Review

Immune System and Psychological State of Pregnant Women during COVID-19 Pandemic: Are Micronutrients Able to Support Pregnancy?

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Abstract: The immune system is highly dynamic and susceptible to many alterations throughout pregnancy. Since December 2019, a pandemic caused by coronavirus disease 19 (COVID-19) has swept the globe. To contain the spread of COVID-19, immediate measures such as quarantine and isolation were implemented. These containment measures have contributed to exacerbated situations of anxiety and stress, especially in pregnant women, who are already particularly anxious about their condition. Alterations in the psychological state of pregnant women are related to alterations in the immune system, which is more vulnerable under stress. COVID-19 could therefore find fertile soil in these individuals and risk more severe forms. Normally a controlled dietary regimen is followed during pregnancy, but the use of particular vitamins and micronutrients can help counteract depressive-anxiety states and stress, can improve the immune system, and provide an additional weapon in the defense against COVID-19 to bring the pregnancy to fruition. This review aims to gather data on the impact of COVID-19 on the immune system and psychological condition of pregnant women and to assess whether some micronutrients can improve their psychophysical symptoms.

Keywords: immune system; pregnancy; stress; COVID-19; vitamins; micronutrients

1. Introduction

Pregnancy is a unique and particular immune state [1]. The maternal immune system must tolerate the paternal antigens present in the fetus and at the same time maintain its ability to defend against possible pathogens. Physiological pregnancy consists of three stages: first pro-inflammatory phase (I trimester), anti-inflammatory phase (II and III trimesters), and second pro-inflammatory phase (late III trimester and childbirth) [2]. During pregnancy, the immune system and the body itself are highly dynamic and subject to several changes [2].

The uterus expands by increasing pressure in the abdominal cavity, lifting the diaphragm. The sub-costal angle of the rib cage increases and the ribs expand outward, decreasing chest compliance by about 35–40% [3,4]. This natural mechanism explains the
“physiological dyspnea” of pregnant women and can complicate a possible diagnosis of lung disease. In addition, the residual functional capacity (RFC) is reduced, leading to compensatory respiratory alkalemia [5], shifting the oxygen balance toward the fetus. This respiratory state, following a viral infection, could easily decompensate, leading to further lung complications [6].

During pregnancy, estrogens and progesterone also play a key role in modulating the immune response [7]. Estrogens implement the response of T helper 2 lymphocytes (Th2) and humoral immunity [8]. These hormones are crucial in modulating the interaction between mother and fetus and in blocking the natural killer cells (NKs) that could be activated against fetal cells [7], showing that these mechanisms are crucial for a successful pregnancy. Plasma volume increases, lowering hemoglobin concentration. Hemoglobin is an oxygen carrier, so its diminishing can cause a decrease in the oxygen content of the blood. Anemia in pregnant women is found in about 38% [9]. In addition, many pregnant women suffer from iron deficiency, further aggravating the anemic condition. Iron is also involved in immunosurveillance mechanisms, modulating the proliferation and activation of immune cells and cytokines [4,10], phylogenetically conserved non-antigen-specific polypeptide mediators that serve as communication signals between immune system cells, organs, and tissues [11]. Moreover, during pregnancy, psychological state and dietary balance play an important role in the modulation of the immune system and the success of pregnancy [12].

The pandemic initiated by coronavirus disease 19 (COVID-19) has spread throughout the world since December 2019, when it was first reported in Wuhan, China. This disease had a globally disastrous effect, causing the death of more than 6 million people by May 2022 [13]. The main symptoms caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are fever, cough, vomit, diarrhea, anosmia, dysgeusia, and, in worst cases, interstitial bilateral pneumonia, multiple organ dysfunction, and consequences that can lead to death [14–17]. To limit the diffusion of COVID-19, urgent measures such as quarantine and isolation were adopted [18].

All these events increased individual psychological stress, exacerbating it in pregnant women, resulting in uncontrolled and compensatory food search, such as snacks and sugar-rich foods [19], and lack of exercise [20]. Stress and depression in quarantine have contributed to the practice of unhealthy and unregulated diets [21]. This has led to metabolic problems, such as increased body fat and insulin resistance, and immune problems, with an increased screening of pro-inflammatory cytokines [22].

Psychological stress is known to be one of the causes of hyperglycemia, which in pregnant women can lead to gestational diabetes [23]. Malnutrition is related to impaired immune function and chronic inflammatory states [24,25]. Adhesion to the Mediterranean Diet before, during, and after pregnancy, could reduce the risks related to the fetus and improve mood and immune system. In this sense, the use of natural and nutraceutical supplements could represent the keystone to support the successful outcome of pregnancy, strengthen the immune system, and counteract stress and depression [26–30].

Recently the use of nutraceuticals and natural compounds as an alternative or integrative therapy is receiving growing interest [31,32]. Polyphenols, such as anthocyanins, and micronutrients, such as minerals and vitamins, are becoming regular supplements in the diet. They possess a wide range of therapeutic biological effects, such as cholesterol-lowering [33], antioxidant [34–37], hypoglycemic, neuroprotective [38], antitumoral [39], antiviral, antibacterial, immunostimulant [31,39,40], and antidepressant [30]. Recently the role of vitamins as a therapeutic complement for SARS-CoV-2 infection has been investigated, with encouraging results [41].

This review aims to provide useful information on how COVID-19 affected the immune system and psychological state of pregnant women during the pandemic and to assess whether some micronutrients can limit or even improve the psycho-physical state of pregnant women and their clinical profile.
2. Immune System of Pregnant Women during COVID-19

Pregnant women represent a vulnerable segment of the population at high risk of serious COVID-19 infection, and they are 1.5 times more subject to be admitted to the Intensive Care Unit (ICU) than non-pregnant women [42]. However, the presence of infection was not related to adverse pregnancy outcomes [43]. Vertical transmission of infection from mother to fetus is extremely limited [44,45], although several studies have shown the presence of the virus in the placenta [46,47]. To date, studies have not shown frequent verticalization events of infection; however, anti-SARS-CoV-2 immunoglobulin G (IgG) has been found in newborns of COVID-19 positive women [48,49]. Subsequently, by laboratory techniques (RT-qPCR), a possible mother-to-fetal transmissibility rate of 11% within the first 48 h of life was estimated [50]. SARS-CoV-2 receptors in fetal organs and the maternal-fetal interface have also been demonstrated [51,52]. During a physiological pregnancy, the immune system changes supporting the tolerance of the fetus and protecting the body from external pathogens. The ratio between regulatory T cells (Treg) and T helper lymphocytes 17 (Th17) is the key to maintain this mechanism [46]. The Treg cells and the cytokines they produce play a key role in the preservation and development of the fetus [53], while the Th17 cells are responsible for the defense against pathogens. This balance during pregnancy shifts in favor of Treg cells, which increase both at the systemic level and on the mother-fetus side [54]. An uncontrolled increase of Th17 cells, and thus a decapensation in this delicate balance, can lead to rejection of the fetus [55] and other severe complications such as abortion, preeclampsia, and preterm birth [46].

Infection with SARS-CoV-2 causes an imbalance of this ratio in favor of an increased level of Th17 cells, leading to a state of uncontrolled systemic phlogosis, risking very serious complications for the outcome of pregnancy [46]. In a normal pregnancy, T and B-cell-mediated immunity decrease, especially during the third trimester [56], with high levels of interleukin 4 and 10 (IL-4, IL-10) and interferon γ (IFN γ) [57]. Several studies have shown that infection with the influenza A virus during pregnancy has enhanced the phlogistic response, exacerbating cytokine levels [7,58]. Pregnant women are more exposed to respiratory viral infections, such as influenza A, SARS-CoV-1, and MERS-CoV-1 [59,60]. The Centre for Disease Control and Prevention (CDC) has shown that COVID-19 positive pregnant patients do not have a higher risk of death than their non-pregnant counterparts [61,62]. In a study by Chen et al., it was noted that the cytokine response was suppressed in pregnant women with SARS-CoV-2 [15,63]. Immunological and hormonal variables have been credited for the low mortality risk. A key role in limiting COVID-19 induced damage is played by estrogens and progesterone.

Estrogen receptors are commonly expressed in white blood cells. CD4+ T cells express high levels of estrogen α receptors, while B cells express higher levels of β receptors [64]. Monocytes and CD8+ cells express lower but almost similar levels of both receptors [64]. In particular, estradiol (E2) shows an immunomodulatory and anti-inflammatory effect [65,66], inhibiting the production of IL-6, IL-1β, and Tumor Necrosis Factor α (TNFα), important in the formation of cytokine storm induced by SARS-CoV-2. It also exhibits inhibitory action on CCL2 chemokine, blocking the migration of monocytes and neutrophils at the sites of flogosis [65]. E2 decreases the release of IL-17 by Th17 and promotes Treg cells, also enhancing fetal tolerance [65]. Estrogens cooperate in limiting COVID-19 pathogenesis by interfering with pro-inflammatory cytokines. In a mouse model, female mice showed lower viral concentrations, with less infiltration of monocyte macrophages and neutrophils with lower levels of IL-6, IL-1β, TNFα, and CCL2, showing less lung damage and lower mortality (20%) than males (80%) [67]. The surgical removal of the ovaries led to equal percentages between male and female mice, demonstrating the protective effect of estrogens.

Progesterone (P4) also exhibits immunomodulatory and anti-inflammatory activity and is secreted in large quantities during pregnancy. P4 receptors are normally expressed by several immune cells, such as macrophages, dendritic cells, lymphocytes, mast cells, and eosinophils [65]. It has an inhibitory effect on cytokines IL-1β and IL-12 and shifts
the immune balance towards Treg cells, promoting and supporting tolerance towards the fetus [65,68] (Figure 1).

Figure 1. Summary of progesterone immunomodulatory mechanism. P4 directly influences T cell activation and differentiation by modulating TCR signal transduction or indirectly by generating tolerant antigen-presenting cells (APCs) such as dendritic cells (DC) that inhibit T cell activation during TCR interaction. P4 can also inhibit cellular cytotoxicity. P4 can promote placental tissue growth and invasion at the maternal-fetal interface by inducing immune-tolerant phenotypes of macrophages, natural killer (NK), and T regulatory (Treg) cells, as well as exhausting activated CD4 and CD8 T cells that have interacted with placental-derived fetal-paternal antigens. Chemoattractant molecules produced on placental tissue help these tolerant leukocytes migrate to maternal-fetal contact. Created with BioRender.com.

Concentrations of P4 similar to those present in the lutein phase conferred protection against influenza A-induced pneumonia in mice, decreasing the inflammatory state, improving lung function, and stimulating cell proliferation [69]. Scientific evidence shows that P4 also has an antiviral activity in VeroE6 cells infected with SARS-CoV-2 [70]. P4 and human chorionic gonadotropin may act by inhibiting Th1, containing cytokine storm, and limiting the evolution of severe forms of COVID-19 [71].

Pregnant women during the first and third trimesters show a pro-inflammatory state that could facilitate the cytokine storm induced by SARS-CoV-2, causing more severe pathological conditions in these patients [72]. The transition during pregnancy from a pro-inflammatory state to an anti-inflammatory phase may depend on estrogens and progesterone, to better assist the fetal tolerance mechanism [73]. Pregnant women appear to be relatively protected from serious COVID-19-induced outcomes [74,75]. During pregnancy, there are several adaptive changes in the respiratory and immune systems that increase morbidity in pregnant women [76]. In the third trimester of pregnancy, there is an intensification in circulating phagocytes and dendritic cells, immune cells that are evolutionarily conserved with the role of antigen-presenting cells (APC) [77–79], capable of producing IFN type I, essential for the antiviral response. In addition, a decrease in T, B, and NK cells is evident [80]. A possible release of viral RNA in cells activates Toll-like receptors
(TLRs), a group of phylogenetically conserved receptors [81–87], which induce the release of pro-inflammatory cytokines. These activate epithelial cells that recruit innate immune cells (NK cells and neutrophils). In addition, dendritic cells exhibit antigen by activating mediated CD4+ and CD8+ T responses [88]. Alterations due to COVID-19 infections can lead to preeclampsia, preterm birth, and emergency cesarean surgery [89]. The immune profile of pregnant and non-pregnant women is almost similar, differing only in lower blood white cell counts in pregnant women COVID-19 positive [15,90].

One of the consequences of COVID-19 infection is lymphopenia, accompanied by a major release of cytokines, called a “cytokine storm”, which leads to a very severe form of bilateral pneumonia, with extensive widespread tissue damage [91]. The susceptibility to this infection varies from individual to individual and is closely related to immune status. Immune dysfunction can therefore play an important role in the evolution of the disease [92,93]. Patients healed from COVID-19 showed a decrease in immature B cells, CD4+ memory T cells, and CD8+ T cells [94], while they had high plasma cell levels [95]. These data were compared with those of pregnant women who were COVID-19 positive after healing. Decreasing Th17 cells, belonging to memory cells and specific NK-virus cells (CD3-CD56+NKP46+) were found. NKP46+ is an NK cell activation receptor involved in interactions against pathogens [91]. Lymphopenia occurs during normal pregnancy. However, in pregnant women with SARS-CoV-2, no major changes were found in this particular condition. Marked infiltration of CD68+ macrophages has been observed in the placenta, which had slight hypoxic characteristics, but it did not cause any particular problem during childbirth [91].

3. Psychological Profile of Pregnant Women during COVID-19

Pregnancy involves a series of changes both hormonal and psychological, altering the emotional and sensitive state, due to the uncertainty, unpredictability, and novelty of the situation [96,97]. This stage of life brings women into a particularly vulnerable psychopathological state. Between 10% and 16% of pregnant women suffer from depression [98], while about 8% suffer from anxiety [99], with serious effects on fetal and maternal health, such as preterm birth, low birth weight, postpartum depression, and hypothalamic-pituitary-adrenal dysregulation in newborns [100,101].

The COVID-19 pandemic, especially in its early stages, has had a very strong psychological impact, with an increasing prevalence and severity of mental health problems in the general population [102], especially in pregnant women, due to the implementation of health precautions such as quarantine, wearing masks, and social distancing [103]. Immunological functions, physiological changes, and susceptibility to infection in pregnant women lead to increased experiences of stress, anxiety, and depression. A cross-sectional study conducted in China between February and March 2020 examined a total of 560 pregnant women with a mean age of 25.8 years, who were given a questionnaire with questions about attitudes and mental health toward COVID-19. The psychological impact caused by this disease has been significantly associated with the trimester of pregnancy in which these women were found. There was more evidence of psychological distress during the second trimester of pregnancy, which also harmed health (work stress, stress at home, apprehension, and helplessness), although pregnant women paid more attention to their mental health and performed relaxation activities [104,105]. A similar result emerged in Italian pregnant women from a recent systematic review on the same subject [106].

During the first year of the pandemic, symptoms of depression, anxiety, and post-traumatic stress were detected. Among the major risk factors for the development of these psychopathologies are increased concern for the health of the other person, previous mental disorders, and lack of social support. Women who have had critical antenatal and postnatal experiences during the dissemination of COVID-19 tend to focus on the other, decentralizing, ignoring, and replacing personal needs to take care of the newborn [107].

A study by Ravaldi et al. (2020), also conducted in Italy, focused on expectations and concerns regarding childbirth of pregnant women during the pandemic. While in the
pre-pandemic period birth was accompanied by joy and excitement, after the spread of COVID-19, birth was associated with fear and sadness in more than half of the women interviewed. Other reasons related to fear were: loneliness, anguish, incapacity, and constraint [108]. In addition, isolation and separation from the family in the vicinity of childbirth have had a traumatic effect on COVID-19 positive women who, feeling lonely in the hospital setting, lacked social support, which is crucial in the perinatal period [109].

In the United States, a recent study (2021) found that 36.4% of pregnant women had clinically significant levels of depression, higher than the generally accepted prevalence of 20% [110]. One in five women also had clinical thresholds for generalized anxiety, and one in ten reported significant levels of post-traumatic stress disorder (PTSD). Women with a pre-existing diagnosis of mental health problems were also 1.5 to almost 4 times more likely to develop symptoms above the clinical threshold for anxiety, depression, and PTSD [111].

It is therefore necessary to provide psychological and social support for pregnant women during this period of uncertainty to avoid and minimize serious and invalidating perinatal and postnatal consequences for parents and the newborn [112]. Individuals with less social support experience greater mental health problems, especially at high levels of negative cognitive assessment. It is therefore considered necessary to raise awareness among health professionals of the increased risk to which pregnant women are exposed to mental health problems and, at the same time, to draw up clear guidelines to provide the best possible care for these patients, even in the event of a pandemic, using e.g., electronic interventions, as suggested by several studies [113,114]. Psychological therapies of choice include Cognitive Behavioral Therapy (CBT) and mindfulness-based approaches: both manage to reduce anxiety and depression in perinatal women through a structured treatment plan that trains people to internalize their attention to regularize their emotions and attention [112,115].

4. Micronutrients Helping Pregnancy

A correct intake of micronutrients can help the success of a physiological pregnancy and enforce the immune system of the mother, through diet or with additional dietary supplements [116]. These micronutrients, such as iron (Fe), zinc (Zn), selenium (Se), and vitamins play a key role in strengthening innate and specific immunity and preventing possible risks of pregnancy [117], while a deficiency of these nutrients can induce alterations in the immune system and make the organism most susceptible to infections [118,119]. A summary of the micronutrients herein described, with recommended intake and further suggestions can be found in Table 1.

Iron (Fe). Iron is an essential micronutrient and strengthens several immune functions. It is involved in the proliferation and differentiation of T cells and is a fundamental component of some enzymes linked to immune cells [120]. In addition, iron promotes the intrauterine growth of the fetus [121]. A deficiency, which in pregnant women is estimated for 50% of cases globally, reduces pro- and anti-inflammatory cytokines and may lead to anemia, morbidity, and prenatal mortality [122,123] and, in childhood, may contribute to the development of cognitive and behavioral problems [124,125]. In addition, low blood levels of Fe are related to altered functions of macrophages, NK cells, neutrophils, T and B cells [126]. Iron deficiency is associated with higher levels of prenatal depression [127,128]. Its integration can reduce the severity of respiratory viral infections and combat them [129].

Selenium (Se). Selenium is an essential micronutrient closely linked to the function of the immune system [124]. It shows immunostimulant effects on the proliferation of T and B cells and the activity of macrophages and NK cells [130,131]. Selenoproteins support the body’s defense system by influencing the functions of leukocytes [116]. Selenium deficiency is related to increased susceptibility to viral infections and, in pregnant women, may contribute to spontaneous abortion and preeclampsia [132]. The integration of this micronutrient increases resistance to viral infections, reduces the risk of prenatal mortality [133], and prevents hypertension [134]. Selenium intake also inhibits the development of postpartum depression, preventing its symptoms [135].
**Zinc (Zn).** Zinc plays a key role in modulating the immune system by promoting the development and function of macrophages, neutrophils, NK cells, inducing CD8+ T-cells proliferation, and assisting in the inflammatory process [120]. This micronutrient shows important antiviral properties, counteracting the replication of RNA viruses and inhibiting the replication of SARS-CoV at low concentrations [136]. Zinc deficiency is related to an altered phagocytic function, and reduced production of macrophages, DCs, and B and T cells [137]. Zn is essential for embryogenesis and fetal development. It is estimated that about 18% of pregnant women have a zinc deficiency. This can lead to premature birth, slowed fetal growth, increased risk of infection and also dwarfism [138], and alterations in brain development [139]. Integration of this micronutrient improves immune functions, protects against respiratory viral infections, reduces the risk of preterm birth, and lowers the incidence of gestational hypertension [140]. Zinc shows anxiolytic and antidepressant properties and its intake in higher quantities can better buffer the impact of stress on the development of symptoms of prenatal depression [141] and postpartum anxiety and depression [142].

**Vitamin A.** Vitamin A is a fat-soluble vitamin also called anti-inflammatory vitamin [116]. It plays an important role in the production, maturation, regulation, and function of macrophages, NK cells, neutrophils, innate lymphoid cells (ILCs), dendritic cells (DCs), T and B cells [143]. Its deficiency is related to respiratory infections [144], congenital fetal defects [145], gestational and diabetes mellitus [146], and schizophrenia [147]. Proper supplementation of this vitamin can reduce the risk of anemia [148] and shows to decrease the morbidity and mortality of some infectious diseases such as HIV [149]. Birth abnormalities have not been linked to vitamin A intakes of less than 10,000 IU per day during pregnancy. However, there are contradictory findings for daily doses ranging from 10,000 to 30,000 IU. Vitamin A intakes of more than 10,000 IU per day are not suggested for pregnant women who are well-nourished [150]. Moreover, excessive doses of vitamin A may be related to an increased risk of developing anxiety, depression, and mood disorders [151].

**Vitamin C.** Vitamin C, or ascorbic acid, is a water-soluble vitamin [152], which has high antioxidant activity and has the ability to fight infection. It modulates the migration of neutrophils to the site of infection and regulates phagocyte cells and NK cells [116]. In addition, it can mitigate the symptoms of respiratory infections [153]. Vitamin C is also able to promote intrauterine growth and childbirth [154]. Its integration contrasts preeclampsia, hypertension, and gestational diabetes [155]. With an average intake of 2000 IU/day of this vitamin, the risk of pregnancy-related complications, such as premature rupture of membranes, is decreased [156]. Vitamin C plays a key role in the biosynthesis of neurotransmitters such as serotonin and norepinephrine, lower levels of this vitamin have been found in patients with depression. Its intake also prevents schizophrenic and depressive symptoms [157,158].

**Vitamin D.** Vitamin D is a fat-soluble vitamin capable of regulating calcium homeostasis in bones [116]; moreover, it has powerful anti-inflammatory and immunomodulatory activities on innate and adaptive immunity, stimulating the differentiation of monocytes-macrophages and inhibiting the production of cytokines [159,160] (Figure 2). Calcium is extremely important for S100 protein expressed by immune cells, in particular macrophages, in immune response [161]. Vitamin D is related to a reduction in viral replication and viral infectivity [162,163]. Vitamin D in pregnant women has shown preventive effects against preeclampsia [164,165], and preterminal birth [166], playing a role in angiogenesis, placental implantation, and endothelial functions [167]. Vitamin D can regulate the immune system through its intracellular receptors (VDRs) present in monocytes, macrophages, B cells, T cells, DCs, and NKs [168]. It also modulates the synthesis of antimicrobial peptides, such as cathelicidin and defensins [169]. Vitamin D is also able to control and regulate the differentiation and function of NKs and DCs, promoting the presentation of antigens to lymphocytes [168]. Moreover, by reducing the secretion of IL-2, it leads to the suppression of Th lymphocytes, inhibiting the secretion of inflammatory cytokines such as IFNγ and IL-17 [168], helping to maintain a tolerogenic state [170,171].
Vitamin D modulates the proliferation of CD4+ lymphocytes [172] and promotes high levels of Treg cells, responsible for fetal tolerance [173]. Women with low vitamin D intake show a higher risk of developing anxiety and depressive symptoms early in pregnancy [174], with a higher probability of developing depression even after childbirth [175].

**Figure 2.** Vitamin D and its role on immune cells. The immunomodulatory effects of 1,25(OH)2D3 are depicted in this diagram. Different actors in the innate (red square) and adaptive immune (blue square) compartments are targeted by 1,25(OH)2D3. Vitamin D has been found to promote innate immune responses by increasing chemotaxis, antimicrobial peptides, and macrophage differentiation. Vitamin D also helps to enhance adaptive immune responses. For example, at the level of antigen-presenting cells, such as dendritic cells, vitamin D inhibits the surface expression of antigen complexed with MHCII, costimulatory molecules, and the production of cytokines IL12 and IL23, causing an indirect change in the Th1 and T-cell polarization. drives the Th17 phenotype towards a Th2 phenotype. Abbreviation: Th—T helper; NK—natural killer; DC—dendritic cells. Created with BioRender.com.

**Vitamin E.** Vitamin E is a fat-soluble vitamin with high antioxidant power and a high immunoregulatory capacity [176]. It modulates macrophages, NK cells, T cells, maturation and function of DCs, improves the humoral response, and reduces oxygen free radicals (ROS), nitrogen-free radicals (RNS), and prostaglandins [177,178]. Its integration improves the protection against viral infections and reduces the viral load of influenza [176,179]. In addition, this vitamin is capable to reduce and counteract oxidative stress during pregnancy, lowering the risk of preeclampsia and preterm birth [180]. Vitamin E levels in maternal blood are also correlated with improved fetal growth [181]. However, high doses of vitamin E (≥400 IU/day) are associated with an apparent decrease in birth weight, and its administration is suggested during the first trimester of pregnancy [182]. Low levels
of vitamin E are also associated with an increased risk of depression, and its intake in the prenatal period could represent a protective factor against the development of depressive symptoms [183].

Table 1. Micronutrients helping pregnancy with recommended intake.

| Micronutrients | Recommended Intake | Beneficial effects and Suggestions | References |
|----------------|-------------------|-----------------------------------|------------|
| Iron           | 16 mg/day         | Strengthens immune functions, helps in resolving anemia and constricting viral infections. Better if administrated during the first and second trimesters. | [120,129] |
| Selenium       | 70–80 µg/day      | Increases resistance to viral infections, reduces the risk of prenatal mortality, prevents hypertension, inhibits the development of postpartum depression. | [140,142] |
| Zinc           | 9.1 mg/day        | Improves immune functions, protects against respiratory viral infections, reduces the risk of preterm birth, lowers the incidence of gestational hypertension, has antidepressant effect and may prevent teratogenesis. | [138,141] |
| Vitamin A      | ≤10,000 IU/day    | Helpful for fetal development and for the regulation of the immune cells, but teratogenic at high doses. | [143,150] |
| Vitamin C      | 2000 IU/day       | Mitigates the effects of respiratory syndromes, helps in the biosynthesis of serotonin and norepinephrine, protects from pregnancy-related complications. | [116,156] |
| Vitamin D      | 600–1500 IU/day   | Implicated in the innate and adaptive immunity, protects against preeclampsia and preterm birth. | [160,166] |
| Vitamin E      | 32.8–44.7 IU/day  | Improves humoral response and protects against viral infections. Better if administrated at suggested doses during the first trimester of pregnancy. | [177,182] |

5. Conclusions

Pregnancy involves changes in women’s immune system and psycho-physical status, which may make them more vulnerable to infection. During COVID-19, altered immune response and stress may contribute to facilitating SARS-CoV-2 infection, exacerbating the symptoms. The use of vitamins and micronutrients, usually taken during pregnancy, can help strengthen the immune system, mood, and psycho-physical state of pregnant women. In addition, they can counteract the severe symptoms of COVID-19, helping to prevent infection.

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