Review Article

CORONAVIRUS IN PREGNANCY: THE ROLE OF MELATONIN

ABSTRACT

The effects of COVID-19 on pregnant individuals are unclear due to a series of physiological changes and immune system adaptations that may affect the development of the fetus. There is evidence supporting the role of melatonin in human pregnancy, and it appears that melatonin is essential for a successful pregnancy. However, in pathological conditions, such as during SARS-CoV-2 infection, melatonin levels can be significantly inhibited. In addition, melatonin, a powerful endogen antioxidant, free radical scavenger, and anti-inflammatory molecule, has been reported to exert beneficial effects on viral diseases such as COVID-19. This review focuses on the current evidence regarding the physiopathology of COVID-19 in pregnancy conditions, the role of melatonin during pregnancy, and the use of melatonin as a promising treatment. Addressing these points should help us understand the knowledge currently available about COVID-19 during pregnancy and explore the possible beneficial effects of melatonin.

Keywords: COVID-19; melatonin; pregnancy.

Abbreviations:

Coronavirus disease-2019 (COVID-19)
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Angiotensin (Ang) II
Angiotensin-converting enzyme 2 (ACE-2)
Interleukin (IL)-18
Interleukin (IL)-6
Interleukin (IL)-8
Interleukin (IL)-20
Interleukin (IL)-12
Interleukin (IL)-1β
Motif chemokine ligand **(**CXCL)
Tumor necrosis factor α (TNF-α)
Type 1 T helper (Th1) cells
Transmembrane serine protease 2 (TMPRSS2)
Ribonucleic acid (RNA)
Nucleocapsid (N) protein
Membrane (M) protein
Envelope (E) protein
Spike (S) protein
Interferon beta (IFN-β)
Interferon gama (IFN-λ)
Acute respiratory distress syndrome (ARDS)
Ang II receptor 2 (AT2R)
Reactive oxygen species (ROS)
Metallothionein (MT)1 and (MT)2
Serotonin-N-acetyltransferase (SNAT)
Hydroxyindole-O-methyltransferase (HOM)
Nuclear factor erythroid 2 (NF-E2)
Factor nuclear kappa B (NF-κB)
Intrauterine inflammation (IUI)

Lipopolysaccharide (LPS)

1. INTRODUCTION

The World Health Organization declared the coronavirus disease-2019 (COVID-19) pandemic on March 11, 2020 (Jin, et al. 2021). At that time, the origin of the disease was yet unclear, but it was known that infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exacerbated respiratory inflammation, resulting in pulmonary oxygen exchange deficit and severe pneumonia (Jin et al. 2021). Alterations in the levels of immune cells, including lymphocytes and thrombocytes, and some C-reactive proteins, lactate dehydrogenase enzymes, and angiotensin (Ang) II are seen in COVID-19 patients (Wastnedge, et al. 2021).

The effects of COVID-19 on pregnant individuals are unclear due to a series of physiological changes and immune system adaptations that regulate the development of the fetus (Wastnedge, et al. 2021). During pregnancy, the respiratory, circulatory, endocrine, reproductive, and immune systems are subject to many changes that may affect the body's responses to viral infections. Such responses may not be observed in non-pregnant individuals (Soma-Pillay, et al. 2016). The immune response to SARS-CoV-2 infection and the pathophysiology and molecular mechanisms of the disease are yet to be understood (Liu, et al. 2020).

Pregnant people represent a high-risk population due to a decrease in the number and activity of lymphocytes during late gestation, which may affect the viral clearance rate and delay the viral infection deterioration (Silasi, et al. 2015). It has also been demonstrated that angiotensin-converting enzyme 2 (ACE-2), a SARS-CoV-2 receptor, is highly upregulated during pregnancy, which may contribute to increasing the susceptibility of this population to SARS-CoV-2 (Zhao, et al. 2020). More importantly, fetuses and newborns are highly susceptible to infections due to their immature innate and adaptive immune systems (Yu, et al. 2018). Dysregulation of factors such as cytokines and the complement cascade caused by infections may have deleterious consequences for brain development and function in fetuses and newborns (Magdalon, et al. 2020).

There is evidence supporting the role of melatonin in human pregnancy; melatonin appears to be essential for successful pregnancy (Tamura, et al. 2008). However, in pathological conditions such as during SARS-CoV-2 infection, melatonin levels can be significantly inhibited (Cardinalli, et al. 2020). Moreover, melatonin permits the transmission of maternal photoperiodic information to generate day/night differences in the fetus and circadian organization during development, which is essential for the maturation of the fetal biological clock (MacCarthy, et al. 2019). In addition, melatonin, a powerful endogen antioxidant, free radical scavenger, and anti-inflammatory molecule, has been reported to exert beneficial effects on viral diseases such as COVID-19 (Juybari, et al. 2020; Moore, Suthar. 2021).

Despite this evidence, there are no studies on the effects of this indoleamine on pregnancy conditions. Therefore, adequate information about the relationship between COVID-19 and pregnancy is required for better management of these patients. Herein, we review the current evidence for the role of melatonin in the treatment of COVID-19 in human pregnancy.

2. PHYSIOLOGICAL CONDITIONS DURING PREGNANCY

The physiologic and immunologic adaptations during pregnancy may result in systemic effects that determine the susceptibility and severity of respiratory infections (Luo, Yin. 2020). Moreover, rather than immunosuppression, a successful pregnancy requires a robust, dynamic, and responsive immune system (Mor, et al. 2017).

During pregnancy the levels of pro-inflammatory and anti-inflammatory cytokine are tightly regulated (Mor, et al. 2017). At first, embryo implantation and placentation benefit from systemic pro-inflammatory cytokines such as C-X-C motif chemokine ligand **(**CXCL), tumor necrosis factor α (TNF-α), Interleukin (IL)-18, IL-6, and CXCL8, after which an anti-inflammatory state leading to angiogenesis and enhancing fetal growth. Then, a subsequent pro-inflammatory state prepares for the initiation of labor in the third trimester (Mor, et al. 2017; Aghaeepour, et al. 2017). In addition, during the second trimester, the inflammatory state is low and Th1

cell-mediated immunity is compromised (Mor, et al. 2017; Kumbel, Manoussaka, 2012), thus increasing the susceptibility of pregnant women to viral and bacterial infections (Mor, et al. 2017; Kumbel, Manoussaka, 2012). Finally, pregnancy could be considered a physiologically hypercoagulable state with raised coagulation factors, fibrinogen and factor VIII included and decreased fibrinolytic proteins (Ferrer-Oliveras, et al. 2021).

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3. PHYSIOPATHOLOGY OF COVID-19

SARS-CoV-2 is transmitted via respiratory aerosols (Wiersinga, et al. 2020). Viral particles are inhaled and bind to nasal mucosa, infecting the epithelial cells (Wiersinga, et al. 2020; Sunganak et al. 2020). In the nasal epithelium, both ciliated and mucus-secreting cells express ACE2 and TMPRSS2 leading to SARS-CoV-2 releasing their RNA inside these cells (Ziegler et al. 2021). It is important to note that the coronavirus is made up of four main structural proteins: the nucleocapsid (N), membrane (M), envelope (E) and spike (S) proteins (Jackson et al. 2022). The S protein of coronaviruses facilitates viral entry into target cells (Hoffmann et al. 2020), the S1 subunit attaches onto ACE2 and the S2 subunit binds the S protein to the membrane (Fehr; Perlman, 2015). The S2 subunit also mediates the mechanism to infect new cells (Fehr; Perlman, 2015). The main mechanism is by TMPRSS2 activation but the cleavage of S2' site can be provided by cathepsins (Jackson et al. 2022). If there is not enough TMPRSS2 expressed or the virus-ACE2 complex is unable to bind, the virus is internalized iva endocytosis and into the late endolysosome the S2' site is then cleaved by cathepsins (Bayati et al. 2021; Inoue et al. 2007). The disease progression is related to infected ciliated cells shedding their ciliary axonemes, which disables mucociliary clearance (Pinto et al. 2021; Zhu et al. 2020). These infections could be asymptomatic or could cause local symptoms (Sunganak et al. 2020).

The virus replicates and releases RNA for further infection of neighboring cells, spreading from the nasal passage to the upper respiratory tract (Subbarao; Mahanty, 2020).

The immune response is intensified due to the release of CXCL10, IFN-β and IFN-λ from the infected cells and leading to symptoms of fever, malaise, and dry cough (Tang, et al. 2005). A great number of patients do not progress do not progress farther than this stage because the immune system is able to contain the infection (Parasher, et al. 2021).

The next stage of the disease occurs after the virus enters the conducting airways, likely by microaspiration of pharyngeal secretions (Bridges et al. 2022). The virus then invades and enters the lower respiratory tract via the host's ACE-2 receptor and starts replication to produce more viral nucleocapsids (Parasher, et al. 2021). The infected pneumocytes release IL-1, IL-6, IL-8, IL-120, and IL-12, TNF-α, IFN-λ and IFN-β, CXCL10, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1α (Parasher, 2021).

The amount of cytokines released attracts immune cells such as neutrophils, CD4 helper T cells, and CD8 cytotoxic T cells, then becoming concealed in the lung tissue (Parasher, 2021). The constant apoptosis of the infected cells releases new viral particles that infect the adjacent type 2 alveolar epithelial cells (Mason, 2020), leading to persistent tissue injury and alveolar damage, resulting in acute respiratory distress syndrome (ARDS)(Batah, Fabro. 2020). In ARDS, pulmonary endothelial cells contribute to the start and broadcast of this condition by changing vessel barrier integrity, supporting a pro-coagulative condition, inducing vascular inflammation, and reconciling inflammatory cell infiltration (Wiersinga, et al. 2020). It should be noted that the majority of COVID-19 patients who die succumb to ARDS (Parasher, 2021).

Many other pathways are also involved in the progression of the cytokine storm in COVID-19 patients, such as dysfunction of the RAS due to the downregulation of the ACE-2 receptor by binding of the S-protein of SAR-CoV-2 with ACE2 (Gheblawi, et al. 2020). Notably, the RAS plays an important role in severe acute lung injury because ACE-2 plays a role in lung protection (Gheblawi, et al. 2020). Since ACE-2 catalyzes the degradation of Ang II into Ang, low levels of ACE-2 increase Ang II levels, which in turn causes AT1R

stimulation and Ang II receptor 2 (AT2R) inactivation (Gheblawi, et al. 2020). AT1R is involved in functions including aldosterone, vasopressin, and adrenocorticotropic hormone secretion, potassium levels, sodium reabsorption, inflammation, cell proliferation, and lung injury, whereas AT2R has a lung-protective function (Gheblawi, et al. 2020). Due to the imbalance between these two receptor functions, the actions of AT1R dominate and result in lung injury and hypokalemia (Gheblawi, et al. 2020). Thus, cytokine storm and ACE-2 downregulation lead to pulmonary vascular hyperpermeability and pulmonary edema, inducing ARDS (Gheblawi, et al. 2020). An increase in vascular permeability due to clot formation occurs, which leads to multiorgan damage and death (Gheblawi, et al. 2020).

4. COVID-19 IN PREGNANCY

SARS-CoV-2 infection in pregnant women can entail several obstetric complications such as thrombosis, poor development of vasculature, premature rupture of the fetal membrane, deposition of fibrin within the fetal vasculature, and vascular malperfusion of the fetus (Smithgall et al. 2020). Notably, obstetric complications in COVID-19 can be induced by both direct viral effects (e.g., via ACE-2 receptors and viral replication) and subsequent hyperinflammatory responses (Racicot; Mor, 2017).

COVID-19 induces hypercoagulability that results from the concurrent activation of clot and fibrinolytic cascades, causing both thrombus and clotting factor consumption (Mei; Hu, 2020). Thus, the manifestations can be either thrombotic or hemorrhagic (Zhou et al. 2020; Tang et al. 2020). Thrombosis has similarly been reported in pregnant women and the general population (Dashraath et al. 2020); however, pregnant women are more likely to suffer from thrombotic-hemorrhagic catastrophic events (Abbassi-Ghanavati et al. 2009; VlachodimitropoulouKoumoutsea et al. 2020).

SARS-CoV-2 can impact the developing fetus as a result of vertical transmission or indirectly by a viral infection of the placenta (Moore et al. 2021). Evidence of viral presence in the human placenta has been reported in the syncytiotrophoblast layer of the chorionic villi (Hosier et al. 2020; Hecht et al. 2020; Menter et al. 2020; Ashary et al. 2020). Previous studies have demonstrated that the virus in inducing immune responses causes fetus rejection and placental compromise, resulting in placental inflammation (Alzemi et al. 2017; Mullins et al. 2012; Ribeiro et al. 2017). Thus, the fetal inflammatory syndrome can occur due to the mother's response to infection, promoting a fetal inflammatory response with high levels of inflammatory cytokines in the placenta (Mor; Cardenas, 2010). The hyperinflammatory environment has a deleterious effect on fetal neurodevelopment (Werenberg et al. 2016) (Figure 2).

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5. ROLE OF MELATONIN IN PREGNANCY

Melatonin is mainly synthesized and secreted by the pineal gland, but other organs in the reproductive system can also synthesize this hormone (Bubenik, 2001). The receptors metallothionein (MT)1 and MT2 were identified in the granulosa luteal cells and the placental villous trophoblasts, and serotonin-N-acetyltransferase (SNAT) and hydroxyindole-O-methyltransferase (HOM) are found in the brain, retinal photoreceptors, immune system, skin cells, and gastrointestinal cells (Soliman et al. 2015). The main role of melatonin synthesis, through the activation of these receptors in these systems, is to reduce the oxidative damage due to different cell stimuli (Tordjman et al. 2017).

Insert Figure 3 about here

Melatonin and cortisol are the main hormones that control the circadian rhythm; however, in pregnant women, estrogen and progesterone levels are also altered in a circadian manner (McCarthy et al. 2019). These two ovarian hormones are secreted during gestation over different temporal patterns. While progesterone levels peak during dark hours, estrogen peaks during the day (Kumar; Magon, 2012). Both hormones are produced by the placenta itself, and the uterus also produces estrogen (Tal; Taylor, 2021). By producing estrogen, the uterus maintains epithelial proliferation to support implantation and promotes progesterone synthesis by the placenta, which maintains immunosuppressive properties and reduces oxidative damage (Napso et al. 2018).

The villous trophoblast cells are not only able to produce melatonin but also express MT1 and MT2 receptors, which provide paracrine, autocrine, and intracrine effects in the placenta, thus maintaining a healthy syncytiotrophoblast layer, protecting it from oxidative stress (Soliman et al. 2015). The placenta also produces the neuropeptide vasoactive intestinal polypeptide (Marzioni et al. 2005). It is known that vasoactive intestinal polypeptide is able to increase SNAT activity and melatonin production and is involved in the control of smooth muscle tissue (Marzioni et al. 2005).

This enhanced production increases maternal plasma melatonin, and during the late third semester, the levels of melatonin are at their highest (McCarthy et al. 2019). This may be attributed to the high placental and leukocyte production of reactive oxygen species (ROS). The imbalance between melatonin and ROS levels can lead to pregnancy complications and conditions such as preeclampsia (Langston-Cox et al. 2021).

In addition to placental adaptation, melatonin also triggers the fetal system to adjust the circadian rhythm, directly affecting neurodevelopment, and protecting the fetus against ROS (McCarthy et al. 2019). Maternal melatonin oscillations help trigger the fetus' circadian rhythm, and disturbances in this process induce negative consequences in newborn babies (McCarthy et al. 2019)

6. MELATONIN AS AN ANTIVIRAL AGENT AGAINST SARS-CoV-2

Melatonin has shown antiviral properties that could help against acute lung injury, thrombosis, sepsis, mortality rate and ARDS induced by bacterial and viral infections (Shneider et al. 2020; Hasan et al. 2022; Farnoosh et al. 2022). Its anti-inflammatory and anti-oxidative properties may be helpful in critically ill patients (Bahrampour Juybari, et al. 2020) and may also interact with ACE-2 and B-cell lymphoma 2-like human proteins that are essential for SARS-CoV-2 development (Behl, et al. 2020). The mechanism of action is illustrated in Figure 4.

Insert Figure 4 about here

The effects are mediated by melatonin receptors (MTs) that channel the response to hormones throughout the organism (Cecon et al. 2018). MT1 is distributed in the retina, hypothalamus suprachiasmatic nuclei, pars-tuberalis of the pituitary gland, liver, and skin and is involved in the modulation of brain functions (Bahrampour Juybari et al. 2020). Melatonin can penetrate cells and interact with both the membrane surface and intracellular receptors, resulting in the regulation of pathways responsible for DNA damage responses, tumor metabolism, angiogenesis, and cell signaling (Hosseinzadeh et al. 2018; Luchetti et al. 2010).

Previous human trials have demonstrated the efficacy of melatonin in the reduction of elevated levels of cytokines in inflammatory pathologies, suggesting that melatonin may be useful in the treatment of COVID-19 (Bazyar et al. 2019; Sanchez-lopez et al. 2018; Kucukakin et al. 2007; Zhao et al. 2018; Shafiei et al. 2018; Zarezadeh et al. 2019). A combination of mercaptopurine and melatonin has been suggested to be a potential treatment for COVID-19, acting synergistically to target papain-like protease, ACE-2 and c-Jun signaling, and

anti-inflammatory cascades (Gurunathan et al. 2020). The possible anti-inflammatory mechanisms of melatonin involve upregulation of sirtuin-1 and suppression of NF-E2-related factor 2, promoting a decrease in the proinflammatory cytokines (TNF, IL-6, IL-10) and an increase in the anti-inflammatory cytokine IL-10 (Hardeland, 2019).

The antioxidant properties of melatonin may be beneficial in relieving the clinical symptoms of COVID-19 (Brown et al. 2021). Melatonin may prolong the survival of infected patients, indicating that the immune system of these patients recovers due to virus elimination (Juybari et al. 2020).

In a mouse model of bacterial pneumonia, melatonin was shown to inhibit pneumonia by interfering with the NLRP3 inflammasome, protecting macrophages from pyroptosis (Zhang et al. 2016). Other studies have indicated that melatonin may be a promising inhibitor of pyroptosis and associated pathologies (Wang et al. 2019; Arioz et al. 2019; Naveenkumar et al. 2019; Onk et al. 2018; Zhang et al. 2017; Liu et al. 2017).

Other possible indirect effects of melatonin in COVID-19 patients include restoring normal sleep habits and reducing anxiety (Wichniak et al. 2021). Long-term sleep deprivation and/or chronic stress leads to the deterioration of immune functions through the disturbance of barrier mechanisms by suppressing phagocytosis, reducing the proliferation and activity of some leukocytes, in particular CD4þ T cells, while increasing T-suppressors, elevating oxidative stress, and inducing a pro-inflammatory background (Besedovsky et al. 2012).

7. SAFETY OF MELATONIN SUPPLEMENTATION

Melatonin has high biological safety, and exogenous melatonin can be used in a variety of doses, including extreme doses (Andersen et al. 2016; Zhang et al. 2020a). Despite the lack of long-term studies exploring the clinical safety of exogenous melatonin (Seabra et al. 2000), some clinical trials show that even at doses higher than physiological concentrations, exogenous melatonin use is safe (Andersen et al. 2016a, 2016b; Brzezinski 1997; Nickkholgh et al. 2011; Seabra et al. 2000). Besides, there is evidence that large doses of melatonin do not cause irreversible damage or intolerable side effects, setting the safe margin to 3750 mg/day for a 75kg individual (Kleszczyński et al. 2020).

Melatonin is available in different administration forms and it is not known wich routes are ideal for pregnant women (Zetner et al. 2015) in order to consider it a potential interventional and prevention of pregnancy complications due to SARS COV-2 infection (Chitimus et al. 2020). It is essential to research more about pharmacokinetic and pharmacodynamics profile of exogenous melatonin in order to guarantee its safe administration and follow up of babies exposed *in utero* (Chitimus et al. 2020).

8. THE ROLE OF MELATONIN IN CORONAVIRUS DURING PREGNANCY

The coronavirus infection in pregnancy induces the production of proinflammatory, antiinflammatory cytokines and oxidized products that activate the maternal immune system and can cross the placental barrier (Ashdown et al. 2006; Gilmore et al. 2004; Presicce et al. 2018). The developing fetus can be impacted directly by viral infection as a result of vertical transmission (i.e. transmission from mother to fetus) or indirectly by viral infection of the placenta (Adams et al. 2013).

Inhibition of melatonin by most viruses suggests that this indoleamine can be useful in the management of viral infections, such as COVID-19 (Anderson et al. 2020). Furthermore, melatonin has protective effects against cellular insults that occur perinatally, leading to neuroprotective properties because of the reduction of proinflammatory response caused by the oxidative stress and avoiding apoptotic cell death (Wang et al. 2018; Welin et al. 2007; Balduini et al. 2012; Hu et al. 2017; Shi et al. 2018; Ding et al. 2014). The melatonin pretreated group showed decreased neuroinflammation and perinatal brain injury with normal neuronal differentiation of neuroblasts in the cortical plate compared to those not pretreated with melatonin (Lee et al. 2019a).

In addition, melatonin prevented the increased apoptotic activity of fetal neurons under hypoxia, possibly induced by a hypercoagulable state as a result of intrauterine inflammation (Yawno et al. 2012). Melatonin can improve hemodynamics at the maternal-placental interface, which is essential for fetal growth under intrauterine inflammation conditions because of the increased risk of hypoxic-induced brain ischemia from a hypercoagulable state in the placenta (Lee et al. 2019b).

Fetal mice that grew under LPS-induced intrauterine inflammation, when pretreated with melatonin, had lower levels of inflammation (NF-κB, IL-1β) in the placenta and increased expression of silent information regulator 2 homolog 1/nuclear factor erythroid 2-related factor 2 in uterine strips than those not pretreated with melatonin (Lee et al. 2019a) In another study, pregnant mice pretreated with melatonin before LPS-induced IUI showed significantly reduced inflammatory mediators, and it prevented an increase of the oxidative stress marker (4-hydroxy-2-nonenal) in the placenta (Lee et al. 2020).

Finally, circadian rhythm and melatonin are essential in controlling the endocrine system and metabolism; these systems are involved in the production of cortisol, which plays a key role in lung maturation of the fetus, and aids the mobilization of glucose and fatty acids from the liver to meet the high metabolic demands of the fetus (de Fencl; Tulchinsky, 1975; McCarthy et al. 2019) (Figure 5).

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9. CONCLUSION

We have provided an overview of the knowledge currently available about COVID-19 during pregnancy and explored the possible beneficial effects of melatonin.

Physiological and immunological adaptations during pregnancy may result in systemic effects that greatly contribute to the development of acute viral infectious diseases such as COVID-19. It is important to note that obstetric complications in COVID-19 could be induced by both direct viral effects (e.g., through ACE-2 receptors or viral replication) and subsequent hyperinflammatory responses.

Melatonin as an adjuvant in COVID-19 treatment has anti-inflammatory, anti-oxidative, and immune response regulatory functions. The strategy that melatonin offers is to slow the cytokine storm observed and reduce oxidative damage to enhance the resistance of individuals and provide additional survival time. Although the direct evidence of melatonin application in COVID-19 is unclear, both its use in experimental animal models and studies on humans has consistently documented its efficacy and safety, and its use by COVID-19 patients would be highly beneficial.

REFERENCES

Abbassi-Ghanavati M, Greer LG, Cunningham FG. 2009. Pregnancy and laboratory studies: a reference table for clinicians. ObstetGynecol 114:1326–1331. https://doi.org/10.1097/AOG. 0b013e3181c2bde8

Acuña-Castroviejo D, Escames G, Figueira JC, de la Oliva P, Borobia AM, Acuña-Fernández C. 2020. Clinical trial to test the efficacy of melatonin in COVID-19. J Pineal Res. 69(3):e12683. doi: 10.1111/jpi.12683.

Adams Waldorf KM, McAdams RM. 2013. Influence of infection during pregnancy on fetal development. Reproduction. 1;146(5):R151-62. doi: 10.1530/REP-13-0232.

Aghaeepour N, Ganio EA, Mcilwain D, Tsai AS, Tingle M, Van Gassen S, Gaudilliere DK, Baca Q, McNeil L, Okada R et al. 2017. An immune clock of human pregnancy. Sci Immunol. 1;2(15):eaan2946. doi: 10.1126/sciimmunol.aan2946.

Agrawal V, Hirsch E. 2012. Intrauterine infection and preterm labor. Semin Fetal Neonatal Med. 17(1):12-19. https://doi.org/10.1016/j.siny.2011.09.001

Ahmed S, Zimba O, Gasparyan AY. 2020. Thrombosis in Coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad. Clin Rheumatol 39:2529–2543. https://doi.org/10. 1007/s10067-020-05275-1.

Alanagreh L, Alzoughool F, Atoum M. 2020. The Human Coronavirus Disease COVID-19: Its Origin, Characteristics, and Insights into Potential Drugs and Its Mechanisms. Pathogens. 29;9(5):331. doi: 10.3390/pathogens9050331.

Al-Azemi M, Raghupathy R, Azizieh F. 2017. Pro-inflammatory and anti-inflammatory cytokine profiles in fetal growth restriction. Clin Exp Obstet Gynecol. 44(1):98-103.

Al-Haddad BJS, Oler E, Armistead B, Elsayed NA, Weinberger DR, Bernier R, Burd I, Kapur R, Jacobsson B, Wang C, et al. 2019. Am J Obstet Gynecol. 221(6):549-562. doi: 10.1016/j.ajog.2019.06.013.

Althaus K, Marini I, Zlamal J, Pelzl L, Singh A, Häberle H, Mehrländer M, Hammer S, Schulze H, Bitzer M, Malek N, Rath D, Bösmüller H, Nieswandt B, Gawaz M, Bakchoul T, Rosenberger P. 2021a. Antibody-induced procoagulant platelets in severe COVID-19 infection. Blood. 25;137(8):1061-1071. doi: 10.1182/blood.2020008762.

Althaus K, Möller P, Uzun G, Singh A, Beck A, Bettag M, Bösmüller H, Guthoff M, Dorn F, Petzold GC, et al. 2021. Antibody-mediated procoagulant platelets in SARS-CoV-2-vaccination associated immune thrombotic thrombocytopenia. Haematologica. 1;106(8):2170-2179. doi: 10.3324/haematol.2021.279000.

Al-Zaqri N., Pooventhiran T., Alsalme A., Warad I., John A.M., Thomas R., 2020.Structural and physico-chemical evaluation of melatonin and its solution-state excited properties, with emphasis on its binding with novel coronavirus proteins. J Mol Liq. 15;318:114082. doi: 10.1016/j.molliq.2020.114082.

Amaral FGD, Cipolla-Neto J. 2018. A brief review about melatonin, a pineal hormone. Arch Endocrinol Metab. 62(4):472-479. doi:10.20945/2359-3997000000066.

Amgalan A, Othman M. 2020. Hemostatic laboratory derangements in COVID-19 with a focus on platelet count. Platelets. 31(6): 740-745.

Anderson G, Vaillancourt C, Maes M, Reiter RJ. 2016. Breastfeeding and Melatonin: Implications for Improving Perinatal Health. Journal of Breastfeeding Biology. 1:8-20.

Anderson G, Reiter RJ, 2020. Melatonin: Roles in influenza, Covid-19, and other viral infections. Rev Med Virol. doi: 10.1002/rmv.2109.

Anderson GM, 2021. Fluvoxamine, melatonin and COVID-19. Psychopharmacology (Berl). Doi: 10.1007/s00213-020-05753-z.

Arioz BI, Tastan B, Tarakcioglu E, Tufekci KU, Olcum M, Ersoy N, Bagriyanik A, Genc K, Genc S. 2019. Melatonin Attenuates LPS-Induced Acute Depressive-Like Behaviors and Microglial NLRP3 Inflammasome Activation Through the SIRT1/Nrf2 Pathway. Front Immunol. 2;10:1511. doi: 10.3389/fimmu.2019.01511.

Artigas L, Coma M, Matos-Filipe P, Aguirre-Plans J, Farrés J, Valls R, Fernandez-Fuentes N, de la Haba-Rodriguez J, Olvera A, Barbera J, et al. 2020. In-silico drug repurposing study predicts the combination of pirfenidone and melatonin as a promising candidate therapy to reduce SARS-CoV-2 infection progression and respiratory distress caused by cytokine storm. PLoS One. 2;15(10):e0240149. doi: 10.1371/journal.pone.0240149.

Ashary N, Bhide A, Chakraborty P, Colaco S, Mishra A, Chhabria K, Jolly MK, Modi D. Single-Cell RNA-seq Identifies Cell Subsets in Human Placenta That Highly Expresses Factors Driving Pathogenesis of SARS-CoV-2. Front Cell Dev Biol. 2020 19;8:783. doi: 10.3389/fcell.2020.00783.

Ashdown H, Dumont Y, Ng M, Poole S, Boksa P, Luheshi GN. 2006. The role of cytokines in mediating effects of prenatal infection on the fetus: implications for schizophrenia. Mol Psychiatry. 11(1):47-55. https://doi.org/10.1038/sj.mp.4001748.

Bahrampour Juybari K, Pourhanifeh MH, Hosseinzadeh A, Hemati K, Mehrzadi S. 2020. Melatonin potentials against viral infections including COVID-19: Current evidence and new findings. Virus Res. 2;287:198108. doi: 10.1016/j.virusres.2020.198108. Epub 2020 Aug 5.

Balduini W, Carloni S, Perrone S, Bertrando S, Tataranno ML, Negro S, Proietti F, Longini M, Buonocore G. 2012. The use of melatonin in hypoxic-ischemic brain damage: an experimental study. J Matern Fetal Neonatal Med. 1:119-24. doi: 10.3109/14767058.2012.663232.

Batah SS, Fabro AT. 2021. Pulmonary pathology of ARDS in COVID-19: A pathological review for clinicians. Respir Med. 176:106239. doi: 10.1016/j.rmed.2020.106239.

Baud D, Greub G, Favre G, Gengler C, Jaton K, Dubruc E, Pomar L. 2020. Second-Trimester Miscarriage in a Pregnant Woman With SARS-CoV-2 Infection. JAMA. 2;323(21):2198-2200. doi: 10.1001/jama.2020.7233.
Bayati A, Kumar R, Francis V, McPherson PS. 2021. SARS-CoV-2 infects cells following viral entry via clathrin-mediated endocytosis. J. Biol. Chem. https:// doi.org/10.1016/j.jbc.2021.100306.

Bazyar H, Gholinezhad H, Moradi L, Salehi P, Abadi F, Ravanbakhsh M, Zare Javid A. 2019. The effects of melatonin supplementation in adjunct with non-surgical periodontal therapy on periodontal status, serum melatonin and inflammatory markers in type 2 diabetes mellitus patients with chronic periodontitis: a double-blind, placebo-controlled trial. Inflammopharmacology. 27(1):67-76. doi: 10.1007/s10787-018-0539-0.

Been JV, Zimmermann LJI. 2008. Histological chorioamnionitis and respiratory outcome in preterm infants. Arch Dis Childhood - Fetal Neonatal Edn. 94(3):F218-F225. https://doi.org/10.1136/ adc.2008.150458

Been JV, Rours IG, Kornelisse RF, Jonkers F, de Krijger RR, Zimmermann LJ. 2010. Chorioamnionitis alters the response to surfactant in preterm infants. J Pediatr. 156(1):10-15.e1. https://doi.org/10.1016/j.jpeds.2009.07.044

Behl T, Kaur I, Bungau S, Kumar A, Uddin MS, Kumar C, Pal G, Sahil, Shrivastava K, Zengin G, Arora S. 2020. The dual impact of ACE2 in COVID-19 and ironical actions in geriatrics and pediatrics with possible therapeutic solutions. Life Sci. 15;257:118075. doi: 10.1016/j.lfs.2020.118075.

Besedovsky L, Lange T, Born J. 2012. Sleep and immune function. Pflugers Arch.463(1):121-137. doi:10.1007/s00424-011-1044-0.

Beyerstedt S, Casaro EB, Rangel ÉB. 2021. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology. 40(5), 905–919.doi.org/10.1007/s10096-020-04138-6

Biran V, Decobert F, Bednarek N, Boizeau P, Benoist JF, Claustrat B, Barré J, Colella M, Frérot A, Garnotel R, et al. 2019. Melatonin Levels in Preterm and Term Infants and Their Mothers. Int J Mol Sci. 27;20(9):2077. doi: 10.3390/ijms20092077.

Bonomini F, Dos Santos M, Veronese FV, Rezzani R. 2019. NLRP3 Inflammasome Modulation by Melatonin Supplementation in Chronic Pristane-Induced Lupus Nephritis. Int J Mol Sci. 15;20(14):3466. doi: 10.3390/ijms20143466.

Bridges JP, Vladar EK, Huang H, Mason RJ. 2022. Respiratory epithelial cell responses to SARS-CoV-2 in COVID-19. Thorax. 77(2):203-209. doi: 10.1136/thoraxjnl-2021-217561.

Brosnihan KB, Neves LA, Anton L, Joyner J, Valdes G, Merrill DC. 2004. Enhanced expression of Ang-(1-7) during pregnancy. Braz J Med Biol Res. 37(8):1255-62. doi: 10.1590/s0100-879x2004000800017.

Brown GM, Pandi-Perumal SR, Pupko H, Kennedy JL, Cardinali DP. 2021. Melatonin as an Add-On Treatment of COVID-19 Infection: Current Status. Diseases. 20;9(3):64. doi: 10.3390/diseases9030064.

Bubenik GA. 2001. Localization, physiological significance and possible clinical implication of gastrointestinal melatonin. Biol Signals Recept. 10(6):350-366. doi:10.1159/000046903

Burton GJ, Jauniaux E. 2015. What is the placenta? Am J Obstet Gynecol. 213(4 Suppl):S6.e1, S6-8. doi: 10.1016/j.ajog.2015.07.050.

Callender LA, Curran M, Bates SM, Mairesse M, Weigandt J, Betts CJ. 2020. The Impact of Pre-existing Comorbidities and Therapeutic Interventions on COVID-19. Front Immunol. 11;11:1991. doi: 10.3389/fimmu.2020.01991.

Cardinali DP, Brown GM, Pandi-Perumal SR. 2020. Can Melatonin Be a Potential "Silver Bullet" in Treating COVID-19 Patients? Diseases. 26;8(4):44. doi: 10.3390/diseases8040044.

Cardinali DP, Brown GM, Reiter RJ, Pandi-Perumal SR. 2020. Elderly as a High-risk Group during COVID-19 Pandemic: Effect of Circadian Misalignment, Sleep Dysregulation and Melatonin Administration. Sleep Vigil. 26:1-7. doi: 10.1007/s41782-020-00111-7.

Cecon E, Oishi A, Jockers R. 2018. Melatonin receptors: molecular pharmacology and signalling in the context of system bias. Br J Pharmacol. 175(16):3263-3280. doi:10.1111/bph.13950

Çelik I, Saatçi, E, Eyüboğlu AF. 2020. Emerging and reemerging respiratory viral infections up to Covid-19. Turkish journal of medical sciences. 50(SI-1), 557–562. https://doi.org/10.3906/sag-2004-126)

Chen YF, Naftilan AJ, Oparil S. 1992. Androgen-dependent angiotensinogen and renin messenger RNA expression in hypertensive rats. Hypertension 19:456–463.https://doi.org/10.1161/01.hyp.19.5.456.

Chen M, Yan R, Zhou K, Li X, Zhang Y, Liu C, Jiang M, Ye H, Meng X, Pang N. 2018. Akt-mediated platelet apoptosis and its therapeutic implications in immune thrombocytopenia. Proc Natl Acad Sci U S A. 6;115(45):E10682-E10691. doi: 10.1073/pnas.1808217115.

Chen L, Li Q, Zheng D, Jiang H, Wei Y, Zou L, Feng L, Xiong G, Sun G, Wang H, et al. 2020. Clinical Characteristics of Pregnant Women with Covid-19 in Wuhan, China. N Engl J Med. 18;382(25):e100. doi: 10.1056/NEJMc2009226.

Chitimus DM, Popescu MR, Voiculescu SE, Panaitescu AM, Pavel B, Zagrean L, Zagrean AM. 2020. Melatonin's Impact on Antioxidative and Anti-Inflammatory Reprogramming in Homeostasis and Disease. Biomolecules. 20;10(9):1211. doi: 10.3390/biom10091211.

D'Souza R, Malhamé I, Teshler L, Acharya G, Hunt BJ, McLintock C. 2020. A critical review of the pathophysiology of thrombotic complications and clinical practice recommendations for thromboprophylaxis in pregnant patients with COVID-19. Acta ObstetGynecol Scand. 99(9):1110-1120. doi: 10.1111/aogs.13962.

D'Agostino A, Zambrelli E. 2020. Reply to 'Delirium, sleep, COVID-19 and melatonin'. Sleep Med. 75:543. doi: 10.1016/j.sleep.2020.05.027.

Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, Choolani M, Mattar C, Su LL. 2020.Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 222(6):521-531. doi: 10.1016/j.ajog.2020.03.021. Epub 2020 Mar 23.

de Fencl M, Tulchinsky D. 1957. Total cortisol in amniotic fluid and fetal lung maturation. N Engl J Med. 292:133-136.

DeBolt CA, Bianco A, Limaye MA, Silverstein J, Penfield CA, Roman AS, Rosenberg HM, Ferrara L, Lambert C, Khoury R, et al. 2021. Pregnant women with severe or critical coronavirus disease 2019 have increased composite morbidity compared with nonpregnant matched controls. Am J Obstet Gynecol. 224(5):510.e1-510.e12. doi: 10.1016/j.ajog.2020.11.022.

Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, Vecchiet J, Nappi L, Scambia G, Berghella V, et al. 2020. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J ObstetGynecol MFM. 2(2):100107. doi: 10.1016/j.ajogmf.2020.100107.

Ding K, Wang H, Xu J, Li T, Zhang L, Ding Y, Zhu L, He J, Zhou M. 2014. Melatonin stimulates antioxidant enzymes and reduces oxidative stress in experimental traumatic brain injury: the Nrf2-ARE signaling pathway as a potential mechanism. Free Radic Biol Med. 73:1-11. doi: 10.1016/j.freeradbiomed.2014.04.031.

Dmitrzak-Weglarz M, Reszka E. 2017. Pathophysiology of Depression: Molecular Regulation of Melatonin Homeostasis - Current Status. Neuropsychobiology. 76(3):117-129. doi:10.1159/000489470

Duhig K, Chappell LC, Shennan AH. 2016. Oxidative stress in pregnancy and reproduction. Obstetric Medicine. 2016;9(3):113-116. doi:10.1177/1753495X16648495

Eisinger F, Langer HF. 2018. The mutual relation of platelet activation and innate immunity. Hamostaseologie. 38(4):186-202.

El-Missiry MA, El-Missiry ZMA, Othman AI. 2020. Melatonin is a potential adjuvant to improve clinical outcomes in individuals with obesity and diabetes with coexistence of Covid-19. Eur J Pharmacol. 5;882:173329. doi: 10.1016/j.ejphar.2020.173329.

Elovitz MA, Wang Z, Chien EK, Rychlik DF, Phillippe M. 2003. A new model for inflammation-induced preterm birth: the role of platelet-activating factor and toll-like receptor-4. Am J Pathol. 163(5):2103-2111.https://doi.org/10.1016/S0002 -9440(10)63567 -5.

Essa MM, Hamdan H, Chidambaram SB, Al-Balushi B, Guillemin GJ, Ojcius DM, Qoronfleh MW. 2020. Possible role of tryptophan and melatonin in COVID-19. Int J Tryptophan Res. 21;13:1178646920951832. doi: 10.1177/1178646920951832.

Farnoosh G, Akbariqomi M, Badri T, Bagheri M, Izadi M, Saeedi-Boroujeni A, Rezaie E, Ghaleh HEG, Aghamollaei H, Fasihi-Ramandi M, et al. 2022. Efficacy of a Low Dose of Melatonin as an Adjunctive Therapy in Hospitalized Patients with COVID-19: A Randomized, Double-blind Clinical Trial. Arch Med Res. 53(1):79-85. doi: 10.1016/j.arcmed.2021.06.006.

Fatima S, Zaidi SS, Alsharidah AS, Aljaser FS, Banu N. 2020. Possible Prophylactic Approach for SARS-CoV-2 Infection by Combination of Melatonin, Vitamin C and Zinc in Animals. Front Vet Sci. 3;7:585789. doi: 10.3389/fvets.2020.585789.

Fehr AR, Perlman S. 2015. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol. Biol. 1282, 1–23.

Feitosa EL, Júnior FTDSS, Nery Neto JAO, Matos LFL, Moura MHS, Rosales TO, De Freitas GBL. 2020. COVID-19: Rational discovery of the therapeutic potential of Melatonin as a SARS-CoV-2 main Protease Inhibitor. Int J Med Sci. 30;17(14):2133-2146. doi: 10.7150/ijms.48053.

Ferrer-Oliveras R, Mendoza M, Capote S, Pratcorona L, Esteve-Valverde E, Cabero-Roura L, Alijotas-Reig J. 2021. Immunological and physiopathological approach of COVID-19 in pregnancy. Arch Gynecol Obstet. 304(1):39-57. doi: 10.1007/s00404-021-06061-3.

García IG, Rodriguez-Rubio M, Mariblanca AR, de Soto LM, García LD, Villatoro JM, Parada JQ, Meseguer ES, Rosales MJ, González J, et al. 2020. A randomized multicenter clinical trial to evaluate the efficacy of melatonin in the prophylaxis of SARS-CoV-2 infection in high-risk contacts (MeCOVID Trial): A structured summary of a study protocol for a randomised controlled trial. Trials. 3;21(1):466. doi: 10.1186/s13063-020-04436-6.

Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, Raizada MK, Grant MB, Oudit GY. 2020. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. Circ Res. 8;126(10):1456-1474. doi: 10.1161/CIRCRESAHA.120.317015.

Gilmore JH, Fredrik Jarskog L, Vadlamudi S, Lauder JM. 2004. Prenatal infection and risk for schizophrenia: IL-1beta, IL-6, and TNFalpha inhibit cortical neuron dendrite development. Neuropsychopharmacology. 29(7):1221-1229.https://doi. org/10.1038/sj.npp.1300446

Grivas TB, Savvidou OD. 2007. Melatonin the "light of night" in human biology and adolescent idiopathic scoliosis. Scoliosis. doi:10.1186/1748-7161-2-6

Guillaumond F, Dardente H, Giguère V, Cermakian N. 2005. Differential control of Bmal1 circadian transcription by REV-ERB and ROR nuclear receptors. J Biol Rhythms. 20(5):391-403. doi: 10.1177/0748730405277232.

Guo L, Rondina MT. The era of thromboinflammation: platelets are dynamic sensors and effector cells during infectious diseases. Front Immunol. 2019;10:2204.

Gurunathan S, Kang MH, Choi Y, Reiter RJ, Kim JH. 2021. Melatonin: A potential therapeutic agent against COVID-19. Melatonin Research. 4(1):30-69. doi: ttps://doi.org/https://doi.org/10.32794/mr11250081.

Hardeland R. 2019. Aging, Melatonin, and the Pro- and Anti-Inflammatory Networks. Int J Mol Sci. 20(5):1223. doi:10.3390/ijms20051223.

Hasan ZT, Atrakji DMQYMAA, Mehuaiden DAK. 2022 The Effect of Melatonin on Thrombosis, Sepsis and Mortality Rate in COVID-19 Patients. Int J Infect Dis. 114:79-84.

Hazra S, Chaudhuri AG, Tiwary BK, Chakrabarti N. 2020. Matrix metallopeptidase 9 as a host protein target of chloroquine and melatonin for immunoregulation in COVID-19: A network-based meta-analysis. Life Sci. 15;257:118096. doi: 10.1016/j.lfs.2020.118096.

Hecht JL, Quade B, Deshpande V, Mino-Kenudson M, Ting DT, Desai N, Dygulska B, Heyman T, Salafia C, Shen D, et al. 2020. SARS-CoV-2 can infect the placenta and is not associated with specific placental histopathology: a series of 19 placentas from COVID-19-positive mothers. Mod Pathol. 33(11):2092-2103. doi: 10.1038/s41379-020-0639-4.

Hentschel R, Bohlin K, van Kaam A, Fuchs H, Danhaive O. Surfactant replacement therapy: from biological basis to current clinical practice. Pediatr Res. 2020;1-8. https://doi.org/10.1038/s4139 0-020-0750-8

Hickman AB, Klein DC, Dyda F. 1999. Melatonin biosynthesis: the structure of serotonin N-acetyltransferase at 2.5 A resolution suggests a catalytic mechanism. Mol Cell. 3(1):23-32. doi:10.1016/s1097-2765(00)80171-9.

Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. 2020. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 16;181(2):271-280.e8. doi: 10.1016/j.cell.2020.02.052.

Honnebier MB, Jenkins SL, Nathanielsz PW. 1992. Circadian timekeeping during pregnancy: endogenous phase relationships between maternal plasma hormones and the maternal body temperature rhythm in pregnant rhesus monkeys. Endocrinology. 131(5):2051-2058. doi:10.1210/endo.131.5.1330486

Hosier H., Farhadian S. F., Morotti R.A., et al, 2020. SARS-CoV-2 infection of the placenta. J Clin Invest. 130(9):4947-4953. doi:10.1172/JCI139569

Hosseinzadeh A, Javad-Moosavi SA, Reiter RJ, Yarahmadi R, Ghaznavi H, Mehrzadi S. 2018. Oxidative/nitrosative stress, autophagy and apoptosis as therapeutic targets of melatonin in idiopathic pulmonary fibrosis. Expert Opin Ther Targets. 22(12):1049-1061. doi:10.1080/14728222.2018.1541318

Hsu CN, Huang LT, Tain, YL. 2019. Perinatal Use of Melatonin for Offspring Health: Focus on Cardiovascular and Neurological Diseases. International journal of molecular sciences. 20(22), 5681. https://doi.org/10.3390/ijms20225681

Hsu CN, Tain YL. 2020. Light and Circadian Signaling Pathway in Pregnancy: Programming of Adult Health and Disease. Int J Mol Sci. 21(6):2232. doi:10.3390/ijms21062232.

Hu Y, Wang Z, Liu Y, Pan S, Zhang H, Fang M, Jiang H, Yin J, Zou S, Li Z, et al. 2017. Melatonin reduces hypoxic-ischaemic (HI) induced autophagy and apoptosis: An in vivo and in vitro investigation in experimental models of neonatal HI brain injury. Neurosci Lett. 13;653:105-112. doi: 10.1016/j.neulet.2016.11.050.

Inoue Y, Tanaka N, Tanaka Y, Inoue S, Morita K, Zhuang M, Hattori T, Sugamura K. 2007. Clathrin-dependent entry of severe acute respiratory syndrome coronavirus into target cells expressing ACE2 with the cytoplasmic tail deleted. J Virol. 281(16):8722-9. doi: 10.1128/JVI.00253-07.

Jackson CB, Farzan M, Chen B, Choe H. 2022. Mechanisms of SARS-CoV-2 entry into cells. Nat Rev Mol Cell Biol. 23(1):3-20. doi: 10.1038/s41580-021-00418-x.

Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, Duan G. 2020. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. Viruses. 27;12(4):372. doi: 10.3390/v12040372.

Juan J, Gil MM, Rong Z, Zhang Y, Yang H, Poon LC. 2019. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. Ultrasound Obstet Gynecol.56(1):15-27. doi: 10.1002/uog.22088.

Kirtsman M, Diambomba Y, Poutanen SM, Malinowski AK, Vlachodimitropoulou E, Parks WT, Erdman L, Morris SK, Shah PS. 2020. Probable congenital SARS-CoV-2 infection in a neonate born to a woman with active SARS-CoV-2 infection. CMAJ. 15;192(24):E647-E650. doi: 10.1503/cmaj.200821.

Kleszczyński K, Slominski AT, Steinbrink K, Reiter RJ. 2020. Clinical Trials for Use of Melatonin to Fight against COVID-19 Are Urgently Needed. Nutrients. 24;12(9):2561. doi: 10.3390/nu12092561.

Koga K, Cardenas I, Aldo P, Abrahams VM, Peng B, Fill S, Romero R, Mor G. 2009. Activation of TLR3 in the trophoblast is associated with preterm delivery. Am J Reprod Immunol. 61(3):196-212. doi: 10.1111/j.1600-0897.2008.00682.x.

VlachodimitropoulouKoumoutsea E, Vivanti AJ, Shehata N, Benachi A, Le Gouez A, Desconclois C, Whittle W, Snelgrove J, Malinowski AK. 2020. COVID-19 and acute coagulopathy in pregnancy. J ThrombHaemost. 18(7):1648-1652. doi: 10.1111/jth.14856.

Kow CS, Hasan SS. 2021. Could melatonin be used in COVID-19 patients with laryngopharyngeal reflux disease? J Med Virol. 93(1):92-93. doi: 10.1002/jmv.26150.

Kücükakin B, Lykkesfeldt J, Nielsen HJ, Reiter RJ, Rosenberg J, Gögenur I. 2008. Utility of melatonin to treat surgical stress after major vascular surgery--a safety study. J Pineal Res. 44(4):426-31. doi: 10.1111/j.1600-079X.2007.00545.x.

Kumar P, Magon N. 2012. Hormones in pregnancy. Niger Med J. 53(4):179-183. doi:10.4103/0300-1652.107549

Kumpel BM, Manoussaka MS. 2012. Placental immunology and maternal alloimmune responses. Vox Sang 102:2–12. https://doi. org/10.1111/j.1423-0410.2011.01533.x

Lee JY, Song H, Dash O, Park M, Shin NE, McLane MW, Lei J, Hwang JY, Burd I. 2019. Administration of melatonin for prevention of preterm birth and fetal brain injury associated with premature birth in a mouse model. Am J Reprod Immunol. 82(3):e13151. doi: 10.1111/aji.13151.

Lee JY, Li S, Shin NE, Na Q, Dong J, Jia B, Jones-Beatty K, McLane MW, Ozen M, Lei J, Burd I. 2019. Melatonin for prevention of placental malperfusion and fetal compromise associated with intrauterine inflammation-induced oxidative stress in a mouse model. J Pineal Res. 67(3):e12591. doi: 10.1111/jpi.12591.

Lee JY, Na Q, Shin NE, Shin HE, Kang Y, Chudnovets A, Lei J, Song H, Burd I. 2020. Melatonin for prevention of fetal lung injury associated with intrauterine inflammation and for improvement of lung maturation. J Pineal Res. 69(3):e12687. doi: 10.1111/jpi.12687.

Li P, Ferrario CM, Ganten D, Brosnihan KB. 1997. Chronic estrogen treatment in female transgenic (mRen2)27 hypertensive rats augments endothelium-derived nitric oxide release. Am J Hypertens 10:662–670. https://doi.org/10.1016/s0895-7061(97) 00039-3.

Lippi G, Plebani M, Henry BM. 2020. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta. 506:145-148.

Liu Z, Gan L, Xu Y, Luo D, Ren Q, Wu S, Sun C. 2017. Melatonin alleviates inflammasome-induced pyroptosis through inhibiting NF-κB/GSDMD signal in mice adipose tissue. J Pineal Res. 63(1). doi: 10.1111/jpi.12414.

Liu H, Wang LL, Zhao SJ, Kwak-Kim J, Mor G, Liao AH. 2020. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. J Reprod Immunol. 139:103122. doi: 10.1016/j.jri.2020.103122.

Lu-Culligan A, Chavan AR, Vijayakumar P, Irshaid L, Courchaine EM, Milano KM, Tang Z, Pope SD, Song E, Vogels CBF, et al. 2021 SARS-CoV-2 infection in pregnancy is associated with robust inflammatory response at the maternal-fetal interface. medRxiv 26:2021.01.25.21250452. doi: 10.1101/2021.01.25.21250452.

Luo Y, Yin K. 2020. Management of pregnant women infected with COVID-19. Lancet Infect Dis 20:513–514. https://doi.org/10.1016/S1473-3099(20)30191-2

Lye P, Dunk CE, Zhang J, Wei Y, Nakpu J, Hamada H, Imperio GE, Bloise E, Matthews SG, Lye SJ. 2021. ACE2 Is Expressed in Immune Cells That Infiltrate the Placenta in Infection-Associated Preterm Birth. Cells. 8;10(7):1724. doi: 10.3390/cells10071724.

Maffei ME. 2020. 5-Hydroxytryptophan (5-HTP): Natural Occurrence, Analysis, Biosynthesis, Biotechnology, Physiology and Toxicology. Int J Mol Sci. 22(1):181. doi:10.3390/ijms22010181

Magdalon J. Mansur F, Teles e Silva AL. 2020. Complement system in brain architecture AND neurodevelopmental disorders. Frontiers in Neuroscience. 14. https://doi.org/10.3389/fnins.2020.00023

Marik PE, Kory P, Varon J, Iglesias J, Meduri GU. 2021. MATH+ protocol for the treatment of SARS-CoV-2 infection: the scientific rationale. Expert Rev Anti Infect Ther. 19(2):129-135. doi: 10.1080/14787210.2020.1808462.

Martín Giménez VM, Inserra F, Tajer CD, Mariani J, Ferder L, Reiter RJ, Manucha W. 2020. Lungs as target of COVID-19 infection: Protective common molecular mechanisms of vitamin D and melatonin as a new potential synergistic treatment. Life Sci. 1;254:117808. doi: 10.1016/j.lfs.2020.117808.

Martín Giménez VM, Prado N, Diez E, Manucha W, Reiter RJ. 2020. New proposal involving nanoformulated melatonin targeted to the mitochondria as a potential COVID-19 treatment. Nanomedicine (Lond). 15(29):2819-2821. doi: 10.2217/nnm-2020-0371.

Martinelli I, Ferrazzi E, Ciavarella A, Erra R, Iurlaro E, Ossola M, Lombardi A, Blasi F, Mosca F, Peyvandi F. 2020. Pulmonary embolism in a young pregnant woman with COVID-19. Thromb Res. 191:36-37. doi: 10.1016/j.thromres.2020.04.022.

Mason RJ. 2020. Pathogenesis of COVID-19 from a cell biology perspective. The European respiratory journal, 55(4), 2000607. doi.org/10.1183/13993003.00607-2020

McCarthy R, Jungheim ES, Fay JC, Bates K, Herzog ED, England SK. 2019. Riding the Rhythm of Melatonin Through Pregnancy to Deliver on Time. Front Endocrinol 213;10:616. doi: 10.3389/fendo.2019.00616.

Mei H Hu Y. 2020. Characteristics, causes, diagnosis and treatment of coagulation dysfunction in patients with COVID-19. Zhonghua Xue Ye Xue Za Zhi 41(3):185–191. https://doi.org/ 10.3760/cma.j.issn.0253-2727.2020.0002

Meyer U, Feldon J, Schedlowski M, Yee BK. 2006. Immunological stress at the maternal-fetal interface: a link between neurodevelopment and adult psychopathology. Brain Behav Immun. 20(4):378-388. https://doi.org/10.1016/j.bbi.2005.11.003

Moore K. M., Suthar M. S., 2021. Comprehensive analysis of COVID-19 during pregnancy. BiochemBiophys Res Commun. 2021 Jan 29;538:180-186. doi: 10.1016/j.bbrc.2020.12.064. Epub 2020 Dec 24. PMID: 33384142; PMCID: PMC7759124.

Mor G, Aldo P, Alvero AB. 2017. The unique immunological and microbial aspects of pregnancy. Nat Rev Immunol 17:469– 482. https://doi.org/10.1038/nri.2017.64 33.

Mullins E, Prior T, Roberts I, Kumar S. 2012. Changes in the maternal cytokine profile in pregnancies complicated by fetal growth restriction. Am J Reprod Immunol. 68(1):1-7. doi: 10.1111/j.1600-0897.2012.01132.x.

NaveenKumar SK, Hemshekhar M, Kemparaju K, Girish KS. 2019. Hemin-induced platelet activation and ferroptosis is mediated through ROS-driven proteasomal activity and inflammasome activation: Protection by Melatonin. BiochimBiophys Acta Mol Basis Dis. 1;1865(9):2303-2316. doi: 10.1016/j.bbadis.2019.05.009.

Niu Z, Li R. 2020. Clinical study of novel coronavirus pneumonia prevention by melatonin. Reprod Biomed Online. 41(6):1156. doi: 10.1016/j.rbmo.2020.09.003.

Numis AL, Foster-Barber A, Deng X, Rogers EE, Barkovich AJ, Ferriero DM, Glass HC. 2019. Early changes in pro-inflammatory cytokine levels in neonates with encephalopathy are associated with remote epilepsy. Pediatr Res. 86(5):616-621. doi: 10.1038/s41390-019-0473-x.

Oelkers WK. 1996. Effects of estrogens and progestogens on the renin-aldosterone system and blood pressure. Steroids 61:166– 171. https://doi.org/10.1016/0039-128x(96)00007-4

Onk D, Onk OA, Erol HS, Özkaraca M, Çomaklı S, Ayazoğlu TA, Kuyrukluyıldız U, Ünver S. 2018. Effect of melatonin on antioxidant capacity, ınflammation and apoptotic cell death in lung tissue of diabetic rats. Acta Cir Bras. 33(4):375-385. doi: 10.1590/s0102-865020180040000009.

Öztürk G, Akbulut KG, Güney Ş. 2020. Melatonin, aging, and COVID-19: Could melatonin be beneficial for COVID-19 treatment in the elderly? Turk J Med Sci. 22;50(6):1504-1512. doi: 10.3906/sag-2005-356.

Pal M, Berhanu G, Desalegn C, Kandi V, 2020. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. Cureus 12(3), e7423.doi: https://doi.org/10.7759/cureus.7423

Parasher A. 2021. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. Postgrad Med J. 97(1147):312-320. doi: 10.1136/postgradmedj-2020-138577.

Parlakpinar H., Polat S., Acet H.A., 2019. Pharmacological agents under investigation in the treatment of coronavirus disease 2019 and the importance of melatonin. Fundam Clin Pharmacol. 2021 Feb;35(1):62-75. doi: 10.1111/fcp.12589. Epub 2020 Oct 14. PMID: 32657483; PMCID: PMC7405383.

Patanè L, Morotti D, Giunta MR, et al. Vertical transmission of COVID-19: SARS-CoV-2 RNA on the fetal side of the placenta in pregnancies with COVID-19 positive mothers and neonates at birth. Am J ObstetrGynecol MFM. 2020; https://doi.org/10.1016/j.

Pinto AL, Rai RK, Brown JC, Griffin P, Edgar JR, Shah A, Singanayagam A, Hogg C, Barclay WS, Futter CE. 2022. Ultrastructural insight into SARS-CoV-2 entry and budding in human airway epithelium. Nat Commun. 25;13(1):1609. doi: 10.1038/s41467-022-29255-y.

Presicce P, Park CW, Senthamaraikannan P, Bhattacharyya S, Jackson C, Kong F, Rueda CM, DeFranco E, Miller LA, Hildeman DA, Salomonis N, Chougnet CA, Jobe AH, Kallapur SG. 2018. IL-1 signaling mediates intrauterine inflammation and chorio-decidua neutrophil recruitment and activation. JCI Insight. 22;3(6):e98306. doi: 10.1172/jci.insight.98306.

Racicot K, Mor G. 2017. Risks associated with viral infections during pregnancy. J Clin Invest 127:1591–1599. https://doi. org/10.1172/JCI87490

Ramos E, López-Muñoz F, Gil-Martín E, Egea J, Álvarez-Merz I, Painuli S, Semwal P, Martins N, Hernández-Guijo JM, Romero A. 2021. The Coronavirus Disease 2019 (COVID-19): Key Emphasis on Melatonin Safety and Therapeutic Efficacy. Antioxidants (Basel). 20;10(7):1152. doi: 10.3390/antiox10071152.

Reiter RJ, Manchester LC, Tan DX. 2010. Neurotoxins: free radical mechanisms and melatonin protection. Curr Neuropharmacol. 8(3):194-210. doi:10.2174/157015910792246236

Reiter RJ, Abreu-Gonzalez P, Marik PE. 2020. Therapeutic Algorithm for Use of Melatonin in Patients With COVID-19. Front Med (Lausanne). 15;7:226. doi: 10.3389/fmed.2020.00226.

Reiter RJ, Sharma R, Ma Q, Dominquez-Rodriguez A, Marik PE, Abreu-Gonzalez P. 2020. Melatonin Inhibits COVID-19-induced Cytokine Storm by Reversing Aerobic Glycolysis in Immune Cells: A Mechanistic Analysis. Med Drug Discov. 6:100044. doi: 10.1016/j.medidd.2020.100044.

Ribeiro VR, Romao-Veiga M, Romagnoli GG, Matias ML, Nunes PR, Borges VTM, Peracoli JC, Peracoli MTS. 2017. Association between cytokine profile and transcription factors produced by T-cell subsets in early- and late-onset pre-eclampsia. Immunology. 2017 Sep;152(1):163-173. doi: 10.1111/imm.12757.

Richard DM, Dawes MA, Mathias CW, Acheson A, Hill-Kapturczak N, Dougherty DM. L-Tryptophan: Basic Metabolic Functions, Behavioral Research and Therapeutic Indications. Int J Tryptophan Res. 23;2:45-60. doi: 10.4137/ijtr.s2129.

Rodríguez-Rubio M, Figueira JC, Acuña-Castroviejo D. 2020. A phase II, single-center, double-blind, randomized placebo-controlled trial to explore the efficacy and safety of intravenous melatonin in patients with COVID-19 admitted to the intensive care unit (MelCOVID study): a structured summary of a study protocol for a randomized controlled trial. Trials. 5;21(1):699. doi: 10.1186/s13063-020-04632-4.

Romero A., Ramos E., López-Muñoz F., et al, 2020. Coronavirus Disease 2019 (COVID-19) and Its Neuroinvasive Capacity: Is It Time for Melatonin? Cell Mol Neurobiol. 2020 Aug 9:1–12. doi: 10.1007/s10571-020-00938-8. Epub ahead of print. PMID: 32772307; PMCID: PMC7415199.

Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. Science. 2014;345(6198):760-765. https://doi.org/10.1126/scien ce.1251816

Salem D, Katranji F, Bakdash T. 2020. COVID-19 infection in pregnant women: Review of maternal and fetal outcomes. Int J Gynaecol Obstet. 152(3):291-298. doi: 10.1002/ijgo.13533.

Salles C. 2020. Correspondence COVID-19: Melatonin as a potential adjuvant treatment. Life Sci. 15;253:117716. doi: 10.1016/j.lfs.2020.117716.

Sánchez-López AL, Ortiz GG, Pacheco-Moises FP, Mireles-Ramírez MA, Bitzer-Quintero OK, Delgado-Lara DLC, Ramírez-Jirano LJ, Velázquez-Brizuela IE. 2018. Efficacy of Melatonin on Serum Pro-inflammatory Cytokines and Oxidative Stress Markers in Relapsing Remitting Multiple Sclerosis. Arch Med Res. 2018 Aug;49(6):391-398. doi: 10.1016/j.arcmed.2018.12.004.

Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, Campagnole-Santos MJ. 2018. The ACE2/Angiotensin-(1-7)/MAS Axis of the Renin-Angiotensin System: Focus on Angiotensin-(1-7). Physiol Rev. 1;98(1):505-553. doi: 10.1152/physrev.00023.2016.

Schumacher A, Brachwitz N, Sohr S, Engeland K, Langwisch S, Dolaptchieva M, Alexander T, Taran A, Malfertheiner SF, Costa SD, et al. 2009. Human chorionic gonadotropin attracts regulatory T cells into the fetal-maternal interface during early human pregnancy. J Immunol. 1;182(9):5488-97. doi: 10.4049/jimmunol.0803177.

Schwartz DA. 2020. An Analysis of 38 Pregnant Women With COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. Arch Pathol Lab Med. 1;144(7):799-805. doi: 10.5858/arpa.2020-0901-SA.

Sehirli AO, Sayiner S, Serakinci N. 2020. Role of melatonin in the treatment of COVID-19; as an adjuvant through cluster differentiation 147 (CD147). Mol Biol Rep. 47(10):8229-8233. doi: 10.1007/s11033-020-05830-8.

Shafiei E, Bahtoei M, Raj P, Ostovar A, Iranpour D, Akbarzadeh S, Shahryari H, Anvaripour A, Tahmasebi R, Netticadan T, Movahed A. 2018. Effects of N-acetyl cysteine and melatonin on early reperfusion injury in patients undergoing coronary artery bypass grafting: A randomized, open-labeled, placebo-controlled trial. Medicine (Baltimore). 97(30):e11383. doi: 10.1097/MD.0000000000011383.

Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA.2020. Placental pathology in COVID-19. medRxiv. doi: 10.1101/2020.05.08.20093229. Update in: Am J Clin Pathol. 8;154(1):23-32.

Silasi M, Cardenas I, Kwon JY, Racicot K, Aldo P, Mor G. 2015. Viral infections during pregnancy. Am J Reprod Immunol. 73(3):199-213. doi: 10.1111/aji.12355.

Shneider A, Kudriavtsev A, Vakhrusheva A. 2020. Can melatonin reduce the severity of COVID-19 pandemic? Int Rev Immunol. 39(4):153-162. doi: 10.1080/08830185.2020.1756284.

Simko F, Hrenak J, Dominguez-Rodriguez A, Reiter RJ. 2020. Melatonin as a putative protection against myocardial injury in COVID-19 infection. Expert Rev Clin Pharmacol. 13(9):921-924. doi: 10.1080/17512433.2020.1814141.

Simko F, Reiter RJ. 2020. Is melatonin deficiency a unifying pathomechanism of high risk patients with COVID-19? Life Sci. 1;256:117902. doi: 10.1016/j.lfs.2020.117902.

Smithgall MC, Liu-Jarin X, Hamele-Bena D, Cimic A, Mourad M, Debelenko L, Chen X. 2020. Third-trimester placentas of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive women: histomorphology, including viral immunohistochemistry and in-situ hybridization. Histopathology. 77(6):994-999. doi: 10.1111/his.14215.

Soliman A, Lacasse AA, Lanoix D, Sagrillo-Fagundes L, Boulard V, Vaillancourt C. 2015. Placental melatonin system is present throughout pregnancy and regulates villous trophoblast differentiation. J Pineal Res. 59(1):38-46. doi: 10.1111/jpi.12236. Epub 2015 Apr 20. PMID: 25833399.

Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. 2016. Physiological changes in pregnancy. Cardiovasc J Afr. 27(2):89-94. doi: 10.5830/CVJA-2016-021.

Subbarao K, Mahanty S. 2020. Respiratory Virus Infections: Understanding COVID-19. Immunity. 52(6):905-909. doi:10.1016/j.immuni.2020.05.004.

Sungnak W., Huang N., Bécavin, C. et al, 2020. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 26, 681–687 (2020).https://doi.org/10.1038/s41591-020-0868-6

Tamura H., Nakamura Y., Terron M. P., et al, 2008. Melatonin and pregnancy in the human. ReprodToxicol. 2008 Apr;25(3):291-303. doi: 10.1016/j.reprotox.2008.03.005. Epub 2008 Apr 1. PMID: 18485664.

Tan D. X., Hardeland R., 2020. Targeting Host Defense System and Rescuing Compromised Mitochondria to Increase Tolerance against Pathogens by Melatonin May Impact Outcome of Deadly Virus Infection Pertinent to COVID-19. Molecules. 2020 Sep 25;25(19):4410. doi: 10.3390/molecules25194410. PMID: 32992875; PMCID: PMC7582936.

Tang N. L., Chan P. K., Wong C. K., et al, 2005. Early enhanced expression of interferon-inducible protein-10 (CXCL-10) and other chemokines predicts adverse outcome in severe acute respiratory syndrome. Clin Chem 2005;51:2333–40

Tang N., Bai H., Chen X., et al, 2020. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J ThrombHaemost 18:1094– 1099. https://doi.org/10.1111/jth.14817 1

Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. 2020.The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 20(6):363-374. doi: 10.1038/s41577-020-0311-8.

Tesarik J. 2020. Melatonin: a fertility-friendly anti-coronavirus agent. Reprod Biomed Online. 2020 Dec;41(6):1155. doi: 10.1016/j.rbmo.2020.09.004.

Tordjman S, Chokron S, Delorme R, Charrier A, Bellissant E, Jaafari N, Fougerou C. 2017. Melatonin: Pharmacology, Functions and Therapeutic Benefits. Curr Neuropharmacol. 2017 Apr;15(3):434-443. doi: 10.2174/1570159X14666161228122115.

Vieira E, Mirizio GG, Barin GR, de Andrade RV, Nimer NFS, La Sala L. 2020. Clock Genes, Inflammation and the Immune System-Implications for Diabetes, Obesity and Neurodegenerative Diseases. Int J Mol Sci. 21;21(24):9743. doi: 10.3390/ijms21249743.

Vriend J, Reiter RJ. 2015. Melatonin feedback on clock genes: a theory involving the proteasome. J Pineal Res. 58(1):1-11. doi:10.1111/jpi.12189

Wang X, Bian Y, Zhang R, Liu X, Ni L, Ma B, Zeng R, Zhao Z, Song X, Liu C. 2019. Melatonin alleviates cigarette smoke-induced endothelial cell pyroptosis through inhibiting ROS/NLRP3 axis. BiochemBiophys Res Commun. 5;519(2):402-408. doi: 10.1016/j.bbrc.2019.09.005.

Wang Z, Zhou F, Dou Y, Tian X, Liu C, Li H, Shen H, Chen G. 2018. Melatonin Alleviates Intracerebral Hemorrhage-Induced Secondary Brain Injury in Rats via Suppressing Apoptosis, Inflammation, Oxidative Stress, DNA Damage, and Mitochondria Injury. Transl Stroke Res. 9(1):74-91. doi: 10.1007/s12975-017-0559-x.

Wastnedge EAN, Reynolds RM, van Boeckel SR, Stock SJ, Denison FC, Maybin JA, Critchley HOD. 2021. Pregnancy and COVID-19. Physiol Rev. 1;101(1):303-318. doi: 10.1152/physrev.00024.2020. 020.

Welin AK, Svedin P, Lapatto R, Sultan B, Hagberg H, Gressens P, Kjellmer I, Mallard C. 2007. Melatonin reduces inflammation and cell death in white matter in the mid-gestation fetal sheep following umbilical cord occlusion. Pediatr Res. 61(2):153-8. doi: 10.1203/01.pdr.0000252546.20451.1a.

Werenberg Dreier J, Nybo Andersen AM, Hvolby A, Garne E, Kragh Andersen P, Berg-Beckhoff G. 2016. Fever and infections in pregnancy and risk of attention deficit/hyperactivity disorder in the offspring. J Child Psychol Psychiatry. 57(4):540-8. doi: 10.1111/jcpp.12480.

Wichniak A, Kania A, Siemiński M, Cubała WJ. 2021. Melatonin as a Potential Adjuvant Treatment for COVID-19 beyond Sleep Disorders. Int J Mol Sci. 11;22(16):8623. doi: 10.3390/ijms22168623.

Wiersinga WJ, Rhodes A, Cheng AC. 2020. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 324(8):782–793. doi:10.1001/jama.2020.12839

Williams WP, McLin DE, Dressman MA, Neubauer DN. 2016. Comparative Review of Approved Melatonin Agonists for the Treatment of Circadian Rhythm Sleep-Wake Disorders. Pharmacotherapy. 36(9):1028-41. doi: 10.1002/phar.1822.

Wongchitrat P, Shukla M, Sharma R, Govitrapong P, Reiter RJ. 2021. Role of Melatonin on Virus-Induced Neuropathogenesis-A Concomitant Therapeutic Strategy to Understand SARS-CoV-2 Infection. Antioxidants (Basel). 2;10(1):47. doi: 10.3390/antiox10010047.

World Health Organization, 2016. Guidance for Managing Ethical Issues in Infectious Disease Outbreaks.

World Health Organization, 2020. Transmission of SARS-CoV-2: implications for infection prevention precautions. 2020 Jul 9. WHO/2019-nCoV/Sci_Brief/Transmission_modes/2020.3

Yan J, Guo J, Fan C, Juan J, Yu X, Li J, Feng L, Li C, Chen H, Qiao Y. 2020. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. Am J Obstet Gynecol. 223(1):111.e1-111.e14. doi: 10.1016/j.ajog.2020.04.014.

Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, Shang Y. 2020. Thrombocytopenia and its association with mortality in patients with COVID-19. J ThrombHaemost. 18(6):1469-1472. doi: 10.1111/jth.14848.

Yawno T, Castillo-Melendez M, Jenkin G, Wallace EM, Walker DW, Miller SL. 2012. Mechanisms of melatonin-induced protection in the brain of late gestation fetal sheep in response to hypoxia. Dev Neurosci. 2012;34:543-551.

Yu JC, Khodadadi H, Malik A, Davidson B, Salles ÉDSL, Bhatia J, Hale VL, Baban B. 2018. Innate Immunity of Neonates and Infants. Front Immunol. 30;9:1759. doi: 10.3389/fimmu.2018.01759.

Zambrelli E, Canevini M, Gambini O, D'Agostino A. 2020. Delirium and sleep disturbances in COVID-19: a possible role for melatonin in hospitalized patients? Sleep Med. 70:111. doi: 10.1016/j.sleep.2020.04.006.

Zarezadeh M, Khorshidi M, Emami M, Janmohammadi P, Kord-Varkaneh H, Mousavi SM, Mohammed SH, Saedisomeolia A, Alizadeh S. 2020. Melatonin supplementation and pro-inflammatory mediators: a systematic review and meta-analysis of clinical trials. Eur J Nutr. 59(5):1803-1813. doi: 10.1007/s00394-019-02123-0.

Zetner D, Andersen LPH, Rosenberg J. 2015. Pharmacokinetics of Alternative Administration Routes of Melatonin: A Systematic Review. Drug Res. 66:169–173. doi: 10.1055/s-0035-1565083.

Zhang JM., An J. 2007. Cytokines, inflammation, and pain. International anesthesiology clinics, 45(2), 27–37. https://doi.org/10.1097/AIA.0b013e318034194e

Zhang Y, Li X, Grailer JJ, Wang N, Wang M, Yao J, Zhong R, Gao GF, Ward PA, Tan DX, Li X. 2016. Melatonin alleviates acute lung injury through inhibiting the NLRP3 inflammasome. J Pineal Res. 60(4):405-14. doi: 10.1111/jpi.12322.

Zhang Y, Liu X, Bai X, Lin Y, Li Z, Fu J, Li M, Zhao T, Yang H, Xu R, et al. 2018. Melatonin prevents endothelial cell pyroptosis via regulation of long noncoding RNA MEG3/miR-223/NLRP3 axis. J Pineal Res. 64(2). doi: 10.1111/jpi.12449.

Zhao X, Jiang Y, Zhao Y, Xi H, Liu C, Qu F, Feng X. 2020. Analysis of the susceptibility to COVID-19 in pregnancy and recommendations on potential drug screening. Eur J Clin Microbiol Infect Dis. 39(7):1209-1220. doi: 10.1007/s10096-020-03897-6.

Zhao Z, Lu C, Li T, Wang W, Ye W, Zeng R, Ni L, Lai Z, Wang X, Liu C. 2018. The protective effect of melatonin on brain ischemia and reperfusion in rats and humans: In vivo assessment and a randomized controlled trial. J Pineal Res. 65(4):e12521. doi: 10.1111/jpi.12521.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 28;395(10229):1054-1062. doi: 10.1016/S0140-6736(20)30566-3.

Zhu N, Wang W, Liu Z, Liang C, Wang W, Ye F, Huang B, Zhao L, Wang H, Zhou W, et al. 2020. Morphogenesis and cytopathic effect of SARS-CoV-2 infection in human airway epithelial cells. Nat Commun. 6;11(1):3910. doi: 10.1038/s41467-020-17796-z.

Ziegler CGK, Miao VN, Owings AH, Navia AW, Tang Y, Bromley JD, Lotfy P, Sloan M, Laird H, Williams HB, et al. 2021. . Impaired local intrinsic immunity to SARS-CoV-2 infection in severe COVID-19. Cell. 2;184(18):4713-4733.e22. doi: 10.1016/j.cell.2021.07.023.

Legends

Figure 1: The physiology of pregnancy

Maternal serum pro-inflammatory and anti-inflammatory cytokine levels are regulated during pregnancy. At the first trimester, embryo implantation and placentation benefit from systemic pro-inflammatory cytokines. In the second trimester, the inflammatory state is low and Th1 cell-mediated immunity is compromised. The inflammatory cytokines are presented in the third trimester.

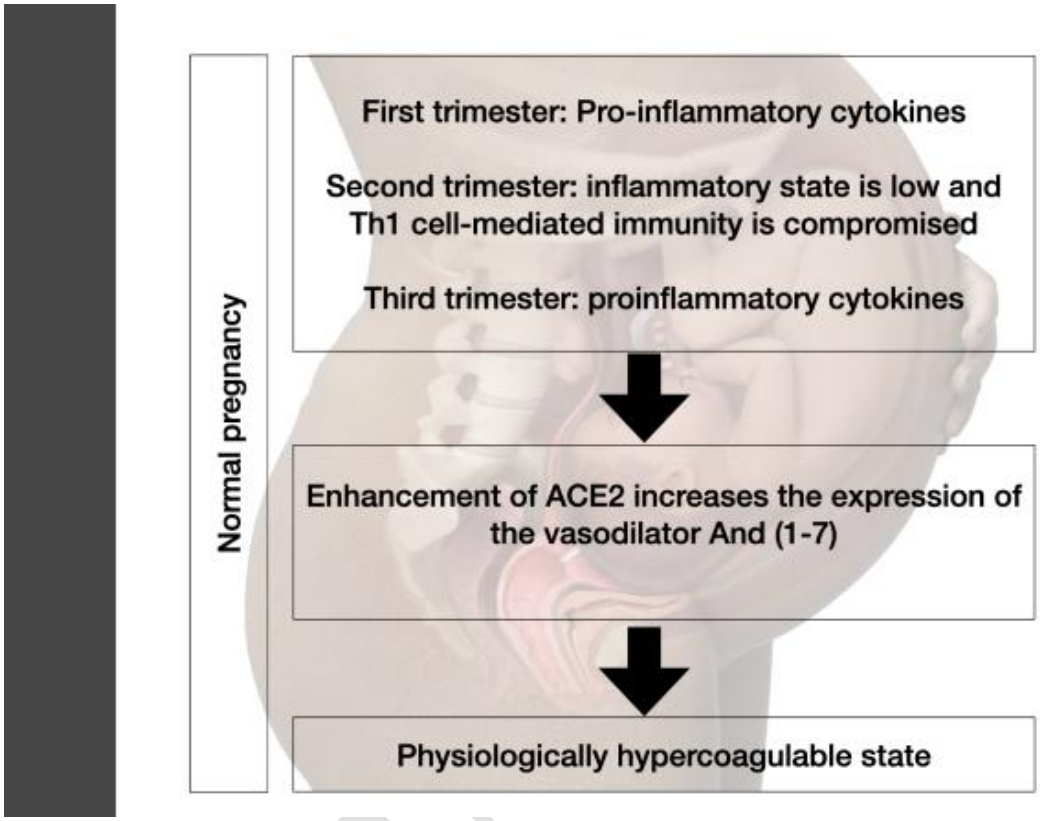

Figure 2: The SARS-CoV-2 infection in pregnant women

The physiologic and immunologic adaptations during pregnancy may result in systemic effects that determine the susceptibility and severity of respiratory infections. Pregnancy could be considered a physiologically hypercoagulable state with raised coagulation factors. Thus, the SARS-CoV-2 infection in pregnant women can entail several obstetric complications such as placental inflammation, vertical transmission, viral infection of the placenta, fetal inflammatory syndrome. These complications can be induced by both direct viral effects (e.g., via ACE-2 receptors and viral replication) and subsequent hyperinflammatory responses.

Figure 3: The melatonin synthesis

Melatonin synthesis depends on dark periods during which the tryptophan hydroxylase enzyme converts L-tryptophan to 5-hydroxytryptophan. Subsequently, 5-hydroxytryptophan is decarboxylated by the aromatic enzyme L-amino acid decarboxylase to form 5-hydroxytryptamine (serotonin). When the light stimulus fades, norepinephrine activates the expression of cAMP, serotonin-N-acetyltransferase (SNAT), and hydroxyindole-O-methyltransferase (HOM). SNAT converts serotonin to N-acetyl-serotonin, and HOM

methylates it to melatonin. Melatonin is mainly synthesized and secreted by the pineal gland, but other organs in the reproductive system can also synthesize this hormone.

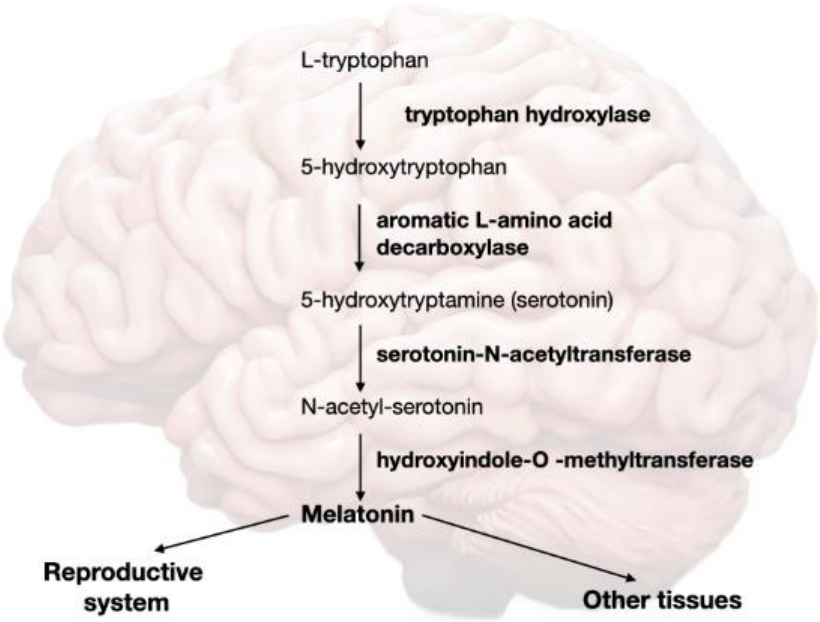

Figure 4: Effects of melatonin in COVID-19

Melatonin is a promising adjunctive drug for viral infections because of its anti-inflammatory, anti-apoptotic, immunomodulatory, and powerful antioxidant properties. The effects are mediated by melatonin receptors (MTs) that channel the response to hormones throughout the organism. The possible anti-inflammatory mechanisms of melatonin involve upregulation of sirtuin-1 and suppression of NF-E2-related factor 2, promoting a decrease in the proinflammatory cytokines (TNF, IL-6, IL-10) and an increase in the anti-inflammatory cytokine IL-10. Also, it could affect the anti-inflammatory cascades and ACE-2 and c-Jung signaling. Melatonin could inhibit NLRP3 inflammasome protecting macrophages from pyroptosis presented in lung pathology caused in SARS-CoV-2 infection. The antioxidant properties of this indolamine are linked to increased activity of superoxide dismutase, glutathione peroxidase, reductase, and catalase.

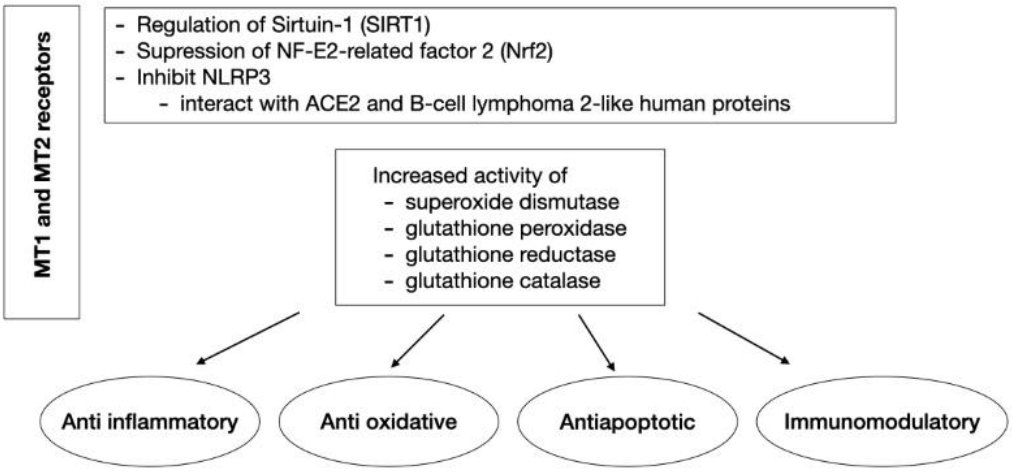

Figure 5: The role of melatonin in pregnant women with coronavirus

Host response to coronavirus infection in pregnancy induces the production of proinflammatory, antiinflammatory cytokines and oxidized products that activate the maternal immune system and can cross the placental barrier. The developing fetus can be impacted directly by viral infection as a result of vertical transmission or indirectly by viral infection of the placenta. Melatonin has several neuroprotective properties through the reduction of oxidative stress, proinflammatory response and apoptotic cell death. This indoleamine could decrease neuroinflammation and perinatal brain injury, thus preventing neuromotor impairment. Circadian rhythm and melatonin are essential in controlling the endocrine system and metabolism; these systems are involved in the production of cortisol, which plays a key role in lung maturation of the fetus.