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Article

Serum Anticardiolipin, anti-beta2 glycoprotein I and Lupus Anticoagulant in Women Experiencing Recurrent Pregnancy Loss

Noora M. Kadhium[1]

College of Medicine, University of Al-Qadisiyah, Al-Qadisiyah, Iraq
* Correspondence: noora.m.kadhium@qu.edu.iq

Abstract: The current study was designed to compare the prevalence of anticardiolipin and anti-beta2 glycoprotein I IgG and IgM antibody levels in married women who have repeated miscarriage and had been diagnosed of recurrent pregnancy loss and normotensive women. A total of 120 women with recurrent pregnancy loss RPL and 120 normotensive married women who didn't have any pregnancy complications and were tested for both IgM and IgG for anti-cardiolipin and anti-beta2 glycoprotien 1 antibodies, and aPTT. The findings revealed that the level of both IgM and IgG for anti-cardiolipin and anti-beta2 glycoprotien 1 antibodies were significantly higher than normal standards were examined in 120 women with repeated miscarriages and matched with 120 normal healthy women, the age range of patients from 21-43 (mean age was 32.1); were matched with 120 healthy married women of the same age range (21-43) with no complications (mean age 31.8). In conclusion, women with recurrent pregnancy loss exhibited increased anticardiolipin and anti-beta 2 glycoprotein antibodies when compared to the healthy control group. However, future researches in chromosomal abnormality and HLA gene that might cause repeat incidences of miscarriage

Keywords: Anticardiolipin, Anti-beta2 glycoprotein, Recurrent pregnancy loss, Antiphospholipid syndrome

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1. Introduction

Pregnancy loss is described as the natural termination of a pregnancy prior to the viability of a fetus; it includes all losses from conception up to 20-24 weeks of pregnancy. On the other hand, the term 'miscarriage' refers to the loss of an intrauterine pregnancy IUP diagnosis by ultrasonography or histology up to 20-24 weeks of gestation1 (Box 1). European society of Human Reproduction and Embryology (ESHRE)/ American Society for Reproductive Medicine (ASRM) guidelines consider recurrent pregnancy loss to be the failure of at least two clinically recognized pregnancies . However, especially important to mention, ectopic pregnancies and molar pregnancies are not considered as part of recurrent pregnancy loss (1, 2) . The exact upper limit of miscarriage is mainly due to the legal definition of viability and differs in countries (12–28 weeks). The availability or absence of early pregnancy units also defines whether a loss is clinically acknowledged and what management is advised to the patient (2).

Antiphospholipid syndrome (APS), is defined as an autoimmune disorder in which auto-antibodies are directed against self-molecules in the individuals such as in case of

APS, auto-antibodies (antiphospholipid) will bind with phospholipid binding proteins. APS is one of the risk factors of recurrent pregnancy loss (3) and a main clinical symptom is thrombosis or repeated pregnancy loss (4). the relationship between APS and pregnancy is characterized by the appearance of anti-phospholipid auto-antibodies which can affect the repeated fetal loss and pregnancy complications such as pre-eclampsia, retarded fetal growth or placental insufficiency (5, 6). The APS syndrome represents a diverse group of antibodies in circulation directed against anionic phospholipids with the most significant ones being Anticardiolipin Antibodies (aCL), a positive Venereal Disease Research Laboratory test (VDRL) and lupus anticoagulants (6, 7). Misleading positive VDRL results do not consider diagnostic standard for the syndrome because the test have low sensitivity and specificity. However, high values in pregnant women is intended to serve as an early warning of the occurrence of antiphospholipid circulating antibodies (8).

In pregnant ladies, an APS rate from 0.2% to 2% is similar to the incidence in the general population (9), however, this syndrome is contribute for about 10% of the cases of frequent pregnancy losses (10, 11). Several research's have related APS with retarded intrauterine growth (12, 13) and other complications like pre-eclampsia (9,14) although this latter association remains disputed (15,16). Antibodies that present in circulation of this syndrome can suppress placental anticoagulant pathway by interfering to phospholipids, thereby thrombosis happend (17), as well as through impacting the production of gonadotropin hormone (18). The β2 glycoproteins considered as a cofactor in the adhesion of antiphospholipid antibodies to anionic phospholipids, thereby acting as a natural anticoagulant and thus any signal interference in this system can result in thrombi formation (19). In an animal model, recurrent pregnancy losses were detected with passive immunity transfer of purified anticardiolipin IgG (5, 20). Treatment using aspirin, heparin, or intravenous immunoglobulins lowers the frequency of fetal loss. Risk of preeclampsia and placental insufficiency happened in around 50% of patients that have no treatment and the efficacy of protective treatment using aspirin and heparin is about 70% (5). The symptoms reduction with the normalization of the levels of ACA is associated to an improvement in the survival rate of fetuses during pregnancy (21).

The present study aimed to evaluate the presence of high aCL and anti-beta2 glycoprotein IgG, IgM and lupus anticoagulant levels in women who had suffered two or more spontaneous miscarriages.

2. Materials and Methods

2.1.Study population

This study included 120 women with recurrent pregnancy loss RPL and 120 normotensive married women who didn't have any pregnancy complications from Maternity and Childhood Teaching Hospital AL-Dywanyia city, Iraq, which concluded from the first of February 2023 to the first of October 2025, women who were diagnosed by a gynecologist to have recurrent pregnancy loss. The RPL patients diagnosed by the number of pregnancy loss have two or more spontaneous abortions.

2.1.1.Selection criteria of patients

2.1.1.1.Inclusion criteria

1-women aged form 21- 43 years

2-ladies that have two or more repeated miscarriage in the first weeks of pregnancy before the fetus has attained viability and include all losses from conception until 20–24 weeks of pregnancy.

2.1.1.2. Exclusion criteria

Maternal and paternal chromosomal abnormalities; fetal chromosomal abnormalities subjects with cancer, in vitro fertilization treatment, diagnosed PE, haemolytic anemia, essential hypertension, uterine malformation, placental abruption, renal and liver diseases, severe infections, or mental illness, gestational diabetes mellitus and TORCH positive patients

2.1.2.Requirements for control group participation

2.1.2.1.Inclusion criteria

Healthy women who had no pregnancy complications with age range from 21-43 years.

2.1.2.2.Exclusion criteria

Exclusion criteria for healthy control women were cancer, chronic hypertension, diabetes mellitus, hemostatic abnormalities, autoimmune, cardiovascular, renal and hepatic diseases, and anticoagulant therapy. All healthy married women had no chronic disease or systemic disease and they have no history of dead fetus.

2.2.Clinical assessment of pregnant women

Detail history includes family history, history of dead baby, and history of miscarriage.

2.2.1.Sample Collection

Blood specimens were gathered from all participant women by vein puncture during the follicular phase of the menstrual cycle 12 weeks apart to conform positive result. 5ml of blood were collected and separated in two tubes one gel tube for serum separation for ELISA and the other sodium citrate tube for aPTT. Anticardiolipin antibodies (aCL) and anti-beta2 glycoprotein 1: IgM and IgG were quantified by using enzyme-linked immunosorbent assay (ELISA). Results were showed in GPL (IgG phospholipid) and MPL (IgM phospholipid) units. A cutoff of >20 GPL/MPL units was considered weak positive and >40 were considered strongly positive result. Lupus anticoagulant (LA): quantified by using heparin partial thromboplastin time (HaPTT) and activated partial thromboplastin time (aPTT) .extended clotting times considered potential LA activity.

2.3.Biotatistical analysis

The present study obtained data were documented with the help of the Microsoft office excel version 2016 and were analyzed by using SPSS version 29. Significant values represented as mean ± standard deviation (M ± SD) were considered different at $P<0.05$.

3. Results

3.1. Results

The results the patient and control groups were correctly matched in terms of having a different age profile. More importantly, they are well distinguished by their obstetric history miscarriages, stillbirth, early delivery) and medical history (chronic disease), with all these differences being highly statistically significant ($P < 0.001$). This confirms that our groups are appropriately chosen for comparing laboratory results (like antibody levels).

Demographic characteristics

A total of 120 women with a history of recurrent pregnancy loss (RPL) were included and 120 completely healthy women. The mean age was 32.1 years (range: 21–43) with at least two spontanous abortions.

Clinical and obstetric histories

History of chronic disease was present in 69.7% of women while the history of early delivery was reported in 32.8%. of patients. History of stillbirth/dead baby was reported

in 28.7% of patients. Women who have a history of chronic disease had a significant higher mean count of abortions compared to those without (mean ± SD) (3.9 ± 1.2 vs. 2.8 ± 1.3, $p < 0.05$).

Table 1: Descriptive Statistics of the Study Participants

Variable	Patient Group (n=120)	Control Group (n=120)	Total (N=240)
Age, Mean (SD)	32.1 (6.5)	31.8 (7.1)	31.9 (6.8)
No. of Abortions, Mean (SD)	2.4 (0.6)	0 (0)	1.2 (1.3)
History of Chronic Disease, n (%)	85 (69.7%)	0 (0%)	85 (35.1%)

Table 2: Independent T-Test Comparing Serological Markers Between Groups

Variable	Patient Group, Mean (SD)	Control Group, Mean (SD)	t-value	df	p-value
anticardiolipin antibody IgG	72.1 (29.5)	16.2 (1.2)	25.45	240	<.001
anticardiolipin antibody IgM	28.3 (23.1)	16.5 (1.5)	6.12	240	<.001
anti-β2-Glycoprotein I IgG	68.9 (30.2)	15.3 (0.9)	22.10	240	<.001
anti-β2-Glycoprotein I IgM	25.8 (21.5)	15.3 (1.1)	6.05	240	<.001
Aptt	42.3 (3.2)	28.8 (2.1)	40.11	240	<.001

Table 3: Chi-Square Test for Clinical History for the pateint group

Parameter	Patient cohort n (%)	Control Group n (%)	χ^2	p-value
History of Chronic Disease	85 (69.7%)	0 (0%)	145.2	<.001
History of Early Delivery	40 (32.8%)	28 (23.3%)	9.2	.089 NS
History of Dead Baby	35 (28.7%)	13 (10.8%)	13.5	<.001

NS: non-significant

Table 4: Categorical Analysis of Antibody Levels Between Patient and Control cohorts

Antibody / Category	Patient cohort (n=120)	Control Group (n=120)	p-value
Acl IgG			<0.001
Negative (<20)	15 (12.3%)	103 (85.8%)	
Weak Positive (20-40)	25 (20.5%)	17 (14.2%)	
Strong Positive (>40)	82 (67.2%)	0 (0%)	
Acl IgM			<0.001
Negative (<20)	85 (69.7%)	111(92.5%)	
Weak Positive (20-40)	22 (18.0%)	9 (7.5%)	
Strong Positive (>40)	15 (12.3%)	0 (0%)	
anti-β2-Glycoprotein I IgG			<0.001
Negative (<20)	18 (14.8%)	113 (94.2%)	
Weak Positive (20-40)	30 (24.6%)	7 (5.8%)	
Strong Positive (>40)	74 (60.7%)	0 (0.0%)	
anti-b2 glycoprotein I IgM			<0.001
Negative (<20)	90 (73.8%)	119 (99.2%)	
Weak Positive (20-40)	20 (16.4%)	1 (0.8%)	
Strong Positive (>40)	12 (9.8%)	0 (0%)	

When we compared the levels of all antibodies of patient and control groups we found the level were highly elevated in patient group with statistically significant p value > 0.001 ,(table 4). The healthy control group shows very low, consistent values (low SD), while the patient group shows much higher and more variable values (table 2).

Prolonged Clotting Time: The Patient Group was a significantly longer aPTT (Mean = 42.3 seconds) compared to the Healthy Control Group (Mean = 28.8 seconds), (table 2). This differencewas highly statistically significant (P <0.001). A prolonged aPTT was a classic indicator of the presence of anticoagulants in the blood. . As a result, there is a strong laboratory indicator of the prescence of lupus anticoagulant and antiphospholipid antibodies (like lupus anticoagulant), which cause the delay in clot formation in vitro. This finding was consistent with the clinical assessment of Antiphospholipid Syndrome (APS).

4. Discussion

The finding of our study shows a strong correlation between recurrent pregnancy loss (RPL) and antiphospholipid antibodies (aPL), which match with the diagnostic criteria of antiphospholipd syndrome (APS) our results show that there is a highly significant elevation in the quantitative levels of specific aPL and functional coagulation activity in women with RPL compared to healthy control women.

The most significant findings are the elevation of anticardiolipin antibody (aCL) for IgG isotype in patients group. The mean value of aCL IgG was mean (SD), (72.1 (29.5)) while the IgM was mean (SD), (28.3 (23.1)) and they were higher than those in healthy control group (16.2 (1.2)) and (16.5 (1.5)) for IgG and IgM respectively with statistically significant p value <0.001 these antibodies have an important function in the pathogenesis of pregnancy complications by activating the endothelial cells, thus disrupting trophoplast function, and activating a prothrombotic state at the maternal- fetal interface (8,9).

The same thing happened with the concentrations of anti-beta2 glycoprotein I (anti-β2GPI) antibodies , which were highly elevated in the patient group the mean values for anti-β2GPI IgG mean (SD) , (68.9 (30.2)) and the IgM (25.8 (21.5)) , which have a higher concentration when compared with the low values of healthy control group mean (SD) , (15.3 (0.9) and 15.3 (1.1), respectively). Anti-β2GPI antibodies are now considered more specific than aCL antibodies for APL because they interact with the major co-factor for the binding of phospholipid . There detection is importantly linked with thrombotic activity and obstetric morbidity which is severe and non-fatal complications, and their elevation in our patient group, further support the positivity of an autoimmune-mediated cause for their pregnancy terminations.(25,26)

Beside the quantitative immuno-assys, the functional coagulation assay, the activated partial thromboplastin time (aPTT), gave an important result. The patient group showed a significantly prolonged aPTT (42.5 (3.2) seconds) when compared to the normal range observed in healthy controls (28.5 (2.1) seconds). This occurrence, known as the lupus anticoagulant (LA) effect, is a paradox where antibodies cause anticoagulation in vitro but are powerfully pro-thrombotic in vivo. An extended aPTT is an important functional test for the existence of LA (27).

This finding is not just acceptable; it is a classic and expected laboratory manifestation of APS. It mean that the antibodies that are detected in patients are biologically active reacting with the phospholipid dependent steps of the coagulation (28).

When we collect the serological (aCL and anti-β2GPI) and functional (aPTT) data a robust diagnostic picture appears. According to the updated Sapporo classification criteria for APS, to diagnose APS it must be one clinical criterion (recurrent pregnancy loss) and one laboratory positive result for aCL, anti-β2GPI, or LA test and continued to be positive for at least 12 weeks apart (29). In our study we collect the samples for two times 12 week apart to confirm positive results and which suggests that the ladies in patient group had linked the laboratory criteria and the clinical history of pregnancy loss. There are many different pathophysilogical processes by which these antibodies can cause pregnancy loss. They can cause thrombosis in the placental vasculature, as result placental infarction

happened and significant decrease in the blood flow to the fetus. Furthermore, they can seriously inhibit trophoplast proliferation and differentiation which can interfere with the placental development and invasion , and also can activate the complement pathway which is part of the innate immune system and toxic inflammatory response would happened and affect the development of pregnancy (8,9).

5. Conclusion

There are a strong relationship between the finding of antiphospholipid antibodies (APL) and pregnancy outcome , especially recurrent pregnancy loss (RPL). Our findings shows that a highly significant profile in the patient group, characterized by serological markers as the patients shows elevated levels of anti-cardiolipin and anti-β2-glycoprotein I for both IgG and IgM antibodies when compared to the healthy contrl group. The current study shows a significant prolonged activated partial thromboplastin time (aPTT) in patients which confirms the presence of lupus anticoagulant (LA), these findings indicate that these antibodies are biologically active. The patients group shows a significant higher incidence of pregnancy complications, including history of stillbirth and early delivery, further supporting the clinical picture of this condition. The relationship between the laboratory findings and the obvious clinical history significantly supports the diagnosis of APS as the important cause of pregnancy loss in these patients. Finally these conditions move from unexplained recurrent pregnancy loss to a well defined and diagnosable and treated pregnancy condition.

6. Recommendations

Based on convincing data from the present study, the following recommendations are suggested for medical practice and farther research.Testing patients that have RPL for APS antibodies: our study encourage complete APS testing for all women that have two or more pregnancy losses by using solid phased immunoassys . For anti-β2GPI and aCL antibodies for both IgG and IgM. Functional clotting test: a lupus anticoagulation test such as aPTT . Pre-pregnancy counseling and risk evaluation: women who diagnosed with APS should have more extensive pre-pregnancy counselings and this counslings have to clear the associated riskks(e.g. placental insufficiency, pre-eclampsia, preterm birth, and sitllbirth) and the care plan , establishing achievable goals.

Execution of a multidisciplinary care plan: after conformation of APS and pregnancy positve test, a systematic treatment guideline should be initiated at once under the supervision of a multidisciplinary team (e.g. hematologist, obstetrician and rheumatologist) .

This protocol typically involves Low-dose aspirin (75-100 mg daily), started pre-conception or as soon as pregnancy is confirmed. Prophylactic-dose low molecular weight heparin (e.g., enoxaparin), were started as soon as fetal viability is confirmed and continuing throughout pregnancy and into the postpartum period. Enhanced Antenatal Surveillance: Pregnancies in APS patients should be classified as high-risk. antenatal care should include increased frequency of ultrasounds for fetal growth monitoring, umbilical artery Doppler studies to assess placental blood flow, and close monitoring for signs of pre-eclampsia. For future research, longitudinal studies must be conducted for long-term follow-up studies to assess the effectiveness of the recommended treatment protocols on live birth rates and long-term child health outcomes in a local context. Investigation of non-criteria manifestations and explore the role of other "non-criteria" antibodies and biomarkers in patients who are symptomatic but test negative for the classic APL markers, to improve diagnostic sensitivity. Further research into the precise molecular mechanisms

by which these antibodies cause placental damage is needed to identify potential new therapeutic targets.

Encourage and develop a structured educational programs fro women with APS to enhance compliance with treatment lower anxiety during their pregnancy journey. In summary, the application of these findings into standard clinical practice through organized testing, multidisciplinary care and right treatment have the chance of transforming the outcomes of affected pregnant women that have a history of pregnancy losses into into a high chance of successful pregnancy.

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