

Renal Prognostic Factors for Clinical Outcome in Pregnant Women with IgA Nephropathy

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The present study was designed to determine the renal prognostic factors influencing the clinical outcome of pregnant women with IgA nephropathy (IgAN). The clinical courses of 10 women, ranging in age from 26 to 36 years (average age of 30.5 years) with biopsy-proven IgAN were studied. The patients were divided into two groups on the basis of their renal function outcome: group I consisted of five patients with no changes in renal function during pregnancy, and group II consisted of five patients who experienced a deterioration in renal function as a result of their pregnancy. The patients in group II had a greater incidence of maternal complications than those in group I. The serum creatinine levels before pregnancy were not significantly different in the two groups. However, patients in group II experienced an increase in proteinuria after pregnancy. The increase in proteinuria was associated with an elevated diastolic blood pressure. Histological features, such as crescent formation and tubulo-interstitial injury, were poor prognostic factors of renal function outcome in pregnant women with IgAN. Careful observation of diastolic blood pressure and a knowledge of the underlying histological pattern in IgAN patients may have predictive value in identifying high risk pregnancies.

Introduction

Immunoglobulin A nephropathy (IgAN) frequently affects women during their childbearing years. Conflicting evidence exists as to whether or not a pre-existing of IgAN condition can adversely influence the clinical course of a pregnancy^{1)~12)}. Therefore, a nephrologist is often consulted to evaluate the advisability of conceiving or to assist in the management of pregnancies already in progress in women who have IgAN^{1)~10)}. The controversy concerning the effects of pregnancy on clinical outcome might be due to the inclusion of women with decreased renal function

and/or hypertension, as well as the decade in which the investigation was performed. Differences in obstetrical and renal care in various localities, disparate ways of collecting and presenting data, and differences in the natural history of the disease among ethnic populations may also account for the conflicting evidence.

More recent reports by Abe¹¹⁾¹²⁾ have described that gestation has no significant consequences on renal function or fetal viability in nephritic women if hypertension is absent and renal function is normal. Moreover, Packham et al¹³⁾ have described that IgAN patients with diffuse prolifera-

tive lesions in accordance with focal and segmental lesions and/or severe vessel lesions, as determined by a diagnostic renal biopsy, were associated with a greater incidence of maternal complications. However, the clinical parameters and histological features that can be used as predictors of pregnancy outcome have not been fully identified in women with IgAN during pregnancy.

The purpose of this study was to determine the renal prognostic factors influencing the clinical outcome of pregnant women with IgAN.

Patients and Methods

Patients

Ten women, ranging in age from 26 to 36 years (average age of 30.5 years), with biopsy-proven IgAN seen in the Department of Medicine, Kidney Center, Tokyo Women's Medical University between 1988 and 1997 were included in the study. Women with the clinical features of Henoch-Schönlein syndrome or with systemic lupus erythematosus were excluded from the study. All patients gave their informed consent to participate in the study.

Clinical assessments

Women with IgAN were divided into two groups on the basis of their renal function outcome after pregnancy: group I consisted of five patients with no changes in renal function after pregnancy, and group II consisted of five patients who experienced a deterioration in renal function as a result of their pregnancy. Preeclampsia was defined as reported in the Criteria of American College of Obstetrics and Gynecology Consensus Report (1990). Intrauterine growth retardation (IUGR) was defined as birth weight below the 10th percentile for gestational age.

Before pregnancy and after delivery, the patient's blood pressure, serum creatinine levels, and 24-hour protein excretion were measured. For each pregnancy, the fetal outcome, gestation, and existence of preeclampsia were also re-

corded. The maternal outcome of each pregnancy was assessed by recording the blood pressure, serum creatinine level, and proteinuria level during each trimester when the blood pressure was 140/90 mmHg or more. Impaired renal function was defined as a serum creatinine level of greater than 1.3 mg/dl or an increase by more than 50% compared to pre-pregnancy levels. Increased proteinuria was defined as a doubling of the proteinuria level.

Histological assessments

Renal biopsy tissue was obtained prior to pregnancy in nine patients, and within one year of post-partum in one patient. The processing and staining of renal tissue has been described elsewhere¹⁴. The degrees of crescent formation, adhesion, extracapillary proliferation, and hyalinosis were scored semiquantitatively using a 4 grade scale: 0 = minimal injury (<10% of the tissue section affected), 1 = mild injury (10 to <30% of the tissue section affected), 2 = moderate injury (30 to <50% of the tissue section affected), and 3 = severe injury (>50% of the tissue section involved). Mesangial proliferation and tubulointerstitial injury were scored using 3 grade scale: 0 = mild injury, 1 = moderate injury, 2 = severe injury. Sclerosing change of the arterioles was scored as positive (1) or negative (0). The pathologic features were assessed using a light-microscope by two investigators who did not have any clinical information on the patients.

Statistical analysis

Values are expressed as means \pm SE. Statistical analysis was performed using Mann-Whitney U test, and p values of <0.05 were considered as statistically significant.

Results

In group I, none of the women experienced preeclampsia of pregnancy and all of the pregnancies resulted in a live infant (Table 1). Of the five normal infants, four were born by vaginal de-

Table 1 Clinical data of women with IgA nephropathy before pregnancy and obstetrical findings

| Patient | Clinical parameters | | | | Obstetrical findings | | | |
|---------------------|---------------------|-------------|---------------------|-----------|----------------------|---------------|----------|---------|
| | Age (yr) | Scr (mg/dl) | Proteinuria (g/day) | BP (mmHg) | Preeclampsia | Fetal outcome | Delivery | |
| Group I (n = 5) | 1 | 26 | 0.97 | 0.95 | 130/60 | No | Normal | Vaginal |
| | 2 | 28 | 0.70 | 0.99 | 110/60 | No | Normal | Vaginal |
| | 3 | 30 | 0.80 | 0.60 | 120/70 | No | Normal | Vaginal |
| | 4 | 33 | 0.92 | 0.80 | 108/62 | No | Normal | c/s |
| | 5 | 35 | 0.74 | 0.76 | 98/68 | No | Normal | Vaginal |
| Group II (n = 5) | 6 | 27 | 1.00 | 0.90 | 152/109 | No | Normal | c/s |
| | 7 | 29 | 0.74 | 0.63 | 102/72 | Yes | Normal | c/s |
| | 8 | 30 | 0.80 | 1.68 | 130/80 | No | IUGR | c/s |
| | 9 | 31 | 0.87 | 0.12 | 102/72 | Yes | Normal | Vaginal |
| | 10 | 36 | 1.32 | 2.84 | 128/85 | Yes | IUGR | c/s |

Scr: serum creatinine, BP: blood pressure, IUGR: intra-uterine growth retardation, c/s: cesarean section.

Table 2 Changes in clinical parameters of women with IgA nephropathy before pregnancy and after gestation

| | Group I (n = 5) | Group II (n = 5) |
|--------------------------|--------------------|---------------------|
| Average age (years) | 30.4 ± 1.6 | 30.6 ± 1.5 |
| Serum creatinine (mg/dl) | | |
| Before | 0.8 ± 0.1 | 1.0 ± 0.1 |
| After | 0.8 ± 0.1 | 1.2 ± 0.2 * |
| Proteinuria (g/day) | | |
| Before | 0.8 ± 0.1 | 1.2 ± 0.1 |
| After | 0.6 ± 0.1 | 2.4 ± 0.5 * |
| Systolic BP (mmHg) | | |
| Before | 113.2 ± 5.5 | 128.4 ± 8.4 |
| After | 109.6 ± 4.8 | 125.4 ± 9.2 |
| Diastolic BP (mmHg) | | |
| Before | 64.0 ± 2.10 | 85.0 ± 5.6 * |
| After | 63.6 ± 1.94 | 78.0 ± 2.0 * |

Values are mean ± SE. Scr: serum creatinine, BP: blood pressure, *: p < 0.05 vs. group I.

livery and one was born after a cesarean section. In group II, however, three out of 5 women experienced preeclampsia of pregnancy and two pregnancies resulted in IUGR. Four of the infants in group II were born after a cesarean section and one was born by vaginal delivery. The gestational age of children in group I (29.2 ± 2.3 week) tended to be longer than those (27.3 ± 2.8 week) in group II, but did not reach to statistical significance.

Table 2 shows the data obtained before pregnancy and after gestation in the present study. Before pregnancy, no significant differences in age, serum creatinine level, proteinuria level, and systolic blood pressure were present between the two groups. However, the diastolic blood pressure was higher in group II than in group I ($p < 0.05$). One to 8 months after gestation, the serum creatinine level, proteinuria level and diastolic blood pressure were higher in group II than in group I. Two years after gestation, increased proteinuria levels were recorded in all of the patients in group II, but in none of the patients in group I. Hypertension occurred in only one group II patient after gestation. Impaired renal function was detected in two of the 5 women in group II and in one of the 5 patients in group I.

Figure 1 shows the changes in serum creatinine levels during pregnancy and after delivery. In both groups, serum creatinine levels tended to decrease during the early stage of pregnancy (16 to 18 weeks) and return to pre-pregnancy levels during the late stage (24 to 36 weeks) of pregnancy.

To evaluate the histological features influencing renal outcome, biopsy specimens were analyzed by two investigators. Renal tissue altera-

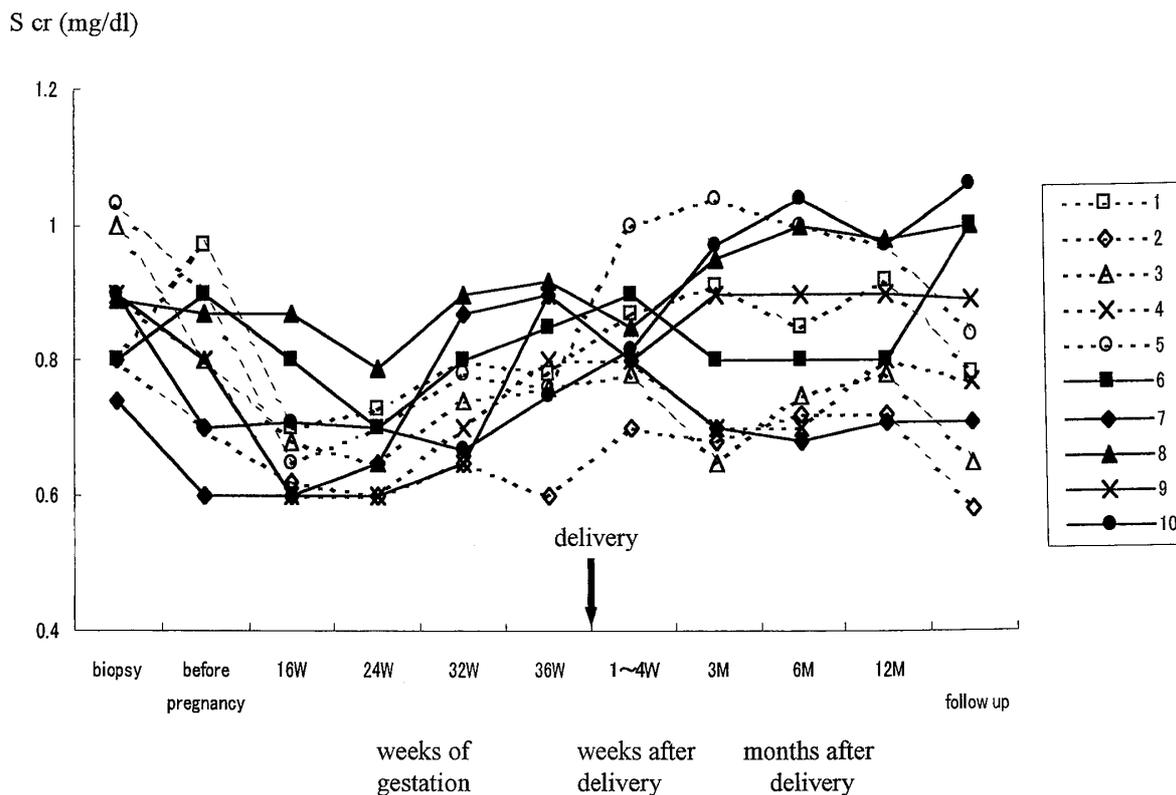


Fig. 1 Changes in serum creatinine of pregnant women with IgA nephropathy
 ... : group I, — : group II.

Table 3 Comparison of histological features in group I and group II of women with IgA nephropathy

| | Group I (n = 5) | Group II (n = 5) |
|------------------------------|--------------------|---------------------|
| Glomerular findings | | |
| Crescent formation | 0.4 ± 0.4 | 1.8 ± 0.2 * |
| Adhesion | 1.6 ± 0.4 | 2.4 ± 0.2 |
| Extracapillary proliferation | 1.6 ± 0.4 | 2.8 ± 0.2 |
| Mesangial proliferation | 1.2 ± 0.2 | 1.6 ± 0.3 |
| Hyalinosis | 1.0 ± 0.5 | 2.6 ± 0.3 |
| Tubulo-interstitial injury | 0.6 ± 0.3 | 1.8 ± 0.2 * |
| Arteriosclerosis | 0.2 ± 0.2 | 0.2 ± 0.2 |

Values are mean ± SE. *: $p < 0.05$ vs. group I.

tions observed using light-microscopy are summarized in Table 3. No significant differences were observed between the groups with regard to the degree of adhesion, extracapillary proliferation, mesangial proliferation, hyalinosis, and arteriosclerosis. However, the grades of crescent

formation and tubulo-interstitial injury were more severe in group II than in group I ($p < 0.05$). Two patients with impaired renal function exhibited widespread tubulo-interstitial lesions, including tubular atrophy, interstitial cell infiltration and fibrosis along with arteriosclerosis.

Recently, corticosteroid therapy has been reported to be effective for the early stage of progressive IgAN. One (case 1) of the 5 patients in group I was treated with prednisolone (initial dose = 20 mg/day), whereas prednisolone (initial dose = 20~40 mg/day) was administered to three of the 5 patients in group II. Medical treatment for IgAN before pregnancy may influence the clinical outcome of pregnant women with IgAN. Figure 2 depicts the clinical course of an IgAN patient (case 10) in group II. She was treated with conventional prednisolone therapy (40 mg/day for 4 weeks, with gradually taper-

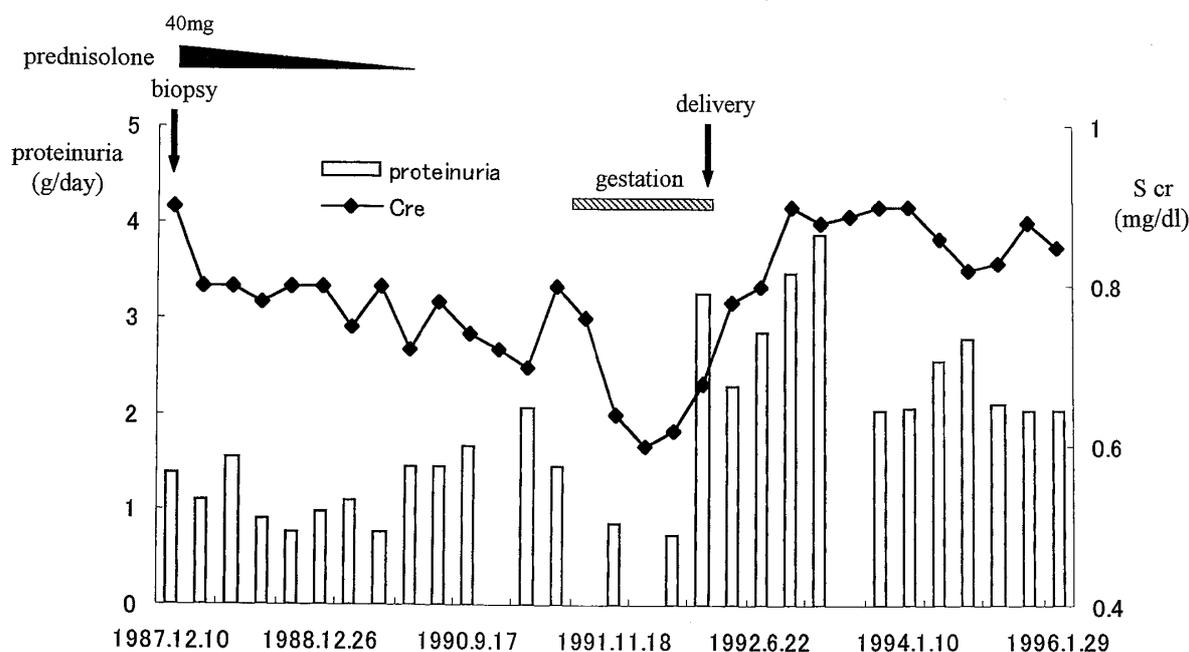


Fig. 2 Effect of prednisolone on serum creatinine and proteinuria in a woman with IgA nephropathy

ing). Thereafter, the serum creatinine levels decreased from 0.9 mg/dl to 0.6 mg/dl, although the proteinuria persisted until gestation. After delivery, the serum creatinine level returned to the level at the time of the renal biopsy and was associated with an increase in proteinuria.

Discussion

IgAN is the most common form of glomerulonephritis affecting women of childbearing age. Therefore, the management of pregnant women with IgAN is an important challenge for obstetricians and nephrologists, especially since the number of women with IgAN who are willing to take on the challenge of a pregnancy is increasing steadily. Although a relatively small number of cases were analyzed in the present study, we characterized the prognostic factors for clinical outcome in pregnant women with IgAN. An increased diastolic blood pressure was a prognostic factor for a reduction in renal function after gestation. In addition, crescent formation and tubulointerstitial injury were histological features that appeared in biopsy specimens from pregnant

women with impaired renal function.

Abe¹¹⁾ reported that most women with IgAN experience few problems with pregnancy as long as they are normotensive and their preconception glomerular filtration rate (GFR) exceeds 70 ml/min. The overall reduction in GFR and the increase in blood pressure and proteinuria at the time of the final follow-up were not significantly higher than those of IgAN patients who had never undergone a pregnancy. However, in patients who were hypertensive or who had GFRs of below 70 ml/min before conception, the long-term prognosis was less optimistic. In the current study, the systolic blood pressure before pregnancy was not significantly different between the groups, indicating that careful observation of the diastolic blood pressure may be important for predicting the renal outcome after gestation.

Packham et al¹³⁾ reported a very high rate of IgAN with superimposed focal and segmental proliferative lesions in their patients who eventually experienced a significant deterioration in renal function. In addition, obstetrical complications

and fetal loss rates were very high among these women. Other investigators did not find any association between either the percentage of sclerosed glomeruli or the presence of active crescents and the maternal or fetal outcome in their series of patients, despite the identification of these factors as prognostic features in other large series of non-pregnant patients¹⁵. Abe¹² has recently reported that among pregnant women with IgAN who progressed to dialysis, their biopsies demonstrated moderate or advanced diffuse proliferative glomerulonephritis with widespread tubulo-interstitial lesion.

In IgAN patients with a GFR value of more than 70 ml/min, a serum creatinine level of less than 1.1 mg/dl, and a blood pressure of less than 140/90 mmHg, an uneventful pregnancy is usually expected. In the present study, all of the women in group I did not experience preeclampsia, and all of the pregnancies resulted in a live infant. On the other hand, three out of the 5 women in group II experienced preeclampsia, and two pregnancies resulted in IUGR. Thus, maternal and fetal complications occurred more frequently in group II than in group I. Koido et al¹⁶ have recently reported that EPH (edema, proteinuria, hypertension)-gestosis and IUGR were correlated with the severity of glomerular abnormalities. Therefore, pregnant patients with severe findings not only in the glomeruli but also in the tubulo-interstitium should be treated with extra care, even if their serum creatinine levels are less than 1.1 mg/dl before pregnancy.

A recent report has suggested that corticosteroids are beneficial in stabilizing long-term renal function during the early stage of progressive IgAN¹⁷. The use of low doses of corticosteroids during pregnancy does not seem to be associated with harmful effects. In an additional study, all of the women with lupus nephritis had successful pregnancies while receiving corticosteroids ther-

apy and no adverse effects on the neonates were reported¹⁸. However, the effects of corticosteroids on the clinical outcome of pregnant women with IgAN has not been evaluated. In the present study, no adverse effects on the neonates appeared in all of the women who were treated with prednisolone. One patient treated with conventional prednisolone therapy (initial dose = 40 mg/day) experienced a reduction in her serum creatinine levels, although her proteinuria persisted until gestation. After delivery, the serum creatinine level returned to the same level present at the time of the renal biopsy and was associated with an increase in proteinuria. This case suggests that corticosteroid therapy before pregnancy may have important benefits for IgAN patients.

Conclusion

In conclusion, pregnancy seems to be safe for women with IgAN who do not have an increased diastolic blood pressure or pathological features such as crescent formation and tubulo-interstitial injury. Careful observation of the diastolic blood pressure and a knowledge of the underlying histological pattern in IgAN patients may have predictive value in identifying high risk pregnancies.

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IgA 腎症を合併した妊娠の予後に影響する腎性因子

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本研究の目的は、IgA 腎症を合併した妊娠の予後に影響する腎性因子を検討することである。対象は、妊娠前に腎生検で IgA 腎症と診断された 10 例の女性で、平均年齢は 30.5 (21~36) 歳である。臨床経過から次の 2 群に分けて検討した。I 群 (5 例) は、妊娠後も血清クレアチニン (Cr) 値の有意な上昇を認めなかったグループで、II 群 (5 例) は妊娠後に腎機能が悪化したグループである。血圧、尿蛋白量、血清 Cr 値、および腎生検所見を比較検討した。I 群に比し II 群では妊娠中毒症などの母体の合併症が多かった。妊娠前における血清 Cr 値は、両群で有意差を認めなかったが、妊娠後には II 群で有意な尿蛋白量の増加を認め、拡張期血圧の高値を伴っていた。また、I 群に比し II 群では半月体形成率が高く、尿細管間質障害の程度が強かった。これらの結果から、IgA 腎症を合併した妊婦は、拡張期血圧のコントロールと腎生検所見に基づいた注意深い経過観察が重要であると考えられた。