Risk of Preeclampsia and Pregnancy Complications in Women With a History of Acute Kidney Injury

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Abstract—An episode of clinically recovered acute kidney injury (r-AKI) has been identified as a risk factor for future hypertension and cardiovascular disease. Our objective was to assess whether r-AKI was associated with future preeclampsia and other adverse pregnancy outcomes and to identify whether severity of AKI or time interval between AKI and pregnancy was associated with pregnancy complications. We conducted a retrospective cohort study of women who delivered infants between 1998 and 2016 at Massachusetts General Hospital. AKI was defined using the 2012 Kidney Disease Improving Global Outcomes laboratory criteria with subsequent clinical recovery (estimate glomerular filtration rate, >90 mL/min per 1.73 m^2 before conception). AKI was further classified by severity (Kidney Disease Improving Global Outcomes stages 1–3) and time interval between AKI episode and the start of pregnancy. Women with r-AKI had an increased rate of preeclampsia compared with women without previous r-AKI (22% versus 9%; $P<0.001$). Infants of women with r-AKI were born earlier (gestational age, 38.2±3.0 versus 39.0±2.2 weeks; $P<0.001$) and were more likely to be small for gestational age (9% versus 5%; $P=0.002$). Increasing severity of r-AKI was associated with increased risk of preeclampsia for stages 2 and 3 AKI (adjusted odds ratio, 3.5; 95% confidence interval, 2.1–5.7 and adjusted odds ratio, 6.5; 95% confidence interval, 3.5–12.0, respectively), but not for stage 1 (adjusted odds ratio, 1.7; 95% confidence interval, 0.9–3.2). A history of AKI before pregnancy, despite apparent full recovery, was associated with increased risk of pregnancy complications. Severity and timing of the AKI episode modified the risk. (***Hypertension*****. 2018;72:451-459. DOI: 10.1161/HYPERTENSIONAHA.118.11161.)** • **Online Data Supplement**

Key Words: acute kidney injury ■ epidemiology ■ hypertension ■ preeclampsia ■ pregnancy

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The global burden of acute kidney injury (AKI) is increasing.[1] AKI severity, duration, and clinical context influence outcomes including the development of hypertension, chronic kidney disease (CKD), and dialysis dependence.[2,3] Although AKI is most often studied in elderly and critically ill populations, it is also observed in children and young adults.[4,5] Young women have been an underrepresented group of study in AKI research, yet the consequences of AKI in young women may be more immediate because of the increased demands on renal function in pregnancy.

Preeclampsia is a multisystem disorder of pregnancy characterized by wide-spread endothelial dysfunction resulting in elevated blood pressure and end-organ damage in the second half of pregnancy.[6] Increased placental production of sFlt-1 (soluble fms-like tyrosine kinase 1), an antagonist of VEGF (vascular endothelial growth factor), plays a central role in the pathogenesis of preeclampsia.[7,8] Many risk factors for preeclampsia are recognized, including nulliparity, obesity, sociodemographic characteristics, and preexisting hypertension.[9]

In a smaller study, we recently demonstrated that a history of AKI, with subsequent complete clinical and laboratory recovery, is associated with higher rates of future preeclampsia.[10] The frequency of fetal complications, including fetal growth restriction, was also higher in these women. Our study identified a novel group of women at high risk for complicated pregnancies and adds to an emerging literature suggesting that subclinical kidney disease is associated with poor pregnancy outcomes.[11–13] Previous studies have demonstrated that the severity of AKI affects long-term prognosis, with stage 3 AKI conferring increased risk of incident CKD and mortality compared with stage 1 AKI.[14,15] Because r-AKI was an infrequent exposure in our original cohort (0.4% of women), we could not address differences in AKI severity and time interval. In

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the present study, we expanded our cohort to include 18 years of data with the aim of confirming our previous findings and to explore whether AKI severity and the time interval between the AKI episode and pregnancy influence outcomes.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Subjects and Data Collection

Massachusetts General Hospital is a quaternary care hospital that serves patients from Boston and surrounding New England. The obstetrics service provides both community and high-risk care, with >3500 deliveries each year. We performed a retrospective cohort study in the Massachusetts General Hospital Obstetric Service Birth Database of all deliveries between September 1, 1998, and March 31, 2016. Clinical information such as medical history, prenatal blood pressure measurements, and delivery information were abstracted into the medical record prospectively and transferred into the study database. We previously reported the outcomes of women from 1998 to 2007, which was combined with data from 2008 to 2016 to increase our analytic power.[10] Detailed past medical history, including previous laboratory results, inpatient and outpatient medical documentation, and billing data, was obtained for the 10 years before pregnancy through the Partners Research Patient Data Registry.[16]

The cohort included all singleton pregnancies that continued beyond 20 weeks of gestation in women who received prenatal care during the study period. In our main analysis, we only included women who had ≥3 assessments of renal function before pregnancy to capture women who had the potential for a diagnosis of AKI before pregnancy. We excluded women with CKD (estimate glomerular filtration rate [eGFR], <90 mL/min per 1.73 m^2 using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation[17] before index pregnancy), patients with structural kidney disease (eg, polycystic kidney disease, congenital solitary kidney), kidney transplant donors and recipients, and patients with known glomerulonephritis or proteinuria (>2+ on urine dipstick) at the first prenatal visit. All women who presented for prenatal care after 20 weeks of gestational age or who were missing baseline blood pressure, urine dipstick, or weight (all part of standard care) at the first prenatal visit were excluded.

Ascertainment of Exposures and Outcomes

We defined AKI using clinical laboratory data obtained before pregnancy. AKI cases were identified using the Kidney Disease Improving Global Outcomes laboratory definition of AKI as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or an increase in serum creatinine to 1.5× baseline, which is known or presumed to have occurred within the prior 7 days.[18] For AKI diagnosed in the outpatient setting, an increase in serum creatinine to 1.5× baseline was used to establish the diagnosis.[19] Stage of AKI was similarly defined using Kidney Disease Improving Global Outcomes criteria (stage 1: serum creatinine elevation of >0.3 mg/dL within 48 hours or 1.5–1.9× baseline; stage 2: serum creatinine elevation of 2.0–3.0× baseline; and stage 3: serum creatinine elevation ≥3.0× from baseline or need for renal replacement therapy). Only the first pregnancy after AKI was considered for analysis. Medical records for all women who met laboratory criteria for AKI in the cohort were reviewed in detail to confirm AKI diagnosis. Before chart review, we identified all women who had a normal eGFR (>90 mL/min per 1.73 m^2) at the closest time point before the start of the index pregnancy. Women who had a GFR <90 mL/min per 1.73 m^2 were considered to have CKD. The cause of AKI was determined by independent chart review (including clinical documentation, laboratory, and radiology review) by 2 nephrologists who were blinded to outcomes. Time interval from AKI to pregnancy was calculated from peak serum creatinine during the AKI episode to estimated date of last menstrual period (delivery date−gestational age at delivery). Preexisting hypertension was defined as a blood pressure before 20 weeks of gestation ≥140/90 mm Hg, use of antihypertensive medications, or documentation of hypertension in the obstetric medical record at initial prenatal visit. Preexisting diabetes mellitus was defined based on documentation in the obstetric medical record at initial prenatal visit or use of insulin or oral hypoglycemic before pregnancy.

Preeclampsia was defined based on blood pressure and spot urine protein measurements made at prenatal visits. In women who were normotensive at their first prenatal visit (blood pressure <140/90 mm Hg), and lacked a diagnosis of chronic hypertension, gestational hypertension was defined as blood pressure ≥140/90 mm Hg after 20 weeks of gestation.[20] In women who were hypertensive at their first prenatal visit (blood pressure ≥140/90 mm Hg), gestational exacerbation of hypertension was defined by the presence of a rise in systolic blood pressure >30 mm Hg or a rise in diastolic blood pressure >15 mm Hg after 20 weeks of gestation. Preeclampsia was defined as the presence of gestational hypertension and ≥2+ proteinuria after 20 weeks of gestation or gestational hypertension and 1+ proteinuria after 20 weeks of gestation with confirmation of the diagnosis in the electronic delivery record. Preterm preeclampsia and early preterm preeclampsia were defined as preeclampsia requiring delivery before 37 and 34 weeks of gestation, respectively. Small for gestational age (SGA) was defined as birthweight in the fifth percentile or lower for completed week of gestational age based on national standards.[21] Perinatal death was defined as fetal death at >20 weeks of gestation or infant death that occurred at fewer than 7 days of age. The composite fetal outcome was defined as preterm delivery (<37 weeks), neonatal intensive care unit (NICU) admission, SGA, or perinatal death.

Statistical Analyses

Baseline characteristics and primary outcomes in women with and without r-AKI were compared using Student *t* test for continuous variables and Fisher exact tests for categorical variables. Univariate and multivariate logistic regression was used to compare the odds of preeclampsia, preterm delivery, delivery by cesarean section, SGA infants, perinatal death, NICU admission, and the composite fetal outcome. Multivariate logistic regression models included variables associated with adverse pregnancy outcomes based on prior literature and included maternal age, body mass index, first-trimester diastolic blood pressure, prepregnancy diabetes mellitus status, race, and parity. The association between maternal baseline characteristics and preeclampsia is summarized in Table S1 in the online-only Data Supplement. The effect estimates in this cohort were similar to previous literature.[22] In a secondary analysis, we included all women who met our initial inclusion criteria regardless of assessment of kidney function before pregnancy (Figure 1). In addition, we conducted a subgroup analysis that included only nulliparous women given the possibility that a prior undocumented pregnancy with preeclampsia could have altered our results.

To assess the relationship between AKI severity and adverse pregnancy outcomes, we modeled AKI stage by Kidney Disease Improving Global Outcomes classification as a 4-category exposure variable (no AKI, stage 1–3 AKI). Main outcomes were compared between groups using ANOVA for continuous variables and Fisher exact tests for categorical variables. Multivariate logistic regression models included variables associated with adverse pregnancy outcomes listed previously.

To assess the relationship between time interval from AKI to pregnancy and risk for adverse pregnancy outcomes, we compared outcomes stratified by time interval ≤18 months from AKI episode to pregnancy and >18 months from AKI to pregnancy. Eighteen months was chosen as this was the upper limit of the lowest quartile of time interval between AKI and pregnancy. Primary outcomes were compared between time groups using ANOVA for continuous variables and Fisher exact tests for categorical variables. In an analysis looking only at women with r-AKI, time interval was treated as a continuous variable in a multivariate logistic regression model including variables associated with adverse pregnancy outcomes listed previously. Statistical analyses were conducted using STATA 14 (Stata Corporation, College Station, TX).

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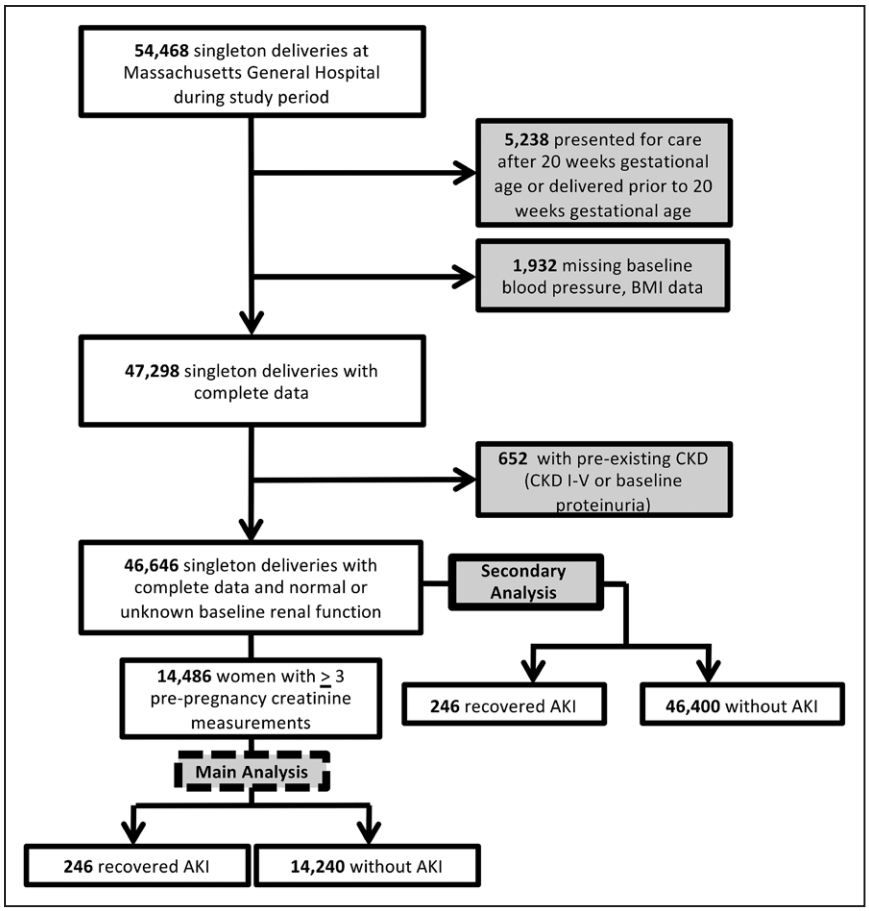

Figure 1. Cohort design. Flow of patients into cohort. AKI indicates acute kidney injury; BMI, body mass index; and CKD, chronic kidney disease.

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Results

Participant Characteristics

From the initial population of 54468 singleton deliveries at Massachusetts General Hospital during the study period, 14486 women met the inclusion criteria for entry into the study cohort (Figure 1). A total of 246 women met the criteria for r-AKI (105 women from 1998 to 2007 and 141 women from 2008 to 2016). Characteristics of the 2 cohorts (1998–2007 and 2008–2016) were similar with respect to both baseline demographics and outcomes.

Baseline characteristics of women with and without r-AKI are summarized in Table 1. Women with r-AKI were of similar age and body mass index at first prenatal visit. Women with r-AKI were more likely to have preexisting diabetes mellitus (9% versus 5%; P=0.006). The cause of AKI episodes is described in Table S2. AKI developed as a complication of a prior pregnancy in 7% of women in the cohort.

Maternal and Fetal Outcomes

Pregnancy outcomes in women with and without r-AKI are summarized in Table 2. Women with r-AKI had increased rates of preeclampsia and preterm preeclampsia (22% versus 9%, P<0.001 and 9% versus 2%, P<0.001, respectively). Rates of delivery by cesarean section were similar between the groups (38% versus 31%, P=0.190). After adjustment for maternal age, body mass index, race, parity, history of diabetes mellitus, and diastolic blood pressure at first prenatal visit, r-AKI remained significantly associated with adverse outcomes. Namely, r-AKI was associated with a 3-fold increased odds of preeclampsia and preterm preeclampsia compared with women without AKI (adjusted odds ratio [OR], 2.9; 95% confidence interval [CI], 1.9–4.4 for preeclampsia and adjusted OR, 3.6; 95% CI, 1.8–7.1 for preterm preeclampsia). Although rates of early preterm preeclampsia (<34 weeks) were higher in women with r-AKI (4% versus 1%, P<0.001), this association did not persist after multivariate adjustment in a logistic regression model (adjusted OR, 1.2; 95% CI, 0.2–8.7).

Offspring of mothers with r-AKI were born earlier (gestational ages, 38.2±3.0 versus 39.0±2.2 weeks; P<0.001). Mean offspring weights in women with and without r-AKI were 3010±690 and 3350±620 g, respectively (P<0.001). Women with r-AKI were more likely to have SGA infants compared with women without AKI (9% versus 5%, P=0.002) and have neonates admitted to the NICU (19% versus 10%, P<0.001). The association between r-AKI and SGA infants persisted after excluding women who developed preeclampsia. There was no significant difference in the rates of perinatal deaths between groups (adjusted OR, 1.9; 95% CI, 0.7–5.5). Recovered AKI was associated with increased odds of SGA infants, requirement for NICU admission, and the composite neonatal adverse outcome (adjusted OR, 2.2; 95% CI, 1.4–3.4, adjusted OR, 2.0; 95% CI, 1.4–2.8, and adjusted OR, 1.9; 95% CI, 1.4–2.6, respectively).

Table 1. Characteristics in Patients With r-AKI Versus No AKI

Characteristic	r-AKI (N=246)			No AKI (N=14 240)	*P* Value
	Stage 1 (N=98)	Stage 2 (N=99)	Stage 3 (N=49)		
Demographics					
Age at first prenatal visit, years	31.0±6.3			31.1±6.2	0.901
	31.3±5.4	31.0±6.8	28.7±6.4		
Non-white race	36% (89)			42% (6033)	0.051
	33% (32)	37% (37)	40% (20)		
Married	59% (144)			66% (9427)	0.012
	64% (63)	57% (56)	51% (25)		
Initial prenatal visit characteristics					
Gestational age at visit, wk	10.7±2.6			11.2±4.1	0.062
	10.3±2.6	11.3±2.8	10.7±2.5		
BMI, kg/m^2	26.8±6.1			26.7±5.7	0.835
	26.7±6.0	26.5±5.2	27.3±5.6		
Nulliparous	38% (94)			43% (6176)	0.105
	32% (31)	36% (36)	55% (27)		
Preexisting hypertension	3% (9)			6% (826)	0.153
	1% (1)	4% (4)	8% (4)		
Preexisting diabetes mellitus	9% (21)			5% (673)	0.006
	3% (3)	9% (9)	18% (9)		
Systolic blood pressure, mm Hg	111±12			110±12	0.392
	109±11	110±12	113±14		
Diastolic blood pressure, mm Hg	68±9			68±8	0.767
	67±9	68±9	72±9		
Preconception creatinine, mg/dL	0.65±0.14			0.66±0.11	0.231
	0.67±0.12	0.64±0.12	0.56±0.15		
Peak creatinine, mg/dL	1.7±0.8			n/a	n/a
	1.2±0.34	1.5±0.46	2.6±1.3		
AKI to LMP, mo	32 [18–60]			n/a	n/a
	32 [18–56]	39 [18–68]	27 [12–42]		

Data are presented as % (n), the mean±SD or median interquartile range. *P* value reflects test of association between all recovered acute kidney injury (r-AKI) and no acute kidney injury (AKI). Peak Creatinine reflects highest creatinine level reported during AKI episode. BMI indicates body mass index; LMP, last menstrual period; and n/a, not applicable.

Outcomes by r-AKI Stage

Baseline characteristics of women by Kidney Disease Improving Global Outcomes AKI stage are summarized in Table 1. Women with stage 3 r-AKI were on average younger, had a higher body mass index, and were more likely to have diabetes mellitus before pregnancy compared with women with no AKI or a history of less severe AKI. Table 2 summarizes the main maternal and fetal outcomes by r-AKI stage. The rate of preeclampsia increased with increasing stage of r-AKI (12% in stage 1, 23% in stage 2, and 40% in stage 3; $P<0.001$). Gestational age at delivery and mean neonatal birthweights decreased with increasing AKI stage (38.7±2.4 weeks and 3240±600 g for stage 1 r-AKI, 38.1+3.3 weeks and 3040±730 g for stage 2 r-AKI, and 37.1±3.5 weeks and 2940±730 g for stage 3 r-AKI; $P<0.001$, respectively). Rates of perinatal death did not significantly differ across r-AKI stage ($P=0.161$). After multivariate adjustment, odds of preeclampsia were highest in women with stage 3 r-AKI (adjusted OR, 6.5; 95% CI, 3.5–12.0) and intermediate in women with stage 2 r-AKI (adjusted OR, 3.5; 95% CI, 1.2–5.7). There was no statistically significant difference in odds of preeclampsia, preterm delivery of need for NICU admission in women with a history of stage 1 AKI as compared with women with no AKI (Figure 2).

Outcomes by Time Interval

Baseline characteristics of women with AKI stratified by time interval between AKI and pregnancy are summarized in Table S3. Women who conceived within 18 months of AKI were more likely to be of non-white race and had higher rates of

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Table 2. Primary Maternal-Fetal Outcomes in Patients With r-AKI Versus No AKI

Outcome	r-AKI (N=246)			No AKI (N=14 240)	Unadjusted Odds	Adjusted Odds	*P* Value
	Stage 1 (N=98)	Stage 2 (N=99)	Stage 3 (N=49)				
Maternal Outcomes							
Cesarean section	38% (94)			31% (4430)	1.4 [1.1–1.8]	1·3 [0.9–1.9]	0.190
	36% (35)	40% (40)	39% (19)				
Preeclampsia	22% (55)			9% (1274)	3.0 [2.2–4.0]	2·9 [1.9–4.4]	<0.001
	12% (12)	23% (23)	40% (20)				
Preterm preeclampsia (<37 wk)	9% (22)			2% (330)	4.1 [2.6–6.5]	3·6 [1.8–7.1]	<0.001
	4% (4)	9% (9)	18% (20)				
Early preterm preeclampsia (<34 wk)	4% (9)			1% (95)	5.7 [2.8–11.3]	1·2 [0.2–8.7]	0.878
	1% (1)	4% (4)	8% (4)				
Gestational hypertension	22% (51)			12% (1621)	2.0 [1.5–2.7]	2.3 [1.7–3.3]	<0.001
	12% (12)	25% (24)	33% (15)				
Fetal outcomes							
Gestation age at delivery, wk	38.2±3.0			39.0±22	n/a	n/a	<0.001
	38.7±2.4	38.1±3.3	37.1±3.5				
Baby weight, g	3010±690			3350±620	n/a	n/a	<0.001
	3240±600	3040±730	2940±730				
Birth weight <10th percentile	20% (50)			9% (1299)	2.5 [1.8–3.5]	2.7 [1.7–4.3]	<0.001
	16% (16)	24% (24)	20% (10)				
Birth weight <5th percentile	9% (23)			5% (718)	1.5 [0.9–2.4]	2.2 [1.4–3.4]	0.001
	7% (7)	10% (10)	12% (6)				
Birth weight <3rd percentile	3% (8)			3% (397)	1.2 [0.6–2.4]	1.3 [0.6–2.6]	0.495
	…	…	…				
Perinatal death	…			1% (108)	2.2 [0.8–5.9]	1.9 [0.7–5.5]	0.209
Neonatal ICU admission	19% (46)			10% (1364)	2.2 [1.6–3.0]	2.0 [1.4–2.8]	<0.001
	13% (13)	19% (19)	30% (14)				
Composite fetal outcome	39% (96)			18% (2621)	2.3 [1.8–3.1]	1.9 [1.4–2.6]	<0.001
	25% (25)	32% (32)	39% (19)				

Data are presented as % (n), the mean±SD and odds ratio (95% confidence interval). Gestational hypertension outcome included only for women without preexisting hypertension. Outcomes are adjusted for age, race, body mass index, diastolic blood pressure at first prenatal visit, history of diabetes mellitus, and parity. *P* values reflect the adjusted analysis for dichotomous outcome variables and *t* tests between for continuous outcome variables entire recovered acute kidney injury (r-AKI) cohort and no acute kidney injury (AKI) cohort. Numbers of perinatal deaths and birthweight <3rd percentile in r-AKI group suppressed to preserve confidentiality because of low numbers. ICU indicates intensive care unit.

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preexisting hypertension. Rates of preeclampsia, preterm delivery, delivery by cesarean section, and need for NICU admission were higher in women who conceived within 18 months of the AKI episode (Figure 3). After multivariate adjustment, women who conceived within 18 months of AKI were at 7-fold increased risk of preeclampsia and 4-fold increased risk of having an infant admitted to the NICU. Women who conceived >18 months from the AKI episode had increased odds of preeclampsia compared with women without r-AKI; however, the magnitude of the risk was attenuated. A similar association was also observed for preterm delivery. The risk of an SGA infant did not differ between time intervals. Among women with r-AKI, risk of preeclampsia decreased by 16% for each 6-month interval time increase between AKI and day of last menstrual period (adjusted OR, 0.84; 95% CI, 0.77–0.92).

Secondary Analyses

We performed a secondary analysis of women who met our initial inclusion criteria except for ≥3 prepregnancy serum creatinine measurements. The frequency of preexisting diabetes mellitus and hypertension was lower in the expanded cohort compared with the restricted population used in the main analysis (Table S4). After multivariate adjustment, we observed a similar association between r-AKI and adverse outcomes when using the expanded cohort (Table S5).

In an analysis of only nulliparous women, women with r-AKI remained at 2-fold increased risk for both preeclampsia

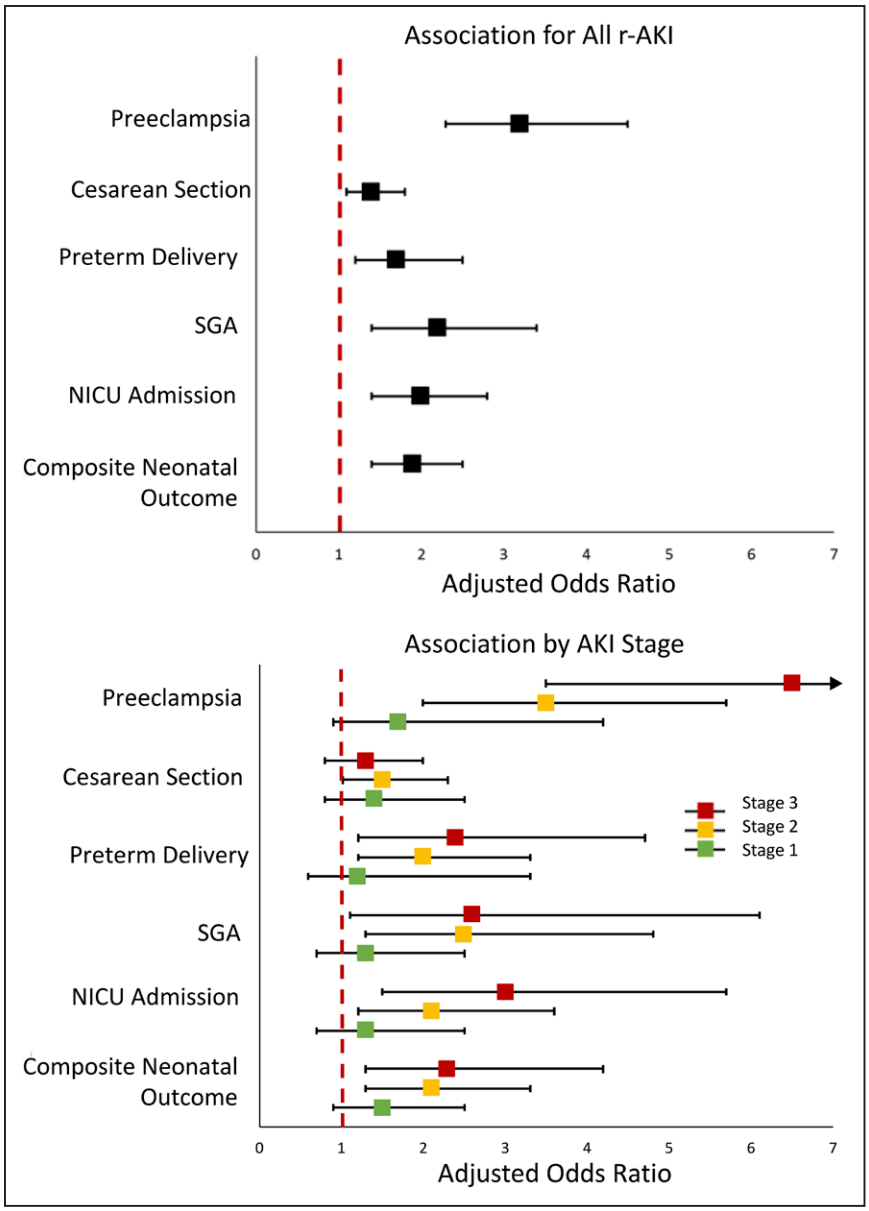

Figure 2. Association between Kidney Disease Improving Global Outcomes (KDIGO) acute kidney injury (AKI) stage and main maternal-fetal outcomes. Association of adverse outcomes with recovered AKI (r-AKI) from logistic regression by severity of AKI episode (KDIGO stages 1–3). Point estimates and 95% confidence intervals are given in the online-only Data Supplement. NICU indicates neonatal intensive care unit; and SGA, small for gestational age.

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and SGA infant. In a subgroup analysis by AKI severity in the nulliparous cohort (N=94 r-AKI), only women with a history of stage 3 AKI were at increased risk for adverse outcomes (Table S6).

Discussion

Despite global improvements in maternal mortality in the last decade, rates of maternal death in the United States are increasing. Hypertensive disorders of pregnancy, including preeclampsia, are a leading cause of maternal morbidity and mortality.[23–25] The effects of preeclampsia are not limited to the duration of pregnancy: women with preeclampsia are at increased risk for future cardiovascular disease and their offspring, if born premature or at low birth weight, are at increased risk for chronic disease in adulthood.[26] The results of our study provide further evidence on the association between r-AKI and adverse pregnancy outcomes including preeclampsia and premature delivery, even when creatinine has completely recovered before gestation, supplementing prior work. New to this study, we demonstrated that severe episodes of AKI and shorter interval between AKI episode and pregnancy were associated with higher risks of preeclampsia.

Studies assessing long-term complications of AKI in humans have largely omitted young populations.[15,27–29] AKI is most often studied in elderly and critically ill populations with high comorbid rates of hypertension, diabetes mellitus, and vascular disease.[15,29,30] AKI, however, is also observed in children.[5] The concept that reversible AKI has long-term consequences has been demonstrated with respect to incident CKD, end-stage renal disease, and death. In a study of clinically recovered hospitalized patients with AKI from a large health system, individuals with r-AKI were at nearly 6-fold increased risk for incident stage 3 CKD.[29] AKI has also been associated with increased mortality.[31,32]

Given that AKI stage was associated with higher risk for gestational hypertensive disorders, one hypothesis is that women with clinically recovered AKI, especially those with severe AKI, have residual subclinical kidney disease and lower nephron mass

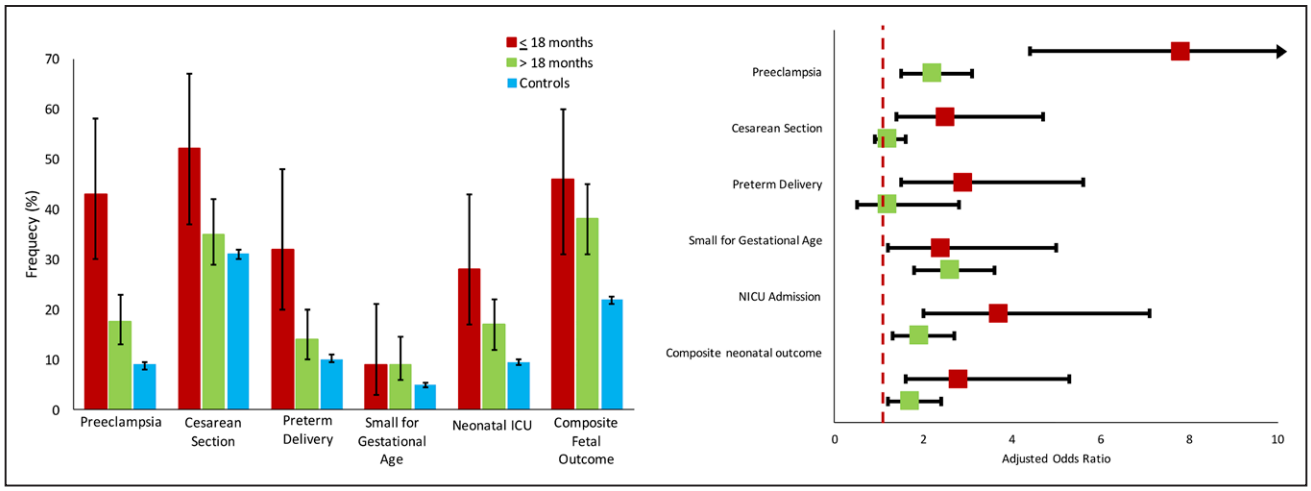

Figure 3. Association between time interval and main maternal-fetal outcomes. **Left**, Frequency (%) of adverse outcomes between recovered acute kidney injury (r-AKI; stratified by time interval of <18 or >18 months from acute kidney injury event to pregnancy). Error bars represent 95% confidence interval (CI). **Right**, Association of adverse outcomes with r-AKI stratified by time interval from logistic regression. Point estimates and 95% CIs are given in the online-only Data Supplement. ICU indicates intensive care unit; and NICU, neonatal intensive care unit.

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before entering pregnancy. Isolated measurements of serum creatinine perform poorly in estimating GFR in individuals with normal kidney function. Nephron number can be reduced by 50% before serum creatinine rises above the normal range. Low nephron number and surrogates for low renal mass have been linked with adverse long-term health consequences, including hypertension and CKD.[26] Low nephron number also seems to be a risk factor for pregnancy complications: both living kidney donors and women with a solitary congenital kidney have been identified as groups at high risk for gestational hypertension and preeclampsia.[11,13] This association is especially relevant in the transplant donor population, who are generally healthy and receive careful medical assessment before donation. Pregnancy is associated with profound changes in renal plasma flow that results in a 50% rise in GFR by midgestation. Impairments in gestational hyperfiltration have been identified as a risk factor for preeclampsia, preterm birth, and low birthweight.[33] Of note, women with stage 3 AKI had a lower prepregnancy serum creatinine than women with milder stages of AKI in our cohort. One hypothesis is that women who recover from more severe AKI were in a state of hyperfiltration before entering pregnancy because of reduced nephron number, which may further lead to impaired renal adaptation during pregnancy. Because creatinine measurements are not part of routine care prenatal care, we were not able to assess GFR changes during pregnancy in this cohort. In addition, the kidney plays a key role in gestational plasma volume expansion which is recognized to be inadequate in early pregnancy in women with preeclampsia. Subclinical reduced renal function may also contribute to impaired hemodynamic adaptation associated with reduced placental perfusion. One potential approach to identify at-risk women would be to assess renal functional reserve before conception in women with a history of severe AKI.

The mechanisms of recovery after AKI are not fully understood. Although renal tubular epithelium can regenerate after an ischemic insult, endothelial cells regeneration may not be complete.[34–36] In animal models, significant vascular dropout has been observed after ischemic AKI, despite clinical recovery.[37] AKI is emerging as a systemic disease with generalized inflammation and endothelial injury.[38] Studies in experimental animals suggest that many of the systemic consequences of AKI persist in the long term.[39] It is possible that women with r-AKI represent a unique group of patients who have underlying endothelial dysfunction and therefore more susceptible preeclampsia. These patients may be particularly susceptible to develop endothelial injury even at lower levels of placental soluble factors made during pregnancy. We identified that shorter time interval between the episode of AKI and pregnancy was associated with increased risk of preeclampsia. Longer time interval may allow for resolution of endothelial dysfunction. Delaying pregnancy after an AKI episode may be 1 strategy to reduce the risk of preeclampsia in this population; however, our findings need to be confirmed in other cohorts before such a recommendation can be made. In addition, this finding should prompt increased efforts to prevent AKI in young women.

The strengths of our study include our use of a large pregnancy database with detailed clinical information on all participants. This allowed us to control for important confounders such as early-pregnancy blood pressure, weight, and previous chronic medical conditions, such as diabetes mellitus and hypertension. AKI cases were identified based on biochemical definitions. In addition, all cases were confirmed by independent chart review by 2 nephrologists.

Our study does have limitations. Because this is a retrospective observational study, there is potential for bias and residual confounding in our analysis, despite efforts to reduce this in our analytic design. The diagnosis of AKI and preeclampsia may not be captured completely. Our definition of preeclampsia deviates from the most recent changes in the definition by the American College of Obstetricians and Gynecologists.[20] As a majority of our data were collected before the current version of these guidelines, this represented a reproducible definition of preeclampsia that was not subject to bias of selection of laboratory testing and diagnostic coding by providers. We could only identify AKI events that

happened in our health network. To diagnose AKI, laboratory samples must be obtained; women with fewer interactions with the healthcare system or who are viewed as healthier by their medical providers may not have renal function checked when presenting with similar types of illnesses. To address this limitation, only women with previous creatinine measurements were included in the main analysis.

Perspectives

An episode of AKI, followed by clinical recovery before conception, is a risk factor for pregnancy complications including preeclampsia. Severity of the AKI episode and duration between AKI episode and pregnancy influence the risk for adverse outcomes. This study adds to the growing literature that reversible AKI is not harmless. Our study has important implications for pregnancy counseling. Practitioners should actively assess for episodes of AKI and counsel women on increased risk. Our findings also highlight the importance of AKI prevention, especially in young women.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This study confirms the previous findings that an episode of kidney injury followed by complete clinical recovery is associated with increased risk of complications in pregnancy including preeclampsia.
- We also found that the severity of kidney injury and the timing of the kidney injury modify the risk of pregnancy complications. Women with the most severe episodes of kidney injury (stage 3 acute kidney injury) and who conceived within 1 year of the kidney injury episode were at the highest risk for preeclampsia and infant growth restriction.

What Is Relevant?

- Preeclampsia is a leading cause of maternal morbidity and mortality across the globe. The findings from our study suggest that some women may develop hypertensive disorders in pregnancy as a consequence of prior kidney injury. In addition, the results of this study will help providers better counsel women with previous kidney injury who are planning pregnancy.

Summary

A history of acute kidney injury before pregnancy, despite clinical recovery, is associated with increased risk of gestational hypertensive disorders including preeclampsia.

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ONLINE ONLY SUPPLEMENT

Title: Risk of Preeclampsia and Pregnancy Complications in Women with a History of Acute Kidney Injury

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Point Estimates, 95% Confidence Intervals from Figure 2:

Results for all r-AKI stages: preeclampsia (adjusted OR 3.2, 95% CI 2.3-4.5), cesarean section (adjusted OR 1.4, 95% CI 1.1-1.8), preterm delivery (adjusted OR 1.7, 95% CI 1.2-2.5), SGA (adjusted OR 1.7, 95% CI 1.0-2.7), NICU (adjusted OR 2.0, 95% CI 1.4-2.8) composite neonatal outcome (adjusted OR 1.9, 95% CI 1.4-2.6). Results for Stage 1 r-AKI: preeclampsia (adjusted OR 1.7, 95% CI 0.9-3.2), cesarean section (adjusted OR 1.3, 95% CI 0.8-2.0), preterm delivery (adjusted OR 1.2, 95% CI 0.6-3.3), SGA (adjusted OR 1.6, 95% CI 0.7-3.7), NICU (adjusted OR 1.3, 95% CI 0.7-2.5) composite neonatal outcome (adjusted OR 1·5, 95% CI 0·9-2·5). Results for Stage 2 r-AKI: preeclampsia (adjusted OR 3.5, 95% CI 1.2-5.7), cesarean section (adjusted OR 1.5, 95% CI 1.0-2.3), preterm delivery (adjusted OR 2.0, 95% CI 1.2-3.3), SGA (adjusted OR 2.5, 95% CI 1.3-4.8), NICU (adjusted OR 2.1, 95% CI 1.2-3.6), composite neonatal outcome (adjusted OR 2.1, 95% CI 1.3-3.3). Results for Stage 3 r-AKI: preeclampsia (adjusted OR 6.5, 95% CI 3.5-12.0), cesarean section (adjusted OR 1.4, 95% CI 0.8-2.5), preterm delivery (adjusted OR 2.4, 95% CI 1.2-4.7), SGA (adjusted OR 2.6, 95% CI 1.1-6.1), NICU (adjusted OR 3.0, 95% CI 1.5-5.7), composite fetal outcome (adjusted OR 2.3, 95% CI 1.3-4.2).

Point Estimates, 95% Confidence Intervals from Figure 3:

Results for time Interval $\leq$18 months: preeclampsia (adjusted OR 7.8, 95% CI 4.4-14.0), cesarean section (OR 2.5, 95% CI 1.4-4.7) preterm delivery (adjusted OR 2.9, 95% CI 1.5-5.6), SGA infant (adjusted OR 2.4, 95% CI 1.2-5.0), NICU (adjusted OR 3.7, 95% CI 3.0-7.1), composite neonatal outcome (adjusted OR 2.8, 95% CI 1.6-5.3). Results for time interval >18 months: preeclampsia (adjusted OR 2.2, 95% CI 1.5-3.1), cesarean section (adjusted OR 1.2, 95% CI 0.9-1.6), preterm delivery (adjusted OR 1.2, 95% CI 0.5-2.8), SGA (adjusted OR 2.6, 95% CI 1.8-3.6), NICU (adjusted OR 1.9, 95% CI 1.3-2.7), composite neonatal outcome (adjusted OR 1.7, 95% CI 1.2-2.4).

Supplementary Tables:

S1. Association between preeclampsia and previously described risk factors in the cohort.

Risk Factor	Odds Ratio [95% CI] MGH Cohort	Odds Ratio [95% CI] *Bartsch et al* Meta-analysis[27]
Maternal Age > 35	1.3 [1.2-1.4]	1.2 [1.1-1.3]
Maternal Age > 40	1.6 [1.3-1.8]	1.5 [1.2-2.0]
BMI > 25	2.4 [2.2-2.6]	2.1 [2.0-2.2]
BMI > 30	2.7 [2.5-3.0]	2.8 [2.6-3.1]
Nulliparity	1.7 [1.6-1.8]	2.1 [1.9-2.4]
Chronic Hypertension	4.3 [3.8-4.9]	5.1 [4.0-6.5]
Pre-gestational Diabetes	2.3 [2.0-2.8]	3.7 [3.1-4.3]
Black race	1.4 [1.1-1.7]	Not reported

Univariable association between previously described preeclampsia risk factors and preeclampsia outcome in the MGH cohort and as described by *Bartsch et al* in large meta-analysis of preeclampsia risk factors.

S2. AKI etiology

Etiology	Recovered AKI N=246
Acute Tubular Necrosis/Pre-renal	48% (117)
Drug-Induced	8% (20)
Pregnancy-associated (prior pregnancy)	7% (18)
Obstruction/Mechanical	5% (12)
Unknown	32% (78)

Data are presented as % (n)

S3. Baseline characteristics in women with AKI stratified by time between AKI episode and date of last missed period.

Characteristic	AKI to LMP ≤18 months (N=63)	AKI to LMP > 18 months (N=183)	
Demographics			
Age at first prenatal visit – years	30.8 ± 6.4	31.1 ± 6.3	p=0.804
Non-white race	48% (30)	32% (59)	p=0.028
Married	58% (37)	58% (107)	p=0.971
Initial PNV Characteristics			
Gestational age at visit – weeks	10.8 ± 3.0	10.7 ± 2.5	p=0.657
BMI– kg/m^2	26.7 ± 6.5	26.8 ± 6.0	p=0.986
Nulliparous	35% (22)	39% (72)	p=0.533
Pre-existing Hypertension	8% (5)	2% (4)	p=0.036
Pre-existing Diabetes	12% (8)	7% (13)	p=0.170
Systolic blood pressure – mm Hg	111 ± 15	110 ± 11	p=0.500
Diastolic blood pressure – mm Hg	69 ± 11	68 ± 8	p=0.859
Pre-conception Creatinine – mg/dl	0.6 ± 0.1	0.6 ± 0.1	p=0.470
Peak Creatinine – mg/dl	1.5 ± 0.9	1.6 ± 0.8	p=0.592

Data are presented as % (n) or the mean ± SD. LMP = Last missed period. BMI = Body mass index. Peak Creatinine reflects highest creatinine level reported during AKI episode.

S4. Baseline characteristics and outcomes in women with no history of AKI stratified by number pre-pregnancy serum creatinine measurements

	Main Analysis No AKI Cohort ≥ 3 Cr measurements N=14,240	**Expanded No AKI Cohort No minimum Cr measurements N=46,400**
Demographics		
Age at first prenatal visit – years	31.1 ± 6.2	31.1 ± 5.8
Non-white race	42% (6,033)	38% (17,482)
Married	66% (9,427)	72% (33,242)
Initial PNV Characteristics		
Gestational age at visit – weeks	11.2 ± 4.1	11.6 ± 4.7
BMI– kg/m^2	26.7 ± 5.7	25.4 ± 5.2
Nulliparous	43% (6,176)	48% (22,456)
Pre-existing Hypertension	6% (826)	4% (1,701)
Pre-existing Diabetes	5% (673)	3% (1,438)
Systolic blood pressure – mm Hg	110 ± 12	109 ± 11
Diastolic blood pressure – mm Hg	68 ± 8	67 ± 8
Maternal Outcomes		
Cesarean section	31% (4,430)	28% (13,002)
Preeclampsia	9% (1,274)	5% (2,232)
Preterm Preeclampsia		
<37 weeks	2% (330)	1% (531)
<34 weeks	1% (95)	0.3% (139)
Fetal Outcomes		
Gestation age at delivery – weeks	39.0 ± 2.2	39.2 ± 2.1
Baby weight (live births) – grams	3,350 ± 620	3,370 ± 570
Birth weight <5^h percentile	5% (718)	5% (2,166)
Neonatal ICU Admission	10% (1,364)	8% (3,631)
Composite Fetal Outcome	18% (2,621)	19% (8,831)

Data are presented as % (n), the mean ± SD. Cr = creatinine.

S5: Association of AKI stage with the development of adverse pregnancy outcomes in the entire cohort regardless of previous kidney function assessment.

	Preeclampsia	**Preterm Delivery**	**SGA**
All r-AKI Stages	5.7 [4.2-8.0]	2.1 [1.5-3.1]	2.4 [1.5-3.8]
AKI Stage 1	3.0 [1.6-5.7]	1.4 [0.7-2.8]	1.8 [0.8-4.1]
AKI Stage 2	6.2 [3.7-10.4]	2.4 [1.4-4.1]	2.7 [1.4-5.3]
AKI Stage 3	11.7 [6.3-21.8]	3.0 [1.5-5.8]	2.8 [1.2-6.7]

Data are presented as OR [95% CI]. Model includes covariates for maternal age, maternal BMI, baseline systolic blood pressure, parity, race and diabetes history. SGA = small for gestational age.

S6: Association of AKI stage with the development of adverse pregnancy outcomes in nulliparous women

	Preeclampsia	Preterm Delivery	SGA
All r-AKI Stages	2.0 [1.2-3.3]	1.5 [0.8-2.6]	2.2 [1.2-4.1]
AKI Stage 1	0.8 [0.2-2.7]	0.6 [0.2-2.4]	1.8 [0.6-5.1]
AKI Stage 2	1.6 [0.7-4.0]	1.1 [0.4-3.1]	1.7 [0.6-5.1]
AKI Stage 3	4.2 [1.8-9.2]	3.1 [1.3-7.2]	3.2 [1.2-8.9]

Data are presented as adjusted OR [95% CI]. Model includes covariates for maternal age, maternal BMI, baseline diastolic blood pressure, race and diabetes history. SGA = small for gestational age.