Does taking an NSAID while on hormonal contraception increase VTE risk?

It could (although the absolute risk is modest), depending on the risk category of the hormonal contraception and the particular NSAID used. Authors of a cohort study in Denmark used national registries to follow more than 2 million women for a median of 10 years to examine the effect of concomitant use of hormonal contraception and NSAIDs on the risk of venous thromboembolism (VTE). A total of 8,710 VTEs were diagnosed. Incidence rate ratios of VTE among women with concomitant use of NSAIDs and hormonal contraception were 50.6 (95% CI, 44.2–57.8) with use of high-risk hormonal contraceptives and 5.7 (95% CI, 3.3–10.1) with use of low-risk hormonal contraceptives. The absolute risk of VTE among women who used NSAIDs with high-risk hormonal contraceptives was modest at 2/10,000.

FAST TRACK

Using national databases, investigators in Denmark conducted a cohort study to assess the impact that independent as well as concomitant use of NSAIDs and combination hormonal contraceptives have on VTE risk

Meaidi A, Mascolo A, Sessa M, et al. Venous thromboembolism with use of hormonal contraception and non-steroidal anti-inflammatory drugs: nationwide cohort study. BMJ. 2023;382:e074450. doi:10.1136/bmj-2022-074450

EXPERT COMMENTARY

Andrew M. Kaunitz, MD, MSCP, is Tenured Professor and Associate Chair, Department of Obstetrics and Gynecology, University of Florida College of Medicine–Jacksonville, and Medical Director and Director of Menopause and Gynecologic Ultrasound Services, UF Health Women's Specialist Services–Emerson. He serves on the OBG MANAGEMENT Board of Editors.

The author reports that the University of Florida receives research funding from Bayer, Merck, Mithra, and Mylan.

doi: 10.12788/obgm.0317

Combination (estrogen plus progestin) hormonal contraceptives as well as non–aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of VTE events, including lower extremity clots and pulmonary embolism. Taking contraceptives formulated with ethinyl estradiol increases hepatic production of clotting factors on a dose-related basis. Newer progestins, including desogestrel and drospirenone, also may contribute to an elevated VTE risk, although this association is controversial.[1] NSAIDs promote platelet aggregation, thereby activating the clotting system and formation of clots. Although studies that assessed the association between NSAID use and thrombosis have focused on arterial

FAST TRACK

Hormonal contraception was classified into 3 VTE risk categories: high, medium, and low/no risk

clots, a substantial literature suggests that NSAIDs, including older NSAIDs (such as ibuprofen, diclofenac, and naproxen), also increase VTE risk.[2]

Although combination contraceptives (oral contraceptives, patches, vaginal rings) and NSAIDs are both commonly used by reproductive-age women, little data have assessed the impact of concomitant use of these medications on VTE risk. Accordingly, investigators in Denmark, using national databases, conducted a retrospective cohort study to assess the impact that independent as well as concomitant use of these medications have on VTE risk.

Details of the study

Meaidi and colleagues included in the cohort reproductive-age women living in Denmark between 1996 and 2017 with no history of thrombosis, thrombophilia, cancer, tubal sterilization, hysterectomy, bilateral oophorectomy, or infertility treatment. National prescription data were used to assess exposure to hormonal contraception.

The investigators classified hormonal contraception into 3 VTE risk categories:

1. high risk—estrogen-progestin patches and vaginal rings; oral contraceptives containing 50 µg of ethinyl estradiol; or the progestins desogestrel, drospirenone, gestodene, or cyproterone (with the latter 2 progestins not available in the United States)
2. medium risk—all other combination oral contraceptives, including those formulated with the progestins norethindrone, norethindrone acetate, norgestrel, and levonorgestrel, as well as depot medroxyprogesterone acetate
3. low/no risk—progestin-only pills, implants, and progestin-containing intrauterine devices (IUDs).

Because in Denmark NSAIDs are prescribed as a single package containing no more than 30 tablets, time exposed to non–aspirin NSAIDs was assumed to last 1 week from the prescription date.

The authors considered first-time diagnoses of lower limb venous thrombosis or pulmonary embolism that were made in hospitals to represent VTE. They also constructed a subgroup of VTE patients in whom the diagnosis was either confirmed with imaging or followed by prescription of an anticoagulant.

To address potential confounding, the authors adjusted their analysis based on age, calendar year, educational attainment, occurrence of pregnancy, surgery, hypertension, diabetes, polycystic ovary syndrome, endometriosis, migraine, systemic connective tissue diseases, inflammatory polyarthropathies, and use of tranexamic acid (a medication that may increase VTE risk). They also censored (temporarily excluded women from analysis) episodes

CONTINUED ON PAGE 14

PHOTOS: RUMAX; ZUURBIERO; MEDSTOCKPHOTOS/SHUTTERSTOCK

CONTINUED FROM PAGE 10

WHAT THIS EVIDENCE MEANS FOR PRACTICE

It is important for clinicians and our patients to recognize that pregnancy—the condition prevented by hormonal contraception—is associated with far higher risks of VTE (10–14 VTE events per 10,000 deliveries) than the use of any modern hormonal contraceptive.[5] Although concomitant use of combination contraceptives and NSAIDs increases VTE risk, the absolute risk is modest, particularly when the NSAID is ibuprofen or naproxen (these are the non–aspirin NSAIDs most commonly used in the United States[6]). Women who regularly take NSAIDs can minimize VTE risk by choosing hormonal contraceptives with little or no impact on the risk of VTE: the progestin implant, progestin IUDs, and progestin-only pills.

ANDREW M. KAUNITZ, MD, MSCP

associated with a transiently elevated risk of VTE: pregnancy and 6 months following delivery, 12 weeks after other pregnancy terminations, 8 weeks following any surgery involving hospital admission, and 8 weeks following prescription of tranexamic acid.

FAST TRACK

Even among women who used NSAIDs concomitantly with high-risk combination hormonal contraceptives, the absolute risk of VTE was 2/10,000

VTEs associated with risk category of hormonal contraception used

Results. The overall cohort included more than 2 million women who were followed for a median of 10 years. During 21.0 million person-years, 8,710 VTE events were diagnosed; almost one-third of these were pulmonary embolisms, with the remainder diagnosed as lower extremity VTE. Of these 8,710 women diagnosed with VTE, 7,043 (81%) were confirmed with either diagnostic imaging or prescription of an anticoagulant. Unfortunately, 228 women (2.6%) died within 30 days of the diagnosis of VTE.

The investigators identified concomitant use of hormonal contraception and NSAIDs in more than 500,000 women. Among women with such concomitant use, 58% were using contraceptives that were high risk while 23% used medium-risk and 19% used low/no-risk contraceptives. Ibuprofen (60%) was the most commonly used NSAID, followed by diclofenac (20%) and naproxen (6%). Between 97% and 98% of high-risk and medium-risk contraceptives were combination pills; 89% of low/no-risk contraceptives were progestin IUDs.

Compared with nonuse of both hormonal contraceptives and NSAIDs, incidence rate ratios of VTE adjusted for age, calendar year, and education were 8.1 (95% confidence interval [CI], 6.9–9.6) for use of NSAIDs only, 4.2 (95% CI, 4.0–4.4) for use of high-risk contraceptives only, 3.0 (95% CI, 2.8–3.2) for medium-risk contraceptive use, and 1.1 (95% CI, 1.0–1.3) for use of low/no-risk hormonal contraception. Risk of VTE was approximately twice as high with the use of diclofenac only compared with the risks associated with ibuprofen or naproxen use only.

With respect to concomitant use of NSAIDs and hormonal contraception, incidence rate ratios of VTE were 50.6 (95% CI, 44.2–57.8), 26.1 (95% CI, 19.6–34.7), and 5.7 (95% CI, 3.3–10.1), respectively, with use of high-risk, medium-risk, and low/no-risk hormonal contraceptives. Adjusting for time updated information on occurrences of migraine, connective tissue disorder, inflammatory polyarthropathies, endometriosis, polycystic ovary syndrome, hypertension, and diabetes did not materially affect these associations.

When analysis was limited to women without these occurring conditions, rate ratios were somewhat higher (5.7 and 4.1) for use of high-risk and medium-risk contraceptives only. Incidence rate ratios in this subcohort of healthier women were substantially higher for NSAID use only (15.0), and 111.7, 43.2, and 13.0, respectively, for concomitant use of NSAIDs with high-risk, medium-risk, and low/no-risk contraceptives. In this analysis of healthier women, diclofenac continued to be associated with substantially higher risks of VTE than ibuprofen or naproxen. When the stricter definition of VTE (confirmed cases) was used, adjusted rate ratios remained similar.

Absolute risks of VTE

Although some of the elevated rate ratios noted in this study might appear alarming, it is important to keep in mind that the baseline incidence of VTE in healthy

reproductive-age women is low. Accordingly, as the authors pointed out, even among women who used NSAIDs concomitantly with high-risk combination hormonal contraceptives, the *absolute* risk of VTE was 2/10,000.

Study strengths and limitations

Strengths of this analysis by Meaidi and colleagues include the use of large, essentially all-inclusive national registries. In addition, nationwide Danish registry data that indicate a diagnosis of VTE have been found to have a high positive predictive value.[3] Another strength is the large number of potentially confounding factors that the authors controlled for.

One potential limitation of their analysis is that the use of only prescribed NSAIDs was considered. Fortunately, however, the prevalence of over-the-counter ibuprofen use in Denmark is not high enough to materially affect the authors' findings.[4] Another potential limitation was that information on smoking and body mass index was not available for most of the women included in the study cohort. The authors countered this limitation by pointing out that, in Denmark, smoking and obesity are highly correlated with educational status, and that all analyses were adjusted for educational status. ●

References

1. Reid RL. Oral hormonal contraception and venous thromboembolism (VTE). *Contraception*. 2014;89:235-236. doi:10.1016/j.contraception.2014.02.002
2. Ungprasert P, Srivali N, Wijarnpreecha K, et al. Non-steroidal anti-inflammatory drugs and risk of venous thromboembolism: a systematic review and meta-analysis. *Rheumatology* (*Oxford*). 2015;54:736-742. doi:10.1093/rheumatology/keu408
3. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6:e012832. doi:10.1136/bmjopen-2016-012832
4. Gaster N, Hallas J, Pottegård A, et al. The validity of Danish prescription data to measure use of aspirin and other non-steroidal anti-inflammatory drugs and quantification of bias due to non-prescription drug use. *Clin Epidemiol*. 2021;13:569-579. doi:10.2147/CLEP.S311450
5. Maughan BC, Marin M, Han J, et al. Venous thromboembolism during pregnancy and the postpartum period: risk factors, diagnostic testing, and treatment. *Obstet Gynecol Surv*. 2022;77:433-444. doi:10.1097/OGX.0000000000001043
6. Chu A. Ibuprofen, naproxen, and more: the 8 most common NSAIDs. GoodRx. July 20, 2023. Accessed October 4, 2023. https://www.goodrx.com/classes/nsaids/nsaid-list