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Maturitas

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Letter to the Editor

Response to “Should estrogen be used in the co-treatment of COVID-19 patients?”



Dear Editor,

We appreciate the comments by Hamzaoglu and Erel [1] on our recommendations concerning the use of menopausal hormone therapy by women suffering with SARS-Cov-2 [2].

The main argument in the letter is that both experimental data and preliminary clinical evidence suggest that estrogens may protect against the development of covid disease. This argument agrees with a previous letter from the Italian Menopause Society [3]. Hamzaoglu and Erel further add that estrogens might prevent cytokine storm, so that the evolution of the disease, even in development, might be milder. They support their position with a series of features of the pathophysiological mechanism, essentially that estrogens favour a decrease in the tissue expression of AT1R, the angiotensin II (A-II) type I receptor, together with an increase in the tissue expression of the anti-inflammatory AT2R and in the serum levels of ACE2, the enzyme converting angiotensin I to angiotensin (1–9) and A-II to angiotensin (1–7). This all is supported by different experimental models and by some clinical evidence, which has been extended in more recent observations during the outbreak in Wuhan [4].

We cannot but reiterate our message already detailed in our response to the letter by Cagnacci et al. [3]. Of course, we absolutely agree in that the emerging data concerning the potential protective effect of estrogens against the progression of the disease is an exciting area, which will require extensive research. But, also as stated in our earlier letter, our recommendations refer to a different setting, in which the disease is already consolidated and in progress. A massive disruption of the endothelium and a tsunami of inflammatory mediators, with the corresponding activation of the extrinsic arm of the coagulation cascade, is the main actor at that stage. This all conditions a generalised status of thrombotic events in organs and systems. We all will probably agree in that, in this context, and this is not recent news [5], oral estrogens will not help, given their well-established pro-coagulative role in the haemostatic balance. These women will be meeting two of the three conditions of the Virchow triad, the injury to the vessel wall plus a pro-coagulative status. This is also the basis for the consensus on the use of heparin, which is present in most protocols worldwide. Distinct is the case of transdermal estrogens, which we have included as an alternative in our algorithm [2].

The case of the severely ill patients, hospitalised in an intensive care unit, is still more compelling. We have singled out that situation in our algorithm, because together with an extremely severe disease, they add prolonged immobility. So, another one, the third condition, of the Virchow triad. We absolutely lack any evidence of how the final balance of estrogens will be in this context. Given the perfect coagulation storm of the situation, and that the interest in using estrogens would

only be to limit the progression of the disease, since the sedated status of these women gives no room for considering menopausal symptoms, we found it common clinical sense to refrain from the use of any form of MHT. Further clinical evidence will be required, and is eagerly expected, to support or refute this recommendation.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this letter.

Funding

No funding was received in relation to this letter.

References

- [1] K. Hamzaoglu, C. Tamer Erel, Should Estrogen be used in the co-treatment of COVID-19 Patients? What is the rationale? *Maturitas* (2020) [Epub ahead of print].
- [2] I. Ramírez, E. De la Viuda, L. Baquedano, et al., Managing thromboembolic risk with menopausal hormone therapy and hormonal contraception in the COVID-19 pandemic: recommendations from the Spanish Menopause Society, Sociedad Española de Ginecología y Obstetricia and Sociedad Española de Trombosis y Hemostasia, *Maturitas* 137 (2020) 57–62, <https://doi.org/10.1016/j.maturitas.2020.04.019>.
- [3] A. Cagnacci, G. Bonaccorsi, M. Gambacciani, V. De Leo, C. Di Carlo, G. Bifulco, S. Alfieri, N. Biglia, S. Caruso, E. Cicinelli, P. De Franciscis, A. Gambera, A. Grasso, F. Murina, A.M. Paoletti, F. Vicariotto, P. Villa, A. Volpe as board of the Italian Society of Menopause, Reflections and recommendations on COVID-19 pandemic: should hormone therapy Be discontinued? *Maturitas* (2020) [Epub ahead of print].
- [4] T. Ding, J. Zhang, T. Wang, P. Cui, Z. Chen, J. Jiang, S. Zhou, J. Dai, B. Wang, S. Yuan, W. Ma, L. Ma, Y. Rong, J. Chang, X. Miao, X. Ma, S. Wang, Potential influence of menstrual status and sex hormones on female SARS-CoV-2 infection: a cross-sectional study from multicentre in Wuhan, China, *Clin. Infect. Dis.* (2020), <https://doi.org/10.1093/cid/ciaa1022> ciaa1022. [Epub ahead of print].
- [5] A. Cano, W.M. van Baal, The mechanisms of thrombotic risk induced by hormone replacement therapy, *Maturitas* 40 (1) (2001) 17–38.

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Received 14 June 2020

Available online 31 July 2020

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