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Commentary on Inherited and Acquired Thrombophilia and Infertility in Infertile Women

Commentary Article

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The effect that inherited and acquired thrombophilias have on embryonic vascularization and implantation is controversial [1]. Therefore, protein S deficiency (DPS), protein C deficiency (DPC), antithrombin (DAT), Factor V Leiden mutation (FVL), prothrombin mutation G20210A, anticardiolipin antibody (ACA), lupus anticoagulant (LA), and anti-β2-glycoprotein I antibody are evaluated for infertility patients. In a convenience sample cross-sectional study of 130 infertile white Brazilian women with 260 fertile white Brazilian women controls, significant differences were found between infertile and fertile white Brazilian women for prevalence of ACA ($p<0.0001$; Odds ratio [OR] = 3.61), DPC ($p = 0.0458$; OR = 0.97), DPS ($p < 0.0001$; OR = 1.70), and DAT ($p = 0.0171$; OR = 1.20). Significant differences were not found for FVL, prothrombin mutation G20210A, or LA. This study did not evaluate anti-β2-glycoprotein I. Some of the cited literature supported the authors' findings for ACA. The authors suggested that prospective studies are needed to confirm this data.

Comment

Failed implantation accounts for the largest group of failed *in-vitro* fertilization (IVF) cycles [2]. It is biologically plausible that inherited and acquired thrombophilias negatively affect embryonic vascularization and implantation [1, 2]. Soligo and colleagues' study is limited by lack of intent-to-treat analysis. As the literature focuses on a wide array of thrombophilia contributors, finding directly comparable studies can be difficult [3, 4]. Nonetheless, the literature supports the presence of a single inherited thrombophilia as a promoter for recurrent IVF failure (2 to 6 failed cycles), OR = 3.15, $p = 0.00$, 95% Confidence Interval [CI]: 1.74 – 5.70 [2]. The literature also supports an association between a single inherited or acquired thrombophilic factor and unexplained infertility, $p < 0.01$, and greater association with at least two thrombophilic factors, $p < 0.0001$ [5]. In contrast with the convenience sample of IVF patients analyzed by Soligo and colleagues, a prospective study of 96 infertile Iranian women associates FVL with recurrent failed IVF, OR = 3.06, $p = 0.01$, 95% CI: 1.26 – 10.27 [2]. Similarly, a prospective case control study of 140 Egyptian women found an association between FVL and unexplained infertility, $p = 0.04$ [5]. However, a smaller sample sized study of 34 patients with 3 or more failed IVF cycles did not find an association between FVL and infertility, $p = 0.6$ [6]. Neither the prospective Iranian study, nor the prospective Egyptian study found DPC, DFS, or DAT to be associated with recurrent IVF failure or unexplained infertility, respectively [2, 5]. The prevalence of ACA in unexplained infertile compared to fertile Egyptian women approached significance, $p = 0.062$, but the smaller sample size may have precluded finding all significant associations [5]. Consistent with this, a retrospective cohort of 2,585 Egyptian women who had undergone 3 or more failed IVF cycles found a higher prevalence of FVL and prothrombin gene mutation than found in the literature [7].

Benefits of knowing which thrombophilias affect infertility and which thrombophilias do not affect infertility include reducing time to a successful pregnancy outcome, while limiting direct and indirect costs of unnecessary laboratory testing and infertility procedures. A stepwise testing cascade can be protocolized whereby those thrombophilias that affect fertility are initially tested for and if negative, then other thrombophilias that also predicate anticoagulation are tested for. Once an infertile women has been identified as having an acquired or inherited thrombophilia, low-molecular weight heparin (LMWH) and low-dose aspirin thromboprophylaxis are recommended [7, 8]. LMWH thromboprophylaxis is associated with increased implantation and on-going pregnancy rates in comparison to placebo, 20.9% versus 6.1%, $p < 0.001$ and 31% versus 9.6%, $p < 0.05$, respectively [8]. Therefore, moving forward it is important for studies on inherited and acquired thrombophilias in infertile women to have adequately powered sample sizes to find exant associations [1].

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