Effect of Pregnancy and Delivery on the Renal Function and the Prognosis of Patients with Chronic Kidney Disease Stage 3 Caused by Immunoglobulin A Nephropathy

Ari Shimizu, Takashi Takei, Takahito Moriyama, Mitsuyo Itabashi, Keiko Uchida and Kosaku Nitta

Abstract

Objective  Immunoglobulin A nephropathy (IgAN) exhibits a peak onset that coincides with the reproductive age. Therefore, many young women with IgAN may become pregnant. However, the outcome of pregnancy in patients with renal diseases remains controversial, and the characteristics and outcome of pregnancy in IgAN patients must be further evaluated.

Methods  A prospective follow-up study of 64 pregnant women with IgAN was performed by analyzing the laboratory data and prognosis. To clarify the influence of renal insufficiency, we compared these patients according to the chronic kidney disease (CKD) stage with special attention to CKD stage 3 [N=16 in total, N=9 for estimated glomerular filtration rate (eGFR) ≥45 mL/min, N=7 for <45 mL/min].

Results  We found that pregnancy and delivery did not produce any significant changes in the renal function for patients with CKD stage 3 (≥45 mL/min) at five years after delivery, although proteinuria was elevated at 30 weeks of pregnancy and at three months after delivery. However, only for patients with CKD stage 3 (<45 mL/min) was there a significant deterioration in the eGFR at five years after delivery. Additionally, the data of pregnant women with CKD stage 3 were compared with those of 22 nonpregnant women with similar clinical and demographic characteristics.

Conclusion  Pregnant patients with IgAN (CKD stage 3, eGFR ≥45 mL/min) did not exhibit any significant reduction in the renal function at five years after delivery as compared with the baseline, which was similar to the findings in nonpregnant patients. Thus, while pregnancy with CKD stage 3 (eGFR ≥45 mL/min) was not a risk factor, patients with CKD stage 3 (eGFR <45 mL/min) showed a worsened renal function five years after delivery.

Key words: chronic kidney disease, immunoglobulin A nephropathy, pregnancy

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common form of glomerulonephritis and the principal cause of end-stage renal disease in daily clinical practice (1, 2). The predominant age at onset of IgAN is 20-30 years. Therefore, many young women with IgAN may become pregnant (1-3). According to some previous reports, renal dysfunction worsens during and after pregnancy, even in normotensive women with only mild renal impairment at the time of conception (3-5). Others have reported that pregnancy does not alter the expected course of maternal renal disease in subjects whose renal function before pregnancy is preserved or nearly normal (6-9). In particular, it remains unclear whether the long-term prognosis is influenced by pregnancy and delivery. We herein compared the outcomes of pregnancy and delivery in patients with IgAN according to the chronic kidney disease (CKD) stage. In our previous study in 2010, we found that pregnancy with CKD stages 2, 3 was not a risk...
factor for renal dysfunction or delivery (10). Recently, CKD stage 3 [estimated glomerular filtration rate (eGFR) 30-59 mL/min/1.73 m²] was divided into G3a (45-59 mL/min/1.73 m²) and G3b (30-44 mL/min/1.73 m²) according to the Kidney Disease Improving Global Outcomes (KDIGO) guideline (11). Therefore, we compared the outcome of patients with CKD stage 3 subpopulations between a group with an eGFR ≥45 mL/min and a group with an eGFR <45 mL/min.

Materials and Methods

Between 1995 and 2008, 64 pregnant women with IgAN visited the Department of Medical Kidney Center at Tokyo Women’s Medical University. This study was approved by the Institute’s Ethics Committee, and all patients provided their written informed consent at the time of pregnancy. The clinical data evaluated at pregnancy were the blood pressure (mmHg), as well as laboratory data including 24-hour urinary protein, urinary red blood cell counts per high-power field (HPF), and serum creatinine (mg/dL). The GFR using the eGFR was also evaluated and the CKD stage was classified as 1 (eGFR >90 mL/min), 2 (89-60 mL/min) or 3 (59-30 mL/min).

The patients were examined at the time of the detection of pregnancy (baseline); at 16, 22, and 30 weeks of pregnancy; at the time of delivery; and at three months and one, two, three, four, and five years after delivery. In addition, the data of the pregnant women were also compared with those of 22 nonpregnant women with IgAN (CKD stage 3) who had similar clinical demographics at baseline and five years after the initial renal biopsy.

Histological examination

All specimens used in this study were obtained using a percutaneous needle biopsy. The specimens were fixed with 10% phosphate-buffered formalin (pH 7.2), embedded in paraffin, and cut into 2-μm-thick sections. Hematoxylin and eosin, periodic-acid Schiff (PAS), silver methenamine, and Masson’s trichrome stainings were performed for light microscopic analyses. Two independent observers blind to the clinical data scored the changes semi-quantitatively.

Statistical analysis

Data are expressed as the means ± SD. The significance of differences between groups was examined using Student’s t-test for non-paired samples and the X² test. The evolution of the clinical parameters was analyzed in both groups using repeated measures analysis of variance (ANOVA). When differences were observed, the values were compared with the baseline values using a paired sample t-test. A p value <0.05 was considered to be statistically significant. A stepwise multiple regression analysis was used to identify the independent risk factors among the parameters selected by the univariate analyses.

Results

The interval from the initial renal biopsy to pregnancy was 0.9±2.3 years. All renal biopsies were performed prior to pregnancy. The 64 pregnancies investigated in this study were all first pregnancies. It is of note that all cases were followed-up for five years after delivery. Among 16 patients with CKD stage 3, all pregnancies resulted in live births and all neonates survived. The mean birth weight of the neonates was 2,870.2±604.0 g. A Caesarean section was performed for 4 cases (25.0%), and no preterm deliveries occurred. The average age at delivery was 32.0±3.8 years in patients with CKD stage 3 (eGFR ≥45 mL/min: 32.0±2.3 years, eGFR <45 mL/min: 33.1±2.5 years). The average gestation time was 38.0±1.6 weeks. There were six complications during pregnancy, such as hypertension (HT) (N=6, 37.5%) and low birth weight infant (<2,500 g, N=3, 18.7%). HT was observed in 4 cases (N=4, 44%) in patients with an eGFR ≥45 mL/min and 2 cases (28.5%) in patients with an eGFR <45 mL/min. Steroid treatment was administered in patients with CKD stage 3 on the basis of both the severity of proteinuria (>1 g/day) and the acute active changes on histology. Accordingly, 13 patients were treated with prednisolone, prednisolone pulse and tonsillectomy (81.3%). For those with mild proteinuria (<0.5 g/day), these treatments had not been administered, and two cases were newly treated with prednisolone pulse and tonsillectomy at five years after delivery.

The clinical data of the patients with CKD stages 1, 2, 3 and CKD stage 3 (eGFR ≥45 mL/min, <45 mL/min) were also evaluated and compared between the time of pregnancy and five years after delivery (Table 1).

The eGFR profile during the study period is shown in Fig. 1. None of the patients received replacement therapy. For patients with CKD stages 1, 2, 3 (eGFR ≥45 mL/min), no significant change was observed in the eGFR profile between the time of the detection of pregnancy and five years after delivery. Only CKD stage 3 patients with an eGFR <45 mL/min showed worsened eGFR profiles from 40.3±2.8 mL/min at baseline to 34.2±7.8 mL/min (p=0.038) at five years after delivery.

The proteinuria profile during the study period in patients with CKD stage 3 is presented in Fig. 2. In patients with CKD stage 3 (eGFR ≥45 mL/min), the severity of proteinuria increased from 1.0±0.8 g/day at baseline to 2.0±0.3 g/day at 30 weeks of pregnancy (p=0.01), and 1.9±0.6 g/day at the time of delivery (p=0.038), however, no change was observed at three months after delivery [0.9±0.4 g/day (p=0.29)]. Similarly, in patients with CKD stage 3 (eGFR <45 mL/min), the severity of proteinuria increased from 1.3±0.4 g/day at baseline to 2.5±0.4 g/day at 22-30 weeks of pregnancy (p<0.001) and 2.0±0.5 g/day at the time of delivery (p=0.02), however, no change was observed at three months after delivery (1.4±0.5 g/day, p=0.14) However, the change in the proteinuria severity observed between the time of
pregnancy and five years after delivery was not statistically significant in any of the CKD groups. Eleven patients with CKD stage 4 were pregnant (eGFR 27.8±4.2 mL/min, proteinuria 2.6 ±0.9 g/day before pregnancy), 10 of whom showed renal death within five years after pregnancy (10/11 patients, 91.0%). The average time to the introduction of continuous renal replacement therapy was 3.9±0.7 years. In addition, 9 out of 11 (81.8%) patients delivered low birth weight infants.

To clarify the factors influencing the risk faced by pregnant women, we compared the data of nonpregnant IgAN patients with CKD stage 3 (N=12, eGFR ≥45 mL/min; N=10, eGFR <45 mL/min) over the course of a five-year period (Table 2). All the parameters were similar between the two groups at baseline. There was no significant difference in the treatment received between the pregnancy and non-pregnancy groups. As shown in Table 2, no significant difference was observed on the histological examination, such as glomerular obsolescence (%), crescent formation (%) and pathological changes (%) between the two sub-groups (Table 2). In the nonpregnant group, the proteinuria and hematuria levels decreased from 1.2±0.6 g/day and 10.9±0.6/HPF at the time of diagnosis to 0.5±0.6 g/day and 4.2±2.5/HPF at five years, respectively, (p=0.038 and p=0.04), in patients with CKD stage 3 (eGFR ≥45 mL/min). The proteinuria and hematuria levels decreased from 1.4±0.7 g/day and 9.0±5.0/HPF at the time of diagnosis to 0.5±0.6 g/day and 4.2±2.5/HPF at five years, respectively, (p=0.038 and p=0.04), in patients with CKD stage 3 (eGFR ≥45 mL/min). The proteinuria and hematuria levels decreased from 1.4±0.7 g/day and 9.0±5.0/HPF at the time of diagnosis to 0.5±0.6 g/day and 4.2±2.5/HPF at five years, respectively, (p=0.038 and p=0.04), in patients with CKD stage 3 (eGFR ≥45 mL/min). The proteinuria and hematuria levels decreased from 1.4±0.7 g/day and 9.0±5.0/HPF at the time of diagnosis to 0.5±0.6 g/day and 4.2±2.5/HPF at five years, respectively, (p=0.038 and p=0.04), in patients with CKD stage 3 (eGFR ≥45 mL/min).
Figure 2. Change of proteinuria in different CKD stages at pre-pregnancy, during pregnancy and five years after delivery.

Table 2. Clinical Data at Baseline and 5 Years of Follow-up in the Pregnancy and Nonpregnancy Groups in CKD3.

<table>
<thead>
<tr>
<th>CKD stage (N)</th>
<th>Baseline (n=9)</th>
<th>Baseline (n=7)</th>
<th>Baseline (n=12)</th>
<th>Baseline (n=10)</th>
<th>After 5 years (n=5)</th>
<th>After 5 years (n=6)</th>
<th>After 5 years (n=8)</th>
<th>After 5 years (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR ≥ 45</td>
<td>55.4 ± 2.3</td>
<td>54.0 ± 2.8</td>
<td>54.6 ± 5.0</td>
<td>50.3 ± 2.8</td>
<td>53.7 ± 2.8</td>
<td>50.6 ± 3.8</td>
<td>53.7 ± 2.8</td>
<td>50.5 ± 3.0</td>
</tr>
<tr>
<td>eGFR &lt; 45</td>
<td>48.0 ± 3.6</td>
<td>43.0 ± 2.8</td>
<td>48.0 ± 5.0</td>
<td>45.0 ± 2.8</td>
<td>48.0 ± 3.6</td>
<td>45.0 ± 3.0</td>
<td>48.0 ± 3.6</td>
<td>45.0 ± 3.0</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (66.7)</td>
<td>5 (71.4)</td>
<td>7 (58.3)</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>Steroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (66.7)</td>
<td>5 (71.4)</td>
<td>7 (58.3)</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>Steroid pulse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (66.7)</td>
<td>5 (71.4)</td>
<td>7 (58.3)</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (66.7)</td>
<td>5 (71.4)</td>
<td>7 (58.3)</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (66.7)</td>
<td>5 (71.4)</td>
<td>7 (58.3)</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>Statins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 (66.7)</td>
<td>5 (71.4)</td>
<td>7 (58.3)</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>ARB, ACE I</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (22.2)</td>
<td>0 (0)</td>
<td>2 (22.2)</td>
<td>2 (28.5)</td>
</tr>
</tbody>
</table>

Histological Examination

- Glomerular obsolescence (%) 17.8 ± 12.5 25.0 ± 26.7 27.8 ± 15.7 29.1 ± 24.4
- Crescent formation (%) 6.2 ± 7.0 8.0 ± 6.4 5.2 ± 7.0 4.2 ± 5.8
- Cellular crescent (%) 2.3 ± 4.7 4.8 ± 2.8 0.9 ± 3.1 1.2 ± 2.3
- Fibrocellular crescent (%) 0.7 ± 2.1 5.3 ± 6.2 3.7 ± 5.0 2.8 ± 4.6
- Fibrosis (%) 3.2 ± 6.0 1.0 ± 2.3 2.0 ± 4.8 0.6 ± 1.7
- Pathological changes (%) 27.3 ± 18.6 33.1 ± 23.7 34.2 ± 12.3 35.3 ± 27.3

*p < 0.05

There was no significant difference in the decrease in eGFR from baseline between the pregnancy and nonpregnancy groups. Next, we further divided the patients into two groups based on the change in proteinuria.
groups according to the level of proteinuria before pregnancy (≥1 g/day, N=10, 62.5% vs. <1 g/day, N=7, 43.8%). The former (proteinuria ≥1 g/day) showed worsened proteinuria (1.6±0.4 g/day before pregnancy to 3.3 g/day at 16 weeks) during pregnancy, however, no significant change was observed after one year. In addition, no significant decrease in the eGFR as compared with the latter group (<1 g/day) was seen during the five-year observation period. However, only patients with >1 g/day proteinuria (N=10) exhibited complications such as HT (N=6, 60%) and low birth-weight infants (N=3, 30%), regardless of their eGFR values.

**Discussion**

IgAN is the most common primary glomerular disease globally, with a peak incidence in young adults aged 20-30 years (1, 2). In previous studies, renal dysfunction at the onset of pregnancy with IgAN was mostly stratified in the classic creatinine classification, i.e., serum creatinine <1.4 mg/dL was defined as normal to mild, 1.5-2.5 or 3.0 mg/dL was defined as moderate, and >2.5 or 3.0 mg/dL was defined as severe renal insufficiency (12). Abe studied patients with a baseline eGFR >60 mL/min/1.73 m² and reported no adverse effects of gestation during the natural history of IgAN during the five-year follow-up period (6). In 2010, we conducted a prospective comparison of eGFRs at the time of pregnancy and three years after delivery in 29 patients with IgAN with CKD stages 1-3 and found that pregnancy did not accelerate the renal dysfunction (10). According to previous reports, a normal pregnancy course can be anticipated in pregnant women with IgAN, and their renal function is not adversely affected after delivery if they have an eGFR value >70 mL/min and a normal blood pressure before pregnancy. Three conditions are necessary for at least two years prior to pregnancy to ensure no deterioration of the renal function: (1) a stable course of nephropathy, (2) U-P less than 1.0 g/day, and (3) blood pressure below 140/90 mm Hg without antihypertensive drugs (13). In these previous reports, no significant differences were noted between the pregnant and nonpregnant groups. However, Limardo et al. reported that while pregnancy does not seem to affect the long-term outcome of kidney disease in woman with IgAN, high ratios of perinatal death (3%) and premature deliveries (10%) were observed (14). Imbasciati et al. reported that in women with renal insufficiency, the presence of both GFR < 40 mL/min/1.73 m² and proteinuria >1 g/day before conception predicts poor maternal and fetal outcomes (15). Physiological changes in the kidneys during pregnancy may be primarily caused by changes in the circulation volume. The blood plasma volume increases by more than 40% starting from the 10th week of gestation and peaks at around 32-34 weeks (16, 17). Although the detailed underlying mechanisms remain to be clarified, some reports have suggested that prolactin may dilate the renal arteries and increase the renal blood flow (18, 19). In addition, an increase in cortisol and lactogen originating from the placenta reportedly affect the renal function and severity of nephritis. During pregnancy, therefore, glomerular hypertension and hyperfiltration become prominent. These factors may damage the glomeruli. In addition, during pregnancy, the blood pressure increases, and relaxation and constriction of import arteries repeatedly occur, injuring the endothelial cells of the glomerular arterioles and capillaries. These factors cause changes in the edematous endothelium of the glomeruli, the penetration of mesangial cells, and ischemia of the loop and focal segmental glomeruli (20-22). However, these factors damage the glomeruli only during pregnancy, and the renal function generally returns to normal after delivery (23).

The patients in the CKD stage 3 groups may have been treated with oral steroids and antiplatelet agents prior to pregnancy. Treatment must be initiated prior to pregnancy if a renal biopsy reveals an active and severe histology. In such cases, treatment should be started prior to pregnancy as early as possible; if the renal function and urinary findings recover, a planned pregnancy might be possible (24). In women who become pregnant, the steroid dosage should be reduced to <15 mg/day (9, 24). Our patients with CKD stage 3 were treated with an average steroid dose of 5.8 mg/day while they were pregnant. For the treatment of IgAN, it is generally accepted that steroids must be used for cases with proteinuria >1.0 g/day, higher histological severity scores and a 24-hour creatinine clearance rate of >70 mL/min. Furthermore, antiplatelet agents, statins and angiotensin receptor blockers may be used in combination. Recently, tonsillectomy and steroid pulse therapy have been used. As a result, at five years after delivery, no significant deterioration of the renal function or urinary findings was observed. In our study, 13 patients had been treated with prednisolone or prednisolone pulse + tonsillectomy (81.3%). Prednisolone <15 mg/day is preferable before pregnancy (9). In this study, the termination of steroid treatments was possible in many cases, thus significant complications were avoided.

In conclusion, pregnant women with IgAN, even those with CKD stage 3, who exhibited progression of the U-P at 30 weeks of pregnancy and who had no pregnancy-related complications did not exhibit a deterioration of the renal function. Pregnant patients with IgAN (CKD stage 3, eGFR ≥45 mL/min) did not exhibit any significant reduction of their renal function at five years after delivery as compared with the baseline function, which was similar to the findings in nonpregnant patients. Furthermore, pregnancy with CKD stage 3 (eGFR ≥45 mL/min) was not a risk factor for renal dysfunction. The group with eGFR <45 mL/min showed deterioration in the eGFR after five years even without pregnancy as a natural course. On the other hand, proteinuria was previously demonstrated to be significantly associated with the deterioration of postnatal maternal outcomes (25). Youxia et al. reported that proteinuria during pregnancy is a predictor of adverse pregnancy outcomes (26). However, only patients with >1 g/day proteinuria (N=10) exhibited complications such as HT (N=6, 60%) and low birth weight infants (N=3, 30%), regardless of the eGFR value. The con-
control of proteinuria before pregnancy is thus highly desirable. Magee et al. reported that there were no significant between-group differences in the risk of pregnancy loss, high-level neonatal care, or overall maternal complications, although a less-tight control was associated with a significantly higher frequency of severe maternal HT (27). In our study, none of the patients exhibited HT prior to pregnancy, and six patients required medication during pregnancy, although their blood pressure was controllable at <135/85 mmHg. Some of these patients were given low doses of ARB after delivery for renal protection and to decrease the proteinuria levels, however, the long-term outcome was not affected. Although pregnancy and delivery did not influence the course of IgAN in the study, further investigations with a longer follow-up period are required for a precise evaluation of the association between IgAN and pregnancy and delivery.

The authors state that they have no Conflict of Interest (COI).

References


© 2015 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html