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Preston et al. indicated that Protein S (PS) deficiency was associated with stillbirths but not miscarriages. The PS-Tokushima missense variant was reported to serve as a genetic risk factor for deep vein thrombosis in the Japanese population. A previous cross-sectional study showed no increase in the prevalence of PS-Tokushima in patients with recurrent early pregnancy loss or in patients with intra uterine fetal death and/or fetal growth restriction. There has been limited number of prospective studies examining the pregnancy outcome in patients with both a PS deficiency and recurrent pregnancy loss (RPL). We examined the association between PS deficiency, PS-Tokushima and RPL. The study group consisted of 355 Japanese women with two or more consecutive pregnancy losses and 101 parous women. The frequency of PS-Tokushima and the subsequent live birth rate in relation to a PS deficiency defined as low PS-specific activity (total PS activity/ total PS antigen) and the presence of PS-Tokushima were examined. There was no significant difference in the frequency of PS-Tokushima between patients and controls. The 8 patients carriers of PS-Tokushima variant were capable of a subsequent live birth without the use of heparin. There was no significant difference in subsequent live birth rates between patients with low or normal PS-specific activity/PS activity without heparin prophylaxis after excluding miscarriages caused by an abnormal embryonic karyotype using multivariate logistic regression analysis. There was no association between PS-Tokushima and RPL and a PS deficiency or low PS activity was shown not to serve as a reliable clinical predictor of subsequent miscarriage.