Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Maturitas 140 (2020) 80

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Letter to the Editor

Should estrogen be used in the co-treatment of COVID-19 patients? What is the rationale?

We have read the recommendations from the Spanish Menopause Society regarding the cessation of menopausal hormone therapy (MHT) in order to prevent the execerbation of TE events in COVID-19 patients [1]. In contrast, our opinion is in accordance with recommendations of the Italian Menopause Society [2] and even goes a little bit further, as we believe the estrogenic component of MHT may prevent a cytokine storm and in turn TE complications. Epidemiological studies have shown a less severe course of COVID-19 and a decreased mortality rate among women. Activation of the coagulation cascade and pulmonary TE due to cytokine storm is the key factor increasing the mortality rates in COVID-19 [3]. The reason for the sex difference in COVID-19 may be the different effects of estrogen and testosterone on ACE2 expression/function and in turn cytokine storm [4].

The spike glycoprotein of the SARS-Cov-2 virus accesses the host cells by using the ACE2 enzyme as a receptor [5]. After SARS-CoV-2 virus binds to ACE2, this complex triggers the activity of a disintegrin and metalloproteinase 17 (ADAM-17) in the membrane. ADAM-17 cleaves the TNF-α and various other cytokines, which in turn initiates and exacerbates the inflammation. Moreover, ACE1 converts angiotensin-I (A–I) into angiotensin-II (A–II), and in turn it binds to A–II type I receptor (AT1R). Activation of the AT1R also further increases ADAM-17 activity. There is also AT2R on the surface of the cell membrane that has an anti-inflammatory effect, functioning contrary to the AT1R.

On the other hand, ACE2 converts both A–I to angiotensin (1–9) (A-1 – 9) and A–II to angiotensin (1–7) (A-1 – 7). A-1–7 also acts through the Mas receptor (MasR). ACE2/A-1 – 7/MasR activation leads to an anti-inflammatory effect as well [7,9]. In summary, there is a balance in the system between ACE1/A–II/AT1R and ACE2/A-1 – 7/MasR. However, SARS-CoV-2 disrupts this balance in favor of ACE1/A–II/AT1R activation, leading to inflammation.

Although there is no sufficient clinical data regarding the effect of estrogen on ACE2, AT1R and AT2R, estrogen have provided a decrease in tissue expression of AT1R but an increase in tissue expression of AT2R and serum ACE2 level in animal models [4]. Interestingly, serum A-1 – 7 levels have been shown to decrease after ovariectomy in female mice. Estrogen administration has provided an increase in the circulating A-1 – 7. Moreover, a study of 42 healthy volunteers has concluded that women exhibit significantly higher plasma concentrations of A-1 – 7 than men [6]. All available evidence suggests that estrogen shifts the balance in favor of the A–II/ACE2/MasR pathway instead of the A–II/ACE2/AT1R pathway. Therefore, estrogen may prevent multiple pathologies leading to cytokine storm and TE complications in COVID-19. However, androgens have the opposite effect to estrogen on both A–II/ACE2/AT1R and A–II/ACE2/MasR pathways [4].

In conclusion, we do not recommend cessation of MHT for postmenopausal women with mild or moderate symptoms of COVID-19. Estrogen would prevent the inflammation and the cytokine storm for women with COVID-19. Transdermal application of estrogen may be preferred to oral administration, and transdermal application of estrogen may even be thought of as a co-treatment for COVID-19 with anti-virals and anti-coagulants in postmenopausal women who were not previously users of MHT. However, we do not have sufficient evidence to recommend cessation of MHT in cases of severe COVID-19. We need further studies to find the right answers.

Funding

No funding was received in relation to this letter.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

References

[1] L. Baquedano, M.J. Cancelo, A. Cano, P. Coronado, E. De la Viuda, P. Llaneza, N. Mendoza, B. Otero, J.A. Páramo, I. Ramírez, S. Sánchez, 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.

[2] 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, Reflections and recommendations on COVID-19 pandemic: should hormone therapy be discontinued? Maturitas (2020) Accepted.

[3] S. La Vignera, R. Cannarella, R.A. Condorelli, F. Torre, A. Aversa, A.E. Calogero, Sex-specific SARS-CoV-2 mortality: among hormone-modulated ACE2 expression, risk of venous thromboembolism and hypovitaminosis d, Int. J. Mol. Sci. 21 (2020) 2948, https://doi.org/10.3390/ijms21082948.

[4] M.C. White, R. Fleeman, A.C. Arnold, Sex differences in the metabolic effects of the renin-angiotensin system, Biol. Sex Differ. 10 (2019) 31, https://doi.org/10.1186/s13293-019-0247-5.

[5] M. Gheblawi, K. Wang, A. Viveiros, Q. Nguyen, J.C. Zhong, A.J. Turner, M.K. Raizada, M.B. Grant, G.Y. Oudit, Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system celebrating the 20th anniversary of the discovery of ACE2, Circ. Res. 126 (2020) 1457–1475.

[6] J.C. Sullivan, P. Rodriguez-Miguelez, M.A. Zimmerman, R.A. Harris, Differences in angiotensin (1-7) between men and women, Am. J. Physiol. Heart Circ. Physiol. 308 (9) (2015) H1171–H1176.

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DOI of original article: https://doi.org/10.1016/j.maturitas.2020.06.014

https://doi.org/10.1016/j.maturitas.2020.06.015
Received 26 May 2020
Available online 31 July 2020