European Journal of Obstetrics & Gynecology and Reproductive Biology 210 (2017) 177–181

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Pelvic organ prolapse and endogenous circulating sex steroids in postmenopausal women: A case control-study

Barbara Bodner-Adler[a,*], Klaus Bodner[a], Cora Schneidinger[a], Oliver Kimberger[b,c], Ksenia Halpern[a], Heinz Koelbl[a], Wolfgang Umek[a]

[a] Department of General Gynecology and Gynecologic Oncology, Medical University of Vienna, Austria
[b] Department of Anesthesiology, Medical University of Vienna, Austria
[c] Outcomes Research Consortium, Cleveland, OH, USA

Abstract *Objective:* We compared sex steroid levels of postmenopausal patients with symptomatic pelvic organ prolapse (POP) with postmenopausal matched patients without any sign of POP. Furthermore, we evaluated a possible relationship between sex steroid levels and various urogynecologic parameters in cases with POP. Main outcome of interest were differences in circulating estradiol levels between the two groups.
Study design: We conducted a case-control study and 46 postmenopausal women with symptomatic POP ≥ stage 2 were matched 1:1 with 46 urogynecologic healthy women. Blood samples were drawn from all patients for assessment for estradiol (E2), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), testosterone (T), androstendion (AEON), dehydroepiandrosterone sulphate (DHEAS) and sex hormone binding globulin (SHBG) with an Electrochemiluminescence immunoassay.
Results: Our study failed to show any statistically significant differences in sex steroid levels between women with and without POP ($p > 0.05$). However, serum concentration of E2 ($p < 0{,}0001$), free testosterone ($p = 0{,}034$) and DHEAS ($p = 0{,}024$) was statistically significant lower in patients with severe prolapse stage. Serum levels of E2 were statistically significant higher in cases with moderate-strong Oxford Grading Scale ($p < 0{,}0001$). Low circulating E2 ($p = 0{,}019$) as well as menopausal age ($p = 0{,}022$) remained independent risk factors for POP in multiple logistic regression analysis.
Conclusion: The significant low hormonal levels in cases with high POP-Q stage as well as the significant higher estradiol levels in patients with strong Oxford Grading Scale may indicate that endogenous circulating sex steroids might have a potential role in the severity and progression of POP.

Introduction

The levels of sex steroids, particularly estrogens and androgens, change markedly during menopause [1]. Estrogen deficiency after menopause causes atrophic changes within the urogenital tract and is also associated with urinary symptoms. Furthermore, the prevalence of prolapse increases in the postmenopausal period, suggesting that a hypoestrogenic state is an important contributing factor [2,3]. Some studies showed that pelvic organ prolapse (POP) is a prevalent condition that increases with age and affects every second elderly woman [4]. Known risk factors contributing to prolapse are childbirth, collagen abnormalities, increasing age and a chronic increase in intraabdominal pressure [2,5]. Whereas it is difficult to separate the effects of declining estrogen levels in menopause from aging in general, it is clear that pelvic organs and their surrounding muscular and connective tissue support are estrogen responsive and that epidemiological studies indicate that menopause is a major risk factor for development of POP with symptoms and severity increasing after menopause [6–9].

The effect of the hormonal milieu during postmenopausal period and the role of circulating endogenous sex steroids in women with symptomatic POP have not been adequately investigated so far. The hormonal deprivation during menopause and the increasing prevalence of pelvic organ prolapse in the postmenopausal period led us to inquire whether sex steroid levels are related to the prevalence of POP. The aim of the present study was to compare the levels of endogenous sex steroids between postmenopausal patients with symptomatic POP and age, parity and BMI matched women without POP. Primary outcome variable was the estradiol level. Furthermore, we investigated a possible correlation between endogenous sex steroid levels and various urogynecologic parameters in cases with POP.

Materials and methods

This case-control study was conducted at the department of general gynecology and gynecologic oncology, Medical University of Vienna (MUV, Austria) with recruitment between December 2015 and July 2016. The study was approved by the ethics committee of Medical University Vienna (EK No.2174/2015) and all participants gave written, informed consent to participate.

Inclusion criteria for cases were patients with symptomatic pelvic organ prolapse ≥ POP-Q stage II and postmenopausal status. The control group consisted of normal postmenopausal volunteers with any benign gynecologic disease and without any evidence for pelvic floor disorder. As controls, mainly women who attended the

* Corresponding author at: Department of General Gynecology and Gynecologic Oncology, Währinger Gürtel 18-20, 1090, Vienna, Austria.
E-mail address: Barbara.Bodner-Adler@meduniwien.ac.at (B. Bodner-Adler).

http://dx.doi.org/10.1016/j.ejogrb.2016.12.027
0301-2115/

general gynecologic outpatient clinic for routine gynecologic examination in the same time interval were available. Exclusion criteria to participate for both groups were: peri, or premenpausal status, unclear menopausal status, medical history of urge, mixed or stress urinary incontinence, cancer, vaginal bleeding of unclear history, intake of systemic or local hormonal treatment or selective estrogen receptor modulators, severe endometriosis, pelvic inflammatory diseases or unable to read and sign informed consent. Following characteristics were assessed for each patient: age, menopausal age, years from menopause, weight, height, BMI, blood pressure, parity with mode of delivery, nicotine abuse, profession and ethnicity.

A thorough history and physical examination was conducted for all patients. These included a standardized urogynecologic interview and complete physical examination to check for genital prolapse according to ICS POP-Q–system [10,11] and controlled provocation with 300 ml saline in the bladder according to the International Continence Society [12]. All patients had pelvic examinations performed in both the supine position and in a 45° upright position while the Valsalva maneuver was performed using maximal effort. Clinical stress test was performed with prolapse reduction (with the support of a vaginal speculum) in supine as well as in a 45° upright position. Cases with positive stress test during prolapse reduction were defined as cases with occult stress urinary incontinence, having no history of incontinence before. Furthermore physical examination included the Oxford Grading Scale to assess pelvic floor strength [13]. Pelvic floor strength, graded on a six-point scale, was dichotomized into weak (no contraction, flicker or weak tone, or 0–2) and strong (moderate, good or strong, or 3–5). Diagnosis of recurrence of prolapse was used in cases with failure of previous surgery, which could be either subjective or objective. Furthermore, we differentiated between direct recurrence, affecting a previously treated compartment and indirect recurrence, affecting another compartment. Women were classified according to their urogenital status in two groups: patients with symptomatic POP (n = 46) and urogynecologic healthy controls (n = 46). Each prolapse patient was matched with a woman without any signs of pelvic organ prolapse or any other existing pelvic floor dysfunction. Matching was based on menopausal status, age, parity and BMI. Menopause was defined as blood-free interval of at least 12 months and menopausal status was confirmed by serum FSH > 20 U/l.

Electrochemiluminescence immunoassay (ECLIA) for the in vitro quantitative determination of circulating sex steroids

Venous blood samples for hormone assay were taken from all cases and controls between 0800 and 1000 am during their first visit at the outpatient clinic. Serum concentrations of Follicle-stimulating hormone [FSH], Luteinizing hormone [LH], 17ß-estradiol [E2], sex hormone binding globulin [SHBG], Testosterone [T], prolactin [PRL], dehydroepiandrosterone sulfate [DHEAS] and androstendion [AEON] were determined by immunoassay using commercial kits according to the protocols specified by the manufacturer (elecsys®2010 Systems, Roche Diagnostics International, Switzerland). Analytic sensitivity and the coefficient of variation (CV%) were as follows: for T 0.02 ng/ml and CV 4–8%; for SHBG 0.5 nmol/L and CV 5%; for E2 10 pg/ml and CV 4–8%; for AEON 0.3 ng/ml and CV 5–7%, for FSH 0.1 mU/ml and CV 7%; for LH 0.1 mU/ml and CV 4%; for DHEAS 0.1 μg/dl; CV 5–8% and for PRL 1.00 ng/ml; CV 4–7%, respectively. Apparent concentrations of free testosterone (fT) were calculated from values for total T, SHBG and a fixed albumin concentration.

Clinical information, including follow-up data was obtained from the database of the department of General Gynecology and Gynecologic Oncology. All patient records were anonymized and de-identified prior to analysis. Body mass index (BMI) was calculated by the formula: weight (kg)/height^2 (m).

Statistical analysis

Comparison between the two groups was made by the chi square statistics for categorical variables and the Student's *t*-test for continuous variables. Main outcome variable of interest were differences of serum estradiol levels between the two groups. Multiple logistic regression analysis (including backward elimination) was performed to identify the impact of different risk factors on POP. The presence of POP was defined as the dependent variable. Independent variables included in the model were age, menopausal age, BMI, parity, smoking, E2, T, SHBG, AEON and DHEAS. A p value <0.05 was considered statistically significant. The SPSS system (IBM, Armonk, NY, USA) was used for the calculations.

A power analysis was conducted using the software GPower [14]. To reach a power of 95%, a sample size of overall 84 patients was calculated with an alpha level of 0,05 and an effect size derived from previously reported serum estradiol levels of 17,30 pg/ml (+/−8,16) for postmenopausal patients with pelvic floor disorder and 24,22 pg/ml (+/−8,99) for postmenopausal patients without pelvic floor disorder [15]. To account for any dropouts and measurement errors we increased the sample size by 10% to a final sample size of 92 patients in all.

Results

This study comprised a cohort of 92 patients, a total of 46 women with symptomatic POP and 46 women were diagnosed as urogynecologic healthy women.

Clinical characteristics of all study participants are shown in Table 1. Clinical parameters did not statistically significant differ between the two groups.

Serum levels of circulating sex steroids in women with POP compared to healthy controls

Mean values of endogenous sex hormones according to the presence of POP are presented in Table 2. No statistically significant difference in circulating sex steroids could be detected between patients with symptomatic POP and women without POP (Table 2).

Serum levels of endogenous sex steroids and urogynecologic parameters in cases with POP

Serum concentrations of E2 ($p < 0{,}0001$), free testosterone ($p = 0{,}034$) and DHEAS ($p = 0{,}024$) were statistically significant lower in the subgroup of patients with severe stage of prolapse. Serum level of E2 was statistically significant higher in the subgroup of patients with higher Oxford Scale ($p < 0{,}0001$). The levels of sex steroids had no statistically significant influence on the recurrence of POP. Subgroups of patients were comparable regarding age and BMI. No statistically significant differences regarding age and BMI could be observed between patients with POP-Q stage II (60,4+−11,3 and 29,7+−6,7), POP-Q stage III (66,5 +−8,6 and 28,0+−5,4) and POP-Q stage IV (68,3+−9,8 and 24,0 +−2,7) ($p = 0{,}124$; $p = 0{,}060$). Besides, no statistically significant differences of age and BMI could be detected between cases with low (65,3+−9,3 and 27,0+−5,7) and high Oxford Grading Scale (65,1+−10,8 and 28,6+−5,5) ($p = 0{,}752$; $p = 0{,}467$) as well as with recurrence (65,2+−9,9 and 28,5+−51,) or without recurrence (64,6 +−9,8 and 27,7+−6,5) ($p = 0{,}915$; $p = 0{,}725$).

Furthermore we observed that patients with low Oxford Grading Scale had statistically significant higher POP-Q stages ($p = 0{,}007$) as well as women with increased age showed significantly more severe prolapse stages ($p = 0{,}056$). Table 3 overviews different urogynecologic, clinical parameters and serum hormonal levels. After multiple logistic regression analysis the strongest factors associated with POP remained low circulating E2 ($p = 0{,}019$) as well as low menopausal age ($p = 0{,}022$) (Table 4).