EDITORIAL

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A point of view on hereditary thrombophilia and low-molecular-weight heparin incorporating the management in pregnancy and involving thyroidology

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INTRODUCTION

Ab initio, the association of hereditary thrombophilia with adverse pregnancy outcomes still remains to be comprehensively understood. Consequently, the demand for screening for hereditary thrombophilia, the introduction of the treatment, the timing of its introduction, and the exact indications are still a matter of debate in most of the clinical studies[1]. Moreover, therapy options for patients with proven hereditary thrombophilia are also a point of discussion. Most physicians use low-molecular-weight heparin (LMWH), but conflicting outcomes remain on whether it improves pregnancy outcomes, hospitalization rates, and quality of life. The resistance index of the uterine artery (RiAu) is a qualified predictor of placental function and vascularization patterns and is therefore involved in pregnancy termination or therapy protocols.

POINT OF VIEW

The first issue that is commonly raised denotes the screening guidelines. Currently, the screening is recommended for pregnant women with a positive history of venous thromboembolism and/or for those having a first-degree relative with a history of high-risk hereditary thrombophilia[1]. There is no screening recommendation for women with a history of fetal loss or adverse pregnancy outcomes. However, studies on the use of anticoagulant therapy, *per se*, among women with hereditary thrombophilia have focused on the prevention of placenta-mediated adverse pregnancy outcomes.

In several studies, published by authors from our center, hereditary thrombophilia was indeed responsible for poor placentation and poor adverse pregnancy outcomes (APO). We have demonstrated that LMWH therapy was negatively associated with RiAu between the 36th and 38th gestational weeks (gw), recently published in *Revista da Associação Médica Brasileira*, Volume 69. Moreover, younger gestational age at delivery, higher D-dimer values, and higher RiAu values were associated with APO, and the LMWH therapy indirectly affected APO via RiAu between the 36th and 38th gw which leads us to believe that previous APO should also be included in the decision-making process for LMWH therapy introduction[2-4]. In addition, the data for that study had been obtained from the hospital's digital database, including comorbid conditions such as thyroid dysfunction. The thyroid hormones such as L-thyroxine (3,5,3',5'-tetraiodothyronine, T4), and L-triiodothyronine (3,5,3'-triiodothyronine, T3) are known to be effective in reproductive functions in humans and animals by regulating the ovarian, uterine, and placental tissues and metabolism in thyroidology[2-7]. Nevertheless, in our previous study, the women with APO in their current pregnancy did not reveal significance compared to the ones without APO in their current pregnancy in terms of thyroid dysfunction[2-5].

In addition, our previous study[3] has proven the requirement for thrombophilia screening when poor vascularization patterns are observed to minimize APO. On the contrary, a recent cohort study and systematic review of the literature[8] has proven similar

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in the setting of recurrent miscarriage without possessing need for thrombophilia screening. Considering this, we believe that thrombophilia screening should be performed when the patients report adverse late pregnancy outcomes in previous pregnancies and recurrent miscarriage as it can be a consequence of poor early placentation. Our viewpoint is that even though there might not be any difference between thrombophilia prevalence between the population of women with regular pregnancy and those with recurrent miscarriage or late APO, the latter might benefit from LMWH introduction and therapy. Specifically, early introduction of the anticoagulant therapy in the early first trimester may have the highest effect on the placentation process and may therefore be able to prevent all the adverse pregnancy outcomes associated with it.

Differences between populations should also be considered since the genetic culprit of inherited thrombophilia is based on gene mutations and polymorphisms. Apart from mutations analyzed in our population, a recent study from India[9] has shown an even greater spectrum of polymorphisms that should be tested in the setting of recurrent pregnancy loss, and similar up-to-date recommendations based on different gene testing studies from Libia[10] and Japan[11]. The prevalence of different hereditary thrombophilia types and especially the differences between the prevalence of homozygous and heterozygous cases might be taken into consideration by decision-making authorities or guidelines in different systems. Factor V Leiden is more common in the population of Northern Europe or Northern European descent and the prothrombin gene mutation is more common in Southern Europe, while MTHFR C677TT mutation is more common among women of European descent, both southern and northern, and of middle east than in Asian populations[12].

Of note, the LMWH therapy has its downsides as well. Although it is proven to have a frequency of adverse effects compared to other anticoagulants and is safe for the fetus, as it does not transfer the placental barrier, it is not without them. The issues with LMWH commonly refer to its expensiveness, the uncomfortable administration, and most worryingly, its association with bleeding. Nonetheless, most women with thrombophilia have stated that they would be willing to take LMWH in future pregnancies to avoid the possibility of pregnancy losses[13].

CONCLUSION

From our point of view, the benefits outweigh the risks and the costs of both screenings for hereditary thrombophilia and treatment of these phenomena. Routine testing scale and treatment modalities with LMWH of inherited thrombophilia in women with previous APO, RPL, and markers of suboptimal placentation (RIAU) are essential. Finally, the tested polymorphisms might be fitted to the population and ethnicity of the mother. This issue merits further investigation. *Several eyes see more than only one.*

AUTHORS' CONTRIBUTIONS

SD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft. **JT:** Investigation, Methodology, Project administration, Validation, Visualization. **MM:** Methodology, Project administration, Validation, Visualization. **SVP:** Investigation, Methodology, Validation, Visualization. **MP:** Investigation, Project administration, Validation, Visualization. **MG**: Investigation, Methodology, Project administration, Validation, Visualization. **DS:** Investigation, Methodology, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **IS:** Investigation, Methodology, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **AP:** Investigation, Methodology, Validation, Visualization, Writing – review & editing. **ECAV:** Investigation, Methodology, Validation, Visualization, Writing – review & editing.

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