IRIS AperTO

UNIVERSITÀ DEGLI STUDI DI TORINO

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Reflections and recommendations on the COVID-19 pandemic: Should hormone therapy be discontinued?

This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1756062 since 2020-09-22T12:31:16Z

Published version:

DOI:10.1016/j.maturitas.2020.05.022

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

12 October 2024

Elsevier Public Health Emergency Collection

Public Health Emergency COVID-19 Initiative

Maturitas. 2020 Aug; 138: 76–77. PMCID: PMC7301099
Published online 2020 Jun 18. doi: 10.1016/j.maturitas.2020.05.022 PMID: 32565009

Reflections and recommendations on the COVID-19 pandemic: Should hormone therapy be discontinued?

A. Cagnacci,[a,*] G. Bonaccorsi,[b] M. Gambacciani,[c] and the board of the Italian Menopause Society

Since the COVID-19 pandemic outbreak, the extent of serious complications and high rate of mortality has concerned all the health authorities worldwide. Death by COVID-19 is mainly due to acute respiratory distress syndrome (ARDS), although heart and multiple organ failure may contribute [1]. Underlying mechanisms are COVID-19-induced endothelial alteration, cytokine storm, inflammation, exudation in the lungs, and vessel occlusion.

1. Difference between sexes

Mortality by COVID-19 is higher in men than in women. Among the advocated reasons are a different exposure to risk factors such as smoking, reduced care of men about their health or different association with other morbidities. Nevertheless, a different expression of ACE2 may explain the different mortality between sexes. COVID-19 disease progression is reduced by ACE2 enzyme expression in endothelial cells mainly at the lung and heart, where it exerts vasodilating, anti-inflammatory and anticoagulant effects [2]. ACE2 is coded by the X chromosome, of which men have only one, and ACE2 expression in endothelial cells is stimulated by estrogens [2]. The possibility that this mechanisms accounts for the lower mortality of women vs. men (Yi et al.) is sustained by the recent evidence that reduced mortality (−72 %) of fertile women vs. men is lost, at least in part, in the postmenopausal years (−49.6 %) [3].

2. Hormone therapy

These data lead to speculation that hormone therapy or even potentiating estrogen stimulus by exogenous estrogens may antagonize the deadly progression of the disease. On the other hand, exogenous estrogens may increase coagulating factors and the risk of thromboembolic events with a potential consequent increase in mortality. Hospitalized individuals with very severe COVID-19 disease have an activated coagulation defined by high levels of D-dimers, products of fibrin degradation, and when D-dimer levels are very high, anticoagulants like heparin may reduce mortality [4]. In order to decrease the risk of thromboembolic events a recent publication has recommended that peri- and post-menopausal women immediately withdraw from exogenous hormone administration after becoming infected by COVID-19 [5]. This position stimulates some considerations.

1) Thrombophilic states are not among the comorbidities that accelerate COVID-19 disease progression. To date, there is no report documenting that the most thrombophilic state in woman life, i.e. pregnancy, or even hormonal contraceptive use [6], is associated with a worst prognosis of COVID-19 infection. 2) Locally formed thrombi, consequent to massive endothelial disruption and local activation of the extrinsic coagulation cascade, rather than cloth emboli, appear to occlude lung vessels of COVID-19-infected individuals in the last stage of disease [4]. Indeed, the evidence that many women with occluded lung vessels lack peripheral vein thrombosis challenges the theory of a massively increased thrombophilic condition [4]. Of the Virchow triad explaining blood clot formation, i.e. increased coagulation, blood stasis and altered endothelium, it is the third component that is highly prevalent in COVID-19 individuals, the contribution of increased coagulation being unknown and probably negligible [4]. 3) The dose of heparin used in COVID-19-infected individuals (80–100 mg) exceeds the prophylactic dose for thrombophilic states. 4) A putative increased risk of venous thrombosis due to increased synthesis of coagulation factors is mainly limited to the first two years of oral estrogen administration, and up to now no study has reported a thrombophilic effect of transdermal estrogens [7]. 5) Perimenopausal women requiring hormonal contraception are usually in their late forties and postmenopausal women start their hormone therapy for symptoms before 60 years of age. In these years, mortality from COVID-19 is below 1 % [3], and there is no report that it is higher in women on hormones.

3. Conclusions

At first sight, indications for COVID-19-positive individuals to withdraw from hormone therapy or oral contraceptives may seem a wise recommendation, but it is not based on real data. It takes into consideration only one side of the coin, the procoagulant activity of exogenous oral estrogens. This effect for COVID-19 patients is likely the least important. In these individuals, increased coagulation is consequent to massive endothelial disruption and to the activation of the extrinsic coagulation cascade, with no evidence that an increase in coagulating factors plays any role [4]. By contrast, the advice to withdraw from estrogens misses a consideration of the main effect of estrogens, i.e. their ability to stimulate ACE2 enzyme expression, a critical factor in reducing mortality from COVID-19 [2].

4. Recommendations

On these bases, we suggest that advice for COVID-19-infected women should be:

a Hormone therapy or hormonal contraceptives [6] should be continued, unless the woman is severely ill, a condition in which hormonal balance is probably not so crucial. In the other conditions, the possibility that hormone withdrawal may accelerate COVID-19 progression cannot be excluded, and withdrawal should be avoided.

b In case of disease progression from a simple flu to more severe symptoms, it seems wise to rely on expertise of specialists who will consider the need of adding heparin, useful as anticoagulant, anti-inflammatory and immune-modulator [4].

c Shifting from oral to transdermal estrogens (patch, gel, spray) may be considered, but is not mandatory.

d In order to start or restart therapy, it is probably useful to use transdermal instead of oral estrogens.

e In the case that hormone therapy is discontinued, it should be remembered that withdrawal bleedings may occur.

Funding

No funding was received in relation to this letter.

Declaration of Competing Interest

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

Contributor Information

the board of the Italian Menopause Society:

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, 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, and A. Volpe

References

1. Yi Y., Lagniton P.N.P., Ye S., Li E., Xu R.H. COVID-19: what has been learned and to be learned about the novel coronavirus disease. *Int. J. Biol. Sci.* 2020;16:1753–1766. doi: 10.7150/ijbs.45134. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

2. Cheng H., Wang Y., Wang G.Q. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *J. Med. Virol.* 2020;(March (27)) doi: 10.1002/jmv.25785. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

3. Cagnacci A., Xholli A. Age-related difference in the rate of COVID-19 mortality in women versus men. *Am. J. Obstet. Gynecol.* 2020 doi: 10.1016/j.ajog.2020.05.039. in press. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

4. Cattaneo M., Bertinato E.M., Birocchi S., Brizio C., Malavolta D., Manzoni M., Muscarella G., Orlandi M. Pulmonary embolism or pulmonary thrombosis in COVID-19? Is the recommendation to use high-dose heparin for thromboprophylaxis justified? *Thromb. Haemost.* 2020;(April (29)) doi: 10.1055/s-0040-1712097. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

5. Ramírez I., De la Viuda E., Baquedano L., Coronado P., Llaneza P., Mendoza N., Otero B., Sánchez S., Cancelo M.J., Páramoc J.A., Cano A. Sociedad Española de Ginecología y Obstetricia and Sociedad Española de Trombosis y Hemostasia; Maturitas: 2020. Managing Thromboembolic Risk with Menopausal Hormone Therapy and Hormonal Contraception in the COVID-19 Pandemic: Recommendations From the Spanish Menopause Society. in press, https://doi.org/10.1016/j.maturitas.2020.04.019. [Google Scholar]

6. Fruzzetti F., Cagnacci A., Primiero F., De Leo V., Bastianelli C., Caruso S., Di Carlo C., Farris M., Grandi G., Grasso A., Guida M., Meriggiola M.G., Paoletti A.M., Cianci A., Nappi C., Volpe A. Contraception during Coronavirus-Covid 19 pandemia. Reccomandations of the Board of the Italian Society for Contraception (SIC) *EJCRHC.* 2020 doi: 10.1080/13625187.2020.1766016. in press. [PubMed] [CrossRef] [Google Scholar]

7. Scarabin P.Y., Oger E., Plu-Bureau G; EStrogen and THrombo Embolism Risk Study Group Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet.* 2003;362:428–432. https//:doi 10.1016/S0140-6736(03)14066-4. [PubMed] [Google Scholar]