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Corona Virus and Effect on Fertility and Reproductive Outcome: Literature Review

Asmaa Abdulrazaq Al-Sanjary
Department of Obstetrics and Gynecology, College of Medicine, University of Mosul, Ninevah, Iraq

Abstract

Human Corona viruses are coronaviridae virus belongs to enveloped single stranded RNA virus. It is a group of viruses that cross species barrier and transmitted from their animal reservoirs to become responsible for human infection with wide genetic diversity. Many of Corona viruses have been responsible for infection in human, which is usually mild in healthy adult, and do not have any concern with treatment or vaccination, like other endemic viruses as infleunza virus, respiratory syncytial virus and rhinoviruses. Until outbreaks of infection with acute respiratory distress syndrome, caused by highly pathogenic strains with severe acute respiratory syndrome coronavirus (SARS CoV). The last outbreaks was at 2019 with the novel SARS-CoV-2 infection, when 91000 people infected and 3120 people dies and by 3rd of march 2020 and it was the start of world pandemic in Wuhan (china), with medical and scientific challenges for china and the world started with many social limitation. The SARS-CoV-2 responsible for the pandemic has 96% similarity to the bat SARS like corona virus and to cause human infection the virus has several adaptation and minor changes in its sequence to improve its fitness to infect the cells of the new host. SARS-Co-2 has high spread rate in human and for each human infected patient there will be 2-3 individuals are infected and the virus remains infectious as aerosols up to three hours and few days on the surrounding surfaces. This review highlighted the impact of coronavirus on fertility.

Keywords: *COVID-19, Fertility, Reproductive Health, SARS-CoV-2.*

Introduction

SARS-CoV-2 virus is enveloped spherical virus with single strand RNA virus contains four types of structural protein: the nucleocapsid, membrane, envelope protein and the spike pretein. The envelope has many projections from glycoprotein, called spike protein, a key determinant for attachment and entry of virus into the target cell [1]. The spike protein consist of 2 subunits, S1 subunits has a receptor binding domain mediated by angiotensin –converting enzyme-2, ACE2 receptors attachments and this affinity was related to virus spread, while the S2 subunits containing a trans membrane domains containing a fusion peptide, that force fusion of viral and host cell membrane. Cleavage of the spike protein at two sites at both subunits by a variety of cellular proteases, is required before activation for fusion. The viral route of infection will be determined by the tissues proteases available and their cleavage sites, and the divergence in the of sequences between the receptor binding domains and cleavage sites SARS-CoV-2 and that bat virus determine what changes were required for adaptation of the animal virus to infect human [2].

The spread of the SARS-CoV-2 virus and infection of human cells occurs by attachment through viral spike (S) protein to the angiotensin converting enzyme receptors

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Corresponding Author: asmaabdulrazaq@uomosul.edu.iq

(ACE receptor) with higher affinity mediate more viral entry to the host cells, infection is 20 fold more than in other viruses explain the wide spread of virus in short time causing the pandemic. These receptors are predominant in the nasal and in respiratory epithelium also expressed in the cornea, ileium, esophagus, colon, lymph nodes, thymus, bone marrow spleen, liver, kidney, brain and reproductive system [3].

Pathogenesis of COVID-19

The course of viral infection includes: cellular invasion and viral replication, dysregulation of immune responses, multiple body organ damage and recovery stage.

The COVID virus after entering the target host cell it replicate and assembled in the cell endoplasmic reticulum, forming syncytia or it lyse the cell, usually if antiviral therapy tried at this time it can reduce the viral load and limit the severity of infection. Viral induced cell apoptosis and damage like mitochondrial damage, alteration of PH or causing enzymatic dysfunction [4]. This direct organ cellular damage caused by the SARS-CoV-2 in addition to altered in appropriate innate and acquired immune response is related to the severity of infection and organ dysfunction, also COVID-19 infect and damage the immune system cells, the spleen and lymphoid tissue since they share the same receptor expression with body organ (ACE2 receptor) or due to systemic effect of the immune response to the virus [5]. Lymphopenia, a common feature can predict presence of pneumonia and progression to severe respiratory distress. Elevated plasma level of TNF-α,IL-2,IL7,IL10, interferon, GCSF, and C-reactive protein, all are markers predict severity of infection even at early stages and it suggest that Hypercytokinemia and cytokines storm may serve fundamental role in severe infection with COVID-19 [6].

Transmission 0f COVID-19 to the Reproductive Organ and Embryo

Theoretical transmission of the virus to the male and female reproductive organ and vertical transmission to the embryo are both possible since immunohistochemistry studies identify ACE receptors and a recently identified Basigin or CD147, both as receptors to facilitate viral entry into the cell, they were expressed in the female reproductive organ as the ovaries, oocyte, uterus, vagina and testes, also they are detected on the early blastocyst and on both trophoctoderm cells and hypoblast cells, and on the epiblast cells of the future embryo [7].

Effect of COVID-19 on Female Infertility

Reis and Colleagues 2011, confirmed that ACE2 receptors was present in the ovary and in all stages of follicle maturation and in the follicular fluid.it is also present in the endometrium, more in the epithelial than in the stromal cells, and it is expression in cell is variable in the menstrual cycle with higher level during the secretory phase that could have a role in controlling endometrial regeneration [8]. Expression of ACE2 receptors and TMPRSS2 is usually low in the endometrium throughout the menstrual cycle and risk of uterine infection was low (0.1%-1.2%) so the endometrium seems to be safe from direct viral infection and most of changes in the endometrium, menstrual cycle and implantation were due to alteration in gene expression due to down regulation of vital function by part of the systemic inflammation and host immune responses [9].

The renin-angiotensin system (RAS) has the Angiotensin –II, Angiotensin (1-7), and ACE receptors with 1 and 2 isoforms, all have a pivotal role in COVID-19 infection and ACE2, a key enzyme in the system, has a synergistic effect in balancing Ang II and Ang (1-7) and their effects on development and maturation of

follicles [10]. Angiotensin II have a role in steroid production, follicle growth and atresia, oocyte maturation and it influence ovulation and maintain corpus luteum progression, while Ang (1-7) promotes production of estradiol and progesterone, enhance ovulation, maturation and resumption of meiosis in the oocyte, So its level were related to higher oocyte quality and normal placentation [11]. The local presence of the virus in the female reproductive system gaining its cellular access through the renin-angiotensin system affecting hormone production and endometrial menstrual function, and could impair endometrial decidualization, and blastocyst implantation through different mechanisms [12].

The COVID-19 infection may induce immune disruption altering type and volume of leucocyte in the endometrium and may also interfere with haemostasis and with endothelial cell function both may have effect on altering menstrual blood loss. Menstrual abnormalities in SARS-COV-2 includes increased premenstrual tension syndrome, protracted periods with decreased menstrual blood volume and even amenorrhea, these changes may be related to transient reduction of ovarian reserve and some of the menstrual changes may be related to treatment with steroids or aspirin and stress of treatment [13].

Infection with COVID-19 could affect the female hormone production through its effect on the hypothalamic–pituitary-gonadal axis, thyroid and adrenal glands changing the amount of sex hormone secretion [14]. Chronic inflammation caused by the infection also induce resistance to the estrogen anti-inflammatory effect thus reduce estrogen potency [15]. In addition inflammatory cytokines induced by COVID -19 will affect the production of GnRH and gonadotrophin secretion from the hypothalamus and pituitary gland interfere with follicle maturation and with steroidogenesis, also it modify estrogen receptor expression and their function, in addition cytokines also induce oxidative stress that disturb ovarian environment and cause DNA damage and disturb cellular function, and stimulate immune cells infiltration to ovarian tissues that will be detrimental for normal ovarian function and disturb maturation of oocyte ovarian follicle[16].

These are the suggested mechanisms for the potential effect of SARS-CoV-2 in causing short term reduction in ovarian reserve and in female reproductive potential as demonstrated in a study by Ding et al. (2021), when a low anti-mullerian hormone was observed in 78 out of 151 patients after COVID-19 infection, the same study also report higher level of follicle stimulating hormone, prolactin and testosterone levels which further suggest that disturbance in ovarian reserve and function. A study by Gullo et al. (2024), indicate that infection with SARS-Cov-2 infection can impair the women reproductive health with significant reduction in AMH (-27.4%) and Antral follicle count (-1 antral follicle) with raised FSH (+13.6%) and LH (+13.4%) [17].

While Many studies shows that there were no any measurable harmful effect on ovarian reserve markers and AMH after acute severe infection although individual cases of premature ovarian failure have been reported in these studies but without clear evidence that COVID-19 being a cause for that. The effect of COVID inflammation, immune dysregulation and cytokine storm, on the ovary is particularly important in case of long COVID when persistent chronic inflammation expose the ovaries to continuous stress exacerbate long lasting ovarian damage [18].

In addition COVID leads to vascular thrombosis and vascular endothelial dysfunction induce ovarian tissue ischemia and hypoxia and cellular damage, disturbing cell metabolism and ovarian function. Evidence of effect of SARS-CoV-2 on the Fallopian tube is lacking now, and it should be paid more attention in the future [19]. The virus was detected by cervical swab in 10.53%

of COVID-19 positive patient [20]. The detection of the virus in vaginal secretions at time of infection with COVID-19 is uncommon, and many studies as that by Barber et al. (2021) and Fenizia et al. (2021), the virus detected only in one patient (1.9%), and detection is possibly is only feasible in the stage of viremia. Larger studies are required to establish the association of vaginal colonization with SARS-CoV-2 with infectivity and risks on patient [21, 22].

Effect of COVID-19 on Male Infertility

Male reproductive organs are prone for SARS-CoV-2 as the ACE-2 receptors and TMPRSS2 have abundantly been expressed in the kidneys, testes, urinary bladder and the prostate, also the virus infect testis through host cell receptor called basigin, which is a glycoprotein abundantly expressed in the testis and has essential role in male reproductive system as a testis blood barrier and as attaching molecule between the germ cells and Sertoli cells in the seminiferous tubules [23]. With detection of virus in semen and its sexual transmission in these men or detection in urine is likely, but studies provide contradictory result without pathological evidence, some studies as that by Paoli et al. (2020), prove the absence of virus RNA from the semen, other report high viral load in the semen in SARS - COV-2 infected individuals [24].

Many of the evidence that SARS-CoV-2 infect the testis comes from autopsy in patient dies from COVID-19, a study by Ma et al. (2021), reveals massive loss of Germ cells from the seminiferous tubules with intact Sertoli cells with higher apoptotic cells in COVID-testes may be responsible for this damage and loss, also there is infiltration of the interstitial tissues with various inflammatory cells as $CD3^+$ T Lymphocytes, $CD20^+$ B-Lymphocyte, CD68+ macrophages [25]. In addition to the presence of activated B cells ($CD38^+$) and plasma cells ($CD138^+$), with extensive precipitation of IgG in the interstitium and in the seminiferous tubules [26], so there were an auto immune secondary response that damage the testis in addition to the primary effect of viral orchitis. Detection of the SARS-CoV-2 nucleic acid and anti – SARS-CoV spike S1 antibody, and viral particles in the interstitial part of testes, all indicate that the virus indeed infecting the testes [26]. Also a study by Li et al reveals interstitial edema and congestion with red blood cells in autopsy from testes of patients with severe Covid-19 infection with elevated seminal IL-6, and TNF-a suggesting presence of auto immune orchitis [27]. Many changes have been described, also indicating acute testicular damage in autopsy of patient died from COVID-19 as presence of sloughed spermatocytes, swollen Sertoli cells, reduced Leydig cells, and microthrombosis in the testicular vasculature [27].

Increased cytokines storm induced by infection will disturb the blood-testis barrier and induce orchitis. Inflammation in COVID-19 orchitis will increase oxidative stress and that will disturb testicular function and spermatogenesis, so hypogonadism develops and reduction in testosterone levels with elevation of luteinizing hormone, unchanged Follicle stimulating hormone and mild elevation in prolactin, the latter is elevated in response to stress of infection and may play a role in development of hypogonadism in COVID-19 infection. Semen parameters in patients recovered from COVID-19 infection shows variable result from azoospermia to normal semen count with lower values in sperm concentration, total sperm count and total motile sperms [28]. A study by Zhang et al. 2024, shows temporal reduction in sperm concentration and total sperm count after COVID infection due to temporal suppression of sperm production which is usually recovered within 3-6 months and there is temporal decline in sperm quality through multiple mechanisms as immune mediated response causing arrest of meiosis, fever has

synergistic effect, which disturb the testicular thermoregulatoty mechanism cause reduction in sperm count and sperm motility, or it could be affected by oxidative stress, causing DNA damage and apoptosis, added to this the drug therapy used for treatment, all will impair sperm quality in temporal self-healing manner [28].

Hu et al., report the median time for recovery of semen parameters to aged matched control was 177.5 days [29]. Testosterone has anti-inflammatory effect reducing cytokines and severity of infection in male, however it was shown that primary damage of testes with infection of leydig cells or due to hypothalamic pituitary gonadal axis dysfunction leads to hypogonadism and reduction of testosterone, and these individuals with reduced testosterone were prone to worse prognosis, longer disease course and longer admission to intensive care units. Over all oligoasthenospermia observed and 18.6% have azoospermia in severe COVID illness and sperm parameters return normal 79 days after fever subside and normal andrological state with no long term impairment after recovery [29].

A study by Hallak et al (2024) were able to detect the virus intracellularly in the spermatozoa till 90 days after hospital discharge, the period of follow up in the study, and electron microscopic examination reveals nuclear (DNA based) extra cellular traps were produced by the spermatozoa similar to those produced by the systemic viral infection. This access of virus to spermatozoa probably because the Blood-testes Barrier has low protection from viral infection including Coronavirus 2, with the virus use the epididymis as his post testicular route to bind, and fuse to mature spermatozoa inducing reverse transcription of proviral DNA and elicit extracellular DNA formation [30].

Effect of COVID-19 on Assisted Reproductive Techniques

The outbreak of SARS CoV-2 had led to limitation in fertility services and impact couples psychology while waiting treatment and there was also a raising concern about outcome of IVF treatment six studies was reviewed by Kaur et al. (2024), have shown no difference in the clinical pregnancy rates between infected and non-infected couples by COVID-19 [31].

A study by Yang et al, 2024 evaluate the outcome of ART cycle between those with acute infection with SARS-CoV-2 at time of controlled ovarian hyperstimulation and those not infected with no difference were observed in their pregnancy outcome between both groups and indicate that those with asymptomatic or mild infection of COVID-19 discovered during ART cycle can safely continue their program with comparable result from cycle as number of blastocyst observed furthermore no any viral RNA was detected in any of the studied patients samples [32]. Also, Tian et al. (2025), study shows that infection before oocyte retrieval have no effect on rate of fertility including good quality embryos, blastocyst formation rate between infected and non-infected groups, although infection in male partner report a lower fertilization rate and infection in the female partner report a lower clinical pregnancy and lower live birth rates [33].

While a study by Eckstein et al. (2024), shows that previous COVID-19 infection in the last 6 months in any of the couples especially the female were result in lower non-significant difference in pregnancy rate associated with significant higher risk of miscarriage accordingly it's better to wait 3-6 months after an infection before attempting ART [34]. Infection acquired shortly after embryo transfer may be not conductive to a clinical pregnancy and infection is better to avoided after embryo transfer and the best is

be vaccinated by 2-3 doses before ART cycle [34].

Effect of COVID-19 on Pregnancy

Pregnancy increase the susceptibility of women to the SARS-CoV-2 as a result of increased expression of the ACE2 receptors in response to blood pressure regulation, and due to changes in immune system induce tolerance to allogeneic embryo, in addition physiological changes, immunomodulation and psychological stress during pregnancy all contribute to severity and morbidity from infection [35].

Pregnant women with SARS-CoV-2 have increased risk of miscarriage, gestational hypertension, gestational diabetes and fetal growth restriction these may be related to placental function disturbance. There were lower platelets count with no significant differences in coagulation condition. Vertical transmission of the virus to the human embryo at early stage of development is theoretically possible since the receptors for entry was expressed on the placental tissues but to date there were no evidence for transmission of infection to the fetuses and many of its effect is due to persistent inflammation and impaired placental perfusion. Maternal inflammatory response can affect the fetal brain development by cytotoxic effect of cytokines and by autoantibodies transferred through the blood brain barriers binding to the receptors of neurotransmitters causing their neurological disorder. Falahi et al. (2023), have reported that in utero exposure may have a risk of neuropsychiatric disorder in the future life, and maternal immune response may be determined by the fetal sex as male fetuses has decreased placental and maternal immune response and fewer antibodies pass to the fetus increase their susceptibility to infection [36].

Sexual and Vertical Transmission of COVID-19

Viral localization in the semen is important to be excluded in studies to determine the possibility of sexual transmission, Abdollalpur et al. (2021), confirmed sexual transmission of the virus [37], while Cannarella R. 2024 describe a low possibility of sexual transmission of virus to partners since the virus is absent in the seminal fluid [38]. It is important to exclude viral transmission not only for the infection transmission but also to verify if spermatogonial cell infection is present and its implication on embryo.

Vertical transmission to the fetus require immunehistochemical or in situ hybridinization studies to diagnose the presence of SARS-CoV-2 by testing intrauterine tissues as chorionic cells from the placenta, amniotic fluid and umbilical cord. Positive PCR for SARS-CoV-2 in the oral, anal and nasopharyngeal swabs and blood samples were 2.5% to 6.5% , where as positive placental samples range from 0%-12%, umbilical cord tissue and blood was 0-3%, amniotic fluid positive cases was raging from 0%-2% and appositive IgM antibodies was 4%-33% a result from systematic review [39]. Ciapponi et al 2020, conclude that risk of intrauterine transplacental transmission is was very low although certainty of these results was lacking [40].

Effect of COVID-19 Vaccination

Mass vaccination for COVID with up to 13.3 billion anti –SARS-CoV-2 vaccine doses were administered worldwide has decrease the disease mortality and morbidity, however many reproductive age women and men are reluctant to take the vaccine because of lacking of information on vaccine safety on female reproductive system. Immunologic studies reveals that the infection with the virus triggers induction of the cascade for ACE2 mediators and TMPRSS2 on infected cells

leads to elevation in the host inflammatory responses cytokines storm as the main fatal factors in COVID these finding make prevention is essential by vaccine production and administration [41].

When female primary granulosa cells in the ovary exposed to the COVID vaccine develops alteration in mRNA transcript without altered viability with up-regulation of Inhibin B and down regulation of Antimullerian hormone and through these endocrine and paracrine hormones graulosa cells can affect and alter the hypothalamic pituitary ovarian axis, and by examining blood sample of women post vaccination there were 2-3 fold change in of FSH/Inhibin values, as altered inhibin expression will impact HPO axis altering endometrial cycle and bleeding pattern. While COVID-19 vaccine have no adverse effect on ovarian reserve parameters as AFC, AMH, FSH, and estradiol [42].

As the pandemic of COVID-19 has potential impact on ovarian reserve and has risk of premature ovarian failure, these issues are raised with long COVID infection and can only prevented by COVID vaccination and social isolation. Vaccine mRNA have no any detrimental effect on semen parameters nor on male reproductive system. Vaccination of couples improve pregnancy outcome in ART probably due to reduced rate on infection and there were no any unfavorable impact on ART program. Vaccination during pregnancy have no any specific pregnancy concern and many evidence support COVID-19 vaccination during pregnancy [43].

Conclusion

Effect of COVID-19 infection on Ovarian reserve marker remains controversial and further investigation is required to prove this and long term. COVID-19 has detrimental effect on spermatogenesis and sperm DNA integrity. Pregnancy and ART and in male and female with COVID-19 should be postponed till 3-6 month after as the virus effect has been resolved. Possibility of sexual transmission is not conformed yet and transplacental transmission to the fetus has low risk. Vaccination is the only methods to prevent COVID-19 and reduce its severity and it is safe on reproductive system and pregnancy.

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