



Potential Role of Zinc in the COVID-19 Disease Process and its Probable Impact on Reproduction

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Abstract

COVID-19 (coronavirus disease 2019) is the current world health crisis, producing extensive morbidity and mortality across all age groups. Given the established roles of zinc in combating oxidative damage and viral infections, zinc is being trialed as a treatment modality against COVID-19. Zinc also has confirmed roles in both male and female reproduction. The possible depletion of zinc with the oxidative events of COVID-19 is especially relevant to the fertility of affected couples. This review aims to present the pathophysiology of COVID-19, especially in relation to reproductive function; the role of zinc in the COVID-19 disease process; and how zinc depletion in concert with cytokine storm and reactive oxygen species production could affect reproduction. It also highlights research areas to better the understanding of COVID-19 and its impact on fertility and potential ways to mitigate the impact.

Keywords Coronavirus · Covid-19 · Reactive oxygen species · Zinc · Infertility

Abbreviations

COVID-19	Coronavirus disease-19
ROS	Reactive oxygen species
MPO	Myeloperoxidase
H ₂ O ₂	Hydrogen peroxide

Zinc Deficiency and COVID-19

The association between zinc deficiency and worse outcomes of respiratory viral infections has been established [1]. Hence, zinc is being trialed as a nutritional supplement that is being used either as a stand-alone intervention or in conjunction with other nutrients for the prophylaxis and the treatment of the coronavirus disease 2019 (COVID-19) infection [2]. The

well-documented roles of zinc in preventing cell damage and its anti-viral properties are helpful in explaining the potential role of zinc in COVID-19 management [3]. Furthermore, there is a degree of overlap between the symptomatology of COVID-19 and that of zinc deficiency.

Like the multiorgan damage and dysfunction characteristic of severe COVID-19 progression, zinc deficiency has far-reaching impacts, affecting the nervous, cardiovascular, thymic, immune, and endocrine systems [4]. Acute effects of zinc deficiency include hair loss, diarrhea, delayed sexual maturation, impotence, hypogonadism in males, and skin lesions [5]. Also, zinc deficiency has been associated with a higher risk of atherosclerosis, diabetes, rheumatoid arthritis, neurodegenerative disease, and obesity secondary to unrestrained chronic inflammation [6–8]. These pathologies, in turn, have been correlated with increased risk for COVID-19 related complications. To a certain degree, patients with these conditions are also likely to have fertility-related and pregnancy-associated complications. Pregnant women infected with COVID-19 have been documented to have poorer outcomes resulting in miscarriages, preterm births, cesarean sections, and perinatal deaths [9, 10]. Hence, reproduction at the time of COVID-19 is fraught with risks and the epigenetic changes on the male and female reproductive organs secondary to COVID-19 exposure is unknown. Reports indicating adverse effects of COVID-19 on male and female gametogenesis are emerging

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[11]. The potential impacts of SARS CoV-2 on the sperm and the oocyte and consequentially the embryo quality remains to be fully investigated.

Cytokine Storm, Reactive Oxygen Species, and Zinc

In COVID-19 infections, acute phase response and the resultant cytokine storm are causative factors for multiorgan damage. The deluge of inflammatory markers secondary to the cytokine storm results in the formation of unlimited quantities of reactive oxygen species (ROS) produced through activation of the mitochondrial respiratory chain, cytochrome P450 enzymes, peroxisomal fatty acid metabolism, and flavoprotein oxidases. In addition, COVID-19 infection is associated with the generation of interleukins, such as IL-6, and tumor necrosis factor (TNF α), which increase neutrophil myeloperoxidase (MPO) activity [12]. Excessive MPO activity can generate free iron through hemoprotein heme destruction, and free iron can in turn mediate the Fenton reaction to further produce ROS, including the highly reactive hydroxyl radical ($\cdot\text{OH}$) [13, 14]. Importantly, overproduction of each of the inflammatory markers and ROS, separately or collectively, has various degrees of impact on the male and the female reproductive system. For example, in the oocytes and embryos, even short-lived ROS such as $\cdot\text{OH}$ ($t_{1/2} = 10^{-9}$ s), superoxide ($\text{O}_2^{\cdot-}$) ($t_{1/2} = 5$ s), and peroxynitrite (ONOO^-) ($t_{1/2} = 10 \sim 20$ ms) have been shown to produce instant and irreversible effects by disimpacting the oocyte spindle and altering the chromosomal alignment [14, 15]. Similarly, mammalian oocytes exposed to IL-6 have a dose-dependent deterioration in microtubule and chromosomal alignment [16]. However, H_2O_2 and hypochlorous acid (HOCl) generated by the neutrophil MPO- H_2O_2 system are longer-lived signaling molecules that cause oocyte damage in a dose-dependent fashion [17, 18]. Also, sperm oxidative stress and resultant ROS are strongly associated with a significant reduction in fertilization rates and IVF/ICSI outcomes in mammals [19].

Another possible factor for the observed pathophysiology in critical cases of COVID-19 is a decline in nitric oxide (NO), a key mediator of vasodilation and also an important regulator of oocyte quality and aging [20] (Fig. 1). Nitric oxide bioavailability can decline in the presence of $\text{O}_2^{\cdot-}$ resulting in the generation of ONOO^- which results in cell damage. ROS overproduction and its detrimental effects on NO are also induced by intracellular zinc depletion, which consequentially causes dysfunction of zinc-dependent antioxidant proteins such as superoxide dismutase (SOD), catalases and glutathione (GSH), NO synthase dimer assembly, and the dysfunction of a number of zinc finger proteins, thereby resulting in mitochondrial damage, which further accentuates oxidative stress [21, 22]. Zinc also serves to inhibit NADPH oxidase and

antagonizes redox activity of the transition metals iron and copper, thereby decreasing ROS production [23]. Thus, zinc deficiency has potential impacts to all organ systems during the COVID-19 disease process and could also leave enduring impacts on the oocyte and sperm quality. Hence, supplementation of zinc to women seeking fertility, especially at the time of the COVID-19 pandemic could be valuable in improving oocyte, sperm, and embryo quality.

Zinc Supplementation and COVID-19

Zinc deficiency places the individual at an increased risk of infections and secondary complications, delayed recovery, decreased wound healing, and increased vulnerability to cell damage from the acute phase response [24]. There is a considerable overlap between the symptomatology of SARS CoV-2 infection and zinc deficiency. Some of the unusual COVID-19 symptoms such as loss of smell and taste are secondary to the enhancement of oxidative stress-mediated by ROS and neutrophil MPO activity and this has been well established in conjunction with zinc deficiency [25]. A comprehensive epidemiological study of childhood mortality identified zinc deficiency as one of the major causes of diarrhea and pneumonia in children [26]. This could also help explain how zinc supplement might help improve outcomes in patients infected with SARS CoV-2. Zinc supplementation in COVID-19 patients could limit the disease process not only by eliminating ROS but also by improving the immune response to the infection. Zinc has anti-inflammatory activity and inhibits NF-KB signaling and regulates T cell function to limit the cytokine storm. In vitro experiments have demonstrated that zinc possesses anti-viral properties through inhibition of SARS-CoV RNA polymerase. Indirect evidence has also established that zinc may decrease the activity of angiotensin-converting enzyme 2 (ACE2) which is a receptor for SARS COV-2 [27]. It also enhances the resistance of the cell to apoptosis by inhibiting caspase-3,-6,-9 [28]. Anti-viral properties of zinc are also related to the metallothioneins (MTs), zinc-binding proteins, the function of which is to store and transport zinc. The presence of reactive compounds or oxidative stress results in modification of the cysteine sulfur ligands of MTs, thereby releasing zinc ions, which in turn leads to increased intracellular free zinc concentrations. An overexpression of MTs has been established in patients infected with flaviviruses (e.g., yellow fever, HCV) and alphaviruses (Venezuela equine encephalitis virus). MTs may sequester zinc away from the viral metalloproteins, thereby facilitating anti-viral signaling [29]. Also, the zinc finger anti-viral protein (ZAP), a key component in interferon-mediated immune response, binds to the CpG dinucleotides in the viral genomes [30]. Subsequently, ZAP inhibits viral replication and mediates viral genome degradation [31].

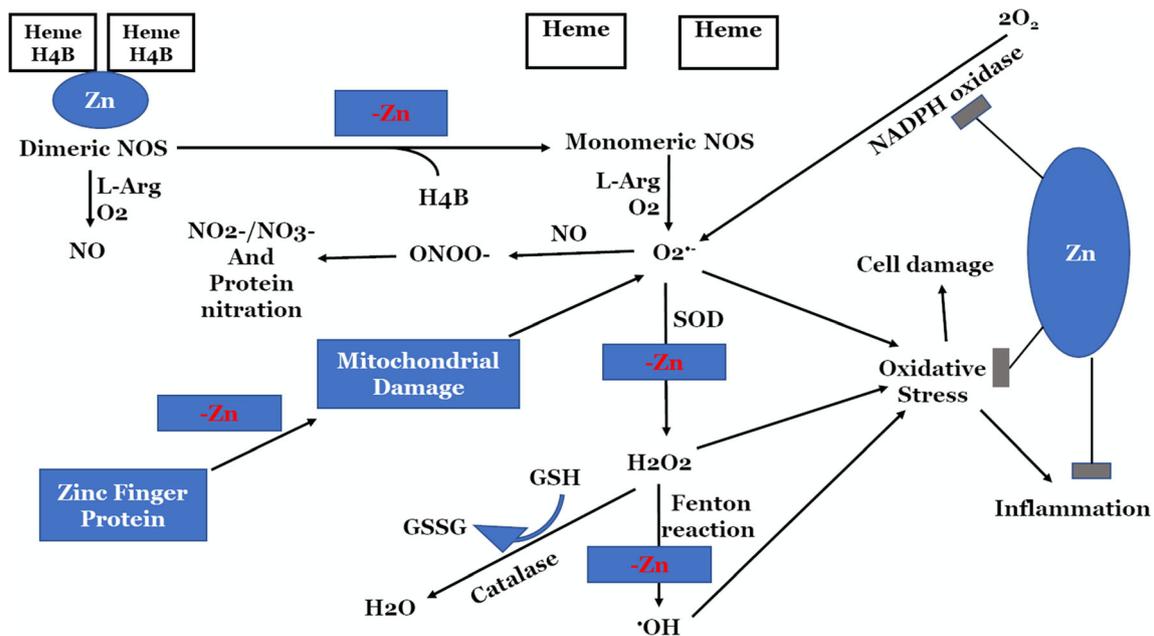


Fig. 1 The relationships between NOS, zinc, ROS, and related pathophysiology. Zinc is involved in attenuating oxidative events and is also required for NOS dimerization. Zinc deficiency not only directly

leads to oxidative stress through increased presence of ROS but also uncouples NOS, causing it to generate superoxide to further compound ROS elevation. These manifest as numerous detrimental conditions

Therefore, zinc has a clearly established role in the immune response to viral infections [32]. Studies show positive effects of therapeutic zinc treatment on viral replication or infection-related symptoms of viruses and viral diseases such as rhinovirus-associated cold symptoms, herpesviruses, picornaviridae, flaviviridae, togaviridae, retroviridae: HIV, and papillomaviridae [33].

Current literature on zinc supplementation in COVID-19 is limited to a very small retrospective study in hospitalized patients that did not demonstrate a causal association between zinc supplements and improved prognosis and survival [34]. While larger and more comprehensive studies are urgently needed to inform this discussion, zinc could indeed be of limited value once the patient is sick enough to be hospitalized. After the patient experiences the cytokine storm, the resultant proinflammatory response causes extensive oxidative damage and ROS production. This would deplete intracellular zinc, more rapidly so in zinc-deficient individuals. Hence, the enzymes that help with the clearing up of the ROS elements become nonfunctional, paving way for acute irreversible cell damage. Zinc supplementation, especially by itself, may be insufficient to reverse the process once widespread acute and oxidative cell damage has occurred. However, if administered to COVID-19 infected individuals in the pre-cytokine storm phase, repletion of zinc in the body might help ameliorate COVID-19 progression in the mild and early phases by both suppressing viral replication as well as by preventing cell damage by acting as a pro-antioxidant.

Zinc and Reproduction

Zinc is an essential element for the functioning of both the male and the female reproductive organs and for completion of meiosis and creating good quality blastocysts. With our current understanding of zinc in the reproductive process, its critical role in determining the sperm, the oocyte, and the embryo quality is well established in mouse and human model [35, 36] (Table 1). Zinc chelation in mouse oocytes and embryos has been demonstrated to decrease intra-oocyte zinc concentration, increased intracellular ROS levels, and changes to the oocyte spindle morphology with poorer quality spindles noted at decreasing intracellular zinc levels [37]. Zinc is the key regulator of meiosis in the oocyte. Zinc spark is the phenomenon whereby the post-fertilization concentration of zinc in the zona pellucida increases by 300%. Zinc spark has direct biological consequence as this results in hardening of the zona pellucida which consequentially blocks polyspermy and is associated with better blastocyst and embryo quality [38, 39]. Hence, maternal zinc deficiency in mammals produces effects ranging from infertility, embryo/fetal death, prematurity, decreased postpartum immunity, impaired wound healing, and an increased risk of neurobehavioral abnormalities [40–43]. Zinc deficiency is associated with teratogenesis and intrauterine growth restriction during pregnancy [44–47].

Zinc is also a crucial modulator of male reproductive function. It is a vital anti-inflammatory factor involved in the oxidative metabolism of the sperm. Its other roles include sperm membrane stabilization, capacitation, and acrosomal reaction

Table 1 Functions of zinc in male and female reproduction

Functions of zinc in male reproduction	Functions of zinc in female reproduction
Oxygen intake of spermatozoa	Sexual maturation
Nuclear chromatin condensation	Development of the breast and genitalia
Acrosomal reaction	Estrous production
Acrosin activity	Oocyte maturation
Sperm chromatin stabilization	Cumulus expansion
Testicular steroidogenesis	Gene expression in vitro
Testosterone synthesis	Maintenance of pregnancy
Testicular development	Fetal growth—teratogenesis/IUGR in deficiency
Conversion of testosterone to dihydrotestosterone (DHT)	Postpartum immunity and emotional well being

[48, 49]. In the testis, zinc is vital for the production and secretion of testosterone from the Leydig cells, maintaining genomic integrity of the sperm and sperm assembly [50]. Accordingly, zinc deficiency is also associated with low serum testosterone concentrations, primary testicular failure, lessening function of the luteinizing hormone receptor, decreased steroid synthesis, and Leydig cell damage due to oxidative stress [51, 52]. Inflammatory process associated with various disorders and higher body temperature induces ROS and also leads to testicular malfunction and altered sperm production [53]. In smokers and infertile men, increased ROS levels in the seminal plasma result in seminal fluid zinc deficiency which sequentially produces abnormal sperm parameters [54]. We believe that the SARS CoV-2 induced cytokine storm, like cytokine storm in other conditions, would similarly increase ROS in the gametogenic cells and deplete intracellular zinc, potentially resulting in oocyte and sperm damage. Zinc deficiency further showed that it can mediate the ROS overproduction and potentiate oocyte and sperm damage through the same mechanism. Hence, zinc depletion and ROS appear to have a bidirectional relationship resulting in a vicious cycle with one aggravating the effects of another.

Zinc Supplementation in COVID-19 Patients Desiring Fertility

Although zinc supplementation in COVID-19 patients has been implemented and analyzed to an extent, data regarding the effects of zinc supplementation on the fertility of couples with COVID-19 exposure remains scarce. The effects of zinc supplementation on the oocyte quality are difficult to reciprocate in vivo, as obtaining and analyzing the oocyte is an invasive procedure. However, zinc deficiency has been established to cause disruption of the post-implantation fetal and placental development in mice [55]. Also, the only available literature of in vitro testing on mouse metaphase 2 oocytes has established that zinc deficiency causes oocyte deterioration and embryo damage through a mechanism involving

overproduction of ROS [56]. The study of zinc supplementation on sperm quality has been undertaken and has been proven to be of value. Zinc supplementation has been demonstrated to protect against chemotherapy-induced testicular damage, with better sperm counts noted in the group of patients treated with zinc supplementation [57]. Also, supplementation of zinc alongside folic acid significantly improved sperm parameters in subjects post varicocelelectomy [58]. In our opinion, supplementation of zinc to both male and female partners seeking fertility during the COVID-19 pandemic could help protect against gametogenic damage, possibly improving embryo quality, and potentially lessening some of the pregnancy complications.

Conclusions

With the initial advent of the SARS CoV-2 virus infection in March 2020, the American Society of Reproductive Medicine (ASRM) noted the highly infectious nature of the disease and the potential complications associated with pregnancies, and advised suspension of all new treatment cycles and cessation of embryo transfers (<https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforce.pdf>). However, the current widespread recent resurgence of SARS COV-2 transmission that has currently exceeded 12 million cases in the USA alone, reaffirms the need to practice reproductive health in a COVID-19 environment for the foreseeable future. Given the crucial roles of zinc in reproduction and its beneficial effects as an anti-oxidant and anti-inflammatory agent, a policy of zinc supplementation to men and women aiming to conceive either through natural or through assisted reproduction may prevent mitochondrial damage and avoid the accumulation of ROS in the oocyte and spermatogonia. It may also enhance immunity against the virus, which could in turn improve pregnancy outcomes. In the general population, zinc supplementation could be beneficial in both enhancing immunity and in fighting against the viral disease process. Though higher doses of zinc have been

used in current COVID-19 clinical trials, until we have robust data, all adults could be supplemented with up to a maximum of 50 mg/day without significant toxic side-effects. Presently, there are multiple studies registered with the WHO that aim to look at the value of zinc, either in the oral or in the intravenous form in patients affected with COVID-19 (<https://www.who.int/ictrp/search/en/>). The results of these studies, when available, will further elucidate the value of zinc in the setting of COVID-19, especially in the reproductive age group.

Compliance with Ethical Standards

Research Involving Human Participants/Animals This manuscript did not make use of human or animal participants or samples.

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent N/A

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