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"Elevated Risk of Thrombosis from Synergistic Downregulation of Protein S by Obesity and Estrogen"

Introduction: Millions of individuals are affected by acquired hypercoagulability, which manifests most prominently as myocardial infarction, stroke, and deep vein thrombosis. Protein S (PS) is an essential natural anticoagulant whose deficiency is a major contributor to acquired hypercoagulability. Many factors cause individual differences in plasma PS level. One factor is the concentration of female sex hormones such as estrogen and progesterone. For example, women who use oral contraceptive pills (OCP) experience a decrease in PS. Importantly, this contraceptive-induced PS decrease enhances the risk of thrombosis by 3-fold. Decreased PS is also associated with obesity, which enhances the risk of thrombosis by 2.5-fold. Dramatically, the risk of thrombosis increases as much as 24-fold for obese women who use OCP. The goal of this project is to determine how obesity and estrogen (present in OCP) synergistically downregulate PS concentration and thereby dramatically elevate thrombotic risk.

Methods: We enrolled pre-menopausal women aged 18-45 years with normal (control) and obese BMIs. Additional participant categories included control women who used OCP and obese women who used OCP. We used aseptic venipuncture to collect blood in sodium citrate tubes. Plasma was isolated immediately via centrifugation, and samples were stored at -80ºC. To determine the effect of obesity and estrogen on clotting time, we performed an activated partial thromboplastin time (aPTT) assay in which 25 mmol/L $CaCl_2$ was used to initiate coagulation. Likewise, we executed a thrombin generation assay (TGA) to measure the effect of PS deficiency on thrombin production in obese and control persons. To quantify the relative amounts of free and bound PS, we used ELISA and immunoblotting techniques.

Results: We observed shorter aPTT times for obese women compared with control and even shorter aPTT times for obese+OCP individuals. Similarly, peak thrombin formed was highest in plasma from obese+OCP women. Using an ELISA assay, we found that free PS levels were lowest in obese+OCP women. Similar trends in PS level were found by immunoblotting assays. In total, our results showed that obesity along with OCP significantly downregulated PS expression.

Conclusion: Our data suggest a synergistic downregulation of PS in obese premenopausal women who use OCP. Downregulation (deficiency) of PS causes thrombosis. Therefore, we suggest that our data explain the high prevalence of thrombosis in premenopausal obese women. We are assaying more plasma samples to ensure the statistical significance of our results.