Research Article

Clinical Predictors Implicated in the Incidence of Acute Pyelonephritis during the Antepartum Period: A Population-Based Cohort Study

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Keywords

Acute pyelonephritis · Risk factors · Antenatal care · Proteinuria

Abstract

Introduction: Acute pyelonephritis (APN) is a common infection during pregnancy that increases the risk of unfavorable maternal and fetal outcomes. However, it has not been clearly elucidated which demographic and clinical characteristics are associated with the incidence of APN during pregnancy. **Objective:** This population-based cohort study aimed to determine the risk factors for APN during pregnancy. **Methods:** Using the database of the Health Insurance Review and Assessment Service of South Korea, we enrolled Korean women who delivered infants between 2010 and 2014 in Korea and had complete health examination records within 1 year of pregnancy. We performed multivariate logistic regression analysis to evaluate the risk factors for APN during pregnancy. **Results:** Of 370,248 women, 2,526 (0.7% of the total participants) were treated for APN while in hospitalization during pregnancy. Younger age, history of previous APN within 1 year of pregnancy, and abnormal results of health examination before pregnancy, such as high fasting glucose level (> 100 mg/dL) and proteinuria, were associated with an increased risk of APN during pregnancy. **Conclusion:** Certain maternal demographic and clinical characteristics were associated with the incidence of APN during pregnancy, and these should be monitored closely during antenatal care.

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Introduction

The risk of acute pyelonephritis (APN) increases during pregnancy owing to anatomic and physiologic changes in the urinary tract [1]. Although the incidence of bacteriuria in pregnant women was estimated to be similar or slightly higher than that in nonpregnant women (2% or 10–13%) in previous studies [2–6], a much higher incidence of symptomatic urinary tract infection (UTI) and progression to APN along with bacteriuria (up to 40%) has been reported [7]. APN is believed to be associated with urinary tract stasis due to hormonal changes during pregnancy, especially increased progesterone level, and is also partly caused by mechanical obstruction as pregnancy progresses. APN is the most frequent bacterial infection during pregnancy and one of the most common causes of antepartum hospitalization besides obstetric indications [8–10]. Given that APN during pregnancy is associated with an increased risk of maternal and fetal morbidity, such as preterm birth, preeclampsia, stillbirth, anemia, sepsis, renal insufficiency, and acute respiratory distress syndrome [11–14], while some resistant organisms are detected in routine urine culture [15], the risk factors for APN should be closely monitored and managed during antenatal care. However, although some risk factors have been reported in previous studies, including multiparity, diabetes mellitus, urinary tract stones or malformation, and low socioeconomic status, it is not yet clear what increases the risk of APN during pregnancy [16]. In the present study, we aimed to investigate the factors associated with the increase or decrease in the risk of APN during pregnancy based on a large health-care system database.

Materials and Methods

Study Population

Study data were retrospectively collected from the Korea National Health Insurance (KNHI) claims database of the Health Insurance Review and Assessment Service (HIRA) over a 5-year period (January 2010 to December 2014). Almost all Koreans are covered by the health insurance policies of the KNHI, except for 3% of the population who are covered by the Medical Aid Program. The KNHI database contains information on all medical claims of approximately 50 million Koreans because health-care providers are required to submit their medical procedures to HIRA for review, which is an essential step in obtaining reimbursement for medical costs. Thus, many epidemiological studies based on this database have been published. Because such studies, including the present study, conceal individual identities by using unidentifiable codes, they are exempted from the requirement for written consent. The International Classification of Diseases 10th revision (ICD-10) diagnosis and procedure codes were used to identify all women who had given birth from 2010 to 2014. This study was approved by the Institutional Review Committees of Korea University Guro Hospital (KUGH17273).

Study Cohort Construction and Outcome Ascertainment

Of the 2,094,332 women with a medical record of pregnancy during 2010–2014, 113,036 individuals with no detailed birth history records were excluded. Further, 1,535,761 participants who did not undergo medical examination through the KNHI examination program within 1 year before pregnancy were also excluded. After the exclusion of 75,287 participants with missing health examination data, the data of 370,248 pregnant women were available. We considered that a previous kidney injury, such as kidney atrophy and vesicourinary reflux, may have an influence on renal function and the incidence of APN. However, information about the diagnosis and treatment of those conditions was not fully available because the data

used in the present study were obtained from medical records between 2010 and 2014 only (older records were not available). Therefore, 2,298 participants with available history of documented underlying kidney diseases (N11: obstructive pyelonephritis, N13.70: vesico-ureteral reflux without reflux nephropathy, N13.71: vesicoureteral reflux with reflux nephropathy without hydroureter, N13.72: vesicoureteral reflux with reflux nephropathy, N13.79: vesicoureteral reflux, N13.8: other obstructive and reflux nephropathy, N13.9: obstructive and reflux nephropathy, N26: atrophy of kidney, N18: chronic kidney disease, N19: unspecified kidney failure, Q62.7: congenital vesico-uretero-renal reflux, Q60.3/4/5: renal hypoplasia) were excluded, and 367,950 participants were finally included in the present study. To assess the clinical and laboratory factors associated with the incidence of APN in pregnant women, APN was defined as a hospitalization for ICD-10 codes N10 (acute tubulointerstitial nephritis, acute infectious interstitial nephritis, acute pyelitis, APN), N12 (tubulointerstitial nephritis, not specified as acute or chronic, pyelitis [not otherwise specified], pyelonephritis [not otherwise specified]), N39.0 (UTI, site not specified), and O23 (infections of the kidney in pregnancy, unspecified infection of the urinary tract in pregnancy, other and unspecified genitourinary tract infection in pregnancy). The study participants were categorized into two groups according to the presence of APN during the pregnancy period.

Sociodemographic and Laboratory Characteristics

Information about demographics (including parity) and comorbid conditions (e.g., previous hospitalization for APN within 1 year of pregnancy) was obtained from the HIRA database. Clinical and laboratory values were acquired from the records of general health examinations provided by the KNHI. The KNHI provides biannual health examinations for the general population. Clinical data such as blood pressure, body size measurements, and smoking history were collected. Laboratory examinations including hemoglobin, creatinine, cholesterol, liver function test, and urine analysis tests were performed. The results within 1 year of pregnancy were adopted as the baseline characteristics of the study population.

Statistical Analysis

The baseline characteristics are summarized as proportions and mean $\pm$ standard deviation. Student's *t* test was used to compare continuous variables between groups, whereas the chi-square test was used to compare categorical variables. We used logistic regression analysis to estimate the association between various clinical characteristics, with the likelihood of APN during pregnancy as the final outcome for the entire study population. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS software version 9.3 (SPSS Inc., Chicago, IL, USA).

Results

Study Population Description

The study population was constructed as shown in Figure 1. A total of 367,950 women who delivered infants between 2010 and 2014 without a history of underlying kidney disease and had complete general health examination records in the KNHI database within 1 year of pregnancy were enrolled. The mean $\pm$ standard deviation age of the overall cohort was 31 ± 4 years. Around 70% of all pregnant women were primiparous, and the rate of multiple pregnancy was $<2\%$. The incidence of APN treated during hospitalization in the overall cohort was 0.7% (2,467 patients). Women who had APN during pregnancy (APN group) were more likely to be younger and primiparous. The prevalence of a history of previous APN within 1 year of

Fig. 1. Construction of the study cohort.

pregnancy was much higher in the APN group (11.3% vs. 1.3%, $p < 0.01$). Other clinical characteristics such as smoking history, body mass index, obesity, and hypertension were not different between groups. In the laboratory findings, blood sugar level, renal function, and liver function were not different between groups. The levels of hemoglobin and total cholesterol were slightly lower in the APN group, although the differences were not clinically significant (Table 1).

Clinical and Laboratory Characteristics Associated with the Incidence of APN during Pregnancy

Table 2 shows the association of clinical and laboratory variables with the risk of APN during pregnancy in univariate and multivariate logistic regression models. Younger age was associated with a higher incidence of APN during pregnancy both in univariate and multivariate analyses (odds ratio [OR] 0.92 for every 5-year increase, 95% confidence interval [CI] 0.87–0.97). A history of previous APN within 1 year of pregnancy was the single most powerful predictor of APN during pregnancy (OR 8.45, 95% CI 7.40–9.65). Although renal function measured using creatinine was not significantly associated with pregnancy, the degree of proteinuria, divided into four groups (negative, $\pm$, 1+, and $\geq 2+$) according to grade from the results of a urinary dipstick test, significantly increased the risk of APN during pregnancy:

Table 1. Baseline characteristics of the study population

Characteristics	APN (–) (n = 365,483)	APN (+) (n = 2,467)	p value
Maternal age at delivery, years	31.5±3.7	31.2±3.9	<0.01
Primiparity	67.1	70.3	<0.01
Multiple pregnancy	1.7	1.9	0.25
Smoking status			0.57
Never	92.9	93.2	
Ever	3.7	3.3	
Current	3.4	3.5	
Previous history of APN treatment	1.3	11.3	<0.01
Body mass index	21.1±2.9	21.0±3.0	0.05
Obesity	9.3	9.1	0.67
Systolic blood pressure, mm Hg	110±11	110±11	0.63
Diastolic blood pressure, mm Hg	69±8	69±8	0.61
Hemoglobin, g/dL	12.9±1.0	12.9±1.0	0.05
Fasting glucose, mg/dL	88±11	88±14	0.25
Total cholesterol, mg/dL	177±32	176±31	0.08
Creatinine, mg/dL	0.9±1.0	0.9±0.9	0.46
Aspartate aminotransferase, IU/L	19±13	19±7	0.54
Alanine aminotransferase, IU/L	15±17	15±12	0.34
Gamma-glutamyl transferase, IU/L	16±13	17±16	0.11

Results are presented as mean ± standard deviation or as %. APN, acute pyelonephritis.

patients with grade 2 or higher proteinuria had a doubled risk of APN during pregnancy (OR 1.83, 95% CI 1.16–2.90). Although the mean fasting blood sugar levels were not different between the two groups (with APN and without APN) during pregnancy (88 ± 14 vs. 88 ± 11 mg/dL, $p = 0.25$), fasting blood sugar >100 mg/dL was a significant factor associated with a high incidence of APN during pregnancy, which increased the risk by more than two times (OR 2.06, 95% CI 1.41–3.01).

The treatment history for UTI other than APN (UTI treated without hospitalization, which was defined as simple UTI) was determined by extending the search for records of ICD-10 codes (N30.0, acute cystitis; N30.1, interstitial cystitis; N30.2, other chronic cystitis; N30.8, other cystitis; N34.1, nonspecific urethritis; N34.2, other urethritis; N37, urethritis in diseases classified elsewhere; B37.4, candidal cystitis and urethritis). A total of 17,468 patients (4.7% of total population) had a history of simple UTI without hospitalization within 1 year of pregnancy, and the comparison of the characteristics of this population with those of participants without a history of UTI was not significantly different from the comparison between patients with and those without a history of APN (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000503788). A history of previous simple UTI within 1 year of pregnancy was not associated with an increased risk of APN during pregnancy, but instead inversely decreased the risk of APN (OR 0.67, 95% CI 0.60–0.75).

Logistic regression analysis was also performed for the association of clinical and laboratory variables with simple UTI during pregnancy (online suppl. Table 2). The association of younger age and primiparity with the incidence of simple UTI was similarly observed in both univariate and multivariate analyses (OR [95% CI], 0.98 [0.96–1.00] and 1.61 [1.55–1.67] for every 5-year increase and primiparity, respectively). Obesity defined as body mass index >25 was associated with the incidence of simple UTI (OR 1.16, 95% CI 1.10–1.22). The degree of proteinuria and fasting glucose level >100 mg/dL was not significantly associated with the

Table 2. Association of clinical characteristics with acute pyelonephritis treated under hospitalization during pregnancy in univariate and multivariate logistic regression models

	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)
Age at delivery, Δ 5 years (ref. age ≤20 years)	0.90 (0.85–0.95)	0.92 (0.87–0.97)
Primiparity	1.16 (1.06–1.26)	1.07 (0.98–1.18)
Multiple pregnancy	1.19 (0.89–1.58)	1.19 (0.89–1.59)
Obesity (body mass index >25 vs. ≤25)	0.96 (0.83–1.10)	1.02 (0.88–1.18)
Previous history of APN treatment	9.48 (8.33–10.78)	8.45 (7.40–9.65)
Previous history of UTI without hospitalization	0.54 (0.48–0.60)	0.67 (0.60–0.75)
Smoking status		
Never	1	1
Ever	0.89 (0.72–1.11)	0.89 (0.71–1.11)
Current	1.01 (0.81–1.25)	0.98 (0.79–1.22)
Systolic blood pressure (>135 vs. ≤135 mm Hg)	0.87 (0.74–1.03)	0.90 (0.76–1.06)
Proteinuria		
Negative	1	1
±	1.12 (0.86–1.45)	1.13 (0.87–1.47)
1+	1.13 (0.78–1.61)	1.05 (0.73–1.51)
≥2+	1.96 (1.24–3.09)	1.83 (1.16–2.90)
Hemoglobin, Δ 1 g/dL	0.96 (0.93–1.00)	0.96 (0.89–1.09)
Fasting glucose (>100 vs. ≤100 mg/dL)	2.01 (1.38–2.93)	2.06 (1.41–3.01)
Total cholesterol (>200 vs. ≤200 mg/dL)	0.96 (0.87–1.06)	0.99 (0.89–1.09)
Creatinine, Δ 1 mg/dL	1.01 (0.98–1.05)	1.01 (0.98–1.05)
Aspartate aminotransferase (>44 vs. ≤44 IU/L)	0.97 (0.79–1.18)	0.96 (0.75–1.22)
Alanine aminotransferase (>44 vs. ≤44 IU/L)	0.94 (0.78–1.14)	0.95 (0.75–1.21)
Gamma-glutamyl transferase (>50 vs. ≤50 IU/L)	1.06 (0.78–1.42)	1.09 (0.79–1.50)

Bold values are statistically significant, $p < 0.05$. ^a Odds ratios (ORs) were adjusted for all variables in the table. CI, confidence interval; APN, acute pyelonephritis; UTI, urinary tract infection.

risk of simple UTI. On the other hand, current smokers and patients with high systolic blood pressure (≥ 140 mm Hg) showed a higher risk of simple UTI.

Discussion/Conclusion

This study demonstrated the clinical and laboratory variables associated with APN during pregnancy, elucidated from a large-scale patient database. Younger age, history of previous APN within 1 year before pregnancy, high fasting glucose level (>100 mg/dL), and proteinuria (grade $\geq 2+$ in urinary dipstick test) were associated with an increased risk of APN during pregnancy.

The strength of our study lies in the examination of a large nationally representative cohort including $>365,000$ pregnant women. However, several limitations should be mentioned. First, the data of comorbidities were not fully included owing to data limitation. Although the prevalence of all major comorbidities affecting the risk of APN, such as diabetes, chronic kidney disease, anatomical abnormality of the urinary tract, kidney atrophy, and vesicoureteral reflux, is expected to be rather low among pregnant women, the exact effect of those findings should be examined further with complete data in the future. Second, records about the time points of APN events and causative organisms were not available. Third, proteinuria was graded using only a urinary dipstick test rather than with a quantitative

method. Lastly, as with all observational studies, our study does not confirm a causal association between the risk factors and real incidence of APN.

During pregnancy, urinary stasis caused by mechanical obstruction and decreased bladder and ureteral tone due to hormonal changes confer increased susceptibility to urinary infection in the mother [1, 17]. Urine concentration and volume might be decreased by the physiologic increase of plasma volume. Moreover, a high incidence of glycosuria and urinary excretion of progesterin and estrogen may lead to reduced resistance of the urinary tract to bacterial infection [18]. All of these anatomic and physiologic changes contribute to the increased risk of APN during pregnancy [19]. Therefore, even asymptomatic pregnant women should be screened for bacteriuria, because it could progress to APN in up to 40% if left untreated [20, 21].

Although the incidence of APN during pregnancy is decreasing in developed countries, it is still considered a significant medical problem during antenatal care [22–24] and is the second most common medical complication during pregnancy next to anemia [23, 25]. Kidney problems have been implicated with the outcome of pregnancy [26, 27], and UTI during pregnancy is reported to have multiple complications, including preeclampsia and preterm labor [23, 28, 29]. However, there is no concrete consensus about the risk factors for APN during pregnancy owing to a lack of previous studies with a large-scale cohort [7, 24]. The incidence of APN during pregnancy in most previous reports was 1–2%; however, it varied from 0.1% to 4.9% among studies [10, 30, 31]. The incidence of APN during pregnancy in the present study was 0.7%, which is relatively lower than that reported in previous studies. This difference may be due to our definition of APN, which was restricted to severe APN treated during hospitalization. This strict definition of APN was used to serve the aim of our study, which was to classify and predict APN and associated factors that could possibly lead to serious complications, and the prevalence of UTI including simple UTI was 5.4% of the total population.

Among the factors associated with the risk of APN during pregnancy, age was a significant determining factor. Younger age was also reported to increase the risk of APN during pregnancy in previous studies, which usually compared two age groups owing to a small sample size [16]. In the present study, a decreasing risk of APN was found across the age groups divided by 5 years. However, the exact reason for this phenomenon is not clear. Higher bacterial inflow or contamination during active sexual intercourse in younger women might be presumed as a cause. The detailed background concerning the association of APN during pregnancy with age should be examined further.

A history of previous hospitalization for APN within 1 year of pregnancy was the most significant factor that tremendously increased the risk of APN recurrence during pregnancy. In the general population, the rate of recurrence of APN in the following year after the first episode is estimated to be around 5–10% [3, 7]. It is also well known that patients with a history of asymptomatic pyuria should be closely monitored for recurrence of the infection during antenatal care [12, 32–34]. A previous study reported that a history of UTI before pregnancy was associated with bacteriuria development during pregnancy [35]. In the current study, a history of APN before pregnancy was also associated with an increased risk of severe symptomatic APN. On the other hand, there was another finding that a history of previous simple UTI, which did not require hospitalization for the treatment, was not associated with an increased risk of severe symptomatic APN during pregnancy. In fact, it showed an inverse association in the present study. The reason for this opposite association between a history of APN or simple UTI and the incidence of severe symptomatic APN during pregnancy is not clear. It can be assumed that close self-monitoring for urinary symptoms or self-adoption of preventive measures for UTI recurrence might be associated with the decreased risk of APN among participants with previous simple UTI. On the other hand, previous APN

might have resulted in vulnerability to the recurrence of severe symptomatic APN regardless of such measures. However, owing to a lack of detailed data about the practice pattern after simple UTI and APN, the exact reason could not be explained in the present study. Further studies should be performed with special attention given to those with a history of previous APN during antenatal care as a high-risk group.

Among the baseline laboratory findings, proteinuria $\geq 2+$ in urinary dipstick test and high fasting glucose level (>100 mg/dL) were considered risk factors for APN during pregnancy. The prevalence of chronic kidney disease and diabetes in the study population was rather low and not different between groups divided according to the presence of APN during pregnancy; however, patients with these diseases could not be included in the analysis because of large missing data. Laboratory abnormalities at one time point may not be enough for a confirmative diagnosis of both diseases. However, the association of proteinuria and high glucose level in the examination taken once before pregnancy with the increased risk of APN during pregnancy suggests that close monitoring during antenatal care should be maintained in patients with abnormal findings for those values in the baseline examination.

In conclusion, clinical and laboratory findings examined before antenatal care, such as younger age, history of previous APN, proteinuria, and high fasting glucose level, were associated with an increased risk of APN during pregnancy. Future studies are needed to determine the underlying mechanisms and to further examine whether optimal and individualized antenatal care, considering the risk factors elucidated from the present study, could decrease the incidence of APN and promote favorable maternal and fetal outcomes.

Statement of Ethics

The study protocol was approved by the Institutional Review Committees of Korea University Guro Hospital (KUGH17273).

Disclosure Statement

The authors have no conflicts of interest to declare. The ICMJE disclosure forms are available as online supporting information.

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Author Contributions

Conducted the research: G.J.K., S.W.H., G.J.C. Performed data analysis or statistical analysis: S.W.H., K.-M.L. Drafted the manuscript: G.J.K., S.Y.A., H.Y.K., G.J.C. Performed quality assurance and critical revision of the manuscript for important intellectual content: G.J.K., S.Y.A., J.E.K., E.J.C., Y.J.K., M.-J.O. Assume primary responsibility for the final content: S.W.H., G.J.C.

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