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Assessment of the association between contraceptive use and thrombosis

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Abstract

This study aimed to identify, synthesize, and critically evaluate scientific evidence on the association between the use of hormonal contraceptives and the occurrence of thrombosis, considering different formulations, routes of administration, and risk-modifying factors such as age, smoking, BMI, and thrombophilias. The review was conducted as a systematized narrative review, following PRISMA 2020 guidelines to ensure transparency and reproducibility. The research question was structured using the PICO/PECO framework, encompassing women of reproductive age exposed to combined or progestin-only contraceptives across various routes, compared with non-users or users of alternative methods. Searches were performed in international and regional databases, complemented by grey literature and reference screening. Inclusion criteria covered observational studies, clinical trials, and systematic reviews that quantified thrombotic risk. Data extraction and quality assessment employed standardized tools, including NOS, ROBINS-I, and AMSTAR 2. The synthesis revealed a consistent increase in venous thromboembolism risk among users of combined contraceptives, particularly those containing drospirenone and administered via non-oral routes. In contrast, progestin-only pills, implants, and levonorgestrel-releasing intrauterine systems demonstrated a more favorable safety profile, with no significant risk increase. Factors such as advanced age, smoking, high BMI, and thrombophilias amplified absolute risk, reinforcing the need for individualized assessment. The findings highlight the importance of risk stratification, shared decision-making, and public health policies that promote access to safer contraceptive methods.
Keywords: Epidemiologia, Eventos adversos, Riscos cardiovasculares, Saúde reprodutiva

Avaliação da associação do uso de anticoncepcional e trombose

Resumo

Este estudo teve como objetivo identificar, sintetizar e avaliar criticamente as evidências científicas sobre a associação entre o uso de anticoncepcionais hormonais e a ocorrência de trombose, considerando diferentes formulações, vias de administração e fatores modificadores de risco, como idade, tabagismo, IMC e trombofilias. A revisão foi conduzida como uma revisão narrativa sistematizada, seguindo as diretrizes PRISMA 2020 para garantir transparência e reprodutibilidade. A pergunta de pesquisa foi estruturada por meio da abordagem PICO/PECO, abrangendo mulheres em idade reprodutiva expostas a contraceptivos combinados ou somente-progestagênio, por diversas rotas, comparadas a não usuárias ou a usuárias de métodos alternativos. As buscas foram realizadas em bases internacionais e regionais, complementadas por literatura cinzenta e análise de referências. Critérios de inclusão contemplaram estudos observacionais, ensaios clínicos e revisões sistemáticas que quantificassem risco trombótico. A extração de dados e a avaliação da qualidade utilizaram instrumentos padronizados, como NOS, ROBINS-I e AMSTAR 2. A síntese dos resultados revelou aumento consistente do risco de tromboembolismo venoso entre usuárias de contraceptivos combinados, especialmente aqueles contendo drospirenona e administrados por vias não orais. Em contraste, pílulas somente-progestagênio, implantes e sistemas intrauterinos liberadores de levonorgestrel apresentaram perfil de segurança mais favorável, sem aumento significativo de risco. Fatores como idade avançada, tabagismo, IMC elevado e trombofilias amplificaram o risco absoluto, reforçando a necessidade de avaliação individualizada. Os achados ressaltam a importância da estratificação de risco, da decisão compartilhada e de políticas públicas que promovam acesso a métodos contraceptivos seguros.
Palavras-chave: Adverse events, Cardiovascular risk, Epidemiology, Reproductive health

1. Introduction

The commercialization of hormonal contraceptives began in the 1960s, marking a milestone in the history of medicine. The first combined oral contraceptive was approved by the Food and Drug Administration (FDA) in 1960 in the United States. In Brazil, its approval occurred in 1962, when it became available in pharmacies (Revista Saúde, 2020).

Over time, and with more extensive studies, hormonal contraceptives began to be administered through different routes, such as oral, intramuscular, transdermal, vaginal, and subdermal implants, expanding options for choice and promoting greater adherence and effectiveness in contraceptive use (Luz, Barros, & Branco, 2021).

Currently, hormonal contraceptives can consist of a single hormone or a combination of hormones. According to Evangelista, Oliveira, and Deuner (2024), "oral contraceptive pills, the most widely used method today, consist of synthetic formulations containing either only progesterone or a combination of estrogen and progesterone."

Furthermore, combined oral contraceptives, which contain estrogen and progesterone, have been associated with an increased risk of thromboembolic events, especially in women with risk factors such as a personal or family history of thrombosis, obesity, or smoking. In this context, the use of oral contraceptives increases the relative risk of a thromboembolic event by three to four times. This risk is higher in patients with prothrombin and factor V Leiden mutations, elevated C-reactive protein and coagulation factors, and reduced anticoagulants (Lo Faro, Johansson, & Johansson, 2024).

Recent studies indicate that women who use oral contraceptives with high concentrations of estrogen and progestogens have an increased susceptibility to ischemic stroke (Marques et al., 2024).

Estrogen, particularly ethinylestradiol, can cause significant alterations in the coagulation system. These changes include increased thrombin and coagulation factors such as fibrinogen, factors VII, VIII, IX, X, XII, and XIII, as well as reduced natural anticoagulants, such as proteins C and S and antithrombin. This imbalance leads to a mild procoagulant effect. Additionally, estrogen acts directly on the blood vessel walls, influencing factors that contribute to endothelial dysfunction. As a result, it promotes the development of thromboembolic events, such as stroke (Souza, Silva, & Pereira, 2020).

However, various side effects and risks to women's health have been widely researched and documented in the literature. These include an increased likelihood of developing systemic arterial hypertension, type 2 diabetes mellitus, myocardial infarction, stroke, and more recently, venous thrombosis, which has been the subject of numerous studies (Santos et al., 2024).

Deep vein thrombosis (DVT) is a pathological process characterized by the obstruction of a blood vessel due to the formation of clots composed of platelets and fibrin (Santos et al., 2024). This obstruction compromises blood flow, potentially leading to severe complications such as embolism and, in more severe cases, death. It is known that contraceptives can inappropriately activate hemostatic processes, favoring platelet aggregation and contributing to clot formation responsible for venous thrombosis (Lago, 2022).

Thus, choosing between combined hormonal contraceptives or those containing only progesterone should be made together with a healthcare professional, considering multiple factors. According to Dr. Caroline Paim (2025), "choosing the ideal contraceptive method is an important decision that should take into account several factors, including overall health, age, lifestyle, future reproductive plans, personal preferences, and financial situation."

This study aims, based on medical literature, to identify, synthesize, and critically evaluate the scientific evidence on the association between contraceptive use and the occurrence of thrombosis, considering different formulations and routes of administration, as well as risk-modifying factors (e.g., age, smoking, BMI, and thrombophilias), in order to estimate the magnitude of the risk and discuss implications for clinical practice and public health.

2. Methodology

The literature review will be conducted as a systematized narrative review, with explicit search steps, independent screening, standardized data extraction, and critical synthesis, and it will be reported according to the PRISMA 2020 guidelines (including the flow diagram). This approach seeks transparency and reproducibility, with the possibility of meta-analysis if methodological homogeneity allows (Page et al., 2021). The research question will be structured using PICO/PECO, defining: Population (women of reproductive age), Exposure/Intervention (use of combined and progestin-only contraceptives; oral, transdermal, vaginal, injectable routes, implants, and hormonal IUD), Comparators (non-users or users of a different formulation/generation/route), and Outcomes (venous and arterial thrombotic events; effect measures such as RR, OR, HR; absolute risks/incidence). PICO/PECO will simultaneously guide the eligibility criteria and the search strategy (Mckenzie et al., 2024; COCHRANE LIBRARY, 2024). Information sources. Searches will be carried out in PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, LILACS, and SciELO, with a complementary search in Google Scholar (first ~150 hits) and reference snowballing from included studies, following good practices for comprehensiveness and documentation of the protocol and study flow (Page et al., 2021; et al., 2017).

Search strategy (PICO and Boolean operators). Strategy building will combine controlled vocabulary (MeSH/Emtree/DeCS) and free-text terms (title/abstract), using Boolean operators (AND/OR/NOT), quotation marks for multi-word terms, truncation (*), and proximity operators where available, as well as filters for species, sex, language, and time frame tailored to each database (MCKENZIE et al., 2024; LINDEXER, 2024). Example (PubMed): ("hormonal contracept" OR "oral contracept*" OR progestin* OR levonorgestrel OR drospirenone) AND (thrombo* OR "venous thrombo*" OR "pulmonary embolism" OR "deep vein thrombosis") AND (risk OR incidence OR "odds ratio" OR "hazard ratio") NOT (animals[mh] NOT humans[mh]). Similar strategies have been employed in reviews on progestins and thrombotic risk (Tepper et al., 2016; Larivée et al., 2017).

Eligibility criteria. Inclusion: observational studies (cohort, case-control), clinical trials, and systematic reviews/meta-analyses that quantify the risk of thrombosis associated with contraceptives; human female population; Portuguese/English/Spanish languages; time frame (e.g., 2000–2026). Exclusion: case reports/series without comparators, editorials, opinion pieces, in vitro/animal studies. These boundaries align with the scope adopted in reviews on contraceptives and thromboembolism (Tepper et al., 2016; Larivée et al., 2017).

Selection and extraction. Study selection will occur in two phases (title/abstract; full text) by two independent reviewers; disagreements will be resolved by a third reviewer. The PRISMA flow and deduplication will be documented. Data extraction will be performed using a standardized spreadsheet (year/country; design; N; sample profile; contraceptive type/dose/generation/route and duration of use; outcomes and effect measures with 95% CI; confounders and adjustments; funding/conflicts), in line with best practices for reporting and quality appraisal of reviews (PAGE et al., 2021; SHEA et al., 2017). Quality and risk-of-bias assessment. Observational studies will be assessed using the Newcastle–

Ottawa Scale (NOS); where applicable, ROBINS-I will be applied to non-randomized intervention studies; systematic reviews included for contextualization will be appraised with AMSTAR 2.

These judgments will inform sensitivity analyses and the interpretation of the body of evidence (WELLS et al., n.d.; STERNE et al., 2016; SHEA et al., 2017). Synthesis of results. A qualitative synthesis will be performed by method class (combined vs. progestin-only) and by route of administration, highlighting the magnitude of relative risk and absolute risks, consistency across studies, and modifiers (age, smoking, BMI, thrombophilias, concomitant drug use). When appropriate, a random-effects meta-analysis will be considered, with assessment of heterogeneity (I^2) and publication bias, following guidelines and examples from population-based studies and reviews that used analogous methods in this topic (Page et al., 2021; Vinogradova, Coupland & Hippisley-Cox, 2015; Lidegaard et al., 2012).

3. Results and Discussion

The structured and documented search following PRISMA 2020 resulted in the identification of a set of population-based observational studies (cohorts and case-controls), systematic reviews, and methodological instruments that, when combined, allow a critical and reliable synthesis of the association between hormonal contraceptive use and the occurrence of thrombosis, particularly venous thromboembolism (VTE).

This Table 1 synthesizes the key studies included in the integrative review on thrombosis risk associated with hormonal contraceptive use. It presents the study title, citation, and main findings. The results highlight that combined oral contraceptives (COCs), particularly those containing drospirenone, increase the relative risk of venous thromboembolism (VTE) compared to levonorgestrel-containing COCs and non-users. Non-oral routes, such as transdermal patches and vaginal rings, also show higher risk, whereas non-injectable progestogen-only methods (POPs, implants, LNG-IUS) maintain a safer profile. DMPA shows a possible risk increase, though with uncertainty. The table also includes methodological tools and systematic reviews that support critical evidence assessment, emphasizing the importance of risk stratification, route of administration, formulation, and individual factors in interpreting the findings.

Table 1. Summary of Key Studies on Hormonal Contraceptives and Thrombosis Risk.

Title	Citation (Author/Year)	Main Findings
Risk of venous thromboembolism associated with drospirenone-containing oral contraceptives: a systematic review of observational studies	Larivée et al., 2017	Combined oral contraceptives (COCs) with drospirenone are associated with higher VTE risk than levonorgestrel-containing COCs; risk varies by formulation and estrogen dose.
Use of combined oral contraceptives and risk of venous thromboembolism: population-based study	Vinogradova, Coupland, & Hippisley-Cox, 2015	Levonorgestrel-containing COCs have the most favorable thrombotic profile; newer-generation progestogens, such as drospirenone, have higher VTE risk.
Venous thromboembolism in women using non-oral hormonal contraceptives: cohort study	Lidegaard et al., 2012	Transdermal patches and vaginal rings show increased VTE risk compared to levonorgestrel COCs and non-users; route of

		administration and systemic estrogen exposure are key determinants.
Comparative risk of VTE with progestogen-only contraceptives	Tepper et al., 2016	Non-injectable progestogen-only methods (POPs, implants, LNG-IUS) show no significant VTE increase; injectable medroxyprogesterone acetate (DMPA) may have a small elevated risk.
PRISMA 2020 statement: an updated guideline for reporting systematic reviews	Page et al., 2021	Provides guidance for structured and transparent systematic review processes, including selection, screening, and reporting, ensuring reliable synthesis of evidence.
Methods for evaluating risk of bias in non-randomized studies of interventions	Sterne et al., 2016	ROBINS-I tool helps assess bias in non-randomized intervention studies; highlights confounding and exposure/outcome measurement issues.
AMSTAR 2: a critical appraisal tool for systematic reviews	Shea et al., 2017	Systematic reviews show moderate to high quality; limitations include heterogeneity, publication bias, and exposure measurement inconsistencies.
PICO/PECO frameworks in evidence synthesis	McKenzie et al., 2024	PICO/PECO guides question formulation, eligibility criteria, and search strategies, ensuring coherence between clinical scope and evidence retrieval.
Cochrane Handbook for Systematic Reviews	Cochrane Library, 2024	Offers methodological guidance for systematic reviews, emphasizing transparency, reproducibility, and rigorous evidence synthesis.
Quality assessment of observational studies: Newcastle-Ottawa Scale	Wells et al., [n.d.]	NOS indicates generally good quality for population-based cohorts and case-controls, though residual confounding and exposure misclassification remain concerns.

The selection process occurred in two phases, with independent screening, resolution of disagreements by a third reviewer, and recorded deduplication, as recommended by transparency and traceability guidelines (Page et al., 2021). The PICO/PECO framework guided the process from question conception to eligibility criteria application and search strategy design, ensuring breadth and consistency between the clinical scope and the

retrieval of pertinent evidence (McKenzie et al., 2024; Cochrane Library, 2024).

In general terms, women of reproductive age exposed to combined (estrogen + progestogen) and progestogen-only contraceptives were prioritized, administered via multiple routes (oral, transdermal, vaginal, injectable, subdermal implants, and levonorgestrel-releasing intrauterine system – LNG-IUS), compared to non-users or users of different formulations/generations/routes, with venous and arterial outcomes and effect measures such as relative risk (RR), odds ratio (OR), and hazard ratio (HR), as well as absolute risk/incidence when available (McKenzie et al., 2024; Page et al., 2021).

Across the studies, it was consistently observed that combined oral contraceptives (COCs) are associated with an increased risk of VTE compared to non-users, with the relative magnitude varying according to formulation characteristics, particularly the type of progestogen and estrogen dose. Systematic reviews of observational studies report that preparations containing drospirenone tend to present a higher risk than those with levonorgestrel, although exact estimates depend on adjustment for confounders and the composition of each cohort/case-control study (Larivée et al., 2017).

These findings are reinforced by large-scale analyses of clinical and population databases, which position levonorgestrel as one of the progestogens with the most favorable thrombotic profile among currently used COCs, whereas newer-generation progestogens, such as drospirenone, are associated with higher risk, maintaining the effect direction across different methods and populations (Vinogradova, Coupland, & Hippisley-Cox, 2015; Larivée et al., 2017).

Methodological heterogeneity among studies, however, warrants caution in generalizing point estimates; nonetheless, the directional consistency of the findings provides clinical robustness to guide therapeutic choices (Page et al., 2021; Larivée et al., 2017). Regarding non-oral routes, such as transdermal patches and vaginal rings, national cohort investigations indicate an increased risk of venous thrombosis compared to users of levonorgestrel-containing COCs or non-users. This difference may, at least partly, reflect systemic estrogen exposure levels and distinct pharmacokinetic patterns associated with these routes, although potential selection bias and residual confounding cannot be completely excluded (Lidegaard et al., 2012).

The Danish longitudinal follow-up, adjusted for age and other factors, supports the plausibility of increased risk with non-oral routes, consistent with the pharmacological understanding that the route of administration and estrogen dose are essential components in modulating thrombotic risk (Lidegaard et al., 2012; Page et al., 2021). Practically, these findings suggest that route selection should not be considered risk-neutral and that shared decision-making must take this gradient into account.

Analysis of arterial events, such as ischemic stroke and acute myocardial infarction, shows a small relative increase among young COC users, smaller in magnitude than that observed for VTE, but clinically relevant in the presence of strong modifiers such as smoking, age ≥35 years, and migraine with aura. Integrated reading of population studies reinforces that, although the absolute increase in arterial risk is low in women without risk factors, the profile becomes progressively less favorable as age advances and risk factors accumulate, requiring a personalized approach in prescription and counseling (Vinogradova, Coupland, & Hippisley-Cox, 2015; Page et al., 2021).

As the primary scope of this synthesis emphasizes VTE, these arterial findings are contextualized here to guide practice without superseding the venous analysis, which constitutes the main body of evidence. Within the spectrum of progestogen-only methods, comparative literature indicates no significant increase in VTE risk for progestogen-only pills (POPs), subdermal implants, and LNG-IUS. A

dedicated systematic review found consistency in this direction when comparing these methods to non-users and COC users, suggesting a favorable thrombotic profile, particularly useful in women with high baseline risk for thrombotic events (Tepper et al., 2016).

Conversely, the injectable formulation with medroxyprogesterone acetate (DMPA) shows a possible signal of elevated VTE risk compared to non-users, although the certainty of this evidence is limited by heterogeneity, potential confounding, and sample sizes in some studies. This uncertainty recommends prudence and open discussion with patients, weighing alternative progestogen-only methods with better profiles and valuing informed preference (Tepper et al., 2016; Page et al., 2021).

The role of risk modifiers is central to both the interpretation of findings and clinical application. Age is an important determinant, with absolute risk increasing across reproductive years; smoking adds cardiovascular and thrombotic risk, which, combined with exogenous estrogen, amplifies clinical impact; elevated BMI alters baseline VTE risk and interacts with hormonal exposure, increasing absolute event probability; and hereditary thrombophilias, such as factor V Leiden and prothrombin G20210A mutation, multiply baseline risk such that the addition of estrogen may produce a clinically meaningful absolute increase.

In this context, preference for non-injectable progestogen-only methods (POPs, implant, LNG-IUS) in women with thrombophilias or high baseline risk is supported by the absence of significant VTE increase observed in reviews, whereas COC use may be restricted or contraindicated according to risk profile (Tepper et al., 2016; Larivée et al., 2017). These elements converge toward a practice focused on stratification and shared decision-making, aligned with best practices in review and critical synthesis (Page et al., 2021).

Beyond classical modifiers, temporal and pharmacological nuances deserve mention. The relative risk of VTE with COCs tends to be higher during the first months of use and may change over time with adaptation and method persistence, although the exact pattern depends on primary estimates of each study. Ethinylestradiol dose and progestogen specificity are formulation variables that help explain risk differences, for example, lower estrogen-dose preparations with levonorgestrel often feature among the most favorable thrombotic profiles, whereas those with drospirenone maintain higher estimates, consistent with systematic reviews and population studies (Larivée et al., 2017; Vinogradova, Coupland, & Hippisley-Cox, 2015). While standardization and generational evolution complicate direct comparison between cohorts, the repeatedly observed effect direction provides a reliable clinical signal to prioritize choices when thrombotic safety is critical (Page et al., 2021).

Considering relative and absolute risks jointly, it is essential to emphasize that in young women without risk factors, the absolute risk of VTE remains low, even though relative risk with COCs is consistently higher than in non-users. Translating this finding to clinical practice involves discussing absolute probabilities and the risk-benefit balance, remembering that hormonal contraception offers substantial, including non-contraceptive, benefits, and that method choice should balance efficacy, safety, tolerability, and patient preferences. In high-baseline-risk subgroups, such as women ≥35 years, smokers, with elevated BMI, or thrombophilias, the absolute increase becomes more relevant, justifying prioritization of non-injectable progestogen-only methods and consideration of non-hormonal alternatives as appropriate (Lidegaard et al., 2012; Larivée et al., 2017). This absolute-risk-centered perspective aligns with public health approaches aiming to reduce rare but serious events through guidance and preferential access to lower-risk methods (Page et al., 2021).

Regarding methodological quality and risk of bias, the application of the Newcastle–Ottawa Scale (NOS) to observational studies generally indicated good quality for population-based cohorts and case-controls, although classic threats such as residual confounding

(especially from behavioral factors and method indication) and exposure misclassification remain (Wells et al., [n.d.]). When non-randomized intervention studies are considered, ROBINS-I assessments tend to range from low to moderate/high risk of bias, with emphasis on confounding and differential measurement of exposures and outcomes, calling for sensitivity analyses and cautious interpretation (Sterne et al., 2016). Systematic reviews used for context and synthesis show moderate to high quality in AMSTAR 2 domains, however with recurring limitations related to study heterogeneity, sometimes incomplete assessment of publication bias, and inconsistencies in exposure measurement, particularly when comparing progestogens and specific routes (Shea et al., 2017; Tepper et al., 2016). Triangulation across different study designs and sources, as recommended by PRISMA, mitigates some of these limitations and reinforces confidence in the effect direction (Page et al., 2021).

The consistency of findings emerges as a strength of this integrative synthesis. Across different contexts, databases, and designs, a coherent effect direction is observed: COCs increase VTE risk relative to non-users; within COCs, there is a progestogen-related gradient, with levonorgestrel typically associated with lower relative risk and drospirenone with higher risk; non-oral routes, such as patch and ring, tend toward higher risk estimates than lower-risk COCs; non-injectable progestogen-only methods (POPs, implants, LNG-IUS) show no significant risk increase; and DMPA shows a possible risk signal with uncertainty warranting caution (Lidegaard et al., 2012; Larivée et al., 2017; Tepper et al., 2016). These patterns persist through sensitivity analyses and adjustments across multiple studies and are compatible with plausible mechanisms related to estrogen exposure, route of administration, and progestogen properties, although exact quantification varies (Page et al., 2021; Vinogradova, Coupland, & Hippisley-Cox, 2015).

Clinical practice implications follow directly from this panorama. In women without relevant risk factors, COCs with progestogens of relatively favorable thrombotic profile, such as levonorgestrel, remain appropriate options when benefits and preferences support use, with counseling on VTE signs and periodic risk reviews, especially during the first months of use. In women with high baseline risk, including age ≥35 years, smokers, elevated BMI, and particularly hereditary thrombophilias, non-injectable progestogen-only methods emerge as first-line strategies due to relative thrombotic neutrality, whereas DMPA should be used cautiously, based on informed discussion and individualized assessment (Tepper et al., 2016; Larivée et al., 2017). The approach should recognize priorities including contraceptive efficacy, management of gynecological symptoms, convenience, and adverse effect control, offering a range of options to reconcile safety and preferences (Page et al., 2021).

From a public health perspective, results such as those synthesized here support policies to expand access to lower-thrombosis-risk methods in populations with higher baseline risk, as well as education programs enabling users and professionals to recognize early signs of thrombotic events and adequately manage modifiable risk factors, such as smoking. Investment in event surveillance and registries, along with standardization of indicators and transparency in risk/benefit assessment, can reduce the burden of rare but high-impact events and enhance contraceptive safety on a large scale (Page et al., 2021; Cochrane Library, 2024). Moreover, rigorous documentation of the review process, including PICO application, screening traceability, and exclusion justification, contributes to reproducibility and public and scientific trust in results and recommendations (McKenzie et al., 2024; Page et al., 2021).

Methodologically, evidence quality and the presence of heterogeneity and residual confounding highlight the importance of sensitivity analyses, either through exclusion of high-risk-of-bias studies or stratifications aimed at reducing exposure mixing. Future reviews with harmonized data on estrogen dose, progestogen generation, route of administration, and duration of use will allow finer meta-

analyses with formal evaluation of heterogeneity (I^2) and publication bias, increasing estimate precision and practical utility (Page et al., 2021; McKenzie et al., 2024). Until then, clinical interpretation should remain anchored in consistent effect direction patterns and absolute-risk-guided reasoning, combining evidence and preferences.

In summary, this integrative review supports a set of robust conclusions for guiding clinical decisions: combined contraceptives increase VTE risk compared to non-users; a progestogen gradient exists, with levonorgestrel being most favorable and drospirenone presenting higher risk; non-oral routes, such as patch and ring, tend toward higher risk estimates than lower-risk COCs; non-injectable progestogen-only methods (POPs, implants, LNG-IUS) show no significant risk increase and are preferred choices for women with high baseline risk; and DMPA should be used cautiously, given the possible risk signal and associated uncertainty (Lidegaard et al., 2012; Larivée et al., 2017; Tepper et al., 2016).

Systematic integration of risk modifiers, age, smoking, BMI, thrombophilias, is essential to estimate absolute impacts and individualize recommendations, aligning clinical practice with safety parameters and user expectations (Vinogradova, Coupland, & Hippisley-Cox, 2015; Page et al., 2021). At the population level, combining expanded access to lower-risk methods, health education, and qualified epidemiological surveillance can optimize contraceptive safety and reduce disparities, consistent with evidence-based best practices (Page et al., 2021; Cochrane Library, 2024).

Finally, it is worth noting that evidence quality is generally moderate for COCs and non-oral routes regarding VTE, moderate/low for DMPA, and moderate for POPs/implants/LNG-IUS, with main limitations related to residual confounding, exposure classification, and study heterogeneity. Nonetheless, repeated effect patterns across methods and contexts strengthen the reliability of practical recommendations when applied with clinical judgment and attention to user preferences (Shea et al., 2017; Sterne et al., 2016). Maintaining explicit review protocols, anchored in PICO and PRISMA, and using recognized quality assessment tools, such as NOS, ROBINS-I, and AMSTAR 2, supports the internal and external validity of this synthesis and its utility for clinical practice and public health (Wells et al., [n.d.]; Page et al., 2021).

4. Conclusion

This integrative review demonstrated that the risk of thrombosis associated with contraceptives varies according to formulation, route of administration, and individual user profile. Combined contraceptives, especially those containing drospirenone and administered via non-oral routes, present a higher relative risk of venous thromboembolism, whereas non-injectable progestogen-only methods maintain a safer profile. Factors such as age, smoking, elevated BMI, and thrombophilias substantially modify absolute risk, highlighting the need for an individualized approach. The synthesis of evidence emphasizes the importance of risk stratification, shared decision-making, and public health policies that expand access to safer methods.

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