A 28-year-old woman presents to your office for a routine health maintenance exam. 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, clinicians often have tried-and-true favorites. However, some of them may be placing patients at increased risk for venous thromboembolic events.

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

In 2012, the European Medicines Agency warned that COCs containing drospirenone were associated with a higher risk for VTE than other preparations, despite similar estrogen content. The FDA produced a similar statement that same year, recommending that providers carefully consider the risks and benefits before prescribing contraceptives containing drospirenone.

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

STUDY SUMMARY
One COC comes out ahead
The authors used an observational cohort model to determine the effects of different doses of estrogen combined with different progestogens in COCs on the risks for pulmonary embolism (PE), ischemic stroke, and MI. Data were collected from the French national health insurance database and the French national hospital discharge database. The study included nearly 5 million women ages 15 to 49, living in France, who had at least one prescription filled for COCs between July 2010 and September 2012.

The investigators calculated the absolute and relative risks for first PE, ischemic stroke, and MI in women using COC formulations containing either low-dose estrogen (20 µg) or high-dose estrogen (30-40 µg) combined with one of five progestogens (norethisterone, norgestrel, norgestimate, desogestrel, and levonorgestrel).
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 for PE, 0.82 for ischemic stroke, and 0.56 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 7,143.

Compared with levonorgestrel, desogestrel and gestodene were associated with higher RRs for PE but not arterial events (2.16 for desogestrel and 1.63 for gestodene). For PE, the ARR with levonorgestrel compared to desogestrel and gestodene, respectively, was 19/100,000 and 12/100,000 person-years of use (NNH, 5,263 and 8,333, respectively). The authors concluded that for the same progesterone, using a lower dose of estrogen decreases risk for PE, ischemic stroke, and MI, and that oral contraceptives containing levonorgestrel and low-dose estrogen resulted in the lowest overall risks for PE and arterial thromboembolism.

WHAT’S NEW?

Low-dose estrogen + levonorgestrel confer lowest risk

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

CAVEATS

Cohort study, no start date, 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 for VTE is highest in the first three months to one year of COC use. Data on tobacco use, a significant independent risk factor for arterial but not venous thromboembolism, was incomplete; however, in other studies, it has only marginally affected outcomes.

CHALLENGES TO IMPLEMENTATION

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 µg of estrogen are associated with spotting in approximately two-thirds of menstrual cycles over the course of a year. That said, women may prefer to endure the spotting in light of the improved safety profile of a lower-dose estrogen pill.

REFERENCES


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