replacement therapy.
- There are high rates of neonatal morbidity in this group, with rates of prematurity and low birth weight inversely related to the severity of renal disease.
- Offspring of mothers with CKD are likely to be at higher risk for cardiovascular morbidity as adults, although there are limited data regarding this.
- There is a need to minimize additional prenatal risk factors that could contribute to intrauterine cardiovascular programming in mothers with CKD, including maternal obesity, excess gestational weight gain, and hypertension.

Research agenda

- To establish prospective studies that determine the long-term outcomes of children born to mothers with renal disease stratifying relative risk by worsening stages of CKD, level of proteinuria, and blood pressure.
- To establish the optimum dialysis schedule to improve maternal and fetal outcomes.
- To make use of emerging registry and database data at a national or an international level to study pregnancy outcomes in rarer renal diseases.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2019.01.018.

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