AJKD
Original Investigation

Pregnancy and Kidney Outcomes in Patients With IgA Nephropathy: A Cohort Study

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Background: The outcomes of pregnancy in immunoglobulin A nephropathy (IgAN) are controversial. This cohort study assessed the effects of pregnancy on kidney disease progression and risk factors for adverse pregnancy outcomes in patients with IgAN.

Study Design: A cohort study.

Setting & Participants: Women of child-bearing age with IgAN and minimum follow-up of 1 year after biopsy from December 2003 to September 2014.

Predictors: Pregnancy, treated as a time-dependent variable; baseline (at time of biopsy) estimated glomerular filtration rate (eGFR), proteinuria, blood pressure, and kidney pathology (Oxford MEST classification).

Outcomes: Kidney disease progression event, defined as 30% decline in eGFR or end-stage kidney disease; rate of eGFR decline; and adverse pregnancy outcomes, including severe preeclampsia and fetal loss.

Results: Of 413 patients enrolled, 266 (64.4%), 101 (24.5%), 40 (9.6%), and 6 (1.5%) had chronic kidney disease (CKD) stages 1, 2, 3, and 4, respectively. During follow-up, 104 had 116 pregnancies, of which 110 continued beyond week 20; 309 patients did not become pregnant. After adjustment for age, eGFR, mean arterial pressure, proteinuria, and pathology class at the time of biopsy, subsequent pregnancy among patients with CKD stages 3 to 4, but not CKD stages 1 to 2, was associated with faster eGFR decline (-7.44 vs -3.90 mL/min/1.73 m^2 per year; $P = 0.007$) and increased incidence of kidney progression events (HR, 5.14; 95% CI, 1.16-22.74) compared with patients who did not become pregnant.

Limitations: Relatively small sample size and single-center experience.

Conclusions: Pregnancy accelerated kidney disease progression in women with IgAN and CKD stage 3, but not in those at stage 1 or 2.

Am J Kidney Dis. 70(2):262-269.

INDEX WORDS: Chronic kidney disease (CKD); immunoglobulin A nephropathy (IgAN); pregnancy; kidney disease outcomes; kidney disease progression; pregnancy outcome; severe pre-eclampsia; fetal loss; estimated glomerular filtration rate (eGFR); proteinuria; hypertension; CKD stage.

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide.[1,2] Female patients with IgAN commonly experience pregnancy because the incidence of IgAN peaks during childbearing age. During pregnancy and after delivery, the 2 major risks are from kidney disease progression and fetal and maternal outcomes related to pregnancy. Whether the prognosis of IgAN is influenced by pregnancy and delivery remains controversial. Some investigators have reported that pregnancy does not alter the expected course of IgAN.[3-6] By contrast, faster loss of kidney function associated with pregnancy has been reported to be observed in a considerable proportion of women with moderate to severe chronic kidney disease (CKD), ranging from 23% to 43%.[7-11]

In contrast to this controversy, it is generally accepted that the risk for adverse maternal and fetal outcomes is higher even in patients with early-stage CKD compared with those without CKD.[12-14] However, risk factors that could predict fetal and maternal adverse events are rarely reported.

To evaluate the long-term outcome of kidney disease in women with IgAN and pregnancy and the risk factors for adverse pregnancy outcomes, we performed a matched-cohort study covering 2003 to 2012 that included 62 patients with IgAN with pregnancies and comparable controls.[15] However, that study did not permit us to reach a definitive conclusion about the effect of pregnancy on kidney progression in IgAN, mainly because of the small sample size. Another key limitation was that we

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Received September 21, 2016. Accepted in revised form January 12, 2017. Originally published online March 18, 2017.

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0272-6386
http://dx.doi.org/10.1053/j.ajkd.2017.01.043

included only patients with preserved kidney function. In this updated cohort study with a much larger population and a wider range of kidney function, we aimed to evaluate the effect of pregnancy on kidney disease progression in IgAN among patients with CKD stages 1 to 4 and explore the unambiguous and clinically feasible risk factors for adverse pregnancy outcomes.

METHODS

Study Cohort and Data Collection

From December 2003 to September 2014, registered patients in the IgAN cohort at Peking University First Hospital were selected. Eligibility criteria for the cohort study were: (1) pre-existing IgAN, (2) women aged 18 to 40 years at the time of diagnosis, and (3) minimum follow-up of 12 months or 3 visits after biopsy. Each included participant may have had none or 1 or more pregnancy. They were divided into a pregnancy group and a nonpregnancy group according to whether they became pregnant during follow-up. We excluded patients with acute kidney failure and pregnancies before the onset of kidney disease.

The method of data collection and follow-up of patients have been reported previously.[15] Briefly, patients were followed up every 1 to 6 months as routine clinical practice, and data were collected at the time of biopsy, during pregnancy, and after delivery, including systolic blood pressure, diastolic blood pressure, proteinuria, serum creatinine level, estimated glomerular filtration rate (eGFR), and therapy with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, steroids, and immunosuppressant medications. Survival status, including death or renal replacement therapy, was also confirmed by telephone annually by the study nurse. Baseline clinical and demographic data were collected from all patients at the time of kidney biopsy. All pathologic sections were evaluated again and graded by 2 experienced pathologists according to the Oxford MEST (M, mesangial, and E, endocapillary, proliferation [hypercellularity]; S, glomerulosclerosis; and T, tubular atrophy and interstitial fibrosis) classification.

Participants who become pregnant were followed up at least every month before delivery and every 1 to 6 months after delivery. To acquire adequate kidney function assessment data, all patients who became pregnant were followed up for at least 12 months after delivery or until dialysis treatment. Proteinuria and blood pressure levels at the beginning of pregnancy were collected from preconception data (when available; within 3 months before conception) or from data at the first checkup during pregnancy. Data concerning delivery mode, gestation age at delivery, maternal and fetal adverse pregnant outcomes, and infant birth weight were collected by medical review and confirmed with the patients.

The study was undertaken in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Peking University First Hospital (number 2013548). All patients gave fully informed written consent.

Outcomes and Definitions

The analysis included kidney and pregnancy outcomes. Based on consensus recommendations from a workshop on kidney end points,[16,17] kidney disease progression event was defined as a 30% decrease in eGFR or end-stage kidney disease without remission after observation for at least 4 weeks or until the end of follow-up. We also performed sensitivity analyses based on outcomes of 50% decline in eGFR or end-stage kidney disease. End-stage kidney disease was defined as eGFR < 15 mL/min/1.73 m^2 or initiation of renal replacement therapy. Worsening of proteinuria was defined as doubling of urinary protein excretion when baseline proteinuria had protein excretion > 1 g/d or an increase in protein excretion > 3 g/d when the baseline value was <1 g/d.[18]

Adverse pregnancy outcomes included infant loss and severe maternal preeclampsia. Infant loss included intrauterine death, neonatal death, and spontaneous and induced abortions because of uncontrolled diseases. Intrauterine death referred to death in the womb at any time before delivery and could be induced by various pregnancy complications, including fetal malformation, fetal growth retardation, embryo arrest, and fetal distress. Neonatal death was defined as death of a live-born infant within 28 days after delivery. Severe preeclampsia was defined as new-onset severe hypertension (blood pressure $>$ 160/110 mm Hg) and severe proteinuria (protein excretion > 5 g/d) after week 20 of gestation. Low birth weight was defined as a live-born infant weighing $<$2,500 g.

GFR was estimated according to the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.[19] Because there is still no validated formula for patients with pregnancy, we used this formula to calculate eGFR during the pregnancy period as a safety evaluation, but this was not used in the primary outcomes evaluation. CKD stages 1 to 4 were classified by eGFR $\geq$ 90, 60 to 89, 30 to 59, and 15 to 29 mL/min/1.73 m^2, according to the KDIGO (Kidney Disease: Improving Global Outcomes) guideline.[20] Hypertension was defined as systolic blood pressure $\geq$ 140 mm Hg and/or diastolic blood pressure $\geq$ 90 mm Hg or receipt of antihypertensive therapy. Mean arterial pressure (MAP) was defined as two-thirds diastolic blood pressure plus one-third systolic blood pressure. For each patient, an average MAP was determined for each 3-month block during pregnancy or follow-up, and the average of every 3-month period's MAP was defined as time-averaged MAP.[21] Similarly, time-averaged proteinuria represented an average of the mean of every 3-month period's proteinuria measurements during pregnancy or follow-up. Proteinuria during the first trimester referred to the mean of protein excretion during the first trimester.

Statistical Analysis

Data were gathered prospectively, periodically controlled, and entered into an electronic database. Quantitative variables were reported as mean $\pm$ standard deviation or median and range. Pregnancy was defined as a time-dependent covariate, being 0 if not pregnant and always remaining 1 if pregnant during the follow-up visit. We used linear mixed-effects modeling with a random participant-specific intercept and a random time effect, by regressing eGFR against pregnancy (as a time-dependent covariate), follow-up time (months since baseline), pregnancy $\times$ time, baseline eGFR, ln(proteinuria), MAP, age, and Oxford MEST classification. The estimated decline in eGFR was derived accordingly. We imputed eGFR as 10 mL/min/1.73 m^2 at the time of end-stage kidney disease onset in the primary analysis. To evaluate whether pregnancy influenced kidney progression events, a time-dependent Cox proportional hazards regression, adjusted for baseline proteinuria, eGFR, age, MAP, and Oxford MEST classification, was used, with pregnancy status as a time-dependent exposure and time of biopsy as the start of follow-up. P values for the interaction term were obtained from likelihood ratio tests. In the pregnancy group, a multivariable logistic regression model was used to evaluate risk factors affecting adverse pregnancy outcomes. Relevant variables that were significantly associated with adverse pregnancy outcomes by univariable analysis were included in the multivariable models. All statistical tests were 2 sided, with significance defined as $P < 0.05$. All statistical analyses were performed using SPSS software, version 16.0 (IBM) and SAS software, version 9.4 (SAS Institute).