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ANTIPHOSPHOLIPID SYNDROME AND PREGNANCY

ANTIFOSFOLIPIDNI SINDROM I TRUDNOĆA

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Abstract

Antiphospholipid syndrome (APS) is a chronic autoimmune disease characterized by the presence of antiphospholipid autoantibodies, such as anticardiolipin antibodies (aCL), antiβ2 glycoprotein 1 antibodies (aβ2GP1), and circulating lupus anticoagulant (LA).

The clinical festures include recurrent thrombosis of the arteries, veins, and microvasculature, which are the main features of vascular APS (vAPS), and/or obstetric complications that are part of obstetric APS (oAPS).

Obstetric complications have a direct effect on maternal and fetal morbidity, causing recurrent pregnancy miscarriages, fetal death, and signs of placental insufficiency that include preeclampsia, intrauterine growth restriction, and HELLP *(Hemolysis, Elevated Liver enzymes, and Low Platelets)* syndrome.

In APS, thrombosis is the most prominent feature of the disease. In oAPS, the main pathological findings include impaired spiral artery remodeling, decidua inflammation with neutrophil infiltration, local tumor necrosis factor (TNF) -α production, deposition of complement split products, and placental infarction, which suggest a state of thrombo-inflammation. Antiphospholipid antibodies have both a direct embryotoxic and an effect on the placenta, causing a pro-inflammatory state, disrupting trophoblast development and implantation, and impaired spiral artery remodeling.

Standard oAPS therapy includes low-molecular-weight heparin and low-dose aspirin.

Approximately 20–30% of oAPS patients do not benefit from standard treatment, and additional therapeutic options are necessary in those refractory cases, which may include small doses of prednisolone, hydroxychloroquine, plasmapheresis, immunoglobulins, TNF-α inhibitors, statins, and eculizumab.

Keywords: antiphospholipid syndrome, obstetric antiphospholipid syndrome, antiphospholipid antibodies, thrombosis, inflammation, pregnancy morbidity

Sažetak

Antifosfolipidni sindrom (APS) je kronična autoimunosna bolest karakterizirana prisutnošću antifosfolipidnih protutijela kao što su lupus antikoagulans (LA), antikardiolipinska protutijela (aCl) i anti-β2 glikoprotein I protutijela (aβ2GPI). Klinička slika može varirati od pojave tromboze vena, arterija i mikrožilja koja je klinička slika tzv. vaskularnog APS-a (vAPS) i/ili *opstetričkih* komplikacija koje su obilježje opstetričkog APS-a (oAPS).

Najčešća su komplikacija oAPS-a višestruki pobačaji, fetalna smrt te prijevremeni porod zbog insuficijencije posteljice koja uzrokuje zastoj u fetalnom rastu, preeklampsiju ili HELLP-sindrom (hemoliza, povišeni jetreni enzimi i niski trombociti; engl. *hemolysis, elevated liver transaminase enzymes, low platelet counts*).

U vAPS-u je tromboza vodeće kliničko obilježje bolesti, dok u oAPS-u vodeća patološka obilježja uključuju nepotpuno remodeliranje spiralnih arterija, upalu decidue uz infiltraciju neutrofila, lokalnu sintezu *čimbenika tumorske nekroze alfa* (engl. *tumor necrosis factor* [TNF] -α), odlaganje komponenti komplementa i infarkte posteljice koji upućuju na stanje tromboinflamacije.

Antifosfolipidna protutijela imaju izravan embriotoksični učinak djelujući i na embrij i na posteljicu, aktivirajući proupalno stanje i uzrokujući prekid normalnog razvoja trofoblasta te posljedično dovode do nemogućnosti implantacije i nepotpunog remodeliranja spiralnih arterija. Standardna terapija u oAPS-u uključuje niskomolekularni heparin i niske doze acetilsalicilne kiseline. U 20 – 30% slučajeva bolesnice s oAPS-om imat će *opstetričke* komplikacije unatoč standardnoj terapiji. U tim refraktornim slučajevima dodatna terapija je potrebna, a može uključivati male doze prednizolona, hidroksiklorokin, plazmaferezu, imunoglobuline, TNF-α inhibitore, statine i ekulizumab.

Ključne riječi: antifosfolipidni sindrom, opstetrički antifosfolipidni sindrom, antifosfolipidna protutijela, tromboza, upala, patologija trudnoće

INTRODUCTION

Antiphospholipid syndrome (APS) is a chronic autoimmune disease with main clinical features that include recurrent thrombosis of the arteries, veins, microvasculature, or/and obstetric complications. The main characteristics of the disease are the presence of antiphospholipid autoantibodies (aPL): anticardiolipin antibodies (aCL) directed against membrane anion phospholipids, antiβ2 glycoprotein 1 antibody *(aβ2GPI)* directed against β2 glycoprotein I (a cardiolipin binding factor), and circulating lupus anticoagulant (LA) (1).

The estimated incidence of the disease is around 2 cases per 100,000, and prevalence is around 45 per 100,000. The prevalence of aPL with obstetric complications is 6–9%, and with vascular complications it is 9–10% (2).

The prevalence of aPL in seemingly healthy individuals is around 5% and it is more likely to be found in elderly patients (3).

Traditionally, APS is subcategorized into 1.) Primary (PAPS), in which no associated systemic autoimmune disease exists, 2.) Secondary (SAPS), which is accompanied by systemic autoimmune disease, such as systemic lupus erythematosus (SLE), and 3.) Catastrophic APS (CAPS) in which thrombosis affects multiple organs in a short period of time (4).

DIAGNOSIS

For the diagnosis of APS to be established, a clinical criterion, such as venous, arterial, or microvasculature thrombosis and/or obstetric complications, in combination with persistently circulating aPL, must be present (5).

The Sapporo criteria were established in 1998 and updated in 2006 as the Sydney criteria. Patients were classified as having APS if they had a clinical event (vascular thrombosis and/or pregnancy morbidity) along with laboratory criteria that were defined as at least double positive aPL (LA, aCL IgG/IgM in medium to high titer, or aβ2GPI IgG/IgM higher than the 99th percentile), and they were tested 12 weeks apart (6).

UVOD

Antifosfolipidni sindrom (engl. *antiphospholipid syndrome*, APS) kronična je autoimuna bolest čija klinička slika najčešće uključuje rekurentnu arterijsku i vensku trombozu, mikrovaskulature i/ili opstetričke komplikacije. Glavne su karakteristike bolesti prisutnost antifosfolipidnih autoantitijela (aPL): antikardiolipinska antitijela (aCL) usmjerena protiv membranskih anionskih fosfolipida, antiβ2 glikoprotein 1 antitijela (aβ2GPI) usmjerena protiv β2 glikoproteina I (faktor vezanja kardiolipina) i cirkulirajući lupus antikoagulans (LA)(1).

Procijenjena incidencija bolesti je oko 2:100.000 u općoj populaciji, a prevalencija je oko 45:100.000 u općoj populaciji. Prevalencija aPL-a s opstetričkom komplikacijom je 6 – 9%, a s vaskularnom 9 – 10% (2).

Prevalencija aPL-a u naizgled zdravih osoba jest oko 5% i vjerojatnije je da će biti prisutna u starijih bolesnika (3).

Što se tiče tradicionalne podjele, APS je bolest koja je podijeljena u tri potkategorije: 1.) primarni APS (engl. *primary antiphospholipid syndrome*, PAPS) u kojem ne postoji pridružena sistemska autoimuna bolest; 2.) sekundarni APS (engl. *secondary antiphospholipid syndrome*, SAPS) u kojem se javlja sistemska autoimuna bolest, poput sistemskoga eritemskog lupusa (SLE) i 3.) katastrofični APS (engl. *catastrophic antiphospholipid syndrom*e, CAPS) u kojem tromboza zahvaća više organa u kratkom razdoblju (4).

DIJAGNOZA

Da bi se postavila dijagnoza APS-a mora postojati klinički kriterij poput venske, arterijske ili mikrovaskularne tromboze i/ili opstetričkih komplikacija, u kombinaciji s trajno cirkulirajućim aPL-om (5).

Kriteriji Sapporo klasifikacije uspostavljeni su 1998. i ažurirani 2006. i to pod nazivom Sydneyevi kriteriji. Bolesnice su klasificirane kao one koje imaju APS ako su doživjele klinički događaj (vaskularna tromboza i/ili morbiditet u trudnoći) zajedno s laboratorijskim kriterijima koji su definirani kao najmanje dva puta pozitivni aPL (LA, aCL IgG/IgM u srednjem do visokom titru ili aβ2GPI IgG/IgM viši od 99. percentila), s tim da su ta testiranja provedena u razmaku od 12 tjedana (6).

For the diagnosis of obstetric APS, the clinical criteria defining pregnancy morbidity included a) one or more unexplained deaths of a morphologically normal fetus at/beyond the 10th week of gestation; b) one or more premature births at/before the 34th week of gestation due to severe preeclampsia (PEC)/eclampsia, or severe placental insufficiency; (PI) c) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation (other possible reasons such as chromosomopathy, hormonal or anatomy abnormalities were excluded) (6).

The 2023 ACR/EULAR APS criteria require an entry criterion of at least one positive aPL test within three years of identification of clinical criterion, followed by additive weighted criteria (1–7 points each) divided into six clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and two laboratory domains (lupus anticoagulant functional coagulation assays, and solid-phase enzyme-linked immunosorbent assays for IgG/IgM aCL and aβ2GPI. For the established diagnosis, at least 3 points in the laboratory domain and 3 points in the clinical domain are needed (7).

When defining pregnancy morbidity, the following clinical criteria are included: a) three or more consecutive pre-fetal (<10th week) and/or early fetal (10w 0d – 15w 6d) deaths, which is weighted as 1 point, b) fetal death (16w 0d – 33w 6d) in the absence of PEC or PI with severe features — 1 point; c) PEC or PI with severe features (<34w 0d) with/without fetal death — 3 points; d) PEC and PI with severe features (<34w 0d) with/without fetal death — weighted the most as 4 points (7).

OBSTETRIC ANTIPHOSPHOLIPID SYNDROME

Obstetric complications are one of the significant manifestations of APS that have a direct effect on maternal and fetal morbidity, causing recurrent pregnancy miscarriages, fetal death, and signs of placental insufficiency, such as preeclampsia, intrauterine growth restriction, and HELLP *(Hemolysis, Elevated Liver enzymes, and Low Platelets)* syndrome (8).

PATHOPHYSIOLOGY OF OBSTETRIC ANTIPHOSPHOLIPID SYNDROME

Thrombosis, the most prominent feature of vascular APS (vAPS), was once thought to be the primary mechanism in the pathophysiology of obstetric APS.

Pathological examinations of the placentas in patients with APS have revealed changes beyond just thrombosis. These changes include impaired spiral artery remodeling, inflammation of the decidua with neutrophil infil-

Za dijagnozu opstetričkog APS-a, klinički kriteriji koji definiraju morbiditet u trudnoći uključivali su a) jednu ili više neobjašnjivih smrti morfološki normalnog fetusa u/nakon desetog tjedna gestacije; b) jedan ili više prijevremenih poroda u/prije 34. tjedna gestacije zbog teške preeklampsije (engl. *preeclampsia*, PEC) / eklampsije ili teške insuficijencije posteljice (engl. *placental insufficiency*, PI); c) tri ili više neobjašnjivih uzastopnih spontanih pobačaja prije desetog tjedna gestacije (drugi mogući razlozi kao što su kromosomopatija, osim hormonalnih ili anatomskih abnormalnosti) (6).

Klasifikacijski kriteriji za APS reumatoloških društava *American College of Rheumatology/European League Against Rheumatism* (ACR/EULAR) iz 2023. zahtijevaju kao ulazni kriterij najmanje jedan pozitivan aPL test unutar tri godine od identifikacije kliničkog kriterija, nakon čega slijede aditivni ponderirani kriteriji (1 – 7 bodova svaki) podijeljeni u šest kliničkih domena (makrovaskularna venska tromboembolija, makrovaskularna arterijska tromboza, mikrovaskularna i opstetrička domena, domena srčanih zalistaka i hematološka domena) i dvije laboratorijske domene (lupus antikoagulans test funkcionalne koagulacije i enzimski povezani imunosorbentni test u čvrstom stanju (engl. *Enzyme-Linked Immunosorbent Assay*, ELISA) za IgG/IgM aCL i aβ2GPI. Za postavljenu dijagnozu potrebna su najmanje tri boda u laboratorijskoj domeni i tri boda u kliničkoj domeni (7).

Pri definiranju morbiditeta u trudnoći uključeni su sljedeći klinički kriteriji: a) tri ili više uzastopnih predfetalnih (< 10 tjedana) i/ili ranih fetalnih (10 tjedana 0 dana – 15 tjedana 6 dana) smrti, što se ponderira 1 bodom, b) fetalna smrt (16 tjedana 0 dana – 33 tjedna 6 dana) bez prisutnosti PEC-a ili PI-a s teškim značajkama: 1 bod; c) PEC ili PI s teškim značajkama (< 34 tjedana 0 dana) s fetalnom smrti ili bez nje: 3 boda; d) PEC i PI s teškim značajkama (< 34 tjedna 0 dana) s fetalnom smrti ili bez nje: ponderirani najviše kao 4 boda (7).

OPSTETRIČKI ANTIFOSFOLIPIDNI SINDROM

Opstetričke komplikacije imaju izravan učinak na morbiditet majke i fetusa, uzrokujući ponavljajuće pobačaje u trudnoći, fetalnu smrt i znakove insuficijencije posteljice, preeklampsije, zastoja rasta fetusa (engl. *intrauterine growth restriction*, IUGR) i HELLP sindrom (hemoliza, povišeni jetreni enzimi i niski trombociti, engl. *Hemolysis, Elevated Liver enzymes, and Low Platelets*) (8).

PATOFIZIOLOGIJA OPSTETRIČKOGA ANTIFOSFOLIPIDNOG SINDROMA

Tromboza, koja je najistaknutija značajka vaskularnog APS-a (vAPS), nekoć se smatrala primarnim mehanizmom u patofiziologiji opstetričkog APS-a.

tration, local production of tumor necrosis factor (TNF)-α, deposition of complement split product, and placental infarction. All these findings suggest that thrombo-inflammation is the primary cause of the condition. (9,10).

Additionally, it is important to note that not all patients with oAPS will develop vAPS, and vice versa. This understanding has helped distinguish vAPS from oAPS as a distinct pathophysiological mechanism.

In 2017. *Taraborelli et al.* performed a multicentric, retrospective study that included 115 women diagnosed with primary APS. During the 18-year follow-up period, 19% (6/31) of patients with a history of pregnancy morbidity but without a prior history of thrombosis developed thrombosis during the follow-up period, and 12% of patients (6/49) with a history of thrombosis developed an obstetrical adverse outcome during the follow-up period (11).

A retrospective multicentric study conducted in Israel revealed that among primary APS patients, 21.2% of patients with oAPS developed arterial thrombosis and 6% of them developed venous thrombosis during the 15-year follow-up period (12).

To facilitate understanding of the pathophysiology of oAPS, it is important to comprehend placental development during a normal pregnancy.

A fertilized egg rapidly undergoes multiple mitotic cleaves and reaches the uterine cavity. There, it is differentiated into blastomere, and then morula until the blastocyst stage is reached.

Blastocystis comprises the inner cell mass (ICM)-embryonic stem cells, and cells surrounding and protecting ICM- trophectoderm cells. From the trophectoderm, cytotrophoblast arises (13). One part of the cytotrophoblast is developed in syncytiotrophoblast by fusing and growing towards the placenta primed for implantation through decidualization. Syncytiotrophoblast has multiple roles: the role of connecting to the uterus by covering the surface of the villi, secreting hormones like progesterone, leptin, lactogen, and human chorionic gonadotropin which are essential to maintain early pregnancy, forming intervillous space by secreting protease in the decidua. One part of the cytotrophoblast is differentiated in extravillous trophoblasts that invade the uterine spiral arteries and remodel them into non-vasoactive large-bore conduits (14). This process is essential for future fetal development because impaired spiral artery remodeling is one of the main culprits in the pathology of placental insufficiency, leading to preeclampsia and fetal growth restriction (15).

In oAPS, antiphospholipid antibodies have a major role in the pathophysiology of the disease. *In vitro* studies have demonstrated that they directly affect the proliferation and growth of trophoblasts and lead to the loss of trophoblast-endothelium interactions. There is a reduced invasion of extravillous trophoblast

Patološkim ispitivanjima posteljica u bolesnica s APS-om otkrivene su i druge promjene osim same tromboze. Te promjene uključuju poremećeno remodeliranje spiralne arterije, upalu decidue s neutrofilnom infiltracijom, lokalnu produkciju faktora nekroze tumora (TNF)-α, taloženje produkta cijepanja komplementa i infarkt posteljice. Svi ovi nalazi upućuju na to da je tromboupala primarni uzrok ove bolesti. (9,10)

Osim toga, bitno je napomenuti da neće sve bolesnice s opstetričkim APS-om (oAPS) razviti i vaskularni (vAPS), i obrnuto. Time se vAPS mogao razlikovati od oAPS-a i to kao zasebni patofiziološki mehanizam.

Godine 2017. Taborelli i suradnici proveli su multicentričnu retrospektivnu studiju u kojoj je sudjelovalo 115 žena s dijagnozom primarnog APS-a. Tijekom 18-godišnjeg razdoblja praćenja, 19% (6/31) bolesnica s poviješću morbiditeta u trudnoći, ali bez prethodne anamneze tromboze, razvilo je trombozu tijekom razdoblja praćenja, a u 12% bolesnica (6/49) s prethodnom anamnezom tromboze došlo je do razvoja opstetrički nepovoljnog ishoda tijekom razdoblja praćenja (11).

Retrospektivna multicentrična studija koja je provedena u Izraelu otkrila je da je među bolesnicama s primarnim APS-om 21,2% bolesnica s oAPS-om razvilo arterijsku, a 6% vensku trombozu tijekom 15-godišnjeg razdoblja praćenja (12).

Kako bi se olakšalo razumijevanje patofiziologije oAPS-a, bitno je shvatiti razvoj posteljice tijekom normalne trudnoće.

Oplođeno jajašce brzo prolazi kroz višestruke mitotičke diobe i dospijeva u maternicnu šupljinu. Ondje se diferencira u blastomeru, zatim morulu i dostiže stadij blastociste.

Blastocista sadrži unutarnju staničnu masu (engl. *inner cell mass*, ICM), embrijske matične stanice i stanice koje okružuju staničnu masu i štite unutarnju staničnu masu, stanice trofektoderma. Iz trofektoderma razvija se citotrofoblast (13). Jedan dio citotrofoblasta razvija se u sinciciotrofoblastu spajanjem i rastom prema posteljici pripremljenoj za implantaciju kroz proces decidualizacije. Sinciciotrofoblast ima više uloga: ulogu povezivanja s maternicom pokrivanjem površine resica, ulogu lučenja hormona poput progesterona, leptina, laktogena i humanoga korionskog gonadotropina koji su bitni za održavanje rane trudnoće te ulogu stvaranja interviloznog prostora lučenjem proteaze u decidui. Jedan dio citotrofoblasta diferenciran je u ekstravilozne trofoblaste koji napadaju spiralne arterije maternice i preoblikuju ih u nevazoaktivne kanale velikog promjera (14). Taj je proces neophodan za budući razvoj fetusa jer je poremećeno remodeliranje spiralne arterije jedan od glavnih krivaca u patologiji insuficijencije posteljice, što dovodi do preeklampsije i zastoja rasta fetusa (15).

with impaired spiral artery remodeling. aPL antibodies also trigger the production of pro-inflammatory cytokines (interleukin (IL)-1, IL-7, IL-8) that attract monocytes and neutrophils, leading to macrophage activation and release of neutrophil extracellular traps (NETosis), which results in inflammation around trophoblast and apoptosis. Additionally, they activate macrophages and complement deposition, thus promoting inflammation around trophoblasts and apoptosis. Complement activation leads to local TNF-α production and secretion, adding to a vicious inflammation circuit. (14,16,17)

Animal models and in vitro research showed the direct embryotoxic activity of aPL. Antibodies taken from women with APS directly affect the growth and viability of animal embryos. (18, 19)

In 2013, Gardiner and the authors conducted research that included around 190 women with APS with vascular and obstetric manifestations. Interestingly, over 50% of women with oAPS, but no known thrombosis had low-titre aCL and/or aβ_2GPI in the absence of LA. The researchers suggested that low-titer aCL and aβ_2GPI should be included in the criteria for the diagnosis of oAPS (20). One possible explanation is that decidual cells and cytotrophoblast usually exhibit high basal levels of β2GPI and represent easily accessible targets for aβ2GPI. This might also explain why a second hit, such as trauma, surgery, infection, primary autoimmune disease or another proinflammatory stimulus needed for developing thrombosis in vAPS is not required to develop oAPS (21).

The different effects of aPL in vAPS and oAPS leading to divergent pathophysiological mechanisms were also confirmed by two in vitro studies. In the first study, aPLs from vAPS and oAPS were observed to activate the monocyte signaling pathway. aPL against β2GPI from vAPS patients were the only ones to induce thrombin factor (TF) production by monocytes, while antibodies from the patient with obstetric manifestations failed to do this. In the second study, purified IgG from patients with obstetric APS, but not the one from non-obstetric APS, inhibited trophoblast invasion (10,22,23).

Clinical manifestations:

1.) Early miscarriages (>10th week of gestation)

Early miscarriages are the most common clinical finding in aPL-positive patients with pregnancy morbidity and were included in the 2006 revised Sapporo classification criteria (6).

According to the 2023 ACR/EULAR classification criteria, it is no longer sufficient to have three or more early miscarriages to fulfill the clinical domain of APS diagnosis. Nonetheless, the authors emphasize that they still remain a part of the high-priority research agenda to guide the future update of the 2023 ACR/EULAR APS classification criteria (7).

U oAPS-u antifosfolipidna antitijela imaju glavnu ulogu u patofiziologiji bolesti. Istraživanja *in vitro* pokazala su da antifosfolipidna antitijela izravno utječu na proliferaciju i rast trofoblasta i dovode do gubitka međudjelovanja trofoblasta i endotela. Postoji smanjena invazija ekstraviloznog trofoblasta s poremećenim remodeliranjem spiralne arterije. Antitijela aPL također pokreću proizvodnju proupalnih citokina (interleukin [IL]-1, IL-7, IL-8) koji privlače monocite i neutrofile, što dovodi do aktivacije makrofaga i oslobađanja izvanstaničnih zamki neutrofila (NEToza), što rezultira upalom oko trofoblasta odnosno apoptozom. Uz to, ta antitijela aktiviraju makrofage i taloženje komplementa, potičući upalu oko trofoblasta i apoptozu. Aktivacija komplementa dovodi do lokalne proizvodnje i izlučivanja TNF-α, što dalje pospješuje začarani krug upale. (14,16,17)

Životinjski modeli i istraživanja *in vitro* pokazali su izravnu embriotoksičnu aktivnost aPL-a, a protutijela uzeta od žena s APS-om izravno utječu na rast i održivost životinjskih embrija. (18, 19)

Godine 2013. Gardiner i suradnici proveli su istraživanje u kojem je sudjelovalo oko 190 žena s APS-om s vaskularnim i opstetričkim manifestacijama. Zanimljiva je činjenica da je više od 50% žena s oAPS-om, ali bez poznate dijagnoze tromboze imalo nizak titar aCL i/ili aβ2GPI u odsutnosti LA. Istraživači su predložili da se aCL i aβ2GPI s niskim titrom uključe u kriterije za dijagnozu oAPS-a (20). Jedno od mogućih objašnjenja jest to da decidualne stanice i citotrofoblast obično pokazuju visoke bazalne razine β2GPI i predstavljaju lako dostupne mete za aβ2GPI. Time se također može objasniti zašto drugi udar, kao što je trauma, operacija, infekcija, primarna autoimuna bolest ili drugi proupalni podražaj koji je potreban za razvoj tromboze u vAPS-u nije potreban za razvoj oAPS-a (21).

Različiti učinci aPL-a u vAPS-u i oAPS-u koji dovode do različitih patofizioloških mehanizama također su potvrđeni u dva istraživanja *in vitro*. U prvom istraživanju primijećeno je da aPLs iz vAPS-a i oAPS-a aktiviraju signalni put monocita. aPL protiv β2GPI u bolesnica s vAPS-om jedini su inducirali proizvodnju faktora trombina (TF) od strane monocita, dok antitijela bolesnica s opstetričkim manifestacijama nisu uspjela u tome. U drugom istraživanju pročišćeni IgG iz bolesnica s opstetričkim, ali ne i neopstetričkim APS-om, inhibirao je invaziju trofoblasta (10, 22, 23).

Kliničke manifestacije:

1.) Rani pobačaji (> 10. tjedan trudnoće)

Rani pobačaji najčešći su klinički nalaz u aPL-pozitivnih bolesnica s morbiditetom u trudnoći i uključeni su u revidirane Sapporo kriterije klasifikacije iz 2006. godine (6).

Prema kriterijima klasifikacije ACR/EULAR iz 2023. više nije dovoljno imati tri ili više ranih pobačaja da bi se

Carvera et al. published a multicentric observational study that included 1000 APS patients (820 women). During the 10-year follow-up period, 127 (15.5%) women got pregnant. The most common obstetric complication was early pregnancy loss (16.5% of pregnancies) (24).

Alijotas-Reig et al. analyzed obstetric outcomes in 1000 patients with oAPS using the European Registry of oAPS. They found that the most prevalent manifestations were miscarriages in 38.6% of the pregnancies (25).

In another study that included 183 patients with oAPS during a 10-year follow-up, recurrent early abortions were found in 58.6% of patients (26).

2.) Stillbirth *(loss of a baby at or after 20 weeks of pregnancy)*

When assessing maternal sera in 582 stillbirth deliveries, elevated levels of aCL and aβ2GPI were associated with a threefold increased odd of stillbirth (27).

A retrospective French study that included 65 women with APS and intrauterine fetal death (IUFD), found that IUFD was the first APS clinical manifestation in 74% of women (28).

3.) Preeclampsia and fetal growth restriction

When assessing the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS), PE was found to be present in 18.1% and fetal growth restriction in 16.1% of cases (25).

The prevalence of aPL is twice as high in pregnant women who develop PE compared to those who have healthy pregnancies. (29).

In a prospective case-control study that compared the frequency of aPL positivity in women who delivered their baby in the period before the 36th week due to PE or placental insufficiency and women with normal pregnancies, it was found that aPL was present in 11.5% of women with PE or placental insufficiency, which was significantly higher compared to 1.4% of women with uncomplicated pregnancies (30).

Carvera et al. found that intrauterine growth restriction (26.3% of live births) and prematurity (48.2%) were the most frequent fetal morbidities.

The observational study of patients with pregnancy loss showed that patients with oAPS who were treated with low-molecular-weight heparin (LMWH) plus low-dose aspirin (LDA) had a lower rate of pregnancy losses but a higher rate of PE than the others, and the study confirmed the greater risk of PE in the oAPS group. (31).

THROMBOTIC EVENTS IN PATIENTS WITH OBSTETRIC ANTIPHOSPHOLIPID SYNDROME

Pregnancy itself carries a risk of thrombotic events; for example, the risk of venous thromboembolism is

ispunili kriteriji za kliničku domenu dijagnoze APS-a. Bez obzira na to, autori naglašavaju da oni ostaju dio visokoprioritetnog istraživačkog programa za usmjeravanje budućeg ažuriranja kriterija klasifikacije ACR/EULAR za APS iz 2023. godine (7).

Carvera i suradnici objavili su multicentrično opservacijsko istraživanje u kojem je sudjelovalo 1.000 bolesnica s APS-om (820 žena). Tijekom desetogodišnjeg razdoblja praćenja zatrudnjelo je 127 (15,5%) žena. Najčešća opstetrička komplikacija bio je rani gubitak trudnoće (16,5% trudnoća) (24).

Alijotas-Reig i suradnici analizirali su opstetričke ishode u 1.000 bolesnica s oAPS-om koristeći se registrom *European Registry on oAPS* (EUROAPS). Otkrili su da su najčešće manifestacije spontani pobačaji u 38,6% trudnoća (25).

U drugom istraživanju, u kojem su sudjelovale 183 bolesnice s oAPS-om tijekom desetogodišnjeg razdoblja praćenja, ponovljeni rani pobačaji dogodili su se kod 58,6% bolesnica (26).

2.) Mrtvorođenče (gubitak djeteta u 20. tjednu trudnoće ili kasnije)

Pri procjeni majčinih seruma kod 582 poroda mrtvorođene djece, povišene razine aCL i aβ2GPI bile su povezane s trostruko većim izgledima za mrtvorođenče (27).

Retrospektivna francuska studija u kojoj je sudjelovalo 65 žena s APS-om i intrauterinom smrti ploda (engl. *intrauterine fetal death*, IUFD), otkrila je da se IUFD javlja kao prva klinička manifestacija APS-a u 74% žena (28).

3.) Preeklampsija i zastoj rasta fetusa

Pri procjeni registra *European Registry on Obstetric Antiphospholipid Syndrome* (EUROAPS), utvrđeno je da je preeklampsija (PE) prisutna u 18,1% slučajeva, a zastoj rasta fetusa u 16,1% slučajeva (25).

Prevalencija aPL-a dvostruko je veća u trudnica koje razviju preeklampsiju (PE) u usporedbi s onima koje imaju zdrave trudnoće (29).

U prospektivnom istraživanju parova u kojem se uspoređivala učestalost pozitivnog aPL-a u žena koje su rodile prije 36 tjedana trudnoće zbog preeklampsije (PE) ili insuficijencije posteljice i žena s normalnom trudnoćom, otkriveno je da je aPL bio prisutan u 11,5% žena s preeklampsijom (PE) ili insuficijencijom posteljice, što je bilo značajno više u usporedbi s 1,4% žena koje su imale trudnoću bez komplikacija (30).

Carvera i suradnici otkrili su da su intrauterini zastoj rasta (26,3% živorođene djece) i prematuritet (48,2%) najčešći fetalni morbiditeti.

Opservacijsko istraživanje bolesnica s prekidom trudnoće pokazalo je da su bolesnice s oAPS-om koje su liječene heparinom niske molekularne mase (engl. *low-molecular-weight heparin*, LMWH) i niskom dozom aspirina (engl. *low-dose aspirin*, LDA) imale nižu stopu prekida trudnoće, ali veću stopu preeklampsije (PE) od

five times higher in a pregnant woman than in a non-pregnant woman of similar age (32).

A retrospective study on 200 APS patients divided into four groups based on previous medical history (obstetric, thrombotic, non-criteria antiphospholipid syndrome, and aPL carriers) showed that 2.5% of patients experienced thrombotic events during pregnancy and puerperium. Most cases were reported in the thrombotic group with prior thrombotic events. Unfortunately, in 85% of these cases, the thrombotic event occurred despite the use of adequate antithrombotic therapy (33).

RISK FACTORS FOR ADVERSE OUTCOMES IN PREGNANCY

Various studies were conducted in search of risk factors for the adverse outcomes in oAPS and found, for example, SLE or hypocomplementaemia to be an additional risk factor (33, 34).

The 2021 meta-analysis, that included 27 eligible records, identified previous thrombosis, double and triple aPL positivity, and lupus anticoagulant positivity as the most important predictors of adverse pregnancy outcomes in APS (35).

These findings should be utilized routinely in preconception counseling and pregnancy follow-up to guide individualized risk assessment for adverse pregnancy outcomes.

MANAGEMENT OF OBSTETRIC ANTIPHOSPHOLIPID SYNDROME

1.) Standard therapy: low-molecular-weight heparin and low-dose aspirin

Anticoagulant therapy plays an essential role in the treatment of APS. In patients with thrombotic APS, vitamin K antagonists (VKAs), such as warfarin, should be included in therapy. Due to warfarin teratogenicity, especially in the first trimester, in pregnant patients with prior thrombosis, warfarin should be discontinued (36).

There is a rising interest in using direct oral anticoagulants (DOACs) in APS patients with vascular manifestations of the disease. Current guidelines recommend that warfarin should be the first-choice treatment in APS, especially in patients with triple aPL positivity and with previous arterial thrombosis due to increased rates of recurrent thrombosis treated with DOAC compared with VKAs (37). Although DOACs may be effective in single/double aPL-positive patients with an exclusively venous thrombotic event, there is no adequate data for the use of DOACs in pregnancy. Limited real-world data and animal studies raised concern for embryo-fetal safety, with a higher rate of miscarriages and possible fetal anomalies, so the current guidelines recommend against DOAC use throughout pregnancy (38).

ostalih, a istraživanjem se potvrdio i veći rizik za preeklampsiju (PE) u skupini bolesnica s oAPS-om (31).

TROMBOTSKI DOGAĐAJI U BOLESNICA S OPSTETRIČKIM ANTIFOSFOLIPIDNIM SINDROMOM

Sama trudnoća podrazumijeva rizik od trombotskih događaja. Primjerice, rizik od venske tromboembolije pet je puta veći u trudnice nego u žene iste dobi koja nije trudna (32).

Retrospektivno istraživanje provedeno na 200 bolesnica s APS-om koje su bile podijeljene u četiri skupine na temelju prethodne povijesti bolesti (opstetrički, trombotski, nekriterijski antifosfolipidni sindrom i nositelji aPL-a) pokazalo je da je 2,5% bolesnica doživjelo trombotske događaje tijekom trudnoće i razdoblja puerperija. Većina slučajeva prijavljena je u trombotskoj skupini s prethodnim trombotskim događajima. Nažalost, u 85% bolesnica došlo je do trombotskog događaja unatoč primjeni antitrombotske terapije u to vrijeme (33).

ČIMBENICI RIZIKA ZA NEPOVOLJNE ISHODE TRUDNOĆE

Provedena su različita istraživanja u potrazi za čimbenicima rizika za nepovoljne ishode kod oAPS-a i utvrđeno je da su, na primjer, sistemski eritemski lupus (SLE) ili hipokomplementemija dodatni čimbenici rizika (33, 34).

U metaanalizi provedenoj 2021. godine, koja je uključivala 27 prihvatljivih nalaza, pronađeni su prethodna tromboza, dvostruka i trostruka pozitivnost na aPL te pozitivnost na lupus antikoagulans, koji su najvažniji prediktori nepovoljnih ishoda trudnoće u APS-u (35).

Ovi se nalazi trebaju rutinski upotrebljavati u savjetovanju prije začeća i praćenju trudnoće kako bi se na pravilan način upravljalo individualiziranom procjenom rizika za nepovoljne ishode trudnoće.

UPRAVLJANJE OPSTETRIČKIM ANTIFOSFOLIPIDNIM SINDROMOM

1.) Standardna terapija: niskomolekularni heparin i niska doza aspirina

Antikoagulantna terapija ima bitnu ulogu u liječenju APS-a. U bolesnica s trombotičnim APS-om u terapiju treba uključiti antagoniste vitamina K (VKA), poput varfarina. Zbog teratogenosti varfarina, osobito u prvom tromjesečju, u trudnica s prethodnom trombozom potrebno je prekinuti primjenu varfarina (36).

Postoji sve veći interes za primjenu direktnih oralnih antikoagulansa (*engl.* direct oral anticoagulants, DOAC) u bolesnica s APS-om s vaskularnim manifestacijama bolesti. Trenutačne smjernice preporučuju da varfarin bude prvi izbor u liječenju APS-a, osobito u bolesnica s trostrukom aPL pozitivnošću i prethodnom arterijskom trombozom zbog povećanih stopa rekurentne

In pregnant patients with prior thrombosis, therapeutic doses of LMWH and LDA are recommended in therapy. For pregnant patients with purely obstetric morbidity and no prior thrombosis, prophylactic dose LMWH and LDA until six weeks postpartum is recommended (36).

Since early recurrent miscarriages are one of the prominent features of oAPS, it is necessary to emphasize the importance of starting the treatment promptly.

In patients with recurrent miscarriages, a prophylactic dose of LMWH should be included since the positive pregnancy test and LDA at least one month before starting attempts for a new pregnancy. For the patients who are in the process of assisted reproductive technique (ART), a prophylactic dose of LMWH should be included since estrogens are started in the substituted cycle or 14 days before the transfer, combined with LDA, at least one month before starting ART (10).

2.) Management of refractory oAPS

Approximately 20–30% of oAPS patients do not benefit from standard treatment (LMWH+LDA), and additional therapeutic options are necessary in those refractory cases (39).

In pregnant patients who receive prophylactic doses of LMWH but still experience recurrent fetal loss, therapeutic doses of LMWH can be administered to prevent adverse events.

Other therapeutic options include small doses of prednisolone, hydroxychloroquine, plasmapheresis, immunoglobulins, tumor necrosis factor (TNF)-α inhibitors, e.g., certolizumab-pegol, statins (pravastatin), and eculizumab, with promising results (36,39–48).

CONCLUSION

Pregnant women with APS must have frequent follow-up visits with both gynecologists and rheumatologists. During these visits, detailed check-ups should be performed, and risk factors for pregnancy morbidity should be screened for. A better understanding of the pathophysiology of the disease will enable the use of new therapeutic options, which can help improve outcomes in oAPS for both the mother and the child.

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tromboze liječenih DOAC-ima u usporedbi s antagonistima vitamina K (VKA) (37). Iako DOAC-i mogu biti učinkoviti u jednostruko/dvostruko aPL-pozitivnih bolesnica s isključivo venskim trombotičnim događajem, nema odgovarajućih podataka za primjenu DOAC-a u trudnoći. Ograničeni podatci iz stvarnog svijeta i studije provedene na životinjama izazvale su zabrinutost za sigurnost embrija i fetusa, s većom stopom pobačaja i mogućih fetalnih anomalija, tako da trenutne smjernice preporučuju da se DOAC-i ne primjenjuju tijekom cijele trudnoće (38).

U trudnica s prethodnom trombozom u terapiji se preporučuju terapijske doze niskomolekularnog heparina (LMWH) i niska doza aspirina (LDA). Za trudnice s opstetričkim morbiditetom i bez prethodne tromboze preporučuje se profilaktička doza niskomolekularnog heparina (LMWH) i niska doza aspirina (LDA) do šest tjedana nakon poroda (36).

Budući da su rani ponovljeni pobačaji jedno od istaknutih obilježja oAPS-a, potrebno je naglasiti važnost pravovremenog početka liječenja.

U bolesnica s ponavljajućim pobačajima potrebno je u liječenju primijeniti profilaktičku dozu LMWH-a od pozitivnog testa na trudnoću i LDA najmanje mjesec dana prije početka pokušaja nove trudnoće. U bolesnica koje su u postupku potpomognute oplodnje (engl. *assisted reproductive technique*, ART) treba primijeniti profilaktičku dozu LMWH-a budući da se s estrogenima počinje u supstituiranom ciklusu ili 14 dana prije transfera, u kombinaciji s LDA, najmanje mjesec dana prije početka postupka potpomognute oplodnje (ART). (10)

2.) Upravljanje refraktornim oAPS-om

Otprilike 20 – 30% bolesnica s oAPS-om nema koristi od standardnog liječenja (LMWH + LDA), a dodatne terapijske opcije potrebne su u tim refraktornim slučajevima (39).

U trudnica koje primaju profilaktičke doze niskomolekularnog heparina (LMWH), ali još uvijek doživljavaju ponovljeni gubitak fetusa, mogu se primijeniti terapijske doze niskomolekularnog heparina (LMWH) kako bi se spriječili nepovoljni događaji.

Druge terapijske opcije uključuju male doze prednizolona, hidroksiklorokina, plazmafereze, imunoglobulina, inhibitora faktora nekroze tumora (TNF)-α, npr. certolizumab pegola, statina (pravastatina) i ekulizumaba te nude obećavajuće rezultate (36, 39–48).

ZAKLJUČAK

Trudnice s dijagnozom APS-a moraju često pohoditi kontrolne preglede i kod ginekologa i kod reumatologa. Tijekom tih pregleda potrebno je obaviti detaljne preglede i ispitati čimbenike rizika za morbiditet u trudnoći. Bolje razumijevanje patofiziologije bolesti omogućit će primjenu novih terapijskih mogućnosti koje mogu biti korisne u poboljšanju ishoda oAPS-a i za majku i za dijete.

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