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A Second Pregnancy may Possibly Worsen the Course of IgA Nephropathy - Ten Years' Experience in a Single Kidney Disease Center

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Abstract

Background

Whether the long-term prognosis of IgA nephropathy is influenced by pregnancy is controversial.

Study Design

A single center, prospective observational study.

Setting & Participants

Twenty-five pregnant women with biopsy-proven, IgA nephropathy were enrolled in this study between January 1, 1995, and December 31, 2002 and were followed up for 10 years.

Outcome & Measures

Rate of change in estimated glomerular filtration rate (eGFR), changes in proteinuria and new-onset hypertension were recorded.

Results

Mean levels of serum creatinine, eGFR and proteinuria at delivery were: 0.78 ± 0.29 mg/dL, 98.3 ± 32.3 mL/min/1.73 m2 and 0.30 ± 0.19 g/24 h, respectively (all patients). During 10 years' follow-up, eight patients underwent a second pregnancy. The remaining women did not show any significant changes in eGFR and proteinuria, except for one case, during 10 years' follow-up. In contrast, except for one out of the eight patients, eGFR levels gradually decreased after the second pregnancy ($P < 0.01$), accompanied by worsening proteinuria ($P < 0.01$); one patient developed end-stage renal disease. There were no significant differences in levels of eGFR, proteinuria and blood pressure between women with one or two pregnancies at the baseline of the first delivery. New-onset hypertension was observed in four women who became pregnant twice, where eGFR was reduced to less than 45 mL/min/1.73 m^2.

Conclusion

A second pregnancy may be a risk factor for worsening renal function in women with IgA nephropathy, although one pregnancy does not jeopardize a prognosis.

Keywords: Proteinuria; eGFR; End-stage renal disease; Pregnancy; IgA; Nephropathy

Introduction

IgA nephropathy (IgA) is the most prevalent glomerular disease, coinciding with the peak reproductive years of affected women. The progression of renal dysfunction in patients with IgA nephropathy is slow but, nevertheless, usually develops to end-stage renal disease (ESRD), 20 to 30 years after its onset [1,2]. Until now, it has been a matter of debate whether the long-term prognosis of IgA nephropathy is influenced by pregnancy [3-7]. Some studies report adverse effects of pregnancy on a prognosis of IgA nephropathy [8] and, in contrast, others note that pregnancy does not alter the course of IgA nephropathy [3,9]. However, since the progression of IgA nephropathy is very slow, at least 10 years' follow-up is necessary to ensure an accurate prognosis of renal function after delivery.

In addition, there have been few reports discussing the effects of multiple pregnancies on women with IgA nephropathy. In the present study, we prospectively followed 25 biopsy-proven, IgA nephropathy female cases, which experienced at least one pregnancy; we describe characteristics and the prognosis of these patients, in the years 1995-2012, from a single center in Japan.

Patients and Methods

This was a prospective, observational, single-center cohort study conducted in accordance with the Declaration of Helsinki. Approval for the study was obtained from Saitama Medical University Ethics Committee, and written informed consent was obtained from each participant at the time of renal biopsy.

Eligibility criteria for the main analysis were: a biopsy-proven, primary IgA nephropathy diagnosis, a pregnancy between January 1, 1995, and December 31, 2002, aged 18-35 years at the time of diagnosis, an eGFR at diagnosis > 60 mL/min/1.73 m^2, and a follow-up of 10 years after the first pregnancy.

Follow-up Methods

At clinical visits, serum creatinine, electrolyte concentrations, a complete blood count, and other serum chemistries (uric acid, glucose, albumin, cholesterol, and liver enzymes) were measured.

During the study, target home blood pressure (BP) was 130/80 mmHg or lower, and home BP measurements were encouraged [10], except during pregnancy. The selection of an antihypertensive agent depended on the physicians' preference, but included renin-angiotensin inhibitors [11] if patients indicated they would forgo further pregnancy. Lipid-lowering drugs, primarily statin derivatives, were administered if serum cholesterol levels exceeded 240 mg/dL [12].

Histopathological Diagnosis

Standard methods of processing and staining biopsy tissues were employed. All specimens were examined by light microscopy and immunohistochemistry (staining for IgG, IgA, IgM, C3 and C1q). When considered necessary, electron microscopy was applied to exclude other types of renal disease. IgA nephropathy was defined as histopathological evidence of IgA deposition by immunofluorescence on renal biopsy.

Clinical data evaluated at the time of pregnancy included blood pressure readings (mmHg), while laboratory data included serum creatinine, uric acid, total protein, albumin and total cholesterol measurements. According to the CKD Guidelines of the Japanese Society of Nephrology, the eGFR was calculated by the following MDRD equation for Japanese: eGFR =194 X Cr(-1.094) X Age(-0.287) (X 0.739, if female) [13].

The primary study outcome was the rate of change in kidney function estimated as the eGFR. Secondary endpoints were changes in proteinuria from baseline, and new-onset hypertension, defined as a change in blood pressure >140/90 mmHg or a need for antihypertensive drugs in previously normotensive patients. The following pregnancy and fetal outcomes were also recorded: pre-eclampsia, spontaneous and voluntary abortions, preterm delivery (live birth before week 37 of gestation), intrauterine death (after week 20 of gestation), birth weight, and neonatal death (live infant dying within 28 days after delivery). Low birth weight was defined as a live-born infant weighing < 2,500 g. Pre-eclampsia was defined as new-onset hypertension and proteinuria with protein excretion > 300 mg/day at baseline; and either worsening hypertension (increase in systolic or diastolic blood pressures > 30 or > 15 mmHg above baseline values, respectively), or a doubling of proteinuria in women, with both hypertension and proteinuria yielding protein excretion > 300 mg/day at baseline.

Statistical Analysis

Statistical analyses were performed using JMP software, version 9 (JMP, A Business Unit of SAS, Cary, NC, USA). Data are presented as mean $\pm$ SEM for normally distributed continuous variables. Significance testing was performed by Student's t-test. Changes in eGFR and proteinuira were analyzed using repeated-measures analysis of variance (ANOVA). A P-value of < 0.05 was considered statistically significant and all tests were two-tailed.

Results

Subject Characteristics

The median age of all 25 subjects was 27.1 $\pm$ 4.4 years. Patients were not treated with antihypertensive agents at the time of pregnancy. The mean levels of serum creatinine, eGFR and proteinuria at delivery were 0.78 $\pm$ 0.29 mg/dL, 98.3 $\pm$ 32.3 mL/min/1.73 m2 and 0.30 $\pm$ 0.19 g/24 h, respectively (all patients). The baseline characteristics of patients with one or two pregnancies at the time of first delivery are shown (Table 1). There were no significant differences in age, systolic and diastolic blood pressures, levels of serum creatinine and eGFR. All patients delivered live births without any complications such as elevated blood pressure or worsening of proteinuria and renal function during the first pregnancy. Preterm delivery was found in two women with one pregnancy and in one woman with two pregnancies; however, low birth weight infants were not noted.

In Table 2, a comparison is made of the clinical data of patients, at time of delivery, who underwent two pregnancies. Although the average age of women was significantly greater at the time of the second pregnancy ($P < 0.05$), there were no significant differences in systolic and diastolic blood pressures, serum creatinine levels or eGFR at the first and second pregnancy. However, with reference to the first pregnancy, proteinuria increased significantly post-delivery by the second pregnancy ($P < 0.01$). Except for two patients who exhibited mild preeclampsia, the course of pregnancy, gestational weeks and birth weights of the newborn were within normal limits. There were slight tendencies for a lower birth weight and a shorter gestational week at the second delivery, but these were not significant.

Table 1. The baseline characteristics of women with one or two pregnancies

	One (n=17)	Two (n=8)
Age (y)	28.3 ± 3.2	27.8 ± 5.0
Systolic blood pressure(mmHg)	124.5 ± 12.8	122.8 ± 11.1
Diastolic blood pressure (mmHg)	69.5 ± 9.5	69.3 ± 7.5
Serum creatinine (mg/dL)	0.80 ± 0.33	0.74 ± 0.23
eGFR (mL/min/1.73m2)	92.7 ± 36.9	104.1 ± 22.7
Birth weight (g)	2861.5 ± 230.0	2886.0 ± 220.2
Gestational weeks	38.5 ± 3.3	38.3 ± 1.7
Urinary excretion of protein (g/24h)	0.31 ± 0.12	0.28 ± 0.33

mean ± SEM

Table 2. A Comparison of women in their first and second pregnancy

	One (n=17)	Two (n=8)
Age (y)	27.8 ± 5.0	33.5 ± 4.5**
Systolic blood pressure(mmHg)	122.8 ± 11.1	124.5 ± 12.8
Diastolic blood pressure (mmHg)	69.3 ± 7.5	69.5 ± 9.5
Serum creatinine (mg/dL)	0.74 ± 0.23	0.78 ± 0.15
eGFR (mL/min/1.73m2)	104.1 ± 22.7	95.7 ± 30.2
Birth weight (g)	2886.0 ± 220.2	2861.5 ± 230.0
Gestational weeks	38.3 ± 1.7	38.2 ± 2.1
Urinary excretion of protein (g/24h)	0.28 ± 0.33	0.53 ± 0.37*

*P<0.05 and **P<0.01

Changes in eGFR during 10 years' Follow-up

During follow-up, all 15 patients with one pregnancy did not exhibit any significant change in eGFR (Figure 1). However, of the eight patients who underwent two pregnancies, all except one experienced significantly worsening renal function over time as assessed by eGFR (Figure 2; $P < 0.01$ vs. year 1). Changes in eGFR in individual cases are shown in Figure 3. In a mirror image of their eGFR data, proteinuria in patients who underwent two pregnancies increased significantly (Figure 4; $P < 0.01$ vs. year 1). New-onset hypertension was observed in four patients who underwent two pregnancies.

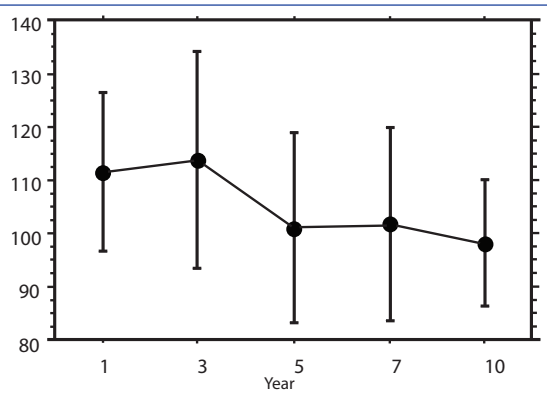

Figure 1. Changes in mean eGFR of women who experienced one pregnancy during 10 years

There were no changes in eGFR (estimated glomerular filtration rate).

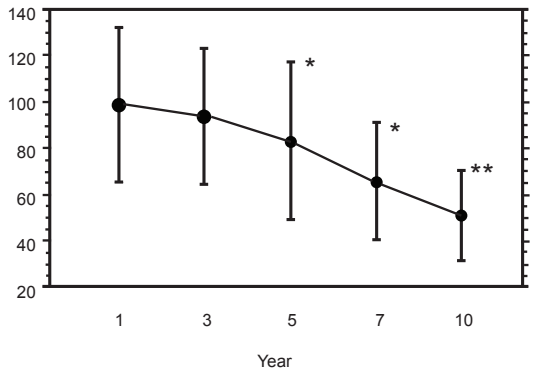

Figure 2. Changes in mean eGFR in women who experienced pregnancy twice

There were significant decreases in eGFR toward the end of the observation period.

*P < 0.05 and **P < 0.01 compared with the baseline value (Year 1).

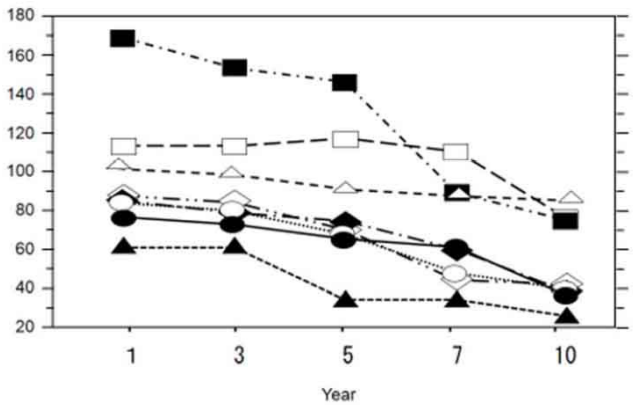

Figure 3. Changes in eGFR of individuals who experienced pregnancy twice All individuals except one tended to show decreased eGFR over time during 10 years' follow-up.

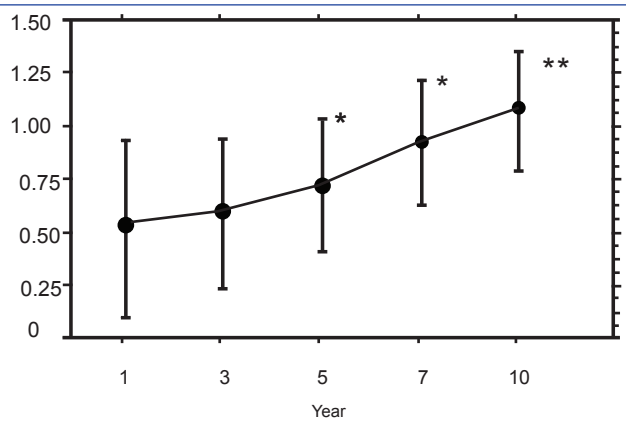

Figure 4. Changes in mean proteinuria in women who experienced pregnancy twice

There were significant increases in proteinuria toward the end of the observation period. *P < 0.05 and **P < 0.01 compared with the baseline value (Year 1).

Discussion

This study shows that pregnancy in IgA patients with nearly normal kidney function did not alter the long-term course of the disease. However, if women with IgA nephropathy underwent a second pregnancy with preserved kidney function, a deterioration of renal function, accompanied by worsening proteinuria, were observed in a long-term follow-up.

Several previous studies clearly demonstrated no adverse influence of gestation on the natural history of IgA nephropathy during 3 to 10 years [3-5]. However, previous observations by Packman et al. [8] revealed unfavorable effects of pregnancy on the course of IgA nephropathy, with an increased loss of kidney function and greater rates of new-onset hypertension or worsening proteinuria, even in normotensive women with normal kidney function [8]. Moreover, a progressive deterioration in kidney function was found, during and after pregnancy, in a greater than expected proportion (6%) of patients [8]. Furthermore, the Packman study of 116 pregnancies in 70 women with IgA nephropathy and pre-pregnancy, normal kidney function, found progressive deterioration in kidney function during and after pregnancy [8]. In their study, it is probable that more than 50% of all patients experienced at least two pregnancies, implying a poor prognosis in comparison with other previous studies. It is uncertain whether these findings come from a mix of single and multiple pregnancies, since they did not separately describe the outcomes of each pregnancy and multiple pregnancies. However, combining our present findings with this previous data, it is likely that one pregnancy does not produce adverse effects on renal function in women with IgA nephropathy in the long-term if they have nearly normal renal function. Moreover, it is postulated that even if a patient has normal renal function, repeated pregnancy invites a poor prognosis of IgA nephropathy and a greater incidence of adverse fetal outcomes.

IgA nephropathy, even when kidney function is relatively well preserved, may increase the risk of unfavorable pregnancy outcomes. For this reason, careful patient counseling and follow-up in a tertiary care center, in which cooperation between nephrologists and obstetricians is available, is highly recommended.

In spite of clear-cut findings, it is difficult to explain why repeated pregnancy produces a worsening of renal function with increased proteinuria. Firstly, the effects of aging should be considered. As is well known, aging is associated with a progression of IgA nephropathy [14]. However, a comparison of nonpregnant women and older women with one pregnancy did not reveal a worsening in renal function. Therefore, the effects of aging as a reason for repeated pregnancy worsening IgA nephropathy are unlikely. Secondly, different physiological changes occur in the kidney between the first and subsequent pregnancies. A large amount of evidence exists within the literature indicating that the rate of urinary protein excretion is a strong predictor of an adverse kidney outcome for patients with IgA nephropathy. In our previous study [15], no physiological changes were found in the kidney between pregnancies. Thirdly, as pregnancy per se exerts deleterious effects on the kidney, some unknown factor may be at work in decreasing renal function. However, pregnancy did not induce a decrease in eGFR over time, even after taking biopsy findings into consideration [14,16-19]. To resolve these enigmatic findings, further study will be needed to assist in nephrology counseling of patients with IgA nephropathy.

Study Limitations

Several potential limitations exist within our study. Although prospective, the study is observational and cross-sectional in design and therefore subject to potential residual confounding. Secondly, our study was limited by a relatively small number of patients. Thirdly, this study was performed at a single renal center; thus, whether findings can be generalized and applied to other a population, including other sites, is unknown; however, this may circumvent the variability in results produced by multiple centers. Moreover, strengths of the present paper include a well-characterized cohort of patients who participated in a rigorously and carefully undertaken follow-up system.

Conclusions

Pregnancy in women with IgA nephropathy and near normal kidney function does not alter the long-term course of the disease.

A second pregnancy may be a risk factor for worsening renal function in women with IgA nephropathy, although one pregnancy does not jeopardize a prognosis. These findings have important prognostic implications and may assist nephrology counseling and clinical decision-making.

Conflict of Interest

The authors declare that they have no conflicts of interest in this study.

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Mrs Sachiko Nakazato, a secretary, calculated the data and typed the manuscript.

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