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In the Literature

Kidney Donation: What Might It Mean for Women Wishing to Become Pregnant

Commentary on Garg AX, Nevis IF, McArthur E, et al. Gestational hypertension and preeclampsia in living kidney donors. N Engl J Med. 2015;372(2):124-133.

Normal pregnancy is characterized by remarkable renal physiologic alterations that are critical to maternal and fetal well-being. Healthy women accommodate to pregnancy by the upregulation of vasodilatory hormones along with downregulation of vasoconstrictor hormones, resulting in a decrease in systemic vascular resistance and mean arterial pressure despite an increase in cardiac output. At the level of the kidney, these hormonal alterations result in vasodilatation and dilatation of the collecting system, with a small increase in kidney size. As such, both renal plasma flow and glomerular filtration rate increase markedly during gestation. The increase in renal plasma flow, together with a decrease in oncotic pressure, are thought to be largely responsible for the increase in glomerular filtration rate, but an increase in glomerular capillary pressure cannot be excluded. Given our understanding of these physiologic alterations that affect the kidney during pregnancy, it is appropriate to wonder whether prior donor nephrectomy leads to maternal or fetal compromise during pregnancy. This is also a public health issue because young women contribute substantially to the pool of eligible kidney donors.

WHAT DOES THIS IMPORTANT STUDY SHOW?

Garg et al[1] conducted a retrospective cohort study of female living kidney donors matched with female nondonors from the general population of Ontario, Canada, to assess the risk of gestational hypertension or preeclampsia (primary composite end point). All cohort members had at least one pregnancy that progressed to at least 20 weeks' gestation during follow-up. To increase comparability, the investigators restricted the pool of non–kidney donors to individuals free of medical conditions that would preclude them from living kidney donation and with a similar tendency to seek out health care services as donors. Six nondonors from this restricted subcohort were matched to each donor based on factors known to predict the risk of gestational hypertension or preeclampsia. Cohort entry was determined by nephrectomy dates for living kidney donors and random cohort entry dates for nondonors based on the distribution of donors' nephrectomy dates. Generalized linear models were used to assess all study outcomes, and clustering induced by the matching schema and repeated pregnancies within cohort participants were addressed using generalized estimating equations and random-effects modeling, respectively. Prespecified subgroup analyses were also conducted.

During a median of 10.9 years or 4,361 person-years of follow-up, 15 gestational hypertension or preeclampsia events occurred among 131 pregnancies in 85 living kidney donors. When compared with the 38 events that occurred among 788 pregnancies in 510 nondonors, the odds ratio (OR) for the primary composite end point was 2.4 times higher (95% confidence interval [CI], 1.2-5.0) in donors versus nondonors. Similar results were noted for each component of the primary composite end point. There was no significant increase in risk of other adverse pregnancy outcomes, such as cesarean section, postpartum hemorrhage, preterm birth, or low birth weight. Subgroup analyses showed that the OR for developing the primary composite end point was significantly greater in individuals older than 32 years compared with those younger than 32 years at the time of pregnancy, suggesting modification of the living kidney donor effect by age.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

The first studies to examine the safety of pregnancy following kidney donation were small, retrospective, uncontrolled, single-center experiences. Further, these early studies provided no data with respect to important confounders known to affect pregnancy outcomes, including maternal age. In 1985, Buszta et al[2] assessed pregnancy outcomes among female donors managed by the Cleveland Clinic Foundation between 1963 and 1984. Of 355 living donors, 191 were women; of these, 23 conceived, resulting in 39 pregnancies and 32 viable births. No evidence of significant pregnancy complications emerged. In women who returned after a mean follow-up of 7.9 years (13/23), no elevations in serum creatinine, urine protein, or blood pressure values were noted. Subsequent data from the University of Minnesota, spanning 1985 to 1992 and using a survey to

Originally published online May 15, 2015.
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0272-6386
http://dx.doi.org/10.1053/j.ajkd.2015.04.002

ascertain outcome data from 45 pregnancies, confirmed that donor nephrectomy was safe with no increased rates of pregnancy-associated complications compared with rates in the general population (miscarriage, 13.3%; preeclampsia, 4.4%; gestational hypertension, 4.4%; proteinuria, 4.4%; and tubal pregnancy, 2.2%).[3]

In 2009, two articles published in the same issue of the *American Journal of Transplantation* challenged this sense of security. Again, investigators from the University of Minnesota used survey data to evaluate pregnancy outcomes in 1,085 donors who reported 3,213 pregnancies.[4] Although overall rates of pregnancy complications were comparable to those in the general population, there were notable differences before and after donation. Postdonation pregnancies, compared with predonation pregnancies, were more likely to result in fetal loss (19.2% vs 11.3%; $P < 0.0001$), preeclampsia (5.5% vs 0.8%; $P < 0.0001$), and gestational hypertension (5.7% vs 0.6%; $P < 0.0001$) and therefore less likely to go to term. In a subgroup of 98 donors who had both a pre- and postdonation pregnancy, there was no difference in the odds of premature delivery, but the odds of adverse maternal outcomes significantly increased in the postdonation pregnancy (OR, 5.21; 95% CI, 1.28-21.22), largely due to increased rates of preeclampsia. Although age is a potential confounder, the vast majority of women were still younger than 35 years at the time of the postdonation pregnancy, suggesting that decreased kidney mass may play a role. A second registry study using the Norwegian Birth Registry compared pre- and postdonation pregnancy outcomes in 326 kidney donors. This study also included a control group of randomly sampled births from their registry. After adjustment for maternal age, parity, and year of birth, a significantly higher incidence of preeclampsia was found in postdonation pregnancies in comparison to predonation pregnancies (5.7% vs 2.6%; $P = 0.026$).[5] However, this result must be interpreted with caution because overall event rates were low and there were no differences in rates of gestational hypertension, preeclampsia, preterm birth, or low birth weight among the 3 groups.

The study by Garg et al[1] extends these prior observations by examining a modern cohort of female living kidney donors and comparing their risk of gestational hypertension or preeclampsia with a matched cohort of female nondonors with comparable indexes of health and health-seeking behavior. Moreover, linkage to multiple large provincial health care databases allowed the investigators to comprehensively assess participant characteristics and clinical outcomes with minimal loss to follow-up. The matched-cohort design and analytical approach allowed efficient estimation of exposure effects despite the relatively small numbers of living kidney donors and primary composite end points. The thoughtful use of sensitivity analyses to examine some of the underlying assumptions increases confidence in the main results. The potential for information bias from differential ascertainment of gestational hypertension or preeclampsia in donors versus nondonors was acknowledged by the investigators, as was the absence of race information and clinical details (eg, blood pressure and proteinuria). Despite these shortcomings, the rigorous study design, sophisticated analytic strategy, and population-level perspective makes the study by Garg et al[1] one of the most informative on the topic to date.

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

The literature to date is encouraging for kidney donation. Although increased gestational hypertension and preeclampsia were more common in donors than in the general population, overall event rates were low. As such, the majority of young women who have donated a kidney can expect a normal pregnancy. It is helpful for clinicians counseling these women to have real numbers and be able to state that overall the rates of either gestational hypertension or preeclampsia are only 11%. Further, these complications, even when they occur, do not increase maternal or fetal mortality and have a limited impact on morbidity, with no statistically significant differences in caesarean section rates, postpartum hemorrhage, preterm birth (<37 weeks), or low birth weight (<2,500 g). As such, these women do not necessarily need burdensome high-risk obstetrical care. Further, untoward future vascular disease, be it coronary artery disease,[6] stroke, peripheral vascular disease,[7] or end-stage renal disease,[8,9] has been demonstrated to be clearly related to the severity of placental disease, and severe placental disease appears to be absent in this patient population.

However, the increased likelihood of gestational hypertension and preeclampsia needs to be followed with further research because decreased kidney mass as an additive risk factor for adverse pregnancy outcomes may factor more prominently if donor criteria change and more high-risk donors are accepted. Outreach of donor programs to ethnic minorities that already have higher baseline rates of preeclampsia (eg. African American and Hispanic) may change the risk-benefit ratio of donation prior to pregnancy in these groups and, critically, most studies to date have not reported race. Expanding donor criteria to include women with higher body mass index may also increase the postdonation pregnancy risk. Further, the societal trend toward delaying pregnancy means that donors are likely to start their families at a more advanced maternal age and more often require assistive reproductive technologies, both of which are independent risk factors for the development of placental

disease. As such, both clinicians and researchers need to remain vigilant with respect to assessing and following up this patient population as the female donor population evolves over time. Finally, there certainly is a role for individualized risk stratification, which might dictate preventative strategies and pregnancy surveillance.

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ACKNOWLEDGEMENTS

Support: None.
Financial Disclosure: The authors declare that they have no relevant financial interests.

REFERENCES

1. Garg AX, Nevis IF, McArthur E, et al. Gestational hypertension and preeclampsia in living kidney donors. *N Engl J Med*. 2015;372:124-133.
2. Buszta C, Steinmuller DR, Novick AC, et al. Pregnancy after donor nephrectomy. *Transplantation*. 1985;40:651-654.
3. Wrenshall LE, McHugh L, Felton P, Dunn DL, Matas AJ. Pregnancy after donor nephrectomy. *Transplantation*. 1996;62:1934-1936.
4. Ibrahim HN, Akkina SK, Leister E, et al. Pregnancy outcomes after kidney donation. *Am J Transplant*. 2009;9:825-834.
5. Reisaeter AV, Roislien J, Henriksen T, Irgens LM, Hartmann A. Pregnancy and birth after kidney donation: the Norwegian experience. *Am J Transplant*. 2009;9:820-824.
6. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ*. 2001;323:1213-1217.
7. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular Health After Maternal Placental Syndromes (CHAMPS): population-based retrospective cohort study. *Lancet*. 2005;366:1797-1803.
8. Wang IK, Muo CH, Chang YC, et al. Association between hypertensive disorders during pregnancy and end-stage renal disease: a population-based study. *CMAJ*. 2013;185:207-213.
9. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. *N Engl J Med*. 2008;359:800-809.