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Original Research Article

Evaluation of factor VIII value in normal women and whom encountered recurrent pregnancy loss: is there any significant difference?

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ABSTRACT

Background: Recurrent pregnancy loss (RPL) is a serious problem on the women, it defined as two or more consecutive pregnancy losses before the fetus has reached birth. The aim of this study is to evaluate the association between the elevation in the factor VIII and RPL. Because women who have thrombophilia have increased risk of fetal loss in most studies.
Methods: A total 72 women were recruited in this case control study. They divided into two groups: the RPL group included 41 women with a history of recurrent pregnancy loss and the control group included 31 healthy women, who had at least one successful pregnancy and none of them had a history of fetal loss or complicated pregnancy.
Results: A majority of the patients of this study didn't have a high level of factor VIII, 9 of 41 (22%) patients of RPL group in comparison with 21 of 32 (65,6%) of control group, that suffer from the increase rate of FVIII, this means that factor VIII doesn't effect on RPL.
Conclusions: The present study showed that the serum elevation in the factor VIII is not significantly associated with RPL.

Keywords: Factor VIII, Recurrent pregnancy loss, Thrombophilia

INTRODUCTION

Recurrent pregnancy loss (RPL), either early or late in the gestational period is a serious problem and has both psychological and social impacts on the women who suffer from it. In some cases, it may lead to divorce or other social problems.[1]

Recurrent pregnancy loss (RPL), defined as two or more consecutive pregnancy losses before the fetus has reached birth at 24 weeks, is a serious reproductive problem, affecting 1-5% of reproductive-age woman.[2,3] There is a strong belief that RPL is a multifactorial condition that many factors affect such as chromosomal abnormalities, uterine anatomic malformation, endocrine dysfunction, immunologic factors, infections, and environmental factors.[4-6]

However, the etiology of RPL remains unknown in ~50% of cases.[7,8] Pregnancy is a hypercoagulable state secondary to an increase in the concentrations of pro-coagulant factors, a reduction in the concentrations of the naturally occurring anticoagulant proteins and a decrease in fibrinolysis.[9] A successful pregnancy requires the development of adequate placental circulation. Multiple studies have shown that thrombophilia increase the risk

of recurrent first and second trimester pregnancy losses through thrombosis of the placental bed.[10-13]

Thrombophilia was identified as a major cause of recurrent pregnancy loss (RPL), after chromosomal abnormalities with a rate of up to 40%, especially in the first half of pregnancy.[14] Although many studies are available on thrombophilia. It is very different from one study to another due to different selection criteria of patients.[13] Thrombophilia describes an increased tendency to develop thrombosis, either venous or arterial.[15]

Thrombophilia may either be inherited or acquired and include protein C deficiency, protein S deficiency, antithrombin deficiency, and the less potent factor V Leiden (FVL) and prothrombin gene mutation (PGM).[15-18] The combined prevalence of these thrombophilia in the general population exceeds one in ten.[15,17-22]

It is hypothesized that thrombophilia may increase the risk of placental insufficiency because of placental micro and/ or macro-vascular thrombosis, as well as effects on trophoblast growth and differentiation.[1,23,24]

Factor VIII (FVIII) is an essential blood-clotting protein, also known as anti-hemophilic factor (AHF). in humans the factor VIII is encoded and produced by the F8 gene shown in (Figure 1).[19,25]

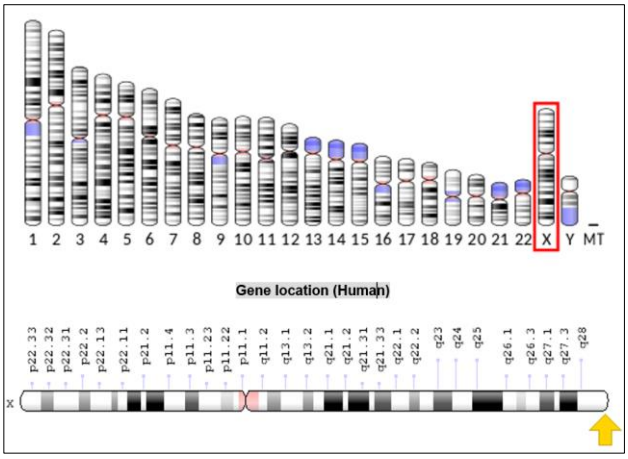

Figure 1: Gene location of factor VIII on human chromosome X.

Factor VIII is produced in liver sinusoidal cells and endothelial cells outside the liver throughout the body.[26] People with high levels of factor VIII are at increased risk for deep vein thrombosis and pulmonary embolism.[27] Copper is a required as cofactor for factor VIII and copper deficiency is known to increase the activity of factor VIII.[28] This objective is to evaluate the association between the elevation of factor VIII level in serum and RPL as a causative factor.

METHODS

The study group included 72 women included 41 women with a history of RPL (two or more abortions before 20th week of gestation, mean±SD: 4±2.31, range 2-11) and 31 healthy women (control group), who had at least one successful pregnancy and none of them had a history of miscarriage or complicated pregnancy, who referred to Orient Hospital, Damascus, Syria, for medical consultation between January 2017 to January 2018.

Study followed the methods of Mohammad et al.[29] All women with known independent risk factor for pregnancy complication, such as endocrine abnormality (prolactin, thyroid stimulating hormone, follicular stimulating hormone and luteal hormone during the early follicular phase), uterine malformation, systemic disease (diabetes mellitus, lupus erythematosus) and women who received induced abortion upon their request, were excluded, in addition to women with other thrombophilic defects, such as deficiency of activities of antithrombin III, protein C, and protein S or antiphospholipid antibodies syndrome.

The control group included 31 healthy women (mean±SD: 28.8±6.8 years, range 17-41 years) from the same ethnic background, who had at least one successful pregnancy, and none of them had a history of miscarriage or complicated pregnancy.

All women in this study had no history or family history of thrombosis. All participants gave informed consent, according to the protocol approved by local Ethics Committee at Damascus University and Health Ministry.

Venous blood samples were collected into Vacutainer tubes containing trisodium citrate, blood centrifuged at 2000-2500g for 15 minutes, plasma was obtained and assayed on STA compact automated coagulations analyzer using STA- Staclot VIII kit, both of Diagnostica Stago, S.A.S. France. The principle of this assay was thoroughly explained by Ali A et al, which is based on the ability of reference plasma and test plasma to correct the prolonged APTT of plasma deficient in the factor VIII that is being assayed. reference plasma with known content of all the factors and factor VIII deficient plasma with factor level less than 1% activity must be available for the assay.[30] One part of test plasma and one part of factor VIII deficient plasma (Stago) and one part of APTT reagent (CK PREST, STAGO) are mixed then incubated at 37^{0}C, in addition, one part of calcium chloride is added, then we note the time taken to clot. Abnormal system control plasma with a factor VIII level of 32-46% and normal system controls with factor VIII level of 87-121% are subjected to the test simultaneously with patient's sample. Normal levels of factor VIII are 50-120%.

Statistical analysis

For the analysis of the data, Pearson chi-square and continuity correction chi-square tests have been used. For all analyses, a value of less than 0.05 was considered statistically significant. SPSS Software (version 25) was used for the analysis.

RESULTS

A majority of the patients of this study didn't have a high level of factor VIII, 9 of 41 (22%) of RPL patients suffer from the increase of the VIII in comparison with 21 of 32 (65.6%) healthy women that suffer from the increase rate of VIII. Normal levels of factor VIII are 50-120%.

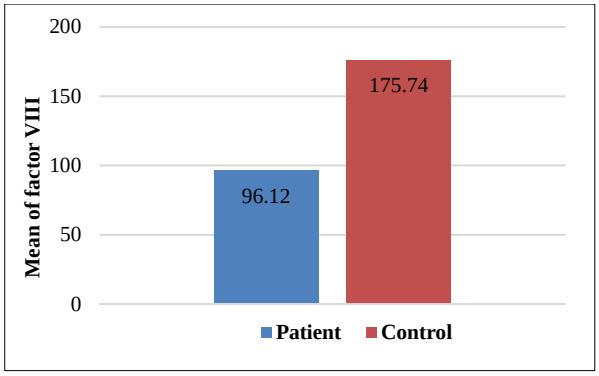

Figure 2: Mean of factor VIII in the patients and controls groups.

Table 1: The Arithmetical averages and the standard deviations of the values of the factor VIII in the blood in RPL patients and controls.

	Low F VIII (% 120 <)		High F VIII (<= 120%)		Total	
	Average	**N**	**Average**	**N**	**Average**	**N**
Patient	74.06±25.78	32	174.56±55.83	9	96.12±53.96	41
Control	85.5±24.37	10	218.71±71.33	21	157.74±87.05	31
Total	**76.79±25.64**	**42**	**205.47±69.23**	**30**	**130.40±80.12**	**72**

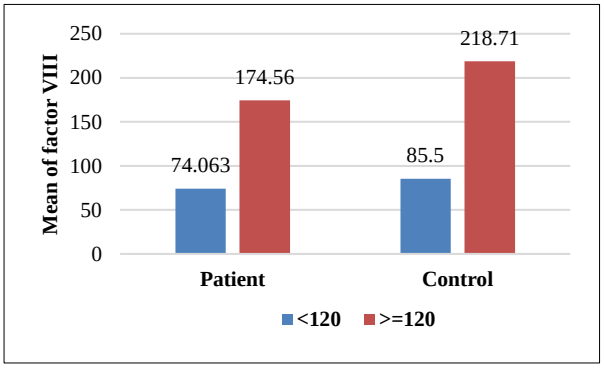

Figure 3: Mean of factor VIII values in both categories (high, low FVIII) in RPL patients and controls.

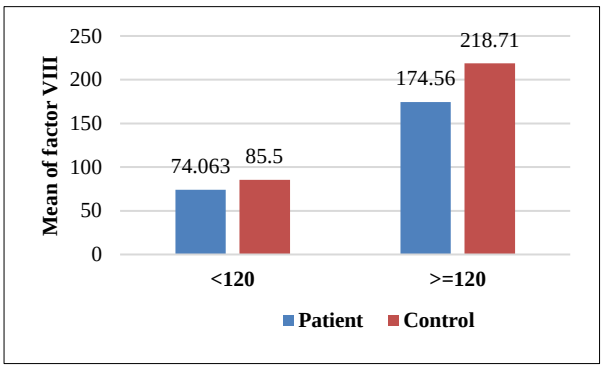

Figure 4: Mean of factor VIII values in RPL patients and controls in the two categories (high, low FVIII).

The following Table 1 and also Figure 2, 3 and 4 explain the arithmetic averages and the standard deviations of the factor VIII in blood for the women's two groups of RPL patients and controls.

There are no variances with a statistical significance to the average of factor VIII values in blood between the two samples of controls and patients in the category in which the values of this factor are less than the value 120%. (where t = 1.24, p value = 0.222 > 0.05) (Figure 4).

DISCUSSION

This Results confirmed that the increase of FVIII levels in blood does not have an effect on RPL.

The rate of RPL patients having an increase of FVIII levels was less than the rate of increase of FVIII in the control group, 9 of 41 RPL patients suffer from the increase of the FVIII, in comparison with 21 of 32 healthy women that suffer from the increase rate of FVIII, which indicate that there is no statistical correlation between FVIII and RPL.

This result show a disagreement with another study carried out in 2012 which concluded a strong correlation between FVIII and RPL, this study shows that the pregnancy complications were found with the increase of the FVIII with a percentage of 66.66%.[31]

Meanwhile, this study is in agreement with multiple studies carried out on thrombophilia in general, a study carried out in 2002 concluded that the thrombophilia has no association with RPL, and with a study carried out in 2011 in Palestine which concluded that there is no statistical correlation between high FVIII levels and RPL, also with two studies carried out in 2016 and 2012 which confirmed the same conclusion.[32-35]

CONCLUSION

According to these results obtained from this study in the middle east about the increase of the FVIII and its effects on RPL, there is no significant statistical correlation between the factor VIII and RPL.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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