

Changes in microscopic analysis of the urinary sediment in postmenopausal women who receive vaginal conjugated oestrogens

Sebastián Carranza-Lira, Miriam Elizabeth Cruz-Ramírez, Diana Sulvarán-Victoria

Research Division in Health, UMAE Gynecology and Obstetrics Hospital "Luis Castelazo Ayala", Social Security, Mexican Institute, Mexico DF, Mexico

Abstract

Introduction: Microscopic haematuria is common in adults and it has been reported in 13% of postmenopausal women.

Objective: To evaluate the changes in urinary sediment after the use of vaginal conjugated oestrogens.

Material and methods: Postmenopausal women with vaginal dryness were studied. In all them a urinalysis was done, looking for density, pH, and the presence of leukocytes and erythrocytes. In order to be included in the study, all of the women had to have microscopic haematuria, considered as the presence of 3 or more erythrocytes in the urinary sediment. All received vaginally 1 g of conjugated equine oestrogens cream 3 times per week for one month, moment in which a new urinalysis was carried out and the same parameters were evaluated.

Results: Twenty-four women were studied. The median age was 62 years (40-83), and the time since menopause was 144 months (24-336). When comparing the values between baseline and end of treatment urinalyses, no significant differences in pH and urinary density were found. The number of leukocytes significantly decreased after treatment (3.0 [1-6] vs. 1.0 [1-6], $p < 0.026$), and the erythrocytes number decreased (4.5 [3-12] vs. 0.0 [0-2], $p < 0.001$).

Conclusion: In postmenopausal women with microscopic haematuria and vaginal dryness, it is worth considering administration of local oestrogen for one month, and after repeat the urine exam, before deciding to begin the microscopic haematuria study protocol.

Key words: conjugated local oestrogens, haematuria, postmenopause.

Introduction

During postmenopause several problems exist, in early postmenopause vasomotor symptoms predominate and can continue for several years [1], afterwards other problems can appear such as cardiovascular risk increase [2] and greater risk of fracture due to osteoporosis [3]. Long-term oestrogen privation is associated with urinary incontinence [4] and vaginal atrophy [5]. It is known that the bladder and the inferior 2 thirds of the vagina are embryologically derived from the urogenital sinus [6]. The vagina has oestrogen receptors of the α type (ER α) and β type (ER β) [7]. However, only ER α is expressed in postmenopausal women, which is increased after local oestrogens use, in the basal epithelium, stroma and connective tissue, while for ER β it is only in the basal epithelium [8]. It has been observed that the increment of ER α correlates directly with the number of blood vessels in the lamina propria [9]. In the urinary bladder ER β has been mainly found in vesical cancer [10], in rats non increase has been observed in ER β after local oestrogens administration;

however, an increase in blood vessel density has been observed [11].

In the postmenopause the decrease of circulating oestrogens conditions at the vagina the decrease in the quantity of superficial and intermediate cells. All this causes a decrease of Doderlein's bacilli, an increase of vaginal pH, and a decrease of the vaginal humidity, finally finishing in atrophy, all of which are corrected with oestrogen use [12]. In the rat urinary bladder, it has been shown that the lack of oestrogens is associated with atrophy of vesical epithelium and inflammation [13], which increases the risk of local infections [14] and vesical activity [15].

Microscopic haematuria is common in adults and often occurs inadvertently; its prevalence ranges from 0.18 to 16.1%, depending on its definition, age, gender and risk factors of the studied group. This entity can be due to menstrual contamination, previous vigorous exercise, or sexual activity [16] and even in situations like the genital prolapse in which the frequency can be up to 20.1% [17]. Microscopic asymptomatic haematu-

Corresponding author:

Dr. **Sebastián Carranza-Lira**, Puente de piedra 150-422, Torre 1 Col. Toriello Guerra, México DF. C.P., 14050, phone. and fax: 55284657, e-mail: drsebastiancarranza@gmail.com

Submitted: 31.03.2017

Accepted: 11.07.2017

ria, is clinically significant because sometimes it can be an early sign of renal or urological potential of serious pathologies. In young women the main causes are: inflammation, cystitis, and lithiasis in 74.3%, and in those older than 65 years these occur in 52.6%, and the other 57.4% are of tumoural origin [18]. This entity has been described in up to 13% of postmenopausal women [19], In a study that evaluated postmenopausal women, vesical cancer was found only in 1.4% of cases [20],

According to the American Urology Association, microscopic haematuria is defined as: 3 or more erythrocytes per high resolution field in the urinary sediment of samples gathered appropriately, which includes recently emitted, clean, in an asymptomatic person and from half urinary stream. The 2012 guidelines from the American Urology Association recommend for any person with microscopic asymptomatic haematuria, without gender and age distinction: urine cytology, cystourethroscopy, renal function tests and image studies [21].

Due to oestrogen receptors existing in the urinary bladder and the vaginal epithelium improving after oestrogen use, the objective of the present study was to evaluate the changes in the urinary sediment, particularly looking for the modification in microscopic haematuria, in postmenopausal women who used vaginal conjugated oestrogens.

Material and methods

Postmenopausal women who attended to a gynaecological endocrinology consultation and who had vaginal dryness were studied. None of them were receiving hormone therapy or any other drug for the relief of vaginal dryness. Age and time since menopause were documented. In all them a urinalysis was carried out looking for density, pH, and the presence of leukocytes and erythrocytes. To be included in the study, all them had to have microscopic haematuria, considered as the presence of three or more erythrocytes in the study of the sediment. A urine culture was carried out which needed to be negative for infection so they can be included. All them received 1 g of conjugated oestrogens vaginally, three times per week for one month, moment in which new urinalysis was done and the same parameters were evaluated.

For sample size calculation a 99.0% confidence interval was considered, a power of 90% and considering a 55% difference between baseline and final parameters, a sample size was esteemed in 24 patients.

Due to the sample distribution, non-parametric statistics were used. The differences among baseline and final results were calculated with Wilcoxon's test.

The protocol was authorised by the Local Committee of Research and Ethics in Research with the registration number R-2015-3606-36; all the patients gave their consent to participate and signed an informed consent form.

Table 1. Previous and after al treatment values in urinalysis.

| Parameter | Baseline | Final | <i>p</i> |
|------------------------|------------------|------------------|----------|
| Density | 1.01 (1.00-1.03) | 1.01 (1.00-1.03) | 0.717 |
| pH | 6.0 (5.0-7.0) | 6.0 (5.0-7.0) | 0.253 |
| Leucocytes per field | 3.0 (1-6) | 1.0 (1-6) | 0.026 |
| Erythrocytes per field | 4.5 (3-12) | 0.0 (0-2) | 0.001 |

Results

Twenty-four women who met the inclusion criteria were included. The median of the age was 62 years (40-83) and the time since menopause was 144 months (24-336).

When comparing baseline and after-treatment urinalysis results, no significant difference in pH and urinary density was found. The leukocytes number significantly decreased after treatment (3.0 [1-6] vs. 1.0 [1-6], $p < 0.026$) and similar occurred with the erythrocytes number (4.5 [3-12] vs. 0.0 [0-2], $p < 0.001$) (Table 1).

Discussion

Microscopic haematuria can be due to multiple reasons. However, given the embryologic similarity [1] and the presence oestrogen receptors in the urinary bladder and vagina, it was decided to evaluate the oestrogen effect in the urinary sediment, in the supposition that the vesical epithelium would have similar oestrogen-mediated changes to those seen in the vaginal epithelium. It is known that persistent microscopic hematuria should be exhaustively studied [16]. Always is recommended to have a second abnormal urinalysis exam before beginning the study, because sometimes this second sample can be normal [16, 18]. This was a limitation of the study because only one sample was taken before inclusion in the study and the start of oestrogenic treatment.

However, in this study the number of leukocytes significantly decreased, which agrees with reports for urinary bladder biopsies in which it has been shown that oestrogen privation is associated with inflammation [13].

Also, to our knowledge, no other report exists in which the effect of local oestrogen in the urinary sediment (included leukocytes and erythrocytes) in postmenopausal women has been evaluated.

Thus it is possible to conclude that in postmenopausal women with microscopic haematuria with vaginal dryness and atrophy, it is worthwhile considering administration of local oestrogens for one month and a repeated urine examination before deciding to begin the study protocol for microscopic haematuria.

Disclosure

Authors report no conflict of interest.

References

1. Carranza-Lira S, Sandoval-Hernández CI. Comparison of the frequency and magnitude of the vasomotor symptoms in premenopausal and postmenopausal women from Mexico City. *Ginecol Obstet Mex* 2013; 81: 127-132.
2. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol* 2016; 1: 767-776.
3. Szamatowicz M. How can gynaecologists cope with the silent killer – osteoporosis? *Prz Menopauzalny* 2016; 15: 189-192.
4. Chmielewska DD, Piecha M, Kwaśna K, et al. Urinary incontinence: a problem of the modern woman. *Prz Menopauzalny* 2013; 17: 378-384.
5. Lindau ST, Dude A, Gavrilova N, et al. Prevalence and correlates of vaginal estrogenization in postmenopausal women in the United States. *Menopause* 2017; 24: 536-545.
6. Aparato urogenital. In: Langman J (ed.). *Embriología médica. Desarrollo humano normal y anormal*. México D.F.: Nueva Editorial Interamericana S.A. de C.V, 1976; 146-182.
7. Chen GD, Oliver RH, Leung BS, et al. Estrogen receptor alpha and beta expression in the vaginal walls and uterosacral ligaments of premenopausal and postmenopausal women. *Fertil Steril* 1999; 71: 1099-1102.
8. Fuermetz A, Schoenfeld M, Ennemoser S, et al. Change of steroid receptor expression in the posterior vaginal wall after local estrogen therapy. *Eur J Obstet Gynecol Reprod Biol* 2015; 187: 45-50.
9. Lara LA, Ribeiro da Silva A, Rosa-e-Silva JC, et al. Estrogen receptor expression and vessel density in the vagina wall in postmenopausal women with prolapse. *Tissue Cell* 2014; 46: 159-164.
10. Shen SS, Smith CL, Hsieh JT, et al. Expression of estrogen receptors-alpha and -beta in bladder cancer cell lines and human bladder tumor tissue. *Cancer* 2006; 106: 2610-2616.
11. Kim ID, Ahn KH, Lee S, et al. Effect of ovariectomy, 17-beta estradiol, and progesterone on histology and estrogen receptors of bladder in female partial bladder outlet obstruction rat model. *J Obstet Gynaecol Res* 2013; 39: 1259-1267.
12. Carranza-Lira S, Cabrera-López TJ, Estrada-Moscoso I, et al. Índice de maduración y sequedad vaginales. Evaluación de dos dosis de estrógenos tópicos vía vaginal. *Rev Med Inst Mex Seguro Soc* 2012; 50: 315-318.
13. Lucan L, Lucan VC, Tabaran FA, et al. Changes in the urinary bladder morphology, mast cell population and estrogen receptor alpha expression following ovariectomy and chronic estrogen replacement therapy in albino rats. *General Endocrinology. Acta Endo (Buc)* 2013; 9: 11-21.
14. Krause M, Wheeler TL II, Snyder TE, Richter HE. Local effects of vaginally administered estrogen therapy: A review. *J Pelvic Med Surg* 2009; 15: 105-114.
15. Cheng CL, Li JR, Lin CH, de Groat WC. Positive association of female ovaractive bladder symptoms and estrogen deprivation. A nationwide population-based cohort study in Taiwan. *Medicine* 2016; 95: 28(e4107).
16. Cohen RA, Brown RS. Clinical practice. Microscopic hematuria. *N Engl J Med* 2003; 348: 2330-2338.
17. 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* 2015; 26: 85-90.
18. Erekson EA, McMahon MD, Moule BA, et al. Microscopic hematuria in women. *Obstet Gynecol* 2011; 117: 1429-1434.
19. Arroyo Maestre JM. Emergencias urológicas I. 1. Hematurias. In: Gil Cebrian J, Diaz Alersi-Rosety R, Coma MJ, Gil Bello D (eds.). *Principios de urgencias, emergencias y cuidados críticos*. <http://tratado.uninet.edu/c0704102.html>.
20. Bradley MS, Willis-Gray MG, Amundsen CL, et al. Microhematuria in postmenopausal women: adherence to guidelines in a tertiary care setting. *J Urol* 2016; 195 (4 Pt 1): 937-941.
21. Davis R, Jones JS, Barocas DA, et al. American Urological Association. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. *J Urol* 2012; 188 (6 Suppl): 2473-2481.