False-positive results of lupus anticoagulant tests should be kept in mind in pregnant patients receiving low molecular weight heparin

To the Editor,

We read the article by Dr Izhar et al. (1), entitled "Anti-phospholipid antibodies in women presenting with preterm delivery because of preeclampsia or placental insufficiency", in the last issue of your journal with great interest. The authors observed a high prevalence of anti-phospholipid antibodies (APLA) in women who have preterm delivery due to preeclampsia or placental insufficiency (PREPI), corroborating the results of previous reports. Their findings are of great interest and finally shed some more light on this interesting topic. Therefore, we would like to commend the authors for addressing this issue. However, several points caught our attention while reading this paper and we would like to highlight these to the reader.

Firstly, as already mentioned by the authors, classification criteria for anti-phospholipid syndrome (APS) includes both clinical and laboratory criteria. The clinical criteria consist of vascular thrombosis and/or pregnancy morbidity. Although the association of APLA with preeclampsia was discussed extensively by the authors, no information was presented regarding the cases in which vascular thrombosis was present. Vascular thrombosis in APS can affect any vascular bed, including venous, microvascular and arterial vessels and can complicate pregnancy (2). Hence it would be beneficial for the authors to perform a subgroup analysis assessing APLA levels in pregnant patients with a history of arterial or venous thrombosis.

Secondly, and more importantly, we think that the authors should have indicated and discussed whether the use of low molecular weight heparin (LMWH) or other anticoagulants had interfered with lupus anticoagulant (LAC) testing in their patient group. Although the detection of LAC according to the guidelines of the International Society on Thrombosis and Hemostasis criteria include screening, mixing and confirmation tests, measured on two or more occasions at least 12 weeks apart, is strictly reliable, both false-positive and false-negative results have been described in literature due to use of heparin or LMWH (3-5). In this context, Martinuzzo et al. (5) study is important for demonstrating an increased rate of false-positive LAC test results in plasma of patients with previous negative LAC tests that receive enoxaparin 40 mg/day. Furthermore, enoxaparin has been shown to affect tests for LAC not only in screening and mixing, but also in confirmatory studies. In accordance with these findings, the Scientific and Standardization Committee for LAC/anti-phospholipid antibodies suggest that anticoagulation with any drug, including unfractionated heparin, LMWH and direct oral anticoagulants, may potentially complicate LAC detection, simply because anticoagulants usually lengthen test clotting times (i.e., the activated partial thromboplastin time and dilute Russell's viper venom time), currently proposed for LAC detection (4,6). Therefore, we think that it would have been advisable for the authors to have mentioned the possible effect of LMWH on positive LAC test results in their patient group. Moreover, further analysis of repeated LAC tests after discontinuation of LMWH in patients who were using LMWH at the time of initial positive LAC should have been included in the article.

In conclusion, we fully appreciate the finding that APLA has a significant effect on preterm delivery due to PREPI. Thus, we suggest that anti-FXa activity should also be measured in patients who are known to be on LMWH treatment and if the activity is within the therapeutic range, LAC testing can be carried out if reagents contain heparin neutralizers.

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Address for Correspondence: *Ece Ünal Çetin*
e.mail: eceunalcetin@gmail.com ORCID: orcid.org/0000-0002-0933-7764

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Fatma Beyazit[1], Ece Ünal Çetin[2], Yavuz Beyazit[2]

[1]Clinic of Obstetrics and Gynecology, Çanakkale Onsekiz Mart University Hospital, Çanakkale, Turkey
[2]Department of Internal Medicine, Çanakkale Onsekiz Mart University Hospital, Çanakkale, Turkey

References

1. Izhar R, Ala SH, Husain S, Husain S. Anti-phospholipid antibodies in women presenting with preterm delivery because of preeclampsia or placental insufficiency. J Turk Ger Gynecol Assoc 2021; 22: 85-90.
2. Svenungsson E, Antovic A. The antiphospholipid syndrome - often overlooked cause of vascular occlusions? J Intern Med 2020; 287: 349-72.
3. Gibbins KJ, Tebo AE, Nielsen SK, Branch DW. Antiphospholipid antibodies in women with severe preeclampsia and placental insufficiency: a case-control study. Lupus 2018; 27: 1903-10.
4. Tripodi A, Cohen H, Devreese KMJ. Lupus anticoagulant detection in anticoagulated patients. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis. J Thromb Haemost 2020; 18: 1569-75.
5. Martinuzzo ME, Barrera LH, D'adamo MA, Otaso JC, Gimenez MI, Oyhamburu J. Frequent false-positive results of lupus anticoagulant tests in plasmas of patients receiving the new oral anticoagulants and enoxaparin. Int J Lab Hematol 2014; 36: 144-50.
6. Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al; Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost 2009; 7: 1737-40.

Author's Response

Dear Editor,

We would like to thank the reader for critically reading and evaluating our article. We would like to clarify to the readers that none of our women had any history of thrombosis or known thrombophilia, so a sub-analysis of such cases was not required. Moreover, we used the standard guideline criteria for detecting LAC, which they also agree is strictly reliable. They have quoted that prolongation of clotting time with use of anticoagulants "can potentially" affect results. We need to take the findings of these studies with a grain of salt. The authors have referred to studies that show anticoagulant use complicates detection of LAC. We tested subjects for all three antibodies and we tested them as per the standard criteria, which still remains the most stringent and widely accepted criteria for identifying anti-phospholipid antibody syndrome. Until a firm evidence base is there, we cannot negate or affirm that detection is altered. However, we would agree that few reports exist that are in agreement with complications in detecting LAC.

Rubina Izhar[1], Syed Hasan Ala[2], Samia Husain[1], Sonia Husain[1]

[1]Department of Obstetrics and Gynecology, Karachi Medical and Dental College, Abbasi Shaheed Hospital, Karachi, Pakistan
[2]Department of Obstetrics and Gynecology, Dow University of Health Sciences, Karachi, Pakistan