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Unravelling the Causal Relationship between Endometriosis and the Risk for Developing Venous Thromboembolism: A Pooled Analysis

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Abstract

Objective To investigate the effect of endometriosis on venous thromboembolism (VTE) in oral contraceptive (OC) users. Pooled analysis on a harmonized dataset compromising international patient-centric cohort studies: INAS-VIPOS, INAS-SCORE, and INAS-FOCUS. Eleven European countries, the United States, and Canada. Individuals being newly prescribed an OC with or without an endometriosis and no VTE history.

Methods Detailed information was captured using self-administered questionnaires at baseline and every 6 to 12 months thereafter. Self-reported VTEs were medically validated and reviewed by an independent adjudication committee. Incidence rates (IRs) were calculated per 10,000 woman-years. The association of endometriosis on VTE was determined in a time-to-event analysis, calculating crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) using stabilized inverse probability of treatment weighting (IPTW).

Results A total of 22,072 women had an endometriosis diagnosis, and 91,056 women did not. Women with endometriosis contributed 78,751 woman-years during which 41 VTE events occurred (IR: 5.2/10,000, 95% CI: 3.7–7.1) compared to 127 VTEs during 310,501 woman-years in women without endometriosis (IR: 4.1/10,000, 95% CI: 3.4–4.9). The hazard ratio of VTE in women with endometriosis was 1.79 (95% CI: 1.24–2.57) using stabilized IPTW controlling for age, body mass index, smoking, education, age at menarche, and family history of VTE. Subgroup and sensitivity analyses showed similar results.

Conclusion These results highlight the importance of considering endometriosis as a potential factor contributing to VTE in women using OC; however, further research on the relationship between endometriosis and VTE is warranted.

Keywords
- endometriosis
- venous thromboembolism
- oral contraceptive

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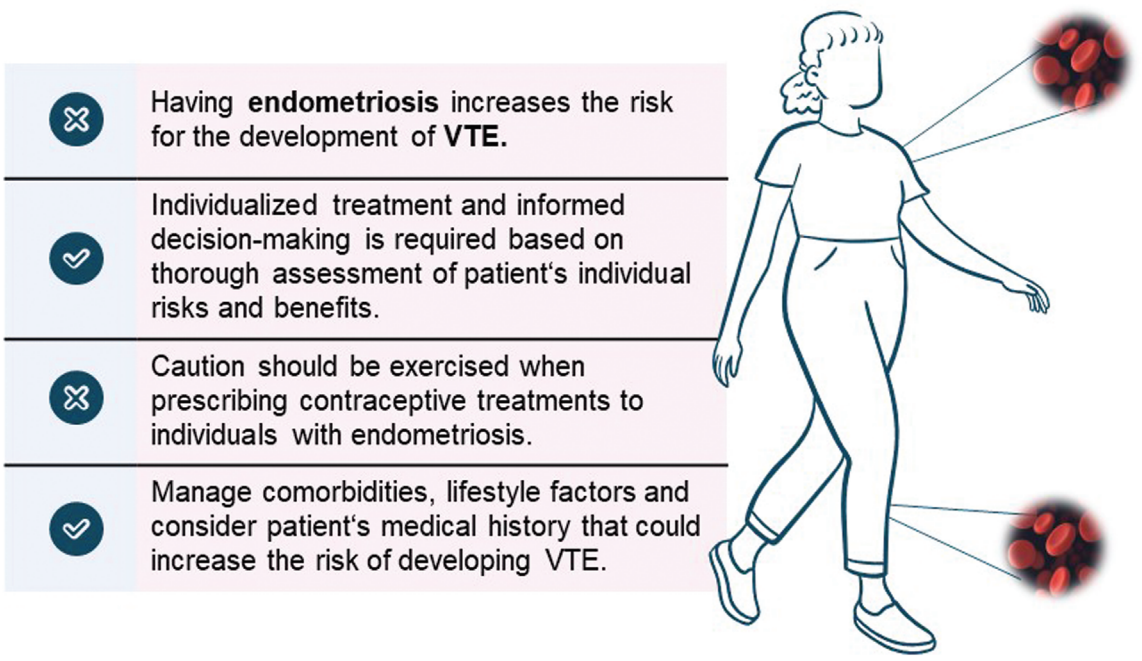

Visual summary. Summary of New Insights into VTE Risk and Management in Endometriosis: Implications for Personalized Care and Treatment.

Introduction

Endometriosis is an estrogen-dependent condition affecting approximately 10% of women of reproductive age worldwide.[1] The mechanisms underlying its development, causes, and clinical burden are not yet entirely understood. Previous research has suggested that women with endometriosis are at higher risk of developing both gynecological and non-gynecological comorbidities (e.g., autoimmune diseases, depression, cardiovascular diseases). This may be because endometriosis interferes with processes that lead to long-term systematic comorbidities.[2–4] Despite the high prevalence of endometriosis, its association with cardiovascular comorbidities remains understudied. However, recent research studies suggest that women with endometriosis may be at increased risk for cardiovascular diseases such as coronary/ischemic heart disease,[5] stroke,[6] and hypertension.[7] In contrast, there is currently a lack of studies examining the risk of venous thromboembolism (VTE) in women with endometriosis compared to those without.

Therefore, we aimed to estimate the causal effect of endometriosis on VTE among women without prior VTE who were newly prescribed an oral contraceptive (OC). We further aimed to compare VTE incidence rates in both groups and describe baseline risk factors and potential mediator mechanisms for the risk of VTE during follow-up.

Materials and Methods

The study was designed as a pooled analysis of previously collected data from three large, International Active Surveillance Studies (INAS) Post-Authorization Safety Studies (PASS), collecting similarly detailed information about underlying factors that could play a role in the development of VTE (e.g., body mass index [BMI], smoking, family history of VTE): INAS-VIPOS,[8,9] INAS-FOCUS,[10] and INAS-SCORE.[11] Prospectively collected information from participants in 11 European countries, the United States, and Canada was obtained by the Berlin Center for Epidemiology and Health Research (ZEG Berlin) between 2009 and 2017, following the same methodology, which is described in detail elsewhere.[12,13] In brief, the included studies shared similar inclusion and exclusion criteria, methods of patient recruitment and follow-up, questionnaire design, and research methods. The dataset covers a wide range of data on women between the ages of 11 and 68. In the INAS-VIPOS study, women were recruited by health care practitioners (HCPs) if they had a diagnosis of endometriosis and were newly prescribed a hormonal treatment such as danazol, gonadotropin-releasing hormone analogs, combined OCs (COCs), or progestogen-only pills (POPs). In INAS-FOCUS and INAS-SCORE, all women of reproductive age were recruited via HCPs if they were newly prescribed an OC, which was the start of their study follow-up.

In all studies, the majority was prescribed a COC, fewer were prescribed other oral preparations such as POPs. Study participants were allowed to stop or switch their prescribed treatment without affecting their study follow-up.

Eligibility for the Pooled Analysis

For this study, women with and without endometriosis who were prescribed a new OC at baseline were selected from the

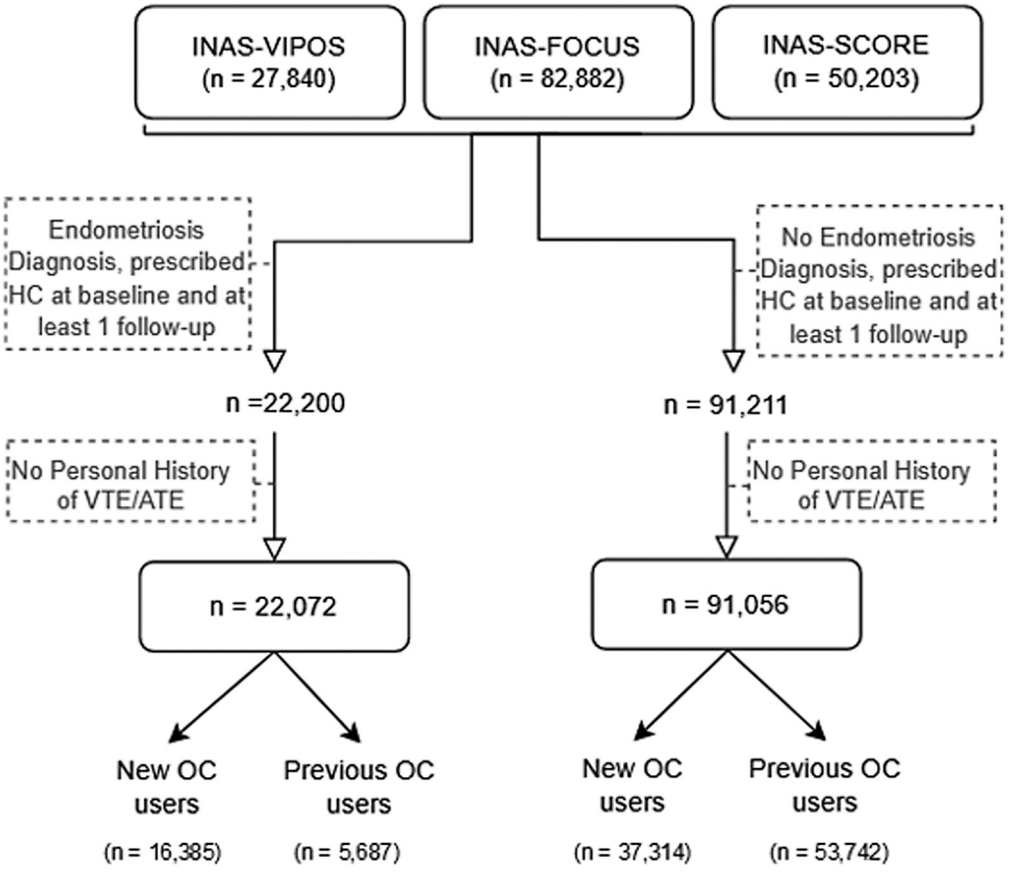

Fig. 1 Selection of study population for the pooled analysis.

pooled dataset. Study participants taking a treatment other than an OC, those without follow-up data, and those with a personal history of VTE or arterial thromboembolism were excluded. Eligible participants were further categorized into new or previous users of OCs. New users were defined as users who did not take any OC before. Previous users were defined as users who switched or re-started any (same or different) OC. Start of follow-up was defined as the date the participant was prescribed new OC treatment. An overview of this selection procedure is shown in ►**Fig. 1**.

Assessment of Endometriosis

The design of the study questionnaires was identical in the different studies, with smaller differences for the INAS-VIPOS study, including questions about endometriosis specifically. In INAS-FOCUS and INAS-SCORE, women were asked at baseline for what purpose the OC was prescribed (e.g., contraceptive use, acne, endometriosis), if they suffered from gynecological problems such as menstrual pain, heavy bleeding, amenorrhea, etc. and if they were diagnosed with any disease, including endometriosis, which enabled the selection of participants without endometriosis from these studies.

Assessment of VTE

Self-reported VTEs by the participants were validated by an expert panel after medical records review at ZEG Berlin. At the end of each study, the categorization of VTEs was again reviewed by an independent adjudication committee, and events were classified until concordance was reached between the members. The outcome of interest was confirmed VTE, including deep venous thrombosis and pulmonary embolism, and was coded consistently by ZEG Berlin's medical event validation team during the outcome validation procedure in the included studies.[11]

Covariate Information

Participants were asked to complete self-administrated questionnaires every 6 to 12 months for a total follow-up period of up to 7 years. Captured baseline information for all studies included age, weight, height, medical history, gynecological history, lifestyle (e.g., smoking), family history of VTE, cardiovascular risk factors (e.g., high blood pressure), regular use of medication, education, and previous and current use of hormonal treatment. All participants were asked about their change in hormonal treatment, the occurrence of a newly diagnosed cardiovascular event such as VTE, any other severe disease, hospitalization, delivery, and regular use of concomitant medication at each point of follow-up. An overview of the data sources can be found in ►**Supplementary Table S1** (available in the online version).

Details of Ethics Approval

The planning and conduct of the studies were subject to the national laws and regulations of the participating countries.

Before documentation of any data, informed consent was obtained by the study participants. The informed consent forms complied with the individual study country law and regulations for observational studies, including approval from local independent ethics committee/institutional review board. All studies were conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices (International Society for Pharmacoepidemiology), the Good Epidemiological Practice (International Epidemiological Association European Federation), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct for Scientific Independence and Transparency, and the ethical principles based on the Declaration of Helsinki. INAS-FOCUS (EUPAS 1597) and INAS-VIPOS (EUPAS 1613) were registered in the EU PAS and received an ENCePP seal. All three studies were registered on clinicaltrials.gov.

Statistical Analysis

Population characteristics and parameters of reproductive, contraceptive, and medical history observed at baseline across all studies were considered as time-invariant continuous or categorical variables in the analysis. Categorical variables were described by absolute and relative frequencies; continuous variables were summarized by the sample mean and standard deviation.

The incidence rates of VTE were calculated per 10,000 woman-years with participants contributing time at risk until the first VTE event, loss to follow-up, death, or reached 60 months of follow-up, whichever occurred first. Participants were censored if no further follow-up information was available, independent of the reason for unavailability of data. If medical confirmation concluded that a death or serious event was caused by a VTE, it was counted as a confirmed VTE event in the analysis. However, if the death was attributed to a cause other than VTE or unknown reasons, the individual was censored after the time of death. Only first confirmed VTE events were considered in the analyses.

To estimate if there is an average effect of endometriosis on VTE, a causal framework was built based on expert knowledge for confounding identification. Inverse probability of treatment weighting (IPTW) was used to control for measured confounding. A pseudo-population was created by weighting each individual by the inverse probability of their exposure status (i.e., having endometriosis or not) given the factors considered contributing to confounding.[14–16] In this weighted population, it is expected that the observed factors considered for confounding are equally distributed across exposure groups and thus, allowing estimation of the population average (marginal) effect.[17] Because of the statistical efficiency, stabilized weights were preferred over unstabilized weights.[18]

Stabilized weights were calculated using the procedure PSMATCH and were used to account for potential differences in baseline characteristics between the two groups.[14] Logistic regression was applied to estimate the probability of exposure (endometriosis) given observed baseline characteristics. Standardized mean differences (SMDs) were used to determine the balance of baseline covariates between the two exposure groups before and after applying the weighting. A covariate was considered adequately balanced if its absolute SMD was lower than 0.25 and its variance ratio was between 0.5 and 2.0. If residual unbalance between the two exposure groups was noticed, the logistic model was modified by including interactions between covariates already available in the initial model, or by introducing nonlinear terms.[19] After confirming adequate balance between the two groups (i.e., similar distribution of observed baseline covariates between endometriosis vs. no endometriosis), a weighted Cox proportional hazards regression was performed.

To check for potential misclassification bias, a sensitivity analysis was performed in women with a surgically confirmed endometriosis diagnosis compared to those without endometriosis.

The selection of observed baseline characteristics to be considered for inclusion in the IPTW model was based on empirical knowledge in endometriosis and cardiovascular outcomes research and on discussions with experts in the field, conceptualized into a Directed Acyclic Graph (DAG)[20] (►**Supplementary Fig. S1**, available in the online version). The following variables were included for the calculation of the weights: age, BMI, family history of VTE, age at menarche, smoking, and education.

Crude and IPTW hazard ratios (HRs) with 95% confidence intervals (CIs) were obtained using a Cox proportional hazards model using PROC PHREG. Ties were optimized using the Efron technique. The fully conditional specification method was applied for multiple imputation (MI) of the selected model covariates.[21] PROC MI was used to create 10 imputed datasets. The results from Cox regression among the imputed datasets were combined with PROC MIANALYZE using Rubin's rules.[22] The proportional hazards assumption was assessed based on a Cox regression model including time-dependent covariates with nonsignificant p-values (>0.05) indicating adherence to the assumption.[23] In ►**Supplementary Fig. S2** (available in the online version), an IPTW-adjusted survival curve was plotted to show the VTE probabilities for each treatment group over time.[24]

Due to the difference in risk of VTE depending on the OC user status,[25] VTE incidence rates and time-to-event analyses were repeated stratifying by new users and previous users of OC.

Lastly, potential baseline risk factors and mediator mechanisms that could play a role in the development of VTE were descriptively summarized per exposure group (endometriosis or no endometriosis).

All data cleaning and analyses were performed with SAS 9.4.

Results

In total, 113,128 women met the eligibility criteria for the pooled analysis. Of these, 22,072 (19.5%) had an endometriosis diagnosis at study entry. The number of available woman-years per cohort was 78,751 for those having endometriosis and 310,501 for those without endometriosis. Of the women with endometriosis, the vast majority were recruited in Eastern European countries (Hungary, Ukraine, Poland, and Russia), whereas only 9.5% came from West-European countries

(Austria, Germany, France, Italy, Switzerland, United Kingdom, and Sweden). For those without endometriosis, two-thirds came from West-European countries or the United States/Canada and a third from Eastern European countries.

►**Table 1** summarizes the distribution of baseline characteristics in women with and without endometriosis. In summary, compared to women without endometriosis, women with endometriosis had a higher mean age (32.6 vs. 27.5 years), lower use of OC before study start (25.8% vs. 59.0%), higher family history of VTE (7.8% vs. 2.6%), higher likelihood of previous (including gynecological) surgery (81.9% vs. 26.3%), took less regular medication at baseline (12.4% vs. 18.8%), and were slightly less likely to have university-level education (46.7% vs. 51.5%). Other measured baseline covariates were similar between the two groups.

►**Supplementary Table S2** (available in the online version) describes the composition of OCs as prescribed to the study participants at study enrollment. Despite wide geographical variations, most participants were prescribed a fourth-generation OC, respectively 50.9 and 41.7% for those with and

Table 1 Baseline characteristics—complete sample

	Before weighting				After weighting			
	Endometriosis		No endometriosis		Endometriosis		No endometriosis	
Number of participants	22,072		91,056		22,072		91,056	
East-EU	19,965 (90.5%)		30,687 (33.7%)		19,445 (88.1%)		31,870	(35.0%)
West-EU/North America	2,107 (9.5%)		60,369 (66.3%)		2,627 (11.9%)		59,186	(65.0%)
Patient characteristics								
Age at study entry (years)[a]	32.6	(± 8.85)	27.5	(± 8.04)	29.2	(± 8.09)	28.6	(± 8.64)
Weight at study entry (kg)	64.7	(± 12.34)	66.7	(± 16.36)	66.2	(± 15.39)	66.0	(± 15.78)
Height at study entry (cm)	166.1	(± 5.94)	164.8	(± 6.63)	166.1	(± 5.90)	164.8	(± 6.62)
BMI at study entry[a]	23.5	(± 4.37)	24.6	(± 5.83)	24.0	(± 5.57)	24.3	(± 5.61)
Gynecological history								
Age at menarche (years)[a]	12.9	(± 1.33)	12.8	(± 1.52)	12.9	(± 1.30)	12.8	(± 1.52)
Ever been pregnant (gravidity)	12,396	(56.2%)	47,727	(52.4%)	9,910	(44.9%)	50,536	(55.5%)
Ever given live birth (parity)	11,419	(51.7%)	42,158	(46.3%)	8,895	(40.3%)	45,164	(49.6%)
Number of live births	1.51	(± 0.66)	1.63	(± 0.81)	1.47	(± 0.56)	1.66	(± 0.85)
Ever used oral contraceptive	5,687	(25.8%)	53,742	(59.0%)	5,717	(25.9%)	54,178	(59.5%)
Cardiovascular risk factors								
Any tobacco smoking[a]	4,364	(19.8%)	15,467	(17.0%)	4,127	(18.7%)	16,026	(17.6%)
Heavy tobacco smoking (>15 cigarettes per day)	547	(2.5%)	1,626	(1.8%)	486	(2.2%)	1,730	(1.9%)
High blood pressure	324	(1.5%)	2,124	(2.3%)	287	(1.3%)	2,276	(2.5%)
Family history of VTE[a]	1,718	(7.8%)	2,365	(2.6%)	817	(3.7%)	3,369	(3.7%)
Medical history								
Diabetes	78	(0.4%)	666	(0.7%)	110	(0.5%)	637	(0.7%)
Thyroid disorder	33	(0.2%)	106	(0.1%)	44	(0.2%)	91	(0.1%)
Cancer	134	(0.6%)	457	(0.5%)	110	(0.5%)	546	(0.6%)
Any surgery	18,065	(81.9%)	23,898	(26.3%)	18,320	(83.0%)	24,494	(26.9%)
Of which, gynecological surgery	17,292	(78.3%)	5,832	(6.1%)	17,459	(79.1%)	6,101	(6.7%)
Medication								
Regular use of medication, excluding vitamins and minerals	2,631	(12.4%)	16,130	(18.8%)	3,090	(14.0%)	21,216	(23.3%)
Education								
Higher than university entrance level[a]	10,311	(46.7%)	46,899	(51.5%)	10,462	(47.4%)	45,710	(50.2%)

Abbreviations: BMI, body mass index; EU, European Union; VTE, venous thromboembolism.
[a]Variables included for calculating the stabilized weights.

Table 2 VTE absolute numbers and IRs—complete sample, new users, and previous OC users

	Endometriosis	No endometriosis
Complete Sample		
Woman-years	78,751	310,501
Number of participants	22,072	91,056
Number of VTE	41	127
IR (95% CI)[a]	5.2 (3.7–7.1)	4.1 (3.4–4.9)
New users		
Woman-years	56,811	123,736
Number of participants	16,385	37,314
Number of VTE	17	24
IR (95% CI)[a]	3.0 (1.7–4.8)	1.9 (1.2–2.9)
Previous users		
Woman-years	21,940	186,765
Number of participants	5,687	53,742
Number of VTE	24	103
IR (95% CI)[a]	10.9 (7.0–16.3)	5.5 (4.5–6.7)

Abbreviations: CI, confidence interval; IR, incidence rate; VTE, venous thromboembolism.
[a]IR and 95% CI are shown per 10,000 woman-years.

without endometriosis. Women without an endometriosis diagnosis were more likely to have been prescribed a first generation OC (25.9% vs. 2.0%), whereas POP was only prescribed to women with endometriosis (20.1% vs. 0%).

VTE Absolute Numbers and Incidence Rates

In total, 168 confirmed VTEs were observed during 60 months of follow-up: 41 were diagnosed in the endometriosis and 127 in the nonendometriosis group; leading to IR of 5.2 per 10,000 woman-years (95% CI: 3.7–7.1) and 4.1 per 10,000 woman-years (95% CI: 3.4–4.9), respectively.

Due to the difference in risk of VTE for new and previous users of OC and the difference in distribution of OC status in women with and without endometriosis, new and previous users were also considered separately (►**Table 2**). In new users, the VTE IRs were 3.0 per 10,000 woman-years (95% CI: 1.7–4.8) and 1.9 per 10,000 woman-years (95% CI: 1.2–2.9) for women with and without endometriosis, respectively. For previous OC users, the VTE IR in women with endometriosis was 10.9 per 10,000 woman-years (95% CI: 7.0–16.3), whereas in women without endometriosis it was 5.5 per 10,000 woman-years (95% CI: 4.5–6.7).

Results from the Time-to-Event Analysis

The results of the analysis of the average effect of endometriosis on VTE are shown in ►**Fig. 2**. In overall comparison, women with endometriosis were at 86% elevated risk of VTE compared to women with no endometriosis (crude HR: 1.86, 95% CI: 1.29–2.68), not taking into account imbalances in population

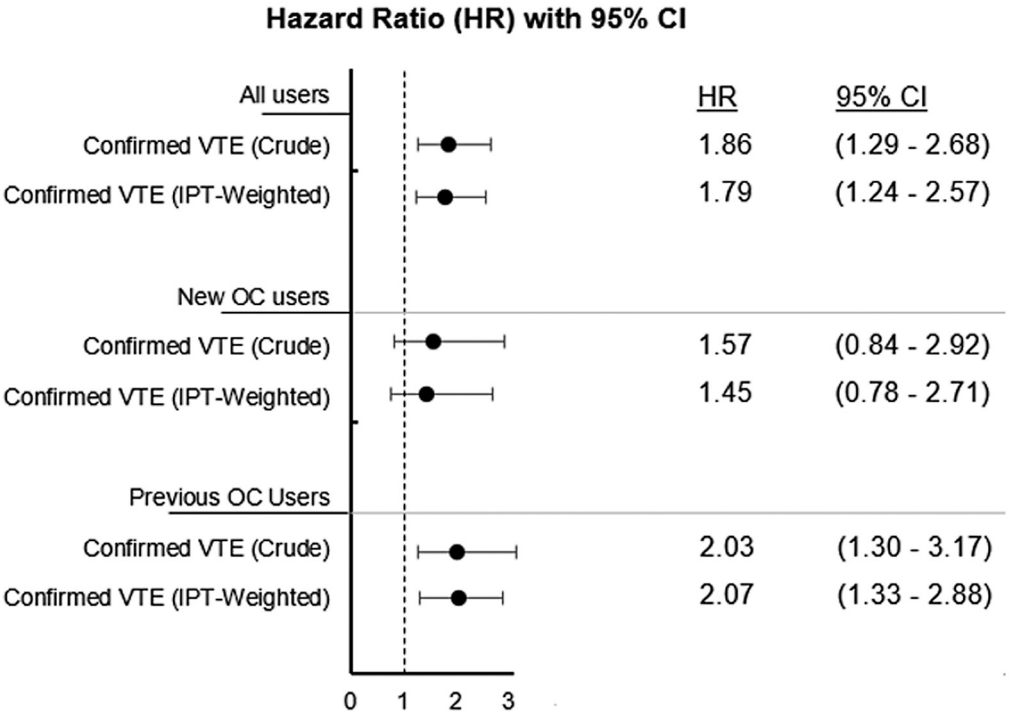

Fig. 2 Crude and IPT-weighted HR with 95% CI—complete sample, new users, and previous users. CI, confidence interval; HR, hazard ratio; IPT, inverse probability of treatment.

characteristics between both groups. For the IPTW model, accounting for observed differences in baseline risk factors including age, BMI, family history of VTE, age at menarche, smoking, and education, women with endometriosis were at 79% elevated risk of VTE compared to women without endometriosis (IPTW HR: 1.79, 95% CI: 1.24–2.57).

The analyses were repeated for the subgroups new and previous OC users (►**Fig. 2**). For new OC users, women with endometriosis had a 57% elevated risk compared to no endometriosis when not accounting for imbalances in risk factors (crude HR: 1.57, 95% CI: 0.84–2.92). The IPTW model resulted in a 45% elevated risk (IPTW HR: 1.45, 95% CI: 0.78–2.71). For previous OC users, women with endometriosis had twice the rate of experiencing a VTE within the observed time for both the imbalanced (crude HR: 2.03, 95% CI: 1.30–3.17) and the weighted (IPTW HR: 2.07, 95% CI: 1.33–3.22) study sample. The mean and range of estimated weights, the balanced statistics and population characteristics after weighting are available in ►**Supplementary Tables SA** and **SB** (available in the online version).

Sensitivity Analyses

To investigate the impact of potential misclassification bias, a sensitivity analysis was performed including only women with endometriosis diagnosed via laparoscopic surgery ($N = 2{,}161$) compared to those without endometriosis. In this surgically confirmed subsample, 6 VTEs were observed, corresponding to an IR of 6.8 per 10,000 woman-years (95% CI: 2.5–14.7). When baseline characteristics were accounted for the IPTW, a 16% (HR of 1.16, 95% CI: 0.38–3.56) elevated risk of VTE was observed for women with a surgically confirmed endometriosis diagnosis compared to those without endometriosis (results available at request).

VTE Baseline Risk and Mediator Factors

When comparing baseline risk factors between those experiencing a VTE and those that did not (►**Supplementary Table SC**, available in the online version), women with a VTE were generally older (mean age of 33.6 vs. 28.5 years) had a higher mean BMI (28.1 vs. 24.3 kg/m^2), had a higher pregnancy history (59.1% vs. 52.2%), reported to have used an OC before (70.2% vs. 51.6%), had a higher number of cardiovascular risk factors (i.e., high blood pressure, family history of VTE, previous surgery), and reported more regular use medication (37.0% vs. 21.0%) compared to women without a VTE. This pattern was similar in women with and without an endometriosis diagnosis.

Regarding the distribution of potential mediators for the development of VTE captured during follow-up, women with endometriosis had a higher proportion of VTE risk factors compared to those without endometriosis including hospital admission (19.7% vs. 13.7%), at least one OC switch during study observation (81.5% vs. 70.5%), reported any new serious disease or surgery (22.6% vs. 9.0%), and were more regularly taking medication during follow-up (25.3% vs. 12.2%; ►**Supplementary Table SD**, available in the online version).

Discussion

Main Findings

The aim of this study was investigating if there is a causal effect of endometriosis on VTE in users of OC. This pooled dataset consisted of 113,128 women, with or without endometriosis, who were newly prescribed an OC and without history of VTE. Despite the overall balanced population characteristics, some heterogeneity in baseline risk was noticed between both groups. Additionally, VTE incidence rates were higher in women with endometriosis, independent of prior OC status. We further observed that endometriosis has an unfavorable effect on the development of VTE. Women with endometriosis had 1.79 times the rate of developing VTE compared with women without endometriosis. This increased rate was stronger in women who had previously used OC compared to those who received their first prescription at inclusion. Further subgroup analyses in different OC user groups and in comparison to those with surgically confirmed endometriosis showed consistent results. Lastly, women with endometriosis were found more likely exposed to baseline and mediator risk factors such as higher number of hospital admissions, (previous) surgeries, serious diseases, regular use of medication, and switching from OC treatment during follow-up, which could contribute to the increased risk of developing a VTE.

Interpretation

This is the first study examining the relationship between VTE and endometriosis in OC users in a large, pooled cohort study. Some imbalances observed when comparing baseline risk between exposure groups could be explained by design of the selected studies of the pooled dataset. First, participants with endometriosis mainly came from Eastern European (Hungary, Poland, Russia, and Ukraine) countries in which OCs were not as commonly prescribed at the time of study conduct compared to West-European countries or the United States/Canada (i.e., from 2009 to 2017). This partially explained the imbalance of prior OC use at baseline between both groups. Additionally, the imbalance in age could be explained by the gap between first occurrence of symptoms and first diagnosis of endometriosis,[26,27] since in INAS-VIPOS only included women with an endometriosis diagnosis being newly prescribed an OC, while in INAS-SCORE and INAS-VIPOS all women of reproductive age being newly prescribed an OC were included. Nonetheless, the imbalance in age and prior OC use was controlled for using stabilized weights and conducting several subgroup analyses which resulted in similar effect estimates. The findings further suggest that OC users with endometriosis have an increased risk of VTE compared to women without endometriosis. Prior research has found women with endometriosis at elevated risk of certain cardiovascular and cerebrovascular outcomes such as hypertension,[7,28] stroke,[6] coronary heart disease,[5,28,29] angiographically confirmed angina,[2] and cerebrovascular incident.[30] While the

underlying reasons for the observed associations are still poorly understood,[31] previous studies have further suggested that several biological mechanisms in women with endometriosis may lead to cardiovascular dysfunction,[32–34] which could potentially also lead to an increased risk of developing cardiovascular comorbidities such as VTE. Additionally, as also supported by our data, women with endometriosis are more likely exposed to nonbiological factors such as surgical interventions or other comorbidities that can increase their risk of developing VTE.

Strengths and Limitations

This study has several strengths that contribute to the validity of the findings. First, during the initial data collection, attention was paid to typical biases in observational research such as bias due to confounding, loss to follow-up, selection bias, and misclassification bias of self-reported outcomes, which is described elsewhere.[8,10,12,13,35] Second, the dataset includes a large variety of information at baseline and follow-up, including detailed information on cardiovascular risk factors. Third, the study has a large sample size, allowing to conduct several prespecified subgroup analyses. Fourth, there is a low number of missing data in the covariates of interest, which reduces the potential for bias. Additionally, the dataset includes a representative population sample from multiple countries, which may enhance the external validity of the findings. Furthermore, we used modern epidemiologic analyses techniques (i.e., IPTW)[14] to estimate the marginal effect of endometriosis on VTE accounting for important confounding factors. Lastly, a study-specific and expert opinion–informed DAG was developed to inform the selection of model covariates. Variables which were considered intermediates were not controlled for to avoid overadjustment bias.[36]

This study also has some limitations. First, despite the broad capture of real-world data, the findings may only be generalized to users of OC. Nevertheless, since OCs are a guideline-recommended therapy for treating endometriosis-related symptoms such as chronic abdominal pain,[37–39] the impact of this limitation is rather limited. Despite that the majority of participants, irrespective of endometriosis diagnosis, were prescribed fourth-generation OCs, it should be noted that variations in prescription patterns and potential differences in hormonal exposures may influence VTE risk. Further investigation into the impact of specific hormonal compositions on VTE risk, particularly in the context of endometriosis, is warranted to inform personalized contraceptive strategies and mitigate thrombotic complications. In addition, the dataset included all OC users, we were not able to distinguish the rate of VTE for COC or POP users. Second, despite the large sample size and long follow-up time, the observed number of VTE was low, which impacted the precision of the research results. Furthermore, women with endometriosis were only followed from the moment they were prescribed a new hormonal treatment for their endometriosis and not from their endometriosis diagnosis which could distort the association between exposure-outcome due to a prevalent user bias.[40] However, the impact of this bias is assumed to be moderate since approximately 80% reported to have experienced their first endometriosis symptoms within the 3 years prior to study inclusion and approximately 70% of women with endometriosis had their endometriosis diagnosis within 1 year before study inclusion. Additionally, among the women without an endometriosis diagnosis, it is plausible that certain women suffer from undiagnosed or asymptomatic endometriosis and were misclassified. Incorrectly classified undiagnosed or asymptomatic cases would lead to bias towards the null, of which the magnitude of underestimation depends on the proportion of cases with an outcome being misclassified. Lastly, stabilized IPTW was applied to improve internal validity by controlling for measured confounding variables. IPTW creates a weighted population with an equal distribution of relevant baseline characteristics, irrespective of the exposure.[17] However, methods such as IPTW only allow for adjustment of characteristics that are measured and included in the model. We cannot rule out that unknown or unmeasured factors leading to confounding may have influenced the found association between endometriosis and VTE.[41] Therefore, further studies with different methodologies that account for unmeasured confounding (e.g., instrumental variable,[16] front-door approach[42,43]) may be needed to further investigate the relationship between endometriosis and VTE. While this study provides epidemiological evidence of an association independent of putative confounding factors, conclusions about the underlying causes are limited by the observational nature of the data. Future research should focus on elucidating underlying biological mechanisms and shared predispositions between endometriosis and thrombotic disorders.

Conclusions

This large observational study evaluated the effect of endometriosis on VTE in users of OC. The findings suggest that OC users with endometriosis have an increased risk of VTE compared to women without an endometriosis diagnosis. These results highlight the importance of considering endometriosis as a potential factor contributing to VTE in women using OC. However, further research is required to better understand the relationship between endometriosis and cardiovascular comorbidities such as VTE, not limited to OC users. Such studies could include larger sample sizes, longer follow-up periods, detailed information on specific OCs, and the exploration of potential confounding factors, such as lifestyle and genetic factors. Our findings have important implications for clinicians and women with endometriosis who are considering the use of OC, and call for individualized and informed decision-making based on a thorough assessment of the risks and benefits of this treatment option.

What is known about this topic?

- Endometriosis has been described as a risk factor for several cardiovascular diseases such as stroke, hypertension, coronary and ischemic heart disease.
- Genetic studies suggest potential shared genetic factors between endometriosis and cardiovascular disease, pointing towards underlying biological pathways that may link these two conditions.
- Current evidence on endometriosis and venous thromboembolism is limited and relies on small sample size studies.

What does this paper add?

- Large pooled analysis reveals elevated rates of venous thromboembolism in endometriosis patients using oral contraceptives.
- Endometriosis emerges as a risk factor for the development of venous thromboembolism.

Authors' Contribution

All authors contributed to the conceptualization and writing (review and editing) of this research; P.D.C., A.S.O., and T.K. contributed to the methodology of the study. P.D.C. contributed to data curation, writing (original draft), and visualization; P.D.C. and I.M. contributed to software, formal analysis, and validation. All authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Conflict of Interest

T.K. reports to have received research grants from the Bundesministerium für Gesundheit (BMG—Federal Ministry of Health, Germany). He further has received personal compensation from Eli Lilly and Company, Teva Pharmaceuticals, Total Energies S.E., The BMJ, and Frontiers. A.S.O. reports to have received research grants from the National Institutes of Health and the Swedish Research Council for Health, Working Life and Welfare. She further has received personal compensation from Abbott. All other authors have nothing to declare.

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