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Risk of Adverse Maternal and Fetal Outcomes during Pregnancy in Living Kidney Donors: A Matched Cohort Study

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Abstract

Background: We examined the risk of adverse pregnancy outcomes in primiparous kidney donors compared to matched controls.

Methods: Fifty-nine women with a history of kidney donation prior to their first pregnancy with normal renal function and no history of kidney disease, diabetes or chronic hypertension were matched 1:4 by age (within 2 years) and race to women with two kidneys using data from an integrated healthcare delivery system. Adverse pregnancy outcomes were defined as preterm delivery (delivery < 37 weeks), delivery via cesarean section, gestational hypertension, preeclampsia/eclampsia, gestational diabetes, length of stay in the hospital > 3 days, infant death/transfer to acute facility and low birth weight (<2,500 gm).

Results: Living kidney donors did not have a higher risk of adverse outcomes compared to matched controls. There was a trend towards an increased risk of preeclampsia/eclampsia in kidney donors but it did not reach statistical significance (OR 2.96, 95% CI 0.98–8.94, p=0.06). However, in kidney donors ≤ 30 years of age, there was a 4-fold increased risk of preeclampsia/eclampsia (OR 4.09, 95% CI 1.07-15.59, p=0.04).

Conclusion: Overall, the risk of pregnancy-associated complications following kidney donation is small but potential female kidney donors should be counseled on the possible increased risk of preeclampsia.

Keywords

pregnancy; kidney donation; preeclampsia; preterm delivery; gestational hypertension

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Introduction

Live kidney donation offers several advantages over cadaveric organ transplantation but requires shared decision-making among the clinician and potential donor, where perceived benefits of kidney donation must be balanced against the potential risks of donor nephrectomy and related comorbidities. Women make up the majority of living kidney donors. In 2015, 63% of living donors were female in which 64% were of child-bearing age[1,2] and may wish to become pregnant in the future. Importantly, there are several adaptive changes in renal physiology during normal gestation, including an increase in renal plasma flow and glomerular filtration rate that culminates in an increase in kidney volume up to 70%.[3,4] In contrast, there is a significant reduction in overall glomerular filtration of 30% at one year following donor nephrectomy despite compensatory hypertrophy and hyperfiltration in the remaining kidney.[5,6] These observations have engendered concerns about the risk of donor nephrectomy on maternal and fetal outcomes.

There is limited and conflicting data in female kidney donors of childbearing age to guide the informed consent process. Prior studies were small, retrospective, single-center experiences[7–9], compared outcomes to randomly sampled controls,[10] or were based on surveys,[11] making it difficult to interpret results.[12–14] To date, there has been only one study comparing maternal and fetal outcomes to matched controls, which demonstrated an increased risk in the combined outcome of gestational hypertension and preeclampsia.[15] The purpose of this study was to broaden our understanding of pregnancy-associated risks following kidney donation by examining adverse maternal and fetal outcomes in first pregnancies of live donors compared with similarly healthy non-donor counterparts.

Materials and Methods

A matched cohort study was performed using the Intermountain Healthcare Enterprise Data Warehouse, which incorporates comprehensive electronic health and administrative data. Intermountain Healthcare is a nonprofit organization with 23 hospitals and more than 150 outpatient clinics and averages 130,000 admissions annually.[16] It serves the states of Utah and Idaho, with facilities ranging from major adult tertiary-level care centers to small clinics and hospitals. ICD coding is entered by the Health Information Management Department with several steps of data validation. The data then interfaces to populate the Administrative Casemix database, which resides in the Enterprise Data Warehouse (EDW). The EDW is used for research population selection and quality improvement processes. This project was reviewed by the Intermountain Healthcare IRB, Protocol #1040486 and has been determined to be exempt from the federal rules governing “human subjects research” and informed consent was not required.[17]

Cohort Definition

The study sample included all adult female patients admitted for childbirth from 1996 through 2015. All participants were required to have clinical and administrative data in the Intermountain Healthcare System. We only included primiparous women and singleton births to reduce bias towards delivery modes (Figure 1). Women with kidney donation prior to their first pregnancy were identified through ICD-9 code V59.4.[18] Women with a solitary

kidney due to renal agenesis (N=228), those with a history of chronic kidney disease (CKD) (N=32), those with a history of chronic hypertension (N=102), and those with a history of diabetes (N=51) were excluded from the analysis. A woman was considered to have CKD if a Charlson ICD-9 code (582.x, 583-583.7, 585.x, 586.x, 588.x)[18] for kidney disease and/or if an ICD-9 code for proteinuria (791)[18] existed prior to pregnancy. Categories of comorbid conditions were included based on individual ICD-9 codes. We identified 59 women with kidney donation prior to their first pregnancy, normal renal function and no history of kidney disease, diabetes or chronic hypertension. Since the initial date of pregnancy was not available we only included women with kidney donation at least 2 years prior to their delivery date to ensure kidney removal did not occur during pregnancy and to allow for recovery from surgery.

Matching

Using a pool of 4710 primiparous women with two kidneys, 59 women who had donated a kidney were matched 1:4 to women with two kidneys by age at delivery (within 2 years) and race. Approach of nearest available neighbor matching without replacement was used.[19]

Outcomes

Outcomes were chosen based on previous studies examining adverse outcomes in pregnancy.[12,17,20] Adverse outcomes were defined as: (1) preterm delivery (delivery < 37 weeks' gestation); (2) delivery by cesarean section; (3) longer length of stay at the hospital (length of stay > 3 days); (4) gestational hypertension (defined as new onset hypertension during pregnancy after 20 weeks); (5) gestational diabetes (defined as any degree of glucose intolerance with onset or first recognition during pregnancy); (6) combined outcome of preeclampsia and eclampsia; (7) combined outcome of gestational hypertension, preeclampsia and eclampsia; (8) low infant birth weight (<2,500 grams); and (9) combined outcome of infant death and/or infant transfer to an acute inpatient facility. All outcomes were identified by ICD-9 code.

Statistical Analysis

Descriptive statistics were used to summarize characteristics of women with and without a prior history of kidney donation. Percentages were used for categorical data and mean ± standard deviation was used for continuous data. Conditional logistic regression models were used to compare outcomes between the matched set data. We considered a finding to be statistically significant for 2-sided $P < 0.05$. Since age is a risk factor for preeclampsia, we performed a subgroup analysis stratifying by age ≤ 30 years vs. >30 years and examined all outcomes using conditional logistic regression models. All statistical analyses were performed with SAS software, version 9.14 (SAS Institute, Cary, NC).

Results

Using a random pool of 4,710 women with two kidneys (Figure 1), 59 women with a history of donor nephrectomy were matched 1:4 by age and race with women with two kidneys (N=236). Mean (SD) age at delivery (years) among donors and non-donors was 30.4 ± 5.5

and 29.6± 5.5, respectively. Over 90% of the women were white. The mean (SD) time from kidney donation to delivery was 2.7 ± 1.8 years.

The prevalence of adverse maternal and neonatal outcomes in donors and non-donors is shown in Table 1. The mean (SD) gestational age (weeks) at delivery was 38.7 ± 1.5 in donors and 38.4 ± 2.3 in non-donors. The mean (SD) birth weight was 3250 ± 483 grams in donors and 3243 ± 820 grams in non-donors. There was no difference in the prevalence of adverse outcomes among donors vs. non-donors in preterm delivery, delivery via cesarean section, length of stay > 3 days in the hospital, preeclampsia/eclampsia, gestational hypertension, gestational diabetes, low birth weight, or infant death/transfer to acute facility.

The association between kidney donation and adverse pregnancy outcomes are shown in Table 1. Compared to non-donors, kidney donors did not have a higher risk of preterm delivery, delivery via cesarean section, gestational diabetes, gestational hypertension, or length of stay > 3 days. There was a trend towards an increased risk of preeclampsia/eclampsia but it did not reach statistical significance (OR 2.96, 95% CI 0.98–8.94, p=0.06). When gestational hypertension was combined with preeclampsia/eclampsia as an outcome, kidney donation was not associated with an increased risk of the combined outcome (OR 1.33, 95% CI 0.53–3.36). Kidney donors did not have a higher risk of adverse infant outcomes including low birth weight or infant death/transfer to acute facility compared to non-donors (Table 1).

We performed a subgroup analysis to determine if the risk of preeclampsia/eclampsia or gestational hypertension differed by age. We divided the kidney donors based on the median age at delivery into ≤ 30 years or >30 years. Kidney donors ≤ 30 years of age had a significantly higher risk of preeclampsia/eclampsia than non-donors (OR 4.09, 95% CI 1.07–15.59, p=0.04). Kidney donors > 30 years of age did not have an increased risk of preeclampsia/eclampsia (OR 1.33, 95% CI 0.14–12.82, p=0.80). There was no difference in the risk of preterm delivery, delivery via cesarean section, length of stay > 3 days, gestational hypertension, gestational diabetes, low birth weight or infant death/transfer to acute facility between donors and non-donors in the subgroup analysis.

We performed a sensitivity analysis matching kidney donors and non-donors on body mass index. Body mass index prior to pregnancy was available only in 26 of the kidney donors and in only 1708 of non-donors. Given the smaller number of non-donors available, we matched women with kidney donation prior to their first pregnancy 1:2 with non-donors on age (within 2 years), race and body mass index (within 0.1 standard deviation). All women with a history of kidney disease, diabetes or chronic hypertension were excluded. The mean (SD) BMI was 26.7 ± 4.2 kg/m^2 in donors and 26.7 ± 4.1 kg/m^2 in non-donors. Kidney donors did not have an increased risk of delivery via cesarean section, gestational diabetes, gestational hypertension, length of stay > 3 days or preeclampsia/eclampsia. After inclusion of BMI, there was no longer a trend towards an increased risk of preeclampsia/eclampsia (OR 1.20, 95% CI 0.3–4.6). Given the small number of events, we were unable to calculate the risk of preterm delivery, infant death/transfer to acute facility or low birth weight.

Discussion

In our cohort, we found the risk of preterm delivery, delivery via cesarean section, gestational hypertension, gestational diabetes, length of stay in the hospital and low birth weight was similar between donors and non-donors. We did find a trend towards an increased risk of preeclampsia/eclampsia in the entire cohort but it did not reach statistical significance. However, a novel finding of our study is that primiparous kidney donors ≤ 30 years of age had a 4-fold increased risk of preeclampsia/eclampsia than non-donors. Our findings suggest that while the majority of women had uncomplicated pregnancies after donation, younger female donors without previous pregnancies may be at a higher risk of preeclampsia/eclampsia.

This study expands upon prior data examining pregnancy outcomes after kidney donation. A study using data from the Norwegian Birth Registry, examined pregnancy outcomes in 326 kidney donors using a control group of randomly sampled births. Similar to our findings, they found no increased risk of preterm birth, low birth weight, gestational hypertension or preeclampsia in the main analysis.[10] However, when they examined outcomes in women who were pregnant before donation with outcomes in pregnancy post-donation, they found an increased risk of preeclampsia post-donation. However, the number of women included in this secondary analysis was small and on average, kidney donors in this study were 5 years older than the non-donors and the analysis did not adjust for this difference. Another study of 1,085 pregnancies found a similar rate of pregnancy complications between kidney donors and the general population.[11] However, women who had pre-donation pregnancies and post-donation pregnancies were more likely to have adverse maternal outcomes post-donation.[11] Specifically, they found a 7-fold increased risk of preeclampsia in adjusted analysis. Limitations of this study include that all data was self-reported on patient surveys completed on average 12 years after first pregnancies and 4 years after post-donation pregnancies and the loss to follow-up after donation was >24%.[11] We limited our analysis to only primiparous women to avoid bias with delivery modes and to exclude women with previous history of preeclampsia so were unable to examine adverse pregnancy outcomes in pre- vs. post-donation.

Similar to our study design was a recent study of 85 living donors matched to 510 controls by age, race, income, urban or rural residence and previous pregnancy numbers in Canada.[15] This study found an increased risk of the combined outcome of preeclampsia and gestational hypertension (OR 2.4, 95% CI 1.2–5.0) in kidney donors.[15] There was no difference in secondary outcomes, including gestational hypertension and preeclampsia alone.[15] We found a trend towards an increased risk of preeclampsia in our study with a similar Odds Ratio to the previous study (OR 2.96, 95% CI 0.98–8.94) but it did not reach statistical significance (p=0.06). We found that kidney donation was not associated with gestational hypertension or with the combined endpoint of preeclampsia and gestational hypertension. Given our small number of patients, it is possible that we were underpowered to detect this difference. However, we did find a 4-fold increased risk of preeclampsia/eclampsia in kidney donors ≤ 30 years of age. Interestingly, in a subgroup analysis of the Canadian study, female donors ≤ 32 years of age did not have an increased risk of preeclampsia/gestational hypertension but female donors >32 years of age did. On average, the subjects in the

Canadian cohort were 2 years older than the subjects in our cohort. Extremes of age are associated with preeclampsia, but usually the risk is greater in older women (age >40 years).[21] In the younger population, once adjustments for parity are made the association between younger age and preeclampsia is usually lost.[22] It is well known that parity influences preeclampsia risk with the highest risk in first pregnancies and most first pregnancies usually occur at a younger age.[23] We only included first pregnancies whereas only 46% of the pregnancies in the previous study were first pregnancies. However, in a subgroup analysis of the Canadian study, primiparous female donors had a significantly higher risk of preeclampsia/gestational hypertension compared to non-donors but multiparous female donors did not. Hence, nulliparous potential kidney donors may be at higher risk of preeclampsia than multiparous donors and should be counseled on this risk.

We only included singleton births as multiple gestation is associated with an increased risk of adverse pregnancy outcomes including preeclampsia,[24] whereas previous studies included all pregnancies. Ninety-three percent of our study population was white and the majority of the Canadian population (70%) was white. Obesity is a significant factor that can influence pregnancy outcomes including preeclampsia. Obesity increases the risk of preeclampsia by 2 to 3 fold.[25,26] BMI data was available in 26 of our patients. When we matched these women to controls by age, race and BMI, there was no longer a trend towards an increased risk of preeclampsia. Most transplant centers exclude donors if the BMI is > 30 kg/m^2. However, the risk of preeclampsia increases with increasing BMI, even within the normal range.[25,26] Unfortunately, with the small number of patients with BMI data included in our analysis make drawing conclusions regarding the confounding of obesity difficult. It remains unclear if the increased risk of preeclampsia seen in kidney donors would persist after adjustment for obesity.

Factors that are responsible for the increased risk of gestational hypertension and preeclampsia in kidney donors are unknown. Kidney donation does result in a reduction of overall kidney function. Even women with mild kidney damage and normal glomerular filtration rate have an increased risk of adverse pregnancy outcomes.[27–29] The cause of increased pregnancy complications in these women is unknown but may be due to endothelial damage, inflammation and oxidative stress, all of which occur with even mild kidney damage.[29,30] Mildly reduced kidney function during pregnancy resulting from kidney donation may be enough to predispose to gestational hypertension and preeclampsia. Additionally, hypertensive disorders of pregnancy in the general population are associated with earlier and higher rates of developing chronic kidney disease.[31] Hence, female donors who develop gestational hypertension and preeclampsia should be monitored long-term to determine if there are higher rates of developing chronic kidney disease. Further studies in pregnant kidney donors are needed to determine the potential mechanisms by which donation may lead to adverse pregnancy outcomes.

Our study has several strengths. It includes a large contemporary cohort of women from a registry of one of the largest health care providers in the Intermountain West. We have complete laboratory and administrative data and this database has been used for other published studies.[17,20,32] Additionally, to our knowledge, we are the first to study only primiparous women. Primiparous women have a higher risk of preeclampsia and thus may

be at higher risk for adverse complications.[23] Only studying primiparous women also reduced bias as women who have had a previous preterm birth are at a higher risk of a recurrent preterm birth and women who have had a prior cesarean section may only be a candidate for a repeat cesarean section.

There are several limitations to this study. Our analysis mainly included women of white race and does not represent other races/ethnicities that collectively comprise approximately 30% of live donors and who may have a higher baseline risk of pregnancy-related complications.[33,34] Secondly, we identified women with a history of donation of a kidney by ICD-9 code rather than chart reviews. Additionally, we identified comorbidities by ICD-9 code and data regarding smoking and laboratory values for renal function were not available in our cohort. All outcomes were also identified by ICD-9 code, and errors or misclassification in coding is possible. Additionally, we were unable to determine the severity of preeclampsia/eclampsia from the dataset. BMI data was only available in a small group of women. We did not have data regarding income or rural or urban residency to match on those factors. We were not able to examine whether the extremes of age (> 40 or < 20 years) were risk factors for preeclampsia given the small number of female donors that fell into these categories. Additionally, we did not have data on prenatal care including ultrasound scans and routine follow-up visits. We also did not have information on PAPP-A protein levels. Low titers of PAPP-A protein levels may indicate higher risk of preeclampsia.[35] Finally, since this is an observational study it may be subject to residual confounding.[36]

Our study suggests that the risk of pregnancy-associated complications following kidney donation is small. While there appears to be an increased risk of preeclampsia, there is no increased risk of preterm delivery, delivery via cesarean section or low birth weight. As such, the majority of female donors can expect a normal pregnancy. Potential donor candidates should be counseled regarding the possible complications of pregnancy including the risk of preeclampsia and gestational hypertension, especially in younger nulliparous women.

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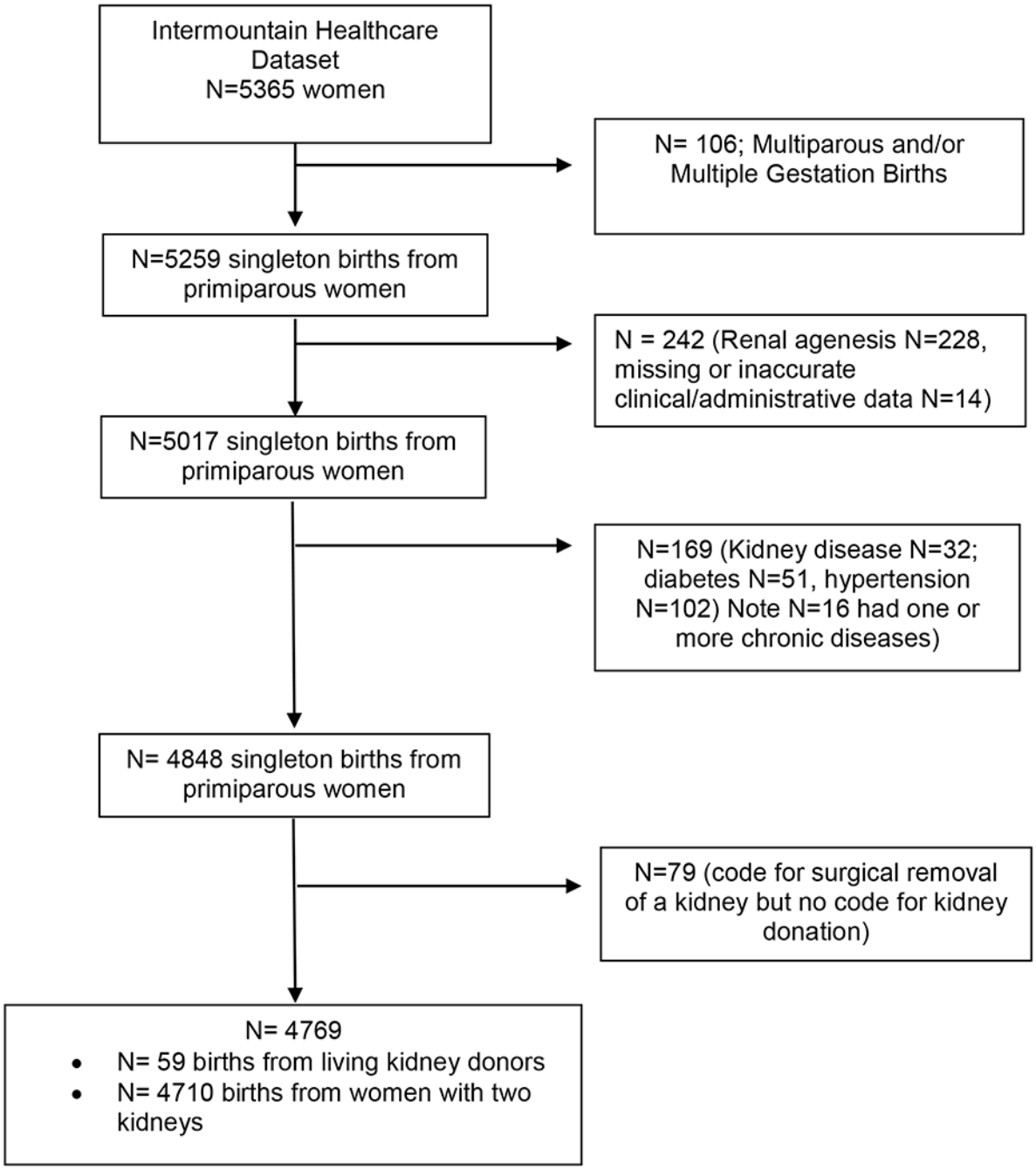

Figure 1.
Flow-Diagram

Table 1.

Association of Kidney Donation with Adverse Pregnancy Outcomes

Outcome	Prevalence of Adverse Outcome N (%)		Odds of Adverse Outcome in Kidney Donors	
	Donors (N=59)	Non-Donors (N=236)	Odds Ratio (95% CI)	P-value
Preterm delivery (<37 weeks)	5 (8.5)	23 (9.7)	0.86 (0.31 to 2.35)	0.77
Delivery via cesarean section	19 (32.2)	57 (24.2)	1.50 (0.80 to 2.81)	0.21
Gestational Diabetes	3 (5.1)	15 (6.4)	0.80 (0.23 to 2.79)	0.72
Gestational Hypertension	7 (11.9)	22 (9.3)	1.33 (0.53 to 3.36)	0.55
Preeclampsia/Eclampsia	6 (10.2)	9 (3.8)	2.96 (0.98 to 8.94)	0.06
Length of stay > 3 days	9 (15.3)	38 (16.1)	0.94 (0.43 to 2.05)	0.88
Infant death/transfer to acute facility	1 (1.7)	3 (1.3)	1.33 (0.14 to 12.8)	0.80
Low birth weight (<2500 grams)	5 (8.5)	21 (8.9)	0.94 (0.34 to 2.58)	0.90

Note: ORs and their 95% CIs were not calculated directly based on number in the table but from conditional logistic regression models because of the nature of matched set data.