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Review Article

Unforeseen effects of COVID-19 on reproductive hormones and health of Indian women

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ABSTRACT

Numerous systematic probes, clinical studies and research papers have been published to depict, interpret, explain and understand the impacts and underlying mechanism of the coronavirus disease 2019 (COVID-19) pandemic and its long-term effects on the female body. COVID-19 affects a number of organs, including the female reproductive function and hormonal profile. However, less attention has been given to the effects of COVID-19 on the female reproductive system due to their low morbidity. The available results of studies involving correlation that COVID-19 infection and ovarian function holds in women of reproductive age has been shown as harmless in most cases. Although, several studies have reported the involvement of COVID-19 infection in oocyte quality, ovarian function, and dysfunctions in the uterine endometrium and the menstrual cycle. The findings of these studies indicate that COVID-19 infection negatively affects the follicular microenvironment and dysregulate ovarian function. Although the COVID-19 pandemic and female reproductive health have been studied in humans and other animals, very few studies have examined how COVID-19 affects the female reproductive system. Our objective in this review is to enumerate, illustrate and categorize the effects of COVID-19 on the female reproductive system, including the ovaries, uterus, and hormonal profiles. We tried to bring forth the possible impact COVID-19 may have caused from the current literature and surveys published in various scientific reports and peer reviewed journal articles. The effects on oocyte maturation, oxidative stress, which causes chromosomal instability and apoptosis in ovaries, in vitro fertilization cycle, high-quality embryos, premature ovarian insufficiency, ovarian vein thrombosis, hypercoagulable state, women's menstrual cycle, the hypothalamus-pituitary-ovary axis, and sex hormones, including estrogen, progesterone, and the anti- Müllerian hormone, are circled around here. The COVID-19 pandemic has significantly impacted the health of women. The scientific community encourages the development of recommendations for specialized care for women and strategies to prevent and respond to violence during and after the COVID-19 pandemic.

Keywords: COVID-19 pandemic, Reproductive hormones, Women health

INTRODUCTION

The COVID-19 pandemic has brought about numerous disruptions to healthcare and daily life. In this context, it is crucial to examine the multifaceted impact of the virus on female reproductive hormones and the frequency of abortions. This abstract provides a concise overview of the key findings in this area of research. Apart from the usual pathogenesis and disease symptoms the pandemic has introduced significant stresses and lifestyle changes, deteriorating the female reproductive health. Studies have reported alterations in menstrual cycles, with increased instances of irregularities and disruptions in hormonal balance. These changes may be attributed to the

physiological stress response to the virus and the influence of psychosocial factors. The COVID-19 pandemic has profoundly affected the lives of the global population. It is known that periods of stress and psychological distress can affect women's menstrual cycles. We, therefore, performed an observational study of women's reproductive health over the course of the pandemic thus far. Furthermore, access to reproductive healthcare services has been constrained during the pandemic, including limited availability of contraceptives and reduced access to safe abortion procedures. As a result, some regions have witnessed a surge in the number of unintended pregnancies and a potentially increased demand for abortions. It becomes the need of the hour to address and face these challenges, healthcare systems must adapt to the evolving needs of women during the pandemic, ensuring access to reproductive healthcare services, psychological support, and information about contraception. Research in this area is ongoing, and a deeper understanding of the complex interplay between COVID-19 and female reproductive health is essential to mitigate the long-term consequences of the pandemic on women's well-being.

Leukopenia, leukocytosis, and lymphopenia are very frequently developed in patients with coronavirus infections, especially observed in cases of COVID-19, wherein the WBC count can be altered. Although lymphopenia appears to be more common.[1,2] It must be emphasized that the lymphocyte count has been found to be directly associated with increased disease severity in COVID-19.[3,4] In patients with COVID-19, the total counts of Natural killer (NK) and cytotoxic T Lymphocytes (CTLs) are generally depleted which a consequence of exhaustion of their function and upregulation of NK inhibitory receptor.[5] Many studies have been performed with different approaches to try to understand the impact of COVID-19 on the materno-fetal binomial. Evidence about COVID-19 and pregnancy has been increasing rapidly since December 2019. However, few studies have raised concerns specifically about gynecology. The pandemic has significantly impacted gynecological health, causing great mental and physical anguish and huge implications on the overall health of females.[6-8] Therefore, the present study was undertaken to summarize the current knowledge on the COVID-19 pandemic in gynecology, including what is known about the potential impact of the disease not only on menstrual abnormalities or steroid hormones, but also on reproduction assistance, fertility care, urogynecological assistance, and the dynamics of interpersonal relationships, including, unfortunately, violence against women.

The authors conducted a meta-analysis of articles published between April 2020 and April 2023 on the PubMed, SciELO, and LILACS databases, using COVID-19 and the following relevant terms: Menstrual change; Ovarian function; Violence against women; Contraception; HPV; Mental health and Urogynecology. The current study is a narrative review of the coronavirus literature to date, with an emphasis on gynaecological outcomes and interventions, with the goal of gathering knowledge to safely approach women with suspected or confirmed COVID-19. There were no linguistic constraints. The authors included editorials and primary research papers that describe the relationship between SARS-CoV-2 infection (the cause of the COVID-19 pandemic) and gynaecological health among the eligible studies found. Data were gathered from the included articles as well as guidelines from national and international gynaecological societies using qualitative synthesis.

EFFECTS OF COVID-19 INFECTION

Soon after binding to target host cells, the coronavirus can create an immune response.

Effect on oocyte maturation

The studies carried out in hospitals across the continents generally lead to conclude that there is no significant effect of COVID-19 infection on oocyte maturation rate, ovulation and telomere reduction upon the infection carrier mothers. it does not affect the fertility scores in mild cases but in females with severe symptoms shortening of telomeres was noticed in case of granulosa cells. Extreme COVID-19 infections however do interfere with the oocyte maturation rates reducing them to much extent. The telomere lengths were found to be lesser in granuloma cells (GCs) compared to controls ($p=0.017$) in severe cases of COVID-19 females.

Distress

Stress developed in prospective mothers is a major cause of reproductive malfunctioning, leading to a wide spectrum of negative consequences ranging from missed periods (before conception) to still births and abortions. Psychological distress associated with missed periods is not only a symptom but also worsening of symptoms associated with menstruation and psychosexual health. Dysmenorrhoea has been shown to be associated with high mental stress levels due to COVID-19.[9,10] Another cause of poor reproductive function during Covid has been recognised as emotional instability and depression.[9,11]

Oxidative stress

Effects have been significant with a marked spike in oxidative stress primarily due to induced chromosomal instability and apoptosis in ovaries.[9,12] Another recent study illustrated that COVID-19 can affect oocyte maturation by increasing oxidative stress.[13-15]

In vitro fertilization cycle

The results of several experiments in vitro showed that COVID-19 and vaccination have no negative effects on sperm parameters and male fertility potential but can affect

gametes or reproductive germ cells.[16] Therefore, the COVID-19 pandemic can be considered to be a problem for natural pregnancy and artificial fertilization, including assisted reproductive technology (ART) and in vitro fertilization (IVF). Given that very few studies have been conducted on the relationship between COVID-19 and human/animal reproduction, investigations on the latest pathophysiological impact of the COVID-19 pandemic on the female reproductive system (ovaries, uterus, and sex hormones) and ART, the main fertility treatment procedure, are important.[15]

Effect on embryo quality

Ovarian tissue is susceptible to COVID-19.[17] During oocyte retrieval in ART, mature follicles and oocyte-cumulus complexes (COCs) are aspirated. In this procedure, the female gamete (oocyte) is naturally out of reach.[18]

Premature ovarian insufficiency

Premature ovarian insufficiency is another ovarian disease that occurs when the ovaries stop functioning before the age of 40. Here, the ovaries do not produce normal amounts of estrogen, and eggs are not released regularly, leading to infertility. This condition is also called premature ovarian failure.[19] In July 2021, Wilkins and Al-Inizi presented the first report of premature ovarian insufficiency that developed in a woman who was infected with COVID-19.[20] Two months before COVID-19 infection, the patient had normal regular periods; normal gonadotropin levels; and follicle stimulation hormone (FSH) and luteinizing hormone (LH) levels of 8 and 2 U/l, respectively. Seven months after the infection, her FSH and LH levels increased to 78 and 43 U/l, respectively. Two months later, when the test was repeated, her gonadotropin level remained high, indicating that she will need assisted reproductive methods to become pregnant A unique case was reported for the first time by Wilkins and Al-Inizi.[20] These authors in their observational study have reported a case of developed premature ovarian insufficiency in a patient who was infected with COVID-19, and hormonal defects are detected in this case.

Ovarian vein thrombosis

COVID-19 infection is associated with a high risk of venous thromboembolism.[21] Ovarian vein thrombosis (OVT) is a rare, serious, and uncommon condition and is mostly reported in the postpartum state.[22] However, cases of OVT associated with COVID-19 have been reported. DeBoer et al reported a case of OVT secondary to COVID-19 infection in a 56-year-old woman without a previous history of thromboembolism.[23]

Hypercoagulable state

A number of studies have reported hypercoagulability in the form of venous and arterial thromboembolism with unknown pathogenesis in patients with COVID-19. Interestingly, changes in thrombotic factors, such as fibrinogen, factor VIII, Willebrand factor, and D-dimer, that can cause a hypercoagulable state have been reported in a number of other studies.[24,25]

Women's menstrual cycle

Women of reproductive age seek healthcare for abnormal uterine bleeding (AUB) more often than for any other condition, and AUB accounts for one-third of women's outpatient visits to a gynecologist during the COVID-19 era. In one of the survey contained 50 questions on demographic information, menstrual cycle and mental health symptoms, diet, exercise and working patterns from before and since the beginning of the pandemic.[9] Missed periods 158/17% (+4%/27) (occasional-93/10%, often-65/7%), 72/9% new missed periods (occasional 56/7%, often 16/2%), Median missed periods=2(1-3), 17/21% who 'occasionally' missed periods pre-pandemic missed periods 'often' during pandemic, 40/31% who had missed periods previously had no missed periods during pandemic, p=0.0003, Heavy periods 447/47%, 18%/100 new heavy periods, 15%/63 less heavy periods, p=0.003, Painful periods 469/49%, 173/30% new painful periods, 49/12% previously painful periods improved, p<0.0001.

The hypothalamus-pituitary ovary axis, and sex hormones, including estrogen, progesterone, and the anti-müllerian hormone

Researchers have suggested that sex steroids may have a protective role against COVID-19.[7,26,27] Estrogen and progesterone, which are both female sex steroids, and their metabolite allopregnanolone have an anti-inflammatory role that can change immune cell responses.[27] Inflammatory responses to pathogens and infections are well known to be mediated by estrogen, and estrogen receptors (ERα/β) have been implicated in the suppression of viral gene transcription.[28] These changes may facilitate the proliferation and repair of respiratory epithelial cells and protect cells against COVID-19 infection.[27] Several studies were designed on the basis of this theory to assess the effect of progesterone and estrogen treatment on COVID-19 infection evaluated the level of AMH in COVID-19 infected women to assess the effects of COVID-19 on AMH.[29-31] They reported that the level of AMH in patients with COVID-19 was not different from that in the control group. The AMH is not influenced by the menstrual cycle, exogenous sex hormones, or pregnancy.[32]

DISCUSSION

On March 11, 2020, the World Health Organisation (WHO) declared the COVID-19 outbreak a pandemic, prompting governments and authorities around the world to implement or strengthen rigorous social distancing measures in order to limit the spread of the sickness. These policies have influenced family dynamics by influencing

income, interpersonal ties, well-being, and mental health.[33] The reason for disturbed menstrual cycle probably is the interaction between the HPA and HPG axes held responsible for menstrual defects after COVID-19 infection.[34] Governments of developed as well as developing countries. Over the globe have initiated special programs for assisted reproductive healthcare during COVID-19 full stop in India. Also, programs were dedicated to welfare and safe childbirth for pregnant women. One such a scheme, called Pradhan Mantri Surakshit Matritva Abhiyan, which was introduced in the 31st July 2016 episode of Man ki Baat. PMSMA played a vital role in providing safe operational care, antenatal care services to mothers in their second and 3rd trimesters of pregnancy. At designated government health facilities PMSMA is a systematic program that works in coordination with engagement of NGO 's and private sector healthcare facilities. It motivates private practitioners for developing awareness, strategies and participate actively. The National Health Mission issued guidelines on operationalization of maternal health services during COVID-19 pandemic.

Another change that greatly impacts women's health during the pandemic can be observed in their menstrual cycles. It is known that periods of stress and psychological distress, like the current pandemic, can affect women's menstrual cycles. The long-term health implications of this are yet to be determined, and future studies should address it. In September 2020, in Dublin, Ireland, Phelan et al conducted a study in which 1,031 women of reproductive age were invited to complete an anonymous digital survey via social media. A total of 441 (46%) respondents reported changes in their menstrual cycle, 483 (53%) reported worsening premenstrual symptoms, and 467 (45%) reported reduced libido since the beginning of the pandemic.

Bentov et al reported that the quality of oocytes in COVID-19-vaccinated women was statistically similar to that in unvaccinated women.[35] These clinical trials suggest that the COVID-19 vaccine has no negative effects on the human reproductive system.[35,36] When blood samples from the early follicular phase were examined for sex hormones and anti-Müllerian hormone in a retrospective, cross-sectional investigation. The severity of the disease appears to be related to more menstrual abnormalities. Patients with comorbidities such as diabetes, liver illness, and malignant tumours, as well as severe cases of confirmed COVID-19 (34% versus 8% of moderate or asymptomatic cases), experienced more changes in the menstrual cycle, primarily longer cycles or a decrease in volume. However, COVID-19 had no effect on average sex hormone concentrations or ovarian reserve in women of childbearing age. From a biological aspect, it is plausible that ovarian function suppression causes hormonal alterations accountable for menstruation abnormalities in these patients suffering from the severe form of COVID-19. Another study looked at how COVID-19 affected partner relationships as well as sexual and reproductive health in China. During the pandemic, 22% of 967 participants reported a drop in sexual desire, 41% reported a decrease in the frequency of sexual intercourse, 30% reported an increase in the frequency of masturbation, and 31% indicated a worsening in partner relationships. Outpatient services in general gynaecology, human reproduction, low-risk prenatal care, family planning, and even contraception access may have been disrupted as a result of the COVID-19 pandemic. A further analysis was carried out of the sex hormone changes in 91 patients during the disease. The data showed no statistically significant differences in all of the sex hormone concentrations between the COVID-19 patients and the controls. Subgroup analysis based on menstrual changes also indicated that there were no significant changes in sex hormone concentrations in either menstrual volume changes, simple cycle changes, or simultaneous volume and cycle changes. This result indicated that the ovarian endocrine system of most female COVID-19 patients was not seriously affected.

However, some patients had abnormal changes in their sex hormone concentrations, such as inappropriately high concentrations of FSH and LH during the early follicular phase, which may indicate ovarian suppression in these patients. When placed under acute stress, ovarian function is usually suppressed to ensure normal operation of essential organs and anovulation has been reported in many acute diseases.[37] With ageing, immune-senescence, characterised by a general decline in immune function is observed. Several of these changes are gender specific and affect post-menopausal women. Levels of estrogen, for example, 17β-estradiol (E2), are variable during the menstrual cycle, high during pregnancy and low after menopause in females. Progesterone (P4) levels are also very high in pregnant women, and P4 is essential to establish and maintain gestation by limiting local and systemic pro-inflammatory immune responses.[38] While progesterone is considered immunosuppressive, estrogens in general are considered immune-stimulatory.[39] Estrogens exert their effects partly through binding to ERα or ERβ, which are expressed in various types of immune cells, including lymphocytes, macrophages, and dendritic cells.[40] E2 thus affects many components of innate immunity, including the functional activity of innate immune cells that influence downstream adaptive immune responses. This is dependent on hormone concentration, in addition to density, distribution and receptor type found in immune cells. As a consequence, lower circulating estrogen levels due to ageing leads to a dampened immune response in older women. For example, in post-menopausal women, a second peak in Human papilloma virus (HPV) prevalence has been reported.[41,42]

New HPV infections in older women with no sexual activity are thought to be due to reduced immune responses.[43] HIV-1 infection is also increasing in post-menopausal women where a European study found that women over 45 have a 4-fold increased risk of acquiring HIV compared to women under 45 years of age.[44] A recent

cohort study of 68,466 patients with COVID-19 from 17 countries found that the fatality risk for women >50 years receiving estradiol therapy was reduced by more than 50% compared with non-users (OR=0.33, hazard ratio (HR)=0.29).[45] Recent results based on the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database of 1,863,478 women show that HRT use was associated with a significantly lower likelihood of all-cause mortality in COVID-19 (unadjusted OR=0.15, 95% CI 0.06-0.37, adjusted OR=0.22, 95% CI 0.05-0.94, p=0.041).[46] If, on the one hand, natural female hormones can hinder the mortality of women by severe COVID-19, on the other hand, exogenous estrogens can increase clotting factors and the risk of thromboembolic events, with a potential consequent increase in mortality, in postmenopausal hormonal therapy users. Hospitalized patients with severe COVID-19 have an activated coagulation demonstrated by high levels of D-dimers (fibrin degradation products), which, in combination with hormonal therapies in postmenopausal women, can favor the development of thromboembolic events. These and other findings even motivated the administration of anticoagulants such as heparin in many protocols for these cases of high levels of D-dimer, in an attempt to reduce mortality, both in men and women.[5,25]

The pandemic can affect gynecological health not only directly through the SARS-CoV-2 infection, but also through the indirect impact in terms of access to assistance or changes in the dynamics of relationships. Difficulty in accessing health systems during the pandemic has also impacted basic family planning rights. The pandemic may have negatively impacted the basic access to contraceptive care, one of the universal women's health services that minimize gender inequality and grant female autonomy. The secondary impact of the pandemic was observed not only in the difficulty in accessing family planning assistance, but also in effects on the production and transportation of contraceptive products, with the consequent unavailability of state-of-the-art contraceptives, favoring unplanned pregnancies.[47,48] The women's health and the COVID-19 pandemic are extremely linked; however, the impact of the pandemic on assistance and public health strategies is not yet clear. The strength of the study is a review focused on gynecology. Due to the nobility of the materno-fetal binomial, most of the articles published on an urgent basis during the pandemic were directed to materno-fetal care. The gynecological patient deserves attention with a collection of studies specifically aimed at health care, not only Obstetrics but also in Gynecology, for non-pregnant women associated with the pandemic. To combat social disruptions connected to women's health, the authors propose ongoing significant reforms, policies, and methods such as telemedicine, hotlines, and online counselling forums. Finally, given the numerous roles that women play in society, the authors would like to reiterate the insightful comment expressed by the WHO Director General: No one will be safe unless every woman is safe.[33]

CONCLUSION

Gynecological measures and guidelines are encouraged to safeguard the sexual and reproductive health of young people during this pandemic. In light of these findings, it is suggested that hormone therapy be discontinued in peri- and postmenopausal women with COVID-19 infection. It is best to advise the patient that discontinuing hormone medication may result in irregular bleeding. Shifting from oral to transdermal oestrogens (patch, gel, spray) may be considered, but each case should be managed individually. Transdermal oestrogens should be recommended when beginning therapy due to the lower risk of thromboembolic events. These findings favour and emphasise the use of treatments that focus on enhancing oocyte maturation rates and reduction in telomere degradation (shortening) in women severely affected by coronavirus undergoing ART who suffered miscarriages during the COVID era.

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