ISGE
GYNECOLOGICAL ENDOCRINOLOGY
THE 18TH WORLD CONGRESS
7-10 MARCH 2018 FLORENCE, ITALY

Impact of progestogenes on hemostasis

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Combined hormonal contraception containing estrogen and progestogen or injectable progestogens for non-contraceptive therapy e.g., dysfunctional uterine bleeding and postmenopausal hormone therapy (HT) with estrogen plus progestogens or estrogen alone, are reported risk factors for deep venous thrombosis (VTE) and with less certainty arterial thrombosis (ATE). The VTE risk associated with oral contraceptives (OCs) appears to vary by estrogen dose and type of progestin. OCs containing lower dose estrogen (< 50 microgram ethinyl estradiol) combined with “newer generation” progestins (e.g., desogestrel, gestodene and drospironone) may have higher VE risk than lower dose estrogen combined with older (second) generation progestin (e.g., levonorgestrel). Among postmenopausal women, VT risk also varies by estrogen type and mode of delivery. However, the risk of VT with progestogen alone or in combination with estrogen is uncertain; with studies to date showing a non-significant to a 1.5 fold increased risk. Within OC users the differences in VTE can be at least partially explained by the association of various combined OCs with differences in resistance to activated protein C (APC) as measured with the thrombin generationbased APC resistance test and quantified via a normalized APC sensitivity ratio (nAPCsr). High nAPCsr indicates increased APC resistance, which is a risk factor for venous thrombosis. Thrombin generation-based APC resistance has been validated in users of combined OCs, with or without the factor V Leiden mutation. The net estrogenicity of a combined OC may serve as a marker for VTE as several studies have shown an association between the clinical risk of causing VTE of combined OCs, APC resistance, and SHBG levels. Similar findings have been done when applying thrombin generation (TG) as marker of VTE as well as the Factor VII-activating protease (FSAP); another marker of thrombosis risk. In postmenopausal women the arterial intima can express tissue factor, and changes in coagulation factor VII (increase) and tissue factor pathway inhibitor (TFPI) (decrease) may be deleterious. We have previously reported on identically deleterious impact on TPFI levels from oral intake of combined HT regardless of type and length of progestin intake. Findings, that contrast reports on hemostatic and clinical effects of non-oral estrogen in combination with oral intake of different progestogens.

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