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DEFICIENCY OF HERITABLE COAGULATION INHIBITORS (PROTEIN C, PROTEIN S AND ANTI THROMBIN III) IN UNEXPLAINED MULTIPLE ABORTION

Physiology

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ABSTRACT

Thrombophilia, both acquired and inherited have been shown to be associated with severe pregnancy complications. Unexplained multiple pregnancy loss subject are evaluated with detailed history procurement, endocrine dysfunction tests, anatomic abnormality detection and data of the functional level of Heritable Coagulation Inhibitors, then analyzed statistically with similar data from age matched controls, so as to assess the impact of the abovementioned factors, in general, and the impact of the altered level of Heritable Coagulation Inhibitors, in particular.

KEYWORDS

unexplained multiple pregnancy loss, Heritable Coagulation Inhibitors

INTRODUCTION

Human hemochorial placentation is unique and inherently unstable. Placental development involves invasion into the maternal decidua and its vasculature and requires precise control of hemostasis and fibrinolysis. Delicate control mechanisms exist locally within the placenta and globally within the pregnant women. [1]

Hormonal and related physiological changes characteristics of pregnancy affect important components of the clotting system, fibrinolytic cascade and platelet physiology. Prothrombotic changes and thrombosis may interfere with these processes leading to miscarriage.[2,3,4] Pregnancy is an acquired hypercoagulable state and maternal thrombophilia has recently been identified as a major cause of thromboembolism, placental thrombosis and adverse pregnancy outcome resulting in recurrent pregnancy loss.[5,6,7,8,9] Thrombophilias, both acquired and inherited have been shown to be associated with severe pregnancy complications such as pre eclampsia, intrauterine growth retardation (IUGR), abruptio placentae and still-birth. Natural anticoagulants like antithrombin III and activated protein C with co-factor protein S, function to confine thrombus formation to the sites of vascular injury and limit thrombus size to prevent vessel occlusion and flow interruption in the affected vessel. The activity of antithrombin III is greatly enhanced by endothelial cell heparan sulfate and pharmacologic heparins. The function of activated protein C is enhanced by its cofactor, protein S.[10]

The inherited disorders deficiencies of antithrombin III, protein C and protein S, activated protein C resistance due to factor V Leiden mutation, mutation in the prothrombin gene (G20210A) and mutation for methylene-tetrahydrofolate reductase C677T, are common and associated with mild thrombotic risks.[6,7,8,9,10,11,12,13,14] Evaluation of recurrent pregnancy loss starts with detailed history of the patient with family history, tests for endocrine dysfunction, detection of anatomic abnormality and laboratory studies to diagnose treatable etiologies.[15,16] Study objective is to record and analyze statistically the data of the functional level of protein C, protein S and antithrombin III obtained from cases of recurrent unexplained fetal loss with the data garnered from age matched controls with live issue and no history of abortion.

MATERIAL AND METHOD

Ladies within age group of 18 to 45 years who voluntarily participated, with complaint of two or more first trimester abortion or one unexplained fetal loss during second or third trimester and with no other clinically detectable abnormality, were tested for random blood glucose level, ABO and Rh grouping & typing, functional level of Protein C, Protein S, Antithrombin III and free T4 & TSH, APLA (anti phopholipid Antibody), VDRL, TORCH (Toxoplasma Rubella Cytomegalovirus Herpes simplex). USG of pelvic organs was also done. This study comprised of 31 cases and equal number of age matched controls with no clinically detectable abnormality, were also subjected to random blood glucose level, ABO and Rh grouping & typing, functional level of Protein C, Protein S, Antithrombin III and free T4 & TSH, APLA (anti phopholipid Antibody), VDRL, TORCH (Toxoplasma Rubella Cytomegalovirus Herpes simplex) and USG of pelvic organs. The tabulated test results were analyzed using appropriate statistical tools.

RESULT AND ANALYSIS

In all the subjects and cases studied, Free T4 & TSH level were found to be within normal limits for all. Random blood glucose was within range for all. VDRL & TORCH were non reactive for all (both subjects and cases), only 1 subject had Rh negative blood. APLA reactivity was found to be negative in all subjects and cases. USG of pelvic organs were found to be within normal limits. The coagulation parameters (functional activity of Protein C, Protein S and Antithrombin III) were tabulated and analyzed as.

Pregnancy loss	AT III	Protein C	Protein S
	r = - 0.184 ; p = 0.322	r = - 0.329 ; p = 0.027	r = - 0.351 ; p = 0.05

Table 1: Correlation Between Pregnancy Loss In Cases And Anticoagulation Factors Under Investigation In The Study Population Is Significant In Case Of Protein C And Protein S.

	AT III	Protein C	Protein S
AT-III	1	0.178	- 0.153
Protein C %	0.178	1	0.324
Protein S %	-0.153	0.324	1

Table 2: Correlation matrix in between the three anti-coagulation factors under investigation is not significant.

Protein C levels			
Pregnancy loss	Elevated	Normal	Totals
2	3	9	12
3	2	10	12
4 or more	0	7	7
Totals	5	26	31

Table 3: Findings: 2 = 2.047; P = 0.359, Thus Inferred That Quantum Of Pregnancy Loss Is Not Significantly Associated With Elevated Protein C Levels.

Protein S levels			
Pregnancy loss	Decreased	Normal	Totals
2	6	6	12
3	12	0	12
4 or more	7	0	7
Totals	25	6	31

Table 4: Findings: 2 = 11.780; P = 0.003, Thus Quantum Of Pregnancy Loss Is Highly Significantly Associated With Decreased Protein S Levels.

AT-III levels			
Pregnancy loss	Elevated	Normal	Totals
2	2	10	12
3	1	11	12
4 or more	0	7	7
Totals	3	28	31

Table 5: Findings: 2 = 1.445; P = 0.485, Quantum Of Pregnancy Loss Has No Significant Association With Elevated AT III Levels.

The amount of pregnancy loss was highly significantly associated with diminished functional activity of protein S levels in cases (p = 0.003) but level of reduced functional activity of protein C deficiency was not significantly associated with the quanta of pregnancy loss in the same group of patients (p = 0.359). It was also evident that no significant association of number of pregnancy loss was detected with elevated functional activity of antithrombin III levels in cases (p = 0.485). T Test gives a highly significant value for diminished functional activity of protein S levels in cases control comparision (p = 0.0015).

CONCLUSION

Protein S deficiency was significantly associated with recurrent pregnancy loss in this study group with all other known risk factors excluded, except Factor V Leiden.

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