



Rescuing fertility during COVID-19 infection: exploring potential pharmacological and natural therapeutic approaches for comorbidity, by focusing on NLRP3 inflammasome mechanism.

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Abstract

The respiratory system was primarily considered the only organ affected by Coronavirus disease 2019 (COVID-19). As the pandemic continues, there is an increasing concern from the scientific community about the future effects of the virus on male and female reproductive organs, infertility, and, most significantly, its impact on the future generation. The general presumption is that if the primary clinical symptoms of COVID-19 are not controlled, we will face several challenges, including compromised infertility, infection-exposed cryopreserved germ cells or embryos, and health complications in future generations, likely connected to the COVID-19 infections of parents and ancestors. In this review article, we dedicatedly studied severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) virology, its receptors, and the effect of the virus to induce the activation of inflammasome as the main arm of the innate immune response. Among inflammasomes, nucleotide oligomerization domain-like receptor protein, pyrin domain containing 3 (NLRP3) inflammasome pathway activation is partly responsible for the inflicted damages in both COVID-19 infection and some reproductive disorders, so the main focus of the discussion is on NLRP3 inflammasome in the pathogenesis of COVID-19 infection alongside in the reproductive biology. In addition, the potential effects of the virus on male and female gonad functions were discussed, and we further explored the potential natural and pharmacological therapeutic approaches for comorbidity via NLRP3 inflammasome neutralization to develop a hypothesis for averting the long-term repercussions of COVID-19. Since activation of the NLRP3 inflammasome pathway contributes to the damage caused by COVID-19 infection and some reproductive disorders, NLRP3 inflammasome inhibitors have a great potential to be considered candidates for alleviating the pathological effects of the COVID-19 infection on the germ cells and reproductive tissues. This would impede the subsequent massive wave of infertility that may threaten the patients.

Keywords COVID-19 · Fertility management · Inflammasome · NLRP3 · SARS-CoV-2

Introduction

The respiratory system was primarily considered the only organ affected by Coronavirus disease 2019 (COVID-19). As the pandemic continues, there is an increasing concern from the scientific community about the future effects of the virus on male and female reproductive organs, infertility,

and, most significantly, its impact on the future generation [1, 2].

While the long-term effects of COVID-19, caused by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), are yet to be investigated, researchers found some insights from previously known coronaviruses [3]. However, it is still controversial whether the infection transmits sexually and impacts the next generation's health and well-being, considering the presence of the virus in the semen and testis tissues [4]. Assessing gene alterations in patients affected by SARS-CoV-2 and understanding how this infection interrupts, various aspects of reproduction provide valuable molecular insights into the infection mechanism. This

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potentially improves our current interventional programs by considering infertility prevention as part of the integrated care strategies at the time of COVID-19 pandemic. In addition, reproductive societies decided to resume assisted reproductive procedures based on inaccurate findings about the long-term consequences of the virus infection [5]. The general presumption is that if the primary clinical symptoms of COVID-19 are not controlled, we will face several challenges, including compromised infertility, infection-exposed cryopreserved germ cells or embryos, and health complications in future generations, likely connected to the COVID-19 infections of parents and ancestors [6].

Since infertility is a time-sensitive situation, by discovering and controlling the main effects of COVID-19, especially at reproductive age or before puberty, the potential side effects of the disease can be suppressed in the acute phase, and subsequently, its accompanying risks on male or female reproductive organs be reduced [7].

In this review article, we dedicatedly studied SARS-CoV-2 virology, its receptors, and the effect of the virus to induce the activation of innate immune response. The activation of innate immunity in SARS-CoV-2 infection results in the systemic elevation of inflammatory biomarkers and the subsequent “cytokine release syndrome” or “cytokine storm,” which is characterized by high levels of cytokines in the plasma. Inflammasomes, as the main arm of innate immunity, play a key role in these processes. Among inflammasomes, nucleotide oligomerization domain-like receptor protein, pyrin domain containing 3 (NLRP3) inflammasome pathway activation is partly responsible for the inflicted damages in both COVID-19 infection and some reproductive disorders, so the main focus of the discussion is on NLRP3 inflammasome in the pathogenesis of COVID-19 infection alongside in the reproductive biology. We also discussed the potential effects of the virus on male and female gonad functions, and further explored the potential natural and pharmacological therapeutic approaches for comorbidity via NLRP3 inflammasome neutralization to develop a hypothesis for averting the long-term repercussions of COVID-19.

SARS-CoV-2, its receptor, and the mechanism of virus entry into cells

Viruses generally attach to the relevant receptors on the target cells in order to enter into the cells and infect them. So, the infectivity and disease severity of the viruses correlates with the abundance of these receptors [8]. SARS-CoV-2 is no exception. It attaches to a cellular transmembrane protein called angiotensin-converting enzyme 2 (ACE2), the key receptor for the SARS-CoV-2 cell entry, and its infectivity [9, 10]. ACE2 is also the cell surface receptor for SARS-CoV,

another member of the human coronaviruses that caused the 2002–2004 outbreak of the severe acute respiratory syndrome (SARS), with about 79% sequence similarity to SARS-CoV-2 [11, 12]. A comprehensive studies have identified 380 amino acid variations between these coronaviruses, which may have resulted in functional and pathogenic divergence of new one [13] that briefly includes important mutations in the receptor-binding domains, 27 amino acid substitutions in the spike protein with a length of 1273 amino acids, and four substitutions in the C-terminal of the receptor-binding subunit S1 domain of SARS-CoV-2, compared with SARS-CoV [14, 15]. Furthermore, it was shown that SARS-CoV-2 ACE2 protein has a stronger binding affinity than SARS-CoV receptor [16, 17].

ACE2 expresses abundantly in lung alveolar epithelium and small intestine enterocytes [18], which might be the reason for the hypervulnerability of respiratory and gastrointestinal organs to COVID-19 infection [19–22]. ACE2 also expresses in the kidney, liver, spleen, and testes and could be responsible for various clinical manifestations of the disease, such as liver diseases [18, 23–25].

The spike (S) glycoprotein of the SARS-CoV-2 contributes significantly to the attachment of the SARS-CoV-2 to ACE2 and the fusion of the virus with the membrane of the target cell [8, 10, 26]. The spike glycoprotein also needs to be proteolytically activated by the host cells to enable the virus to enter the cell. It seems that SARS-CoV-2 infiltration of lung cells can lead to the down-regulation of membranous ACE2 in the host cell [27]. Underexpression of ACE2 has been reported in the lung tissue of SARS-CoV-infected mice [28, 29]. Angiotensin II, an octapeptide that enhances blood pressure through a vascular contraction with pro-inflammatory activities, also increases in COVID-19 patients' circulation [27, 30]. Angiotensin II is converted from angiotensin I by ACE. In this process, ACE2 plays a protective role by converting angiotensin II to heptapeptide angiotensin-(1-7), an antagonist for angiotensin II [8, 28]. So, severe complications in SARS-CoV-2 infected patients could be explained, in part, by the loss of ACE2-expressing lung epithelium, leading to perturbation in the renin-angiotensin system that eventually escalates inflammation [31].

SARS-CoV-2 S protein is a trimer glycoprotein comprised of S1 and S2 subunits. S1 heads are the receptor-binding domains (RBD) responsible for the attachment of the virus to the ACE2 on the target cell, and S2 stalks are the responsible section for the membrane fusion. SARS-CoV-2 also uses the trans-membrane protease serine 2 (TMPRSS2) for S protein priming [32]. In fact, the S-protein of SARS-CoV-2 utilizes TMPRSS2 and ACE2 to get primed and enter into target cells [32–34].

The significance of the NLRP3 inflammasome pathways in the pathophysiology of SARS-CoV-2 infection

In SARS-CoV-2 infection, the activation of innate immunity leads to the systemic elevation of inflammatory biomarkers (such as D-dimer, ferritin, and C-reactive protein) and the subsequent “cytokine release syndrome” or “cytokine storm” characterized by high levels of cytokines including IL-6, TNF- α , IL-8, IL-10, IL-1RA, and CXCL10 in the plasma [35]. Inflammasomes, as an important arm of innate immunity, have a crucial role in these processes [36, 37]. NLRP3 inflammasome is one of the most studied mechanisms in innate immune cells, such as macrophages, neutrophils, dendritic cells [38–40], and tissues [41, 42]. NLRP3 consists of a sensor (NLRP3), an adaptor protein (apoptosis-associated speck-like protein containing a caspase recruitment domain, ASC), and an effector (procaspase 1) [43].

SARS-CoV-2 induces NLRP3 inflammasome activation by different mechanisms. It has shown that open reading frame 3a (ORF3a), a viroporin encoded by SARS-CoV-2, mediates cellular K⁺ efflux, a common trigger of NLRP3 activation [44]. Viroporins are virus-encoded proteins that integrate into the plasma membrane and mediate ions influx/efflux in the cell [43, 45]. Protein E, another viroporin of SARS-CoV-2, also enhances Ca²⁺ influx across the plasma

membrane and endoplasmic reticulum membrane. Excessive intracellular calcium causes lysosomal rupture and leakage of digestive proteases into the cytosol leading to cell death [46, 47]. Mitochondrial damage and generation of reactive oxygen species (ROS) are other downstream of intracellular ion imbalance that contribute to NLRP3 inflammasome activation [47, 48]. NLRP3 inflammasome activation is a two-phase process and can be described as follows: The first step is priming, resulting in NF- κ B activation and higher expression of NLRP3 inflammasome components. The second step is inflammasome assembly, during which ASC interacts with the NLRP3 and recruits procaspase-1 [49, 50]. Then, NLRP3 inflammasome activation induces cleavage of inactive procaspase-1 to active cysteine protease caspase-1, leading to activation of pro-interleukin 1 β (pro-IL1 β) and pro-interleukin-18 (pro-IL18) to form IL1 β and IL18, respectively, both of which recruit neutrophils to the inflammatory sites and cause resultant tissue damage (Fig. 1) [49, 51]. In addition, following inflammasome activation, activated Caspase 1 cleaves gasdermin D (GSDMD), which is incorporated into the plasma membrane and forms a pore. GSDMD increases the release of IL-1 β and IL-18 and causes H₂O influx. It leads to cell swelling and programmed cell death “pyroptosis,” and the release of pro-inflammatory intracellular components and cytokines (Fig. 1a) [36, 52, 53].

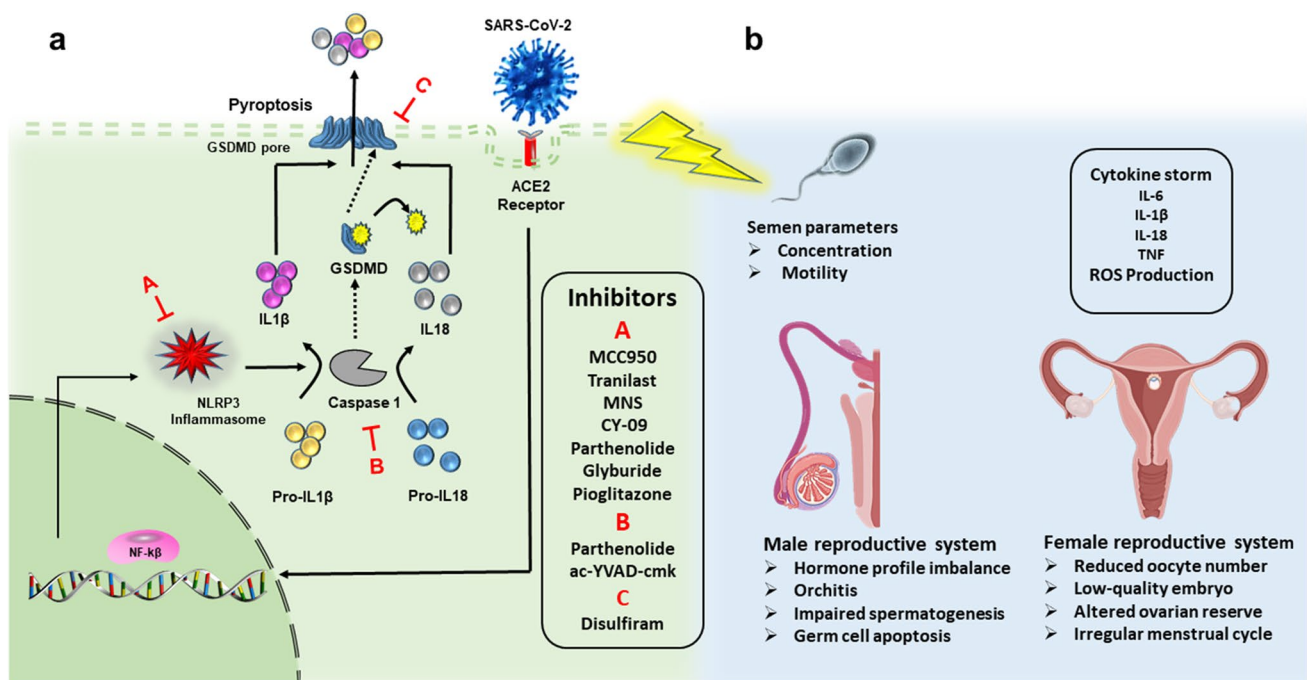


Fig. 1 NLRP3 Inflammasome activation, its inhibitors, and consequences of SARS-CoV-2 on reproductive organs. **a** NLRP3 inflammasome activation by virus-intrinsic pathway and different inhibitors.

b Some of the known consequences of SARS-CoV-2 on male and female reproductive organs. Some icons were created with BioRender.com

NLRP3 inflammasome can be antagonized via several pathways in order to hinder the excessive inflammatory response. For example, the generation of destabilized subunits via proteolytic cleavage of caspase-1 leads to the termination of caspase-1 activation [54]. Chaperone-mediated suppression of NLRP3 inflammasome was also reported previously [55]. Furthermore, pyrin-only protein (POP2) and CARD-only proteins (COPs) have been shown to inhibit inflammasome assembly by interacting with ASC and caspase-1, respectively [37, 56]. Although precise cellular mechanisms regulate and terminate NLRP3 inflammasome activity, the aberration in NLRP3 inflammasome function is the main reason for tissue damage and cytokine storm in COVID-19 patients [35].

Considering the critical role of NLRP3 and inflammasomes in COVID-19 pathophysiology, better understanding of the mechanisms of antagonizing this pathway can offer new interventional strategies for current and/or future SARS-CoV outbreaks [35, 57, 58].

Potential effects of COVID-19 on the reproductive systems

Male reproductive organ: a plausible target for the SARS-CoV-2 virus

A growing body of research suggests COVID-19 can infect several organs expressing ACE2 receptors, including the male reproductive system [59, 60]. The presence of the virus or its particles in COVID-19 patient semen has been reported, leading to the speculation that the SARS-CoV-2 could penetrate the blood-testis barrier (BTB), entering the testicular micro-environment [61, 62]. Besides, scrotal discomfort and orchitis have been reported in 19% of COVID-19 men as clinical manifestations of the disease [63]. The pathophysiology mechanisms underlying these symptoms may be related to the vital role played by the ACE receptor and the cytokine storm in the manifestation and transmission of pain in COVID-19 patients [64]. Increased thickening of the seminiferous tubule basement membranes, leukocyte infiltration, orchitis, and impaired spermatogenesis have been reported in postmortem studies of SARS-CoV infected cases, and the high similarity of genome sequences between SARS-CoV and SARS-CoV-2 suggests that the same complications might develop in COVID-19 patients [2, 61, 65, 66].

SARS-CoV-2 could indirectly or directly attack the male reproductive system. Higher levels of both ACE2 and TMPRSS2 were reported in seminiferous tubules of COVID-19 patients [67], and the elevated concentration of ACE2 receptors in this tissue was reported to lead to lower spermatogenesis [60]. ACE2 receptor could mediate activation

of NLRP3 inflammasome in male reproductive organs in two ways: first, facilitating SARS-CoV-2 entry into the cell and triggering NLRP3 activation in the testicular tissue, particularly in Leydig and Sertoli cells, disrupting the organ functions [68]. Furthermore, COVID-19-induced ACE2 downregulation in testicular cells promotes Angiotensin II upregulation, which in turn activates the NLRP3 inflammasome and pro-inflammatory response in testes [69, 70].

On the contrary, several studies reported the absence of virus (or viral particles) in patients' semen and summarized that COVID-19 directly damage testes by increasing pro-inflammatory cytokines in the organ [71, 72]. A recent study on the testes of 12 deceased COVID-19 patients demonstrated that although RT-PCR did not detect the virus genome in the semen of 90% of patients, and the electron microscopy yielded negative results in all cases, Sertoli and Leydig cells were extensively damaged in infected patients [73]. Injured Sertoli cells lose their ability to nourish developing sperm cells, eventually disrupting spermatogenesis [74]. The damage to Leydig cells also dysregulates testosterone production [75], which could explain the decreased ratio of testosterone to LH and FSH to LH in COVID-19 male patients, as such disruption pattern is highly associated with Leydig cells dysfunction and hypogonadism [76–78].

In addition, TMPRSS2 expression has been reported in spermatogonial stem cells, epididymal luminal epithelial cells, elongated spermatids, and prostate luminal epithelial cells. As a result, these tissues can potentially serve as a host if they are exposed to the virus [79].

Female reproductive system is vulnerable to SARS-CoV-2 infection

Until now, there is known and unknown information about SARS-CoV-2 in female reproductive organs [80]. Meta-analysis of high-throughput gene and protein expression data from online repositories revealed that various reproductive organs and tissues are possible SARS-CoV-2 contamination sites [1, 81]. Several cell types in human female reproductive organs, such as fallopian tubes, the ovary, cervix, and endometrium, have been shown to express putative receptors (like ACE2) for SARS-CoV-2 infection [2, 82]. ACE2 plays crucial roles in the different functions of the ovary, including promoting steroid hormone production and secretion, aiding follicle growth and oocyte development, regulating early stages of ovulation, and maintaining the function of the corpus luteum [83–85].

Recent studies revealed the effects of SARS-CoV-2 infection on the different aspects of female fertility and investigated whether the female reproductive system is vulnerable to SARS-CoV-2 infection [86–89]. Expression patterns of SARS-CoV-2 receptor proteins, ACE2 and TMPRSS2, in endometrial tissue, uterine smooth muscle, decidual stromal

cells, and extravillous trophoblast suggest the vulnerability of these organs to viral infection [90]. Interestingly, the susceptibility to diseases rises with the patient age because ACE2 shows a moderately increased endometrial expression with age [91]. Moreover, altered ovarian reserve, considerable menstrual changes, and hormonal imbalance were reported in females with SARS-CoV-2 infection [86]. Bentov et al. (2021) evaluated three groups of females in a cohort study, including vaccinated, recovered from confirmed COVID-19, and non-vaccinated, and reported that COVID-19 has no negative impact on ovarian follicle activities such as the number of retrieved oocytes, oocyte yield, mature oocytes, and oocyte quality biomarkers in the follicular fluid [92]. Interestingly, a comparison of FSH levels in patients undergoing IVF treatment before and after the pandemic revealed a trend of increased FSH levels in post-pandemic patients, which has been associated with lower pregnancy rates [93]. However, anti-Müllerian hormone (AMH) levels were not different between women with COVID-19 and the control group in any of the published studies [86, 94, 95]. Wang et al., in a retrospective cohort study, compared SARS-CoV-2 exposed and unexposed women and reported a significant difference in blastocyst formation rate but not in the number of recovered oocytes, maturation rate, fertilization rate, and biochemical and clinical pregnancies [96]. On the other hand, Herrero et al. [88] and Orvieto et al. [97] reported a lower number of retrieved and mature oocytes and a reduced number of top-quality embryos in the women exposed to SARS-CoV-2.

Taken together, the expression patterns of the ACE2 and TMPRSS2 in the male and female reproductive tissues support the idea that the virus can infiltrate these compartments and promote a chain of pathophysiological processes leading to tissue architecture change and host cell apoptosis. Some of the known consequences of SARS-CoV-2 on male and female reproductive organs are shown in Fig 1b.

SARS-CoV-2, fertility disorders, and their common players

Since SARS-CoV-2 infection causes a variety of humoral and cellular immunological responses, one way to overcome COVID-19 long-term implications and reverse the deterioration of patient health is to control cytokine storm or inflammation responses [98]. In this context, several candidates have been suggested. Among them, NLRP3 is a common immune mediator in organ damage, either respiratory system or reproductive tissues, accompanied by multisystem infections [47]. Excess activation of NLRP3, as the most important and best-studied inflammasome, and its signaling pathway in male and female reproductive systems have recently been shown to induce an imbalance of inflammatory

and pro-inflammatory cytokines, resulting in infertility, miscarriage, preeclampsia, gestational diabetes, preterm labor, reproductive aging, PCOS, and endometriosis [99, 100]. Therefore, developing an approach to its blockade might be a hopeful and promising treatment strategy for both comorbidities [101].

Inflammasome in reproductive biology

NLRP3 in male infertility

Several inflammatory and non-inflammatory mechanisms have been associated with male sub/infertility pathologies. Some reports are showing the involvement of NLRP3 inflammasome in conditions leading to male infertility, including spinal cord injury (SCI), varicocele, and, more recently, COVID-19. In testes, NLRP3 is expressed in Sertoli cells and its overexpression by infection or sterile stimuli can lead to dysregulation of spermatogenesis and male infertility [102]. Studies revealed that following SCI, BTB disruption, leukocyte infiltration, increased apoptosis of sperm cells, and elevated inflammatory cytokines lead to induction of an inflammatory niche in the testis [103–105]. NLRP3 inflammasome and its end products (IL1 β and IL-18) are elevated in the semen of these patients, which has a toxic effect on sperm quality. They present lower motility and viability while the normal concentration of sperm compared to the control group. Ibrahim et al. supported these findings in their study of treating semen with an antibody against ASC, leading to the inhibition of NLRP3 inflammasome and a subsequent significant improvement in sperm motility in SCI patients [106]. A research study found that malondialdehyde, which serves as a marker of oxidative stress, increased significantly in the testis of rats after seven days of SCI. The simultaneous increase in malondialdehyde and NLRP3 expression suggests that the generation of high levels of ROS in the testis might be responsible for NLRP3 inflammasome activation and impaired function of the testis in these patients [107].

Studying infertile men with oligozoospermia and accessory gland inflammatory alterations, Milardi et al. reported that the treatment with prednisolone, which acts as an anti-inflammatory agent, could improve sperm motility and concentration, possibly by reducing leukocyte infiltration and pro-inflammatory cytokines in their genital tract [108]. Considering the role of leukocytes in inflammation response, in some experiments, the leukocytes were removed from the sperm suspension to evaluate the contribution of sperm alone to NLRP3 inflammasome activation. The findings showed that the high expression of ASC and caspase-1 in these patients is not a sequel of either leukocytes or

sperm cells, but both act in concert. The generation of high amounts of reactive oxygen species (ROS) by leukocytes and sperm cells results in oxidative stress, which is a significant reason of inflammasome activation [109–111].

Varicocele, a major cause of male infertility, has been shown to be associated with NLRP3 inflammasome activation [112]. A recent study confirmed that the level of IL-1 β , ASC, and NLRP3 significantly increased in the seminal plasma of varicocele patients and that resveratrol, a powerful antioxidant, diminished the expression levels of NLRP3 inflammasome components in the testis of varicocele rats. Therefore, ROS production has been linked to NLRP3 inflammasome activation in the testis of infertile varicocele men [113, 114].

Muckle-Wells syndrome, a rare auto-inflammatory disorder caused by gain-of-function mutations in NLRP3, may contribute to perturbed spermatogenesis and male sterility [115]. Overproduction of IL-1 β due to the permanent activity of the NLRP3 inflammasome is demonstrated to inhibit testosterone production in Leydig cells, which is considered a key contributing factor of male infertility in this syndrome [102].

In testicular ischemia/reperfusion injury, inflammatory cell infiltration, high levels of ROS, and NLRP3 inflammasome activation are particularly involved in testicular dysfunction and disturbed spermatogenesis [116, 117]. A study on a mouse model of testicular ischemia/reperfusion injury reported NLRP3 signaling blockade resulted in reduced pro-inflammatory cytokines and improved testicular function [118].

Obesity linked to chronic inflammation and inflammatory status in reproductive tissue might lead to male infertility. A study reported that high-fat-diet-induced obese mouse model shows poor sperm quality and a lower fertility rate. In a subsequent study on a high-fat-diet-induced obese mouse model and overweight males, they showed a direct relation between obesity-related infertility and high levels of NLRP3 and pro-inflammatory cytokines in the epididymis, prostate, and especially in the testis, suggesting an association between the NLRP3 inflammasome complex and obesity-induced infertility [119, 120].

Inflammasome and female infertility

The NLRP3 inflammasome has been linked to several different high-risk female reproductive diseases, including recurrent spontaneous abortion (RSA), polycystic ovarian syndrome (PCOS), especially in overweight patients, endometriosis, gestational diabetes mellitus, and preterm birth [121].

The pathophysiology of PCOS is still controversial, and numerous studies have suggested that chronic inflammation is implicated. Some PCOS women appear to have

higher levels of androgen, oxidative stress, and free fatty acid (FFA) elements that act as danger signals to trigger the inflammasome pathway, particularly the NLRP3 one [122]. The cytokines implicated in the NLRP3 pathway have critical roles in regulating ovarian steroidogenesis and ovarian follicle development. Also, IL-18 expression was dramatically enhanced in PCOS patients. On the other hand, because IL-1 β reduces adipose tissue insulin sensitivity by decreasing insulin signaling, reducing its activity or synthesis may improve insulin signaling [123, 124].

Aging is a physiological process in which various parameters play roles, entailing progressive destruction of physiological and metabolic homeostasis, inflammation included [125, 126]. Female infertility is a process that can be affected by aging as one of its physiological contributors [127, 128]. Studies have shown that NLRP3 is involved in the process of infertility related to physiological aging. Interestingly, the ovarian aging process can be hindered, to some extent, by using NLRP3 inhibitors [125, 126].

As mentioned earlier, inflammation is involved in different aspects of a normal and pathological pregnancy, such as implantation, pregnancy maintenance, and parturition [129–131]. More interestingly, various components of the inflammasome pathway are detectible in gestational tissue. NLRP3 has been detected in peripheral leukocytes of pregnant women, in placentae throughout the pregnancy, in the chorioamniotic membranes, as well as in myometrial tissues at term pregnancy [132–135]. In contrast, an unrestricted level of inflammation can have negative impacts on female fertility [136]. Intra-amniotic infection and sterile intra-amniotic inflammation are two conditions associated with inflammation that may result in pathological at-term pregnancies. The former is inflammation with detectible microorganisms in the amniotic fluid, but the latter is inflammation without detectible microorganisms [137]. Studies have demonstrated that NLRP3, activated forms of caspase-1, IL-1 β , and IL-18, are involved in the inflammation that occurs in histologic chorioamnionitis [138–140]. Therefore, Gomez-Lopez et al. suggested that inflammasomes play roles in the pathological inflammation that occurs in the pregnancies at term, which are associated with intra-amniotic infections [141]. It has also been revealed that inflammasome and NLRP3 are involved in the preterm labor associated with sterile intra-amniotic inflammation [142, 143]. NLRP3 inflammasome plays a role in the progression of preeclampsia, as the escalated levels of NLRP3, caspase-1, and IL-1 β in the placentas of women with severe preeclampsia has been reported [144, 145].

In summary, based on the above-mentioned studies, inflammation, which comes from the earlier activation of the inflammasome, is a game-changing factor in physiological and pathological pregnancy, female reproductive disorders;

on the other side, uncontrolled activation of inflammasome can also affect female fertility.

NLRP3 inflammasome inhibitors: killing two birds with one stone

Since NLRP3 inflammasome is linked to a wide variety of disorders, there is a substantial amount of investment in the scientific community to find inhibitors of NLRP3 inflammasome that are both efficient and reliable. An array of targets is available for suppressing the NLRP3 inflammasome by utilizing its complicated signaling cascade [146]. For instance, inhibition of NLRP3 inflammasome activation, suppression of upstream and/or downstream signals, blockade of inflammasome assembly and Gasdermin D (GSDMD) cleavage, inhibition of caspase-1 activation, and neutralization of the cytokines produced by the NLRP3 inflammasome can all be tailored for the prospective inhibition of the NLRP3 inflammasome [147].

Because SARS-CoV-2 can provoke humoral and cellular immunological responses, one proposed approach to overcome COVID-19 long-term implications is to reduce inflammasome activation using inhibitors targeting the NLRP3 inflammasome and its downstream pathways [57]. Taken together, pathological effects on reproductive tissues and germ cells may also be prevented by using inflammasome inhibitor drugs.

Natural NLRP3 inflammasome inhibitors

Dietary micronutrients may have preventive or therapeutic effects on NLRP3 as the upstream activators of inflammatory responses [148]. The immune system-boosting, antiviral, and anti-inflammatory properties of different nutraceuticals have been well-documented [149]. Among them, 1,25-dihydroxyvitamin D₃ (1,25(OH)₂ D₃, VitD₃, calcitriol), γ -tocopherol (vitamin E), vitamin C (ascorbic acid), and cinnamaldehyde (organic compound in cinnamon) could be effective against inflammation via down-regulation of the inflammatory response mediated by NF- κ B/NLRP3 [150–153]. Interestingly, serum vitamin D levels are shown to be inversely associated with the prevalence or severity of COVID-19 in several studies [154, 155].

Nicotinic acid (NA, vitamin B₃) and pyridoxine (vitamin B₆) exert their anti-inflammatory effects by inhibiting NLRP3-dependent caspase-1 processing and the subsequent secretion of mature IL-1 β and IL-18 [156, 157]. VitD₃ (as the co-activator of vitamin D receptor (VDR)) also suppresses NLRP3 inflammasome via a different mechanism, including inhibiting caspase-1 activation,

reducing IL-1 β secretion, and preventing NLRP3-mediated ASC oligomerization. Interestingly, there is a direct interaction between VDR and NLRP3 by which vitamin D treatment results in attenuating the inflammatory response mediated by NF- κ B/NLRP3 [150].

Riboflavin (vitamin B₂) prevents mitochondrial ROS production and DNA damage, which triggers the NLRP3 inflammasome assembly. Furthermore, this vitamin disrupts the activity of caspase-1 and inhibits the absence in melanoma 2 (AIM2), NLR family-CARD domain containing 4 (NLRC4), and non-canonical inflammasomes [158]. It seems that zinc has a double-edged sword role in the inflammatory pathways [159, 160]. Both the deficiency and high doses have adverse effects. In deficient samples, zinc promotes autophagy, activates the protein expression of ubiquitin, and suppresses high levels of NLRP3 [161]. Zinc deficiency has been reported to be associated with NLRP3 inflammasome activation and the production of IL-1 β in macrophages by nuclear factor erythroid 2-related factor 2 (Nrf2) pathway activation [162].

Pharmacological NLRP3 inflammasome inhibitors

Until now, various inhibitors for each component of the inflammasome signaling cascade acting directly or indirectly have been presented through in vitro and in vivo experimental studies. Some of them directly inhibit NLRP3, such as the MCC950 (specifically binds to NLRP3), 3,4-methylenedioxy- β -nitrostyrene (MNS), CY-09, and Tranilast (N-[3',4'-dimethoxycinnamoyl]-anthranilic acid, TR) [163]. Other inhibitors, in contrast, target NLRP3 indirectly; for instance, glyburide inhibits ATP-sensitive K⁺ channels and ASC aggregation [147, 164, 165].

Some inhibitors can act on different targets simultaneously, such as parthenolide, which is an inhibitor with a broad spectrum and various anti-inflammatory characteristics. NF- κ B, caspase-1, IKK β , and several inflammasomes, including NLRC4, NLRP1, and NLRP3, are among its targets [166]. The powerful and irreversible caspase-1 inhibitor known as ac-YVAD-cmk has been shown to have anti-apoptotic, antipyrptotic, and anti-inflammatory properties [167]. Disulfiram (an FDA-approved drug) inhibits the GSDMD pores formation and hence suppresses the IL-1 β release and subsequent pyroptosis of cells [163].

Interestingly, there are NLRP3 inhibitors with multiple functions that improve some infertility pathology. Pioglitazone, an insulin sensitizer, is used to promote ovulation in PCOS patients with insulin resistance; on the other hand, it is a potent NLRP3 inhibitor and exerts an anti-inflammatory effect, declining NLRP3 levels and downstream inflammatory cytokines in patients with diabetes mellitus [168, 169]. MCC950 and CY-09 were used to attenuate dysmenorrhea and reduce the development of endometriotic lesions by

suppressing the NLRP3, respectively [170, 171]. In addition, Tranilast improves the semen parameters in severe oligoasthenozoospermia [172].

Conclusion

Female and male reproductive organs express ACE2 and TMPRSS2 receptors; therefore, these systems are vulnerable to SARS-CoV-2 infection. NLRP3 inflammasome and its end pathway products (IL1 β and IL-18) activation are responsible for the inflicted damages in both COVID-19 infection and some reproductive pathophysiology. An array of NLRP3 inflammasome inhibitors that are both efficient and reliable is available for suppressing the NLRP3 inflammasome by utilizing many targets in its complicated signaling cascade.

Expert opinion

Since COVID-19 infection and some reproductive disorders have common players for the inflicted damages especially NLRP3 inflammasome pathway activation, its inhibitors have a great potential to be considered candidates for alleviating the long-term repercussions of the COVID-19 infection on the germ cells or embryos, reproductive tissues, and health complications in future generations. This would impede the subsequent massive wave of infertility that may threaten the patients. Therefore, better understanding of the mechanisms of antagonizing these pathways can offer new interventional strategies for current and/or future SARS-CoV outbreaks.

Author contribution E. H., M. B.: conceptualization, supervision, and writing — original draft preparation. H.-R. K.-G., C. A. A., and M. N.: supervision and writing — reviewing and editing. M. A., A. Z., S. N. M., R. K., P. A., and S. E.: made impressive contributions to writing the manuscript. All authors read and approved the final manuscript.

Declarations

Conflict of interest The authors declare no competing interests.

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