Yee Lam, MD, PhD; Catherine Coe, MD; Anne Mounsey, MD
University of North Carolina School of Medicine, Department of Family Medicine, Chapel Hill

DEPUTY EDITOR
Shailendra Prasad, MBBS, MPH
University of Minnesota, Department of Family Medicine and Community Health, St. Cloud

Which combined OC to prescribe with CV safety in mind?

With various formulations available, which combined OC should you recommend to minimize not only the risk of PE, but also the risk of stroke and MI?

PRACTICE CHANGER

When prescribing combined oral contraceptives, choose one containing levonorgestrel and low-dose estrogen (20 mcg) to minimize the risks of pulmonary embolism, ischemic stroke, and myocardial infarction.

STRENGTH OF RECOMMENDATION

B: Based on a good quality, patient-oriented cohort study.

Weill A, Dalichampt M, Raguideau F, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. *BMJ*. 2016;353:i2002.[1]

ILLUSTRATIVE CASE

A 28-year-old woman presents to your office for a routine health maintenance examination. She is currently using an oral contraceptive containing desogestrel and ethinyl estradiol for contraception and is inquiring about a refill for the coming year. What would you recommend?

When choosing a combined oral contraceptive (COC) for a patient, physicians often have "go-to" favorites—tried and true agents that are easy to prescribe on a busy clinic day. However, some of these may be placing patients at increased risk for venous thromboembolic events.

In general, when compared with nonusers, women who use COCs have a 2- to 4-fold increase in risk of venous thromboembolism (VTE) and an increased risk of myocardial infarction (MI) and stroke.[2,3] More specifically, higher doses of estrogen combined with the progesterones gestodene, desogestrel, and levonorgestrel, are associated with a higher risk of VTE.[2-6]

In 2012, the European Medicines Agency warned that COCs containing drospirenone were associated with a higher risk of VTE than other preparations, despite similar estrogen content.[7] The US Food and Drug Administration (FDA) produced a similar statement that same year, recommending that physicians carefully consider the risks and benefits before prescribing contraceptives containing drospirenone.[8]

The risks of ischemic stroke and MI have not been clearly established for varying doses of estrogen and different progesterones. This large observational study fills that informational gap by providing risk estimates for the various COC options.

STUDY SUMMARY

One combined oral contraceptive comes out ahead

The authors used an observational cohort model to determine the effects of different doses of estrogen combined with different progesterones in COCs on the risks of pulmonary embolism (PE), ischemic stroke, and MI.[1] Data were collected from the French national health insurance database and the French national hospital discharge database.[9,10] The study included just under 5 million women

15 to 49 years of age, living in France, with at least one prescription filled for COCs between July 2010 and September 2012.

The investigators calculated the absolute and relative risks of first PE, ischemic stroke, and MI in women using COC formulations containing either low-dose estrogen (20 mcg) or high-dose estrogen (30-40 mcg) combined with one of 5 progesterones (norethisterone, norgestrel, levonorgestrel, desogestrel, gestodene). The relative risk (RR) was adjusted for confounding factors, including age, complimentary universal health insurance, socioeconomic status, hypertension, diabetes, and consultation with a gynecologist in the previous year.

The absolute risk per 100,000 woman-years for all COC use was 33 for PE, 19 for ischemic stroke, and 7 for MI with a composite risk of 60. The RRs for low-dose estrogen vs high-dose estrogen were 0.75 (95% confidence interval [CI], 0.67-0.85) for PE, 0.82 (95% CI, 0.7-0.96) for ischemic stroke, and 0.56 (95% CI, 0.39-0.79) for MI. The absolute risk reduction (ARR) with low-dose estrogen vs high-dose estrogen was 14/100,000 person-years of use; the number needed to harm (NNH) was 7143.

Compared with levonorgestrel, desogestrel and gestodene were associated with higher RRs of PE but not arterial events (2.16; 95% CI, 1.93-2.41 for desogestrel and 1.63; 95% CI, 1.34-1.97 for gestodene). The ARR with levonorgestrel use as opposed to desogestrel for PE was 19/100,000 person-years of use (NNH=5263); the ARR with levonorgestrel use as opposed to gestodene was 12/100,000 person-years of use (NNH=8333). The authors concluded that for the same progesterone, using a lower dose of estrogen decreases risk of PE, ischemic stroke, and MI, and that oral contraceptives containing levonorgestrel and low-dose estrogen resulted in the lowest overall risks of PE and arterial thromboembolism.

WHAT'S NEW?

Low-dose estrogen and levonorgestrel confer lowest risk of 3 CV conditions

Prior studies have shown that COCs increase the risk of PE and may also increase the risks of ischemic stroke and MI.[3,11] Studies have also suggested that a higher dose of estrogen in COCs is associated with an increased risk of VTE.[11,12] This study shows that 20 mcg of estrogen combined with levonorgestrel is associated with the lowest risks of PE, MI, and ischemic stroke.

CAVEATS

A cohort study, no contraceptive start date, and incomplete tobacco use data

This is an observational cohort study, so it is subject to confounding factors and biases. It does, however, include a very large population, which improves validity. The study did not account for COC start date, which may be confounding because the risk of VTE is highest in the first 3 months to one year of COC use.[12] Data on tobacco use, a significant independent risk factor for arterial but not VTE, was incomplete, but in other studies has only marginally affected outcomes.[3,13]

CHALLENGES TO IMPLEMENTATION

Low-dose estrogen is associated with increased vaginal spotting

One potential challenge to implementing this practice changer may be the increased rate of vaginal spotting associated with low-dose estrogen. COCs containing 20 mcg of estrogen are associated with spotting in approximately two-thirds of menstrual cycles over the course of a year.[14] That said, women may prefer to endure the spotting in light of the improved safety profile of a lower-dose estrogen pill. JFP

ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center For Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

References

1. Weill A, Dalichampt M, Raguideau F, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. *BMJ*. 2016;353:i2002.
2. Lidegaard Ø, Løkkegaard E, Svendsen AL, et al. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ*. 2009;339:b2890.

CONTINUED

Oral contraceptives containing levonorgestrel and low-dose estrogen resulted in the lowest overall risks of PE and arterial thromboembolism.

3. Lidegaard Ø, Løkkegaard E, Jensen A, et al. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med.* 2012;366:2257-2266.
4. Stegeman BH, de Bastos M, Rosendaal FR, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. *BMJ.* 2013;347:f5298.
5. US Food and Drug Administration. Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints. Available at: https://www.fda.gov/downloads/drugs/drugsafety/ucm277384. Accessed February 23, 2017.
6. Seeger JD, Loughlin J, Eng PM, et al. Risk of thromboembolism in women taking ethinyl estradiol/drospirenone and other oral contraceptives. *Obstet Gynecol.* 2007;110:587-593.
7. European Medicines Agency. PhVWP Monthly report on safety concerns, guidelines and general matters. 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/01/WC500121387.pdf. Accessed February 23, 2017.
8. US Food and Drug Administration. FDA Drug Safety Communication: Updated information about the risk of blood clots in women taking birth control pills containing drospirenone. 2012. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm299305.htm. Accessed February 23, 2017.
9. Tuppin P, de Roquefeuil L, Weill A, et al. French national health insurance information system and the permanent beneficiaries sample. *Rev Epidemiol Sante Publique.* 2010;58:286-290.
10. Moulis G, Lapeyre-Mestre M, Palmaro A, et al. French health insurance databases: what interest for medical research? *Rev Med Interne.* 2015;36:411-417.
11. Farmer RD, Lawrenson RA, Thompson CR, et al. Population-based study of risk of venous thromboembolism associated with various oral contraceptives. *Lancet.* 1997;349:83-88.
12. Lidegaard Ø, Nielsen LH, Skovlund CW, et al. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. *BMJ.* 2011;343:d6423.
13. Zhang G, Xu X, Su W, et al. Smoking and risk of venous thromboembolism: a systematic review. *Southeast Asian J Trop Med Public Health.* 2014;45:736-745.
14. Akerlund M, Røde A, Westergaard J. Comparative profiles of reliability, cycle control and side effects of two oral contraceptive formulations containing 150 micrograms desogestrel and either 30 micrograms or 20 micrograms ethinyl oestradiol. *Br J Obstet Gynaecol.* 1993;100:832-838.