DOI: https://www.doi.org/10.36719/2663-4619/74/68-72

Nurana Ariz Hamidova
Azerbaijan Medical University
Phd in medicine
kombc@mail.ru

NEW APPROACHES AND ALL-ROUND OVERVIEWS TO THE MENSTRUAL CYCLE AND FEMALE GENITAL HORMONES COMPARABLY IN WOMEN OF DIFFERENT AGE GROUPS (REPRODUCTIVE AND MENOPAUSAL) IN COVID-19

Abstract

The changes in serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FHS), estradiol, and progesterone that occur both early and late in reproductive life were characterized and compared with findings in young, normal women and in patients with certain menstrual disorders. Since the beginning of the COVID-19 pandemic, there have been accumulating discussions on social media and blogs indicating that women have experienced menstrual changes, including altered menstrual duration, frequency, regularity, and volume (heavier bleeding and clotting), increased dysmenorrhoea and worsened premenstrual syndrome.

Key words: *SARS CoV-2, COVİD-19, reproduction, changing in hormonal balans*

Nurana Ariz Hamidova

COVİD-19-da müxtəlif yaş qruplarında (reproduktiv və menopauzal) qadınlarda müqayisəvi mənstrual siklə və qadın genital hormonlarına yeni yanaşmalar

Xülasə

Reproduktiv həyatın həm erkən, həm də gec dövrlərində baş verən luteinləşdirici hormon (LH), follikül stimullaşdırıcı hormon (FHS), estradiol və progesteronun serum səviyyələrindəki dəyişikliklər səciyyələndirilmiş və gənc, orta yaşlı qadınlarda və müəyyən menstrual siklin müəyyən dövründəki məlumatlar müqayisə edilmişdir. COVID-19 pandemiyasının başlanğıcından etibarən qadınların menstrual dəyişiklikləri, o cümlədən menstruasiya müddəti, tezliyi, nizamlılığı və həcminin dəyişməsi (daha ağır qanaxma və laxtalanma), dismenoreyanın artması və daha da pisləşdiyini göstərən məlumatlar öyrənilir.

As soon as it will be almost two year that the COVİD-19 pandemic has spread all over the world. Approximately in December 2019, an outbreak of the novel coronavirus disease 2019 (COVID-19) first time occurred in Wuhan, China, is becoming a serious calamity influencing the health of the world's population.

According to the retrospective studies by 14 June 2020, a total of 7,865,794 people had been diagnosed with COVID-19 globally, with a cumulative death amount of 432,394 (https://www.worldometers.info/coronavirus/). The local and International Public Health responses, practically synchronous imposed various restrictions to the minimize spread of this virus, overloading of health system capacity, deficit of personal protective equipments (PPE). However at the recently— **5 February 2021**, there have been **104,370,550 confirmed cases** of COVID-19, including **2,271,180 deaths**, reported to WHO, which also means that the infections with new SARS-CoV-2 virus were continuously rising with climbing numbers of deaths globally and continues to grow. All the COVID-19 patients have been reported multisystem complications with respiratory, cardiovascular and digestive system symptoms [1]. The clinical and laboratory parameters of were hospitalized coranovirus patients have been dynamically monitored for a long time.

The aim of our review is to summarize current knowledge regarding the novel SARS CoV-2, including its pathophysiology, as well as, what is known about the potential impact of COVID-19 on

reproduction, fertility care, pregnancy and changing hormonal balance in women of different age groups.

According to the latest research on the pathophysiology of SARS-CoV-2 viruses (CoVs) are round and enveloped, positive sense, single strained RNA viruses, ~ 30 kb in size, and ranging 65-125 nm in diameter [2]. They are classified in four genera: Alfa, Beta, Gama and Delta [3]. SARS-CoV-2 is a Beta CoV, part of subgroup 2B, with a crown-like appearance on its surface. Its genetic sequence has at least 70% homology with the SARS-CoV and ~ 50% with the Middle East Respiratory Syndrome (MERS) CoV [4]. SARS-CoV-2 consists of three following structural proteins: 1) Spike (S), - transmembrane glycoprotein protruding from the virus surface, which determines the diversity of corona viruses and host tropism, with two subunits: a)S1, which is responsible for attachment to the host cell receptor; and b)S2 which is responsible for the fusion of the membranes of the virus and the cell; 2) membrane (M), which determines the shape; and 3) envelope (E), a protein responsible for passage and assembly during viral morphogenesis. The capsid of SARS-Cov-2 includes the RNA genome complexed with a nucleocapsid (N) protein that has three major regions: 1) N-terminal domain (NTD), responsible for RNA binding, 2) central linker domain, and 3) C-terminal (tail) domain (CTD), responsible for dimerization of N-proteins, which regulate replication, transcription and translation in the host cell [5].

The first step in the life cycle of the SARS-CoV-2 within the host is attachment to the host cell receptors, and consequently penetrating the cell through fusion with the host cell membrane (endocytosis). When the virus is intracellular, viral RNA enters the nucleus to replicate, and viral mRNA is utilized to make viral proteins (biosynthesis). The next steps are maturation of new viral particles, packaging in vesicles, transfer to the cell membrane, and release [5, 6].

Angiotensin converting enzyme 2 (ACE2) is a functional receptor on alveolar epithelial type 2 (AT2) cells and an entry point for the SARS-CoV-2 [7]. The spikes of SARS-CoV-2 (S-protein) have strong affinity for the ACE2 receptor, and after attachment, the viral genome and nucleocapsid are liberated into the host cell cytoplasm [7,8]. SARS-CoV-2 needs TMPRSS2 (transmembrane, serin protease-2) to cleave the viral S-protein, and enable fusion between the viral and host cellular membrane. The co-expression of both ACE2 and TMPRSS2 genes is necessary for infection to occur, since SARS-CoV-2 uses the ACE2 receptor for entry and the serine protease TMPRSS2 for S protein priming.

ACE2 expression is found in the heart (7.5% of myocardial cells), ileum (30%), kidney (4%), bladder (2.4%) and in the respiratory tract (~ 2%). All tissues that have more than 1% expression of ACE2 receptors could be a target for the SARS CoV-2 [6].

The SARS-CoV-2 susceptibility of reproductive tissues is closely related with ACE2 too in men and women with different ages.

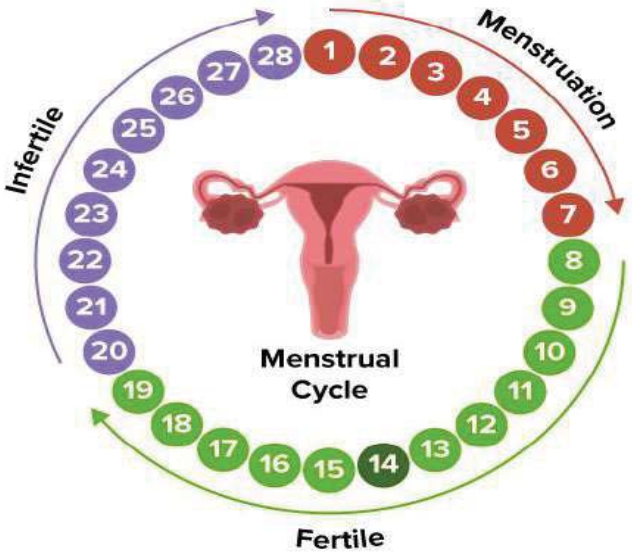
That such reasoning is possible, ACE2- is the functional receptor fsor SARS-CoV-2, is a key component of the renin-angiotensin system (RAS), modulating the cleavage of angiotensin II (Ang II) and Ang (1–7) [6]. After cell invasion, COVID-19 disrupts the RAS system, by downregulating ACE2 expression in the host cells, leading to an increased proinflammatory response by Ang II. Ang II, ACE2 and Ang (1–7) regulate basic functions in the male and female reproductive systems.

In the female, these include folliculogenesis, steroidogenesis, oocyte maturation, ovulation, and endometrial regeneration. In the male, testicular ACE2 may regulate testicular function, plays a role in sperm function, and may be important for sperm's contribution to embryo quality. Since SARS-CoV-2 enters the cell by binding to the ACE2 receptor, reproductive cells and/or tissues expressing it are potentially vulnerable to the virus, and their functions may theoretically be disturbed.

ACE2 receptors are much more abundant in the male reproductive system than the female reproductive system, and this is a gynecologically important point. Low expression of ACE2 was demonstrated in the fallopian tube (ciliated and endothelial cells), ovary, vagina, cervix and endometrium [8]. On the other hand, ACE2 expression in the testis is among the highest observed, with high expression in Leydig and Sertoli cells and medium expression in glandular cells of the seminal vesicle [8,9]. As a result, it is expected that the testes will be more vulnerable than the ovaries to the detrimental effects of a SARS-CoV-2 infection. One of the most pressing problems in women of

different ages (reproductive; menopausal) with coronavirus disease is the study of changes in their hormonal balance, menstrual cycle and female sex hormones (figure 1). Over the last decade, female reproductive health has become increasingly important, and attention to the effects of COVID-19 on the reproductive system has been called for globally. Various retrospective clinical studies in this field are examining the effects of Covid-19 virus infection on endocrine disorders and ovarian depletion in women of childbearing potential on the basis of proven results.

figure 1.



According to a retrospective study of reproductive aged (18-42ages) 177 women were registered at Tongji Hospital in China between January 19 and April 1, 2020 and confirmed to be diagnosed with acute illness such as SARS-CoV2, it may alter the hypothalamic-pituitary gonadal (HPG) axis function, decreasing the endogenous production of estrogens and progesterone. It was determined by characterizing the menstrual function of these patients that, 132 (75%) patients had no change in menstrual volume, 36 (20%) patients had a significant decrease in menstrual volume, and only 9 (5%) patients had an increased volume. As a result, generally, patients with COVID-19 showed decreased menstrual volume. But based on the result obtained for the day of the menstrual period, there were 25 (14%) patients with a menstrual cycle shorter than 28 days, 66 (37%) between 28 and 32 days, 31 (18%) between 33 and 37 days, 43 (24%) patients had cycles longer than 37 days, and 12 (7%) patients showed a cycle disorder. As a result, generally, severely ill patients had longer menstrual cycles [6,9]. In total, the median concentrations of hormones, including FSH, LH, oestradiol, progesterone, testosterone and AMH, were marginally higher in both mildly and severely ill patients than in the control group. However, no significant difference was found between COVID-19 patients and control or between mild and severe patients. Further subgroup analysis of sex hormones and AMH in patients with menstrual changes showed no significant differences in the average concentrations of all hormones in patients with either menstrual changes alone or periodic changes, or both.

Besides, where studied the concentrations of gonadotropin-releasing hormones (GnRH) and AMH comparable in the early follicular stage (3rd-5th days of menstruation) in 91 COVID-19 patients and 91 controls. In total, the median concentrations of GnRH, including FSH, LH, oestradiol, progesterone, testosterone and AMH, were marginally higher in both mildly and severely ill patients than in the control group. However, no significant difference was found between COVID-19 patients and control or between mild and severe patients. Further subgroup analysis of sex hormones and AMH in patients with menstrual changes showed no significant differences in the average concentrations of all hormones in patients with either menstrual changes alone or periodic changes, or both.

In conclusion, there was no evidence to support that SARS-CoV-2 causes substantial impairment of fertility in female COVID-19 patients on reproductive ages. Nevertheless, transient abnormal changes in menstruation were observed in some patients, along with hormone concentration changes. For COVID-19 patients with menstrual abnormalities, home observations are recommended after excluding pregnancy, which could avoid both wasting medical resources and hospital infections, especially in the current serious epidemic situation. It is also suggested that patients should undergo an examination of GnRH concentrations and ovarian function before planning a pregnancy. At the beginning of the pandemic, many governments and health organizations released guidelines on who may be more vulnerable to severe symptoms of the Covid-19. A study has suggested that, people with lower levels of estrogen or rather women on menopausal and postmenopausal period are suffering from estrogen deficiency seem to be at higher risk of developing serious complications after being diagnosed with Covid-19 [10]. Research published in medRxiv and led by King's College London found that high levels of estrogen may have a protective effect against Covid-19, leaving people who have gone through menopause vulnerable.

Researchers used the Symptom Study App to look at about 400,000-500,000 people for a several time. They concluded that estrogen could be another protection against Covid-19. Alongside maintaining the menstrual cycle, estrogen plays a key role in cognitive and bone health, immune system, and cardiovascular system.

According to a study of menopausal women infected with the COVİD-19 virus, it turned out that this virus infection is not likely to be a significant additional risk to menopausal women per se, but menopause is a time women begin to have increased risk for heart disease and type 2 diabetes, once they lose the protective effects of estrogen. These co-morbidities definitely increase risk for women who may contract COVID-19. In fact, the Centers for Disease Control and Prevention (CDC) guess age, heart disease, and diabetes can all increase your chance of being severely ill with the Coronavirus. More so, weight gain, which may be caused by menopause, can also complicate matters.

Frustratingly, for women in menopause, a decrease in estrogen could potentially cause increased vulnerability to severe symptoms. And there is some investigational research data which suggested estrogen may be somewhat protective for women exposed to the Coronavirus too.

As noted in one of the considerations, menopause itself can therefore impact immunity. Immunity is a complex issue that is impacted by multiple factors — some of them are controllable, but anothers are not.

Estrogen hormone has been shown to play a protective role in women, so women who are not on hormone therapy during menopause may be at greater risk than those who are not on estrogen [10].

Menopause is also associated with a risk of cancer, as well as a decrease in T cells that the immune system works to fight cells and foreign invaders and generally boost the immune response.

If we take into account the age of women and the most common inflammatory-infectious infection as the main factors in menopause, we will see a direct correlation. So that as women get older, the levels of inflammation increase, causing pain, autoimmune problems, weight gain and susceptibility to disease. Thus, it is not menopause that is at risk, but menopausal-related health factors that can cause complications.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
2. Li F. Structure, function, and evolution of coronavirus spike proteins. Annu Rev Virol. 2016;3(1):237–61.
3. Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe. 2020;27(3):325–8.
4. Bosch BJ, van der Zee R, de Haan CA, Rottier PJ. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. J Virol. 2003;77(16):8801–11.

5. Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiol Mol Biol Rev. 2005;69(4):635–64.
6. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020;14(2):185–92.
7. Reis FM, Bouissou DR, Pereira VM, Camargos AF, dos Reis AM, Santos RA. Angiotensin-(1-7), its receptor mas, and the angiotensin-converting enzyme type 2 are expressed in the human ovary. Fertil Steril. 2011;95(1):176–81.
8. Qiu L, Liu X, Xiao M, Xie J, Cao W, Liu Z, et al. SARS-CoV-2 is not detectable in the vaginal fluid of women with severe COVID-19 infection. Clin Infect Dis. 2020;71(15):813–7.
9. Female age-related fertility decline. Committee Opinion No. 589. Obstetrics and gynecology. 2014;123(3):719–21.
10. Ding T, Zhang J, Wang T, Cui P, Chen Z, et al. (2020) Potential Influence of Menstrual Status and Sex Hormones on female SARS-CoV-2 Infection: A Cross-sectional Study from Multicentre in Wuhan, China [published online ahead of print, 2020 Jul 22]. Clin Infect Dis ciaa1022. Link: https://bit.ly/3bRuZZC
11. World Health Organization. Tracking SARS-CoV-2 variants. 2022
12. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020 Apr;5(4):536-44.

Göndərilib: 30.12.2021 Qəbul edilib: 17.01.2022