Does administration of vaginal estrogens increase the risk of venous thromboembolism

A case–control study

Svendsen, Andreas Ludvig Ohm; Esbech, Peter Skov; Nielsen, Emma; Hallas, Jesper; Lund, Lars Christian

Published in:
Basic & Clinical Pharmacology & Toxicology

DOI:
10.1111/bcpt.13644

Publication date:
2021

Document version:
Accepted manuscript

Citation for pulished version (APA):
Svendsen, A. L. O., Esbech, P. S., Nielsen, E., Hallas, J., & Lund, L. C. (2021). Does administration of vaginal estrogens increase the risk of venous thromboembolism: A case–control study. *Basic & Clinical Pharmacology & Toxicology*, *129*(5), 385-388. https://doi.org/10.1111/bcpt.13644

Svendsen Andreas (Orcid ID: 0000-0001-8050-6447)
Esbech Peter Skov (Orcid ID: 0000-0001-8147-5515)

Does administration of vaginal estrogens increase the risk of venous thromboembolism: a case-control study

Article Type: Short Communication

Andreas Ludvig Ohm Svendsen [1,3]

Peter Skov Esbech [1,2]

Emma Nielsen [1]

Jesper Hallas [1,3]

Lars Christian Lund [3]

1. Dept. of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark
2. Dept. of Internal Medicine, Odense University Hospital Svendborg, Svendborg, Denmark
3. Clinical Pharmacology, Pharmacy and Environmental Medicine, Department of Public Health, University of Southern Denmark, Odense, Denmark

Running title: Vaginal estrogens and venous thromboembolism

Keywords: Pharmacoepidemiology, vaginal estrogen, venous thromboembolism, adverse drug reactions, case-control study

Correspondence
Andreas Ludvig Ohm Svendsen
Clinical Pharmacology, Pharmacy and Environmental Medicine
Department of Public Health
University of Southern Denmark
J.B. Winsløws Vej 19, 2
5000 Odense C, Denmark
E-mail: alosvendsen@health.sdu.dk

Introduction and background

Vaginally administered estrogen is an effective treatment of vaginal atrophy [1] and recurrent urinary tract infections [2] in postmenopausal patients. The systemic absorption of vaginal estrogen is low, and thus unlikely to substantially raise the systemic estrogen level among users [3]. However, the United States Food and Drug Administration has issued a black box warning against the use of vaginal estrogen in patients with current or former venous thromboembolism (VTE) based on an increased risk of VTE among users of systemic estrogens. Whether this increased risk associated with systemic therapy also applies to vaginal estrogen has not been thoroughly investigated. Of note, this warning is also listed in the Danish package inserts of vaginal estrogen. Consequently, postmenopausal women with a history of VTE may unnecessarily be withheld a safe and effective treatment for vaginal atrophy and recurrent urinary tract infections. Therefore, we aimed to investigate whether postmenopausal women, with and without a history of VTE, using vaginal estrogen are at increased risk of VTE.

Materials and Methods

Using the Danish health registers, we conducted a population-based, nested case-control study. This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [4].

Eligible individuals were women above 55 years of age residing in Denmark from 1 January 2010 to 31 December 2018. We used a cut-off of 55 years as most women can be assumed to be postmenopausal at this age. Cases were defined by a first hospital diagnosis of venous thrombosis or pulmonary embolism during the study period. We matched up to four controls to each case based on the year of birth and history of prior VTE between 1995-2010. Controls were assigned an index date similar to the diagnosis date of the matched case. Cases were eligible to be sampled as controls before the date of receiving a VTE diagnosis. By this control sampling (risk-set sampling), the derived odds ratio (OR) is an unbiased estimate of the incidence rate ratio that would have emerged in a cohort study from the same source population [5].

We applied the following exclusion criteria to the cases and controls: dispensing of systemic estrogen within 12 months prior to index date, dispensing of oral anticoagulants within 12 months prior to index date, a history of cancer or hematologic malignancy, inflammatory bowel disease, or coagulopathy. We also required that the subject had not been hospitalized within 3 months prior to index date to avoid confounding by surgical procedures, trauma, or critical illness. For a flowchart over the selection of study cases, see **Figure S1**.

We considered a case or control exposed if they redeemed a prescription for vaginal estrogen during the three months prior to the index date. This choice of exposure window was validated by analysing the waiting time distribution for local estrogen dispensing (**Figure S2**) [6].
The OR associating local estrogen with VTE was estimated using multivariable conditional logistic regression. Potential confounders and risk factors of VTE were included as covariates in the regression model, e.g., frequency of recurrent UTI, a hospital diagnosis of obesity or venous insufficiency, and use of drugs to treat cardiovascular disease. Confounding by age, calendar time, and history of VTE was controlled for by employing conditional logistic regression stratified on the individual risk-set. For a detailed list of covariates, prescription and diagnosis codes used to define exposures, outcomes, and covariates, see **Table S1**.

Results

Out of 1,223,474 women aged 55 years or older, we identified 13,748 incident cases of VTE and 54,948 age-matched controls. The median age in the study population was 74 years (interquartile range 66 to 82). Compared to controls, cases had a higher prevalence of most comorbidities and were more often users of prescription drugs used in the treatment of chronic conditions (**Table 1**).

Among cases, 1296 (9.4 %) filled a prescription for vaginal estrogen within three months before receiving a VTE diagnosis, compared to 5482 (10 %) controls. We did not find an increased risk of VTE (adjusted OR 0.87, 95% confidence interval: 0.81 to 0.93), deep venous thrombosis (adjusted OR 0.90, 0.83 to 0.98) or pulmonary embolism (adjusted OR 0.81, 0.73 to 0.91) when comparing users of vaginal estrogens to unexposed individuals (**Table 2**).

We mostly found null associations in stratified analyses (**Table 2**). Most importantly, we found no association between vaginal estrogen therapy and VTE among women with a history of VTE (adjusted OR 1.13, 0.91 to 1.42).

We performed several post-hoc analyses. To investigate the effect of exposure misclassification, we shortened the exposure assessment window to 30 days, which yielded unchanged risk estimates (adjusted OR 0.89, 0.81 to 0.99). To investigate whether the risk of VTE increases with the cumulative dose, we estimated ORs for the following dose strata (0, 1-39, 40-119, 120-199, 200-399, 400+ DDD) compared to never use of vaginal estrogens. The cumulative-dose analysis yielded a slight tendency towards an inverse association between a higher cumulative dose and the risk of VTE (Table S2). Finally, we investigated whether the slightly reduced risk of VTE in users of vaginal estrogen could be related to a healthy-user bias. We performed a case-time-control analysis[7] among the previously sampled cases and controls. The case-time-control design is unaffected by confounders that are stable over time, such as a healthy lifestyle. We used one focal window and four referent windows, all with a duration of 90 days spaced equally apart. Using conditional logistic regression, we obtained an OR of 0.99 (0.87 to 1.11) among cases.

Discussion

In this population-based case-control study, we found no increased risk of VTE among women exposed to vaginal estrogens. Furthermore, we found reassuring results regarding patients with prior VTE, as vaginal estrogen therapy was not associated with an increased risk of VTE in this group either.

Our study had the following strengths: It was based on the highly valid Danish nationwide registers and Denmark's universal tax-funded healthcare system. The risk of selection bias in our study was minimal, as health care is free for all residents, and all hospital contacts are registered in the Danish National Patient Registry. The codes used to identify patients with VTE have been validated, with a reported positive predictive value of 88% and 72% for first-time and recurrent VTE, respectively [8]. The main limitation of our study was the lack of information on potential confounders such as smoking, alcohol consumption, and body weight. We sought to adjust for these using hospital diagnoses as proxies (**Table S1**). Furthermore, we saw no reason to suspect that any of these factors are strongly associated with the use of vaginal estrogen, thus limiting their potential to confound our associations. Another limitation of our study was the potential presence of non-differential exposure misclassification, i.e. a redeemed prescription of vaginal estrogen not necessarily leading to continuous use of the drug, which may bias results towards the null. We addressed this bias by shortening the exposure assessment window in post-hoc analyses, and found comparable results.

The supplementary analysis on the effect of the cumulative dose revealed a dose-related fall in risk of VTE. Slightly reduced risks of VTE in the main and cumulative dose analysis may be explained by a healthy-user bias. This bias was eliminated in the case-time-control analysis.

Our findings are compatible with the results from two recent cohort studies, which found no increased risk of pulmonary embolism or venous thrombosis among users of vaginal estrogen [9,10]. However, both studies lacked statistical power to rule out a non-trivial risk, having upper limits of confidence intervals of 1.28 and 1.93. Neither of these studies addressed the risk among women with a history of VTE. Our study may reassure clinicians that vaginal estrogen use is safe and that it should not be withheld with reference to VTE risk, not even in women with a history of VTE.

Acknowledgements

Funded by the University of Southern Denmark.

Conflict of interests

None.

References

1. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause*. 2020;27(9):976-992. doi:10.1097/GME.0000000000001609

2. Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(2). doi:10.1002/14651858.CD005131.pub2

3. Santen RJ, Mirkin S, Bernick B, Constantine GD. Systemic estradiol levels with low-dose vaginal estrogens. *Menopause N Y N*. 2020;27(3):361-370. doi:10.1097/GME.0000000000001463

4. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med*. 2007;4(10):e296. doi:10.1371/journal.pmed.0040296

5. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed., thoroughly rev. and updated. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.

6. Hallas J, Gaist D, Bjerrum L. The waiting time distribution as a graphical approach to epidemiologic measures of drug utilization. *Epidemiol Camb Mass*. 1997;8(6):666-670. doi:10.1097/00001648-199710000-00009

7. Suissa S. The case-time-control design. *Epidemiol Camb Mass*. 1995;6(3):248-253. doi:10.1097/00001648-199505000-00010

8. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6(11):e012832. doi:10.1136/bmjopen-2016-012832

9. Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study: *Menopause*. 2018;25(1):11-20. doi:10.1097/GME.0000000000000956

10. Bhupathiraju SN, Grodstein F, Stampfer MJ, et al. Vaginal estrogen use and chronic disease risk in the Nurses' Health Study: *Menopause*. 2019;26(6):603-610. doi:10.1097/GME.0000000000001284

Tables

Table 1. Characteristics of cases and controls. A case-control study on the association between vaginal estrogen therapy and venous thromboembolism, based on Danish registers during 2010-2018.

	Cases	**Controls**
	(n=13,748)	(n=54,948)
Demographics		
Age 55-64	2,940 (21.4)	11,740 (21.4)
Age 65+	10,808 (78.6)	43,208 (78.6)
History of		
Recurrent UTI	600 (4.4)	1,651 (3.0)
Venous thromboembolism	1,196 (8.7)	4,744 (8.6)
Hypertension	8,732 (63.5)	30,261 (55.1)
Atrial fibrillation	699 (5.1)	1,885 (3.4)
Heart failure	725 (5.3)	1,747 (3.2)
Ischaemic heart disease	2,096 (15.2)	6,406 (11.7)
Ischaemic stroke	933 (6.8)	3,001 (5.5)
Peripheral arterial disease	596 (4.3)	1,423 (2.6)
Venous insufficiency	87 (0.6)	126 (0.2)
Chronic liver disease	207 (1.5)	566 (1.0)
Alcohol-related disorders	374 (2.7)	898 (1.6)
Markers of smoking	1,575 (11.5)	3,593 (6.5)
Diabetes	1,214 (8.8)	4,503 (8.2)
Prescription drug use		
Lipid-lowering agents	4,013 (29.2)	16,174 (29.4)

Platelet inhibitors	3,865 (28.1)	13,488 (24.5)
Systemic glucocorticoids	1,645 (12.0)	3,295 (6.0)
Inhaled glucocorticoids	1,843 (13.4)	4,726 (8.6)
Antidepressants	2,746 (20.0)	8,628 (15.7)
Opioids	3,273 (23.8)	8,855 (16.1)
Benzodiazepines and derivatives	2,528 (18.4)	8,922 (16.2)
Non-steroidal anti-inflammatory drugs	3,304 (24.0)	9,620 (17.5)

Table 2. Main results of a case-control study on the association between the use of vaginal estrogen and venous thromboembolism

Subgroup	Cases, exposed/unexposed	Controls, exposed/unexposed	Crude odds ratio	Adjusted odds ratio
All	1296/12452	5482/49466	0.94 (0.88 to 1.00)	0.87 (0.81 to 0.93)
Outcomes				
Pulmonary embolism	458/4580	2047/18086	0.88 (0.79 to 0.98)	0.81 (0.73 to 0.91)
DVT	838/7872	3435/31380	0.97 (0.90 to 1.05)	0.90 (0.83 to 0.98)
Subgroups				
Age < 65*	221/2719	1077/10663	0.81 (0.69 to 0.94)	0.74 (0.63 to 0.86)
Age 65+*	1075/9733	4405/38803	0.97 (0.91 to 1.04)	0.90 (0.84 to 0.97)
History of VTE	117/1079	404/4340	1.16 (0.94 to 1.44)	1.13 (0.91 to 1.42)
No history of VTE	1179/11373	5078/45126	0.92 (0.86 to 0.98)	0.85 (0.79 to 0.91)

DVT = Deep vein thrombosis, VTE = Venous thromboembolism

*Crude odds ratios may deviate minimally from manual calculations, due to age stratification in rare cases dropping all controls from a risk set.