Renal Complications in Pregnancy Preceding Glomerulonephropathy Diagnosis

To the Editor: Primary glomerulonephropathies (GNs) and preeclampsia share a common phenotype of proteinuria, hypertension, and renal dysfunction. Precise mechanisms for these disease manifestations in each setting are not fully elucidated; however, both preeclampsia and active glomerular disease are associated with podocyturia and altered expression of podocyte-specific proteins.[1–3] Preeclampsia may lead to immediate adverse pregnancy outcomes and also increases the odds of developing cardiovascular disease[4] and end-stage renal disease.[5] Given the epidemiologic and hypothesized pathophysiologic parallels between glomerular disease and hypertensive disorders of pregnancy, we studied a cohort of patients with biopsy-proven GN (Cure Glomerulonephropathy) to assess whether preeclampsia, proteinuria, worsening hypertension, or decreased kidney function ("renal-relevant complications") during a first pregnancy altered the timing and nature of the subsequent GN presentation.

RESULTS

A total of 318 women reported their first pregnancy before their GN diagnosis. Clinical and demographic information at the time of their diagnostic kidney biopsy is reported in Table 1. Estimated glomerular filtration rate ($P = 0.786$), severity of proteinuria ($P = 0.096$), and hematuria ($P = 0.420$) at the time of biopsy were similar between women with and without renal-relevant complications during their first pregnancy. Women with a renal-relevant pregnancy complication were younger at biopsy than those without ($P < 0.001$). Women with IgA nephropathy or focal segmental glomerulosclerosis (FSGS) were more likely to report a renal-relevant pregnancy complication during their first pregnancy than those with minimal change disease or membranous nephropathy ($P = 0.005$). Among pregnancies with renal-relevant complications, 76.9% of infants (50/65) were delivered at full term, with a mean birth weight of 3.0 kg, compared to 91.0% (202/222) ($P = 0.009$) and 3.4 kg ($P < 0.001$), respectively, among pregnancies without these complications.

Although women with and without renal-relevant pregnancy complications were phenotypically similar at

Table 1. Demographic and clinical characteristics at diagnostic kidney biopsy among women with and without complications during their first pregnancies

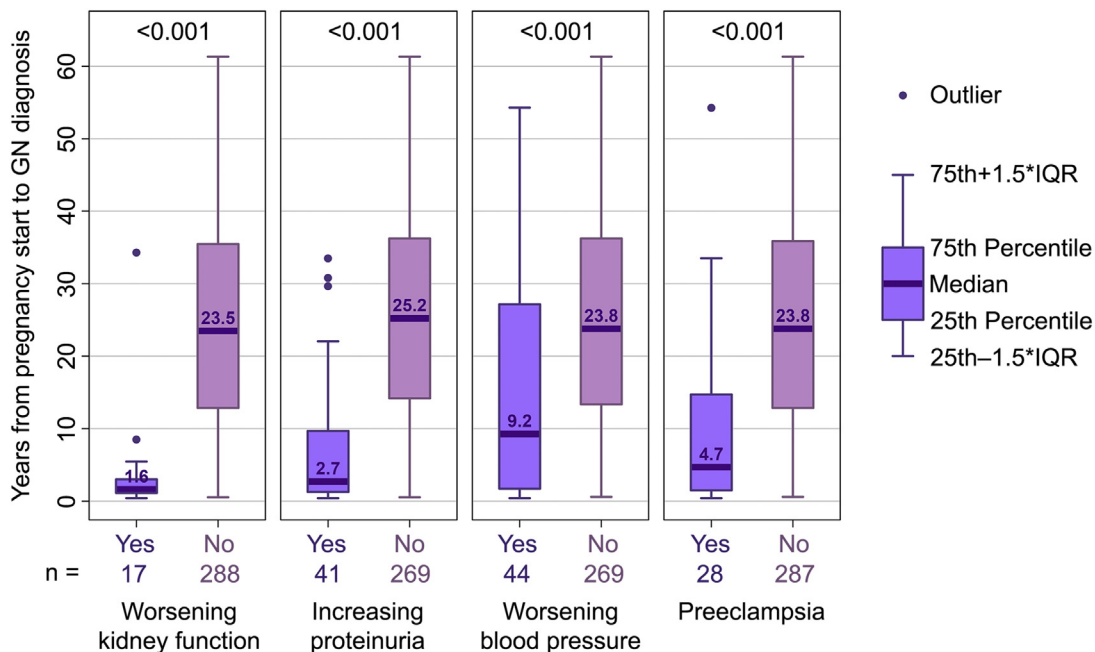|	No Complications during first pregnancy	Any complication during first pregnancy	P value[a]
n	251	67	
Age, yr, mean (SD)	50.2 (13.4)	39.2 (12.9)	<0.001
Hispanic	16.1% (40/248)	15.2% (10/66)	0.997
Race			0.207
Black	21.1% (51/242)	33.9% (21/62)	
White	64.5% (156/242)	54.8% (34/62)	
Asian	11.2% (27/242)	8.1% (5/62)	
Other	3.3% (8/242)	3.2% (2/62)	
Cohort			0.005
MCD (incl. IgM nephropathy)	13.1% (33/251)	11.9% (8/67)	
FSGS (incl. C1Q)	29.1% (73/251)	35.8% (24/67)	
MN	31.5% (79/251)	11.9% (8/67)	
IgAN (incl. IgAV/HSP)	26.3% (66/251)	40.3% (27/67)	
Family history of kidney disease	35.9% (88/245)	35.4% (23/65)	0.999
eGFR,[b] mean (SD)	68.5 (34.1)	69.9 (33.8)	0.786
UPCR,[b] median (IQR)	5.0 (1.9-8.4)	3.1 (1.5-5.3)	0.096
Immunosuppression use	13.1% (26/199)	15.3% (9/59)	0.830
Hematuria			0.420
Negative or trace	30.7% (47/153)	40.8% (20/49)	
1+	20.3% (31/153)	16.3% (8/49)	
2+ or 3+	49.0% (75/153)	42.9% (21/49)	

C1Q, C1Q nephropathy; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; HSP, Henoch-Schonlein purpura; IgAN, IgA nephropathy; IgAV, IgA vasculitis; inc., including; IQR, interquartile range; MCD, minimal change disease; MN, membranous nephropathy; UPCR, urine protein-to-creatinine ratio.
[a]P values from χ^2 test for categorical variables and t tests for continuous variables. UPCR was log transformed before testing.
[b]Missingness (no complications n, any complications n): eGFR (51,8); UPCR (78,16).

the time of subsequent kidney biopsy, we found that the latency time between a complicated first pregnancy and subsequent GN diagnosis was significantly shorter than after an uncomplicated first pregnancy (Figure 1). This was most prominent in women with worsening kidney function or increasing proteinuria during their first pregnancy (all $P < 0.001$), after adjusting for differences in age at pregnancy, race, and Hispanic ethnicity. The adjusted differences in latency time between complicated and uncomplicated pregnancies also varied by ultimate GN diagnosis (Figure 2), with between-group differences being greatest for FSGS and IgA ($P = 0.003$). Similarly, age at GN diagnosis was earlier after complicated first pregnancies (all $P < 0.001$), especially among individuals ultimately diagnosed with FSGS or IgA ($P = 0.022$). Models were adjusted for age at pregnancy, race, and ethnicity, of which younger age at pregnancy and non-Hispanic ethnicity were independently associated with decreased latency time and white race was associated with increased latency time (Supplementary Table S1).

In our secondary analysis, 318 women had a total of 730 pregnancies before GN diagnosis. Accounting for repeated pregnancies in individuals and adjusted for

Figure 1. Distribution of latency time between start of first pregnancy and subsequent diagnosis of glomerulonephropathy (GN) by complication status. Differences were tested using linear models with square root transformation for time. Models were adjusted for age at pregnancy, race, and Hispanic ethnicity. IQR, interquartile range.

the presence of prior renal-relevant pregnancy complications, we found a persistent decrease in latency time after any pregnancy complicated by worsening kidney function, increasing proteinuria, worsening blood pressure, or preeclampsia (all $P \leq 0.001$) (Supplementary Table S2).

DISCUSSION

We found that among women with GN, those who experienced worsening kidney function, increasing proteinuria, worsening blood pressure control, and/or preeclampsia during prior pregnancy were diagnosed with GN sooner than their counterparts without these pregnancy complications. Although we considered recall bias as a potential explanation for this difference (i.e., women newly diagnosed with GN recall recent pregnancy complications more readily), literature suggests that maternal recall of even distant pregnancy events is generally accurate,[6,7] and recent validation of the question "Did you have a hypertensive disorder in pregnancy?" in a Dutch population of women was found to be 84% sensitive and 94% specific when compared to medical chart review.[8] In our study, pregnancies with reported renal-relevant complications were also objectively more likely to deliver prematurely with a lower mean birth weight, disputing recall bias as the sole explanation for the findings. Our study design is limited by an inability to adjust for potential confounders beyond age, race, and ethnicity; however, continued prospective observation within this cohort

study (Cure Glomerulonephropathy) should allow for future in-depth analyses of pregnancies occurring after study enrollment.

We have considered a number of hypotheses for our finding of decreased latency time between pregnancy and GN diagnosis after pregnancies with renal-relevant complications. Given the phenotypic similarities between GN and preeclampsia, GN occurring during pregnancy may have been misdiagnosed as preeclampsia. We found a more prominent difference in latency time among women who ultimately were diagnosed with IgA nephropathy or FSGS. IgA nephropathy and FSGS are more likely to affect women of childbearing age than is membranous nephropathy or minimal change disease, and therefore would be the most likely of the GNs to confound a preeclampsia diagnosis. In addition, IgA may have an indolent presentation, making possible both a missed diagnosis during pregnancy and an unrecognized increased risk for preeclampsia when compared to other GNs.[9]

Alternatively, the podocyte depletion hypothesis may also explain the phenomenon of decreased latency of GN development.[10] This theory suggests that podocyte loss from an episode of preeclampsia results in decreased podocyte density and accelerates the subsequent clinical presentation of GN. Although this study is unable to determine a relative risk of GN after renal-relevant pregnancy complications, prior work by Vikse *et al.* found the relative risk of future kidney biopsy in women with preeclampsia to be three to six times that of childbearing women without
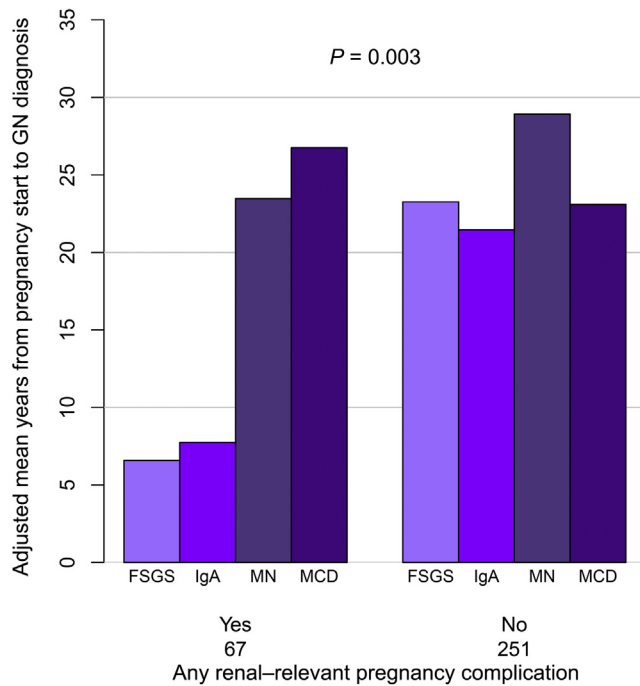
Figure 2. Adjusted mean latency times between start of first pregnancy and subsequent diagnosis of glomerulonephropathy (GN) by complication status and diagnosis. Adjusted means were estimated using a linear model with an interaction between complication status and diagnosis. The model was adjusted for age at pregnancy, race, and Hispanic ethnicity, and included a square root transformation for time.

preeclampsia.[11] This effect was most prominent in the first 5 years after childbirth, and a subset of these women were diagnosed with GNs such as FSGS and minimal change disease.[11] This supports our findings and suggests that preeclampsia may accelerate or unmask a GN diagnosis. Finally, GN and preeclampsia may share common genetic, immunologic, or environmental risk factors. The immunologic underpinnings of primary GNs and aberrant placentation in preeclampsia are a continued focus of study. Future study is needed to better elucidate common mechanisms.

Pregnancy is an opportunity to engage young women in health care. A subset of these women will have pregnancy complications that may be harbingers of kidney disease. Our study highlights the need for close *post partum* follow-up for persistent signs of renal disease after renal-relevant pregnancy complications, akin to existing U.S. obstetric guidelines recommending follow-up of cardiovascular disease risk factors after preeclampsia.[12] Notably, these guidelines recommend yearly measurement of blood pressure, body mass index, lipids, and fasting blood glucose. Based on our findings, we suggest that assessment of serum creatinine, urinalysis, and urine protein-to-creatinine ratio be performed for women with acute kidney injury, preeclampsia, or proteinuria in pregnancy at the routine 6-week obstetric *post partum* follow-up and annually thereafter. Abnormal results of these low-cost tests should trigger a nephrology referral for further evaluation. By recognizing renal complications in pregnancy and subsequent risk for GN, we may be able to alter a trajectory otherwise headed toward irreversible renal injury.

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AUTHOR CONTRIBUTIONS

Research idea and study design: AO, LM, JZ, MH; statistical analysis: JZ; data interpretation: AO, MR, JZ, MOS, EMH, EH, DVR, CN, JS, NA, KT, LM, MH. Supervision or mentorship: LH, MH. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriate investigated and resolved.

SUPPLEMENTARY MATERIAL

Short Methods.

Table S1. Linear regression models of latency time from first pregnancy.

Table S2. Linear generalized estimating equation models of latency time from any pregnancy.

Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

1. Garovic V, Wagner S, Petrovic L, et al. Glomerular expression of nephrin and synaptopodin, but not podocin, is decreased in kidney sections from women with preeclampsia. *Nephrol Dial Transplant*. 2007;22:1136–1143.

2. Barisoni L, Kriz W, Mundel P, et al. The dysregulated podocyte phenotype: a novel concept in the pathogenesis of collapsing idiopathic focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol*. 1999;10:51–61.

3. Craici IM, Wagner SJ, Bailey KR, et al. Podocyturia predates proteinuria and clinical features of preeclampsia: longitudinal prospective study. *Hypertension*. 2013;61:1289–1296.

4. Zoet GA, Koster MP, Velthuis BK, et al. Determinants of future cardiovascular health in women with a history of preeclampsia. *Maturitas*. 2015;82:153–161.

5. Vikse BE, Irgens LM, Leivestad T, et al. Preeclampsia and the risk of end-stage renal disease. *N Engl J Med*. 2008;359:800–809.

6. Carter EB, Stuart JJ, Farland LV, et al. Pregnancy complications as markers for subsequent maternal cardiovascular disease: validation of a maternal recall questionnaire. *J Womens Health (Larchmt)*. 2015;24:702–712.

7. Chin HB, Baird DD, McConnaughey DR, et al. Long-term recall of pregnancy-related events. *Epidemiology*. 2017;28:575–579.

8. Paauw N, van der Graaf AM, Bozoglan R, et al. Kidney function after a hypertensive disorder of pregnancy: a longitudinal study. *Am J Kidney Dis*. 2017;71:619–626.

9. Piccoli GB, Attini R, Cabiddu G, et al. Maternal-foetal outcomes in pregnant women with glomerulonephritides. Are all glomerulonephritides alike in pregnancy? *J Autoimmun*. 2017;79:91–98.

10. Wiggins RC. The spectrum of podocytopathies: a unifying view of glomerular diseases. *Kidney Int*. 2007;71:1205–1214.

11. Vikse BE, Irgense LM, Bostad L, et al. Adverse perinatal outcome and later kidney biopsy in the mother. *J Am Soc Nephrol*. 2006;17:837–845.

12. American College of Obstetrics and Gynecology. Hypertension in pregnancy. Available at: https://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy. Accessed December 18, 2017.