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Kidney Disease and Maternal and Fetal Outcomes in Pregnancy

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Abstract

Background—Pregnancy in kidney disease is considered high risk but the degree of this risk is unclear. We tested the hypothesis that kidney disease in pregnancy is associated with adverse maternal and fetal outcomes.

Study Design—Retrospective study comparing pregnant women with and without kidney disease.

Setting & Participants—Using data from an integrated healthcare delivery system from 2000 through 2013, 778 women met the criteria for kidney disease. Using a pool of 74,105 women without kidney disease, we selected 778 women to use for matches for the women with kidney disease. These women were matched 1:1 by age, race, and history of diabetes, chronic hypertension, liver disease and connective tissue disease.

Predictor—Kidney disease was defined using the NKF-KDOQI definition for chronic kidney disease or ICD-9 codes prior to pregnancy or serum creatinine >1.2 mg/dL and/or proteinuria in first trimester.

Outcomes & Measurements—Maternal outcomes included preterm delivery, delivery via cesarean section, preeclampsia/eclampsia, length of stay at hospital (>3 days) and maternal death.

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Supplementary Material: Table S1: Basis for diagnosis of kidney disease.

Note: The supplementary material accompanying this article (doi:) is available at www.ajkd.org

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Fetal outcomes included low birth weight (weight <2500 g), small for gestational age, number of admissions to neonatal intensive care unit (NICU) and infant death.

Results—Compared to women without kidney disease, those with kidney disease had 52% increased odds of preterm delivery (OR, 1.52; 95% CI, 1.16-1.99) and 33% increased odds of delivery via cesarean section (OR, 1.33; 95% CI, 1.06-1.66). Infants born to women with kidney disease had 71% increased odds of admission to NICU or infant death compared to infants born to women without kidney disease (OR, 1.71; 95% CI, 1.17-2.51). Kidney disease was also associated with two-fold increased odds of low birth weight (OR, 2.38; 95% CI, 1.64-3.44). Kidney disease was not associated with increased risk of maternal death.

Limitations—Data on level of kidney function and cause of death not available.

Conclusions—Kidney disease in pregnancy is independently associated with adverse maternal and fetal outcomes when other comorbid conditions are controlled by matching.

Index words

pregnancy; kidney disease; chronic kidney disease (CKD); decreased renal function; maternal outcomes; fetal outcomes; preterm delivery; cesarean delivery; neonatal intensive care unit (NICU) admission; low birth weight; death

Chronic kidney disease (CKD) is a global public health problem, and the incidence and prevalence continues to increase. It is estimated that the prevalence of CKD is around 3% in women of childbearing age,¹ but kidney disease is often underappreciated in pregnancy. Pregnancy in CKD is considered high risk. It is possible that diseased kidneys are unable to adapt to the normal physiologic changes of pregnancy, resulting in adverse outcomes. Pregnancy in CKD has a high rate of adverse maternal and fetal outcomes including miscarriage, preterm delivery, preeclampsia and fetal death.² Even pregnant women with mild decrease in glomerular filtration rate (GFR) are at an increased risk of adverse events compared to women without kidney disease.^{1,2} The magnitude of this risk is unclear as most studies are small, the definitions of CKD vary and many studies do not report important outcomes such as maternal mortality.² Furthermore, many of these studies did not take into account important comorbid conditions that may confound the relationship between pregnancy with kidney disease and adverse outcomes. Hence, we performed a retrospective study to provide an assessment of the risk of kidney disease during pregnancy on important maternal and fetal outcomes including death. We tested the hypothesis that pregnant women who have kidney disease have an increased risk of adverse maternal and fetal outcomes.

Methods

Data Source

A retrospective study was performed using the Intermountain Healthcare Enterprise Data Warehouse, which incorporates comprehensive electronic health and administrative data.³ Intermountain Healthcare is a non-profit organization with 23 hospitals and over 150 outpatient clinics and averages 130,000 admissions annually.³ It serves the states of Utah and Idaho, and its facilities range from major adult tertiary-level care centers to small clinics and hospitals that are the only source of care in rural communities.

Cohort Definition

The study sample included all adult female patients admitted for childbirth from 2000 through 2013. All participants (women with and without kidney disease) were required to have clinical and administrative data in the Intermountain Healthcare system. Only singleton pregnancies were included; we excluded all multiple gestation pregnancies. Even though several women had multiple pregnancies, only one pregnancy was used per participant in this study. In order to identify cases of pre-existing kidney disease, we defined kidney disease based on data obtained prior to pregnancy or in the first trimester. Cases were identified based on ICD-9 code as well as the NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) definition of CKD (presence of kidney damage or $\text{GFR} < 60 \text{ ml/min/1.73 m}^2$ for ≥ 3 months).⁴ A woman was considered to have kidney disease if the following occurred: a Charlson ICD-9 code (582.x, 583-583.7, 585.x, 586.x, 588.x)⁵ for kidney disease existed prior to pregnancy or in the first trimester; proteinuria (based on ICD-9 code 791)⁵ existed prior to pregnancy or in the first trimester; prior to pregnancy the participant met NKF-KDOQI criteria for CKD (presence of kidney damage or $\text{GFR} < 60 \text{ ml/min/1.73 m}^2$ for ≥ 3 months); or if her serum creatinine was $> 1.2 \text{ mg/dL}$ in the first trimester. We chose a serum creatinine $> 1.2 \text{ mg/dL}$ in the first trimester as a definition of kidney disease based on previous studies using this definition.^{6,7} A Charlson ICD-9 code is a comorbidity index that is an indicator of disease burden. Categories of comorbidities are included based on individual ICD-9 codes, and the patient must be actively managed for the condition in order for it to be included as a comorbidity.⁵

Seven hundred seventy-eight women met the criteria for kidney disease (Table S1, available as online supplementary material). Using a pool of 74,105 women without kidney disease we selected 778 women to use for matches for the women with kidney disease. Women with kidney disease were matched in a 1:1 fashion by age, race, and history of diabetes, chronic hypertension, liver disease and connective tissue disease to women without kidney disease. An exact or approximate (within 2 years) match criterion was used for age. A woman was considered to have diabetes, liver disease and/or a connective tissue disorder if a Charlson ICD-9 code for these comorbidities existed. Connective tissue disorders included lupus, Sjögren's syndrome, dermatomyositis, polymyositis, rheumatoid arthritis, unspecified connective tissue diseases, polymyalgia rheumatic and other inflammatory polyarthropathies. Hypertension prior to pregnancy was also defined by ICD-9 code.

Outcomes

Our main objective was to examine if women with kidney disease have a higher risk of adverse maternal and fetal outcomes compared to women without kidney disease. Outcomes were chosen based on previous studies examining adverse outcomes in pregnancy.² Adverse maternal outcomes were defined as: 1) gestational age at birth (four different dichotomous groupings: a) preterm delivery (delivery < 37 weeks' gestation), b) extremely preterm (< 28 weeks' gestation), c) early preterm (28-33 weeks' gestation), and d) late preterm (34-36 weeks' gestation); 2) delivery via cesarean section; 3) longer length of stay at the hospital (length of stay > 3 days); 4) combined outcome of preeclampsia and eclampsia (outcome was combined given the low number of patients with eclampsia; and 5) maternal death (since there was only 1 death within 1 year of delivery, we defined maternal death as death

occurring at any time). Adverse fetal outcomes were defined as: 1) low birth weight (< 2500 g); 2) small-for-gestational-age infant (infant <10th percentile of birth weight for given gestational age); 3) combined outcome of number of admissions to the neonatal intensive care unit (NICU) and fetal death (death during the hospitalization).

Statistical Analysis

Descriptive statistics were used to summarize characteristics of women with and without kidney disease. Percentages were used for categorical data and means $\pm$ standard deviations were used for continuous data. Two-sample t-tests were used to compare characteristics and outcomes between the two groups. Conditional logistic regression was used to examine the association between kidney disease and maternal and fetal outcomes. We considered a finding to be statistically significant if the two-sided *P*-value was less than 0.05. All statistical analyses were performed with SAS software, version 9.13 (SAS Institute Inc, Cary, NC).

Results

Study Participants

Seven hundred seventy-eight women met the criteria for kidney disease (Table S1). These women were matched 1:1 by race, and history of diabetes, chronic hypertension, liver disease, and connective tissue disease, and near-matched (within 2 years) by age with 778 women without kidney disease. As seen in Table 1, the women with kidney disease were well matched with women without kidney disease. The mean age was 28.66 ± 5.40 (standard deviation) years for women with kidney disease versus 28.67 ± 5.39 years for women without kidney disease. In the whole study population, there were 209 (13.4%) preterm deliveries, 458 (29.4%) cesarean sections, 138 (8.9%) cases of preeclampsia/eclampsia, 17 (1.1%) maternal deaths, 149 (9.6%) infants with low birth weight, 118 (7.6%) admissions to the NICU and 3 (0.2%) infant deaths.

Maternal Outcomes

Maternal and fetal outcomes in women with and without kidney disease are shown in Table 2. The mean gestational ages at delivery in women with and without kidney disease were 37.5 ± 2.5 weeks and 38.2 ± 1.8 weeks, respectively ($p < 0.001$). Women with kidney disease were more likely to have preterm deliveries and delivery via cesarean sections compared to women without kidney disease. There was no difference in the length of stay in the hospital and in the incidence of maternal death between the two groups. The mean time to maternal death following delivery in women with and without kidney disease was 5.2 ± 3.8 years and 5.2 ± 4.4 years, respectively. The association of kidney disease with maternal outcomes is shown in Table 3. Compared to women without kidney disease, those with kidney disease had 33% increased odds of delivery via cesarean section than women without kidney disease (odds ratio [OR], 1.33; 95% confidence interval [CI], 1.06-1.66). Women with kidney disease did not have a longer length of stay in the hospital than women without kidney disease (medians 2.0 [interquartile range, 2.0-3.0] versus 2.0 [interquartile range, 2.0-3.0] days, respectively). Of note, when length of stay was defined as > 3 days, women with kidney disease did not have significantly higher odds of prolonged hospitalization (OR,

1.28; 95% CI, 0.95-1.72). Women with kidney disease had a 52% increased odds of preterm delivery compared to women without kidney disease (OR, 1.52; 95% CI, 1.16-1.99). When preterm delivery was categorized as extremely or early preterm, compared to women without kidney disease, those with kidney disease had a 10-fold increased risk of having an extremely preterm infant (OR, 10.00; 95% CI, 1.28-78.11) and a 4-fold increased risk of having an early preterm infant (OR, 4.30; 95% CI, 2.16-8.56). There was no significant difference in late preterm births between the two groups. Kidney disease was not associated with increased odds of preeclampsia/eclampsia, but the point estimate did trend towards an increased risk (OR, 1.13; 95% CI, 0.76-1.68). Women with kidney disease did not have higher odds of death than women without kidney disease (OR, 1.13; 95% CI, 0.43-2.92). However, there were only 17 deaths in the entire cohort.

Fetal Outcomes

The incidence of fetal outcomes in women with and without kidney disease is shown in Table 2. The means of infant weight at birth in women with and without kidney disease were 3106 ± 675 g and 3314 ± 560 g, respectively ($p < 0.001$). Women with kidney disease were more likely to have low birth weight infants compared to women without kidney disease ($p < 0.001$). Infants born to women with kidney disease were more likely to have an admission to the NICU ($p = 0.002$) and the combined endpoint of admission to the NICU/infant death ($p < 0.001$). The association of kidney disease with adverse fetal outcomes is shown in Table 3. Kidney disease was associated with a 2-fold increase in odds of low birth weight (OR, 2.38; 95% CI, 1.64-3.44). However, women with kidney disease did not have higher odds of small-for-gestational-age infants compared to women without kidney disease (OR, 1.37; 95% CI, 0.94-2.00). Infants born to women with kidney disease had 71% higher odds of the combined outcome of admission to the NICU or infant death compared to those born to women without kidney disease (OR, 1.71; 95% CI, 1.17-2.51). When examined as separate variables, kidney disease was not associated with a higher risk of infant death (OR, 0.50; 95% CI, 0.05-5.51) but was associated with an 80% increased risk of admission to the NICU (OR, 1.80; 95% CI, 1.22-2.65).

Discussion

This study demonstrates that adverse maternal and fetal outcomes remain high in women with kidney disease notwithstanding advances in obstetric and neonatal care. Kidney disease was associated with adverse outcomes independently of other significant comorbid conditions including diabetes, chronic hypertension and connective tissue disorders. To our knowledge, this is the first study to show that kidney disease is associated with adverse maternal and fetal outcomes after matching pregnant women with and without kidney disease for significant comorbid conditions.

Our study confirms other findings from previous studies.^{1,2,8-12} A recent systematic review found that in pregnancy with kidney disease, the overall risk of adverse maternal events was five-fold higher and adverse fetal events was two-fold higher than in women without kidney disease.² However, the authors did note that the existing literature has several limitations. Most studies were small (N range, 16-675), did not use comparison groups, did not clearly

define the maternal and fetal outcomes, and did not adjust for important confounding factors such as chronic hypertension. Only one other study has examined the risk of kidney disease in a large number of pregnancies (>21,000) but they did not clearly define kidney disease or adjust for other confounding variables.⁸ A key strength of our study was the large number of patients we were able to include for analyses. We were able to compare over 700 pregnancies from women with kidney disease to a matched population of high risk pregnancies in the same time period. Hence, our study is one of the first to compare pregnancies in those with kidney disease to other high risk pregnancy groups and find an independent association of kidney disease with adverse outcomes.

Women with kidney disease had much higher odds of preterm delivery and delivery via cesarean section. Similar to our findings, a study by Fink et al.¹¹ found that women with kidney disease had a higher risk of preterm delivery and cesarean section compared to women without kidney disease. Even though they did adjust for age, diabetes, hypertension and smoking, they were unable to adjust for other maternal risk factors that may affect pregnancy outcomes. In our analyses, women with kidney disease did not have a longer length of stay in the hospital. Fink et al. found that women with kidney disease did have a higher risk of longer length of stay.¹¹ Interestingly, to our knowledge, these are the only two studies examining length of stay following delivery in women with and without kidney disease. Further studies are needed to determine if women with kidney disease are requiring more resources and incurring more hospital charges than women without kidney disease. We did not find an association between kidney disease and preeclampsia/eclampsia. However, the point estimate did suggest an increased risk for preeclampsia/eclampsia. This finding suggests that most of the women may have had early stages of kidney disease, and, given the low number of events, we may have not had enough power to find a significant association. Additionally, it can be very difficult identifying superimposed preeclampsia in women with kidney disease and some events may not have been identified. Unfortunately data on the degree of decreased kidney function was not available; so, we were unable to assess the risk via stages of kidney disease. Like previous studies, we did not find an association between kidney disease and maternal death. The lack of an association was likely due to the small number of women who died (only 1 death within 1 year of delivery).

We also found a high rate of adverse fetal outcomes in women with kidney disease. Infants born to women with kidney disease had a two-fold increased odds of low birth weight and a 71% increased risk of admission to the NICU or death compared to infants born to women without kidney disease. Holley et al. performed a matched control study of 40 women with kidney disease and found they had a higher risk of fetal death, prematurity and low birth weight compared to women without kidney disease.¹² However, they did not adjust for diabetes, hypertension or other comorbid conditions. We were able to match pregnant women with and without kidney disease for important maternal factors that are associated with kidney disease and adverse outcomes in pregnancy. Similar to our findings, Fink et al. found that women with kidney disease had a higher rate of premature infants independent of age, race, smoking, parity hypertension and diabetes.¹¹ A drawback of Fink's study was the inability to adjust for other important maternal confounders such as connective tissue disorders, which we were able to do in our study. Our findings give a more complete account of the role of kidney disease toward fetal and maternal outcomes.

Our study has several limitations worth mentioning. As is inherent with all secondary data analyses, our results are limited by the quality and completeness of the data from Intermountain HealthCare System. However, this is a large healthcare system with complete laboratory and administrative data and this database has been used for other published studies.¹³ Second, since this is an observational study, a causal relationship between kidney disease and adverse maternal and fetal outcomes cannot be established. Third, the patients with kidney disease were identified through ICD-9 codes and serum creatinine and GFR data. It is possible that mild cases of kidney disease were not reported. Nonetheless, our definition of kidney disease included both administrative and laboratory data, and we only included data obtained prior to pregnancy or in the first trimester. Furthermore, data on the degree of decreased kidney function was not available so we were unable to assess the risk via stages of kidney disease. Additionally, we were unable to address the impact of pregnancy on the progression of kidney disease. Finally, we did not have data on cause of maternal or fetal death.

In conclusion, our data indicate that kidney disease is a significant and independent risk factor for adverse maternal and fetal outcomes. Considering the potential for adverse outcomes, women with kidney disease who want to become pregnant should have preconception counseling. Our results should aid the healthcare provider in counseling women with kidney disease about pregnancy. A multidisciplinary approach involving obstetricians and nephrologists is needed in order to improve pregnancy outcomes in women with kidney disease. Future research should focus on dedicated interventions and education programs to improve pregnancy outcomes in women with kidney disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Baseline Characteristics of Women with and without Kidney Disease

Characteristic	Kidney Disease (n=778)	No Kidney Disease (n=778)
Age (y)	28.66 ± 5.40	28.67 ± 5.39
Race/Ethnicity		
Black	0 (0)	0 (0)
White	684 (87.9)	684 (87.9)
Hispanic	52 (6.7)	52 (6.7)
Native Hawaiian/Pacific Islander	9 (1.2)	9 (1.2)
Asian	10 (1.3)	10 (1.3)
American Indian/Alaskan Native	2 (0.3)	2 (0.3)
Other	21 (2.7)	21 (2.7)
Diabetes	99 (12.7)	99 (12.7)
Chronic Hypertension	197 (25.3)	197 (25.3)
Liver Disease	59 (7.6)	59 (7.6)
Connective Tissue Disorders	43 (5.5)	43 (5.5)

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation.

Table 2
Maternal and Fetal Outcomes in Women with and without Kidney Disease

Outcome	Kidney Disease	No Kidney Disease	P
Delivery timing*			
Preterm	151 (19.4)	106 (13.6)	0.002
Extremely preterm	10 (1.3)	1 (0.1)	0.007
Early preterm	44 (5.7)	11 (1.4)	<0.001
Late preterm	97 (12.5)	94 (12.1)	0.8
Delivery via cesarean	251 (32.3)	207 (26.6)	0.01
LOS in hospital > 3 d	117 (15.0)	95 (12.2)	0.1
Gestational age at delivery (wk)	37.5 ±2.5	38.2 ± 1.8	<0.001
Preeclampsia/Eclampsia	72 (9.3)	66 (8.5)	0.6
Maternal death	9 (1.2)	8 (1.0)	0.8
Infant weight at birth (g)	3106 ±675	3314 ±560	<0.001
Low birth weight, ie <2500 g	102 (13.1)	47 (6.0)	<0.001
SGA infant	71 (9.1)	54 (6.9)	0.1
Infant death	1 (0.1)	2 (0.3)	0.6
Admission to NICU	75 (9.6)	43 (5.5)	0.002
Admission to NICU/Infant death	75 (9.6)	45 (5.8)	<0.001

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation.

LOS, length of stay; NICU= neonatal intensive care unit; SGA, small-for-gestational-age.

* Preterm, <37 weeks; extremely preterm, <28 weeks; early preterm, 28-33 weeks; late preterm, 34-36 weeks.

Table 3
Association of Kidney Disease with Adverse Maternal and Fetal Outcomes

Outcome	OR (95% CI)
Maternal	
Delivery timing*	
Preterm	1.52 (1.16 to 1.99)
Extremely preterm	10.00 (1.28 to 78.11)
Early preterm	4.30 (2.16 to 8.56)
Late preterm	1.04 (0.77 to 1.40)
Delivery via Cesarean section	1.33 (1.06 to 1.66)
LOS in hospital > 3 d	1.28 (0.95 to 1.72)
Preeclampsia/eclampsia	1.13 (0.76 to 1.68)
Maternal death	1.13 (0.43 to 2.92)
Fetal	
Low birth weight, ie <2500 g	2.38 (1.64 to 3.44)
SGA	1.37 (0.94 to 2.00)
Admission to NICU/infant death	1.71 (1.17 to 2.51)
Admission to NICU	1.80 (1.22 to 2.65)
Infant death	0.50 (0.05 to 5.51)

CI, confidence interval; LOS, length of stay; NICU=neonatal intensive care unit. OR, odds ratio; SGA, small for gestational age

* Preterm, <37 weeks; extremely preterm, <28 weeks; early preterm, 28-33 weeks; late preterm, 34-36 weeks.