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"Estrogen, Protein S, and Obesity Contribute to Thrombosis in Premenopausal Obese Women Who Use Oral Contraceptives"

Blood coagulation occurs by a finely tuned cascade of enzymatic reactions that result in fibrin formation. Central to this process is a complex of a vitamin K-dependent proteases, factor IXa (FIXa), and factor VIIIa (FVIIIa), assembled on a phospholipid-containing membrane. The FXa/FVIIIa complex is the kinetically significant activator of factor X (FX). During thrombin formation by activated FX (FXa), several anticoagulant reactions prevent systemic activation of coagulation. Impairment of these anticoagulant activities increases the risk of venous thrombosis. Common causes of high-risk venous thrombosis are hereditary and acquired deficiencies of the plasma anticoagulant Protein S (PS). PS (also vitamin K-dependent) negatively regulates coagulation by inhibiting FIXa, thereby limiting factor FXa and thrombin formation.

The female hormone estrogen depresses plasma PS level. Thus, women who use estrogen-based oral contraceptive agents experience reductions in PS abundance, and these women are at higher risk for thrombosis. Estrogen suppresses PS level by inhibiting PS gene transcription; estrogen receptor α and transcription factor SP1 mediate this transcriptional inhibition. Additionally, we found that decreased plasma PS level was associated with obesity. PS is synthesized in the liver, which becomes hypoxic in obese individuals. Hypoxia causes hypoxia inducible factor 1 alpha to downregulate PS expression in obese individuals; this effect explains why obesity increases the risk of thrombosis. Importantly, the combination of obesity and estrogen-based oral contraceptives dramatically increases thrombotic risk.

In this project, we used ELISA assays to measure the amounts of total and free PS in plasma from non-obese and obese individuals (based on BMI). We also measured the free PS levels in obese individuals who used oral contraceptives. Finally, we used a specific thrombin generation assay to measure thrombin formed by these plasma samples. We observed that obesity and estrogen, individually and synergistically, were associated with lower than control levels of plasma PS. Therefore, premenopausal, obese women who use oral contraceptives have greater thrombin generation potential compared with obese women who do not use oral contraceptives.

In further research, we will focus on 1) determining the molecular mechanism by which hypoxia, associated with obesity, and estrogen, from contraceptives, affect PS level and 2) investigate therapies to elevate PS level in obese ± estrogen premenopausal women.