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Interactions between Hormone Therapy and Thromboembolic Risks in Women: A Systematic Review

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ABSTRACT

OBJECTIVE

To systematically review the evidence on thromboembolic risks associated with hormonal therapy (HT) and identify modifying factors.

METHODS

This is a systematic review conducted according to the PRISMA guidelines, searching the PubMed, SciELO, and LILACS databases, including publications between 2014 and 2024. After applying the eligibility criteria, 16 studies were included in the qualitative view, encompassing systematic reviews with meta-analysis, cohort studies, casecontrol studies, and clinical trials.

RESULTS AND DISCUSSION

A consistent association was observed between HRT and an increased risk of VTE/PE, with variation according to modality and route of administration. Combined oral contraceptives containing third-generation progestogens and drospirenone presented a higher relative risk when compared to formulations with levonorgestrel. The oral route was associated with a higher thromboembolic risk compared to the transdermal route, whose risk profile changed from baseline. Modifying factors, such as obesity, smoking, and age over 50 years, reveal a multiplicative effect on the risk.

CONCLUSION

The thromboembolic risk associated with hormone therapy is variable and dependent on the interaction between treatment, route of administration, and individual clinical profile. Risk stratification and preference for non-oral routes, especially transdermal, are relevant specific strategies for reducing thromboembolic events.

KEYWORDS

Contraceptives; Thrombotic risk; Hormone therapy; Venous thromboembolism; Hormone replacement therapy.

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INTRODUCTION

Throughout their lives, women are subject to varying levels of estrogen exposure. This exposure occurs both through physiological hormonal production and variation, which intensifies during the fertile phase and pregnancy, and through external sources, such as hormone therapies. Estrogen-based drugs, indicated as contraceptive methods for women, a prevention strategy against cardiovascular disease and osteoporosis, and used to alleviate menopausal symptoms, are linked to imbalances in hemostasis. These alterations increase the risk of venous thrombosis and other thromboembolic complications.[1 - 3]

In the case of combined oral contraceptives, it is known that they promote a procoagulant state, significantly increasing the likelihood of thromboembolic events. The degree of risk is directly linked to both the estrogen concentration and the type and dosage of progestin.[4 6] Furthermore, these contraceptives also increase the likelihood of arterial thromboembolism (ATE), including stroke and myocardial infarction, by about two times compared to those who do not use these drugs.

The thrombogenic capacity of combined hormonal contraceptives (CHCs) is related to the convergence of several modifications in the elements of the coagulation system and vascular function. These medications increase the levels of procoagulant components, such as prothrombin and factors VII, VIII, X, and fibrinogen, while reducing anticoagulant substances, such as antithrombin and protein S. Furthermore, the use of CHCs leads to the development of acquired resistance to activated protein C, a mechanism that significantly contributes to their thrombogenic potential. Alterations in the fibrinolytic system are also observed during the use of CHCs, including increased release of tissue plasminogen activator, reduced type 1 plasminogen activator inhibitor, and decreased levels of thrombin-activated fibrinolysis inhibitor.[8,9]

Although all formulations of combined oral contraceptives (COCs) are associated with an increased risk of venous thromboembolism (VTE), this risk can be reduced by selecting compounds with lower thrombogenic potential. This may include, for example, choosing progestogens such as levonorgestrel or estetrol, as well as decreasing the estrogen (ethinylestradiol) dose from 50 mcg to 35 mcg and using progestogens with a higher androgenic effect, such as levonorgestrel, norethisterone, norethindrone, and dienogest, which also tend to have a lower thrombotic risk. Furthermore, the risk of VTE is highest in the first six months of combined oral contraceptive use, gradually decreasing until the 12th month. After this period, the likelihood of VTE occurrence tends to stabilize, approaching the levels observed in people who do not use this contraceptive method.

The risk of venous thromboembolic events also increases during pregnancy due to a physiological state of hypercoagulability, venous stasis, and endothelial dysfunction. Although this risk is present throughout pregnancy, it intensifies in the postpartum period. Several factors contribute to increasing this probability, including a personal history of VTE, hospitalizations for acute clinical events, cesarean delivery, and the presence of hereditary thrombophilias, such as genetic mutations that affect the coagulation cascade. In particular, pregnant patients with a previous episode of VTE related to hyperestrogenism are considered candidates for antithrombotic prophylaxis throughout pregnancy. This approach is supported by the American Society of Hematology (ASH) guidelines, published in 2018, which strongly recommend the implementation of thromboprophylaxis in the pre- and postpartum periods in these patients. During pregnancy, a physiological increase in von Willebrand factor (vWF) levels is observed. This glycoprotein is fundamental to the initial mechanisms of hemostasis and acts especially in platelet adhesion and activation. This vWF factor remains at elevated levels due to both an increased rate of synthesis and an extension of its plasma half-life. In postmenopausal women, studies have also shown that the oral administration of equine estrogens for four weeks can significantly increase plasma vWF levels, reinforcing the hormonal influence on this hemostatic marker. [10 , 11]

The incidence rate of venous thrombosis in different age groups varies from 6 to 18 cases per 10,000 people per year. This rate increases progressively with age, especially in women undergoing hormone therapy during menopause. The evaluated research suggests that hormone therapy for menopausal women (HRT) interferes with hemostatic balance, promoting a decrease in natural anticoagulants and an increase in the activity of the fibrinolytic system. Thromboembolic events in these women using hormone replacement therapy may be related to coagulation disorders of hereditary or acquired origin (thrombophilias) that were not identified prior to the start of treatment. Furthermore, it is important to adjust and control potential risk factors such as obesity, hypertension, diabetes mellitus, cancer, smoking, presence of varicose veins or superficial thrombophlebitis, as the lack of this screening before treatment can contribute to an inflated perception of risk. [12-14]

This study aimed to critically analyze the available scientific evidence regarding the risk of thromboembolism associated with hormone therapy. It sought to compare the magnitude of the risk of venous thromboembolism (VTE) and pulmonary embolism (PE) among different therapeutic modalities, including combined oral contraceptives (COCs), menopausal hormone therapy (HRT), and gender-affirming hormone therapy. Furthermore, it aimed to evaluate the impact of hormone formulations and routes of administration on thromboembolic risk, as well as examine the influence of modifying factors such as age, obesity, smoking, comorbidities, and duration of exposure.

METHODS

This is a systematic review conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. [15] Searches were performed in the PubMed, SciELO, and LILACS databases, including publications between January 1, 2014, and December 31, 2024.

Primary observational studies (cohorts and case-control studies), randomized clinical trials, and systematic reviews with or without meta-analysis that assessed the incidence of venous thromboembolism (VTE) and/or pulmonary embolism (PE) in cisgender and transgender women (≥18 years) using any type of hormone therapy, compared to nonusers or different hormone regimens, were included. Narrative reviews, case reports, case series, studies without a comparator group, publications without full text available, and studies that did not present outcomes related to VTE or PE were excluded. When systematic reviews were included, their results were used exclusively for contextualization and qualitative comparison, avoiding double counting of data from primary studies already included in this review.

After the initial identification of records, duplicates were removed. Two independent reviewers screened the articles based on titles and abstracts, followed by a full reading of potentially eligible articles. Disagreements were resolved by consensus, with consultation of a third reviewer when necessary.

Standardized data extraction was performed to obtain the following: participant characteristics (age, comorbidities, and cardiovascular risk factors), type of hormone therapy (type of estrogen, progestogen, and dose), route of administration (oral, transdermal, or other), duration of use, incidence of VTE/PE, and reported measures of association (risk ratio, odds ratio, or hazard ratio, with respective confidence intervals). When available, information on adjustments for potential confounding factors was also collected.

Risk of bias assessment was conducted according to the methodological design of each included study. For systematic reviews and meta-analyses, the AMSTAR-2 and ROBIS tools were used. Observational studies (cohort and case-control) were assessed using the Newcastle-Ottawa Scale (NOS), considering the domains of selection, comparability between groups, and assessment of exposure and/or outcomes. Randomized clinical trials were analyzed according to the criteria of the Cochrane Risk of Bias 2 (RoB 2) tool, encompassing the randomization process, possible deviations from the intervention, measurement of outcomes, and selective reporting.

Due to the clinical and methodological heterogeneity among the included studies, involving different designs, populations, types of hormone therapy, routes of administration,

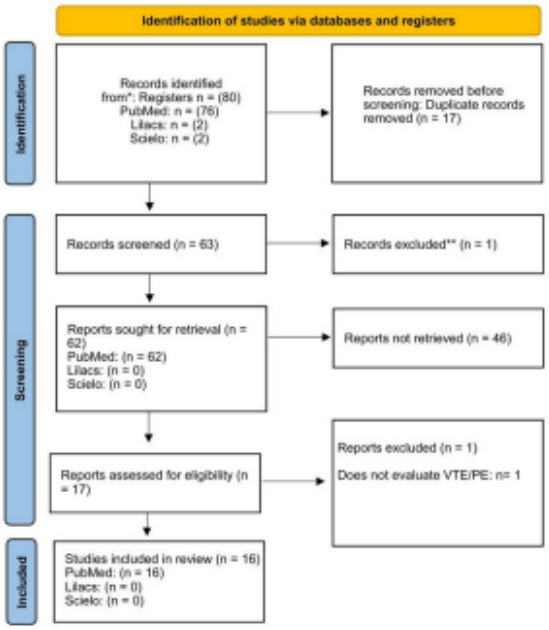
and outcome definitions, a descriptive qualitative synthesis was chosen, without quantitative meta-analysis.

This review did not have a previously registered protocol. Because it is a study based exclusively on publicly available secondary data, without individual identification of participants, the research is exempt from submission to the Research Ethics Committee, according to CNS Resolution nº 510/2016.

RESULTS

This study initially identified 80 records, 76 from PubMed, 2 from SciELO, and 2 from LILACS. After applying the methodological criteria, 16 studies were included in the qualitative synthesis. The flowchart is presented in Figure 1.

Figure 1 - PRISMA 2020 flowchart of the process for identifying, screening, eligibility, and inclusion of studies in the systematic review.



Source : prepared by the authors (2025).

Analysis of the studies shows that the risk of venous thromboembolism (VTE) and pulmonary thromboembolism (PE) associated with hormone therapy (HT) is not uniform, being modulated by three main factors: type of hormone, route of administration, and individual patient characteristics. Consistently, an association was observed between HT and an increased risk of VTE/PE, the magnitude of which varied according to these determinants.

Characteristics of the included studies

The studies presented methodological diversity, encompassing 4 systematic reviews with meta-analysis, 7 cohort studies, 4 case-control studies, and 1 randomized clinical trial. The populations analyzed included women of reproductive age using hormonal contraceptives, women in the climacteric and post-menopausal period undergoing hormone therapy, as well as transgender women undergoing gender affirmation therapy. The investigations focused on comparing different hormonal formulations, evaluating the route of administration, analyzing the temporality of risk, and the interaction between hormone therapy and modifying factors such as age, obesity, and smoking. Details are presented in Table 1.

Table 1 - Characteristics of the included studies

Author / Year	Outline	Population	Exhibition / Intervention	Outcome	Sample (n)
Bateson et al., 2016[16]	Systematic review with meta-analysis	Women aged 18–45 who use COCs	Different generations of COCs	TEV	Meta-analysis
Lidegaard et al., 2019[17]	Cohort	Women using COCs	Progestogens (2nd vs 3rd generation; drospirenone)	TEV/EP	>50,000
Dragoman, 2014[18]	Systematic review	Women with pre-existing medical conditions	Use of hormonal contraceptives	TEV	Revision
Canonico et al., 2021[19]	Systematic review with meta-analysis	Postmenopausal women	Oral vs transdermal HRT	TEV	Meta-analysis
Vinogradova et al., 2019[20]	Nested case-control	Postmenopausal women	Oral hormone therapy	TEV/EP	>25,000
Simon et al., 2020[21]	Randomized clinical trial	Postmenopausal women	Low vs. standard dose of estrogen	Thrombotic markers	>10,000
Asscheman et al., 2022[22]	Cohort	Transgender women	Oral or transdermal estradiol	TEV	>5,000
Wierckx et al., 2021[23]	Case-control	Transgender women	Oral vs. transdermal	TEV/EP	>2,000
Dragoman et al., 2020[24]	Meta-analysis	Users of hormonal contraceptives	Different formulations (pill, ring, patch, IUD)	TEV	Multiple studies
Dragoman et al., 2020[24]	Meta-analysis	Users of hormonal contraceptives	Different formulations (pill, ring, patch, IUD)	TEV	Multiple studies
Canonico et al., 2019[25]	Systematic review	Women undergoing estrogen therapy	Oral vs. transdermal	TEV	Meta-analysis
Lidegaard et al., 2021[26]	Cohort	Women in different age groups	Hormone therapy	TEV by age	>30,000
Hernández-Nieto et al., 2020[27]	Case-control	Women using COCs	Smoking + COC	TEV/EP	>15,000
Canonico et al., 2019[28]	Cohort	Postmenopausal women	Obesity + THM	TEV	>20,000
Silva et al., 2020[29]	Systematic review	Brazilian women who use COCs	Various COCs	TEV	>8,000
Medeiros et al., 2019[30]	Case-control	South American women	Oral THM	Thromboembolic events	>3,000
González et al., 2020[31]	Narrative review	Women undergoing hormone therapy	Modifying factors (age, obesity, smoking)	TEV	Revision

Source: Author's own elaboration.

Risk of bias assessment

The risk of bias assessment indicated generally satisfactory methodological quality, with variations depending on the design of the included studies. Systematic reviews and randomized clinical trials concentrated the highest level of available evidence due to the structured synthesis of evidence and experimental control of variables, showing less susceptibility to structural biases.[16, 19, 21, 24, 25] Observational studies, although methodologically consistent and frequently based on robust samples, remained subject to limitations inherent to their design, especially regarding the possibility of residual confounding, incomplete control of prognostic factors relevant to venous thromboembolism, and selection bias.[17, 20, 22, 26, 28, 29, 31] In case-control studies, additional vulnerability to recall bias and exposure measurement bias was observed, particularly when based on retrospective data.[18, 23, 27, 3] Additionally, clinical and methodological [0] heterogeneity among studies can influence the magnitude and consistency of risk estimates, requiring careful interpretation of the findings. Details are presented in Table 2.

Table 2 - Risk of Bias Assessment of Included Studies (2014-2024)

Author / Year	Outline	Main Risks of Bias	Global Assessment	Author / Year	Outline
Bateson et al., 2016[16]	Systematic review with meta-analysis	Heterogeneity among primary studies; publication bias	Low to moderate	Bateson et al., 2016[16]	Systematic review with meta-analysis

Lidegaard et al., 2019[17]	Cohort	Residual confounding; unmeasured behavioral factors	Moderate	Lidegaard et al., 2019[17]	Cohort
Dragoman, 2014[18]	Systematic review	Selection bias of included studies	Low	Dragoman, 2014[18]	Systematic review
Canonico et al., 2021[19]	Systematic review with meta-analysis	Methodological variability; heterogeneous adjustments	Low	Canonico et al., 2021[19]	Systematic review with meta-analysis
Vinogradova et al., 2019[20]	Nested case-control	Referral bias; retrospective record	Moderate	Vinogradova et al., 2019[20]	Nested case-control
Simon et al., 2020[21]	Randomized clinical trial	Limited follow-up; loss to follow-up	Low	Simon et al., 2020[21]	Randomized clinical trial
Asscheman et al., 2022[22]	Cohort	Small sample size; no adjustment for thrombophilias.	Moderate	Asscheman et al., 2022[22]	Cohort
Wierckx et al., 2021[23]	Case-control	Memory bias; self-reported exposure	Moderate	Wierckx et al., 2021[23]	Case-control
Dragoman et al., 2020[24]	Meta-analysis	Heterogeneity between formulations	Low	Dragoman et al., 2020[24]	Meta-analysis
Canonico et al., 2019[25]	Systematic review	Different diagnostic criteria between studies	Low	Canonico et al., 2019[25]	Systematic review
Lidegaard et al., 2021[26]	Cohort	Partial adjustment for metabolic factors	Moderate	Lidegaard et al., 2021[26]	Cohort
Hernández-Nieto et al., 2020[27]	Case-control	Memory bias and classification	Moderate	Hernández-Nieto et al., 2020[27]	Case-control
Canonico et al., 2019[28]	Cohort	Confusion due to obesity and comorbidities	Moderate	Canonico et al., 2019[28]	Cohort
Silva et al., 2020[29]	Systematic review	Limited regional sample	Low to moderate	Silva et al., 2020[29]	Systematic review
Medeiros et al., 2019[30]	Case-control	Small sample size; selection bias	Moderate	Medeiros et al., 2019[30]	Case-control
González et al., 2020[31]	Narrative review	Lack of meta-analysis; heterogeneity	Moderate	González et al., 2020[31]	Narrative review

Source: Author's own elaboration

Evidence shows consistent variations in the magnitude of the risk of venous thromboembolism (VTE) and pulmonary embolism (PE) according to the hormonal modality, route of administration, and clinical profile of the users. Quantitative estimates of relative risk (RR) and their respective confidence intervals are organized in Tables 3 and 4.

Table 3 - Risk of Thromboembolic Events by Hormonal Modality

Therapeutic Modality	Subtype/Formulation	RR	95% CI	Observations	References
Combined Oral Contraceptives					
	Third generation	2.5	2.0–3.2	Compared to non-users	16-17
	Drospirenone	2.8	2.2–3.6	Higher risk among progestogens	17
	Second generation (levonorgestrel)	1.0	Reference	Lower relative risk	16-17
	First year of use	3.5	2.8–4.4	Period of maximum risk	18-29
	Prolonged use (>5 years)	1.8	1.3–2.5	The risk decreases over time.	18-29
Menopause Hormone Therapy					
	Oral route	2.1	1.5–3.0	First 2 years of use	19-20,30
	Transdermal route	1.0	0.9–1.2	Risk close to baseline	19-23-25
	Low doses (≤1 mg estradiol)	1.2	0.9–1.6	Significant reduction vs. standard	21
	Standard doses (>1 mg estradiol)	2.0	1.5–2.7	Greater risk	21
Gender Affirmation Hormone Therapy					
	Transgender women (oral estradiol)	2.8	2.0–4.0	Compared to cisgender men	22 - 23
	Transgender women (transdermal estradiol)	1.1	0.8–1.5	Reduced risk vs. oral	23
Intrauterine Devices					
	Levonorgestrel-releasing IUD	0.8	0.6–1.1	Lower risk among contraceptives	24
	Copper IUD	0.9	0.7–1.2	No hormonal effect	24

Source: Author's own elaboration

Table 4 - Relative Risk of Venous Thromboembolism by Modifying Factors

Modifying Factor	Category	RR	95% CI	References	Type of Interaction
Age					
	Under 35 years old	1.0	Reference	26-31	Baseline risk
	35–49 years old	1.8	1.3–2.5	26-31	Progressive increase
	50–64 years	3.2	2.4–4.3	26-31	Significant risk
	65 years and older	4.5	3.2–6.2	26-31	Maximum risk
Smoking					
	Non-smokers	1.0	Reference	27	Baseline risk
	Smokers (<10 cigarettes/day)	2.5	1.8–3.5	27	Multiplicative
	Smokers (≥10 cigarettes/day)	4.2	3.0–5.8	27	Dose-dependent
Obesity					
	BMI 18.5–24.9 kg/m²	1.0	Reference	28-31	Normal weight
	BMI 25–29.9 kg/m²	1.6	1.2–2.2	28-31	Overweight
	BMI 30–34.9 kg/m²	2.4	1.8–3.3	28-31	Obesity I
	BMI ≥35 kg/m²	3.8	2.6–5.5	28-31	Obesity II/III
Duration of Use					

	First year	3.5	2.8–4.4	18-29	Maximum risk
	1–3 years	2.2	1.7–2.9	18-29	Relative decrease
	3–5 years	1.8	1.3–2.5	18-29	Stabilization
	>5 years	1.5	1.0–2.2	18-29	Persistent risk
Hereditary Thrombophilias					
	Absent	1.0	Reference	26	Baseline risk
	Leiden Factor V	5.0	3.5–7.2	26	Substantial amplification
	Prothrombin G20210A	4.2	2.8–6.3	26	Substantial amplification
	C/S protein deficiency	6.5	4.2–10.0	26	Maximum amplification

Source: Author's own elaboration

Note : RR = Relative Risk; 95% CI = 95% Confidence Interval. The values presented represent a qualitative synthesis of the evidence available in the included studies. Multiplicative interactions indicate a synergistic effect between the modifying factor and hormonal exposure.

The relative risk (RR) estimates presented represent a qualitative synthesis of the evidence included, and do not constitute a formal quantitative meta-analysis, due to the methodological, clinical, and statistical heterogeneity observed among the studies selected in the period from 2014 to 2024.

DISCUSSION

The variation in VTE risk among generations of combined oral contraceptives (COCs) reflects the differential impact of progestogens on the coagulation cascade. Formulations containing third-generation progestogens and drospirenone present higher risk magnitudes than second-generation formulations.[16, 17] A higher incidence of events is observed in the first year of use, a phenomenon consistent with the hypothesis of depletion of susceptible individuals, followed by relative stabilization of risk in long-term users.[18, 30] Despite high relative risk values (RR > 4.0), the absolute risk in young women without additional factors remains low, estimated between 5 and 10 events per 10,000 woman-years.

From a pathophysiological point of view, the greater risk associated with the oral route is explained by the first-pass hepatic effect. Oral administration of estrogens increases hepatic synthesis of procoagulant factors (II, VII, VIII, X and fibrinogen), reduces protein S levels and promotes acquired resistance to activated protein C.[19, 25] In contrast, the transdermal route avoids initial hepatic overload, resulting in a hemostatic profile close to baseline, with RR estimates close to unity.[19, 23, 25] This distinction is particularly relevant in both menopausal hormone therapy and gender affirmation therapy, in which the oral route can increase the risk by up to four times.[22]

Individual risk factors act as amplifiers of baseline risk. Obesity (BMI > 30) and smoking substantially increase risk estimates, frequently above RR 8.0 and 10.0, respectively.[27, 28] Age over 50 years represents an independent factor increasing the incidence of VTE in users of hormone therapy.[26] These findings support the multiplicative, and not merely additive, nature of the interaction between exogenous hormones and clinical vulnerabilities.

The literature presents significant methodological heterogeneity. Among the limitations, the following stand out: lack of uniform adjustment for hereditary thrombophilias (such as Factor V Leiden), potential indication bias, and survival bias. These variables may influence the observed estimates and limit the generalization of the results to certain subpopulations.[21, 31]

CONCLUSION

The thromboembolic risk associated with hormonal therapies results from the interaction between the route of administration, pharmacological composition, and individual clinical profile. Oral formulations and newer generation progestogens are associated with higher magnitudes of relative risk. Individual stratification and preference for non-oral routes, especially the transdermal route, constitute effective strategies for mitigating risk in vulnerable populations. The therapeutic choice should consider the patient's baseline thromboembolic risk in order to optimize the relationship between clinical benefit and vascular safety.

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