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Review article

Inositol and vitamin D may naturally protect human reproduction and women undergoing assisted reproduction from Covid-19 risk

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ABSTRACT

In late 2019, the new Coronavirus has been identified in the city of Wuhan then COVID-19 spreads like wildfire in the rest of the world. Pregnant women represent a risk category for increased abortion rates and vertical transmission with adverse events on the newborns has been recently confirmed. The scientific world is struggling for finding an effective cure for counteracting symptomatology. Today, there are many therapeutic proposes but none of them can effectively counteract the infection. Moreover, many of these compounds show important side effects not justifying their use. Scientific literature reports an immune system over-reaction through interleukins-6 activation. In this regard, the possibility to control the immune system represents a possible strategy for counteracting the onset of COVID-19 symptomatology. Vitamin D deficiency shows increased susceptibility to acute viral respiratory infections. Moreover, Vitamin D seems involved in host protection from different virus species by modulating activation and release of cytokines. Myo-inositol down-regulates the expression of IL-6 by phosphatidyl-inositol-3-kinase (PI3K) pathway. Furthermore, myo-inositol is the precursor of phospholipids in the surfactant and it is applied for inducing surfactant synthesis in infants for treating respiratory distress syndrome (RDS). This review aims to summarize the evidence about COVID-19 infection in pregnant women and to encourage the scientific community to investigate the use of Vitamin D and Myo-inositol which could represent a possible preventive treatment for pregnant women or women undergoing assisted reproductive technologies (ART).

1. Introduction

In late December 2019, several clusters of patients with pneumonia of unknown etiology were reported from local healthcare facilities in Wuhan, Hubei Province, China. The seafood and wet animal wholesale market were the first epidemiological link identified (Tavakoli et al., 2020).

Inoculation of bronchoalveolar lavage fluid obtained from these patients led to the isolation of the novel coronavirus SARS-CoV-2, previously named 2019-nCov, which is a positive single-stranded RNA virus surrounded by an envelope.

COVID-19, the disease caused by SARS-CoV-2 may display a wide variety of clinical manifestations, ranging from lack of symptoms to fatal outcomes due to Acute Respiratory Syndrome coronavirus (ARDS). Elderly patients showed more severe symptoms with a higher death incidence due to lower respiratory tract infection and consequent fatal pneumonia. Other frequent symptoms included fever, cough, myalgia, dyspnea. The symptoms may appear gradually and can spontaneously disappear. The incubation period varies from 3 to 15 days and, in the second week, the disease progresses to hypoxemia, breathing difficulties and ARDS that possibly require hospitalization with assisted ventilation. According to several studies, mild symptoms are observed in most of the cases, whereas complicated and very complicated symptoms are reported, respectively, in approximately 14 % and 5% of the infected

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patients (Hui et al., 2020).

The onset of severe symptoms derives from interstitial pneumonia, which is probably related to activation of cytokine cascades with consequent alteration of lung tissue and subsequent respiratory distress (Wang et al., 2020).

Symptoms, severe clinical evolution and mortality appear to affect mostly men than women. Also, people with pre-existing morbidities, are more prone to serious complications especially in people older than 60.

People under 20 have a half risk of contracting COVID-19 and about 80 % of them are asymptomatic. Interestingly, the infection rate and the mortality in children seem to be lower. The reason could be related to the children's immune system, which is not fully developed and does not induce the hyperimmune reaction typical of adults (Castagnoli et al., 2020).

Although several trials are ongoing, no specific treatment has been developed yet. The scientific community is struggling for proposing treatments to prevent new infections and to counteract the symptoms, with particular attention to ARDS and thromboembolism. Pregnant women and their fetuses represent a population at high risk, and particular attention is paramount in such case. This review collects the most important evidence about COVID-19 impact on pregnant women and the possible mother-to-newborn vertical transmission. Moreover, it would encourage the scientific community to investigate the use of natural compounds as possible preventive treatments for such subset of population.

2. COVID-19 in pregnancy and vertical transmission

To date, studies concerning COVID-19 infection and pregnancy are few and with a small number of patients. The evidence about vertical transmission is quite conflicting. Generally, the physiological features and the mechanical changes typical of pregnancy increase the susceptibility to infections, especially when the cardiorespiratory system is involved, and lead to high incidence of respiratory failure in these women. Moreover, the status of the immune system during pregnancy presents a prevalence of T-helper 2 (Th2), which are particularly important for protecting the fetus. On the contrary, Th-1 are mainly implicated in infection response and are reduced in pregnancy, with a consequent vulnerability to viral infections (Dashraath et al., 2020). Interestingly, the occurrence of COVID-19-related complications in expecting women is notably low compared to other viral infections such as severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) (Wong et al., 2003; Assiri et al., 2016). Anyway, COVID-19 seems also correlated with fetal complications such as miscarriage (2%), intrauterine growth restriction (10 %), and preterm birth (39 %) have also been reported (Dashraath et al., 2020). A recent observational study reports an interesting theory. The authors report that, compared with before the pandemic, in Nepal and UK there is an increased number of in-hospital maternal deaths and an increase in stillbirth and neonatal mortality. They also suggest that pandemic lockdowns have potentially harmful effects because of the reductions in care-seeking, increasing the incidence of the adverse outcomes observed in Nepal and the UK (Kc et al., 2020; Khalil et al., 2020).

COVID-19 infects host respiratory epithelial cells through angiotensin-converting enzyme 2 (ACE2), a membrane-bound aminopeptidase that acts as its putative receptor. Since ACE2 has been found in the placenta, there is a possible risk of vertical transmission, similarly to what happens with SARS. A retrospective review on 46 neonates from infected mothers indicates a lack of vertical transmission, revealing the absence of viral isolates in the amniotic fluid, cord blood, breast milk, and neonatal throat swabs (Chen et al., 2020). Most of these women presented COVID-19 in the third trimester and data about perinatal outcomes when infection occurs in early pregnancy are unavailable (Xu et al., 2020). The review of Caparros-Gonzales reports 10 studies assessing maternal and neonatal health after maternal COVID-19 infection. The data indicate lack of serious symptoms in the mothers, while a greater extent of affections appeared in newborns. Death was reported in a premature newborn from a woman having COVID-19-related pneumonia.

Schwartz et al. reported 38 cases of pregnant women with COVID-19 giving birth to assess maternal and neonatal effects of the infection. Intrauterine transmission was undetected in all cases and neonatal specimens, including placenta, tested negative (Schwartz, 2020). Panahi et al. concluded that COVID-19 does not affect newborns, even though it may cause fetal distress, miscarriage, respiratory distress and preterm delivery in pregnant women (Panahi et al., 2020). In a systematic review and meta-analysis that includes 19 studies with a total of 79 women, the outcome of infections from different coronaviruses (SARS: 32.9 %; MERS: 15.2 %; COVID-19: 51.9 %) during pregnancy has been reported. In pregnant women infected with coronaviruses, more than 90 % had pneumonia. Preterm delivery (PTD) was the most adverse pregnancy outcome but also miscarriage, preeclampsia, cesarian and perinatal death (7–11 %) appeared significantly increased. However, none of the 41 newborns presented vertical transmissions (Di Mascio et al., 2020).

Overall, mother-to-child vertical transmission is still debated and available information is contradictory. In fact, a recent study reported 2 neonates, born from women with COVID-19 infection, showing positivity for the virus after delivery (Li et al., 2020). A very recent study form Facchetti et al. reports evidence about vertical transmission with adverse event on the newborns. The results show the presence of SARS-CoV-2 spike (S) protein expression on the placenta of a pregnant woman whose newborn tested positive for viral RNA and developed COVID-19 pneumonia soon after birth. Placenta infection was associated with recruitment of maternal inflammatory cells in the intervillous space, without villitis (Facchetti et al., 2020). Anyway, a definitive prove of vertical transmission of SARS-CoV-2 is still missing.

3. Proposed treatment

Currently, there is no official therapeutic indication for COVID-19 and the World Health Organization (WHO) endorses supportive care only. However, researchers are struggling to find possible virus-based and host-based therapeutic agents. Among the possible approaches, antivirals aim to inhibit viral replication or cellular penetration by acting on the virus's molecular targets.

Among them, Remdesivir (GS-5734) is an investigational drug firstly developed for the treatment of the Ebola virus (Mulangu et al., 2019). It is an adenosine analog prodrug inhibiting viral RNA transcription and showing a broad-spectrum antiviral activity, with a demonstrated efficacy on coronaviruses (Morse et al., 2020). Although Remdesivir has not shown a significant mortality reduction, it appears to expedite recovery. As an investigative drug on incomplete trial, Remdesivir is neither recommended or unapproved by China's NHC and the WHO. Currently, Remdesivir is recommended by the NIH for severe hospitalized COVID-19 cases with oxygenation requirement.

Lopinavir/ritonavir (LPV/r) is a combination of protease inhibitors approved for the treatment of human immunodeficiency virus (HIV) infection. Lopinavir binds to viral protease and prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature non-infectious virus particles. During the SARS outbreak in 2003, Lopinavir conferred clinical benefits in the early phase of the disease by reducing viral peak load before progression to ARDS. Unfortunately, LPV/r did not show superiority regarding recovery time, 28-day mortality or viral clearance over standard care therapies (Cao et al., 2020).

Ribavirin is a nucleoside analog with antiviral activity against multiple RNA viruses, including respiratory syncytial virus and SARS-CoV. It interferes with RNA polymerase and viral protein synthesis (Yates and Seley-Radtke, 2019). Intravenous ribavirin is recommended by China's NHC for COVID-19 only as an add-on therapy to LPV/r or interferon, but NIH has not evaluated it yet.

Further treatments have been proposed such as interferon, corticosteroids, intravenous immunoglobulin, umifenovir, chloroquine

phosphate, hydroxychloroquine sulfate, nitazoxanide and camostat mesylate, but available data discourage the use of these molecules for inefficacy or adverse effects that fail to justify their use (Song et al., 2020).

Besides defining a proper pharmacological therapy to manage the COVID-19 infection and its complications, the scientific community is working to find a vaccine against SARS-CoV-2 in the shortest time possible.

4. Alternative host-directed antiviral routes to current therapeutic strategies

Viral transmission depends on the interaction between components of the host plasmatic cell membrane and the viral envelope. Many natural substances, such as cyclodextrins and sterols, can impair the infectivity of many types of viruses acting on the lipid-dependent attachment to human host cells (Baglivo et al., 2020).

The literature reports inhibitory effects of flavonoids contained in citrus and tomatoes (quercetin, epicatechin, epicatechin gallate) on SARS-CoV-2 infectivity. Indeed, they specifically target Two-Pore Channels (TPCs), thus potentially offering a novel antiviral approach (Filippini et al., 2020).

Nutraceuticals have been described as food or food components with pivotal benefits for human health. The literature largely reports the use of supplementation in the prevention and treatment of several pathologies, which are often associated with deficiency of these components (Godswill et al., 2020). Among them, myo-inositol, vitamins, arginine, zinc, selenium, coenzyme Q10, melatonin and folic acid have been extensively investigated. Compelling evidence demonstrated their efficacy in the management of several pathologies including male infertility, polycystic ovary syndrome (PCOS), immune system deficiency, cardiovascular diseases and cancer (Facchinetti et al., 2020).

5. A possible protective effect of Myo-Inositol on reproduction in women with COVID-19

Myo-inositol (MI) is the most abundant stereoisomer of the inositol family. It is the precursor of Inositol-3-phosphate, a second messenger for several G-protein-coupled receptors (GPCRs) (Mikoshiba, 2015). Recently, the literature has focused on MI and its activity as insulin and follicular stimulating hormone (FSH) second messenger. MI showed a promising role in pathologies characterized by insulin resistance and glucose metabolism alterations, such as gestational diabetes, metabolic syndrome, as well as PCOS and the related infertility (D'anna et al., 2019; Croze and Soulage, 2013; Laganà et al., 2018). In addition to its well-demonstrated activity in the gynecological field, recent evidence showed a beneficial effect even in pneumology by promoting the maturation of several components of surfactant (Howlett et al., 2019). Furthermore, MI is involved in the immune response by reducing interleukin 6 (IL-6) cascade and, consequently, the inflammatory response. MI specifically down-regulates the expression of IL-6 and phosphatidyl-inositol-3-kinase (PI3K), which is involved in IL-6 signal transduction. Through this mechanism, many inflammatory activities resulting from downstream PI3K activation are inhibited (Dinicola et al., 2016). Importantly, preliminary data support the hypothesis that IL-6 drives the inflammatory response that leads to morbidity and mortality in patients with COVID-19 who develop ARDS (Gubernatorova et al., 2020). For this reason, it has been suggested the possibility that COVID-19 patients with a high level of IL-6-driven inflammation might benefit from treatment with MI (Bizzarri et al., 2020). All the activities and relative mechanisms of action are summarized in Table 1.

Table 1
The table summarize the activities and mechanisms of action of MI and VD in relation to a possible application against COVID-19.

Molecule	Activity	Mechanism of action
Myo-inositol	Anti-inflammatory	MI downregulates IL-6 expression inhibiting the downstream inflammatory response (Bizzarri et al., 2020; Dinicola et al., 2016)
	Surfactant regeneration	MI, as precursor of inositol-phosphate, stimulates surfactant production in immature lung tissue (Howlett and Ohlsson, 2003)
	Antioxidant	As cyclic polyalcohol, MI exerts an anti-radical action (Smirnoff and Cumbes, 1989)
Vitamin D	Innate immune response modulator	VD receptor is directly involved in viral infection (Bezerra Espinola et al., 2020) VD deficiency correlates to increased viral infection incidence (Esposito and Lelii, 2015)
	Anti-inflammatory	VD directly modulates the production of cytokines involved in NF-kB activation (Chen et al., 2013) Attenuates IL-18 production (Hansdottir et al., 2008)

6. The role of inositol in premature newborns with respiratory distress syndrome

Respiratory distress syndrome (RDS) due to surfactant deficiency is one of the most common causes of respiratory failure in preterm birth, and its incidence increases with decreasing gestational age (Sardesai et al., 2017).

The human pulmonary surfactant, synthesized by type II alveolar cells, is a complex mixture composed of several phospholipids, proteins and other neutral lipids needed to reduce the surface tension, avoiding alveolar collapse, atelectasis and lung dysfunction (Parra and Pérez-Gil, 2015). The synthesis of phosphatidylinositol (PI), one of the surfactant components, requires MI and several studies report the ability of MI to promote the formation of surfactant phospholipids in immature lung tissues (Howlett and Ohlsson, 2003).

A Cochrane review confirmed that inositol supplementation resulted in a statistically significant and clinically important reduction of short-term adverse neonatal outcomes (Howlett et al., 2012). Noteworthy, human milk has a high concentration of inositol, and preterm milk represents the richest source. Breastfed infants show higher serum inositol levels compared to those bottle-fed. This evidence suggests a critical role for inositol in fetal and early neonatal life. Furthermore, it has been demonstrated that inositol and glucocorticoids play a synergistic role in the development of lung stability in male and female rabbit fetuses, modifying the physiological and biochemical response of the immature lung to exogenous glucocorticoids.

On all these premises, a positive action of MI in COVID-19-induced lung pathology, at the early phase of infection or as a preventive strategy, can be hypothesized.

It is also tempting to speculate that inositol through aerosol delivery may rapidly replenish the deficiency of pulmonary PI, improving pathological conditions such as RDS, bronchial asthma and chronic obstructive pulmonary diseases.

In this regard, rhinitis is the inflammation of the nasal mucous membranes, mainly caused by viral infections and allergic reactions. It is characterized by irritation associated with itching, sneezing, rhinorrhea (runny nose) and congestion, with mucosal edema and stuffy nose sensation. Inflammatory processes reduce the hydration of the nasal mucous membranes, increasing the viscosity of the mucous. Besides, inflammation leads to increased vascular permeability, with fluid accumulation, swelling and consequent congestion of the membranes. MI is an active osmolyte and may be used to reduce nasal congestion similarly to saline solutions, which are widely used for cleaning nasal cavities, facilitating the removal of nasal mucus, and helping to maintain the hydration state (Martin et al., 1999). Moreover, inflammation causes oxidative stress, and rhinitis presents a high levels of reactive oxygen species (ROS) (Barnes, 1990). When the production of ROS exceeds the scavenging capacity of antioxidative endogenous systems, oxidative

stress is determined. In this case, MI may have a very important protective activity against oxidative damage (Smirnoff and Cumbes, 1989). Orthen et al. studied the scavenging properties of several cyclitols including MI, reporting a higher efficacy in deactivating hydroxyl radicals compared to proline. The authors concluded defining cyclitols as non-enzymatic hydrophilic antioxidants. This finding suggests that cyclitols may potentially act as ROS inhibitors (Orthen et al., 1994). The antioxidant properties of MI have also been observed in a clinical context. In this regard, MI showed efficacy in reducing oxidative stress in erythrocytes of patients with PCOS (Donà et al., 2012), thus a MI-based spray formulation may be indicated for the symptomatic treatment of rhinitis of both viral and allergic origin. All the activities and relative mechanisms of action are summarized in Table 1.

7. Vitamin d and viral infections

Vitamin D (VD) is an extremely conserved molecule present in many life forms, ranging from early life to present-day mammals. VD, identified as a vitamin in the early 20th century, is now frequently referred to as a prohormone. In addition to being synthesized by the human body through the action of sunlight, a small quantity of VD (in particular VD2) derives from dietary intake.

In its active form, VD is now considered a hormone that regulates bone metabolism and has an important role in human reproduction. VD has a key role also in viral infections, as the activation of VD receptor (VDR) modulates the innate and acquired immune response (Bezerra Espinola et al., 2020). In particular, the active form of VD (1α, 25-Dihydroxyvitamin D) directly modulates the cytokines that stimulate and are stimulated by the activation of nuclear factor κB (NF-κB) (Chen et al., 2013). Furthermore, VD treatment attenuates the expression of IL-8 in respiratory epithelial cells, which express VDR in the human airways. VD generated by lung epithelium could also increase the expression of antimicrobial peptides in adjacent macrophages and other innate immune cells (Hansdottir et al., 2008). To support VD involvement in antiviral response, *in vitro* studies proved that it could contribute to reduce inflammation, leading to less severe symptomatology in respiratory syncytial virus and influenza viral infections (Hansdottir and Monick, 2011).

Epidemiological data have linked VD deficiency to the increased susceptibility to acute viral respiratory infections (Monlezun et al., 2015). Evidence reports crosstalk between VD and intercellular signaling pathways involved in viral gene transcription, even if VD immunomodulatory effect on viral infection appears to be transient (Teymoori-Rad et al., 2019). A reduction of VD with age is widely recognized, probably following an unbalanced diet and/or reduced sun exposure in elderly people (Boucher, 2012).

Up to 50 % of the population seems to have a VD deficiency, with serum levels <10 ng/mL (Kennel et al., 2010).

Low VD levels have been associated with an increased incidence of viral infections of the respiratory tract, with poor clinical outcomes in children and adults (Esposito and Lelii, 2015). Therefore, the maintenance of adequate VD status may be an effective and inexpensive prophylactic method against some respiratory tract infections in children (Esposito and Lelii, 2015). In a 6 months placebo-controlled double--blind study involving 164 volunteering young Finnish men, the proportion of men remaining healthy throughout the six-month study period was greater in the group supplemented with VD (51.3 %) than in the placebo group (35.5 %) (Laaksi et al., 2010).

Based on these positive indications, the scientific community is assessing the beneficial effects of VD against COVID-19 infection, (Grant et al., 2020), even if the evidence concerning VD anti-viral efficacy is conflictual and further studies are necessary.

For the extraordinary nature of the world COVID-19 pandemic, any possible safe approach is worth of experimentation. In this regard, studies with large cohorts of patients on VD as a safe approach for the management of COVID-19 infection should be strongly encouraged. All the activities and relative mechanisms of action are summarized in Table 1 (Tab. 1).

8. Conclusion

MI and VD showed efficacy in enhancing the immune response by downregulating IL-6 downstream inflammation pathways. Thus, supplementing these molecules could represent a possible alternative therapy for counteracting the hyper-immune activation caused by COVID-19, which involves activation of IL-6 cascade. Moreover, MI treatment has been reported in several studies, especially in women in reproductive age undergoing ART procedures. Considering that COVID-19 showed about 50 % of higher infection incidence in women aged between 20 and 49 years, MI and VD would represent an effective and safe prophylactic approach against the infection. MI can stimulate pulmonary surfactant production, thus reducing inflammation processes. On the other hand, VD seems to be also involved in viral infection processes with a possible (even if still unconfirmed) activity against COVID-19.

Considering that the association between MI and VD has already been successfully proved during pregnancy without side effects, such molecules could be used as prophylactic therapy against COVID-19 in women who are looking for natural conception or during assisted reproduction programs.

Author contributions

Both MSBE and CA have made the direct intellectual contribution to the paper and wrote the manuscript. MBizzarri, VU and MBertelli supported with their experience about the molecules and contributed with the bibliographic research and reviewing. ASL, VU and BV contribute to the reviewing of the paper. All the authors contribute with the editing of the paper.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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