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Prospective study of perinatal outcome in pregnancies with primary antiphospholipid syndrome

Prospektivna analiza perinatalnih ishoda kod trudnica sa antifosfalipidnim sindromom

Aleksandar Ćetković*, Biljana Kastratović†, Ivana Novaković‡

***Clinic of Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade; Serbia; †Faculty of Medicine, University of Belgrade, Belgrade, Serbia; ‡Institute of Human Genetics, Faculty of Medicine, University of Belgrade, Belgrade, Serbia**

Abstract

Background/Aim. Pregnancies complicated with antiphospholipd syndrome are associated with the increased perinatal mortality and morbidity. The aim of this study was to assess perinatal outcome in pregnancies with primary antiphospholipd syndrome. **Methods.** This prospective study evaluated perinatal outcome in 25 pregnant women with antiphospholipid syndrome. After establishing vital pregnancy all the patients were treated with low-molecular-weight heparin and aspirin. The perinatal outcome was measured by rates of miscarriages, preterm deliveries, live births and neonatal complications. **Results.** Of the 25 pregnancies, 20 (80%) resulted in live birth, 3 (12%) in spontaneous abortion and 2 (8%) were stillbirths. The mean gestational age at delivery was 37.2 ± 1.0 weeks, mean neonatal birth weight was 2,930.4 ± 428.0 g. Prematurity occurs in 4 (20%) live births, and there were 4 (20%) intrauterine growth restriction with mean birth weight 2,060 ± 210.6 g. Neonatal complications were present in 6 (30%) newborns. Adverse perinatal outcome was significantly associated with anticardiolipin IgG antibodies ($p < 0.01$) and development of hypertension during pregnancy ($p < 0.01$). **Conclusion.** Despite a high incidence of adverse perinatal outcomes in pregnancies with primary antiphospholipid syndrome, early treatment with aspirin and low-molecular-weight heparin, combined with meticulous fetomaternal monitoring could be associated with a relatively high probability of favorable perinatal outcome.

Key words:
antiphospholipid syndrome; pregnancy outcome; aspirin; heparin, low-molecular-weight.

Apstrakt

Uvod/Cilj. Trudnoća komplikovana antifosfolipidnim sindromom udružena je sa povećanim perinatalnim morbiditetom i mortalitetom. Cilj rada bio je procena perinatalnog ishoda u trudnoći sa primarnim antifosfolipidnim sindromom. **Metode.** U prospektivnoj studiji analizirali smo perinatalni ishod kod 25 trudnoća sa antifosfolipidnim sindromom. Po utvrđivanju vitalnosti trudnoće sve ispitivane bolesnice dobijale su niskomolekularni heparin i aspirin. Procena perinatalnog ishoda bazirana je na učestalosti pobačaja, prevremenih porođaja, živorođenosti i neonatalnih komplikacija. **Rezultati.** Ishod 25 analiziranih trudnoća bio je sledeći: 20 (80%) živorođenih, 3 (12%) spontana pobačaja i 2 (8%) mrtvorođenih. Prosečna gestacijska starost na rođenju iznosila je 37,2 ± 1,0 nedelja, a prosečna telesna masa novorođenčadi 2 930,4 ± 428,0 g. Prevremeni porođaj registrovan je kod 4 (20%) živorođenih, bilo je 4 (20%) slučaja intrauterinog zastoja u rastu ploda sa prosečnom težinom na rođenju od 2 060 ± 210,6 g, a neonatalne komplikacija bile su prisutne kod 6 (30%) novorođenčadi. Nepovoljan perinatalni ishod bio je značajno povezan sa antikardiolipinskim IgG antitelima ($p < 0,01$) i razvojem hipertenzije tokom trudnoće ($p < 0,01$). **Zaključak.** Uprkos visokoj incidenciji nepovoljnog perinatalnog ishoda trudnoća sa antifosfolipidnim sindromom, rano započinjanje tretmana sa niskomolekularnim heparinom i aspirinom, uporedo sa intenzivnim nadzorom majke i fetusa, moglo bi biti udruženo sa relativno velikom verovatnoćom povoljnog perinatalnog ishoda.

Ključne reči:
antifosfolipidni sindrom; trudnoća, ishod; aspirin; heparin, niskomolekulski.

Correspondence to: Aleksandar Ćetković, Clinic of Gynecology and Obstetrics, Clinical Center of Serbia, Koste Todorovića 26, 11 000 Belgrade, Serbia. Phone: +381 11 366 3575. E-mail: aleksa_cetkovic@vektor.net

Introduction

Antiphospholipid syndrome (APS) is an immune-mediated thrombophilia, presenting as recurrent vascular thrombosis and pregnancy morbidity, in association with positive tests for antiphospholipid antibodies [1]. Antiphospholipid syndrome is classified as secondary if there is present underlying autoimmune disease such as systemic lupus (SLE) or rheumatoid arthritis [2]. In contrast, in primary APS thrombosis and/or pregnancy failure occur in isolation.

Women with APS have an unusually high proportion of pregnancy losses within the pre-embryonic, embryonic and fetal period [1]. Pregnancies with APS can also be complicated by preterm delivery due to pregnancy-associated hypertensive disease and placental dysfunction [1].

Pathophysiological mechanism present in this syndrome includes antibody-mediated interference with coagulation homeostasis, platelet and endothelial cell activation, placental tissue injury, T-cell immune response and complement activation [3].

Since this syndrome has a tremendous impact on maternal and fetal morbidity and mortality, there has been continued interest and efforts to better define therapy for the condition.

A combination of heparin and aspirin represents the most frequently applied therapeutic protocol, resulting in a live birth rate of up to 70–80 % of cases [4–6].

Steroids have also been used during pregnancy in patients with APS, however a significant maternal and fetal morbidity reported discourage this treatment modality [7].

Intravenous immunoglobulin (IVIG) is a form of therapy usually combined with heparin and low-dose aspirin, especially in women with unfavorable obstetric history or recurrent pregnancy loss during heparin treatment [4]. However, a randomized study of IVIG treatment during pregnancy in unselected APS cases found no benefit of this expensive therapy compared to heparin and low-dose aspirin [8]. It is currently unclear whether IVIG may have therapeutic significance in refractory APS cases, and it would be vise to limit its use to patients with APS who have had poor pregnancy outcome despite treatment with aspirin and heparin [8].

A recent update of the classification criteria for definite APS introduced the concept of stratification of APS patients on the basis of laboratory and clinical characteristics [9]. According to these reports, different therapeutic regimens should be used in the various subsets of APS patients [9].

Methods

In this study we followed 25 monofetal pregnancies in women who had been diagnosed preconceptionally with APS according to the International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome [9]. Clinical criteria were: 1) one or more clinical episodes of arterial, venous or small vessel thrombosis; 2) pregnancy morbidity that included: a) one or more unexplained deaths of morphologically normal fetus before 10th week of gestation; b) one or more premature births of morphologically normal neonate before 34th week of gestation because of eclampsia or severe pre-eclampsia, or recognized features of placental insufficiency; c) three or more unexplained consecutive spontaneous abortions before 10th gestation. Laboratory criteria were: 1) Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis; 2) Anticardiolipin (aCL) antibody of IgG or IgM isotype in serum or plasma present in medium or high titer on two or more occasions at least 12 weeks apart measured by standard ELISA; 3) Anti-β2 glycoprotein-I antibody of IgG or IgM isotype in serum or plasma present on two or more occasions, at least 12 weeks apart measured by standardized ELISA.

The diagnosis of antiphospholipid syndrome requires the combination of at least one clinical and one laboratory criterion.

Women with uterine abnormality and multiple pregnancies were excluded from the study on the basis of ultrasound examination. Other thrombophilias such as activated protein C resistance, protein C/S deficiency, G 20210A prothrombin mutation that may mimic APS were diagnosed using appropriate hematological laboratory testing and were also excluded from the study [10]. Patients with abnormal karyotype detected on standard cytogenetic analysis were not included in the study.

All women in our study had the history of recurrent miscarriage and persistently positive results for antiphospholipids antibodies.

The study was approved by the Ethics committee of the Belgrade University Clinical Center.

All the patients received aspirin 100 mg/daily when they had positive serum β-hcG (> 50 IU/mL) indicating that they are pregnant. When fetal heart activity was detected on vaginal ultrasound all women received additional therapy of subcutaneous low-molecular-weight heparin (deltaparin sodium) 5000 IU 24 hourly. The last heparin injection was made 12 hours before planned caesarean delivery and was begun again 12 hours after delivery. Aspirin was stopped three weeks prior to labor.

During first hospitalization clinical history, physical examination, complete blood count, routine biochemistry were evaluated. Coagulation screening included prothrombin time, partial thromboplastin time, fibrinogen, anti-thrombin III and D-dimer levels. Patients were hospitalized every four week until the delivery.

From the 24th week of gestation Doppler analysis of fetal uteroplacental and cerebral circulation was performed during hospitalization, and from 32nd weeks of gestation cardiotocography was also introduced as a part of fetal monitoring.

Uterine artery mean pulsatility index (PI) values ≥ 1.45 were considered abnormal, and umbilical artery Doppler PI value > 95th for gestation or absent/reversed end-diastolic flow were considered abnormal [11].

Definitions of adverse perinatal outcome were: fetal deaths defined as stillbirths ≥ 22 weeks of gestation or an infant weighting ≥ 500 gr; neonatal death defined as the death of a liveborn infant before the 28th day of life; perinatal mortality comprised both fetal and neonatal deaths; spontaneous abortion was defined as spontaneous loss of a fetus before 24 weeks of gestation; preterm delivery comprised delivery < 37 weeks of gestation; newborn were considered small (intrauterine growth restriction – IUGR) when their

birth weight was below the tenth percentile, on the basis of standard growth and development for Serbian population [12].

Anticardiolipin antibodies (IgM and IgG) were identified with an enzyme-linked immunosorbent assay (ELISA) and lupus anticoagulant (LA) was detected with standard activated partial thromboplastin time (aPTT) followed by the dilute Russell`s viper venom time (dRVVT) [13]. Data for anticardiolipin antibodies were expressed as Immunoglobulin G Phospholipid (GPL) or Immunoglobulin M Phospholipid (MPL) units using international reference material [13]. Cutt-off values for medium/high titers were 15 GPL and 16 MPL, respectively [13].

Statistical analysis was performed using SPSS statistical software (SPSS for Windows, release 10.0, Chicago, IL). Descriptive statistics are presented as mean values ± standard deviation (SD), frequency and percentage. The differences between the groups were compared with parametric Student's *t*-test or χ^2-test. A statistical significance was set up at *p* less than 0.05 ($p < 0.05$).

Results

The clinical characteristics of patients and laboratory parameters are presented in Table 1.

Treatment with aspirin began at the mean gestational age of 4.2 ± 1.2 weeks and treatment with heparin at the mean gestational age of 7.33 ± 1.73 weeks. Eight (32%) women developed hypertension during pregnancy, of whom 2 (8%) had pre-eclampsia.

Abnormal uterine artery PI was detected in 5 (20%) pregnancies, and abnormal umbilical artery PI in 3 (12%) pregnancies. There was 1 (4%) patient with absent umbilical artery end-diastolic velocity.

The parameters of perinatal outcome are presented in Table 2. The live birth rate was 20 (80%), 3 (12%) pregnancies ended in spontaneous abortion and there were 2 (8%) stillbirths. Spontaneous abortion occurred at the mean of 12.0 ± 4.1 weeks. The mean gestational age at delivery was 37.2 ± 1.0 weeks, mean neonatal birth weight was 2,930.4 ± 428.0 g. Prematurity occurs in 4 (20%) live births, and there were 4 (20%) intrauterine growth restriction with the mean birth weight 2,060 ± 210.6 g.

Six (30%) newborns were admitted to the neonatal intensive care unit (three with respiratory distress, two with perinatal asphyxia and one with intraventricular hemorrhage grade I/II) of whom none had fatal outcome or did developed permanent disability.

Poor perinatal outcome was significantly associated with anticardiolipin IgG antibodies ($p < 0.01$) and development of hypertension during pregnancy ($p < 0.01$).

Discussion

In the last three decades many efforts have been made to define the best approach for treatment and monitoring pregnancies with primary APS.

In patients with primary APS treated with heparin and aspirin, according to the different studies, live births ranges between 70–80%, early fetal loss between 10–20%, IUGR between 15–30%, preterm deliveries between 10–25%, maternal complications other than preeclampsia are present in 8–13%

Table 1

Clinical characteristics and antiphospholipid antibody profile of patients with primary antiphospholipid syndrome (APS)

Patients characteristics	Values
Age (year), $\bar{x}$ ± SD	31.0 ± 4.95
Number of previous abortion, $\bar{x}$ ± SD	2.41± 0.87
Lupus anticoagulant positive, (%)	58.82
Anticardiolipin IgM positive, (%)	35.29
Anticardiolipin IgG positive, (%)	29.41
Antikardiolipin IgM + IgG positive, (%)	17.64
Anticardiolipin IgM titre (MPL), $\bar{x}$ ± SD	12.46 ± 4.72
Anticardiolipin IgG titre (GPL), $\bar{x}$ ± SD	19.43 ± 8.31
Abnormal uterine artery pulsatility index (PI), (%)	5 (20)
Abnormal umbilical artery pulsatility index (PI), (%)	3 (12)
Absent umbilical artery end-diastolic velocity, n (%)	1 (4)

GPL – immunoglobulin G phospholipid units;
MPL – immunoglobulin M phospholipid units.

Table 2

Perinatal outcome in pregnancies with primary antiphospholipid syndrome (APS)

Perinatal outcome	Values
Live birth, n (%)	20 (80)
Spontaneous abortions, n (%)	3 (12)
Stillbirth, n (%)	2 (8)
Preterm delivery, n (%)	4 (20)
IUGR, n (%)	4 (20)
Neonatal complications, n (%)	6 (30)
Neonatal gestational age at birth (weeks), $\bar{x}$ ± SD	37.2 ± 1.0
Neonatal birth weight (g), $\bar{x}$ ± SD	2,930.4 ± 428.0

IUGR – intrauterine growth restriction.

and preeclampsia develops in 11–60% of patients [3, 13–16]. In our group of patients with primary APS live birth rate was 80%, early fetal loss was 3%, preterm delivery rate was 20%, IUGR was present in 20%, preeclampsia developed in two patients, and the rate of neonatal complications were 30% of whom neither had fatal outcome or did result in permanent disability. This relatively high rate of live births and moderate level of preterm deliveries could be regarded as good results despite small number of patients that were enrolled in the study. The explanations for these outcomes may be sought in fact that lupus anticoagulant antibodies were positive in 60% of patients and that anticardiolipin antibodies titers were moderately elevated without higher titres of IgG anticardiolipin antibodies present. Therefore, the group of patients analyzed in our study could represent a milder form of antiphospholipid syndrome.

Primarily, anticardiolipin (aCL) antibodies are not as strong risk factor for development of trombosis and other complications as lupus anticoagulant antibodies (LA). LA is considered the most powerful predictor of thrombosis [14]. Antibodies titer and isotype are also important: IgG aCL is more strongly associated with clinical manifestations than IgM aCL, ant the risk of thrombosis and other complications increases with high titers (> 40 U) [15].

However, there are still present controversies about the significance of the titer of anticardiolipin antibodies (particulary IgG) and its contribution to maternal morbidity and perinatal outcome that deserves further comprehensive studies. The current problem of laboratory standardization and the clinical heterogeneity inherent in the antiphospholipid syndrome have resulted in difficulties to interprete the significance of various factors for the clinical outcome.

Uterine artery Doppler blood flow analysis provides a noninvasive indirect method of screening women with risk of uteroplacental insufficiency. In our study abnormal uterine artery Doppler waveform pattern was present in 20% of pregnancies, and abnormal Doppler waveform, in umbilical artery in 12% of pregnancies. All these pregnancies developed hypertension, and 60% of these women had some unfavorable perinatal outcome. Despite a high incidence of adverse perinatal outcome in pregnancies with hypertension and abnormal uterine or umbilical artery Doppler waveforms because of a small number of patients in this subgroup we could not find any statistically significant association between these two variables.

Overall, our findings indicate that poor perinatal outcome was significantly associated with anticardiolipin IgG antibodies ($p < 0.01$) and development of hypertension during pregnancy ($p < 0.01$).

Conclusion

The results of our study show that despite a high incidence of adverse perinatal outcomes in pregnancies with primary antiphospholipid syndrome, early treatment with aspirin and low-molecular-weight heparin combined with meticulous fetomaternal monitoring could be associated with a relatively high probability of favorable perinatal outcome. Accurate preconceptional counseling and multidisciplinary approach are essential to achieve these results.

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