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The correlation between the concentration of ovarian steroid and the severity of COVID-19 in females

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***Abstract*---**Background: Coronaviruses are positive single-stranded RNA viruses that have a spherical shape and some spike-shaped proteins (spike proteins) that project from their surface, from which they derive their name because they resemble a solar corona. The RNA sequence of SARS-CoV-2 is approximately thirty thousand nucleotides in length and encodes both structural and non-structural proteins. Objective: To assess the relation between the concentration of ovarian steroid and the severity of covid-19 in females. Patients and method: A cross sectional study carried at Consulting clinic for chest and respiratory diseases in Babylon Governorate at the period from 1st of January 2021 to the 1st of June 2021. Patients were female infected with COVID-19 with in age between 25-65 years old. Results: mean age in the studied group was (44.75±13.87) years and the main age group between 40-49 years (29.6%), the majority of the patients (96.3%) were married women, and (71.6%) were obese. fever was found in 68 (84.0%) of patients, diarrhea in 40 (49.4%), loss of smell in 48 (59.3%) of patients and loss of taste were found in 59 (72.8%) of them, and 46 (56.8%) of patients with COVID-19 presented with cough, the level of progesterone and estrogen were decreased with increase of lobe involvement. Conclusion: Ovarian steroid play an important role to decrease the severity of COVID-19.

***Keywords*---**estrogen, progesterone, COVID-19, total severity score, CT scan.

Introduction

Since 2020, the world faces a new pandemic caused by the SARS-CoV-2 virus, with an increase that already exceeds hundred million positive cases with more than million deaths. [1] Coronaviruses are positive single-stranded RNA viruses that have a spherical shape and some spike-shaped proteins (spike proteins) that project from their surface, from which they derive their name because they resemble a solar corona. The RNA sequence of SARS-CoV-2 is approximately thirty thousand nucleotides in length and encodes both structural and non-structural proteins. The SARS-CoV-2 genome is only 79.5% identical to that of SARS-CoV-1, while 96.2% to that of the bat Rhinolophus affine is (CoV RaTG13), which is why it was thought that this animal would be the natural host, but its peak diverges in the receptor-binding domain, so it would not bind efficiently to the converting enzyme of human angiotensin 2 (ECA2). [2]

For the virus to enter host cells, the receptor-binding domain (RBD) of the S1 subunit of the S protein is required to act as a mediator to bind the virus to cell receptors, while the S2 subunit is the mediator of membrane fusion events. Different cellular receptors have been described for coronaviruses. Protein S on the surface of the virus is the one that binds to this ECA2 receptor, being a critical point for the virus to enter cells. [3] This suggests that fur in cleavage occurs during viral exit from the host cell. Some in vitro experiments showed that cathepsin L inhibitors could inhibit infection by SARS-CoV-1, as well as other viruses that depend on cathepsin L for admission. The presence of a cleavage site for cathepsin L in the SARS-CoV-2 opens the possibility that inhibitors of this protease are useful for inhibiting HIV infection. [4]

Antibodies against RBD and the S2 subunit of protein S in SARS-CoV and MERS-CoV have shown effectiveness in neutralizing cell infection in vitro. Moreover, these antibodies were tested in experiments on animals and patients infected during outbreaks of these diseases. Different specific monoclonal antibodies against RBD failed to bind to the SARS-CoV-2 protein S 21, but CR3022 did bind with high affinity to the RBD of SARS-CoV-2. These studies demonstrate that there are differences between the RBDs of SARS-CoV1 and those of SARS-CoV-2 that impact the cross-reactivity of many antibodies. Developing effective antibodies against SARS-CoV-2 RBD could be a promising way to curb this pandemic. [5]

Because of the efficient way in which its RBD binds to the human ECA2 receptor, which is different from those previously predicted, it is impossible that this new virus is the product of laboratory genetic manipulation. It has originated by natural selection, either in a host animal before zoonotic transfer, or in humans after it. [6] The main cause of mortality from SARS-CoV-2 is respiratory failure due to ARDS (53%) and the second myocardial damage with heart failure (7%), 33% dying from a combination of both. Myocardial damage is often due to fulminant myocarditis. The cytokine storm is a state of self-sustained hyperinflammation that occurs, along with inadequate immune stimulation, due to the fact that the patient is unable to clear the virus antigens, in this case those of SARS-CoV-2. The dysfunction of the innate immune system that involves IL-1 is fundamental in the pathogenesis of the disease. [7]

Mortality among patients with SARS-CoV-2 who are hospitalized is 32%, but if they are admitted to the ICU, this percentage rises to 61.5%, even more if they are subjected to mechanical ventilation (81% -97%). [8] Schwartz DA et al in their epidemiological study confirmed that coronaviruses (SARS-CoV-2) could have adverse effects on fetuses and infants, including preterm delivery, intrauterine growth restriction, spontaneous abortion and even death. [9] Moreover, Hsu AL et al study has recognized the presence of virus across the placenta even in pregnant patients with mildly disease, actually leading to fetal growth restriction (FGR) and other gestational complications. Accumulating evidence now suggests that 2019-nCoV/ACE2 may interfere with the female reproductive functions, leading to menstrual disorder, infertility and fetal distress. [10] Computed tomography (CT) imaging is considered to be the most effective method for detection of lung abnormalities, especially in the early stage of the disease. Moreover, serial chest CT imaging with different time intervals is also effective in estimating the evolution of the disease from initial diagnosis to discharge from hospital. [11]

Estrogens / progesterone and COVID-19

In an animal model, used to study infection by the SARS-CoV virus, it was found that gonadectomy or treatment with estrogen receptor antagonists in female rats increased mortality from viral infection, results that suggest that the estrogenic signal protects female rat from lethality. [12] From the results of experimental studies and animal models, it is known that 17β estradiol through its α and β receptors: 1) contributes to the activation and proliferation of T lymphocytes and induces high levels of interferon (IFN) γ, which together IFNβ (Interferon Beta) would have a synergistic anti-SARS-CoV effect; 2) increases immune response with faster clearance of pathogens and more effective response to vaccines; 3) improves Th1 immune response and reduces Th2; 4) favors the increase in the number of CD4 + cells and the population of T reg cells; 5) has anti-inflammatory effects by reducing the release of inflammatory cytokines, delays apoptosis of neutrophils and increases the expression of annexin 1 in neutrophils, without increasing its activation; 6) offers greater efficiency to phagocytosis with the elimination of NADPH oxidase (adenine phosphate dinucleotide); 7) it favors the increase of new dendritic cells (mainly involved in the antiviral response); 8) it promotes the activation of innate pathways inducible by INF type 1; and the genes of the IFN pathway are expressed in women, regulating innate immunity; 9) inhibits the metabolism of the virus (influenza A). [13, 14]

Estriol (E 3) during influenza A virus infection reduces the transcriptional activity of genes associated with pro-inflammatory cytokines and chemokines, which is associated with decreased recruitment of immune cells in the lungs, which improves lung function, reduces morbidity and clinical disease. Altogether, these results suggest that E3 treatment protects against infection through immunomodulatory mechanisms, and that in women, high concentrations of this hormone cause a worse (better) evolution of the disease. Progesterone modifies the immune environment, promotes homeostasis by reducing inflammation by inducing the anti-inflammatory response. In gonadectomized female rats infected by influenza A virus, progesterone treatment mitigated the effects on morbidity and mortality; made rats more tolerant to infection by limiting inflammation and

lung damage, without acting on virus replication; did not affect the cell-induced antiviral immune response; it promoted repair, increased the number of Th17 regulatory cells, increased II22 expression, and regulated antiregulin epidermal growth factor (AREG), which appears to mediate the actions of progesterone in the lung epithelium. [15]

In a laboratory model in rats, it turned out that treatment with progesterone or a synthetic analog (Levonorgestrel), present in hormonal contraceptives, affected sequential infection to the influenza A virus by modulating antibody responses and decreasing the number and the activity of memory CD8 T cells. After challenge with an H3N2 virus, progestin-treated female rats experienced increased mortality with increased lung inflammation, and a reduction in the number and activity of CD8 T cells, suggesting that these drugs modify the immune response to influenza A virus infection, and that its effect on prognosis depends on the history of exposure. [16]

The effect of 17β estradiol on the immune system could explain the lower mortality in COVID-19, but not the higher incidence of the disease in women, particularly in ages between 40-59 years, so it is pertinent to consider the influence of other factors, among them, the social determinants derived from the family and social responsibilities of this subgroup of women, who in general are responsible for the care and attention of the family, not only in the solution of the problems of daily life, but also to collaborate with the family economy, comply with the measures for the prevention of infection by the SARS-CoV-2 virus (physical isolation, social distancing, use of a mask, hand hygiene), without forgetting to adapt to working conditions in a pandemic situation such as remote work, the risk of infection when working on the red line, etc.). [17, 18]

Aim of the study

To assess the relation between the concentration of ovarian steroid and the severity of covid-19 in females.

Patients and Method

A cross sectional study carried at Consulting clinic for chest and respiratory diseases in Babylon Governorate at the period from 1st of January 2021 to the 1st of June 2021. Eighty-one patients were female infected with COVID-19 with in age between 25-65 years old. 5 cc of venous blood drawn from the patients and after centrifuge the serum divided into 2 tubes to investigate blood parameters and other tube to detect the level of ovarian steroid, in addition to that CT scan done for patients to detect the severity of the disease according to involvement of the lung lobes which divided 4 groups (1-25%, 26-50%, 51-75%, and 75-100 %). Data were revied by the researcher many times and enter to the excel then after the arrangement of the data we convert it to SPSS program version 25 to analyze it. Informed consent was obtained from all participants before the beginning of the study.

Results

Table 1 show that the mean age in the studied group was (44.75±13.87) years and the main age group between 40-49 years (29.6%), the majority of the patients (96.3%) were married women, and (71.6%) were obese.

Table 1
Demographic criteria of the patients in the studied group

		No.	%
Age Group	<30	9	11.1
	30-39	21	25.9
	40-49	24	29.6
	50-59	11	13.6
	≥60	16	19.8
	Mean±SD	44.75±13.87	
Marital Status	Single	3	3.7
	Married	78	96.3
BMI Group	Thin	1	1.2
	Normal	3	3.7
	Overweight	19	23.5
	Obese	58	71.6

As shown in table 2, fever was found in 68 (84.0%) of patients, diarrhea in 40 (49.4%), loss of smell in 48 (59.3%) of patients and loss of taste were found in 59 (72.8%) of them, and 46 (56.8%) of patients with COVID-19 presented with cough.

Table 2
Clinical presentations of the patients in the studied group

		No.	%
Fever	Yes	68	84.0
	No	13	16.0
Diarrhea	Yes	40	49.4
	No	41	50.6
loss of smell	Yes	48	59.3
	No	33	40.7
loss of taste	Yes	59	72.8
	No	22	27.2
Cough	Yes	46	56.8
	No	35	43.2

CT done to the patients, then according to lobe involvement they divided into 4 groups depending on Total severity score classification of the COVID-19 severity, 51 (63.0%) of patients were found in score 1 (1-25%), 24 (29.6%) of patients in score 2, 4 (4.9%) in score 3, and only 2 (2.5%) in score 4, (table 3). Table 3: CT group and hospital entry of the patients in the studied group

	Total severity score (TSS)	No.	%
CT Group	Score 1 (1-25%)	51	63.0
	Score 2 (26%-50%)	24	29.6
	Score 3 (51%-75%)	4	4.9
	Score 4 (75-100%)	2	2.5
Hospital entry	Yes	3	3.7
	No	78	96.3

As shown in table 4, the level of progesterone and estrogen were decreased with increase of lobe involvement

Table 4
Distribution of ovarian steroid level and the severity of disease

	CT Group			
	1-25 (n=51)	26-50 (n=24)	51-75 (n=4)	75-100 (n=2)
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
progesterone (ng/ml) 0=<1.4	6.07±3.02	5.71±2.1	5.43±3.51	1.6±0.34
Estrogen (pg/ml)	131.02±67.8	127.07±49.2	121.91±77.29	60.9±66.3

Discussion

In the current study we found that fever was the most common symptoms as it presented in (84%) of the patients which is in agreement with Tian S et al, [11] study as mentioned that fever is the most frequent symptom (from 76.51% to 93.5%). Wu C et al, [19] concluded that when it exceeds 39 ° C is associated with more severe and, paradoxically, also decrease the risk of death box. Diarrhea was found in in (49.4%), which is more than that recorded in other study carried by Li LQ et al, [20] (diarrhea between 4.8% and 7.4%). This may be attributed to the viral mutation or development from the Chinese study to our study. The cough varies in frequency from 45.8% to 82% and to a lesser extent it can be productive (from 32.2% to 41.3%). [21] which is in agreement with that found in the current study (cough presented in 56.8%).

According to previous studies the immunity of the women was stronger than men and there is heightened immune responses compared to males. Butterworth et al, in 1967 described that woman produce higher levels of circulating immunoglobulins IgG and IgM than that produced by men. [22] Graham JH, et al, revealed that both estrogen and progesterone when used as replacement therapy to the menopausal women as combined contraceptive pills lead to increase immune response and give a protection against viral infections. [23] Nevertheless, type 2 immune response activated by progesterone while its inhibit type 1 immune response, and this might explain the association between the use of progestin-only contraceptive depot and the risk of human immune deficiency virus (HIV). [24] Moreover, progesterone has powerful anti- inflammatory and immunomodulation effects and E2 inhibits innate immunity through suppression

of immune cell migration, mainly neutrophils and monocytes to the inflamed area. This effect weakens the development and progression of cytokine storm (CS) via inhibition of pro- inflammatory cytokine release. [25,26] CS is regarded as a major cause for the development of ALI, ARDS, multiorgan failure, and death in Covid-19. [27] According to the total severity score presented by Li K et al, [28] we divided the severity of COVID-19 into 4 scores depending on the severity of the disease, and we noticed that level of ovarian steroid was decreased with increase of lobe involvement. This is in agreement with Costeira R et al, [29] that found a protective effect of estrogen on COVID-19.

Conclusion

Ovarian steroid play an important role to decrease the severity of COVID-19

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References

1. Bar-On YM, Flamholz A, Phillips R, Milo R. Science Forum: SARS-CoV-2 (COVID-19) by the numbers. elife. 2020 Mar 31;9:e57309.
2. Malik YA. Properties of coronavirus and SARS-CoV-2. The Malaysian journal of pathology. 2020 Apr 1;42(1):3-11.
3. Wang L, Xiang Y. Spike glycoprotein-mediated entry of SARS coronaviruses. Viruses. 2020 Nov;12(11):1289.
4. Li F. Structure, function, and evolution of coronavirus spike proteins. Annual review of virology. 2016 Sep 29;3:237-61.
5. Tai W, He L, Zhang X, Pu J, Voronin D, Jiang S, Zhou Y, Du L. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cellular & molecular immunology. 2020 Jun;17(6):613-20.
6. RM ER. Origin of SARS-CoV-2 theories, keys and unknowns of an emerged disease. Revista Espanola de Salud Publica. 2020 Sep 30;94.
7. Gibson PG, Qin L, Puah SH. COVID‐19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre‐COVID‐19 ARDS. Medical Journal of Australia. 2020 Jul;213(2):54-6.
8. Rodríguez A, Moreno G, Gómez J, Carbonell R, Picó-Plana E, Bofill CB, et al. Severe infection due to the SARS-CoV-2 coronavirus: Experience of a tertiary hospital with COVID-19 patients during the 2020 pandemic. Medicina Intensiva (English Edition). 2020 Dec 1;44(9):525-33.
9. Schwartz DA, Graham AL. Potential maternal and infant outcomes from (Wuhan) coronavirus 2019-nCoV infecting pregnant women: lessons from SARS, MERS, and other human coronavirus infections. Viruses 2020;12:194.
10. Hsu AL, Guan M, Johannesen E, Stephens AJ, Khaleel N, Kagan N, Tuhlei BC, Wan XF. Placental SARS‐CoV‐2 in a pregnant woman with mild COVID‐19 disease. Journal of medical virology. 2021 Feb;93(2):1038-44.
11. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. J Thorac Oncol. 2020.

12. Sharma G, Volgman AS, Michos ED. Sex differences in mortality from COVID-19 pandemic: are men vulnerable and women protected?. Case Reports. 2020 Jul 15;2(9):1407-10.
13. Li Y, Jerkic M, Slutsky AS, Zhang H. Molecular mechanisms of sex bias differences in COVID-19 mortality. Critical care. 2020 Dec;24(1):1-6.
14. Vom Steeg LG, Klein SL. Sex and sex steroids impact influenza pathogenesis across the life course. InSeminars in immunopathology 2019 Mar (Vol. 41, No. 2, pp. 189-194). Springer Berlin Heidelberg.
15. Hall OJ, Nachbagauer R, Vermillion MS, Fink AL, Phuong V, Krammer F, Klein SL. Progesterone-based contraceptives reduce adaptive immune responses and protection against sequential influenza A virus infections. Journal of virology. 2017 Mar 29;91(8):e02160-16.
16. Artiles Visbal L: Living conditions as determinants of the health-disease process in climacteric women. In: Artiles- Visbal L, Navarro Despaigne DA, Manzano Ovies BR, editors. Climacteric and menopause. Havana: Scientific-Technical Editorial; 2007. p.58.
17. Walter LA, McGregor AJ. Sex-and Gender-specific Observations and Implications for COVID-19. Western Journal of Emergency Medicine. 2020 May;21(3):507.
18. Cagnacci A, Xholli A. Age-related difference in the rate of coronavirus disease 2019 mortality in women versus men. American Journal of Obstetrics and Gynecology. 2020 Sep;223(3):453.
19. Wu C, Chen X, Cai Y. Xia J'an, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43.
20. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. Journal of medical virology. 2020 Jun;92(6):577-83.
21. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. J Infect. 2020; 80 (4): 388-393
22. Butterworth M, McClellan B, Allansmith M. Influence of sex in immunoglobulin levels. Nature. 1967;214(5094):1224-1225.
23. Graham JH, Yoachim SD, Gould KA. Estrogen receptor alpha signaling is responsible for the female sex bias in the loss of tolerance and immune cell activation induced by the lupus susceptibility locus Sle1b. Front Immunol. (2020) 11:582214
24. Curtis KM, Hannaford PC, Rodriguez MI, Chipato T, Steyn PS, Kiarie JN. Hormonal contraception and HIV acquisition among women: an updated systematic review. BMJ Sex Reprod Health. (2020) 46:8–16. doi: 10.1136/bmjsrh-2019-200509
25. Ruggieri A, Gagliardi MC, Anticoli S. Sex-dependent outcome of hepatitis B and C viruses infections: synergy of sex hormones and immune responses?. Front Immunol. (2018) 9:2302.
26. AbdulHussain G, Azizieh F, Makhseed MA, Raghupathy R. Effects of progesterone, dydrogesterone and estrogen on the production of Th1/Th2/Th17 cytokines by lymphocytes from women with recurrent spontaneous miscarriage. J Reprod Immunol. (2020) 140:103132.

27. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. Front Immunol. (2020) 11:1446.
28. Li K, Fang Y, Li W, Pan C, Qin P, Zhong Y, et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). European radiology. 2020 Aug;30(8):4407-16.
29. Costeira R, Lee KA, Murray B, Christiansen C, Castillo-Fernandez J, Lochlainn MN, et al. Estrogen and COVID-19 symptoms: associations in women from the COVID Symptom Study. MedRxiv. 2020 Jan 1
30. Suryasa, I.W., Sudipa, I.N., Puspani, I.A.M., Netra, I.M. (2019). Translation procedure of happy emotion of english into indonesian in kṛṣṇa text. *Journal of Language Teaching and Research, 10*(4), 738–746
31. Suryasa, W. (2019). Historical Religion Dynamics: Phenomenon in Bali Island. *Journal of Advanced Research in Dynamical and Control Systems*, *11*(6), 1679-1685.
32. Akbarov, A. N., & Xabilov, D. N. U. (2021). The condition of the oral cavity in patients who have had a viral infection COVID-19. International Journal of Health & Medical Sciences, 4(4), 381-383. https://doi.org/10.21744/ijhms.v4n4.1796