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Incidence of Female Urethral Diverticulum: A Population-Based Analysis and Literature Review

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Abstract

Introduction and Hypothesis—Urethral diverticulum (UD) is a protrusion of the urethra through the periurethral fascia. We aimed to determine the population-based incidence of female UD.

Methods—Using the records-linkage system of the Rochester Epidemiology Project (REP), we identified women 18 years and older with a new diagnosis of UD in Olmsted County, Minnesota, from January 1, 1980, through December 31, 2011. We also identified cases meeting the same criteria diagnosed at Mayo Clinic, regardless of county of residency. Incidence rates were calculated and trends for changes in incidence over time were tested. We conducted a systematic search of the MEDLINE, EMBASE, Cochrane Systematic Reviews, CENTRAL, Web of Science, and Scopus databases from inception through March 30, 2013, to identify published reports of UD incidence or prevalence.

Results—We identified 164 incidence cases, including 26 women residing in Olmsted County. Age-adjusted annual incidence of UD in Olmsted County was 17.9 per 1,000,000 women (<0.02%) per year (95% CI, 10.9–24.9). We observed a trend for increased incidence during the past 3 decades ($P=.03$). In our literature review, only 7 studies included an estimate of incidence

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or prevalence of UD; these estimates ranged from 6.4 per 1,000,000 per year (<0.01%) having surgical intervention related to UD to a 4.7% rate of UD diagnosed in asymptomatic women admitted for gynecologic or obstetric issues.

Conclusion—In this population-based study, female UD was a rare disease, affecting fewer than 20 per 1,000,000 women (<0.02%) per year.

Keywords

Urethra; diverticulum; urogynecology; urology

Introduction

Urethral diverticulum (UD) is a congenital or acquired protrusion of the urethra through the periurethral fascia [1–3]. For acquired cases, the cause is not well defined but might be related to periurethral infection or trauma [4–7]. Irrespective of the cause, UD can cause significant morbidity. Symptoms at presentation are commonly nonspecific, which usually delays the diagnosis. Complications include recurrent urinary tract infections, stone formation, and (more rarely) malignancy [3].

From a gynecologic perspective, UD is the most common differential diagnosis for a periurethral mass, accounting for 84% of all periurethral masses [8]. Despite frequently quoted incidence or prevalence rates (ranging from 0.6% to 6%), to our knowledge, no population-based study has validated those rates [2, 3, 9–12]. In this study, we report the incidence rate of symptomatic UD in adult females in Olmsted County, Minnesota, from January 1, 1980, through December 31, 2011. In addition, we conducted a systematic literature review of the incidence and prevalence of UD.

Materials and Methods

This study included a historical cohort and a systematic review of the literature. The Institutional Review Boards of Mayo Clinic and Olmsted Medical Center approved the study protocol. All participants provided their consent for use of their medical records in research. The manuscript was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [13, 14].

Incidence Study

Rochester Epidemiology Project—Almost all residents of Olmsted County, Minnesota, receive their primary and subspecialty care at Mayo Clinic or Olmsted Medical Center and their affiliated hospitals, and about 83% of the county's population is examined at least annually in 1 of these 2 facilities. To allow proper calculation of population-based incidence of UD in Olmsted County, we utilized the Rochester Epidemiology Project (REP). The REP is a records-linkage system that includes the medical records generated by Mayo Clinic and Olmsted Medical Center for Olmsted County residents [15]. In the past 4 decades, more than 1 million medical records were linked to about 500,000 individuals in the REP. The REP Census was validated using lists of county residents obtained from

various sources, and REP census counts were valid when compared with recent decennial US censuses, obtaining counts that sometimes were higher than the US census counts [16, 17].

Case Identification—Using the REP database, we identified all female Olmsted County residents, age 18 years and older, who received a new diagnosis of UD from January 1, 1980, through December 31, 2011. To identify cases of UD, we conducted a search using diagnostic codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Codes included 599.2 (“urethral diverticulum”), 599.5 (“prolapsed urethral mucosa”), and 599.84 (“other specified disorder of the urethra”) [18]. We also searched for Hospital Adaptation of the International Classification of Diseases (HICDA) codes 05994110 (“rupture, urethra, nontraumatic”), 05994210 (“prolapse, urethra, and NOS”), 05994300 (“sacculum, urethra”), 05994310 (“outpouching urethra [cystic]”), 05994320 (“diverticulum, urethral”), 05994710 (“cyst, urethra”), and 05994712 (“cyst, urethral gland”).

When searching the Mayo Clinic databases, we included all female patients age 18 years and older (regardless of their area of residence) who received a new diagnosis of UD during the study period. To meet the incidence criteria, patients who received the UD diagnosis or were treated before the start of the study period were excluded. Retrieved cases were verified through chart review.

Systematic Review

To identify previous studies that reported the incidence or prevalence of UD, we conducted a systematic search of the MEDLINE, EMBASE, Cochrane Systematic Reviews, CENTRAL, Web of Science, and Scopus databases from inception through March 30, 2013. Search terms included those referring to UD. Two investigators (S.A.E. and S.K.-F.) reviewed all identified studies in 2 parts. First, all studies were evaluated for relevance and number of cases. Studies with no UD cases or those including only a case report or a small case series (<10 cases) were excluded. Second, the text was reviewed in full to identify incidence or prevalence estimates. Disagreement in study inclusion was resolved by consensus, and agreement in the study selection was evaluated using κ statistics (κ estimates were interpreted according to Landis and Koch with values < 0 indicates no agreement and 0–0.20 indicates slight agreement, 0.21–0.40 indicates fair agreement, 0.41–0.60 indicates moderate agreement, 0.61–0.80 indicates substantial agreement, and 0.81–1 as almost perfect agreement [19]. One investigator (S.A.E.) reviewed bibliographies of the retrieved articles to identify additional eligible studies. Finally, only studies that reported incidence or prevalence rate of UD were included in the review. Data abstracted included study authors and publication date, type of rate reported, study population, and the reported estimate. No meta-analysis was intended or performed.

Statistical Methods

The primary outcome of the study was the age- and sex-specific population-based incidence of UD in Olmsted County, using cases from the population-based cohort. Rates were calculated with the assumption that the adult (18 years and older) female population of

Olmsted County was at risk. The numerator was the number of female Olmsted County residents with an incident diagnosis of UD during the duration of the study. The denominator was calculated from census data from 1980 through 2011. Rates were adjusted for age and sex based on the US Caucasian population in 2000 to increase generalizability to the US population.

Ninety-five percent CIs for the rates were calculated assuming a Poisson error distribution. The relation of incidence rates to 5-year intervals was assessed by fitting a generalized linear model, assuming a Poisson error structure, using the SAS procedure GENMOD (SAS Institute, Inc). A similar approach was used to calculate admission-based incidence rates to allow comparison with previous studies. The numerator was the number of female patients with an incident diagnosis of UD at Mayo Clinic during the study period. Separate denominators were obtained from the admission numbers for females to the 2 hospitals affiliated with Mayo Clinic, the Division of Gynecologic Surgery, and the Department of Urology, from January 1, 1980, through December 31, 2011.

Normally distributed continuous variables were reported as mean (SD); nonnormally distributed continuous variables were reported as median (range). Categorical variables were reported as number (%). Trends in the detection methods and management approaches were descriptively summarized across 5-year intervals and tested using the Cochran-Armitage test for trend. All statistical tests were 2-sided, and *P* values less than .05 were considered statistically significant. Statistical analysis was performed using SAS version 9.2 and JMP version 9.0 (SAS Institute, Inc).

Results

Incidence Study

We identified 595 women with a diagnosis code suggestive of UD from the REP and Mayo Clinic databases. After removing those who did not meet inclusion criteria, UD was verified in 182 women, with ascertainment of 164 new cases (Figure 1). Of these, 26 patients resided in Olmsted County and were included in the population-based incidence analysis (3 cases were diagnosed in the 1980s, 7 in the 1990s, 14 in the 2000s, and 2 cases after 2010). Accordingly, the age-adjusted incidence of UD in Olmsted County was 17.9 per 1,000,000 women per year (95%CI, 10.9–24.9) with a significant trend of increased cases through the past 3 decades (*P*=.03) (Table 1).

All 164 new cases, regardless of their county of residency, were used to calculate admission-based incidence estimates for the six 5-year intervals from 1980 through 2009. The incidence estimates were calculated using 3 separate denominators (the number of female admissions to the 2 affiliated Mayo Clinic hospitals, the Division of Gynecologic Surgery, and the Department of Urology) to facilitate comparison with previously published rates. The incidence was significantly higher when calculating the incidence based on Department of Urology admission numbers compared to Division of Gynecologic Surgery and All admission number with an overall estimate of 12,480.6 (95%CI; 10,552.7–14,408.5) per 1,000,000 compared to 1,512.3 (95%CI; 1,278.7–1,745.9) and 261.9 (95%CI; 221.4–302.3) per 1,000,000, respectively. (Table 1) (Figure 2).

Systematic Literature Review

Of the 774 studies identified by the primary search, 66 studies described UD cases and were considered for inclusion in the review. The κ agreement between the 2 investigators for study selection was graded as “almost perfect agreement” [$\kappa=0.88$; 95% CI, 0.80–0.95]. Of the identified studies, only 7 reported an estimate of incidence or prevalence, and none included a population-based incidence [5, 9–12, 20, 21] (Table 2).

Discussion

The main finding of our current study was the low incidence rate of female UD (17.8 in 1,000,000 women per year) in Olmsted County, Minnesota. This population-based incidence rate was lower than rates previously reported in previous research that ranged from 0.6% to 6% [3] [5, 9–12, 20, 21]. Out of 774 studies identified by our primary search, only 7 reported an estimate of incidence or prevalence, and none included a population-based incidence [5, 9–12, 20, 21]. The current study is the first to report incidence of UD on a population level, using valid epidemiologic methodology [22–24].

The higher estimates previously reported might be attributable to variations in population characteristics, presence of symptoms, diagnostic modality used, and era of diagnosis. For example, in studies from the 1940s and 1950s, the differences might be attributable to variations in clinical practice and diagnostic modalities [11, 20]. Nevertheless, the calculated estimates in relation to total admissions to Charity Hospital in New Orleans in the 1940s resulted in a rate of 25.4 per 1,000,000 women admissions [20]; this rate is slightly higher than that calculated in the current study, but it is still within the 95% CI of our rate and supports the observation that the disease is rare. Other causes of variation include the detection of asymptomatic diverticulum, whether by postmortem evaluation [11], by performing urethrography in women with an early diagnosis of cervical cancer [10], or by evaluating new admissions to an obstetrics and gynecology practice [9]. Notably, such reports might represent an estimate of UD in asymptomatic women.

Incidence estimates of 1.6% and 1.4% were reported in patients treated in a urology practice and in patients referred for evaluation of urinary incontinence by cystoscopy, respectively [5, 12]. Although those estimates are much higher than our calculated population-based incidences, they are comparable to our estimates when considering the total number of women presenting to our institution with UD and the total number of women admitted to the Division of Gynecologic Surgery and Department of Urology. This is an example of referral bias and its effect on overestimation of the incidence of the condition. The higher rate also may be because of a higher incidence of UD in patients with other urologic diseases [5, 12] or because the denominator is relatively small for the total number of patients admitted for treatment in the Department of Urology or the Division of Gynecologic Surgery compared with the denominator used to calculate the population-based incidence in Olmsted County.

Although this is the first report of a population-based incidence rate for UD in adult females, the study was limited by its retrospective design. However, the incidence was measured in relation to actual number of women at risk, with appropriate adjustment for age and time of the study. Another limitation was the high percent of whites in the Olmsted County

population compared with the US population. Nevertheless, 14% of cases were nonwhites, and we adjusted the incidence to the US population to allow better generalizability of the findings. Finally, the number of cases in the population-based cohort was small and might add some instability to the calculations of the incidence rates. We believe that the length of the study period (30 years) add assurance that those rates are still representative of the incidence in the population studied, even if they are estimated from small numbers in each year.

One of the main concerns about the use of the REP is the generalizability of the epidemiologic findings from Olmsted County population to the US population. In a previous study, the age, sex, and ethnic characteristics of Olmsted County were overall comparable to those of the state of Minnesota, the Upper Midwest, and overall US population. The only significant difference was that Olmsted County is less ethnically diverse than the US population (90.3% vs 75.1% white), has more educated residents (91.1% vs 80.4% high school graduates), and has higher median household income (\$51,316 vs \$41,994). In addition, Mortality rates in Olmsted were similar that of the state of Minnesota, and the United States [16, 17]. Thus, we believe that the findings of this study are generalizable to the Upper Midwest, with some limitation in application to the whole US population in nonwhite population.

In conclusion, female UD is a rare condition affecting less than 20 per 1,000,000 women (<0.02%) per year. Further validation of this finding in other areas of the United States and other countries with greater demographic diversity would be of value.

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Abbreviations

ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
HICDA	Hospital Adaptation of the International Classification of Diseases
REP	Rochester Epidemiology Project
UD	urethral diverticulum

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Brief Summary

Female urethral diverticulum is a rare disease, affecting fewer than 20 per 1,000,000 women (<0.02%) per year.

Figure 1.

Flow Chart of the Study Population and Case Identification. MRI denotes magnetic resonance imaging.

Figure 2.
Incidence of Female Urethral Diverticulum. Rates are stratified by population- and admission-based data. Log scale is used.

Table 1

Incidence of Urethral Diverticulum in Olmsted County, Minnesota (January 1, 1980, through December 31, 2009)

Calendar Period	Population-Based, Age-Adjusted Incidence per 1,000,000 Women (95% CI)	Incidence per 1,000,000 Admissions (95% CI)		
		All Hospital Admissions	Division of Gynecologic Surgery	Department of Urology
1980–1984	3.4 (0 – 10.1)	275.4 (171.5 – 379.3)	1,599.1 (995.9 – 2,202.2)	12,080.5 (7,523.7 – 16,637.3)
1985–1989	7.8 (0 – 18.6)	238.7 (141.2 – 336.3)	1,379.1 (815.5 – 1,942.7)	10,712.6 (6,334.5 – 15,090.7)
1990–1994	21.1 (0 – 42.3)	198.6 (106.9 – 290.4)	1,112.9 (598.8 – 1,627.0)	10,309.3 (5,546.6 – 15,071.9)
1995–1999	12.7 (0 – 27.1)	258.9 (153.1 – 364.7)	1,463.2 (865.2 – 2,061.2)	14,724.7 (8,706.9 – 20,742.5)
2000–2004	20.5 (2.4 – 38.6)	237.2 (142.3 – 332.0)	1,363.5 (818.0 – 1,909.0)	10,963.9 (6,577.4 – 15,350.4)
2005–2009	33.8 (11.4 – 56.1)	341.9 (228.6 – 455.2)	2,040.1 (1364.2 – 2,716.0)	15,660.0 (10,471.8 – 20,848.1)
Overall	17.9 (10.9 – 24.9)	261.9 (221.4 – 302.3)	1,512.3 (1,278.7 – 1,745.9)	12,480.6 (10,552.7 – 14,408.5)
<i>P</i> value, test for trend*	.03	.36	.31	.27

* Testing for a linear trend across the six 5-year intervals.

Table 2
Published Estimates for Incidence or Prevalence of Female Urethral Diverticulum

Study	Year	Study Population (Denominator)	Diagnostic Test	Type of Study	Estimate (Prevalence or Incidence)
Menville and Mitchell [20]	1944	510,585 (265,815 white, 244,770 nonwhite) admissions to Charity Hospital in New Orleans from January 1, 1892, through June 1, 1943	Usual evaluation	Incidence	13 (25.4 per 1,000,000) [11 reported: 8 nonwhite, 3 white]
Bruning [11]	1959	500	Autopsy (information about symptoms was not available)	Prevalence	9 (0.6%)
Adams [9]	1964	129 asymptomatic cases (82 consecutive gynecologic admissions, 47 postpartum patients)	Urethrograms	Prevalence	6 (4.7%)
Andersen [10]	1967	300 asymptomatic cases with newly diagnosed early cervical cancer	Urethrograms	Prevalence	9 (3%)
Davis and Roberinson [12]	1970	6,481 [972 blacks, 5,509 whites] hospitalized in Urology in the same time of surgery	Usual evaluation	Incidence	110 (1.6%) [blacks, 6%; whites, 1.1%]
Aldridge et al [5]	1978	279 with urinary incontinence, undergoing cystoscopy	Usual evaluation	Prevalence	4 (1.4%)
Burrows et al [21]	2005	Data from the National Hospital Discharge Survey (1979–1997) for diagnosis and procedure codes using the ICD-9-CM classification system	Surgery for urethral diverticulum	Urethral surgery rate	Age-adjusted rate per 1,000,000 women: 1979–1988, 14.2 1989–1997, 6.4 Three-fold higher rate for blacks compared with whites

Abbreviation: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.