Does the Progestogen Used in Combined Hormonal Contraception Affect Venous Thrombosis Risk?

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KEYWORDS

• Progestin • Progestogen • Venous thromboembolism • Oral contraceptive
• Drospirenone

KEY POINTS

- All combined oral contraceptive pills carry a small, but increased risk for venous thromboembolism (VTE).
- Existing studies rely on observational data to estimate the risk for VTE of different progestogen subtypes.
- These studies vary in their ability to account for preexisting risk factors, confounders, and cohort-related effects.
- Despite heterogeneity in study results regarding the safety of different progestogens, the risk of VTE overall with combined oral contraceptives remains very low compared with pregnancy.
- The decision to prescribe a pill should be based on the unique risk factors and medical history of the individual woman.

INTRODUCTION

Almost 60 years after the pill first became available for contraception, more than a quarter of US women choose combined hormonal contraception (CHC) for birth control.[1] Over the years, the pill has undergone substantial modifications in chemistry, formulations, and dosing regimens, and transdermal patches and vaginal rings have been introduced. As a result, there is now a variety of combined hormonal methods to choose from. These different formulations contain both objectively demonstrated and theoretic differences in side effects and noncontraceptive benefits. Despite the

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options, the basic formula for CHC remains the same: an estrogen coupled with a synthetic progestogen. Consequently, the most important risk of CHC has also remained the same: venous thromboembolism (VTE).

VTE is a life-threatening condition. Two-thirds manifest as deep vein thrombosis (DVT), whereas another third present as pulmonary embolism (PE). Mortality and morbidity for these conditions are serious.[2] Studies estimate that 20% to 25% of all PE cases present as sudden death.[3] Moreover, recurrent thromboembolism, chronic venous insufficiency, and pulmonary hypertension are important nonfatal sequelae of these diseases.[4] Even in the most benign scenarios of simple, detected VTE, treatment requires a course of anticoagulation therapy that affects patient quality of life and confers risk from adverse bleeding scenarios.[5]

VTE was recognized almost immediately as a serious risk of combined oral contraceptive (COC) use. Once estrogen was identified as the culpable hormone, pharmaceutical companies scaled back the estrogen dose from what now seems like a massive load of 150 μg of mestranol per pill to modern levels of 10 to 35 μg of ethinyl estradiol (EE). As predicted, reducing estrogen doses decreased VTE risks without sacrificing efficacy. Clinicians now accept that the risk of VTE is about 2-fold higher in COC users on a background rate of about 5 to 10 per 10,000 woman-years in healthy nonpregnant women.[6] CHCs also increase the risk of arterial thromboembolism (ATE).[7] Although ATE events such as myocardial infarction (MI) and stroke are extremely rare in reproductive-aged women, the consequences are severe. However, in healthy, nonsmoking women, less than 35 years old, using low-dose (eg, <50 μg of EE) pills, the increase in risk is negligible.[8,9] Furthermore, although age, smoking, hypertension, and to a lesser extent migraine headache with aura have been reported to modify the risk of ATE[8] associated with CHC use, the type of progestogen in a formulation has not been implicated as an additional risk factor.[7] In contrast, considerable scientific debate continues regarding whether the type of progestogen used in a combined method modifies VTE risk.[10]

Because all but the most recently introduced COCs use the same synthetic estrogen, EE, the progestogen used differentiates most formulations. New progestogens were developed to address side effects related to androgenic properties of the 19-nortestosterone derivative progestogens norethindrone and levonorgestrel (LNG). This steady evolution of less androgenic progestogens led to grouping formulations into generations so that pills of similar characteristics could be discussed together. Although this classification system does not provide a true representation of structural chemistry, a body of literature had adopted the convention. However, regulatory approval of these new formulations as contraceptives did not require proof of additional health benefit or tolerability compared with existing low-dose formulations. Therefore, controversy developed because these newer progestogens were linked to an increased risk of VTE in some epidemiologic studies.[11–15]

For more than 2 decades, this controversy has persisted. Because VTE is an uncommon to rare event, phase 3 premarketing studies are underpowered to evaluate these outcomes, and are typically not conducted using an active comparator. Although case-control and database studies can provide useful insights on rare events, inherent limitations of these designs prevent ascertainment of key confounders.[10] This article examines the complex problems that obscure this debate, and highlight the merits and shortcomings of the most important and recent research contributions.

TYPES OF PROGESTOGENS

In addition to androgenicity, progestogens differ in several significant ways, including bioavailability, potency, and metabolism.[16] Individual variation in metabolism may