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# Prevalence of vascular thrombosis and obstetriccomplications in systemic lupus erythematosuspatients with antiphospholipid antibody

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# Prevalence of vascular thrombosis and obstetric complications in systemic lupus erythematosus patients with antiphospholipid antibody

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**Background :** *The European League Against Rheumatism (EULAR) recommends primary prophylaxis with aspirin and hydroxychloroquine in systemic lupus erythematosus (SLE) patients with antiphospholipid antibodies without prior thrombosis. However, Asian populations may have lower incidence of thrombosis and the role of primary prophylaxis is unclear. Therefore, we examined the prevalence of thrombosis in Thai antiphospholipid-positive SLE patients.*

**Methods :** *The medical records of SLE patients (N = 715) admitted to King Chulalongkorn Memorial Hospital from 2002 - 2012 were studied. Two hundred and eighteen patients were investigated for antiphospholipid antibodies, and 82 of them (37.6%) were positive. These 82 patients were studied for baseline characteristics, the types of antiphospholipid antibodies, prevalence of thrombosis and other potential risk factors.*

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**Results** : *The mean age of antiphospholipid - positive patients was 31 years, and 80.5% of them were female. The mean duration of SLE was 7.7 years, and the median follow up time was 3 years. The positive rates for lupus anticoagulant, low-titer anticardiolipin, high-titer anticardiolipin and anti-$\beta_2$ glycoprotein I were 61% (50/68), 40% (33/73), 23% (19/73) and 17% (1/6), respectively. Without aspirin prophylaxis, 23 (28%) antiphospholipid-positive cases developed vascular thrombosis (24.4%) and/or obstetric complications (6.1%). Venous thrombosis was more common than arterial sites. The thrombotic rate of medium to high titer and low titer of anticardiolipin was 36.8% and 21.2%, respectively (p = 0.22). On the other hand, 2.2% (3/136) antiphospholipid-negative patients developed thrombosis or pregnancy complication with the odds ratio (OR) of 17.28 (95% confidence interval [95%CI] 5.0 - 59.8, p < 0.0001). Upon multivariate analysis in antiphospholipid-positive SLE, the age of SLE diagnosis of over 30 years and hydroxychloroquine use showed odds ratios of 2.94 (95% CI 1.02 - 8.43, p = 0.045) and 0.28 (95% CI0.08 - 0.96, p = 0.043), respectively.*

**Conclusion** : *This study reveals that antiphospholipid antibodies are strong risk factors for thrombosis in patients with SLE in Thailand. Additionally, hydroxychloroquine may prevent thrombosis in these patients.*

**Keywords** : *Antiphospholipid antibodies, systemic lupus erythematosus, prevalence.*

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**ไพลิน มหาพรรณ, พลภัทร โรจน์นครินทร์. ความชุกของภาวะหลอดเลือดอุดตันและภาวะแทรกซ้อนทางสูติศาสตร์ในผู้ป่วยซิสทีมิคลูปัสอีริทีมาโทซัสที่มีแอนติฟอสโฟลิปิดแอนติบอดี. จุฬาลงกรณ์เวชสาร 2557 พ.ย. – ธ.ค.; 58(6): 577 – 87**

**ที่มา** : *The European League Against Rheumatism (EULAR) ได้แนะนำการป้องกันหลอดเลือดอุดตันชนิดปฐมภูมิด้วยแอสไพริน (aspirin) และไฮดรอกซีคลอโรควิน (hydroxychloroquine) ในผู้ป่วยซิสทีมิคลูปัสอีริทีมาโทซัส (systemic lupus erythematosus) หรือเอสแอลอี (SLE) ก่อนที่จะเกิดภาวะหลอดเลือดอุดตัน อย่างไรก็ตามอุบัติการณ์ของภาวะหลอดเลือดอุดตันในผู้ป่วยชาวเอเชียอาจจะต่ำกว่าชาวตะวันตก บทบาทของการป้องกันปฐมภูมิจึงยังไม่ชัดเจน จึงได้ศึกษาความชุกของภาวะหลอดเลือดอุดตันในผู้ป่วยเอสแอลอีชาวไทย ที่มีแอนติฟอสโฟลิปิดแอนติบอดีเป็นบวก*

**วิธีการศึกษา** : *จากเวชระเบียนผู้ป่วยเอสแอลอี 715 รายที่เข้ารับการรักษาแบบผู้ป่วยในที่โรงพยาบาลจุฬาลงกรณ์ ระหว่างปี พ.ศ. 2545 - 2555 มีผู้ป่วย 218 รายที่ได้รับการตรวจหาแอนติฟอสโฟลิปิดแอนติบอดี และ 82 ราย หรือร้อยละ 37.6 มีผลการตรวจเป็นบวก ผู้ป่วย 82 รายนี้ได้รับการศึกษาลักษณะพื้นฐาน ชนิดของแอนติฟอสโฟลิปิดแอนติบอดี ความชุกของภาวะหลอดเลือดอุดตัน และปัจจัยเสี่ยงอื่น ๆ*

**ผลการศึกษา** : *อายุเฉลี่ยของผู้ป่วยที่แอนติฟอสโฟลิปิดแอนติบอดีเป็นบวกเท่ากับ 31 ปี และร้อยละ 80.5 เป็นผู้หญิง ระยะเวลาเฉลี่ยที่ได้รับการวินิจฉัยเอสแอลอีเท่ากับ 7.7 ปี และค่ามัธยฐานของการติดตามผู้ป่วยเท่ากับ 3 ปี ระยะเวลา อัตราของผลบวกต่อ lupus anticoagulant, low-titer anticardiolipid, high-titer anticardiolipin ระดับสูง และ anti - $\beta_2$ glycoprotein I เท่ากับร้อยละ 61 (50/68), 40 (33/73), 23 (33/73) และ 17 (1/6) ตามลำดับ ไม่มีผู้ป่วยได้รับแอสไพรินป้องกัน ผู้ป่วยจำนวน 23 ราย หรือร้อยละ 28 ที่มีผลบวกต่อแอนติฟอสโฟลิปิดเกิดภาวะหลอดเลือดอุดตัน (ร้อยละ 24.4) และ/หรือภาวะแทรกซ้อนทางสูติศาสตร์ (ร้อยละ 6.1) ภาวะหลอดเลือดดำอุดตันพบบ่อยกว่าหลอดเลือดแดงอุดตัน อัตราการเกิดหลอดเลือดอุดตันในผู้ป่วย medium to high titer และ low titer ของ anticardiolipin เท่ากับร้อยละ 36.8 และ 21.2 ตามลำดับ (p = 0.22) ในขณะที่ร้อยละ 2.2 ของผู้ป่วยที่มีแอนติฟอสโฟลิปิดแอนติบอดีเป็นลบเกิดภาวะหลอดเลือดอุดตัน หรือภาวะแทรกซ้อนทางสูติศาสตร์ odds ratio (OR) เท่ากับ 17.28 (95%*

*confidence interval [95%CI] 5.0 - 59.8, p < 0.0001) การวิเคราะห์พหุตัวแปร (multivariate analysis) ในผู้ป่วยเอสแอลอีที่มีแอนติฟอสโฟลิปิดแอนติบอดี พบว่าผู้ป่วยที่วินิจฉัยเอสแอลอีตอนอายุมากกว่า 30 ปี และการใช้ไฮดรอกซีคลอโรควินมี odds ratios เท่ากับ 2.94 (95% CI 1.02 - 8.43, p = 0.045) และ 0.28 (95% CI 0.08 - 0.96, p = 0.043) ตามลำดับ*

**สรุป** : *การศึกษานี้แสดงให้เห็นว่าแอนติฟอสโฟลิปิดแอนติบอดีเป็นปัจจัยเสี่ยงสำคัญของภาวะหลอดเลือดอุดตันในผู้ป่วยเอสแอลอีชาวไทย นอกจากนี้ไฮดรอกซีคลอโรควินอาจป้องกันภาวะหลอดเลือดอุดตันในผู้ป่วยเหล่านี้*

**คำสำคัญ** : *แอนติฟอสโฟลิปิดแอนติบอดี, ซิสทีมิคลูปัสอีริทีมาโทซัส, ความชุก.*

Systemic lupus erythematosus (SLE) has a high risk of thrombosis when compared with other autoimmune diseases.[1] The most important contributing factor is the presence of antiphospholipid antibodies in these patients. Furthermore, proteinuria from lupus nephritis can cause urinary antithrombin loss predisposing to venous thrombosis. In addition, other conventional thrombotic risk factors, e.g., hypertension, diabetes, infections and hospitalization, are common in SLE patients receiving corticosteroid therapy and probably attribute to thrombosis.[2] Strategies to prevent this complication in SLE will be very helpful in reduction of morbidity and mortality in these patients.

In 2008, the European League Against Rheumatism (EULAR) recommended that SLE patients with positive antiphospholipid antibodies with no prior thrombosis should have primary prophylaxis with low - dose aspirin at least 2 times at $\geq$ 12 weeks and hydroxychloroquine (strength of statement D); and, also stated that aspirin has benefit that outweighs its risks. However, the conclusion was based on retrospective, case-control or cohort studies. There have been no randomized control trials to strongly support the recommendation of the primary prevention in these patients.[3-7]

Asian populations may have lower incidence of thrombosis compared with the Caucasian.[8] In Thailand, there are no recommendations regarding primary prophylaxis aspirin in SLE patients with persistently positive antiphospholipid antibodies. There is a lack of data on the prevalence of thrombosis in this population. If the prevalence is high, it may be beneficial to have primary prophylaxis.

Although aspirin shows lower rates of bleeding compared with anticoagulants, SLE patients also have high risks of bleeding from the disease itself or treatments, such as thrombocytopenia or non-steroidal anti-inflammatory drugs (NSAIDs). Therefore, the prevalence and outcomes of thrombosis in this population should be carefully reviewed. This information is helpful to appropriately weigh the risk against the benefit of the primary prophylactic measures.

The primary objective of the study was to determine the prevalence of thrombosis in SLE patients with positive antiphospholipid antibody in Thailand. The secondary objective was to investigate risk factors of thrombosis in these patients. In addition, the protective role of hydroxychloroquine in Thai patients was explored.

**Patients and methods**

According to the discharge summary of medical in-patients, there were 715 SLE patients admitted to King Chulalongkorn Memorial Hospital from 2002 - 2012. Of these SLE patients, 218 cases were worked up for antiphospholipid antibodies, and 82 patients yielded positive results (37.6%). All eligible patients were studied for baseline characteristics, antiphospholipid antibody tests, the presence of thrombosis and/or obstetric complications and other associated risk factors. Due to the retrospective nature of the study, informed consent was exempted by the Ethical Committee of the Faculty of Medicine, Chulalongkorn University.

The SLE diagnosis was confirmed under the criteria of the American College of Rheumatology (ACR) 1997. The patients must have been able to

follow up for at least 6 months or until the events of thromboembolism (arterial or venous thrombosis or pregnancy complications). The patients who were loss to follow up or died within 6 month after positive antibody test were excluded.

Baseline data included demographic information and clinical characteristics. The examined potential predictor variables included age at SLE diagnosis, sex, duration of SLE, history of nephritis, aspirin uses and immune-modulating medications.[9,10] Medication history was collected by the online pharmacy information supplemented by medical record information and classified as 'ever' *versus* 'never' uses.

Medical records obtained from patients' rheumatologists or other treating physicians were reviewed to document thrombosis and pregnancy complications. Thrombosis events included deep vein thrombosis, pulmonary embolism, cerebral vascular disease, coronary disease and retinal vein thrombosis. The obstetric complications were defined as three consecutive miscarriages in the first trimester or more than 1 in the second or third trimesters. Nephritis was defined according to the meeting of American College of Rheumatology renal criteria, confirmed by review of medical records and/or renal biopsy consistent with lupus nephritis. Immune - modulating drugs included cyclophosphamide, azathioprine, cyclosporine and/or mycophenolate mofetil.

Medical records were also reviewed for the results of antiphospholipid (aPL) testing, including lupus anticoagulant (LA) measured by Russell viper venom time (RVVT) and diluted activated partial thromboplastin time (dAPTT). Anticardiolipin (ACL) IgG and IgM antibodies and anti-$\beta_2$glycoproteinI IgM and IgG antibodies were tested using ELISA methods (Euroimmun, Lubeck, Germany). The normal values of anticardiolipin and anti-$\beta_2$glycoproteinI were below 12 GPL and 20 RU/ml, respectively. The medium to high titer anticardiolipin was defined as the titer over 40 GPL. Subjects were considered aPL positive, if at least one of these autoantibodies were documented at least once. Low titer anticardiolipin positivity was also included in the study.

The potential thrombotic risks were examined in unbivariate analysis using the Chi square test (for categorical variables) and Student's t - test (for continuous variables). These variables included aPL status, duration of disease, age at SLE diagnosis, medication history and history of nephritis. Odds ratios and 95% confidence intervals were calculated. The multivariate analysis used binary logistic regression. Statistical analysis was performed by SPSS 16.0 program.

## Results

### Baseline Characteristics

During the 10-year study period, 82 SLE cases with positive antiphospholipid antibodies were enrolled. Sixty-six of them (80.5%) were female. The baseline characteristics were summarized in Table 1. The mean age of SLE diagnosis was 31.5 years old. The mean duration from SLE diagnosis to the time of study was 7.7 years.

Forty-five patients (54.1%) had history of lupus nephritis. Most cases (97.6%) had received prednisolone, and 42.4% had taken other immuno-suppressive drugs. The history of hydroxychloroquine was noted in 32 cases (39%). Chloroquine use was not included.

As for the antiphospholipid antibody tests, lupus anticoagulants were positive in 61% (50/68), anticardiolipin IgG and/or IgM positive in low titer in 40% (33/73), positive in medium to high titerin 23% (19/73) and anti-$\beta_2$glycoglobulinI positive in 16.7% (1/6).

**Table 1.** Characteristics of the 82 SLE patients with positive antiphospholipid antibody.

| Variable | N (%) |
|---|---|
| Female | 66(80.5%) |
| Age (yr) | |
| • Median (range) | 31.5 years (range 8 - 67) |
| Age at SLE diagnosis (years) | 31.5 years (range 5 - 66 years) |
| • <= 20 years | 40 (48.8%) |
| • 20- <=40 years | 34 (41.5%) |
| • >40 years | 8 (9.8%) |
| Duration of SLE until the time of study | 7.7 years (range 1 - 23) |
| Number of thrombosis | 23 (28%) |
| • 1 site | 15 (18.3%) |
| • 2 sites | 5 (6.1%) |
| • Obstetric complications (with or without thrombosis) | 5 (6.1%) |

**Prevalence of thrombosis (venous and/or arterial and/or obstetric complication)**

All but one patient received no primary aspirin prophylaxis. The patient who took aspirin did not develop thrombosis. During the median follow-up time of 3 years, 23 patients developed thrombosis and/or obstetric complications showing the thrombotic prevalence of 28% (Table 1). The obstetric complications were 2 abortions, 2 dead fetuses *in utero* and 1 pre-eclampsia. The characteristics of patients with thrombosis were summarized in Table 2. Eighteen of them (22%) fit in with the criteria for diagnosis of antiphospholipid syndrome.

Thirteen (56.5%) thrombotic SLE patients had positive antiphospholipid antibodies tests at the clinical thrombotic setting, while 10 (43.5%) patients had positive antiphospholipid antibodies before clinical thrombosis for the mean of 3.6 years, ranging from 1 to 6 years.

Seven of 19 SLE patients (36.8%) with medium-to-high titer anticardiolipin suffered from thrombosis and/or obstetric complications. In this group, there were 13 patients with one thrombosis, 4 patients with recurrent thrombosis and 3 patients with pregnancy complications. Seven of 33 SLE patients (21.2%) with low titer antiphospholipid progressed to thrombosis, and no obstetric complication was found. The difference in thrombotic rate between low *vs.* high titers of anticardiolipin was not significant ($p = 0.22$).

After thrombotic events, 13 patients were still on anticoagulants, and one was on aspirin at the time of the study. Anticoagulation was discontinued in 2 patients due to serious bleeding complication or death. Two patients expired from other causes than thrombosis. The mean duration of follow up was 3.71 years.

Among 136 SLE patients with negative antiphospholipid antibody, only 2 thrombotic events (sinus venous thrombosis and deep vein thrombosis) and 1 pregnancy complication (unexplained two consecutive abortions at gestational age over 10 weeks) have been reported yielding the prevalence of 2.2%. The odds ratio for thrombosis in SLE patients with antiphospholipid antibody compared with SLE without antiphospholipid was 17.3 (95% confidence interval [95%CI] 5.0 - 59.8, $p$ <0.00001).

**Factors associated with thrombosis in SLE patient with antiphospholipid antibodies**

The patients who had thrombosis showed older ages of SLE diagnosis compared with cases without thrombosis (37.7 ± 12.2 *vs.* 29.1 ± 14.9 years, $p$ = 0.016). In addition, hydroxychloroquine use was negatively associated with thrombosis (OR 0.29, 95% CI 0.09 - 0.95, $p$ = 0.034). On the other hand, male sex, history of nephritis and history of immune-modulators were not significantly associated with thrombosis and/or obstetric complications (data not shown).The other known risk factors, which were hypertension (3), immobility (2), diabetes mellitus (2) and morbid obesity (1), were found in 34.5% of patients with thrombosis. These factors were not reported in cases without thrombosis (p < 0.001).

Upon multivariate analysis, both older age of diagnosis (30 years or older) and absence of hydroxychloriquine use were independently related to thrombosis in SLE patients with detectable antiphospholipid antibodies (Table 3). The relationship with the presence of traditional risk factors of thrombosis was not significant.

**Table 2.** Characteristics for the 23 SLE patients with antiphospholipid antibody positive with thrombosis (N = 23).

| Variables | N (%) |
|---|---|
| Female | 21(91.3%) |
| Age at the testing (yr) | |
| • Median (range) | 37.7 years (17 - 63) |
| Duration of SLE (yr) | 10 years (1 - 23) |
| History of nephritis | 15 (65.2%) |
| History of immunomodulator therapy | 15 (65.2%) |
| History of prednisolone treatment | 23 (100%) |
| History of hydroxychloroquine treatment | 5 (21.7%) |
| History of aspirin treatment | 0 |
| Lupus anticoagulant | |
| • positive | 19 (82.6%) |
| • negative | 3 (13%) |
| • not done | 1 (4.3%) |

**Table 2.** Characteristics for the 23 SLE patients with antiphospholipid antibody positive with thrombosis (N = 23). (Continue)

| Variables | N (%) |
|---|---|
| Anticardiolipin | |
| • not done | 32 (39%) |
| • low titer | 2 (8.7%) |
| • medium to high titer | 7 (33.4%) |
| • negative | 7 (33.4%) |
| Thrombotic sites | |
| • venous | 12 (52.1%) |
| • arterial | 4 (17.4%) |
| • both venous and arterial | 2 (8.7%) |
| • obstetric complication | 3 (13%) |
| • obstetric and arterial site | 2 (8.7%) |

**Table 3.** Multivariate analysis for the factors associated with thrombotic events.

| Variables | Thrombosis OR (95%CI) | p Value |
|---|---|---|
| Hydroxychloroquine uses | 0.28 (0.08 - 0.96) | 0.043 |
| Age of SLE onset > 30 yrs | 2.94 (1.02 - 8.43) | 0.045 |

## Discussion

This study shows that the high prevalence of thrombosis in SLE patients with positive antiphospholipid in Thailand (28% with the median follow-up time of 3 years) compared to previous reports.[11-14] A study in Hong Kong revealed the incidence of 22.0% (18/82) with the median follow-up of 11 years.[13] The study in Korea showed the prevalence of 12.2% (6/49).[14] In addition, it confirms the risks of antiphospholipid antibodies for thrombosis in SLE patients with the odds ratio of over 17. Notably, the patients did not receive primary aspirin prevention and heparin prophylaxis was not routinely given for hospitalization. Interestingly, low titers of anticardiolipin in this study also showed higher risks of thrombosis with the prevalence of over 21.2%. However, high-titer anticardiolipin and lupus anticoagulant positivity showed greater prevalence rates of 36.8% and 38.0%, respectively. The differences were not statistically significant, probably due to the small sample size. Although we mostly did not repeat the test, one time positivity in this group of patients was a strong risk factor for thrombosis and/or obstetric complications.It remains to be determined whether the persistent antibodies is more predictive for thrombosis.

In this study, the only positive factor associated with thrombosis in SLE with antiphospholipid is the age of SLE diagnosis. This is not surprising as age is also a strong risk factor of thrombosis in non-SLE patients. Interestingly, hydroxychloroquine is found to be a significant protective factor in our population that is supportive of the recommendation in the EULAR's guideline. Hydroxychloroquine contains many potential mechanisms to prevent thrombosis, such as inhibition of platelet aggregation and adhesion, cholesterol-lowering, blockade of antiphospholipid antibody binding to the targets, as well as immune modulation.[15] Unlike previous studies, we could not find the association of thrombosis with history of nephritis or immunosuppressive drugs, probably due to the small sample size and the retrospective nature of the study. In addition, other confounding factors may contribute to thrombosis, such as smoking history, obesity, etc. In this study only one patient received primary aspirin prophylaxis. Therefore, the association between aspirin and thrombosis could not be determined.

Because antiphospholipid antibodies were not tested in all patients, there might be a bias in recruitment of SLE patients to be tested and the actual thrombosis might be lower. Fifty-seven percent of the patients were tested for antiphospholipid antibodies before thrombosis. If we included only those who had thrombosis after the laboratory tests, the prevalence would be 14.5%. This is still comparable to other reports. Therefore, primary aspirin and hydroxychloroquine prophylaxis as recommended for the Caucasian[3, 16] should also be considered in Thai SLE patients with detectable antiphospholipid antibodies. However, our study included only patients who used to be admitted to the hospital, which was a risk factor of venous thrombosis. This may not be applicable to patients who were treated solely as outpatients.

In conclusion, the prevalence of thrombosis in antiphospholipid-positive SLE was 28%. Primary prophylaxis should be considered. Future prospective multicenter studies are, however, warranted.

**References**

1. Romero-Diaz J, Garcia-Sosa I, Sanchez-Guerrero J. Thrombosis in systemic lupus erythematosus and other autoimmune diseases of recent onset. J Rheumatol 2009 Jan; 36(1): 68 - 75
2. Giron-Gonzalez JA, Garcia del Rio E, Rodriguez C, Rodriguez-Martorell J, Serrano A. Antiphospholipid syndrome and asymptomatic carriers of antiphospholipid antibody: prospective analysis of 404 individuals. J Rheumatol 2004 Aug; 31(8):1560 - 7
3. Bertsias G, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, Font J, Gilboe IM, Houssiau F, Huizinga T, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2008 Feb; 67(2): 195 - 205
4. Metjian A, Lim W. ASH evidence-based guidelines: should asymptomatic patients with antiphospholipid antibodies receive primary prophylaxis to prevent thrombosis?

Hematology Am Soc Hematol Educ Program 2009; 247 - 9

5. Erkan D, Harrison MJ, Levy R, Peterson M, Petri M, Sammaritano L, Unalp-Arida A, Vilela V, Yazici Y, Lockshin MD. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. Arthritis Rheum 2007 Jul; 56(7): 2382 - 91
6. Tarr T, Lakos G, Bhattoa HP, Shoenfeld Y, Szegedi G, Kiss E. Analysis of risk factors for the development of thrombotic complications in antiphospholipid antibody positive lupus patients. Lupus 2007; 16(1): 39 - 45
7. Hereng T, Lambert M, Hachulla E, Samor M, Dubucquoi S, Caron C, Launay D, Morell-Dubois S, Queyrel V, Hatron PY. Influence of aspirin on the clinical outcomes of 103 anti-phospholipid antibodies-positive patients. Lupus 2008 Jan; 17(1): 11 - 5
8. White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res 2009; 123 Suppl 4: S11 - 7
9. Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. Ann Rheum Dis 2009 Feb; 68(2): 238 - 41
10. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. Arthritis Rheum 2009 Jan; 61(1): 29 - 36
11. Tarr T, Lakos G, Bhattoa HP, Soltesz P, Shoenfeld Y, Szegedi G, Kiss E. Clinical thrombotic manifestations in SLE patients with and without antiphospholipid antibodies: a 5-year follow-up. Clin Rev Allergy Immunol 2007 Apr; 32(2): 131 - 7
12. Erkan D, Yazici Y, Peterson MG, Sammaritano L, Lockshin MD. A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. Rheumatology (Oxford) 2002 Aug; 41(8): 924 - 9
13. Mok MY, Chan EY, Fong DY, Leung KF, Wong WS, Lau CS. Antiphospholipid antibody profiles and their clinical associations in Chinese patients with systemic lupus erythematosus. J Rheumatol 2005 Apr; 32(4): 622 - 8
14. Woo KS, Kim KE, Kim JM, Han JY, Chung WT, Kim KH. Prevalence and clinical associations of lupus anticoagulant, anticardiolipin antibodies, and anti-beta2-glycoprotein I antibodies in patients with systemic lupus erythematosus. Korean J Lab Med 2010 Feb; 30(1): 38 - 44
15. Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody-positive patients. Curr Rheumatol Rep 2011 Feb;13(1): 77 - 80
16. Wahl DG, Bounameaux H, de Moerloose P, Sarasin FP. Prophylactic antithrombotic therapy for patients with systemic lupus erythematosus with or without antiphospholipid antibodies: do the benefits outweigh the risks? A decision analysis. Arch Intern Med 2000 Jul; 160(13): 2042 - 8