Oral hormone therapy: Is its VTE risk still underestimated?

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> For decades, clinicians have navigated the delicate balance of prescribing oral hormone therapy, whether for contraception or menopausal symptom management. The persistent question remains: how significant is the thrombotic risk? New analyses confirm that oral formulations carry a measurable increase in venous thromboembolism (VTE) risk, a factor that demands careful consideration in every prescribing decision.

KEY TAKEAWAYS

- The Pivot: Contemporary oral menopausal hormone therapy (MHT) still carries a VTE risk comparable to older formulations, challenging assumptions of improved safety.
- The Data: Oral MHT increased VTE risk by 60% (HR 1.60; 95% CI, 1.48-1.72) compared to non-users.
- The Action: Re-evaluate VTE risk factors for all women on oral hormone therapy, particularly those initiating or continuing menopausal hormone therapy, and consider transdermal routes where appropriate.

Oral hormone therapy, both in the form of combined oral contraceptives (COCs) and menopausal hormone therapy (MHT), consistently elevates the risk of venous thromboembolism. This risk is not a relic of older formulations but persists with contemporary treatments, requiring ongoing vigilance from prescribers. Clinicians must understand the magnitude of this risk across different patient populations.1,2

A systematic review and meta-analysis published in BMJ Sex Reprod Health evaluated the safety of continuous or extended-cycle COCs compared with conventional cyclic regimens.1 This comprehensive analysis included a broad range of studies, aiming to clarify the safety profile for women using COCs for contraception. Another nationwide nested case-control study, published in BMJ, specifically examined contemporary MHT and thrombotic disease, drawing on extensive population data to provide robust real-world evidence.2

The persistent VTE signal

Oral combined oral contraceptives (COCs) increase the risk of venous thromboembolism, a well-established fact that continues to be reinforced by current evidence. The meta-analysis of COCs found that while continuous or extended-cycle regimens offer similar contraceptive effectiveness to conventional cyclic regimens, the VTE risk remains a significant consideration for patient safety. This risk is inherent to the oral route of administration and the systemic estrogen exposure it entails.1

For women using contemporary oral menopausal hormone therapy, the VTE risk is also substantial. A nationwide nested case-control study in Denmark, involving 1,008,189 women aged 50-70, identified 12,149 VTE cases and 121,490 controls.2 The study found that current oral MHT use increased the risk of VTE by 60% (HR 1.60; 95% CI, 1.48-1.72)

compared to non-users. This elevation in risk was consistent across various estrogen types and progestin combinations, indicating a class effect for oral administration.2

The study further detailed that the VTE risk was highest during the first year of oral MHT use, showing an adjusted hazard ratio of 1.86 (95% CI, 1.66-2.09). This initial heightened risk suggests that the thrombogenic effects are most pronounced upon initiation of therapy. But, the risk remained elevated even with longer-term use, diminishing only slightly after the first year.2 Clinicians should counsel patients about this early risk, particularly when starting MHT. For a deeper dive into managing complex obstetric conditions, clinicians might consult resources on obstetric antiphospholipid syndrome, where thrombotic risk is also a central concern.

Transdermal MHT, however, presented a different picture. The Danish study found no statistically significant increase in VTE risk with transdermal MHT (HR 1.05; 95% CI, 0.94-1.17). This distinction between oral and transdermal routes is important for clinical decision-making, as it points to the first-pass hepatic metabolism of oral estrogen as a key driver of thrombotic potential.2 The Oxford Handbook of Clinical Medicine (11th ed) offers a concise reference for navigating such treatment considerations in general practice.

What the evidence does not establish

While the evidence for increased VTE risk with oral hormone therapy is clear, the specific mechanisms driving this risk are not fully elucidated by these studies. The meta-analysis on COCs focused on effectiveness, safety, and acceptability, but did not examine the precise biological pathways that lead to thrombosis.1 Similarly, the Danish study, while robust in its population-level data, is an observational study and cannot definitively establish causality, though the association is strong and consistent with known pharmacology.2

The studies also do not provide granular data on individual patient risk factors beyond broad demographic categories. For example, while the Danish study adjusted for factors like age and comorbidities, it did not fully explore the relationship of genetic predispositions to thrombosis with oral MHT use. This gap matters, as some women may have an inherently higher baseline risk that is further exacerbated by oral hormones.2 The Cochrane review on long-term hormone therapy for perimenopausal and postmenopausal women, while broad, also highlights the need for more detailed safety data across diverse populations.3

The long-term implications of continuous or extended-cycle COCs on cardiovascular health beyond VTE were not the primary focus of the meta-analysis.1 This means clinicians still need to consider the broader cardiovascular profile of patients, especially those with existing risk factors, when prescribing these regimens. For women experiencing postpartum haemorrhage, understanding the immediate and long-term risks of various interventions is critical, as discussed in our coverage on tranexamic acid in postpartum haemorrhage.

The studies also do not definitively guide the optimal duration of oral MHT for minimizing VTE risk while maximizing symptom relief. The Danish study showed a higher risk in the first year, but an elevated risk persisted.2 This leaves clinicians to balance symptom control against a sustained, albeit slightly lower, thrombotic risk in longer-term users. The decision to continue oral MHT beyond the initial symptomatic period requires a careful, individualized risk-benefit assessment.

Clinical implications for prescribing

The evidence is clear: oral hormone therapy, whether for contraception or menopause, carries a definite risk of venous thromboembolism. For combined oral contraceptives, clinicians must continue to screen for VTE risk factors meticulously before initiation. The choice between continuous and cyclic regimens does not mitigate this fundamental risk, as the systemic exposure to estrogen remains.1

For menopausal hormone therapy, the distinction between oral and transdermal routes is paramount. The Danish study provides compelling evidence that transdermal MHT does not significantly increase VTE risk, unlike its oral counterpart.2 This should prompt clinicians to favor transdermal estrogen for women with existing VTE risk factors or those who express concern about thrombosis. It is a straightforward way to reduce a known hazard without sacrificing symptom control.

The heightened VTE risk during the first year of oral MHT use demands particular attention. Clinicians should counsel patients thoroughly about this initial period of increased vulnerability and ensure they understand the symptoms of VTE. Regular reassessment of VTE risk factors should be standard practice for all women on oral MHT, especially as comorbidities or lifestyle factors change over time. The ongoing debate around one-step versus two-step screening in other obstetric contexts underscores the importance of clear, evidence-based protocols.

CLINICAL IMPLICATIONS

The persistent VTE risk associated with oral hormone therapy, particularly oral menopausal hormone therapy, is not a new revelation, but these recent analyses reinforce its clinical significance. It is a reminder that while formulations evolve, the fundamental pharmacology of oral estrogen's first-pass hepatic effect on coagulation factors remains. Clinicians should not assume that newer oral MHTs are inherently safer regarding thrombosis; the data simply do not support that. The Danish study, with its large population, provides a clear signal that the oral route itself is the primary driver of VTE risk.2

This means a pragmatic shift in prescribing habits is warranted. For women requiring MHT, transdermal estrogen should be the default choice where VTE risk is a concern, given its demonstrated lack of significant thrombotic risk. Oral MHT should be reserved for those without VTE risk factors or where transdermal options are unsuitable, and even then, with clear patient counseling on the initial heightened risk. It is a simple, evidence-based adjustment that can meaningfully impact patient safety.

The implications extend beyond MHT to combined oral contraceptives. While the meta-analysis confirmed their effectiveness, the VTE risk remains.1 This necessitates a rigorous pre-screening process for all women considering COCs, ensuring that individual risk factors are thoroughly assessed. We must move beyond a one-size-fits-all approach to hormonal contraception and menopausal management, tailoring therapy to each woman's unique thrombotic profile.

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