PREVENTION OF MISCARRIAGE IN WOMEN WITH ANTIPHOSPHOLIPID SYNDROME, DEPENDING ON THE THERAPY AND THE PRESENCE OF TORCH INFECTION

Nasriddinova Kamola Pulatovna,
Department of Obstetrics and Gynecology №2, ASMI.
E-mail: www.kamolka-91@mail.ru

Shermukhamedova Maftunabonu Pulatovna,
Department of Oncology and Medical Radiology, ASMI.
E-mail: maftun_temirova@icloud.com

Nasriddinov Shohruh Bakhodirovich
Andizhan State Medical Institute (ASMI),
Department of Oncology and Medical Radiology, ASMI. Andizhan, Uzbekistan
E-mail: nasriddinov.shohruh@bk.ru

ABSTRACT

Objective — to study the features of the course of pregnancy in women with antiphospholipid syndrome (APS), depending on the therapy and the presence of TORCH infection.
Material and methods. 137 cards of women with a history of pregnancy termination were analyzed, divided into 2 groups according to the principle of presence/absence of plasmapheresis in the treatment regimen at the stage of pregravid preparation, followed by ranking into 2 subgroups according to the principle of presence/absence of TORCH infection activity.

Key words: antiphospholipid antibodies, antiphospholipid syndrome, miscarriage, plasmapheresis, TORCH infections.

Results. The features of the course of pregnancy in women with APS depending on the complex therapy and the presence of TORCH infection were as follows: early toxicosis developed more than 2 times more often, regardless of the treatment regimen used, the presence or absence of TORCH infection. The threat of spontaneous miscarriage in the first trimester was almost 10 times higher than in the control group. The absence of efferent therapy in patients with TORCH infection against the background of APS led to an increase in the risk of spontaneous miscarriage up to 73%, which was more than twice as much as in patients whose plasmapheresis was included

in the treatment regimen. Placental insufficiency developed 3 times more often than in the control group and 2 times more often than in the main group. In the third trimester, an increase in the risk of preterm birth was observed in all subgroups, with the exception of I2, which did not differ from the control group and was 2.9 times smaller than in the comparison subgroup. Fetal hypoxia in patients with APS, but without TORCH infection, regardless of the therapy, developed with the same probability as in the control group. The presence of TORCH infection in women with APS, whose plasmapheresis was included in the complex therapy, increased the probability of developing fetal hypoxia by more than 50%, while the absence of efferent therapy methods led to a three-fold increase in the probability of fetal suffering in relation to the control group and double — in relation to the main subgroup. Conclusion. Combined therapy for miscarriage in women with APS with the inclusion of plasmapheresis at the preconception stage, which developed against the background of TORCH infection, significantly reduces the development of pregnancy complications.

ПРОФИЛАКТИКА НЕВЫНАШИВАНИЙ БЕРЕМЕННОСТИ У ЖЕНЩИН С АНТИФОСФОЛИПИДНЫМ СИНДРОМОМ В ЗАВИСИМОСТИ ОТ ПРОВОДИМОЙ ТЕРАПИИ И НАЛИЧИЯ TORCH ИНФЕКЦИЙ

Насриддинова Камола Пулатовна
Кафедра акушерства и гинекологии №2 АГМИ.
E-mail: www.kamolka-91@mail.ru

Шермухамедова Мафтунабону Пулатовна,
Кафедра онкологии и медицинской радиологии АГМИ.
E-mail: maftun_temirova@icloud.com

Насриддинов Шохрух Баходирович
Андижанский государственный медицинский институт(АГМИ),
Кафедра онкологии и медицинской радиологии АГМИ.
Андижан, Узбекистан
E-mail: nasriddinov.shohruh@bk.ru

Ключевые слова: антифосфолипидные антитела, антифосфолипидный синдром, невынашивание беременности, плазмаферез, TORCH-инфекции.

РЕЗЮМЕ. Цель исследования — изучить особенности течения беременности у женщин с антифосфолипидным синдромом (АФС) в зависимости от проводимой терапии и наличия TORCH-инфекций. Материал и методы. Проведен анализ 137 медкарт женщин с прерываниями беременности в анамнезе, разделенных на две группы по принципу наличие/отсутствие плазмафереза в схеме терапии на этапе прегравидарной подготовки с последующим ранжированием на две подгруппы по принципу наличие/отсутствие активности TORCH-инфекций. В 1-ю группу (основную) вошли женщины (n=73), которым на прегравидарном этапе проводилась комплексная терапия с включением плазмафереза, во 2-ю группу (сравнения, n=64) — женщины, которым эфферентная терапия не проводилась. У женщин 1-й (–) и 2-й (–) подгрупп по результатам лабораторных исследований признаков активности TORCH-инфекций не наблюдалось. У пациенток 1-й (+) и 2-й (+) подгрупп обнаружена активность TORCH-инфекций. Результаты. Определены особенности течения беременности у женщин с АФС в зависимости от проводимой комплексной терапии и наличия TORCH-инфекций. Ранний токсикоз у женщин с АФС развивался более чем в 2 раза чаще вне зависимости от используемой схемы терапии, наличия или отсутствия TORCH-инфекций по сравнению с беременными контрольной группы. Угроза самопроизвольного патологического прерывания беременности в I триместре была практически в 10 раз выше, чем у женщин контрольной группы. Отсутствие эфферентной терапии у пациенток с TORCH-инфекциями на фоне АФС привело к росту угрозы самопроизвольного патологического прерывания беременности до 73%, что более чем в 2 раза больше по сравнению с пациентками, которым проведен плазмаферез. Плацентарная недостаточность развивалась в 3 раза чаще, чем у женщин контрольной группы и в 2 раза чаще, чем у женщин основной группы. В III триместре рост угрозы преждевременных родов наблюдался у беременных всех подгрупп, за исключением 1-й (+). Показатели угрозы преждевременных родов у беременных 1-й (+) подгруппы не отличались от таковых у беременных контрольной группы и были в 2,9 раза меньше, чем у женщин 2-й (+) подгруппы. Гипоксия плода у пациенток с АФС, но без TORCH-инфекций, вне зависимости от проводимой терапии развивалась с такой же частотой, как и у женщин контрольной группы. Наличие TORCH-инфекций у женщин с АФС, в комплексной терапии которых использовался плазмаферез, способствовало росту количества случаев развития гипоксии плода более чем на 50%, в то время как отсутствие методов эфферентной терапии приводило к трехкратному росту числа случаев страдания плода по сравнению с

беременными контрольной группы и двукратному — по сравнению с беременными 1-й (+) подгруппы. Вывод. Комплексная терапия невынашивания беременности у женщин с антифосфолипидным синдромом, развившемся на фоне TORCH-инфекций, которая включала в себя на прегравидарном этапе плазмаферез, значительно снижала риск развития осложнений беременности.

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic process that affects all organs and tissues and is determined by clinical and laboratory criteria [1, 2]. The currently established clinical manifestations of APS affect two systems: the vascular system , causing thrombotic phenomena, and the uteroplacental blood flow, which leads to pregnancy complications [2]. At the same time, infectious diseases are still one of the main causes of perinatal losses worldwide. Clinical symptoms of TORCH infections remain mild, which causes certain difficulties in diagnosis and treatment [3, 4]. Effects on the fetus and newborn range from asymptomatic infection to sepsis, malformations, and fetal death. Examination of pregnant women for the presence of infectious agents is an important part of the antenatal care program [4]. The relevance of studying TORCH infections in pregnant women is determined not only by significant perinatal losses, but also by the fact that a fetus that has had an infection often has a congenital pathology that leads to serious health problems and disability. During the primary infection of the embryo in the early stages of its development, the development of fetopathy occurs, leading to spontaneous pathological termination of pregnancy [5, 6]. Researchers have described the role of pathogenic agents in the theory of the origin of antiphospholipid antibodies (APA) [7, 8]. APAs are a heterogeneous group of autoantibodies directed against phospholipid-protein complexes. Their role in the pathogenesis of APS, the most common form of thrombophilia with a genetic predisposition, has been proven. There are various theories explaining the involvement of AFA in the development of clinical manifestations of APS. The origin of AFA remains less studied. Particular attention is paid to the mechanisms of infection-induced production of antibodies and their role in modeling the further course of the disease. The association of infections with the development of APA has been described in a number of review epidemiological and experimental works [9, 10]. Many infectious diseases are accompanied by an increase in APL titers, which in some cases can lead to the appearance of clinical symptoms of APS [11, 12]. In rare cases, more than one agent has been identified as the source of infection. Viral infections have been most frequently described as an infectious trigger for AP induction [13]. The most interesting aspect of the association of viral infection with APA is the fact that

thrombosis develops in many patients who have had an infection. And although the fact of the occurrence of thrombosis under the influence of APA is unproven, the frequency of such coincidences leads to the question of whether the association of viruses with APA is pathogenic. There is a known relationship between APA and antibodies to β 2-glycoprotein I (β 2 -GpI), APS and infectious agents. Among the infectious diseases in which antibodies (AT) to β 2 -GpI are determined , there are viruses (parvovirus B 19, cytomegalovirus , HIV, varicella -zoster virus, Epstein - Barr virus, hepatitis B and C viruses , adenovirus, human T-lymphotropic virus type 1), bacteria (Streptococcus pyogenes , Staphylococcus aureus , Helicobacter pylori , Salmonella typhi , Mycobacterium leprae , Escherichia coli , Rickettsia typhi , Mycobacterium tuberculosis , Coxiella burnetti , Chlamydophila psittaci , Mycoplasma pneumoniae) and parasites (Plasmodium falciparum , Borrelia burgdorferi , Leptospirosis , Leishmania). APS, β2 - GpI - linked synthetic peptides, and infectious agents have high homology and show molecular mimicry between synthetic β2-GpI-related peptides designed to provide epitopes for anti - β2 - GpI antibodies and pathogenic structures [12]. β 2 -GpI is a “cleaner” molecule with a specific binding site for the negatively charged phospholipid phosphatidylserine (PS) [13]. By binding to PS, β 2 -GpI facilitates the removal of particles and apoptotic bodies from the circulatory system. Cellular microparticles are the main sources of PS expression. Thus, antibodies to β 2 -GpI can cause damage to cellular microparticles by masking β 2 -GpI molecules, resulting in the accumulation of cellular “garbage” that affects autoimmunity and the development of inflammation [12].

The purpose of the study was to study the features of the course of pregnancy in women with APS, depending on the therapy and the presence of TORCH infections.

MATERIALS AND METHODS

A prospective analysis of 137 individual records of pregnant women with abortions and APS was carried out. Examined women are divided into two groups according to the principle of the presence / absence of plasmapheresis procedures in the treatment regimen for miscarriage at the pregravid stage. In the 1st group (main) included women (n = 73) who were on preconception stage, complex therapy was carried out with the inclusion of plasmapheresis, in the 2nd group (comparisons, n = 64) - women who did not receive efferent therapy. The main element of complex therapy patients of both groups served the standard protocol treatment and prevention of venous thromboembolic complications according to clinical guidelines. Written informed consents were obtained. Each of the groups was divided into 2 subgroups according to the principle of the presence / absence of laboratory signs of active TORCH infections. So, in women of the 1st (–) and 2nd (–) subgroups, according to the results of laboratory studies, signs of TORCH infection activity were not observed.

In patients of the 1st (+) and The 2nd (+) subgroups showed activity of TORCH infections. Women of the 1st (+) and 2nd (+) subgroups up to the onset of pregnancy, therapy aimed at deactivating TORCH infections was carried out according to clinical recommendations. After leveling the signs of the activity of the infectious process and carrying out in patients of the 1st (+) subgroup plasmapheresis started planning pregnancy. The number of miscarriages suffered is comparable in groups and subgroups. The main laboratory criteria for the diagnostic verification of APS were not statistically significant. differences. The 3rd group (control, n = 28) included practically healthy women with a singleton, the first in a row, physiologically proceeding pregnancy, without spontaneous pathological interruptions of pregnancy in the anamnesis. The average age of the studied patients was 26.1±2.7 years. Statistically significant differences in age between patients of all groups was not revealed ($p > 0.05$). In order to identify infectious process, tracking the dynamics of its development, the effectiveness of treatment and verification of clinical and laboratory cure used the determination of antibodies - immunoglobulins of classes G (IgG) and M (IgM), their avidity, presence/absence of antigens infectious agents, their titer. The studies were carried out on automatic analyzers Architect 2000 (" Abbott ", USA) and Immulite 2000 (" Siemens healthcare Diagnostics, Germany). Key parameters of links hemostasis was determined using the study of platelet and plasma components. For this, we used an impedance aggregometer Multiplate (Roche, Switzerland). fibrinogen concentration, activity and content of blood coagulation factors, heparin, plasmin inhibitor, plasminogen, proteins C, S were determined on an automatic coagulometer ACL -700 (Instrumentation Laboratory, USA). All women examined had the most common polymorphisms of the genes of the system hemostasis: Leiden mutations, prothrombin gene, methylenetetrahydrofolate reductase, inhibitor mutations plasminogen activator. The study included only those patients who did not have laboratory evidence of the mutations listed above. Molecular studies of venous blood were performed using the polymerase chain reaction (PCR) on amplifiers Rotor - Gene (Qiagen GmbH, Germany) and DT-96 (NPO DNA-Technology LLC, Russia). Laboratory diagnosis of APS was carried out by identifying autoantibodies: lupus anticoagulant (LA), antibodies to phospholipids (IgG, IgM, IgA antibodies to cardiolipin, phosphatidylserine, glycoprotein, annexin , prothrombin) and/or to the β subunit of human chorionic gonadotropin (IgM and IgG). The presence of antibodies was determined on the analyzer MultiScan EX (Labsystems, Finland). Plasmapheresis was performed in patients included in the main group, observing clinical recommendations for the application of this procedure in preparation for pregnancy in order to remove from the blood (decreased concentration) of autoantibodies, and also indications and contraindications for efferent therapy. Statistical data processing was

carried out using the Statistica 6 program. The normality of the distribution of the results obtained in the variation series was assessed using the criterion Kolmogorov-Smirnov, as well as according to the rule of two and three sigma (σ). When comparing quantitative signs of two sets of unrelated samples, obeying the law of normal distribution, used Student's t -test. The Mann-Whitney test was applied if the compared sets of unrelated samples did not obey the law of normal distribution. The Wilcoxon test was used to compare two related samples. When comparing qualitative features, χ 2 was used. Critical level of significance statistical hypotheses in this study were taken equal to 0.05.

RESULTS AND DISCUSSION

According to the data, early toxicosis developed more than 2 times more often in the examined women of the 1st and 2nd groups, regardless on the therapy regimen used, the presence or absence of TORCH infections. The threat of spontaneous pathological termination of pregnancy in the first trimester in women of the 1st and 2nd groups was almost 10 times higher than in the control group. The lack of efferent therapy in patients with TORCH infections on the background of APS led to an increase in the risk of spontaneous pathological abortion up to 73%, which is more than 2 times more than in patients whose treatment regimen included plasmapheresis. In the second trimester, patients of all subgroups showed an increase in the incidence of preeclampsia, in women of the 1st (–) subgroup - almost 2 times compared with women in the control group. A different picture in the II trimester was formed by the frequency of the threat of abortion. So, if pregnant women of the main group have an increase frequency of this pathology is 2 times compared with pregnant in the control group was only a trend, the absence of plasmapheresis in the treatment regimen in preconception period in pregnant women of the comparison group led to a fivefold increase in the frequency of threatened abortion compared with pregnant women in the control group and a twofold increase compared to women of the 1st (–) subgroup (who underwent plasmapheresis). The presence of TORCH infections only exacerbated this dynamics, since in pregnant women of the 2nd (+) subgroup, who did not undergo efferent therapy, the threat of abortion developed 6 times more often than in women of the control group and 3 times more often than in women of the main group. Apparently, the structural trigger for such a clinical picture in the second trimester could be changes in the microcirculatory bed of the placenta, which was reflected in the development of placental insufficiency in patients. If in pregnant women of the main group, the increase in the detection of this pathology was only a trend, then in women of the comparison group, regardless of the presence or absence of TORCH infections, placental insufficiency developed 3 times more often than in the studied control group and 2 times more often than in women of the main group. In the third trimester, an

increase in the risk of preterm birth was observed in pregnant women of all subgroups, except for the 1st (+). The indicators of the threat of preterm birth in pregnant women of the 1st (+) subgroup did not differ from those in pregnant women of the control group and were 2.9 times less than in women of the 2nd (+) subgroup. The incidence of preeclampsia statistically significantly increased only when pregnant women had APS, TORCH infections and the absence of plasmapheresis in the therapy regimen during preconception preparation (2nd (+) subgroup), in other subgroups, the increase in the incidence of preeclampsia was only a trend. Placental insufficiency developed 2–3 times more often than in women of the control group in pregnant women with APS, regardless of the presence or absence of TORCH infections, as well as complex therapy, which was reflected in the absence of statistically significant differences in this parameter between subgroups. Fetal hypoxia in patients with APS, but without TORCH infections, regardless of the therapy (with or without plasmapheresis), developed with the same probability as in pregnant women in the control group. The presence of TORCH infections in women with APS, in the complex therapy of which plasmapheresis was used, contributed to an increase in the number of cases of fetal hypoxia by more than 50%, while the absence of efferent therapy methods led to a threefold increase in the number of cases of fetal suffering compared with pregnant control group and twice — in comparison with patients of the 1st (+) subgroup. Violation of fetal hemodynamics I A degree, according to cardiotocography, developed statistically significantly more often in all pregnant women with APS compared with women in the control group. At the same time, if in the studied main group the frequency of development of this pathology increased 3 times, then in the studied group of comparison - 6-10 times compared with pregnant women in the control group. It should be noted that in the subgroups of the main group, differences in the incidence of hemodynamic pregnant women did not have a fetus, while in the comparison group in TORCH -infected women, fetal hemodynamic disturbances occurred 2 times more often than in patients of the same group, but without TORCH infections. The use of plasmapheresis in the complex preparation of women for pregnancy against the background of APS, habitual miscarriage and TORCH -infections turned out to be much more effective than even the use of efferent therapy in TORCH -uninfected women, and even more so in women who did not undergo plasmapheresis. Probably, one of the key factors in the development of clinical signs of placental insufficiency, the threat of abortion, signs of fetal suffering was a pathogenic change in the parameters of the hemostasis system. The key change in the parameters of the hemostasis system, which was recorded in the dynamics of observation of pregnant women with APS, was an increase in blood thrombotic activity against the background of a decrease in the ability of the anticoagulant blood system to prevent the formation of blood clots. This

clinical picture was aggravated by the presence of TORCH infections and the absence of plasmapheresis in complex therapy in preparing women for pregnancy. Thus, fibrinolytic activity decreased almost 2 times below the norm only in women with APS on the background of TORCH infections and without the use of plasmapheresis (2nd (+) subgroup), while plasmapheresis in patients of the 1st (+) subgroup contributed to prevention of these changes. Moreover, if in women of the 2nd (+) subgroup in the first trimester of pregnancy there was a steady decrease in the number of platelets, which was only a trend, then in the II and III trimesters this decrease was already statistically significant compared with the indicators in pregnant women of the control group and 1st (–) subgroups. Changes in platelet aggregation with ristomycin, as well as the total number of active forms of platelets, which mainly increased significantly in patients of the comparison group, especially against the background of TORCH infections, indicated the state of thrombophilia in women in this group.

Output.

The features of the course of pregnancy are determined in women with antiphospholipid syndrome, depending on the ongoing complex therapy and the presence of TORCH infections. Early toxicosis developed more than 2 times more often in the studied women outside depending on the therapy regimen used, the presence or absence of TORCH infections. The threat of spontaneous pathological abortion in women with antiphospholipid syndrome in the first trimester was almost 10 times higher than in pregnant control group. Lack of efferent therapy in patients with TORCH infections on the background of antiphospholipid syndrome led to an increase in the risk of spontaneous pathological termination of pregnancy up to 73%, which is more than 2 times more than in patients whose therapy regimen included plasmapheresis. In the II trimester, in patients of the main group, an increase in the frequency of threatened abortion by 2 times compared to women in the control group was only a trend, while the absence of plasmapheresis in the treatment regimen for women in the comparison group led to a five-fold increase in this complications compared with patients in the control group and twice as compared with pregnant women who underwent plasmapheresis. The presence of TORCH infections exacerbated this dynamics, since in patients with TORCH infections who did not undergo efferent therapy, the threat of abortion developed 6 times more often than in pregnant women of the control group, and 3 times more often than in the studied main group. Placental insufficiency in women of the 2nd (+) subgroup developed 3 times more often than in pregnant women control group, and 2 times more often than in pregnant women of the main group. In the third trimester, an increase in the risk of preterm birth was observed in women of all subgroups, with the exception of the 1st (+), this indicator did not differ from that of women in the control group and was 2.9

times less than in pregnant women of the 2nd (+) subgroup. Fetal hypoxia in patients with antiphospholipid syndrome, but without TORCH infections, regardless of the therapy, developed with such the same frequency as in the control group. The presence of TORCH infections in women with APS, in complex therapy which used plasmapheresis, contributed to an increase in the number of cases of fetal hypoxia by more than 50%, while how the absence of methods of efferent therapy led to a threefold increase in the number of cases of fetal suffering compared with pregnant women in the control group and a twofold increase in comparison with pregnant women of the 1st (+) subgroup. Antiphospholipid syndrome combined with TORCH -infections and physiological hypercoagulability, as well as against the background of the absence of selective sorption of pathogenic autoimmune antibodies, caused a state of thrombophilia, the development of which also supported the decreasing capabilities of the anticoagulant system of the blood. Thus, in the course of the study The mutual influence of antiphospholipid syndrome, TORCH infections, the hemostatic system, as well as the inclusion of plasmapheresis in complex therapy on the likelihood of developing a new pregnancy and its course has been comprehensively studied. Mutual reinforcing shown the effect of antiphospholipid antibodies - class G immunoglobulins, TORCH infections and the number of previous miscarriages on the likelihood and physiological course of this pregnancy. An exceptionally positive effect on both the course of the antiphospholipid syndrome, as well as the deactivation of TORCH infections, was provided by plasmapheresis included in complex therapy in preparing the female body for pregnancy.

REFERENCES:

1. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, DE Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). Journal of Thrombosis and Haemostasis . 2006;4(2):295-306. 2. Bitsadze V.O., Khizroeva D.Kh. , Makatsaria N.A., Egorova E.S., Baimuradova S.M., Mashkova T.Ya. Antiphospholipid antibodies, their pathogenetic and diagnostic significance in obstetric pathology. Obstetrics, gynecology and reproduction. 2014;8(2):39-60. 3. Adamyan L.V., Kuzmin V.N., Arslanyan K.N., Kaznacheeva T.V., Kharchenko E.I. Modern approaches to the diagnosis and treatment of intrauterine infections. reproduction problems. 2015; 21(5):115-119. 4. Kuzmin V.N., Adamyan L.V. The problem of intrauterine infection in modern obstetrics. Infectious Diseases: News, Opinion, Learning . 2017;3(20):32-36. 5. Naumenko N.S.,

Nikonov A.P., Astsaturova O.R., Belova A.V. The structure of infectious screening of pregnant women: Russian and global practice. Archive of Obstetrics and Gynecology V.F. Snegirev. 2018;5(1):26-30. 6. Okhtyrskaya T.A., Yavorovskaya K.A., Shurshalina A.V., Nazarenko G.A. Implantation losses in IVF programs: the role of hereditary and acquired thrombophilia (literature review). reproduction problems. 2010;16(2):53-57. 7. Tetruashvili N.K. Habitual miscarriage. Obstetrics and Gynecology. News. Opinion. Training . 2017 ;4 (18):70-87. 8. Makatsariya AD, Khizroeva J, Bitsadze VO. Catastrophic antiphospholipid syndrome (ronald asherson syndrome and obstetric pathology. Journal of perinatal medicine . 2018;46(4):387-400. https :// doi . org /10.1515/ jpm -2017-0092 9. Martirosyan A.A., Manukyan G.P. Theories of the origin of antiphospholipid antibodies: the role of infectious pathogenic agents. Advances in modern biology. 2018;138(2):148-160. 10. Cervera R. Antiphospholipid syndrome. Thrombosis Research.2017 ;151 (suppl. P):43-47. https://doi.org/10.1016/S0049-3848(17)30066-X 11. Shoenfeld Y, Blank M, Cervera R, Font J, Raschi E, Meroni PL. Infectious origin of the antiphospholipid syndrome. Annals of the Rheumatic Diseases. 2006 ;65 (1):2-6. 12. Asherson RA, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, Lim E, Lau TC, Gurjal A, Jedryka-Góral A, ChwalinskaSadowska H, Dibner RJ, Rojas-Rodriguez J , García - Carrasco M, Grandone JT, Parke AL, Barbosa P, Vasconcelos C, Ramos-Casals M, Font J, Ingelmo M. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. medicine. 2001 ;80 (6): 355-377. 13. Abdel- Wahab N, Lopez- Olivo MA, Pinto- Patarroyo GP, SuarezAlmazor ME. Systematic review of case reports of antiphospholipid syndrome following infection. Lupus . 2016;25(14):1520-1531.