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Priority Updates from the Research Literature from the Family Physicians Inquiries Network

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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

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