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Review Article

Selected Micronutrients: An Option to Boost Immunity against COVID-19 and Prevent Adverse Pregnancy Outcomes in Pregnant Women: A Narrative Review

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Abstract

The coronavirus disease-19 (COVID-19) negatively affects immune system. It is linked with adverse pregnancy outcomes. These complications may be linked with the infections mediated deficiency of micronutrients in pregnant women. COVID-19 cause's malabsorption of micronutrients thereby increases the risk of their deficiency. Both micronutrients deficiencies and poor micronutrients intake can compromise immune function and may increase the risk of pregnancy complications associated with COVID-19 infection. Vitamin A, C, D, E, and selected minerals iron (Fe), selenium (Se), and zinc (Zn) are the micronutrients essential for immuno-competency and play a significant role in the prevention of adverse pregnancy outcomes. Immune function and pregnancy outcomes can be improved by adequate intake of micronutrients in diet or in supplements form. Based on regulatory links between viral infection, micronutrients, immunity, and pregnancy outcomes, this review highlights the role of micronutrients in boosting immunity to reduce or prevent pregnancy complications in COVID-19 infected women.

Keywords: COVID-19; Micronutrients; Immune function; Pregnancy outcomes

Introduction

Nowadays, the coronavirus disease 2019 (COVID-19) is one of the most challenging public health threats across the globe. The emergence of COVID-19 infection was reported in Wuhan, Hubei Province, China, in Dec 2019 (1), declared as global pandemic by WHO on 11th Mar 2020 (2). COVID-19 infection is highly contagious and escalating rapidly around the world. Globally, it has infected more than 28 million people as of 11th Sep, 2020, including the general population and pregnant women (3).

Pregnancy is a state of physiological changes and partial immune suppression of the body predisposes pregnant women to viral infections. These changes can put pregnancy at higher risk and may increase the risk of pregnancy complications

through respiratory viral infection (4). Changes in immunological responses such as the development of immunologic adaptations that allow pregnant women to tolerate an antigenically distinctive fetus eventually may increase the risk of COVID-19 infection (5). COVID-19 infection may have adverse effects on pregnancy outcomes, causing problems such as fetal distress, premature birth, newborn respiratory distress syndrome, and even neonatal death (6). Moreover, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) are also known to be responsible for adverse pregnancy outcomes (7, 8).

Successful pregnancy outcomes and healthy maternal immune systems rely on adequate intake of micronutrients. Micronutrients including vitamins (A, C, D, E,) and minerals (Fe, Se, Zn) have a vital role in sustaining immune competency and preventing adverse pregnancy outcomes. The immune response is compromised with inadequate nutrition that predisposes individuals to infection. During pregnancy, deficiency of certain vitamins and minerals may increase the risk and severity of infection that result in pregnancy complications. Enrichment and fortification of diet with micronutrients can boost immunity against infection and prevent such consequences (9-11).

Viral Infection and Immunity in Pregnancy

Pregnancy is a unique immunological state, in which maternal immune system protects maternal health and growing fetus from invading foreign pathogens. Immune cells such as natural killer (NK) cells and monocytes respond more strongly to viral infection, however, some immune cells function (T and B cells) are down-regulated during pregnancy (12). In response to Hepatitis C virus in pregnant women, trophoblast cells and immune cells constantly produce Toll-like receptors (TLRs) and Nod-like receptors (NLRs) to combat such virus. Trophoblast cells can control viral replication by secreting interferon-beta (IFNβ) which further induces antiviral responses in the body (13). However, it is not surprising that one of the molecular pathways called type-1 interferon (type 1 IFN) can actively inhibited by viruses (14). Furthermore, Epstein–Barr virus (EBV) can also reduce IFNβ expression by inhibiting placental interferon regulatory factor 3 phosphorylation (IRF3), resulting in decrease antiviral responses (15). In animal models, the influenza A virus protein non-structural 1 (NS1), associated with reduced production of interferon-alpha (IFNα) and IFNβ (16). The decreased production of IFNα and IFNβ would reduce the receptivity of the immune cells at the maternal-fetal interface and would decrease their capability to respond and control microorganisms. The presence of viral infection can decline IFNβ signaling and inhibit IFNβ regulators, leading to abolish its immunomodulatory effects and may induce inflammation (17). Based on the recent literature, COVID-19 infection is associated with cytokine-storm, lymphopenia, and inflammation. Pregnant women in their first and third trimester are produced pro-inflammatory state and the cytokine-storm because of COVID-19 infection that may induce more severe inflammation and leads to pregnancy complications (18-20).

Effect of Viral Infection on Pregnancy Outcomes and Micronutrients Absorption

Inflammation induced by COVID-19 infection may associate with adverse pregnancy outcomes such as miscarriage, preterm birth, still birth; affect several aspects of fetal brain development, and even preeclampsia in pregnancy. In such cases, the increased level of maternal inflammatory responses and the level of inflammatory cytokines including interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)-α may affect fetal brain development and circulatory system, and can increase the risk of fetal mental disorders (21). Moreover, coronavirus including SARS-CoV, MERS-CoV, and SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2) are associated with miscarriages, intrauterine growth restriction (IUGR), preterm birth, low birth weight, and perinatal death. However, there is no vertical transmission of SARS-CoV, MERS-CoV and SARS-CoV-2 from mothers with SARS,

MERS, and COVID-19 to their fetuses (22). There has always been an intricate link between COVID-19 infection and micronutrients absorption. COVID-19 infection may affect absorption of micronutrients, cause certain complications such as diarrhea, and fever (22). The malabsorption and nutrients losses during diarrhea, can lead to weak immune system, micronutrients deficiency and aggravate infection. In addition, fever substantially increases micronutrients requirements in viral infected individuals (22, 23).

Role of Micronutrients in Immunity and Pregnancy Outcomes

The immune system plays a key role in protecting body against infections; consist of innate and adaptive immunity. Innate immunity considered as first line of defense against infections through physical protectors (skin and epithelial lining of the gastrointestinal and respiratory tracts), biochemical barriers (secretions, gastric acids and mucus), phagocytes, leukocytes, and natural killer cells. If innate immunity fails to combat with infection, a more complex adaptive immunity is triggered, mediated by T and B lymphocytes, which produces specific antibodies to kill and destroy the invading pathogens (24).

Pregnancy is a critical period for fetal growth and insufficient micronutrients intake can lead to impaired fetal development, predisposing neonates to chronic conditions later in life, poor maternal health, and adverse neonatal outcomes (25). Pregnancy complications including preeclampsia, pregnancy-induced hypertension, intrauterine growth restriction (IUGR), low birth weight (LBW), and preterm delivery predict maternal-neonatal lifelong morbidity and mortality (26). Poor or insufficient micronutrients intake may associate with compromised immune system. However, micronutrients such as vitamins (A, C, D, E,) and minerals (Fe, Se, Zn) can improve the immune system and prevent adverse pregnancy outcomes (9, 25).

Vitamin A

Vitamin A is one of the fat-soluble vitamins known as "anti-inflammatory vitamin". It contributes in the production, regulation, maturation, and functions of the immune cells including macrophages, neutrophils, natural killer T cells, dendritic cells (DCs), innate lymphoid cells (ILC), T cells (Thymus cell), and B cells (Bone marrow cells) (27). Its deficiency is associated with impaired intestinal immune responses and increased the risk of mortality associated with respiratory infection (28). Moreover, its supplementation has shown a significant reduction in morbidity and mortality in different infectious diseases such as diarrheal disease, measles-related pneumonia, and human immunodeficiency virus (HIV) infection (29, 30). Level of vitamin A in serum is reduced with the advancing of gestational age, thus favoring its deficiency (31). Human and animal models studies demonstrated that its deficiency is associated with congenital defects (32), IUGR (33), schizophrenia spectrum disorders (34), diabetes mellitus, gestational diabetes (35), and anorectal malformations (36). However, its sufficient intake can reduce the risk of anemia, LBW, vertical transmission of HIV (37), while excessive supplementation should also be avoided in pregnancy (38). Therefore, an adequate vitamin A intake can be chosen as a basic option for enhancing the immune system prevents COVID-19 infection and adverse pregnancy outcomes.

Vitamin C

Vitamin C, a water-soluble vitamin known as ascorbic acid (39) is a potential antioxidant that reduces the risk of inflammation and susceptibility to infections (40). It supports various functions of the innate and adaptive immunity including epithelial barrier function, protecting leukocytes from oxidative stress, migration of neutrophils to the infection site, regulation of antimicrobial activities of phagocyte cells, natural killer (NK) cell functions, and reduction of lymphocyte proliferation and differentiation. Its administration to patients enhances the functions of various immune cells and ameliorates the severity of respiratory infection such as pulmonary tuberculosis, pneumonia, and coronavirus infections (41-43). In human-controlled trials, vitamin C supplementation significantly reduced the incidence

of pneumonia, suggesting that it might prevent the susceptibility of lower respiratory tract infections under certain conditions (44). Vitamin C is crucial for embryogenesis, promoting fetal growth, progression of pregnancy, and delivery (45). In an animal model, fetus was protected against lipopolysaccharide-induced intrauterine fetal death and IUGR (46). Vitamin C in plasma decreases with advancing in gestational age (47) and its deficiency is associated with various pregnancy complications, especially in the third trimester (48). Its supplementation found to reduce the risk of oxidative stress and may be important to prevent pregnancy complications, including preeclampsia, gestational hypertension, gestational diabetes, IUGR, and endothelial dysfunction (49, 50). Therefore, sufficient vitamin C intakes could be a promising option to strengthen immune system that prevent COVID-19 infection and reduces negative pregnancy results.

Vitamin D

Vitamin D, a fat-soluble vitamin that is crucial to maintain calcium homeostasis and bone health (40). In addition to these classical functions, its anti-inflammatory and immunomodulatory effects could not be ignored in the immune system. It plays a fundamental role both in innate and adaptive immunity (41). To protect the body against pathogens, it promotes the differentiation of monocytes to macrophages; reduce immune cell proliferation and cytokine production. During influenza infection, through immune response the lungs epithelial cells start the conversion of inactive vitamin D to active vitamin D, which in turn promotes the production of cathelicidin. Increased production of cathelicidin is associated with reduce severity of infection and viral replication (47, 48). However, reduced vitamin D level in calves is reported to increase risk of the bovine coronavirus infection (51). However, therapeutic dose of vitamin D showed a statistically significant (42%) reduction in the incidence of influenza infection (52). It has various kinds of actions in pregnancy, including its effect on angiogenesis, placental implantation, oxidative stress, and endothelial functions (53). In the COVID-19 pandemic, many people are advised to stay at home. Therefore, they will not be able to spend time outdoors and expose skin to the sun, which may increase the risk of vitamin D deficiency. Deficiency of maternal vitamin D is common in pregnancy due to insufficient dietary intake and less exposure to sun that associated with preeclampsia (54, 55), preterm birth (56), LBW (57, 58), and also later in life associated with autoimmune diseases (59), asthma (60), and type 1 diabetes (61). Moreover, many observational and randomized clinical trials found that its supplementation is beneficial to both mother and developing fetus (62). Therefore, vitamin D could be one of the effective choices to boost immunity, reduce severity of COVID-19 infection, and prevent adverse maternal-neonatal outcomes.

Vitamin E

Vitamin E, a fat-soluble vitamin is known as an antioxidant and its immunomodulatory effect has been observed in different animal and human studies (63). It regulates macrophages which serve as antigen presenting cells (APC) and regulate NK cells and T cells by producing cytokines, while reduces reactive oxygen species (ROS), reactive nitrogen species (RNS), and prostaglandins (64). It expedites activities of NK cells; regulates the maturation and functions of dendritic cells (DCs), increases interleukin-2 (IL-2) producing capacity of T cells, and enhances the humoral response of immune system (65-68). The decreased vitamin E status in calves associated with increased risk of bovine coronavirus (51). Its supplementation enhances resistance against infectious disease and loweres viral titer of influenza (63, 69, 70). It decreases oxidative stress during pregnancy that may cause preeclampsia, preterm delivery, and LBW (50, 71). In a population-based study, maternal vitamin E status was positively associated with fetal growth (72). It has shown positive effect on pregnancy outcomes under some conditions (73, 74). Therefore, vitamin E supplementation is likely to amplify immunity, promote resistance against COVID-19 infection and improve pregnancy outcomes.

Iron (Fe)

Iron (Fe) is one of the essential micronutrients and involved in many immunological functions such as production and regulation of cytokines, generation of ROS that kill pathogens, differentiation and proliferation of T lymphocytes and essential component of certain enzymes which are important for the functioning of immune cells (75, 76). Its deficiency affects the functions of macrophages, neutrophils, NK cells, B cells, and T cells. Moreover, Fe deficiency harms both pro- and anti-inflammatory cytokines including IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, TNF-α, and IFN-γ (77). Medicinal Fe and food fortification may reduce the risk and severity of respiratory infections (78). It promotes normal growth and development of fetus (79). Its deficiency affects more than 50% of all pregnant women in both developed and developing countries and may lead to anemia, IUGR, SGA, perinatal morbidity and mortality, induces maternal-neonatal stress, and can damage fetal erythrocytes. Furthermore, Fe deficiency can cause long-term cognitive and behavioral problems in childhood. Iron supplementation in pregnancy showed significantly higher mean birth weight and lower incidence of LBW (80, 81). Fe supplementation could be effective for strengthening immunity, reduce the risk and severity of COVID-19 infection and prevent maternal-neonatal morbidity and mortality.

Selenium (Se)

Selenium (Se) is also an essential micronutrient that plays a significant role in optimal immune responses. Selenium-dependent enzymes (selenoproteins) are crucial for the antioxidant host defense system affecting leukocytes function. Selenium has found an immuno-stimulator of innate immune cell functions, T cells proliferation, and NK cells activities (76, 82). Macrophages activity, functions of NK cells, activation and functions of T and B cells are impacted by dietary Se intake (83). Its insufficient intake is associated with susceptible immune system and increased incidence, severity, and progression of viral infections such as influenza, HIV and Coxsackie virus. However, its sufficient intake above the recommended levels has been shown to enhance immune competence and resistance against influenza infections in both human studies and animal models (84, 85). In general, pregnancy associated with increased oxidative stress. It reduces oxidative stress and prevents perinatal morbidity and mortality (86, 87). During pregnancy, Se level in maternal blood reduces significantly and cause miscarriage, pre-eclampsia, and IUGR (88, 89). Its supplementation has a positive effect on hypertension (90) therefore; Se may have the potential to boost immunity, reduce pregnancy complications and severity of COVID-19 infection.

Zinc (Zn)

Zinc (Zn) promotes the development and functions of macrophages, neutrophils, and NK cells (91). It modulates cytokine release, induces proliferation of CD8+ T cells, activates and develops T lymphocyte (75, 76) and prevents free radical-induced injury during inflammatory process (91). Its deficiency is associated with decreased phagocytosis, reduced production of macrophages, cytokines, decreased DCs maturation, and adversely affects the growth and function of T and B cells (92). Its supplementation increases immune functions and decreases the risk and severity of acute lower respiratory infections (91, 93). Increased intracellular concentration of Zn with pyrithione can efficiently reduce the RNA viruses' replication and at low concentrations inhibits the replication of SARS-CoV (94). Zn is essential for embryogenesis and normal fetal growth and its requirement in third trimester of pregnancy is two times higher than non-pregnant women. Due to its increased transfer from mother to developing fetus, concentration of Zn in maternal serum declines (95, 96). Its deficiency limits fetal growth and can be teratogenic in severe cases. Its supplementation reduces preterm birth, increases neonatal birth weight, reduces incidence of gestational hypertension and increases neonatal head circumference (96-98). Hence, Zn supplementation alone or in combination with pyrithione can enhance immunity, inhibit SARS-CoV-2 replications, and improve maternal-neonatal outcomes. The Recommended Dietary Allowances (RDA) of micronutrients is shown in Table 1.

Table 1: Recommended Dietary Allowances (RDA) during pregnancy

Micronutrients	*Units*	*Maternal age*		*Rich natural sources*
		≤18 years	*19-50 years*	
Vitamins				
Vitamin A	IU	2,500 (UL= 9,240)	2565 (UL= 10,000)	Mango, Carrots, Pumpkin, Sweet potato, Spinach
Vitamin C	Mg	80 (UL= 1800)	85 (UL = 2000)	Oranges, Grapefruit, Citrus fruits, Strawberries, Broccoli
Vitamin D	IU	200 (UL= 2000)	200 (UL= 2000)	Salmon, Fish, Milk, Cereals, Skin exposure to sunlight
Vitamin E	Mg	15 (UL= 800)	15 (UL= 1000)	Cereals, Tomato, Sunflower seeds, Nuts, Spinach
Minerals				
Iron (Fe)	Mg	27 (UL= 45)	27 (UL= 45)	Beef, Chicken, Spinach, Tomato, Chickpeas, Soybeans
Selenium (Se)	Mcg	60 (UL= 400)	60 (UL= 400)	Chicken, Fish, Duck, Nuts, Wheat flour, Ricotta chees
Zinc (Zn)	Mg	12 (UL =34)	11 (UL = 40)	Beef, Chicken, Duck, Cereals, Kidney beans

Note: IU (International Unit), mg (Milligram), mcg (Microgram), UL (The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects) (100-102)

Conclusion

The novel coronavirus disease (COVID-19) is highly contagious. It has infected more than three million people around the globe. Pregnant women are more susceptible to respiratory viral infections compared to non-pregnant women due to physiological and immunological changes. The COVID-19 infection may suppress the immune system in pregnancy and put pregnant women at higher risk of complications. The COVID-19 infection associated with inflammation and cytokine-storm that can cause adverse perinatal outcomes. Moreover, COVID-19 infection associated with diarrhea may affect absorption of micronutrients and increase the risk of micronutrients deficiency in pregnant women. Micronutrients deficiency in pregnancy associated with decline immune responses and adverse pregnancy outcomes including preeclampsia, preterm birth, LBW, IUGR, congenital anomalies, and perinatal mortality (Fig. 1).

In pregnancy, increased physiological changes require increased nutrients intake to support the fetus development, placental tissue, and hence successful pregnancy outcomes. Sufficient intake of micronutrients can prevent negative pregnancy outcomes and may boost immunity against COVID-19 infection in pregnant women. Due to malabsorption of micronutrients in COVID-19 infection and increased requirement of micronutrients in pregnancy, it is highly recommended for pregnant women to take the tolerable upper intake level (UL) of micronutrients. Pregnant women are encouraged to take variety of foods including, fresh vegetables and legumes, fruits, grains (high cereals fiber varieties), dairy products (milk, yogurt, cheese), meat (lean meat, fish, poultry, egg), and micronutrient supplements. However, excessive intake of micronutrient supplements should be avoided in pregnancy, which may increase the risk of adverse pregnancy outcomes (38, 99). We would suggest that randomized clinical studies to be conducted to explore the individual vitamins impact on immune function and pregnancy complications associated with micronutrients absorptions. In addition to develop specific mechanisms through which specific micronutrient modulates physiological, biochemical and immunological responses during pregnancy in context of precision nutrition.

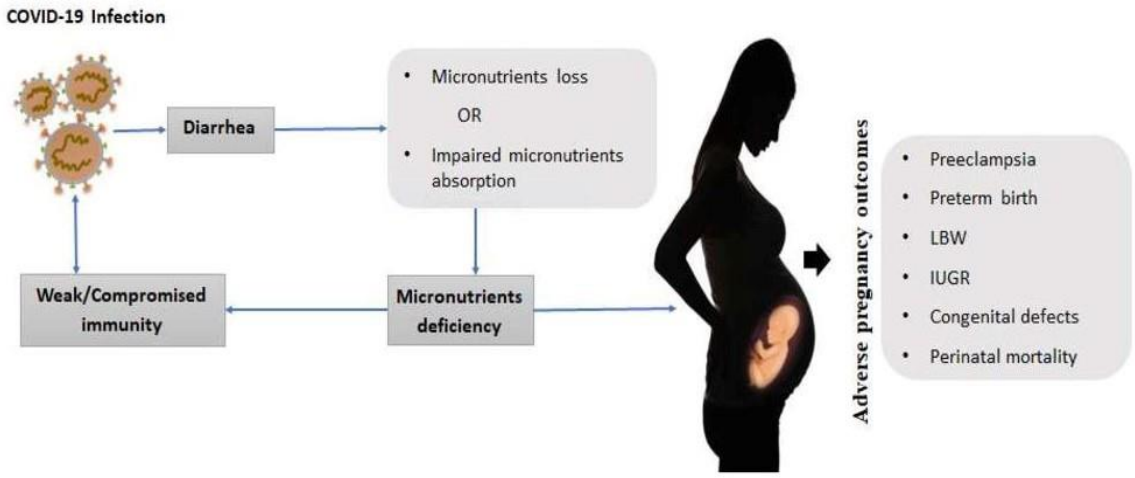

Fig. 1: A vicious cycle of COVID-19 infection and micronutrients deficiency with compromised immunity and adverse pregnancy outcomes (Original figure)

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest

The authors have no conflict of interest regarding this review.

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