An update on progestins and venous thromboembolism risk: What clinicians need to know*

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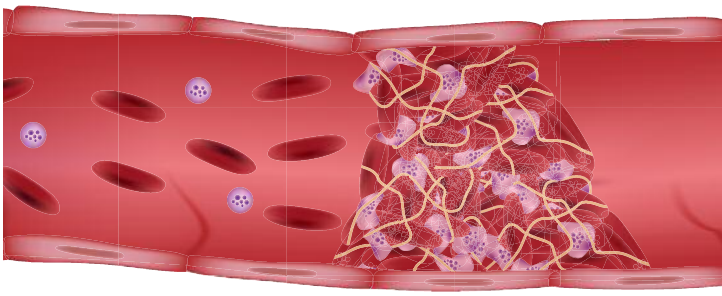
A mandated FDA warning about the risk for venous thromboembolism (VTE) is included in package inserts for all hormonal contraceptives. However, many practitioners do not consider VTE risk with use of the progestin-only "mini-pill" containing norethindrone, the progestin-releasing intrauterine device containing levonorgestrel (LNG), or the depot medroxyprogesterone acetate (DMPA) injection as being equal to that linked to combined hormonal contraceptives (CHCs) containing estrogen and a progestin. During an educational session about insertion of the progestin-only implant Nexplanon, which contains the progestin etonogestrel (ENG), the speaker emphasized that this product was absolutely contraindicated in women with a history of thrombosis or an increased risk for thrombosis. A session participant asked why the ENG implant was singled out in this way. It was explained that ENG is "estrogen friendly, whereas DMPA is an estrogen antagonist" (personal communication, December 1, 2012). The speaker's comment implied a risk beyond that of the routine FDA warning about VTE with respect to all hormonal contraceptives, and prompted this review of the literature on progestins and VTE risk.

The media and professional healthcare journals have reported conflicting information regarding the relationship between the progestin type used in CHCs and VTE risk. According to a meta-analysis,[1] the data from studies showing an increased VTE risk with some progestins used in third-generation oral contraceptives (OCs), including desogestrel (DSG), gestodene (not available in the United States), and drospirenone (DRSP), may have been flawed.[2-4] No controversy exists regarding the level of estrogen and VTE risk, however. Experts agree that estrogen doses greater than 35 mcg are associated with increased risk.[5] However, what does the evidence show about the presence of DSG or DRSP in combined OCs (COCs) or of ENG, which is derived from DSG, and which is used in combination with estrogen in a vaginal contraceptive ring and by itself in subdermal implants?

In 2010, the Society of Obstetricians and Gynaecologists of Canada (SOGC) released a clinical practice guideline concluding that all COCs increase VTE risk.[5] In the guideline, the rate of VTE risk rose from 4-5/10,000 woman-years in COC nonusers to 9-10/10,000 woman-years in COC users, independent of progestin type. VTE risk was greatest in the first few months of use. The guideline also identified risk for VTE in pregnancy as 29/10,000 woman-years. The authors of the guideline concluded that for most healthy women of reproductive age, COC benefits will outweigh the risks.[5]



The SOGC guideline implied that the various types of progestin do not differ with respect to their association with VTE risk. However, if that is the case, why would the ENG implant, but not DMPA, be absolutely contraindicated in women with a history of VTE? One small statement in the Canadian guideline points to a possible reason: "The precise effects of different hormonal contraceptives on the hemostatic system continue to be studied and debated…."[5 p 1194]

Reports suggest that the use of DSG and DRSP, as compared with LNG, in COCs is associated with higher levels of sex hormone-binding globulin (SHBG) and greater resistance to the anticoagulant action of activated protein C (APC).[4] However, these changes

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have not been thought to fully explain an increase in risk for thrombosis. The impact of higher levels of SHBG and greater resistance to APC was further evaluated in a study of the metabolic effects of another progestin, Nestorone, which is combined with estrogen in a contraceptive ring.[6] Rad et al[6] used discriminant analysis to identify which hemostatic variables might be affecting VTE risk. These investigators hypothesized that the increase in SHBG is indeed associated with APC resistance, but that there also are associated changes in procoagulant factor VII (FVII) and the fibrinolytic factor plasminogen (PLG). These changes cause an imbalance, the magnitude of which may explain the difference in thrombotic risk.

By stating that ENG was estrogen friendly, perhaps the speaker meant that its use is associated with higher levels of SHBG and, therefore, increased risk for changes in APC, FVII, and PLG, which increase VTE risk. This finding provides some explanation as to why the ENG implant is absolutely contraindicated for women with a history of thrombosis. The findings of Rad et al[6] may also provide support for old warnings regarding increased risk for clotting with use of contraceptives that contain DSG or DRSP. Perhaps the studies by Rosing et al,[2] Vandenbroucke et al,[3] and van Vliet et al[4] were flawed in relationship to the outcome measured rather than other methodology.

The European Medicines Agency (EMA), the European equivalent of our FDA, announced in late January 2013 that its Pharmacovigilance Risk Assessment Committee (PRAC) would study whether a need exists to restrict use of third- and fourth-generation CHCs because of VTE risk. In 2001, the EMA had conducted a similar review and concluded that women using third-generation pills have a small increased risk for VTE. On balance, however, the benefits and risks were favorable for all CHCs.

Conclusions from the PRAC's recent review were released in October 2013.[7] A baseline VTE risk of 2/10,000 was reported for women not pregnant and not taking CHCs. Women taking CHCs containing LNG, norgestimate, or norethisterone (norethindrone) had the lowest increase in risk (5-7/10,000). The intermediate risk category included CHCs containing either ENG or norelgestromin, which is used in the patch (6-12/10,000), and the highest risk was noted with CHCs containing gestodene, DSG, or DRSP (9-12/10,000). The PRAC recommends that women taking CHCs without problem continue with their regimen. However, the use of certain progestins can be associated with a small increased risk for VTE. Therefore, prescribers should take into consideration both individual- and progestin-related risk factors for women just starting CHCs.[7,8]

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