Case Report **Open Access**

Hristina Andreeva*, Marit Seip, Stanislava Koycheva

Live birth pregnancy outcome after first in vitro fertilization treatment in a patient with Systemic Lupus Erythematosus and isolated high positive IgA anti-β2glycoprotein I antibodies: a case report

DOI 10.1515/med-2017-0003
received October 7, 2016; accepted January 12, 2017

Abstract: IgA anti-β2glycoprotein I antibodies **(**IgA-anti-β2GPI) seems to be the most prevalent isotype in patients with Systemic Lupus Erythematosus (SLE) with a significant association to thrombotic events. Both SLE and antiphospholipid syndrome (APS) can be associated with implantation failure, fetal loss and obstetric complications. Recent reports highlight the clinical value of IgA-anti-β2GPI determination in supporting in vitro fertilization (IVF) treatment and IVF pregnancy outcomes. We report a 36-year-old female diagnosed with SLE, endometriosis and unexplained infertility. Conventional APS markers were consistently negative: anti-cardiolipin (aCL) and anti-β2GPI: IgG/IgM. She was then tested with reports of repeatedly high IgA-anti-β2GPI and tested positive from 2014 after IgA (aCL; anti-β2GPI) were established in our APS diagnostic panel. She underwent successful first IVF procedure with a 30 week live birth pregnancy outcome. During the follow up no lupus flare, thrombosis or ovarian hyperstimulation syndrome were registered. Serum IgA-anti-β2GPI and anti-dsDNA levels declined statistically significant during the second and third trimester. Titres of IgA-anti-β2GPI remained lower postpartum as well. This case highlights the clinical importance of IgA-anti-β2GPI testing for family planning, assisted reproduction and pregnancy in women with SLE and/or APS.

Keywords: IgA anti-beta2 GPI antibodies; Systemic lupus erythematosus; Antiphospholipid syndrome; Infertility; In vitro fertilization; assisted reproductive technology

1 Introduction

IgA anti-β2 glycoprotein I antibodies (IgA-β2GPI) seem to be the most prevalent isotype antiphospholipid antibody in patients with Systemic Lupus Erythematosus (SLE) with a significant association to thrombotic events [1]. Other conditions have also been described, such as unexplained recurrent spontaneous abortion/pregnancy loss, acute cerebral ischemia, cognitive dysfunction or transient ischemic attack [2]. IgA antiphospholipid antibodies are not currently recognized as formal laboratory criteria for antiphospholipid syndrome (APS), but according to the last international consensus guidelines on antiphospholipid antibodies (aPL), testing for IgA isotype is recommended for both anticardiolipin antibodies (aCL) and anti-*β*2GPI when results of conventional markers (IgG and/or IgM isotypes) are negative and APS is still suspected [3]. Indeed, the updated classification criteria for SLE proposed by the international group SLICC has included for the first time IgA aCL and IgA anti-β2GPI as valid tests for definition of SLE [4].

Regarding the assisted reproductive technology procedures (ARTs), which include ovarian stimulation, oocyte retrieval, in vitro fertilization (IVF), and transfer of the fertilized embryo into the uterus, recent studies attest to the relative safety of ART in patients with SLE and/ or APS. Especially, neither lupus flare nor thrombosis showed

***Corresponding author: Hristina Andreeva,** Division of Immunology and Transfusion Medicine, Department of Laboratory Medicine, University Hospital of North Norway, Tromsoe, Norway, E-mail: hristina.andreeva@unn.no
Marit Seip, Department of Rheumatology, University Hospital of North Norway, Tromsoe, Norway
Stanislava Koycheva, Division of Immunology and Transfusion Medicine, Department of Laboratory Medicine, University Hospital of North Norway, Tromsoe, Norway

unusually high prevalence in patients with SLE and/or APS undergoing ARTs [5]. On another hand, the clinical relevance of isolated IgA anti-β2GPI has also been suggested for unexplained recurrent spontaneous abortions, fetal death [6, 7] and recently for IVF pregnancy outcome [8]. Here, we report a case of a SLE patient with isolated high positive IgA-anti-β2GP which underwent successful first IVF procedure with a 30 weeks live birth pregnancy outcome.

2 Case report

We report a case of a 36 years old Caucasian female with a 17 year history of SLE, characterised by malar rash, leucopenia, photosensitivity, alopecia, Raynaud's phenomenon, arthritis, 3 episodes of peripheral facial paresis and endometriosis. Pregnancy was desired but not achieved naturally. No tubal obstruction found on laparoscopy.

After being repeatedly negative for "classical" APS markers: aCL and anti-β2GPI: IgG/IgM, was she tested high (≥40U/ml) IgA-anti-β2GPI positive in 2014 after IgA (aCL; anti-β2GPI) had been established in our APS diagnostic panel. Other members of aPL family such as anti-prothrombin, anti-phosphatidylserin, anti-annexin V, anti-phosphatidylglycerol antibodies were not performed in our patient. These newly discovered and persistently positive IgA aPL have been taken into account in preconception counseling and risk stratification for choice of assistant reproductive techniques (ovulation induction therapy and in vitro fertilisation). The patient underwent successful ARTs according the guidelines for ovarian stimulation and IVF in patients with SLE and/or APS published by Bellver and Pellicer [9]. Briefly, mild ovarian simulation, single frozen embryo transfer in a natural cycle and luteal phase support. Complications such as lupus flare, thrombosis or ovarian hyperstimulation have not been registered during the ARTs. Gravidity was obtained for the first and only IVF attempt. The fetal surveillance monitoring followed the local protocols of our hospital applied to high-risk pregnancies. Her pregnancy finished successfully with preterm (30 weeks) delivery and live birth. Some complications of prematurity were registered in the new-born during the early and late neonatal period. The placenta pathology showed signs of maternal vascular malperfusion with increased perivillous fibrin deposition and architectural disturbances without thrombosis (Figure 1). There were also moderate acute chorioamnionitis and funicitis.

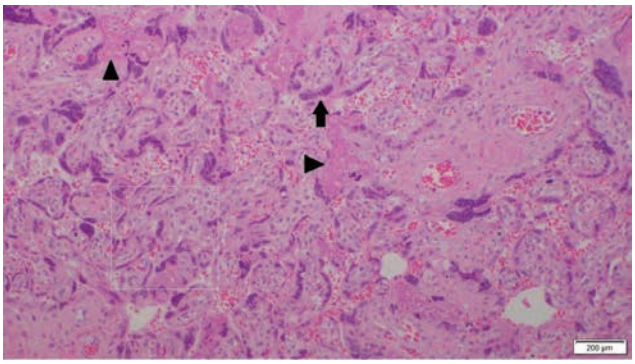

Figure 1: Histopathology of the placenta. A photomicrograph showing areas with accelerated maturation-increased perivillous fibrin deposition (arrowheads), increased amount syncytial knots (arrow) and agglutinated villi (square). These pathological changes are characteristic for maternal vascular malperfusion. Hematoxylin and eosin staining X10.

Conventional SLE treatment consisted of prednisolone, azathioprine and hydroxychloroquine during all assessment periods. Current antithrombotic treatment included low-dose aspirin and prophylactic doses of low molecular weight heparin and was administrated during ovarian stimulation, pregnancy and 6 weeks postpartum according the European League Against Rheumatism (EULAR) recommendations for ART and pregnancy in women with SLE and/or APS [10].

The disease course was evaluated as low to moderate SLE activity (SLEDAI: 4-6) with mild increase in the lupus activity in the form of arthritis, without renal involvement, pre-eclampsia or hypocomplementemia. During pregnancy she was diagnosed with two urinary tract infections treated with antibiotics, and one viral respiratory tract infection with mild elevation in liver enzymes at the time.

The routine laboratory studies: renal function tests, urine analysis, complete blood count and platelet count remained normal during all studied periods. Predictive serological biomarkers for maternal SLE disease activity (serum C3, C4 complement's fractions, anti-dsDNA titres), aPL antibodies levels as well as lupus anticoagulant have been monitored monthly before, during ARTs, first, second trimester and three months postpartum. The same parameters were tested every 2,5 weeks during the first (7½) month of the third trimester.

All SLE-autoantibodies and aPL were performed routinely using EliA kits (Thermo Fisher Scientific, Phadia AB, Uppsala, Sweden). Samples were considered positive when above the established cut-off points for each test. Statistical analysis of titres changing for anti-dsDNA and IgA-β2GPI was performed using SPSS Advanced Statistics 10.00. The results are expressed as the mean±SD. Anti-dsDNA and IgA-β2GPI values at all-time points were

compared with each other using Student's paired T-test. A probability (P) value <0.05 was considered as statistically significant (Table 1).

The fractions of complement (C3, C4) remained in normal range. Lupus anticoagulant was negative. Anti-SmD antibodies persisted always-high positive. Very low titres of aCL IgM were registered but not constantly. Their presence was interpreted of not great clinical significance. The serum levels of both anti-dsDNA and IgA-anti-β2GPI showed statically significant decrease at the second and third trimester compared to other checkpoints. In addition, titres of IgA-anti-β2GPI remained lower postpartum as well (Figure 2).

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the

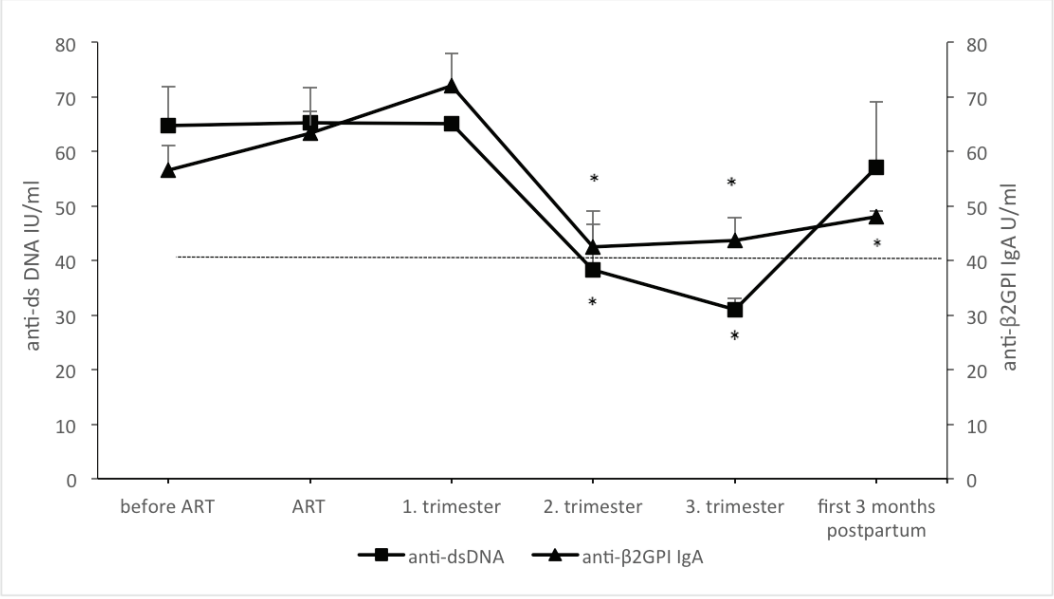

Figure 2: Course of anti-dsDNA (squares) and IgA-β2GPI (triangles) antibodies in the patient. The figure shows titers of anti-ds DNA (IU/ml) and IgA-β2GPI (U/ml) antibodies during different checkpoints of the follow-up compared to each other. Threshold for high positivity (dotted line) was ≥40 IgA-antiβ2GPI U/ml. Bars represent standard deviations of the means. (*: P<0.05). **Abbreviations:** ART: assistant reproductive treatment.

Table 1: Laboratory data of the patient

Follow-up period	Anti-ds DNA (IU/ml) (mean±SD)	Anti-SmD (EliA U/ml)	C3 g/l (mean±SD)	C4 g/l (mean±SD)	IgA-anti-β2GPI U/ml (mean±SD)	Other apL Abs MLP-U/ml (mean±SD)	LA
Before ART	64,8±7,3	>481	0,73±0,1	0,09±0,01	56,6±4,4	aCL IgM 13,2±1,7	negative
ART	65,3±6,4	>481	0,87±0,1	0,11±0,03	63,3±4,1	aCL IgM 18±1	negative
1. trimester pregnancy	65±1	>481	0,89±0,01	0,125±0,01	72±6	aCL IgM 16±0	negative
2. trimester pregnancy	38,3±8,4*	>481	0,89±0,02	0,1±0	42,5±6,5*	negative	negative
3. trimester pregnancy	31±2*	>481	1,11±0,04	0,11±0,03	43,6±4,3*	negative	negative
first 3 months postpartum	57±12	>481	1,1±0,11	0,15±0,01	48±1*	aCL IgM 16±0	negative

Abbreviations: ART: assistant reproductive treatment, aPL Abs: antiphospholipid antibodies, LA: lupus anticoagulant, aCL: anticardiolipin antibodie, MLP-U/ml: 1MPL-Unit corresponds to binding activity of 1mg/ml of cardiolipin IgM antibody purified from standard serum. **Normal ranges:** anti-ds DNA<15 IU/ml; anti-SmD<10 EliA U/ml; C3: 0,84-2,15g/l; C4: 0,08-0,33g/l; IgA-anti β2GPI<7U/ml; aCL IgM <10 MLP-U/ml- negative, aCL IgM 10-39 MPL-U/ml- low positive. **Statistical significance:** * p<0.05.

authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from the patient included in this case report.

3 Discussion

Despite the increasing evidence in the last twenty years for the diagnostic values of isolated IgA-β2GPI, they are not currently recognized as formal laboratory criteria for APS but recommended, when results of conventional markers are negative and APS is still suspected [3]. Probably, because of this fact the routine testing for IgA aPL is not yet wide available in Norway. Consequently, the real prevalence of isolated IgA-β2GPI positive patients with primary APS, SLE-related APS or miscellanea of others autoimmune and non-autoimmune conditions is underestimated.

In our case, the patient was repeatedly negative for "classical" APS criteria. With previous unremarkable history for thrombosis or obstetric APS was she tested from 2014 persistently high positive for exclusively IgA-anti-β2GPI. Of note, our patient has confirmed SLE but does not meet the clinical criteria for definite APS. Her repeated isolated peripheral seventh cranial nerve neuropathy is the only neurological manifestation, which is described in both SLE and APS [11]. Nevertheless, in the choice of ARTs, IVF procedure, anticoagulation treatment and pregnancy monitoring was she stratified as moderate-to-high risk group due to the presence of SLE and IgA-anti-β2GPI antibodies [10]. The most important risk factors, which were taken into consideration during the follow-up, are discussed separately below.

3.1 The impact of ARTs and IVF on SLE / APS complications

During the follow-up either ARTs or IVF induced raise in the lupus activity and/or thrombosis in our patient. In agreement with our findings, previous studies have also shown that, when controlled clinically and medically, SLE and APS do not express complications during ART/ IVF procedures [9].

The literature data are relative insufficient with only 3 reported studies with a total of 61 patients and 186 induction ovulation/IVF procedures. Lupus flare tend to be the most prevalent complication with prevalence 8%, 25% and 31% in these reports, while no thrombosis or only 5% prevalence was observed [12]. Recently review article by Levin and Lockshin also discussed that ART and/or IVF do not appear to increase the risk of SLE flare or thrombosis [5]. Stable autoimmune diseases for at least 6-12 months without major organ damage, like in our patient, do not seem to affect ART/IVF outcome.

3.2 The effect of IgA-anti-β2GPI on IVF outcome

In contrast to another reports, the presence of IgA-anti-β2GPI in our SLE patient did not cause failed first IVF procedure. Several studies have reported controversial significance of aPL (including IgA-anti-β2GPI) for IVF success. Chilcott et al. found that the prevalence of anti-β2GPI (IgG/IgM isotype) antibody in women referred for IVF was only 3.4% (11 of 328) and these antibodies do not affect the IVF outcome [13]. In a recent retrospective study of 594 women undergoing IVF, Steinvil et al. found no association between anti-β2GPI (IgG isotype) and the number of IVF cycles or fertility success rates [14]. In contrast, another report underlined significantly higher abortion rates and lower delivery rates in aCL-positive women undergoing IVF [15]. Recently, two small studies highlighted the high prevalence of IgA-β2GPI antibodies in the population of women undergoing IVF, but they did not find association between the presence of IgA-β2GPI and the numbers of IVF attempts or IVF outcome [8, 16]. Altogether these data summarized that the presence of aPL and in particular IgA-β2GPI antibodies are not predictive for success or failure of IVF, but should be regarded as a debasing factor for IVF pregnancy outcome.

3.3 APL and SLE as a risk factors for pregnancy morbidity and fetal health

The clinical relevance of isolated IgA anti-β2GPI has also been suggested for pregnancy morbidity. We performed regular measurement of routine biomarkers for SLE activity (anti-dsDNA, C3, C4) together with serum levels of all aPL including IgA-anti-β2GPI in our patient before, during pregnancy and postpartum. This is routine procedure for all SLE-pregnant women regardless pregnancy achievement (naturally or assistant). We aimed to evaluate the dynamics changes in the SLE disease activity and titres of IgA-β2GPI during the pregnancy and the impact for outcome. Our findings that IgA-β2GPI decreased significantly during the second and third trimester compared

to initial screening are in agreement with other studies which reported modest decrease in anti-β2GPI IgG [17] or aCL IgG [18] levels during pregnancy. There are only a few studies that have longitudinal evaluated aPL titres (but not IgA-β2GPI) throughout pregnancy. Despite the limitation in the providing evidences, it is generally agreed that aPL titres more often decline during pregnancy and that favorable pregnancy outcomes are associated with lower aPL levels [17], including the group of SLE patients [18]. Several potential mechanisms might explain the reason for aPL decline during pregnancy [17], but our report does not address these topics in details. To our knowledge, a serial IgA-β2GPI determination throughout pregnancy in SLE patients undergoing ART/IVF procedures has not been previously reported.

Furthermore, elevated levels of anti-dsDNA in SLE patients seem to correlate with adverse pregnancy outcomes or development of active lupus nephritis [18]. The association of anti-dsDNA with aPL antibodies may suggest an increased risk for prematurity or fetal loss [19]. In addition, decreasing titers and/or disappearance of aCL have been related with improved fetal prognosis in a subset of pregnant women with APS or with APS secondary to SLE [18]. Our results are in agreement with these clinical observations. The declined titres of both anti-dsDNA and IgA-β2GPI antibodies during the pregnancy in our patient could be associated with lack of SLE complications and favorable pregnancy outcome (preterm live birth), rather than with no accomplished pregnancy.

3.4 The impact of isolated IgA-β2GPI on pregnancy outcome

With respect to clinical values of IgA-β2GPI for IVF pregnancy outcome, Paulmyer-Lacroix et al. showed that positivity of IgA-β2GPI was significantly associated with abnormal IVF pregnancy outcome such as premature embryo or fetal losses [8]. In a population of 40 IVF patients in their study, no accomplished pregnancy with full term live birth was observed in IgA-β2GPI positive (5 of 40) IVF patients. Previous studies have also reported association of IgA isotype with clinical manifestations of obstetric APS. A study by Lee SR et al. showed that in sub-group of women with intra-uterine fetal demise and unexplained miscarriages who were previously negative for aPL antibodies, IgA anti-β2GPI was most commonly found [15]. Similar findings have been reported in case series of five patients with isolated elevation of IgA anti-β2GPI antibodies and history of unexplained recurrent abortion, intrauterine fetal death or preterm delivery because of pre-eclampsia [2]. Similarly, in a group of 36 women with unexplained recurrent abortions and negative for IgG anti-β2 GPI, the presence of isolated IgA-β2GPI was found in nearly 14% of these women [6]. Although SLE disease in our patient was an additional risk factor for adverse pregnancy outcome or unfavourable fetal health, the presence of isolated IgA anti-β2GPI could be associated only with preterm live birth (from all above mentioned possible complications).

3.5 The impact of IgAβ2-GPI antibodies on the maternal-fetal interface

They are postulated several mechanisms about the pathogenic role of IgA isotype β2-GPI antibodies during pregnancy. In particular, Yamada et al. have proposed the local thrombogenic action of IgA-β2GPI antibodies in syncytiotrophoblast and/or uterine spiral artery, which might lead to early pregnancy loss [6]. With respect to thrombogenic effect of IgA aPL antibodies, Ruiz-Lemon et al. demonstrated that affinity-purified IgA anti-β2GPI isolated from patients with exclusive IgA isotype positivity induced thrombus formation in femoral vein in a mouse model [20]. Recently, Pericleous et al. evaluated in a multicenter cohort study (using sera from 230 APS patients, 119 SLE but not APS patients, and 200 healthy controls) the utility of IgG, IgM, IgA assays to each of aCL, β2GPI and Domain I antibodies in APS [21]. The authors found an association between the presence of IgA-β2GPI and anti-Domain I antibodies and thrombotic but not obstetric complications in patients with APS. Alternatively, non-thrombotic mechanism for anti-β2GPI antibodies action during early pregnancy was also proposed. IgA anti-β2GPI may directly influence the normal fertilization and embryo development likewise IgG anti-β2GPI, which has been known to inhibit in vitro proliferation of extravillous trophoblast and choriocarcinoma cells [22]. However, and to date, they are limited data on IgA anti-β2GPI antibody and its association with thrombosis or other complications during pregnancy. Regarding our patient it is unclear whether these antibodies alone were directly pathogenic and caused maternal vascular malperfusion on placenta or they were "only" a persistent marker of an underlying SLE placenta damage. In particular, such patients with SLE and/or APS are at high risk for placental insufficiency and intrauterine growth restriction as a result of inflammation rather than thrombosis at the maternal-fetal interface [23]. In our case, it is perhaps more likely that the placental dysfunction has led to a premature rupture of membranes and the later developed acute chorioamnionitis is a second finding in this context.

As father research, the pathogenicity of IgA-β2GPI for both normal and assistant fertilization, and embryo development, as well as the origin of IgA anti-β2GPI secretions in the genital tract remains to be clarified.

4 Conclusion

In summary, this case suggests that measurement of IgA-anti-β2GPI may be useful and may enable the clinician to identify additional group of patients with incomplete APS clinical expression, who do not meet the current diagnostic criteria for APS. In addition, the detection of IgA isotype aPL antibodies might influence the appropriated management of family planning, risk stratification, ARTs and pregnancy monitoring in SLE and/or APS patients.

To our knowledge, such a longitudinal determination of isolated high IgA-anti-β2GPI antibodies in SLE patient, who successfully underwent first IVF procedure with live birth pregnancy outcome have not been previously reported. Further studies are warranted to investigate the clinical and pathological value as well as the prognostic power of isolated IgA-β2GPI antibodies in women's reproductive health.

Acknowledgments: We would like to thank Dr. Cecilie Nordbakken (Department of Pathology, University Hospital of North Norway) for the provision of pathology report and photomicrograph of histological findings.

Conflict of interests: No authors report any conflict of interest.

References

[1] Andreoli L., Fredi M., Nalli C., Piantoni S., Reggia R., Dall 'Arra F., et al., Clinical Significance of IgA Anti-Cardiolipin and IgA anti-β2glycoprotein I antibodies. Curr rheumatol Rep., 2013, 15, 343

[2] Kumar S., Papalardo E., Sunkureddi P., Najam S., González EB., Pierangeli SS., Isolated elevation of IgA anti-β2glycoprotein I antibodies with manifestations of antiphospholipid syndrome: a case series of five patients. Lupus, 2009, 18, 1011-1014

[3] Miyakis S., Lockshin M.D., Atsumi T., Branch D.W., Brey R.L., Cervera R., et al., International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS), J Thromb Haemost., 2006, 4 (2), 295-306

[4] Petri M., Orbai A.M., Alarcón G.S., Gordon C., Merrill J.T., Fortin P.R., et al., Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus, Arthritis Rheum., 2012, 64 (8), 2677-2686

[5] Levine A.B., and Lockshin M.D., Assisted reproductive technology in SLE and APS, Lupus, 2014, 23, 1239–1241

[6] Yamada H., Tsutsumi A., Ichikawa K., Kato E.H., Koike T., Fujimoto S., IgA-class anti-beta2-glycoprotein I in women with unexplained recurrent spontaneous abortion, Arthritis Rheum., 1999, 42 (12), 2727-2728

[7] Lee R.M., Branch D.W., Silver RM., Immunoglobulin A anti-beta2-glycoprotein antibodies in women who experience unexplained recurrent spontaneous abortion and unexplained fetal death, Am J Obstet Gynecol., 2001, 185 (3), 748-753

[8] Paulmyer-Lacroix O., Despierres L., Courbiere B., Bardin N., Antiphospholipid antibodies in women undergoing In vitro fertilization treatment: clinical value of IgA anti-β2glycoprotein I antibodies determination, Biomed Res Int., 2014 https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC4055657/314704

[9] Bellver J. and Pellicer A., Ovarian stimulation for ovulation induction and in vitro fertilization in patients with systemic lupus erythematosus and antiphospholipid syndrome, Fertil Steril., 2009, 92, 1803-1810

[10] Andreoli L., Bertsias G.K., Agmon-Levin N., S Brown S., Cervera R., Costedoat-Chalumeau N., et al., EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome, Ann Rheum Dis Published Online First: [25.0. 2016] DOI:10.1136/ annrheumdis-2016-209770

[11] Honczarenko K, Budzianowska A, Ostanek L., Neurological syndromes in systemic lupus erythematosus and their association with antiphospholipid syndrome, Neurol Neurochir Pol., 2008, 42 (6) 513-517

[12] Orquevauxa P., Masseaub A., Le Guernc V., Gayetd V., Vauthiere D., Boutin D., et al., In vitro fertilization and systemic lupus erythematosus or antiphospholipid syndrome: An update, La revue de medicine interne, 2015, 36, 154-158

[13] Chilcott I.T., Margara R., Cohen H., Rai R., Skull J., Pickeringe W.,et al., Pregnancy outcome is not affected by antiphospholipid antibody status in women referred for in vitro fertilization, Fertil Steril., 2000, 73, 526-530

[14] Steinvil A., Raz R., Berliner S., Steinberg D.M., Zeltser D., Levran D., et al., Association of common thrombophilias and antiphospholipid antibodies with success rate of in vitro fertilization, Thromb Haemost., 2012, 108, 1192-1197

[15] Lee S.R., Park E.J., Kim S.H., Chae H., Kim C.H., Kang B.M., Influence of antiphospholipid antibodies on pregnancy outcome in women undergoing in vitro fertilization and embryo transfer. Am J Reprod Immunol., 2007, 57, 34-39

[16] Sanmarco M., Bardin N., Camoin L., Beziane A., Dignat-George F., Gamerre M., et al., Antigenic profile, prevalence, and clinical significance of antiphospholipid antibodies in women referred for in vitro fertilization. Ann N Y Acad Sci., 2007, 1108, 457-465

[17] Yelnik C.M., Porter T.F., Branch D.W., Laskin C.A., Merrill J.T., Guerra M.M., et al., Brief Report: Changes in Antiphospholipid Antibody Titers During Pregnancy: Effects on Pregnancy Outcomes. Arthritis Rheumatol., 2016, 68 (8), 1964-1969

[18] Salazar-Paramo M., Jara L., Ramos A., Barile L., Machado G., Garcia-De La Torre I., Longitudinal study of antinuclear and anticardiolipin antibodies in pregnant women with systemic

lupus erythematosus and antiphospholipid syndrome, Rheumatol Int., 2002 22, 142-147
[19] Khamashta M.A., Ruiz-Irastorza G., Hughes G., Systemic Lupus erythematosus flares during pregnancy, Rheum Dis Clin N Am., 1997, 1:15-29
[20] Ruiz-Limon P., Romay-Penabad Z., Carrera Marin A.L., IgA anti-β2glycoprotein I antibodies are pathogenetic in a mouse model of APS, Arthritis Rheum., 2012, 64, S742 [abstract 1731]
[21] Pericleous C., Ferreira I., Borghi O., Pregnolato F., McDonnell T., Garza-Garcia A., et al., Measuring IgA Anti-β2-Glycoprotein I and IgG/IgA Anti-Domain I Antibodies Adds Value to Current Serological Assays for the Antiphospholipid Syndrome, 2016, PLOS ONE / DOI: 10.1371/ journal.pone.0156407
[22] Chamley L.W., Duncalf A.M., Mitchell M.D., Johnson P.M., Action of anticardiolipin and antibodies to b2-glycoprotein-I on trophoblast proliferation as a mechanism for fetal death, Lancet, 1998, 352, 1037-1038
[23] Cervera R., Balasch J., Autoimmunity and recurrent pregnancy losses, Clin Rev Allergy Immunol., 2010, 39 (3):148-152