Microhematuria in postmenopausal women: adherence to guidelines in a tertiary care setting

Megan S. Bradley, MD,
Duke University Medical Center, Department of Obstetrics and Gynecology, Division of Urogynecology and Reconstructive Pelvic Surgery, 5324 McFarland Drive, Suite 210, Durham, NC 27707, (c) 248-770-1681 (w) 919-401-1000 (f) 919-401-1033

Marcella G. Willis-Gray, MD,
University of North Carolina – Chapel Hill, Department of Obstetrics and Gynecology, Division of Urogynecology and Reconstructive Pelvic Surgery

Cindy L. Amundsen, MD, and
Duke University Medical Center, Department of Obstetrics and Gynecology, Division of Urogynecology and Reconstructive Pelvic Surgery

Nazema Y. Siddiqui, MD, MHSc
Duke University Medical Center, Department of Obstetrics and Gynecology, Division of Urogynecology and Reconstructive Pelvic Surgery

Megan S. Bradley: Megan.bradley@duke.edu

Abstract

Purpose—In 2012, the American Urological Association released a revision of their asymptomatic microscopic hematuria (AMH) guidelines. Our objectives were to assess adherence to these guidelines and to describe the prevalence of urinary tract malignancy in postmenopausal women at our institution.

Materials and Methods—This is a cross-sectional analysis of women over age 55 evaluated by Urogynecology or Urology from 8/2012-8/2014 for a diagnosis of AMH. Women who underwent evaluation for 3 RBC/HPF on microscopic urinalysis were considered "true AMH." Those who were evaluated after a dipstick with blood and had <3 RBC/HPF on urinalysis or no urinalysis were considered "positive dipstick." Demographics, laboratory values, imaging results, and cystoscopy findings were extracted from electronic medical records.

Results—Our study population included 237 women (mean age 67.1±8.3 years). In our overall population 169/237(71.3%) had true AMH, 48/237(20.3%) had a positive dipstick, and 20/237(8.4%) underwent evaluation in the setting of a urinary tract infection. We detected 3(1.4%)

urinary tract malignancies. One kidney cancer was identified in a 56 year-old, current smoker with a urine dipstick of 1+ blood. Two instances of bladder cancer were detected in women aged 58 and 64, one current and one nonsmoker with 6 and 42 RBC/HPF on urinalyses respectively.

Conclusions—In postmenopausal women evaluated for AMH, the overall prevalence of urinary tract malignancy was low (1.4%). In our population, 28.7% underwent evaluation without meeting guideline criteria for AMH. This demonstrates an opportunity to improve adherence to existing guidelines to provide high-quality care and avoid unnecessary, expensive testing.

Keywords

Asymptomatic Microscopic Hematuria; Postmenopausal Women; Clinical Guidelines

Introduction

The prevalence of asymptomatic microhematuria (AMH) ranges from 2–30% depending on the definitions used and the age and gender of the population studied.[1] AMH is clinically significant as it may be a sign of underlying urinary tract malignancy (including bladder and upper tract urothelial cancer), but there is often controversy regarding which patients should be investigated and if similar guidelines should be used for male and female patients.[2,3] In 2012, the American Urological Association (AUA) revised the AMH guidelines to maximize detection rates of urinary tract malignancies, but unfortunately the guidelines do not explicitly address gender-specific recommendations.[1] In summary, the guidelines propose a thorough evaluation of any patient with three or greater red blood cells per high powered field (3RBC/HPF) on one properly collected urinary specimen in the absence of an obvious benign cause.[1] They recommend cystoscopy for all patients over 35 years old as well as upper tract imaging using multi-phasic computed tomography (CT) urography. Since microhematuria may be intermittent, even when caused by malignancy, the guidelines specifically now require only one positive urine sample as opposed to the 2001 guidelines that required the presence of AMH in two out of three samples.[4]

The above recommendations may be appropriate in some patient populations, but postmenopausal women pose a unique challenge since bladder cancer is 3–4 times less common in females as compared to the equivalent male population[5], while the prevalence of microhematuria is as high as 20.1% in postmenopausal women, presumably due to factors such as pelvic organ prolapse or vaginal atrophy.[6] The AUA guidelines are vague as to how to consider these potentially confounding conditions in postmenopausal women and many clinicians pursue full AMH evaluations even if vaginal prolapse and atrophy are present, possibly leading to unnecessary, expensive testing and undue patient concern.

Furthermore, there are data that, in the primary care community, few patients with appropriately diagnosed AMH receive complete evaluations,[7] but there are limited data on the urologic community's adherence to AUA diagnostic criteria prior to initiation of AMH evaluation. The objective of this study was to describe adherence to AUA AMH guidelines by urology and urogynecology providers in a population of postmenopausal women at a tertiary care center. Additionally, we sought to assess the prevalence of urinary tract malignancy in our population of postmenopausal women.

Materials and Methods

After Institutional Review Board approval, we performed a cross-sectional analysis of postmenopausal women evaluated for AMH at Duke University Medical Center. We used our electronic medical record to identify women who were evaluated by the Divisions of Urogynecology or Urology for ICD-9 codes 599.71 (gross hematuria), 599.7 (hematuria), 599.70 (hematuria, unspecified) and 599.72 (microscopic hematuria) from 8/2012 to 8/2014. For purposes of our analysis, we only included women 55 years of age or older, and after medical records were reviewed, women with gross hematuria were excluded from our analysis. The AMH diagnosis was assigned by the clinician either based on a urine specimen sent from the initial office visit, or based on referral diagnosis for a new patient consultation.

Demographics, past medical and surgical histories, laboratory results, cystoscopy findings and imaging results were extracted from the medical record. For our study, the degree of hematuria was ascertained from the first positive urinalysis if multiple positive urinalyses were found. The American Urological Association (AUA) recommends further evaluation for AMH (defined as 3 RBC/HPF on microscopic urinalysis) when benign causes such as urinary tract infection (UTI) have been excluded. Women who underwent evaluation based on these guidelines were considered "true AMH". Those who were evaluated after a dipstick with any blood and negative microscopic urinalysis (<3 RBC/HPF) or no microscopic urinalysis were considered "positive dipstick." We also assessed for concomitant UTI, based on urine culture, at the time of urinalysis or dipstick analysis. A complete evaluation was defined per the AUA AMH guidelines as cystoscopy and upper tract imaging via multi-phase computed tomography (CT) urography.

Data were analyzed using SPSS 22.0 (SPSS Inc., Chicago, IL). Results are presented as means with standard deviations (SD) for continuous normally distributed variables and medians with full ranges for continuous not normally distributed variables. Categorical variables are presented as counts and percentages.

Results

During our two year study period, we identified 348 hematuria diagnoses in women > 55 years of age. After excluding those with gross hematuria, our study population included 237 women with mean age 67.1±8.3 years. The majority of women were white (74.7%), nonsmokers (57.4%) and overweight (Body Mass Index [BMI] 28.1 ±5.9). Irritative voiding symptoms, defined as self-reported urinary urgency, frequency or nocturia, were reported in 107/237 (45.1%) and 36/237 (15.2%) met one of the following definitions of recurrent urinary tract infection: 1) current antibiotic prophylaxis use; 2) 2 documented positive urine cultures in the last 6 months; or 3) 3 positive urine cultures in the last year.[8] Oral or vaginal estrogen was used in 62/237 (27.0%) of patients.

Only 150/237 (63.3%) women underwent full genitourinary exam documenting vaginal tissue quality and presence of prolapse. Of these, 90/150 (60.0%) had objective atrophy. In this group, there was no prolapse in 134/150 (89.3%) and only 17/150 (11.3%) had stage II or greater prolapse on exam.

Of the 228 women that had a microscopic urinalysis performed at some point in their evaluation, the mean number of RBC/HPF was 10.9 +/− 14.8 (range 0–117). In total, 40/228 (17.5%) had <3 RBC/HPF, 123/228 (53.9%) had 3–10 RBC/HPF and 65/228 (28.5%) had >10 RBC/HPF. Of the microscopic urinalysis specimens, 206/237 (86.9%) were voided specimens, 19/237 (8.0%) were catheterized specimens and 12/237 (5.1%) had unknown collection methods.

With regards to our adherence to the AUA guidelines, in our overall population 169/237 (71.3%) had true AMH, 48/237 (20.3%) had a positive dipstick, and 20/237 (8.4%) underwent evaluation for AMH in the setting of a urinary tract infection (UTI). Of these 20 with UTI, only two women had follow up urinalyses documenting presence of AMH in the absence of infection. Additionally many patients were given a diagnosis of AMH without microscopic urinalysis. Only 60/237(25.3%) patients had a microscopic urinalysis sent on the same day that they had a dipstick that prompted referral or further evaluation for AMH. Amongst these 60 patients, there was a weak, positive correlation between urine dipstick amount and number of RBC/HPF (r=0.44 p<0.001). Of the remaining patients, 9/237 (3.8%) never had a microscopic urinalysis sent while 168/237 (70.9%) had urinalyses sent, but on a different date than their initial dipstick and often after they had already undergone expensive testing (cystoscopy and/or CT urogram).

In total, 210/237 (88.6%) women underwent complete evaluation, including 151/169 with true AMH and 59/68 with either positive dipstick or AMH in the setting of UTI. (Table 1) Amongst the patients with incomplete evaluation, 3 patients had magnetic resonance imaging (MRI) that was not specifically for urography and 1 patient had a renal ultrasound as their imaging modality. All women had a recently documented estimate of renal function.

Overall, among patients with complete evaluations, we detected 3/210 (1.4%) urinary tract malignancies. (Table 2) One woman with positive dipstick was diagnosed with kidney cancer. She was a 56 year-old, current smoker with a urine dipstick of 1+ blood without a full urinalysis. In those with true AMH, there were two instances of bladder cancer. They were in women aged 58 and 64, one current and one nonsmoker with 6 and 42 RBC/HPF on urinalysis respectively. Importantly, there were no patients with urinary tract malignancy that had only trace blood on initial dipstick analysis. In our study population we did not detect any intervention for nephrolithiasis. Of the 43/213 (20.2%) patients with benign renal cysts on imaging, none required intervention. Of patients that underwent cystoscopy, 12/234 (5.1%) had a biopsy. Results included the two aforementioned bladder cancer cases and ten additional biopsies that resulted in findings of benign cystitis cystica.

Discussion

This study provides real-word insight into adherence to the current AUA asymptomatic microhematuria guidelines. In this cross-sectional study, we have several notable findings. Ultimately, 71.3% of patients were evaluated for a diagnosis of AMH that was adherent to the current AUA guidelines, but many of the urinalyses were sent after upper tract imaging and cystoscopy had already been performed. In our population of postmenopausal women, 28.7% underwent evaluation for "hematuria" without actually being diagnosed with AMH or

had MH in the setting of a UTI. If referral or evaluation for AMH had been deferred until a confirmatory microscopic urinalysis had been sent or urine culture had resulted there would have been a significant decrease in the amount of expensive evaluations incurred by this patient population. As we are a tertiary care center, many of these patients were referred from primary care for a diagnosis of AMH and, in the majority of these cases, evaluation was likely initiated because of the patients' presentation to a new provider for consultation. However, there were also evaluations initiated by either a urologic or urogynecologic provider after only a urinary dipstick showing MH. These variations in practice patterns may be amenable to interventions to improve workflows between primary care providers and specialists and is a potential target for quality improvement.

The greatest strength of our study is the size of the female, postmenopausal population reviewed and the number of patients with complete evaluations in order to comment on malignancy rates. Furthermore, since the data is based on real-world evaluation of patients, regardless of whether they met rigid AUA criteria for AMH; it is applicable to current practice patterns. The characteristics of our population of postmenopausal women are also consistent with other published studies. We had a high rate of recurrent UTI (15.2%) in our population that is inline with reported rates of bacteriuria and symptomatic UTI occurring in 10%–15% of women aged 65–70 years and 15%–20% of women aged 80 years.[9] This is an important factor in postmenopausal women that is not often discussed in risk factors for AMH. Since postmenopausal women have such a high rate of recurrent UTIs there could be low levels of persistent MH. This speculation is supported by the fact that the majority of the bladder biopsies performed in our study population were consistent with findings of cystitis cystica.

This study has several potential limitations that should be taken into consideration. Firstly, due to the retrospective, observational nature of our study, only 63.3% of patients had documented genitourinary exams. This limits our ability to comment on potentially confounding factors, such as atrophy or prolapse that may contribute to the presence of AMH. A significant proportion of patients with exams (60.0%) did have objective atrophy but we are unable to comment on the remainder of the patients. We know that estrogen deficiency after menopause causes atrophic changes within the urogenital tract. In addition to vaginal atrophy, these changes have been associated with urinary symptoms including frequency, urgency, nocturia, incontinence and recurrent infection.[10,11] It is not unreasonable to assume that these atrophic changes to the bladder and urethra may lead to asymptomatic microhematuria in postmenopausal women although a direct link between urogenital atrophy and microhematuria has not been established. Although additional studies are needed in order to assess if it is safe to forego AMH evaluations in postmenopausal women with vaginal atrophy, clinicians should perform and document a genitourinary exam to determine if treatment of vaginal atrophy is necessary. Additionally, the higher presence of AMH (up to 20.1%)[6,12,13] in women with pelvic organ prolapse, compared to the general population, despite a low risk of malignancy, has been used as an argument for separate AMH guidelines for women. Our particular population had a low rate of pelvic organ prolapse with only 11.3% of the documented exams with stage 2 or greater prolapse. This could limit generalizability of our data and the contribution of prolapse to AMH may be

significantly underestimated as upwards of 30% of postmenopausal women may have stage 2 or greater prolapse on clinical exam.[14]

In our population of postmenopausal women evaluated for AMH, the overall prevalence of urinary tract malignancy was low, which is consistent with other published literature. Overall, regardless of gender, urinary tract malignancy rate amongst studies reviewed by the AUA was 3.3%[1], but amongst studies evaluated by the AUA with large numbers of female patients, bladder cancer rates were noted to be 0–0.3%.[15] As our data are consistent with the aforementioned studies, we again raise the question as to the most cost-effective screening strategies in this population. When considering large populations of patients, screening tests should not result in over-utilization of invasive testing, without improving the detection rate of malignancy - as this could actually result in harm. For example, the US Preventative Services Task Force (USPSTF) updated their breast cancer screening guidelines in 2009 to decrease mammographic frequency to limit unnecessary evaluations for benign breast disease.[16] Improving gender-specific guidelines that allow for high detection rates of malignancies while limiting unnecessary evaluations is imperative for cost-effective health care. In the meantime, it is also of the utmost importance that providers adhere to the AUA guidelines and only pursue costly evaluations on patients who actually have AMH.

Importantly, in our study, we found all patients with urinary tract malignancy had 1+ or greater blood on initial dipstick analysis. We did not find any malignancy or clinically significant findings in patients with trace blood on dipstick. There was a weakly positive correlation between amount of blood on dipstick and level of hematuria. Studies have attempted to evaluate if urine dipsticks reliably predict microhematuria in various populations[17], but additional research would need to be done in postmenopausal women to determine these associations. This would potentially lead to a decrease in the number of AMH evaluations for very low levels of microscopic hematuria and limit unnecessary testing.

Our data describes urinary tract malignancy rates in postmenopausal women evaluated for AMH and real-world adherence to the current AUA guidelines in the urology and urogynecologic community. In this cost-conscious era of health care it is important for clinicians to critically evaluate screening strategies. Our study not only demonstrates an opportunity to improve adherence to existing guidelines in consulting practices, but also that there is significant need for education in the primary care community. If microscopic urinalyses were universally sent as follow-up for dipstick tests concerning for AMH, a significant number of unnecessary referrals and evaluations might have been prevented.

Conclusion

This study provides important, real-world information on the adherence to the current AUA asymptomatic microhematuria guidelines in a tertiary care referral center. Our urinary tract cancer rate was low in our population of postmenopausal women, which continues to raise questions as to whether current guidelines are cost-effective for screening in this particular population.

Future directions should include continued research into the confounding risk factors for AMH in postmenopausal women including vaginal atrophy, pelvic organ prolapse and recurrent urinary tract infection. Investigation into the exact correlation of urinary dipstick to microscopic urinalysis may also be a way to decrease the number of unnecessary and costly evaluations if definitive evidence shows that trace blood is not associated with AMH.

Key of Definitions for Abbreviations

AMH	Asymptomatic Microscopic Hematuria
AUA	American Urological Association
UTI	Urinary Tract Infection
CT	Computed Tomography
BMI	Body Mass Index
RBC	Red Blood Cells
HPF	High Powered Field

References

1. Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. J Urol. Dec; 2012 188(6 Suppl):2473–2481. [PubMed: 23098784]

2. Wollin T, Laroche B, Psooy K. Canadian guidelines for the management of asymptomatic microscopic hematuria in adults. Can Urol Assoc J. Feb; 2009 3(1):77–80. [PubMed: 19293985]

3. Harmanli O, Yuksel B. Asymptomatic microscopic hematuria in women requires separate guidelines. Int Urogynecol J. Feb; 2013 24(2):203–206. [PubMed: 23149599]

4. Grossfeld GD, Wolf JS Jr, Litwan MS, et al. Asymptomatic microscopic hematuria in adults: summary of the AUA best practice policy recommendations. Am Fam Physician. Mar 15; 2001 63(6):1145–1154. [PubMed: 11277551]

5. Jung H, Gleason JM, Loo RK, et al. Association of hematuria on microscopic urinalysis and risk of urinary tract cancer. J Urol. May; 2011 185(5):1698–1703. [PubMed: 21419446]

6. Pillalamarri N, Shalom D, Sanidad S, et al. The prevalence of microscopic hematuria in a cohort of women with pelvic organ prolapse. Int Urogynecol J. Jan; 2015 26(1):85–90. [PubMed: 24980137]

7. Friedlander DF, Resnick MJ, You C, et al. Variation in the intensity of hematuria evaluation: a target for primary care quality improvement. Am J Med. Jul; 2014 127(7):633–640. e611. [PubMed: 24486290]

8. Raz R, Gennesin Y, Wasser J, et al. Recurrent Urinary Tract Infections in Postmenopausal Women. Clin Infect Dis. Jan 1; 2000 30(1):152–156. [PubMed: 10619744]

9. Nygaard IE, Johnson JM. Urinary tract infections in elderly women. Am Fam Physician. Jan; 1996 53(1):175–182. [PubMed: 8546044]

10. Robinson D, Cardozo LD. The role of estrogens in female lower urinary tract dysfunction. Urology. Oct; 2003 62(4 Suppl 1):45–51. [PubMed: 14550837]

11. Elia G, Bergman A. Estrogen effects on the urethra: beneficial effects in women with genuine stress incontinence. Obstet Gynecol Surv. Jul; 1993 48(7):509–517. [PubMed: 8355926]

12. Brazell HD, O'Sullivan DM, Steinberg AC. Do patients with pelvic organ prolapse have an increased frequency of asymptomatic microscopic hematuria? Urology. Jun; 2014 83(6):1236–1238. [PubMed: 24745798]

13. Toz E, Kurt S, Canda MT, et al. Comparison of frequency of asymptomatic microhematuria in patients with stage 2–4 versus stage 0–1 pelvic organ prolapse. Pak J Med Sci. 2015; 31(3):654–657. [PubMed: 26150862]

14. Nygaard I, Barber MD, Burgio KL, et al. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. Sep 17; 2008 300(11):1311–1316. [PubMed: 18799443]

15. Murakami S, Igarashi T, Hara S, et al. Strategies for asymptomatic microscopic hematuria: a prospective study of 1,034 patients. J Urol. Jul; 1990 144(1):99–101. [PubMed: 2193173]

16. Screening for breast cancer: U S. Preventive Services Task Force recommendation statement. Ann Intern Med. Nov 17; 2009 151(10):716–726. w-236. [PubMed: 19920272]

17. Moore GP, Robinson M. Do urine dipsticks reliably predict microhematuria? The bloody truth! Ann Emerg Med. Mar; 1988 17(3):257–260. [PubMed: 3345019]

Table 1

AMH work-up and findings

Type of patient	n (%)
Asymptomatic Microscopic Hematuria	169/237 (71.3%)
Full work-up	151/169 (89.3%)
No cystoscopy	3/169 (1.8%)
No imaging[*]	15/169 (8.9%)
Positive Dipstick	48/237 (20.2%)
Positive dipstick, negative urinalysis	39/237 (16.5%)
Positive dipstick, no urinalysis sent	9/237 (3.8%)
Microscopic hematuria in setting of UTI	20/237 (8.4%)
Full work-up	59/68 (86.8%)
No imaging[*]	9/68 (13.2%)

[*] Also includes non-urography MRI or renal ultrasound

Table 2

Imaging and Cystoscopy Findings

Finding	n/N (%)
Urinary Tract Cancer	3/210 (1.4%)
Bladder Cancer	2/210 (0.9%)
Kidney Cancer	1/210 (0.5%)
Kidney Stone requiring Surgery	0/213 (0%)
Cystoscopy requiring Biopsy	12/234 (5.1%)
Cystitis Cystica	10/12 (83.3%)
Bladder cancer	2/12 (16.7%)
Imaging finding	70/213 (32.9%)
Kidney mass	1/213 (0.5%)
Non-obstructing stone	26/213 (12.2%)
Benign Renal Cyst	43/213 (20.2%)