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General Medicine

PROPOSED ESTROGEN THERAPY FOR COVID 19 AND OTHER MICROBIAL INFECTIONS

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ABSTRACT The novel coronavirus or SARS CoV-2 infection or COVID 19, which originated in Wuhan, China is an infection with a new coronavirus. Since there was no previous human exposure to this virus, there was no herd immunity. Despite this universal absence of herd and adaptive immunity, there are considerable gender differences in mortality among men and women. In addition, mortality in children is considerably low as compared to adults (https://www.worldometers.info/coconavirus/Coronavirus-age-sex-demographics/ Coronavirus Age, Sex, Demographics (COVID 19) – Worldometer).

This implies stronger innate and adaptive immunity are at play in children and women as compared to that in adult men. Less severe affliction of women may be due to higher levels of estradiol in pre-menopausal women that in men. Estradiol has a favorable influence on innate and adaptive immunity (Carmen Giefing-Kröll et al. Aging Cell. 2015 Jun; 14(3): 309–321). Arsenicum Album 30, a homeopathic medicine, recommended by the Ministry of AYUSH, Government of India, (https://www.ayush.gov.in/docs/homeopathy-guidelines.pdf) has arsenic, which is a metalloestrogen (P D Darbre J Appl Toxicol. May-Jun 2006; 26(3):191-7); which appears to be the reason for its effectiveness in the treatment of COVID 19 or SARS Cov-2. Estradiol has thromboembolic effects when administered orally. However, transdermal estradiol is safer, without thromboembolic effects and is already in use in some countries (Archer DF et al. Climacteric. 2012 Jun;15(3):235-40.; Marianne Canonico et al Circulation. 2007;115:840–845).

Estrogen therapy is given in some forms of prostatic cancer in men. In view of these potential benefits of estrogen, estradiol transdermal therapy should be tried as a repurposed or investigational drug along with routine treatment of COVID 19 in men and post-menopausal women and in similar infections with new microbes in the absence of specific treatment.

KEYWORDS : Estradiol, Metalloestrogen, COVID 19, SARS CoV-2

INTRODUCTION:

The ongoing COVID 19 pandemic which originated in Wuhan, China has been spreading all over the world leading to considerable morbidity and mortality. Unfortunately, this being a new virus, there is no herd immunity and specific medicines for its treatment. All the medicines and therapies being tried are investigational. Many clinicians and scientists are trying to develop medical management protocols, specific medicines and vaccines.

In absence of rapid antibody testing and scarcity of Reverse Transcription PCR test in many parts of world, many asymptomatic cases and mild cases of COVID 19 are thus missed. The most severe outcome of the disease is, obviously, death and this outcome is being reported more reliably all over the world. There is however, a stark difference in mortalities between men and women and between paediatric and non-paediatric populations.

The age distribution of COVID 19 cases in New York City reveals that there were only 0.04% deaths in age group 0-17 years. There was considerable difference in the gender distribution of deaths in New York City. Mortalities in males and females were 61.8 % and 38.2% respectively.

Older data from China reveal that death rate probably attributable to COVID 19 in 0-9 age group and 10-19 age group were 0% and 0.2 % respectively. The same data show that death rate among confirmed cases of COVID 19 were 4.7% and 2.8% in males and females respectively(https://www.worldometers.info/coconavirus/Coronavirus-age-sex-demographics/Coronavirus Age, Sex, Demographics (COVID 19) – Worldometer).

DISCUSSION:

The immune system gradually matures during infancy. Critical early protection against many infectious diseases previously experienced by the mother is given by the passive IgG antibody transferred from the mother transplacentally and in milk. Once that fades away, young children become more vulnerable to infections, though by then better armed with the maturing innate and adaptive immune systems. The risks are now much reduced by vaccinations, which stimulate protective immune responses in the maturing immune system. Nevertheless, children may still acquire viral, bacterial and parasitic infections that have to be fought off and controlled by immune responses. Besides promoting recovery, such antigen stimulation results in immunological memory. Thus, over time, protection provided by the immune response increases, and young adults suffer fewer infections. This accumulation of immunological memory is an evolving feature of the adaptive immune response. The memory persists into old age but then may fade (A. Katharina Simon et al, 2015; Proc Biol Sci.282(1821): 20143085).

COVID 19 is a new disease due to novel corona virus. Mothers are less likely to transfer passive IgG antibody to this virus transplacentally and in the breast milk. Even if this is considered to be the case, this is likely to fade away after 6 to 9 months, making infants and young children more vulnerable to COVID 19 due to their immature immune system. This risk is not reduced by vaccination as applicable to other childhood vaccine preventable diseases since no vaccine for COVID 19 has been administered to children so far. Children suffer from infections more frequently than adults as their immune system is immature as compared to that of adults. Both innate and adaptive immunity are less developed in children. Due to less developed immune system, children are more vulnerable to infections. In spite of immature immune system, absence of immunological memory due to lack of previous exposure to COVID 19, negligible death rate among children, although desirable, is unexplainable.

Absence of work place exposure, less active social life, less exposure to community outside the residence may be protective factors working in favour of children. But COVID 19 is highly infectious virus. Its high infectivity is likely to negate the protective effects of the above factors. It is evident that despite having less developed immune system, children are not seriously affected by COVID 19.

Children have more lymphoid tissue per kilogram of body weight. Lymphoid tissue mass gradually declines over the years. Lymphoid tissue reaches its maximum just before adolescence, and then declines to its adult value as the reproductive organs rapidly increase as shown in the figure 1.

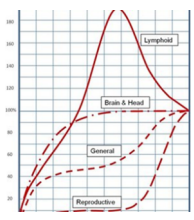

Figure 1

Developmental growth curves. Developmental growth curves of different parts and tissues of the human body, each plotted as a percentage of the total gain from birth to 20 years of age (i.e. size at age 20 is 100 on the vertical scale). Height and most body measurements follow the "general" curve. Note that the brain (and the head containing it) develops earlier than any other tissue; at birth it is already 25% of its adult weight, and 90% at age five. Lymphoid tissue reaches its maximum just before adolescence, and then declines to its adult value as the reproductive organs rapidly increase.

(https://www.researchgate.net/figure/Developmental-growth-curves-Developmental-growth-curves-of-different-parts-and-tissues_fig1_221681384 [accessed 29 Apr, 2020]).

Possibly higher lymphoid tissue mass to body mass ratio compared to that present in adults has protected children by some unknown mechanism.

There is also age –related thymic involution. Thus infants and children have more thymic tissue mass as compared to that in adults.

The size of thymus decreases as the age advances. Thus, mass of thymus and other lymphoid tissue considered together is greater in children than that in adults. This higher total lymphoid mass to body mass ratio, more particularly thymic to body mass ratio, in children may be a protective factor by some unknown mechanism.

Women seem to more immune to COVID 19 infection as evident from less mortality in women (https://www.worldometers.info/coconavirus /Coronavirus-age-sex-demographics/ Coronavirus Age, Sex, Demographics (COVID 19) – Worldometer).

Women have two X chromosomes. They by virtue of this fact mount stronger immune responses against many viruses and bacteria as compared to their male counterparts. But this also predisposes them to exaggerated immune response leading to more chances of developing autoimmune diseases.

Females are protected many bacterial and viral infections due to protective effects of sex hormones. Apart from sexual maturation and role in reproductive mechanism, sex hormones also have effects on immunity. In females, after menopause, levels of these sex hormones falls, which increases vulnerability of females to infections.

There are gender specific differences in immunological function and vulnerability to infections.

Among men, susceptibilities toward many infectious diseases and the corresponding mortality rates are higher. Responses to various types of vaccination are often higher among women thereby also mounting stronger humoral responses. Women appear immune-privileged. The major sex steroid hormones exhibit opposing effects on cells of both the adaptive and the innate immune system: estradiol being mainly enhancing, testosterone by and large suppressive. However, levels of sex hormones change with age. At menopause transition, dropping estradiol potentially enhances immunosenescence effects posing postmenopausal women at additional, yet specific risks. Conclusively during aging, interventions, which distinctively consider the changing level of individual hormones, shall provide potent options in maintaining optimal immune functions.

Oestrogens largely have immunoenhancing effects. Androgens and progesterone mainly have immunosuppressive effects (Carmen Giefing-Kröll etal. Aging Cell. 2015 Jun; 14(3): 309–321. Published online 2015 Feb 26. doi: 10.1111/acel.12326).

With regard to inflammation, oestradiol can be considered to be anti-inflammatory (Kenneth W. Beagley et al. FEMS Immunology & Medical Microbiology, Volume 38, Issue 1, August 2003, Pages 13–22, https://doi.org/10.1016/S0928-8244(03)00202-5).

Higher physiological or supraphysiological levels of estrogens most often foster anti-inflammatory responses that attenuate inflammation (Susan Kovats. –Cell Immunol. 2015 Apr; 294(2): 6369.

Published online 2015 Feb 7. doi: 10.1016/j.cellimm.2015.01.018).

Estradiol (E2) has genomic and non-genomic actions on cells. It has receptors on cells of the cardiovascular system and endothelial cells of blood vessels. It has protective effects on endothelium. It also leads to vascular relaxation and dilatation.

Estradiol leads to endothelium dependent vasodilatation in premenstrual women (J. Miner et al.https://www.fertstert.org/article/S0015-0282(10)00091-9/fulltext).

It has same vasodilatory effect in postmenopausal women (Marie Gerhard et al. Originally published 22 Sep 1998 https://doi.org/10.1161/01.CIR.98.12.1158 Circulation. 1998; 98:1158–1163https://www.ahajournals.org/doi/full/10.1161/01.CIR.98.12.1158). Progesterone has vasoconstrictory effects (Marie Gerhard et al. Originally published 22 Sep 1998 https://doi.org/10.1161/01.CIR.98.12.1158Circulation. 1998; 98:1158–1163 https://www.ahajournals.org/doi/full/10.1161/01.CIR.98.12.1158).

There is a body of evidence suggesting that sex hormones interfere with the synthesis and bioavailability of endothelium-derived nitric oxide (NO). Animal studies show that the release of NO from the endothelium is greater in female than in male rats. Indeed, estradiol induces endothelial nitric oxide synthase (eNOS) expression, mediated via the estradiol receptor alpha. Moreover, estradiol interacts with estradiol receptors in the cell membrane and causes rapid non-genomic signaling pathways that regulate eNOS activity, partly by eNOS translocation to the cell membrane. In addition to stimulating NO synthesis, estradiol has antioxidant effects and inhibits superoxide formation and, thereby, increases NO bioavailability.

Estradiol attenuates endothelin 1 (ET-1) and endothelin beta receptor messenger RNA (mRNA) expression and inhibits ET-1 production in endothelial cells (ET1 is an endogenous vasoconstrictor) (Uta Hillebrand et al. Pflügers Archiv - European Journal of Physiology volume 456, pages51–60(2008) https://link.springer.com/article/10.1007/s00424-007-0411-3).

In COVID 19, there is immune dysadaptation and uncontrolled inflammation. There is also, endothelitis, which has been reported recently (Zsuzsanna Varga et al. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30937-5/fulltext VOLUME 395, ISSUE 10234, P1417-1418, MAY 02, 2020 Published: April 20, 2020DOI:https://doi.org/10.1016/S0140-6736(20)30937-5).

Both oestrogen and progesterone are present in both men and women. The levels of these hormones are higher in women. COVID 19 is a new disease. There is no specific drug or time-tested and effective treatment protocol for the same. All the drugs being used are investigational.

Considering these facts and beneficial effects of estradiol on immunity and endothelium, and its role in endothelium dependent vasodilatation, estradiol in supraphysiological doses should be administered to both men and post-menopausal women to improve prognosis. Already there is some evidence of improvement of immunological function with HRT (Hormone Replacement Therapy) in post-menopausal women (V.R. Porter et al. Experimental Gerontology Volume 36, Issue 2, February 2001, Pages 311-326 https://doi.org/10.1016/S0531-5565(00)00195-9).

Estrogen therapy has a small risk of thromboembolism. This risk pertains to estradiol in oral form. Transdermal ESTROGEN-ONLY implants are safe (Archer DF et al. Climacteric. 2012 Jun;15(3):235-40. doi: 10.3109/13697137.2012.664401.

https://www.ncbi.nlm.nih.gov/pubmed/22612609) and (Marianne Canonico et al. Originally published20 Feb2007 https://doi.org/10.1161/CIRCULATIONAHA.106.642280Circulation.2007;115:840–845 https://www.ahajournals.org/doi/full/10.1161/circulationaha.106642280).

In fact, such transdermal estrogen-only implants may have beneficial effects on pro-inflammatory markers (The American College of Obstetricians and Gynecologists WOMEN'S HEALTH CARE PHYSICIANS

Postmenopausal Estrogen Therapy: Route of Administration and Risk of Venous Thromboembolism COMMITTEE OPINION NUMBER 556 APRIL 2013 Committee on Gynecologic Practice).

Platelet inhibiters like aspirin may be co-administered with estradiol.

Aspirin, being an NSAID, has anti-inflammatory action. Earlier, W.H.O. in its earlier treatment protocol had warned against use of NSAIDs in the management of COVID 19. After a meta-analysis, it has stated that there are no significant side effects of NSAIDs in viral respiratory infections including COVID 19 (World Health Organization Scientific Brief 19 April 2020https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19)

Apart from estrogen and estradiol, there are some inorganic xenoestrogens called metalloestrogens which include aluminium, antimony, arsenite, barium, cadmium, chromium (Cr (II)), cobalt, copper, lead, mercury, nickel, selenite, tin and vanadate. These metalloestrogens are capable of binding to cellular oestrogen receptors and then mimicking the actions of physiological oestrogens (P D Darbre. J Appl Toxicol. May-Jun 2006;26(3):191-7. doi: 10.1002/jat.1135).

Some of these like chromium, cobalt, copper are already recognised as micronutrients and thus can be safely used for clinical trials. A homeopathic medicine known as 'Arsenicum album', recommended by Ministry of AYUSH, Government of India and having arsenic; may be working as metalloestrogen mimicking actions of natural estrogen (https://www.ayush.gov.in/docs/homeopathy-guidelines.pdf).

RCTs should be conducted in COVID 19 patients using estradiol transdermal patch in one study (RCT trial) arm, metalloestrogens in second trial arm and none of these in the third arm.

In an outbreak of an infectious disease due to a new micro-organism, human population is not exposed to it earlier. Development of drugs and vaccines specific for the new micro-organism takes long time. Role of immunomodulators thus, becomes crucial for treatment of such infection. Several drugs like chloroquine, vitamin D3 and estradiol are known to have immunomodulatory actions. Their role in the management of COVID 19 and other infections in general should be investigated. As regards transdermal estradiol, it can be removed in case of any unanticipated effects or complications. Anti-oestrogens are also available to titre or counter its effects.

A combination therapy of estradiol and aspirin or transdermal estradiol alone may be considered for postmenopausal women and adult men with moderate or severe COVID 19 infection. This therapy should be considered reasonably early, giving time for hormonal actions to take place before the stage of irreversible clinical decompensation begins.

Considering relative sparing of children and menstruating women as regards mortality, role of adequately functioning immune system and especially innate immunity appears to be important. Other immunomodulators and metalloestrogens should also be used as investigational drugs.

REFERENCES

1. The American College of Obstetricians and Gynecologists WOMEN'S HEALTH CARE PHYSICIANS
2. Postmenopausal Estrogen Therapy: Route of Administration and Risk of Venous Thromboembolism
3. COMMITTEE OPINION NUMBER 556 APRIL 2013 Committee on Gynecologic Practice
4. Archer DF, Oger E.
5. Estrogen and progestogen effect on venous thromboembolism in menopausal women.
6. Climacteric. 2012 Jun;15(3):235-40. doi: 10.3109/13697137.2012.664401.
7. https://www.ncbi.nlm.nih.gov/pubmed/22612609
8. https://www.ayush.gov.in/docs/homeopathy-guidelines.pdf
9. Kenneth W. Beagley, Christine M. Gockel
10. Regulation of innate and adaptive immunity by the female sex hormones oestradiol and progesterone
11. FEMS Immunology & Medical Microbiology, Volume 38, Issue 1, August 2003, Pages 13– 22, https://doi.org/10.1016/S0928-8244(03)00202-5
12. Marianne Canonico, Emmanuel Oger, Geneviève Plu-Bureau, Jacqueline Conard, Guy Meyer,
13. Hervé Lévesque, Nathalie Trillot, Marie-Thérèse Barrellier, Denis Wahl, Joseph Emmerich,
14. Pierre-Yves Scarabin
15. Hormone Therapy and Venous Thromboembolism Among Postmenopausal Women
16. Impact of the Route of Estrogen Administration and Progestogens: The ESTHER Study
17. Originally published20 Feb 2007 https://doi.org/10.1161/CIRCULATIONAHA.106.642280Circulation. 2007; 115:840–845
18. https://www.ahajournals.org/doi/full/10.1161/circulationaha.106.642280
19. P D Darbre
20. Metalloestrogens: An Emerging Class of Inorganic Xenoestrogens With Potential to Add to the Oestrogenic Burden of the Human Breast
21. J Appl Toxicol
22. . May-Jun 2006;26(3):191-7.
23. doi: 10.1002/jat.1135.
24. Developmental allometry and paediatric malaria - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Developmental-growth-curves-Developmental-growth-curves-of-different-parts-and-tissues_fig1_221681384 [accessed 29 Apr, 2020]
25. Marie Gerhard, Brian W. Walsh, Ahmed Tawakol, Elizabeth A. Haley, Shelly J. Creager, Ellen W. Seely, Peter Ganz, and Mark A. Creager
26. Estradiol Therapy Combined With Progesterone and Endothelium-Dependent Vasodilation in Postmenopausal Women
27. Originally published 22 Sep 1998 https://doi.org/10.1161/01.CIR.98.12.1158 Circulation.1998; 98:1158–1163
28. https://www.ahajournals.org/doi/full/10.1161/01.CIR.98.12.1158
29. Carmen Giefing-Kröll, Peter Berger, Günter Lepperdinger, and Beatrix Grubeck-Loebenstein
30. How sex and age affect immune responses, susceptibility to infections, and response to vaccination
31. Aging Cell. 2015 Jun; 14(3): 309–321. Published online 2015 Feb 26. doi: 10.1111/acel.12326
32. Uta Hillebrand, Martin Hausberg, Detlef Lang, Christian Stock, Christoph Riethmüller, Chiara Callies & Eckhart Büssemaker
33. How steroid hormones act on the endothelium—insights by atomic force microscopy
34. Pflügers Archiv - European Journal of Physiology volume 456, pages51–60(2008)
35. https://link.springer.com/article/10.1007/s00424-007-0411-3
36. Susan Kovats
37. Estrogen receptors regulate innate immune cell and signalling pathways
38. Cell Immunol. 2015 Apr; 294(2): 63–69.
39. Published online 2015 Feb 7. doi: 10.1016/j.cellimm.2015.01.018
40. J. Miner, M. Smith, E. Martini, V. Brunt, P. Kaplan, J. Halliwill, C. Minson
41. Progesterone Administration Antagonizes the Effect of Estradiol on Endothelium-Dependent Vasodilation and Cardiovagal Baroreflex Sensitivity in Young Healthy Women
42. V.R. Porter G.AGreendale MSchocken XZhucR. BEffros
43. Immune effects of hormone replacement therapy in post-menopausal women
44. Experimental Gerontology
45. Volume 36, Issue 2, February 2001, Pages 311-326
46. https://doi.org/10.1016/S0531-5565(00)00195-9
A. Katharina Simon, Georg A. Hollander, and Andrew McMichael
47. Evolution of the immune system in humans from infancy to old age
48. Proc Biol Sci. 2015 Dec 22; 282(1821): 20143085.
49. Zsuzsanna Varga, Andreas J Flammer, Peter Steiger, Martina Haberecker, Rea Andermatt, Annelies S Zinkernagel, Mandeep R Mehra, Reto A Schuepbach, Frank Ruschitzka, and Holger Moch
50. Endothelial cell infection and endotheliitis in COVID-19
51. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30937-5/fulltext
52. VOLUME 395, ISSUE 10234, P1417-1418, MAY 02, 2020
53. Published: April 20, 2020DOI:https://doi.org/10.1016/S0140-6736(20)30937-5
54. World Health Organization
55. The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19
56. Scientific Brief 19 April 2020
57. https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19
58. Coronavirus Age, Sex, Demographics (COVID 19) – Worldometer
59. https://www.worldometers.info/coconavirus/Coronavirus-age-sex-demographics/