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Association Between Recurrence of Urinary Calculi and Childbirth: A Population-Based Case-Control Study

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We examined the recurrence rate of urinary calculi (UC) in women after childbirth. The recurrence of UC is common, but no previous studies mentioned the risk of recurrence after childbirth. We performed a nationwide population-based cohort study to investigate whether childbirth could correlate with the recurrence of UC by using data from the National Health Insurance Research Database in Taiwan. Nulliparous women (age ≥20 years) receiving a diagnosis of first episode of UC between 2000 and 2002 were enrolled. We recorded the events of recurrence between parous patients (n = 737) and matched-control nulliparous patients (n = 737). The average ages for parous patients and controls were 27.41 and 27.54, respectively. The recurrence rate was 11.67% (86 of 737) in the childbirth cohort group and 21.57% (159 of 737) in the nonchildbirth cohort group. The childbirth cohort group was associated with a significantly decreased risk of

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secondary UC (adjusted hazard ratio, 0.45; 95% confidence interval, 0.35–0.59) compared with those who did not deliver a child. This relationship should be studied further.

Key words: Childbirth – Urinary calculi – Recurrence

The incidence of urinary calculi (UC) has increased considerably throughout the world in the last three decades.[1] Despite the progress in minimally invasive stone management, the prevention of further recurrence still remains the most important issue. According to various studies, factors such as hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, low urinary output, multiple stones, and family history have been considered causes for stone recurrence; however, the exact mechanism still remains unclear.[2–4]

For women, incidence rates seem to be increasing worldwide, along with the male-to-female ratio, which has increased from 1.7:1 to 1.3:1.[1] The risk of UC occurring is highest for females in their late 20s (2.5 per 1000 per year), but this decreases to 1 per 1000 per year by age 50 years,[5] thereby overlapping the childbearing period. UC during pregnancy is a special issue that accounts for 1 in 250 to 1 in 3000 pregnancies. Most UCs occur during the second and third trimesters, which increases the prevalence of preterm labor, lower birth weights, and cesarean deliveries.[6] During pregnancy, the glomerular filtration rate and renal plasma flow increase up to 30% to 50%, which subsequently increases the filtration load of calcium, sodium, oxalate, and uric acid, which are lithogenic factors.[7] This rise in lithogenic factors is coexistent with a rise in the levels of inhibitors of stone formation, such as urinary citrate, magnesium, and glycoproteins.[8] Overall, gravid and nongravid women are known to have similar risk of UC.[9] Stone components also differ from nonpregnancy; it was found that in pregnancy 74% of stones were predominantly calcium phosphate,[10] implying a different pathophysiology in stone formation during pregnancy.

Riley *et al*[11] also reported a significant increase in UC incidence in females, but the frequency of stone formation in pregnant women showed no change over a two-decade–long period. Although most studies focused on issues related to UC during pregnancy, recurrence of UC after childbirth was not yet well examined.

The application of big data analysis to health care has developed rapidly and convincingly, as in other fields in recent decades, and using this new approach to identify the factors associated with urolithiasis may bring us new insights into the pathophysiology of stone formation. This study aims to assess the influence of childbirth on stone recurrence in previous stone-forming patients. To our knowledge, this is the first population study to analyze the effect of childbirth on the recurrence of stone formation.

Patients and Methods

Data sources

The National Health Insurance Administration, Ministry of Health and Welfare, Taiwan, implemented a single-payer program for the National Health Insurance (NHI) in 1995, where joining the program is compulsory for all residents. Since 1997, the coverage rate has approached 99% of Taiwan's 22.9 million residents, whereas 97% of hospitals and 92% of clinics have contracts with NHI.

The Longitudinal Health Insurance Database 2000 (LHID2000) contains all of the original claim data for 200,000 individuals randomly sampled from the 2000 Registry for Beneficiaries (ID) of the NHI research database, which maintains the registration data of everyone who was a beneficiary of the National Health Insurance program during the period of 1996–2000.

In this study, we used the hospitalization claims data of all enrollees (23 million residents) in Taiwan, which contained information such as sex, birthdate, dates of admission and discharge, diagnoses, discharge status, and expenditures by admission. Diseases were coded based on the International Classification of Disease Diagnoses, 9th Revision of Clinical Modification (ICD-9-CM codes). The study was approved by the Institutional Review Board of China Medical University and Hospital (CMUH104-REC2-115).

Study design and population

We identified patients 20 years and older and those newly diagnosed with UC (ICD-9-CM: 592.0, 592.1, 592.9, 594.1) according to the data in the LHID2000 from 2000 to 2002. The follow-up concluded on December 31, 2011. Patients with UC from 2000 to 2002 following childbirth (ICD-9-CM: 650-659) classified by benefits for natural spontaneous delivery or cesarean delivery were defined as the cohort group. Patients with UC who did not give a birth during the study period were defined as the comparison cohort group. The date of the first UC occurring during the index years was designated as the index date for each group. The follow-up period ended either on the date of the secondary UC or on December 31, 2011. In order to exclude patients with UC during pregnancy, patients with secondary UC during pregnancy and those who had secondary UC 42 days after delivery were not taken into account.

For each patient in the cohort group, one comparison cohort patient was frequency-matched by age and index year. Overall, 737 individuals for the cohort group and 737 for the comparison cohort group were enrolled in the study. The potential confounders taken into account included urbanization level (4 levels) and insurance premium [New Taiwan dollars (NT$); categorized as $<$20,000; 20,000 $\leq$ insurance premium $<$ 40,000; 40,000 $\leq$ insurance premium $<$ 60,000; and $\geq$60,000).

The primary outcome was a secondary calculus of the kidney after the index date. All individuals were followed from the index date to the date of the diagnosis of a secondary calculus of the kidney or the end of the year 2011.

Statistical analysis

Means and standard deviations were described for continuous variables, and percentages were described for categoric variables. Comparisons between the two groups were performed using the Student *t*-test for continuous variables and Pearson χ^2 test for categoric variables, including age (20–30 years and $>$30 years), urbanization level (4 levels, with 1 being the most urbanized and 4 being the least), and insurance premium (NT$, $<$20,000; 20,000–39,999; 40,000–59,999; and $\geq$60,000). We intentionally matched the variable of urbanization level between the cohort group and comparison cohort group to ensure the cases and controls were reasonably similar in terms of unmeasured neighborhood socioeconomic characteristics. We used Cox proportional hazard regression models to estimate the effect of childbirth on survival analysis determined by adjusted hazard ratio (HR) with a 95% confidence interval (95% CI). The Kaplan-Meier method was used to estimate the cumulative event rate, and the log-rank test was used to examine differences between the groups. All analyses were carried out with SAS statistical software (version 9.4 for Windows, SAS Institute Inc, Cary, North Carolina). All statistical tests were determined at a significance level of 0.05 in 2-tailed tests.

Results

Of the total 737 cohort patients and 737 controls included with an initial UC during 2000–2002, the mean age was 27.54 years in the control group and 27.41 years in the cohort group. Overall, there were 245 patients with recurrent UC in the study: 86 patients who gave birth and 159 who did not.

Table 1 shows the results of the Pearson χ^2 tests performed to examine differences in the distributions of age, urbanization level, and insurance premiums between cohort patients and controls. The cohort group and comparison cohort group had similar ages (P = 0.631) and insurance premium distributions (P = 0.52). However, the comparison cohort group had a higher urbanization level ($P <$ 0.001) than the cohort group. The mean follow-up period was 10.0 years for the cohort group and 7.84 years for the comparison cohort group, respectively.

Table 2 further shows the crude and adjusted hazard ratios (HRs) of secondary UC for patients who did or did not give birth. Compared with nonpregnancy, childbirth was significantly associated with a decreased risk of secondary UC [HR, 0.44, 95% confidence interval (95% CI, 0.34–0.58] without adjusting for sociodemographic factors. After adjusting for age, urbanization level, and insurance premium, there was also a significantly decreased hazard for the cohort group compared with those without pregnancy (HR, 0.45; 95% CI, 0.35–0.59). Additionally, we categorized age into patients between 20 and 30 years and those older than 30 years. Compared with the younger group, the adjusted HR for women older than 30 years was 1.39 (95% CI, 1.07–1.80).

Table 3 shows the subgroup analysis for the two groups. The overall incidence rate of recurrent UC was 11.67 per 1000 person-years in the cohort group and 27.53 per 1000 person-years in the comparison cohort group. We further explored the association between recurrent UC disease and childbirth by stratifying age, urbanization level, and insurance premium (NT$). When stratified by age, the childbirth group had a lower risk of recurrent UC than the comparison cohort group among the 20- to 30-year-olds (HR, 0.45; 95% CI, 0.32–0.62) and women older than 30 (HR, 0.46; 95% CI, 0.30–0.72).

The Kaplan-Meier analysis was conducted in order to compare the cumulative incidence of UC between the childbirth and the nonchildbirth groups within

Table 1 Demographic characteristics in UC patients with and without childbirth

Variate	First UC between 2000 and 2002		*P* value
	Nonchildbirth (n =737)	Childbirth (n =737)	
Age, y, mean ± SD	27.54 (5.18)	27.41 (4.82)	0.6312
20–30 y, n (%)	527 (71.51)	527 (71.51)	0.99
More than 30 y, n (%)	210 (28.49)	210 (28.49)	
Urbanization level, n (%)[a]			<0.0001
1 (highest)	370 (50.2)	290 (39.35)	
2	302 (40.98)	344 (49.68)	
3	53 (7.19)	80 (10.85)	
4 (lowest)	12 (1.63)	23 (3.12)	
Insurance premium in NT$, n (%)			0.5201
<20,000	226 (30.66)	210 (28.49)	
20,000 ≤ insurance premium < 40,000	232 (31.48)	255 (34.6)	
40000 ≤ insurance premium < 60,000	126 (17.1)	131 (17.77)	
≥60,000	153 (20.76)	141 (19.13)	
Follow-up time, y, mean (SD)	7.84 (4.28)	10.00 (2.03)	

[a]The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

the follow-up periods of 7368 and 5776 person-years. The log-rank test result showed a higher incidence rate of UC in the nonpregnant group than in the childbirth group ($P < 0.0001$; Fig. 1).

Discussion

Although no one had previously reported women with decreased risk of UC after childbirth, we found that women who experienced child delivery were less prone to secondary stone recurrence compared with those who did not give birth during the 11-year follow-up period. The HR was 0.45 after adjusting for confounders (insurance premium, urbanization levels).

About 50% of recurrent stone patients experience stones once during their lifetime.[12] A high recurrence of stone disease was observed in about 10% of patients.[13] Risk factors for recurrence include male sex, multiple and lower calyx stones, familial history, and complications after stone removal.[13] Females did show a significant difference in the risk ratio of stone development for different variables, including body mass index, hyperinsulinemia, and hypertension.[14,15]

Table 2 Cox model with HRs and 95% CIs of secondary UC associated with childbirth

Variable	Secondary UC patients (n = 245)	Crude		Adjusted[a]	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Childbirth					
No	159	1; reference		1; reference	
Yes	86	0.44 (0.34–0.58)	<0.0001	0.45 (0.35–0.59)	<0.0001
Age					
20–30 y	157	1; reference		1; reference	
Older than 30 y	88	1.41 (1.09–1.83)	0.0101	1.39 (1.07–1.80)	0.0141
Urbanization level					
1	111	1; reference		1; reference	
2	112	0.95 (0.73–1.23)	0.6729	0.79 (0.57–1.08)	0.1395
3	20	0.8 (0.49–1.28)	0.347	0.85 (0.59–1.25)	0.411
4 (lowest)	2	0.29 (0.07–1.16)	0.079	0.85 (0.60–1.22)	0.3799
Insurance premium, NT$					
<20,000	82	1; reference		1; reference	
20,000 ≤ insurance premium < 40,000	73	0.79 (0.57–1.08)	0.1351	0.96 (0.74–1.25)	0.7774
40,000 ≤ insurance premium < 60,000	41	0.86 (0.59–1.25)	0.4256	0.86 (0.53–1.39)	0.5256
≥60,000	49	0.89 (0.62–1.27)	0.5157	0.29 (0.07–1.17)	0.0825

[a]Adjusted the variables of age, urbanization level, and insurance premium.

Table 3 Incidence rates, HRs, and CIs of secondary UC for patients with and without childbirth stratified by age, urbanization level, and insurance premium

	Childbirth							
	No (n = 737)			Yes (n = 737)				
Variables	Event	Person-years	IR	Event	Person-years	IR	Crude HR (95% CI)	Adjusted HR (95% CI)
Total	159	5776	27.53	86	7368	11.67	0.44 (0.34–0.57)***	0.45 (0.35–0.59)***
Age								
20–30 y	102	4083	24.98	55	5328	10.32	0.43 (0.31–0.6)***	0.45 (0.32–0.62)***
Older than 30 y	57	1693	33.67	31	2040	15.19	0.47 (0.3–0.72)***	0.46 (0.3–0.72)***
Urbanization level								
1	83	2611	31.79	28	2899	9.66	0.33 (0.22–0.51)***	0.33 (0.21–0.5)***
2	64	2569	24.92	48	3426	14.01	0.57 (0.39–0.83)**	0.6 (0.41–0.88)**
3	11	473	23.27	9	806	11.16	0.49 (0.2–1.19)	0.5 (0.2–1.21)
4 (lowest)	1	124	8.07	1	238	4.21	0.53 (0.03–8.53)	0.78 (0.04–14.56)
Insurance premium (NT dollars)								
<20,000	55	1799	30.57	27	2085	12.95	0.44 (0.28–0.69)***	0.44 (0.28–0.7)***
20,000 ≤ insurance premium < 40,000	47	1850	25.4	26	2553	10.19	0.42 (0.26–0.68)***	0.43 (0.27–0.7)***
40,000 ≤ insurance premium < 60,000	27	948	28.49	14	1308	10.71	0.4 (0.21–0.76)**	0.4 (0.21–0.77)**
≥60,000	30	1179	25.44	19	1423	13.35	0.54 (0.3–0.97)*	0.53 (0.29–0.95)*

IR, incidence rates, per 1000 person-years.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

Onset of UC at a younger age is also an independent risk factor for stone recurrence.[13] In our study, we collected more early-onset patients with UC in their childbearing age. About 71.5% of the cohort group was between the ages of 20 and 30 years.

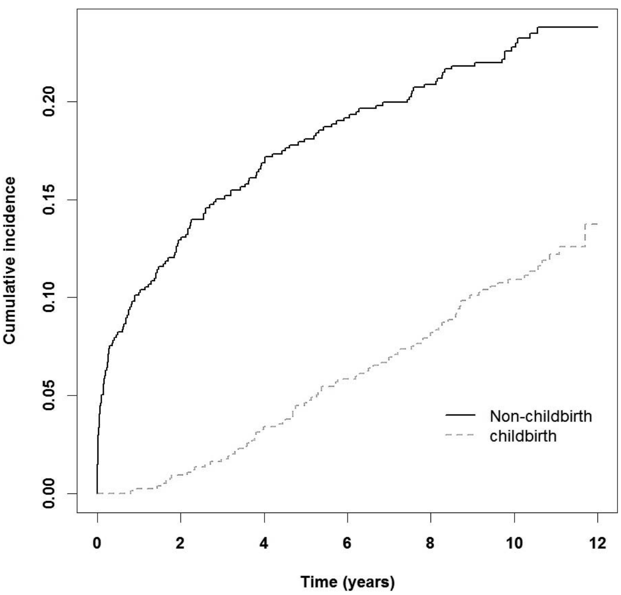

Fig. 1 The estimated cumulative incidence of UC with and without childbirth cohort by Kaplan-Meier analysis.

As we know, pregnancy at an early childbearing age and breast-feeding may reduce the risk of breast cancer.[16] How childbirth is linked with lower UC recurrence is unclear. We assume physiologic and hormonal changes during pregnancy and lactation may influence the recurrence of UC.

The low urine calcium levels are a response to the postpartum decreased glomerular filtration and increased tubular reabsorption of calcium after childbirth.[17–19] Breast-feeding also came with increases in bone turnover rate, reductions in bone mineral density, and reductions in urinary calcium excretion, which may also play a role in the postpartum period for reducing the incidence of UC.[20] The reduction of calcium excretion generally persists during the restoration period of bone density to the skeleton, even after the childbirth.[19]

Oxytocin, a neurohypophyseal hormone crucial for uterine contraction and lactation, may have a wide variety of physiologic functions.[21,22] In recent research, oxytocin has shown positive metabolic effects on insulin sensitivity, glucose metabolism, and lipid profile in diabetic rats.[23] Moreover, it has an anabolic effect on bone biology.[24,25] As we know, UC is implied as a systemic disease associated with diabetes mellitus, hypertension, gout, and osteoporosis.[26–28] Oxytocin may represent a promising role for decreasing the risk of UC recurrence.

Furthermore, estrogens appear to inhibit kidney stone formation, as reported in experimental animal studies.[29,30] Because estrogen may help to prevent the formation of kidney stones, nephrolithiasis is generally more common in men than in premenopausal women.[31] Moreover, the incidence of stones rises after menopause in women to where it equals that of men. Estrogen treatments may decrease the risk of stone recurrence in postmenopausal women by lowering urinary calcium and calcium oxalate saturation.[31,32] However, after childbirth, estradiols drop to their low prepregnancy levels. Therefore, estrogen may not play a major role in UC inhibition after child delivery.

Additionally, various studies reported that married individuals were known to have better health than those remained single.[33,34] Marital status and marital satisfaction may help to improve women's health, physical, and psychosocial conditions. Although unfavorable marital stress was associated with 3-fold increased risk of recurrent cardiovascular disease,[35] unmarried status may also intensify the risk of cardiovascular disease and metabolic syndrome.[36] Overall, women in high-quality marriages are known to have a lower risk of metabolic syndrome.[37] Interestingly, UC is associated with systemic metabolic and cardiovascular disorder.[38,39]

Studies on the pathophysiology of UC have provided knowledge from basic experiments, human metabolic studies, and population-based epidemiology. Lessons from population databases are valuable. The major limitation to such studies is their correlation with the conditions of an individual person. The stone component, body mass index, blood pressure, urine biochemistry, and metabolic profile were highly correlated with UC recurrence, but in this population cohort study, we could not correlate these parameters with stone recurrence. In addition, the NHI Research Database lacks information on the severity of UC; therefore, we could not account for severity in evaluating the relationship between childbirth and stone recurrence.

To the best of our knowledge, this is the largest and most complete nationwide population-based study to investigate the relationship between participants who gave birth and the subsequent risk of stone recurrence. Childbirth and lactation may be protective factors in the prevention of stone formation.

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