History of Adverse Pregnancy on Subsequent Maternal-Fetal Outcomes in Patients with Immunoglobulin A Nephropathy: A Retrospective Cohort Study from a Chinese Single Center

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Keywords

Immunoglobulin A nephropathy · Chronic kidney disease · Pregnancy outcome · Kidney disease outcome

Abstract

Background: Gestation complications have a recurrence risk and could predispose to each other in the next pregnancy. We aimed to evaluate the relationship between a history of adverse pregnancy and maternal-fetal outcomes in subsequent pregnancy in patients with Immunoglobulin A nephropathy (IgAN). **Methods:** A retrospective cohort study from a Chinese single center was conducted. Pregnant women with biopsy-proven primary IgAN and aged ≥ 18 years were enrolled and divided into the 2 groups by a history of adverse pregnancy. The primary outcome was adverse pregnancy outcome, which included maternal-fetal outcomes. Logistical regression model was used to evaluate the association of a history of adverse pregnancy with subsequent adverse maternal and fetal outcomes. **Results:** Ninety-one women with 100 pregnancies were included, of which 54

(54%) pregnancies had a history of adverse pregnancy. IgAN patients with adverse pregnancy history had more composite maternal outcomes (70.4% vs. 45.7%, $p = 0.012$), while there was no difference in the composite adverse fetal outcomes between the 2 groups (55.6% vs. 45.7%). IgAN patients with a history of adverse pregnancy were associated with an increased risk of subsequent adverse maternal outcomes (adjusted odds ratio [OR], 2.64; 95% CI, 1.07–6.47). Similar results were shown in those with baseline serum albumin < 3.5 g/dL, 24 h proteinuria ≥ 1 g/day, and a history of hypertension. There was no association between a history of adverse pregnancy and subsequent adverse fetal outcomes in IgAN patients (adjusted OR, 1.56; 95% CI, 0.63–3.87). **Conclusion:** A history of adverse pregnancy was associated with an increased risk of subsequent adverse maternal outcomes, but not for adverse fetal outcomes in IgAN patients.

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Introduction

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular nephropathy worldwide, especially in Asian populations [1]. Overall, 30–40% of patients may progress to end-stage kidney disease in 20–30 years after diagnosis [2]. Most female patients with IgAN are diagnosed during the childbearing period due to its higher incidence in those aged 20–30 years [3, 4]. Therefore, the impact of IgAN on mother or newborn has been a major concern.

Previous studies have showed that gestation complications, including stillbirth, spontaneous preterm birth, intrauterine growth restriction, and preeclampsia in general population have a recurrence risk and could predispose to each other in the next pregnancy [5, 6]. It is essential for health providers to be conscious of and identify the at-risk pregnancies with a history of adverse birth outcomes, which may be helpful for antenatal surveillance and target interventions to prevent adverse outcomes in continuing pregnancy. Currently, most of the studies focused on the effects of pregnancy on kidney disease progression and risk factors associated with adverse pregnancy outcomes in patients with IgAN [7–9]. There is limited evidence regarding on the impact of a history of adverse birth outcomes on maternal-fetal outcomes and long-term renal outcome in IgAN patients. Therefore, in this study, we aimed to evaluate the association of a history of adverse pregnancy with recurrent maternal-fetal outcomes in subsequent pregnancy in IgAN patients. We also compared kidney function and proteinuria after delivery and during follow-up between IgAN patients with and without a history of adverse pregnancy outcomes.

Materials and Methods

Study Design and Population

This is an observational cohort study. Patients in the IgAN registry of the First Affiliated Hospital, Sun Yat-sen University (FAH-SYSU) (<http://igan.medidata.cn>) during January 1, 2003 to December 31, 2019 were screened. Female pregnant patients with biopsy-proven primary IgAN and aged ≥ 18 years were enrolled. We excluded patients who experienced pregnancy before diagnosis of IgAN, and had missing baseline or gestational information. Eligible patients were divided into 2 groups based on a history of adverse pregnancy. A history of adverse pregnancy was defined as fetal loss, pre-eclampsia, and premature birth.

Demographic and Clinical Data

Baseline demographic, clinical, and biochemistry data of the participants were collected at the time of kidney biopsy from medical charts. Demographic and clinical characteristics (age, body

mass index, gestation history, and blood pressure) and biochemistry variables (hemoglobin, serum creatinine, albumin, blood urine nitrogen, and proteinuria) were collected. We also collected the medicine history of angiotensin receptor blockers, angiotensin converting enzyme inhibitors, corticosteroids, and immunosuppressant agents at the kidney biopsy. Maternal and fetal outcomes were ascertained through reviewing medical electronic health record database. Estimated glomerular filtration rate (eGFR) was calculated using Chronic Kidney Disease Epidemiology Collaboration creatinine formula [10] and renal histologic lesions were evaluated and graded according to the Oxford MEST-C classification criteria of IgA nephropathy (M, mesangial hypercellularity; E, endocapillary proliferation; S, segmental glomerulosclerosis/adhesion; T, tubular atrophy/interstitial fibrosis; and C, crescent formations) [11].

Study Outcomes

The primary outcomes were adverse pregnancy outcomes, which included adverse maternal outcomes and fetal outcomes. Adverse maternal outcomes were defined as delivery by cesarean section, premature rupture of fetal membrane, or pre-eclampsia. Adverse fetal outcomes were defined as low birth weight, preterm deliveries, fetal loss, or fetal distress.

Pre-eclampsia was diagnosed when a new-onset hypertension (blood pressure $>140/90$ mm Hg) and proteinuria (24-h urine protein excretion >0.3 g) occurred after week 20 of gestation [12]. Preterm birth was defined as a live-born infant delivery with a gestational age <37 weeks and low birth weight was defined as an infant weight <2.5 kg [13]. Fetal loss was defined as spontaneous abortion (intrauterine fetal demise before the 20th week of gestation caused by natural factors), stillbirth (intrauterine fetal demise after 20th week of gestation), neonatal death (live infant dying within 28 days after delivery), and therapeutic and induced abortions because of uncontrolled diseases [8]. We also investigated the change of maternal kidney function and proteinuria after delivery.

Statistical Analysis

Data were presented as mean $\pm$ standard deviation (SD) or median (25th, 75th) for continuous variables, as appropriate, as well as the number (percent) or frequency for categorical variables. Patients were divided by previous history of adverse pregnancy. Baseline demographic and laboratory variables were compared between patients with and without history of adverse pregnancy using Student's *t* test or Mann-Whitney U test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables, as appropriate.

Univariate and multivariate logistic regression model was used to evaluate the association of a history of adverse pregnancy with subsequent adverse maternal and fetal outcomes. The following potential confounding covariates were adjusted in the multivariate model: age, mean arterial pressure, proteinuria, serum albumin, and eGFR.

A priori subgroup analyses were conducted and defined by baseline serum albumin (≥ 3.5 g/dL vs. <3.5 g/dL), 24-h urine protein excretion (≥ 1 g/day vs. <1 g/day), eGFR (≥ 60 mL/min/1.73 m² vs. <60 mL/min/1.73 m²), and hypertension status (yes vs. no). We further compared the proteinuria and eGFR levels between patients with and without previous history of adverse pregnancy at the time of delivery and follow-up until July 1, 2020 using Whitney U test.

Table 1. Baseline clinical characteristics at the time of kidney biopsy

Variables	Overall	With adverse pregnancy history	Without adverse pregnancy history	<i>p</i> value
<i>N</i>	100	54	46	
Age, yr	27.2 (4.0)	27.0 (3.5)	27.5 (4.5)	0.57
Body mass index, kg/m ²	20.1 (18.8, 22.1)	20.7 (19.5, 22.5)	19.5 (18.4, 21.2)	<0.01
Time from biopsy to pregnancy, yr	4.0 (2.0, 6.0)	4.0 (2.0, 7.0)	2.0 (1.0, 4.0)	<0.01
Time from biopsy to delivery, yr	3.0 (1.0, 5.0)	5.0 (3.0, 8.0)	3.0 (1.0, 5.0)	<0.01
Hypertension, <i>n</i> (%)	21 (21.0)	11 (20.4)	10 (21.7)	0.41
Systolic BP, mm Hg	119.1 (18.3)	119.7 (18.0)	118.5 (18.9)	0.75
Diastolic BP, mm Hg	77.0 (13.7)	77.0 (13.1)	77.0 (14.5)	0.99
Mean arterial pressure, mm Hg	86.7 (80.0, 97.0)	86.7 (81.3, 97.0)	86.8 (79.7, 97.0)	0.54
Proteinuria category, <i>n</i> (%), g/d				
<1	65 (65.0)	35 (64.8)	30 (65.2)	0.55
1–2	27 (27.0)	16 (29.6)	11 (23.9)	
>2	8 (8.0)	3 (5.66)	5 (10.9)	
Hemoglobin, g/L	121.0 (115.0, 128.0)	122.0 (115.0, 129.0)	121.0 (113.0, 127.0)	0.82
Serum creatinine, mg/dL	0.7 (0.6, 0.9)	0.7 (0.7, 0.8)	0.8 (0.7, 0.9)	0.57
eGFR, mL/min/1.73 m ²	110.6 (90.7, 121.8)	112.3 (94.5, 121.0)	105.2 (87.0, 121.8)	0.47
Serum albumin, g/dL	3.8 (3.6, 4.1)	3.9 (3.7, 4.1)	3.7 (3.5, 4.1)	0.08
Oxford classification, ^a <i>n</i> (%)				
M1	88 (100.0)	47 (100.0)	41 (100.0)	
E1	14 (15.9)	7 (14.9)	7 (17.1)	0.74
S1	47 (53.4)	22 (46.8)	25 (61.0)	0.08
T1/2	22 (25.0)	10 (21.3)	12 (29.3)	0.34
C1/2	29 (32.9)	15 (31.9)	13 (31.7)	0.82
Treatment before pregnancy, <i>n</i> (%)				
RAS blocker treatment alone	71 (71.0)	37 (68.5)	34 (73.9)	0.55
Glucocorticoids and/or immunosuppressive drugs	43 (43.0)	23 (42.6)	20 (43.5)	0.76

Data are expressed as mean and standard deviation and median and range. $p < 0.05$. eGFR, estimated glomerular filtration rate; BP, blood pressure; RAS, renin-angiotensin system. ^aAnalysis was based on 41 patients without adverse pregnancy history and 47 patients with adverse pregnancy history.

All analyses were performed using Stata version 15 (Stata Corp LP, College Station, TX, USA) and R (version 3.6.3; Free Software Foundation Inc, www.r-project.org). A p value <0.05 was considered as statistically significant.

Results

Clinical Characteristics of Pregnant Patients with IgAN at Baseline and the Time of Delivery

A total of 91 women with 100 pregnancies who experienced pregnancy after IgAN diagnosis were included in this study (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000520586). At the time of biopsy, compared to patients without a history of adverse pregnancy, patients with a history of adverse pregnancy had higher body mass index, and longer time from biopsy to pregnancy and delivery. However, most of base-

line characteristics were similar between the 2 groups, including age, baseline serum creatinine, eGFR, proteinuria, hemoglobin, serum albumin, blood pressure, pathologic characteristics, and treatment (Table 1). At the time of delivery, patients with a history of adverse pregnancy had a higher body mass index and blood pressure, and there were not statistical differences in other characteristics between the 2 groups (online suppl. Table 1).

Adverse Pregnancy Outcomes

There were 51 (51.0%) adverse fetal outcomes and 59 (59.0%) maternal outcomes in 100 pregnancies. For fetal outcomes, patients with a history of adverse pregnancy had higher frequency of preterm birth than those without adverse pregnancy history (31.5% vs. 13.0%, $p = 0.04$). However, there were no statistical differences in frequency of fetal death, low birth weight, fetal distress, and composite adverse fetal outcomes between the 2 groups. For maternal

Table 2. Pregnancy outcomes of pregnant patients with IgA nephropathy

Variables	With adverse pregnancy history	Without adverse pregnancy history	<i>p</i> value
Fetal outcomes, <i>n</i> (%)			
Fetal death	5 (9.3)	9 (19.6)	0.27
Preterm delivery	17 (31.5)	6 (13.0)	0.04
Low birth weight	10 (18.5)	7 (15.2)	0.73
Fetal distress	4 (7.4)	3 (6.5)	0.91
Composite measure ^a	30 (55.6)	21 (45.7)	0.32
Maternal outcomes, <i>n</i> (%)			
Premature rupture of membranes	8 (14.8)	1 (2.2)	0.030
Pre-eclampsia	8 (14.8)	1 (2.2)	0.030
Delivery by cesarean section	33 (61.1)	19 (41.3)	0.06
Composite measure ^a	38 (70.4)	21 (45.7)	0.012

^a Adverse pregnancy outcome occurred for a single pregnancy was defined as a composite measure. *p* < 0.05.

Table 3. Association of a history of adverse pregnancy with fetal and maternal outcomes

Variables	Fetal outcomes				Maternal outcomes			
	OR	lower	upper	<i>p</i> value	OR	lower	upper	<i>p</i> value
Unadjusted model	1.49	0.68	3.28	0.324	2.82	1.24	6.44	0.013
Adjusted model								
A history of adverse pregnancy ^a	1.56	0.63	3.87	0.33	2.64	1.07	6.47	0.034
Age (per 1 year)	0.99	0.88	1.11	0.83	0.98	0.88	1.10	0.74
Mean arterial pressure (per 1 mg/Hg)	1.00	0.96	1.03	0.94	1.00	0.97	1.04	0.81
Proteinuria (per 1 g/24 h)	1.00	0.44	2.28	1.00	0.64	0.28	1.45	0.28
Serum albumin (per 1 g/dL)	0.92	0.82	1.03	0.17	0.99	0.89	1.10	0.82
eGFR (per 1 mL/min/1.73 m ²)	0.98	0.96	1.00	0.07	1.00	0.99	1.02	0.66

eGFR, estimated glomerular filtration rate. ^a Analysis was based on adjusted model.

outcomes, patients with a history of adverse pregnancy had higher frequency of premature rupture of membranes (14.8% vs. 2.2%, *p* = 0.03), pre-eclampsia (14.8% vs. 2.2%, *p* = 0.03), and composite adverse maternal outcomes (70.4% vs. 45.7%, *p* = 0.012) than those without adverse pregnancy history, but no statistical differences were found on the frequency of delivery by cesarean section (Table 2).

Effect of Pregnancy History on Subsequent Adverse Pregnancy Outcomes

There were no associations between a history of adverse pregnancy and subsequent composite adverse fetal outcomes either in unadjusted model (OR, 1.49; 95% CI, 0.68–3.28) or adjusted model (OR, 1.56; 95% CI, 0.63–3.87). For composite adverse maternal outcomes, patients with a history of adverse pregnancy was associated with an increased risk of subsequent composite adverse

maternal outcomes in unadjusted (OR, 2.82; 95% CI, 1.24–6.44; *p* = 0.013) and adjusted models (OR, 2.64; 95% CI, 1.07–6.47; *p* = 0.034) (Table 3).

In subgroup analysis, patients with a history of adverse pregnancy had higher risk of subsequent adverse maternal outcomes in those with serum albumin <3.5 g/dL (OR, 5.06; 95% CI, 1.43–17.83; *p* = 0.012), proteinuria greater than 1 g/day (OR, 6.02; 95% CI, 1.15–31.63; *p* = 0.034), and diagnosis of hypertension at kidney biopsy (OR, 2.83; 95% CI, 1.11–7.19; *p* = 0.029). There was no relationship between history of adverse pregnancy and subsequent adverse maternal outcome in patients with different kidney functions at the time of kidney biopsy (Fig. 1).

Kidney Function and Proteinuria after Delivery

There were 19 patients with 21 pregnancies without follow-up data. During a median (25th, 75th) follow-up of 2.2

Fig. 1. Subgroup analysis of a history of adverse pregnancy with fetal and maternal outcomes. GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate.

Fig. 2. Changes in eGFR (a) and protein urine (b) at the time of kidney biopsy, during delivery and after delivery. eGFR, estimated glomerular filtration rate.

(1.1–4.7) years after delivery, the eGFR levels were not different between the 2 groups (99.3 [59.3, 115.4] mL/min/1.73 m² vs. 112.0 [88.0, 118.2] mL/min/1.73 m², $p = 0.06$) (Fig. 2a; online suppl. Table 2); while the 24-h urine protein

excretion in patients with a history of adverse pregnancy was borderline higher than those without a history of adverse pregnancy (0.78 [0.36, 1.61] g/day vs. 0.39 [0.05, 0.85] g/day, $p = 0.048$) (Fig. 2b; online suppl. Table 2).

Discussion

In the current study, we demonstrated that a history of adverse pregnancy in pregnant patients with IgAN was not associated with subsequent adverse fetal outcomes, but associated with an increased risk of subsequent adverse maternal outcomes, especially in those with potential risk factors, including decreased serum albumin, overt proteinuria, and hypertension. At the end of follow-up, the levels of eGFR were not different between the 2 groups, while the proteinuria levels were borderline higher in patients with a history of adverse pregnancy than those without a history of adverse pregnancy.

Several studies have evaluated the possible relationship between obstetrical complications and adverse pregnancy outcomes in later pregnancies. A nationwide Swedish cohort including 354,676 women without predisposing chronic diseases showed that women with previous preterm preeclampsia had a higher risk of adverse pregnancy outcomes, including stillbirth, placental abruption, and preterm births in a second pregnancy [12]. Recently, a large population-based registry study reported similar results, that women who deliver with obstetrical complications (including pre-eclampsia, placental abruption, stillbirth, neonatal death, and small for gestational age infants) in a first birth even at term had substantially increased risks of subsequent preterm delivery [14]. These studies indicated the persistent causal factors in the mother and the possibility of shared biologic linking pregnancy conditions and outcomes [12, 14], due to the disorders of placental function (such as ischemic placental disease) [14, 15]. Evidence also showed that pregnancy-related complications were independent risk factors for kidney and other cardio or cerebrovascular disease outcomes [9, 16]. It indicated that metabolic, endothelial, and inflammatory changes may be responsible for the early onset of subsequent disease propensity in patients who experience a complicated pregnancy [16]. IgAN is an autoimmune renal disease arising from consequences of increased levels of galactose-deficient circulating IgA1. The mechanisms involved the formation of pathogenic IgA1-containing immune complexes in intercapillary and mesangial, which causes the cell activation and initiation of glomerular injury [17]. Therefore, IgAN patients with pregnancy may have such impact of immunologic microenvironment on maternal-fetal interface. However, whether the presence of history of adverse pregnancy in pregnant patients with IgAN could increase the risk of unfavorable maternal-fetal interface has not been elaborated in previous studies.

In this study, we separately defined the history of adverse pregnancy and subsequent maternal and fetal outcomes as a composition instead of a single exposure, which was different from previous studies [12, 14, 18]. Our study demonstrated that a history of adverse pregnancy in IgAN patients was associated with an increased risk of subsequent adverse maternal outcomes, but not for adverse fetal outcomes. The potential interpretation was that women with a history of adverse pregnancy had more extensive follow-up during subsequent pregnancy compared to those without such history. One recent meta-analysis showed IgAN had high risk of preeclampsia (OR, 11.80; 95% CI, 7.53–18.48), pregnancy-induced hypertension (OR, 10.39; 95% CI, 5.45–19.80), and preterm birth (OR, 3.37; 95% CI, 1.91–5.95) and low birth weight (OR, 2.36; 95% CI, 1.52–3.66) [19]. However, the increased risk of adverse fetal outcomes was not correspondingly high as that of preeclampsia and pregnancy-induced hypertension [19]. Similar results were reported by Piccoli et al. [20] that there was a higher risk of preeclampsia in IgAN pregnancy patients, but the risk of preterm delivery was not increased. Such a discrepancy indicated that the occurrence of “late” or “maternal” preeclampsia in IgAN pregnancy patients had less effect on early fetal growth. The occurrence of adverse maternal outcomes in the present study was similar as “late” or “maternal” preeclampsia, which may result in less severely fetal growth or shorten gestation.

Our study also noted that a history of adverse pregnancy was associated with increased risks of adverse maternal outcomes in those with a decreased serum albumin, overt proteinuria, and pre-existing hypertension, although the sample size of subgroup analysis was small. The possible explanation was that adverse maternal outcomes and renal progression shared common risk factors. Previous studies have found that proteinuria during pregnancy, hypertensive disorders, and decreased kidney function were key risk factors associated with adverse maternal outcomes [21–23]. Although we cannot prove a causal relationship in this study, the presence of history of adverse pregnancy was associated with subsequent adverse maternal outcomes after adjustment for multiple risk factors in IgAN patients. Interventions to reduce proteinuria, optimal blood pressure control, and balance nutrition for these high-risk mothers were required during the course of pregnancy.

There were several limitations in the present study. First, this retrospective cohort study was conducted in a single Chinese center. We could not exclude the possibility of residual confounding from unmeasured or un-

known covariates and selection bias because of the nature of retrospective analysis with limited sample size. In addition, the demonstration of the effect of the present study was limited to Chinese pregnancy IgAN patients. Therefore, it should be interpreted with caution for patients with other kidney diseases and races. Second, few patients with eGFR <60 mL/min/1.73 m² were involved, which limited the study's power to assess adverse pregnancy outcomes in those with decreased level of eGFR. Third, we only have the information of RAS blocker and immunosuppressive agents at the time of kidney biopsy, but had no corresponding information during the course of pregnancy and follow-up, which may place restrictions on research of treatment strategy. However, due to limited evidence regarding on the effect of the history of adverse pregnancy on recurrent maternal-outcomes in IgAN patients, it is important to highlight the requirement for further studies on the topic.

In conclusion, a history of adverse pregnancy in pregnant patients with IgAN was associated with a high risk for adverse maternal outcomes in subsequent pregnancy, while it was not associated with increased risk of adverse fetal outcomes. After delivery, both eGFR and proteinuria levels were stable at the end of follow-up. Further studies with large sample size and long-term follow-up are needed.

Statement of Ethics

This study was approved by the First Affiliated Hospital of Sun Yat-sen University Institutional Review Boards, Guangzhou, China (No. [2020] 207). All participants provided their written informed consent prior to inclusion in the registry.

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Conflict of Interest Statement

The results presented in this article have not been published previously except in abstract form. The authors declare no relevant conflicts of interest. Co-author Xueqing Yu is an Editorial Board Member of Kidney Diseases.

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Author Contributions

W.C. and X.Q.Y. were involved in the research idea and study design; X.J.L. and L.F. analyzed data and interpreted and drafted the manuscript; X.N., C.W., and Y.L. contributed to data acquisition; W.F.C. was involved in supervision or mentorship. All authors were involved in the revision of manuscript and responsible for providing intellectual content of critical importance to the work described as well as for final approval of the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary files. Further inquiries can be directed to the corresponding author.

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