Hormonal contraception and thrombosis

Regine Sitruk-Ware, M.D.

Population Council, Center for Biomedical Research, New York, New York

The safety of combined hormonal contraceptives (CHCs) has been documented by years of follow-up, and the occurrence of venous thromboembolism (VTE) possibly related to their use is rare in the young population exposed to these agents. The balance between the benefits and risks of contraceptive steroids is generally positive, in particular when compared with pregnancy's risks. Epidemiological studies led to different results showing either no difference in VTE risk between CHCs (active surveillance prospective studies) or an increase in risk (observational or database studies). The discrepancy may be explained by different study designs and the fact that important risk factors such as overweight, family history of thrombosis, and smoking were not adjusted for in some observational studies. To improve the safety of CHC, modifying the estrogen dose and type, selecting newer progestins, and alternative routes of delivery were implemented. Ethinyl- E_2 (EE) exerts a stronger effect than E_2 on estrogen-dependent markers such as liver proteins and coagulation factors. To circumvent the metabolic changes induced by EE, more natural compounds such as E_2 and E_2 valerate (E_2V) were developed, as well as new progestins structurally closer to P. Progestins when given alone do not increase VTE risk, and their risks and benefits depend upon their chemical structure, the type and dose of combined estrogen, and the delivery route. The lower impact of E_2-based CHCs on metabolic markers may result in an improved safety profile. A recent study on clinical outcomes supports this hypothesis. In conclusion, CHCs remain a safe and effective choice to prevent unwanted pregnancy, and the risk of VTE is in general low. Careful consideration of individual risk factors should be given before prescribing to avoid cumulative risks and minimize the occurrence of unwanted events. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

Key Words: Estrogen, progestin, venous thromboembolism, risk factors, hormonal contraception

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Oral contraceptives (OCs), which contain either a combination of an estrogen and progestin or only progestin, offer safe, effective, and reversible fertility regulation. Since the approval of the first steroidal OC pill in the 1960s, this method has been the most commonly prescribed family planning method (1).

Concerns over its adverse cardiovascular (CV) effects led to modifications of the composition of OCs with the goal of decreasing the risk of venous thromboembolism (VTE) and CV events, which, although rare in the young population exposed to these agents, had raised public health concern (2).

EPIDEMIOLOGICAL STUDIES ON CHC AND VTE RISK

VTE is a rare event in women of reproductive age, and its incidence increases with age (2). An increased risk has been demonstrated in users of combined hormonal contraceptives (CHCs) containing ethinyl-estradiol (EE) and different progestins, as reviewed in recent studies and meta-analyses (3–7). Although the risk is increased approximately by 4-fold as compared with nonusers, the absolute risk is low (about 7/10,000 women-years) and lower than the risk associated with pregnancy (8). The overall incidence of pregnancy-associated VTE is about 20 per 10,000 women-years (8).

The dose of EE used with high-dose OC pills was first implicated as the cause, leading to its reduction in current formulations. In a recent large cohort study of five million French women, Weill et al. (9) showed that, for the same type of progestin, an estrogen dose of 20 μg versus 30–40 μg was associated with lower risks of pulmonary embolism, ischemic stroke, and myocardial infarction, justifying the recommendation for lower EE content of CHCs.

The type of progestin associated with EE, either less androgenic or antiandrogenic, has recently been suggested as a second factor possibly related to an increased incidence of VTEs (3, 10, 11). These findings are still controversial, since data from prospective active surveillance studies, which have certain advantages over database studies, showed no difference in the incidence of VTE between different CHCs (12, 13).

One of the still active controversies relates to the possible increase in

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Reprint requests: Dr. Regine Sitruk-Ware, M.D., Population Council, Center for Biomedical Research, 1230 York Avenue, New York, New York 10065 (E-mail: regine@popcbr.rockefeller.edu).

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thrombosis risk in women using OC combinations of EE and the antiandrogenic progestin, drospirenone (DRSP) (14–17). Several studies of different design led to different results showing either no difference in risk as compared to second generation pills containing the progestin levonorgestrel (LNG; active surveillance prospective studies) (13, 14) or an increased risk (observational or database studies) (3,16–18).

OBSERVATIONAL STUDIES

Large studies comparing users of oral or nonoral contraceptives to nonusers or to users of LNG-containing OCs have been published in the last decade (16–18).

The largest study was commissioned by the Food and Drug Administration Office of Surveillance and Epidemiology to assess CV outcomes for recently marketed CHCs, including the DRSP/EE oral tablet, norelgestromin/EE transdermal patch (NGMN), and etonogestrel/EE vaginal ring (ETN) (18). This was a retrospective cohort study using data from four geographically diverse health plans, which included 835,826 women with 898,251 person-years of CHC use, designed to evaluate the risk of thrombotic and thromboembolic events. In adjusted analyses, CHCs combining EE with DRSP, NGMN, or ETN were associated with a significantly higher risk of VTE relative to standard CHC comparators (Table 1).

In another large cohort study conducted in Denmark (17), 5,287 first venous thrombosis events were recorded, of which 3,434 were confirmed. In nonusers of hormonal contraception, the incidence rate of confirmed events was 2.1 per 10,000 woman-years. Compared with nonusers of hormonal contraception, and after adjustment for age, calendar year, and education, the relative risk (RR) of confirmed venous thrombosis in users of transdermal combined contraceptive patches was higher than for nonusers (RR, 7.9; 95% confidence interval [CI], 3.5–17.7) or users of EE+LNG combinations (RR, 2.3; 95% CI, 1.0–5.2).

Lidegaard et al. (17) indicated also higher risks for use of EE/ETN vaginal rings with an RR of 6.5 (95% CI, 4.7–8.9) as compared with nonuse of hormonal contraception. However, the authors clearly state that the results were not controlled for family history of VTE or for body mass index (BMI).

Progestin-only methods did not show any significant increase in VTE risk. The RR was increased in women who used SC implants, but the difference was not statistically significant and not increased in those who used the LNG intrauterine system (0.6; 95% CI, 0.4–0.8).

PROSPECTIVE STUDIES

Dinger et al. (12) used a prospective cohort design that enrolled a population representative of usual OC users and measured validated outcomes. An independent data safety and monitoring board blinded to product used provided oversight of the protocol outcomes. They found that DRSP-containing combined OCs are associated with similar risks of venous and arterial thromboembolism, fatal outcomes, cancer, severe depression, and other serious adverse events compared with OCs without DRSP and with LNG (12, 13).

In another prospective study from the same authors, including 33,295 users of the EE/ETN vaginal ring or of combined OCs, no difference in venous or arterial risk was found between the vaginal ring delivering EE and ETN and other CHCs (19) (Table 1).

HOW TO EXPLAIN THE DISCREPANCIES—CUMULATIVE EFFECT OF RISK FACTORS

Among the known risk factors for thrombosis, overweight, family history of thrombosis, and smoking are prominent independent factors, besides the existence of thrombophilia, which increases considerably the risk (8, 20).

Pomp et al. (20) in the Multiple Environmental and Genetic Assessment study of risk factors for venous thrombosis conducted in the Netherlands showed that height, weight, and obesity are independent risk factors of venous thrombosis and that the risk of VTE occurrence is further enhanced in obese women using OCs (Table 2). The risk of venous thrombosis

TABLE 1

Venous thromboembolism risk in combined hormonal contraceptive users according to the route of administration and type of progestin associated with ethinyl- E_2.

Author (Ref.)	DRSP + EE (oral)	NGMN + EE (transdermal patch)	ETN + EE (vaginal ring)
FDA-CDC cohort 2012 (18)			
RR of VTE	1.74	1.55	1.56
95% CI	1.42–2.14	1.17–2.07	1.02–2.37
Lidegaard cohort 2012 (17)			
RR vs. non-use		7.9	6.5
95% CI		3.5–17.7	4.7–8.9
RR vs. LNG users		2.3	1.9
95% CI		1.0–5.2	1.3–2.7
Dinger (12, 19)			
Adjusted HR vs. OCs	0.8[a]		0.8[b]
95% CI	0.4–1.5		0.5–1.6

Note: Results from large observational studies (17, 18) or from prospective longitudinal surveillance studies (12, 19). The results are expressed as RR or HR, respectively. CI = confidence interval; DRSP = drospirenone; EE = ethinyl- E_2; ETN = etonogestrel/EE vaginal ring; FDA-CDC = Federal Drug Administration-Centers for Disease Control; HR = hazard ratio; LNG = levonorgestrel; NGMN = norelgestromin/EE transdermal patch; OC = oral contraceptive; RR = risk ratio; VTE = venous thromboembolism.

[a] Adjusted HR versus LNG oral contraceptives (12).

[b] Adjusted HR versus other oral contraceptives (19).

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