The Effect of Coronavirus Disease 2019 on Reproduction System and Fertility

Muhammad Fidel Ganis Siregar*1, Effinia Kamila Hanum Siregar

Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Abstract

As of October 9, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was recorded to have infected more than 235 countries and 36,361,054 people globally, and 1,056,186 people died from coronavirus disease 2019 (COVID-19). In early October 2020, it was reported that the rate of increase in new cases reached 300,000 cases per day. A scientific reference source about COVID-19 in pregnancy and fertility system based on the results of previous research. By conducting a literature search that was carried out until October 12, 2020, through the PubMed and Google Scholar databases using the keyword COVID-19 and pregnancy, 20 articles were used as a reference source. Human SARS-CoV appeared in China, causing a deadly epidemic 18 years ago. Novel coronavirus-2019 infects target cells by binding to angiotensin-converting enzyme 2 (ACE2) through its surface spike protein, nCoV-2 modulates ACE2 expression and causes serious injury, similar to SARS-CoV. There is the possibility that the SARS-CoV-2 mechanism can affect fertility on female, namely, SARS-CoV-2 can harm ovarian tissue and granulosa cells, and reduce ovarian function and quality of oocytes, and can make infertility or miscarriage; also damage the endometrial epithelium and affect early embryo implantation. COVID-19 is caused by SARS-CoV-2 which is an acute infectious disease that mostly affects the respiratory system, but can also attack the reproductive system.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) which is an acute infectious disease that mostly affects the respiratory system, first discovered in December 2019 in Wuhan, China. It was then declared a pandemic by the World Health Organization on March 11, 2020 [1], [2]. As of October 9, 2020, SARS-CoV-2 was recorded to have infected more than 235 countries and 36,361,054 people globally, and 1,056,186 people died from COVID-19. In early October 2020, it was reported that the rate of increase in new cases reached 300,000 cases per day. The United States, India, and Brazil are the three countries with the highest total cases of the spread of COVID-19 in the world [3].

There were 324,658 confirmed cases of COVID-19 in Indonesia until October 9, 2020, of which 247,667 people had recovered and 11,677 people died. Based on data released by the Medan City Health Office, there were 6090 COVID-positive patients in Medan City as of October 9, 2020, 260 people died, and 3938 patients recovered. This figure may continue to grow [3], [4], [5].

This virus enters the target cells through the glycoprotein spike SARS-CoV-2 (S) which binds to the host's angiotensin-converting enzyme 2 (ACE2) receptor. Moreover, host cellular proteases such as transmembrane serine two protease (TMPRSS2) then cleavage viral S protein which allows fusion of the viral and host cell membranes permanently [1]. This study aimed to report the effect of COVID-19 on the reproduction and fertility system. We hypothesized that there is an effect of COVID-19 on pregnancy and fertility.

Pathogenesis of COVID-19: ACE2 as SARS-CoV and SARS-CoV2 Receptors

ACE2 is a functional receptor by which SARS-CoV enters the target host cell. The transmembrane nail glycoprotein (protein S) of SARS-CoV binds to the ACE2 cell membrane; SARS-CoV then attaches to the target cell, followed by priming the S-SARS-CoV protein by cell surface proteases, such as TMPRSS2, 11A, 11D, and 11E allowing fusion between the virus...
and the cell membrane resulting in the entry of SARS-CoV and replication occurs in target cells. In addition, phosphatidylinositol 3-phosphate 5-kinase, two-pore channel subtype 2, cathepsin L, and cathepsin B, which are a lysosome, are also reported to be important molecules that play a role in the entry of SARS-CoV-2 to the target cell. Low ACE2 levels greatly reduced infection and viral replication in the SARS-CoV infection trial in mice. Thus, the S-SARS-CoV protein and ACE2 binding are very important in the process of SARS-CoV infection [6], [7].

Effects of SARS-CoV-2 on the Male Reproductive System

In early October 2020, it was reported that the rate of increase in new cases reached 300,000 cases per day. There were 324,658 confirmed cases of COVID-19 in Indonesia until October 9, 2020, of which 247,667 people had recovered and 11,677 people died. Based on data released by the Medan City Health Office, there were 6090 COVID-positive patients in Medan City as of October 9, 2020, 260 people died, and 3938 patients recovered (Table 1). This figure may continue to grow [3], [4].

Experts are currently focusing on studying the characteristics of the SARS-CoV-2 virus and the mechanisms that lead to the development of the COVID-19 disease. In fact, intense efforts are being made to find a possible cure or vaccine. Then, there are only limited studies which have explored the possible effects of SARS-CoV-2 infection and its sequel on the reproductive systems of both men and women, as well as the potential outcomes in the context of reproductive medicine [6].

The Human Protein Atlas database reports the expression of the ACE2 receptor in male and female reproductive organs. These receptors have an important role in sperm function and the fertilization of oocytes. Increased expression of the ACE2 receptor was reported in testicular tissue, particularly in spermatogonia, Sertoli, and Leydig cells, as well as in prostate epithelial cells, fibroblasts, and pericytes (Figure 1) [8], [9].

**Figure 1: Severe acute respiratory syndrome coronavirus 2 in spermatogenesis** [8]

The effects of SARS-CoV-2 on the male reproductive system are not fully explained. The effects of SARS-CoV-2 on the male reproductive system are

| Table 1: COVID-19 data in Indonesian Provinces4 |
|-----------------------------------------------|
| No. Province | Total cases on October 9, 2020 | Recovered cases on October 9, 2020 | Deceased cases on October 9, 2020 |
|--------------|-------------------------------|----------------------------------|----------------------------------|
| 1 Aceh       | 5423                          | 3949                             | 254                             |
| 2 Bali       | 9759                          | 8317                             | 313                              |
| 3 Banjarmasin| 6570                          | 6711                             | 86                               |
| 4 Bangka Belitung | 440          | 454                             | 31                              |
| 5 Bengkulu   | 774                            | 751                             | 14                              |
| 6 Di Yogyakarta | 2904                      | 2590                            | 313                             |
| 7 DI Jakarta  | 83,372                         | 84,315                           | 650                             |
| 8 Jambi      | 715                            | 760                             | 30                              |
| 9 Jawa Barat | 26,259                         | 26,763                           | 34                              |
| 10 Jawa Tengah | 25,261                     | 25,673                           | 210                             |
| 11 Jawa Timur | 46,095                        | 46,405                           | 306                             |
| 12 Kalimantan Barat | 1108             | 1136                            | 30                              |
| 13 Kalimantan Timur | 10,203          | 10,338                           | 182                             |
| 14 Kalimantan Tengah | 3866                | 3890                            | 314                             |
| 15 Kalimantan Selatan | 10,816             | 10,897                           | 8                               |
| 16 Kalimantan Utara | 629                       | 632                             | 5                               |
| 17 Kapuas Riau | 2450                           | 2450                            | 182                             |
| 18 NTB       | 3486                           | 3513                            | 22                              |
| 19 Sumatera Selatan | 6614                     | 6677                            | 65                              |
| 20 Sumatera Barat | 7824                        | 8119                            | 66                              |
| 21 Sulawesi Barat | 4885                        | 4704                            | 35                              |
| 22 Sulawesi Utara | 11,064                      | 11,159                           | 95                              |
| 23 Sulawesi Tenggaro | 3306                     | 3419                            | 63                              |
| 24 Sulawesi Selatan | 16,298                     | 16,299                           | 101                             |
| 25 Sulawesi Tenggaro | 528                         | 539                             | 33                              |
| 26 Lampung   | 1089                          | 1089                            | 17                              |
| 27 Riau      | 9226                          | 9430                            | 66                              |
| 28 Maluku Utara | 2082                        | 2082                            | 60                              |
| 29 Maluku Barat | 3272                        | 3272                            | 4                              |
| 30 Papua Barat | 2754                          | 2854                            | 87                              |
| 31 Papua     | 7312                          | 7428                            | 4                              |
| 32 Sumbawa   | 866                            | 878                             | 8                               |
| 33 NTB       | 532                            | 551                             | 6                               |
| 34 Gorontalo | 2931                          | 2933                            | 106                             |
| **TOTAL**    | 320,564                       | 324,658                          | 244,060                         |
Effects of SARS-CoV-2 on the Female Reproductive System

Until now, the damage of female reproductive system due to COVID-19 patients has not been reported. There is evidence that the renin-angiotensin (Ang)-aldosterone system is involved in female reproductive processes such as folliculogenesis, steroidogenesis, oocyte maturation, and during ovulation. Reis et al. confirmed the presence of the Ang- (1–7)-axis Mas-ACE2 receptor, and the ACE2 marker at all stages of follicular maturation in the human ovary. ACE2 is also found in the endometrium, in epithelial cells higher than stromal cells, and ACE2 expression changes according to the phase of the menstrual cycle, becoming more during the secretory phase than in the proliferative phase; this may interfere with local Ang-II homeostasis and regulate endometrial regeneration [10], [11], [12].

Furthermore, the previous studies have shown that ACE2 is expressed in the ovaries and granulosa cells of cattle and mice, is regulated by gonadotropins, and is involved in follicular development. Hence, it can be said that the possibility of the SARS-CoV-2 mechanism can affect fertility on female, namely: (1) SARS-CoV-2 can harm ovarian tissue and granulosa cells, and reduce ovarian function and oocyte quality, can make infertility or miscarriage; and (2) SARS-CoV-2 also damage the endometrial epithelium and affect early embryo implantation. However, there is still little evidence explaining the effects of SARS-CoV-2 on the Fallopian tubes, so it needs to be more attention in the future [10], [11].

ACE2 in Uterine and Vagina

ACE2 mRNA has been identified in the uterus of humans and mice. ACE2 mRNA is more common in epithelial cells than in stromal cells, and higher in the secretory phase than in the proliferative phase. Moreover, it has been confirmed the presence of ACE2 in the uterus and vagina based on data analysis from the Human Protein Atlas and Gene Card Database. It is noteworthy, however, that there are reports which found that the transmission rate of infection was quite high among the sexual partners of 35 women with nCoV2-2019 positive, which may explain the possibility of transmission through sexual contact. However, transmission by sexual contact still requires further research [2].

ACE2 in Pregnancy

ACE2 is widely revealed in the human placenta. In the placental villi, ACE2 is revealed in the syncytiotrophoblast, cytotrophoblast, smooth muscle, and vascular endothelium of the primary and secondary villi. In the maternal stroma, ACE2 is expressed in invading trophoblasts and in intravascular trophoblasts, as well as in decidual cells. ACE2 is also found in arterial and venous endothelium and umbilical cord smooth muscle. Hence, ACE2 reaches its highest level in early pregnancy. Lately, early-onset nCoV-2019 infection was found in infants based on positive nasopharyngeal and anal swabs on days 2 and 4 of birth and an infant born from a mother with COVID-19 positive had elevated IgM antibodies 2 h after birth. The identification of nCoV-2019 in human airway epithelial cells requires at least 96 h for culture, there is speculation that intrauterine transmission of nCoV-2019 may occur and may allow the fetus to become infected during pregnancy [2].

One of three breast milk samples were positive for nCoV-2019 when tested for nucleic acid, showing
the possibility of transmission through breastfeeding. Although there was no virus in breast milk, transmission by contact during breastfeeding must be taken into account. Given the weak immune system in newborns, it is highly recommended that pregnant patients who are positive for nCoV-2019 should do breastfeeding or start breastfeeding after 14 days of self-isolation and symptoms improve. However, considering the benefits of breast milk in lowering the risk of respiratory, gastrointestinal infections, sudden infant death syndrome, and diabetes in infants, breastfeeding may not be completely prohibited. However, it was reported that of two postpartum women who were diagnosed with COVID-19 and did not wear a mask while breastfeeding, their newborns tested positive [10].

Gynecological Surgery during the COVID-19 Pandemic

Surgery on patients who are suspected or confirmed positive for COVID-19 is a high-risk procedure. In infected patients, COVID-19 can be found in their body cavities. Aerosols generated in the operating room during surgery can contain viruses or particles that are thought to survive in the aerosol for at least 3 h (Figure 3). During surgery, the droplets may be exposed and theoretically could infect the surgical team involved at that time. However, there are several operations on gynecological disorders that cannot be delayed [14], [15] (Table 2).

Figure 3: Guide to priority gynecological operations in 3-phase lockdown during the coronavirus disease 2019 pandemic [14]

Table 2: Operation triage category [14]

| Category       | Description                                                                 | Desirable Maximum Waiting Time |
|----------------|------------------------------------------------------------------------------|--------------------------------|
| Urgent         | Has the potential to deteriorate quickly to the point where it may become an emergency  |
|                | Causes pain, dysfunction, or disability                                      | Within 30 days                  |
| Semi-urgent    | Unlikely to deteriorate quickly                                             | Within 60 days                  |
|                | Causes pain, dysfunction, or disability                                      |                                |
| Elective       | Unlikely to deteriorate quickly                                             | Within 180 days                 |
|                | Does not have the potential to become an emergency                           |                                |

Telemedicine during the COVID-19 Pandemic

Providing primary health care during this pandemic seemed to be challenging as health-care services are being interrupted due to inadequate protective gears, lockdown, and also the risk of infection spread to patients and medical practitioners. To make a better decrease and manage the spread of coronavirus, hospitals need to improve the efficiency of their medical system by replacing physical treatments with digital technologies [16].

Telemedicine promotes social distancing and helps medical centers in managing prolonged waiting times and risk of disease progression. However, only few physicians and patients are adequately educated on how best practice to utilize these digital services. Hence, there is a need to make guidelines and recommendation to educate both physicians and patients on how they can use telemedicine and virtual care effectively [16].

In Indonesia, telemedicine activities have been implemented according to the POGI guideline called TeleMed POGI where TeleMed POGI refers to the Minister of Health Regulation number 20/2019 and Regulation of the Indonesian Medical Council number 74/2020, which state that providing of remote health-care services by the obstetricians and gynecologists to patients is used by information and communication technology [17].

The POGI TeleMed service is limited to 30 min per patient consultation, however, this service can facilitate the administration of mild drugs prescription to pharmacies in non-emergency complaints of obstetrics and gynecology. TeleMed POGI is not allowed to handle emergency complaints and cases, as well as oncology-gynecology cases. Cases that can be served by TeleMed POGI are non-emergency cases including [17]:

- Mild pregnancy-related complaints such as delayed menstruation, infertility, vaginal discharge, and pregnancy control without complaint
- Mild complaints related to the menstrual cycle such as menstrual pain and irregular cycles
- Mild complaints related to the urinary tract and genitalia such as urinary tract infections and mild degree of pelvic organ prolapse
- Mild post-operative complaints such as control of the anatomical pathology results
- Mild complaints related to precancerous lesions such as control of pap smear results
- Consultation on laboratory and radiological results in obstetrics and gynecology.

At least 59 hospitals (including RSCM Jakarta, RSUD Hasan Sadikin Bandung, RSUP Haji Adam Malik Medan, RSUD Sorong Papua, and many others) and 173 primary health centers in Indonesia have been participated in telemedicine services and are
connected to each other. However, there are several limitations of telemedicine. It might not be ideal if focusing sensitive topics, especially if there is patient's inconvenience or concern for privacy. There is also a certain situation in which in-person visits are more suitable due to urgency, a person's underlying health conditions, or the fact that a physical examination or laboratory testing is needed for medical decision making. Limited access to technological devices or connectivity may make telemedicine not suitable for some people, especially for those living in rural environment [18], [19].

**Assisted Reproductive Technology During the COVID-19 Pandemic**

In the early stages of the pandemic, the American Society for Reproductive Medicine (ASRM) and European Society of Human Reproduction and Embryology (ESHRE) recommend discontinuation of infertility therapy except for the urgent cases mostly. In March 2020, the ESHRE recommended “to avoid getting pregnant at this time.” For undergoing treatment patients, they suggest “considering delaying pregnancy by freezing the embryo or oocytes to delay embryo transfer.” The ASRM also issued a statement delaying “non-urgent” treatment and embryo transfer whenever possible [10], [20], [21].

![Figure 5: Age and reproductive in woman](image)

This condition led to have significant impacts on psychological status and live birth. It is reported that 38% of patients with failed *in vitro* fertilization (IVF) cycles of 2 were detected with anxiety or depression. About 37.4% of patients declared that they would like to undergo the IVF treatment despite the COVID-19 pandemic. The unsustainable of fertility treatment for even 1 month in the USA could make in 369 fewer women having live birth, due to the mount in patients' age during the lockdown [22].

Infertility is a time-sensitive problem, due to its correlation with decreased of egg quality (Figure 4). The optimal age for fertility rate is considered to be in range of 18–31 years old, subfertility stage is 31–41 years, while woman at 41–51 years is thought to have sterility and irregular cycle, which means she is in perimenopause state. The average age of menopause is 47.5 years according to Indian Menopause Society (Figure 5) [22], [23].

However, recently, with mitigation strategies that have worked in several areas and the presence of additional data, as well as resistance to this policy, infertility therapy has resumed. ASRM, ESHRE, and International Federation of Fertility Societies have come asserted the importance of serial reproductive care during the COVID-19 pandemic [20], [23], [24], [25].

![Figure 4: Egg count overtime](image)

There is no evidence to suggest the presence of virus in follicular fluid. Data on the infectivity potency of semen are controversial. Even though the presence of SARS-CoV-2 in the semen of infected and hospitalized patients has been proven, no conclusions about transmission can be ascertained and further studies are needed to confirm this hypothesis (Figure 6) [10], [26].

![Figure 6: Summary of the infertility therapy cycle](image)
Conclusion

COVID-19 caused by SARS-CoV-2 which is an acute infectious disease that affects the respiratory system mostly, but can also attack the reproductive system. This is because this virus enters the target cells through the glycoprotein spike SARS-CoV-2 (S) which binds to the host’s ACE2 receptor. And host cellular proteases such as TMPRSS2 then cleavage viral S protein which allows permanent fusion of the viral and host cell membranes.

In the reproductive organs, ACE2 was also expressed predominantly in spermatogonia, Leydig cells, and Sertoli cells, while TMPRSS2 was revealed only in spermatogonia and spermatids. ACE2 is also found in the ovaries, uterus, vagina, and placenta. Hence, viral infection can also impact reproductive function if the cells of the male and/or female reproductive systems also shown ACE2.

Given that this pandemic has only occurred in early March 2020, so there are still little data being reported, therefore, further investigation with sufficient timeframes is needed regarding the effects of COVID-19 on this reproductive system so that clear evidence can be obtained so that appropriate action can be taken.

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