Review Article

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Micronutrients Supplementation in Pregnant Women during COVID-19 Pandemy: Pros and Cons

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Abstract

Coronavirus can negatively affect the immune system. This complication can be exaggerated in pregnant women with micronutrient and elemental deficiencies. Also, coronavirus itself can induce micronutrients malabsorption and result in their severe deficiencies that can lead to increased risk of infection in these groups of patients. Serum calcium, zinc, iron, and selenium values have a positive correlation with PO2 values and a negative correlation with severe COVID-19 infection, lung involvement, fever, and C-reactive protein (CRP) concentration. In this mini-review study, the safety and efficacy of different suggested micronutrients including zinc, selenium, iron, vitamin A, C, D, E, and myo-inositol in pregnant women with COVID-19 have been discussed. According to the clinical practice findings and previous reports, administration of essential micronutrients including zinc, selenium, and iron and vitamins including vitamin A, B8, C, D, and E with optimum recommended dietary allowances (RDAs) during pregnancy would be promising and suggestive to improve maternal/neonatal complications during COVID-19 infection due to the enhanced immunity system against viral infection and COVID-19 pneumonia.

Keywords: COVID-19, coronavirus, pregnancy, micronutrients.

1. Introduction

More than one year has been passed since the first report of COVID-19 from Wuhan city of China. Soon this new virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was spread around the world and became a pandemic and till now, over 122 million people have been infected and over 2.69 million of them have been died due to COVID-19 infection. Many efforts have been done regarding different aspects of COVID-19 pharmacotherapy and its challenges (1-4). Coronavirus can negatively affect the immune system. This complication can be exaggerated in pregnant women with micronutrient and elemental deficiencies. Also, coronavirus itself can induce micronutrients malabsorption and result in their severe deficiencies that can lead to increased risk of infection in these group of patients. The most important micronutrients that can support the immune system are zinc, selenium, iron, vitamin A, C, D, and E. Results of a recent study reported that serum calcium, zinc, iron, and selenium values had positive correlation with PO2 values and negative correlation with severe COVID-19 infection, lung involvement, fever, and C-reactive protein (CRP) levels (5). So, it has been suggested that administration of supplemental micronutrients would be helpful to prevent the severe complications of COVID-19 infection in pregnant women (6). In this study the possible mechanisms, recommended dietary allowances (RDA), and suggested dose of

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different micronutrients in pregnant women with COVID-19 have been summarized.

2. Materials

Scientific publications on PubMed, Scopus, Google Scholar, and Up-to-date® databases were considered. The key search terms were COVID-19, pregnancy, vitamin A, vitamin C, vitamin D, vitamin E, myo-inositol, iron, selenium, zinc, and recommended daily allowance (RDA). In this regard, at first titles and abstracts of the related articles were reviewed. Then, suitable papers were considered to draft this review article.

3. Micronutrients

3.1. Vitamin A

Vitamin A and its metabolites have a pivotal role in immune cell response and susceptibility to infection. Vitamin A could play its role through the contribution in normal epithelial tissue differentiation, optimum maturation and function of immune cells including neutrophils, enhance phagocytic function of macrophages, and enhanced oxidative burst potential. So, vitamin A deficiency can result in altered immune response, barrier dysfunction, and increased susceptibility to different viral and bacterial infections (7). Furthermore, vitamin A deficiency during pregnancy can result in congenital defects, anorectal malformation, schizophrenia, gestational diabetes, and diabetes mellitus. Also, excessive administration of supplemental vitamin A should be avoided during pregnancy (6). Administration of excessive doses of vitamin A in pregnant women with COVID-19 would be associated with teratogenicity craniofacial malformation, and central nervous system (CNS), heart, and thymus abnormalities (8). It has been reported that the incidence of teratogenicity was significantly higher in pregnant women who consumed vitamin A over the threshold daily dose of 10000 units (9). So, the maximum dose of 10000 units/day or 25000 units once weekly should be considered during vitamin A administration in pregnant women with COVID-19 (10).

3.2. Vitamin C

Vitamin C deficiency during pregnancy could be accompanied by several pregnancy complications including gestational diabetes, gestational hypertension, and preeclampsia. So, administration of supplemental vitamin C would be promising in pregnant women who are infected with new coronavirus to prevent these complications during pregnancy and boosting of the immunity system (6). Vitamin C is an essential micronutrient that can exhibit its beneficial role in COVID-19 management through its antioxidant effects and acting as a co-factor and/or modulator of different immune pathways. Although many studies have been done on the clinical efficacy of vitamin C administration in COVID-19 management, results are still controversial and inconclusive. So, further larger studies and trials are required. The suggested doses of vitamin C administration in COVID-19 is too wide and controversial. Also, it has been considered both in oral and intravenous route of administration (11). The safety and efficacy of administration of high-dose intravenous vitamin C during pregnancy should be considered due to the possible passage of vitamin C through the placenta to the fetus (12). The RDA of vitamin C in pregnant women is 80 mg/day and the upper limit dose administration should not exceed over 1800 mg/day (10).

3.3. Vitamin D

Vitamin D3 (cholecalciferol) plays an important role in protection against respiratory tract viral infection through the modulation of the process of cytokine release and activation (13). Vitamin D deficiency during pregnancy would be associated with the risk of preeclampsia, preterm birth, and low weight birth, and respiratory tract viral infection. So, vitamin D administration would be essential to prevent maternal and neonatal complications and reduce the severity of COVID-19 infection during pregnancy by enhancing the potential of the immunity system against viral infection (13). Also, it has been reported that vitamin D deficiency was associated with higher rate of hospitalization due to acute respiratory tract infection (14). Further larger clinical trials are required to confirm the efficacy of vitamin D for COVID-19 prevention and treatment in different subgroups of patients with a minimum of 8-week follow up (15). The RDA for vitamin D during pregnancy would

be 15 mcg/day (600 unit/day). In pregnant women with concurrent vitamin D deficiency the total daily dose could be enhanced to 1000-2000 unit/day but in others who are not at risk of vitamin D deficiency, administration of doses that exceed the RDA should be avoided (10). Administration of high doses of vitamin D over a long period of time would be associated with hypercalcemia that can induce further heart and kidney injuries and bone weakness (15).

3.4. Vitamin E

Vitamin E is a fat soluble vitamin with antioxidant and immunomodulatory potential. Also, vitamin E administration could alleviate stress ulcer during pregnancy and furthermore could prevent from preeclampsia, low birth weight, and preterm delivery occurrence. It has been reported that administration of supplemental doses of vitamin E during pregnancy would be associated with immunity system amplification, improves resistance against COVID-19 infection, and better pregnancy outcomes (6). Vitamin E might also reduce the risk of infection through the positive effects in the interleukin 2 (IL-2) and T cell levels, augmentation of natural killer cell (NK cell) activity, and increment in the mitogenic lymphocyte responses. So, administration of supplemental doses of vitamin E would be associated with increased resistance against respiratory infection including COVID-19 infection (16). Administration of vitamin E in combination with other micronutrients during pregnancy was associated with decreased risk of placenta abortion (17). The RDA for pregnant women with COVID-19 is dependent on the age of the pregnant women, for pregnant female ≤18 years old would be 15 mg and the upper limit dose should not exceed the daily dose of 800 mg and for pregnant women between 19 and 50 years old is 15 mg and the upper limit dose should not be exceeded over the daily dose of 1000 mg (10).

3.5. Myo-inositol (vitamin B8)

Myo-inositol (vitamin B8), the precursor of inositol-3-phosphate, with the potential mechanism of anti-inflammatory, antioxidant, surfactant regeneration, and immune response regulation through the IL-6 cascade reduction can induce protective effects against COVID-19 especially in pregnant women (13). Also, myo-inositol could induce insulin sensitizing properties that can be considered as an additional therapeutic agent for the management of diabetes mellitus (DM) during pregnancy. Furthermore, myo-inositol with its anti-inflammatory, anti-oxidant, and insulin sensitizing properties could alleviate the pathogenesis of inflammation, oxidative stress, and insulin resistance during pregnancy (18). There is no RDA available for myo-inositol but myo-inositol with a daily dose of 4 g in 2 divided doses has been considered in pregnant women to prevent gestational diabetes mellitus (GDM) (18).

3.6. Iron

Iron as an essential trace element could affect host cell immunity and susceptibility to various infectious disease. Iron supplementation during pregnancy could be associated with a lower risk of low birth weight, a strengthened immunity system, and higher resistance against COVID-19 infection. Also, iron supplementation can prevent maternal/neonatal mortality and complications. So, iron is one of the most essential micronutrients that should be administered in pregnant women especially those who are infected with COVID-19 (6). Iron deficiency can induce thymus atrophy that can result in reduced naïve T cell counts and further effects on human immune response against infections. So, iron deficiency can enhance the susceptibility to respiratory tract infection including COVID-19. Also, iron overload can induce impaired immunity and harmful inflammatory consequences (7). So, the sufficient amount of iron supplement and regular serum iron monitoring is essential to avoid iron deficiency or iron overload during pregnancy in the current COVID-19 outbreak. The dietary reference intake for iron during pregnancy is 27 mg/day (10). Since iron overload would be a possible complication of COVID-19 infection, excess administration of iron supplement in pregnant women with COVID-19 should be avoided and administration of iron chelating agents including deferoxamine and lactoferrin in symptomatic patients with hyperferritinemia and plasma iron level of >500 µg/dL might be considered (3, 19).

3.7. Selenium

Selenium, as an anti-oxidant agent, can prevent oxidative stress during pregnancy and induce the immunity system. Selenium can act as a cofactor of glutathione peroxidase enzyme and further prevent oxidative cell damage of reactive oxygen species (ROS). The potential antiviral effect of selenium would be attributed to the anti-oxidant characteristic of selenite (Se4+) that can block the viral protein disulfide isomerase (PDI) and prevention from virus penetration to healthy cells (20). So, selenium administration during pregnancy would be accompanied by the reduced severity of COVID-19 infection and complications during pregnancy (6). There are several reports on the potential role of selenium in host cell immune response and susceptibility to infection (7). Selenium deficiency could be potentially associated with impaired acquired and innate immune response by affecting the B cells, T cells, reduced the ability of antibody production, and diminished NK cells activity. It has been reported that administration of supplemental doses of selenium (100-300 mcg/day) could induce immune response in elderly patients. Also, selenium supplementation with a daily dose of 50-100 mg in adult patients could improve the immune response against poliovirus (7). Results of a recent study revealed that selenium deficiency was associated with higher mortality rate among COVID-19 patients. Also, another study from china reported that selenium status was positively correlated with cure rate among COVID-19 patients. The potential mechanism of these associations would be the impact of selenium deficiency on viral mutation, replication, and the pathogenicity of RNA viruses such as SARS-CoV-2. Also, selenium might counteract with the harmful oxidative damage of the lung during COVID-19 infection (21). Further larger clinical trials are required to confirm the beneficial effects of selenium supplementation against COVID-19 infection. The RDA for selenium administration during pregnancy is 60 mcg/day (10).

3.8. Zinc

Zinc as an essential trace element with anti-inflammatory, immunomodulatory, antioxidant, and antiviral properties would be considered as a supplementary therapy in the management of infectious diseases including COVID-19 infection. Also, zinc might prevent from viral binding angiotensin-converting enzyme 2 (ACE2) through the reduction in Sirtuin 1 (SIRT-1) induced ACE (22). Severe zinc deficiency during pregnancy can result in limited fetal growth and teratogenic effects. So, administration of supplemental zinc during pregnancy would be valuable to boost the immune system, reduce coronavirus replication, and avoidance of maternal/neonatal complications during the COVID-19 pandemy (6). The potential antiviral effects of zinc could be attributed to the inhibition of RNA polymerase which is an essential enzyme for the replication RNA viruses including SARS-CoV-2. Also, zinc deficiency could result in reduced naïve B cell and T cell counts and impaired innate immune response through disabled phagocytosis process and reduced NK cell activities. Furthermore, zinc deficiency would be associated with recurrent respiratory tract infection and zinc supplementation was accompanied with shorter duration of common cold symptoms and could reduce the incidence and prevalence of pneumonia (7). Also, it has been reported that severe pre-existing zinc deficiency would be an important risk factor for progression to the severe type of COVID-19 infection (23). Results of a recent study revealed the impaired zinc-copper balance (Zn/Cu ratio) in pregnant women infected with COVID-19. Serum zinc level has been decreased in the mentioned pregnant women with COVID-19 during all their three semesters. Also, it has been shown that serum zinc level was inversely correlated with the inflammatory markers of COVID-19 including IL-6, erythrocyte sedimentation rate (ESR), and CRP (24). In the pregnant women involved with COVID-19, administration of supplemental zinc would be helpful to prevent COVID-19 severe complications and reduce the duration of hospitalization. COVID-19 in pregnant women can result in higher serum copper levels in first and third trimesters. In this regard, a diminished Zn/Cu ratio would be predicted in pregnant women with COVID-19 (6, 24). The RDA for zinc administration during pregnancy is 11 mg/day (10).

Table 1. The possible mechanism(s) and recommended dietary allowances (RDAs) of essential micronutrients for COVID-19 management in pregnant women.

Micronutrients	Possible mechanism(s)	Recommended daily allowance (RDA)
Vitamin A	Vitamin A might contribute in normal epithelial tissue differentiation, maturation and function of immune cells including neutrophils, enhance phagocytic function of macrophages and enhanced their oxidative burst potential.	10000 units/day or 25000 units once weekly
Vitamin C	Vitamin C, as an essential micronutrient, can exhibit its beneficial role in COVID-19 management through its antioxidant effects and acting as a co-factor and/or modulator of different immune pathways.	80 mg/day (up to 1800 mg/day)
Vitamin D3	Vitamin D3 (cholecalciferol) can play an important role in protection against viral respiratory tract infection through the modulation of the process of cytokine release and activation.	600 units/day (up to 1000-2000 units/day)
Vitamin E	Vitamin E with antioxidant and immunomodulatory properties might also reduce the risk of infection through the enhancement in the interleukin 2 (IL-2) and T cell levels, enhancement in natural killer cell (NK cell) activity, and increment in the mitogenic lymphocyte responses.	15 mg/day (up to 1000 mg/day)
Myo-inositol (vitamin B8)	Myo-inositol with its anti-inflammatory, anti-oxidant, and insulin sensitizing properties could alleviate the pathogenesis of inflammation and oxidative stress. Also, myo-inositol with the potential mechanism of anti-inflammatory, antioxidant, surfactant regeneration, and immune response regulation through the IL-6 cascade reduction can induce protective effects against COVID-19 infection.	4 g/day
Iron	Beneficial effect on host cell immunity and susceptibility to infection at optimum supplemental daily doses. Also, iron deficiency can induce thymus atrophy that can result in reduced naïve T cell counts and diminished immune responses against viral infection.	27 mg/day
Selenium	Selenium can act as a cofactor of glutathione peroxidase enzyme and further prevent from oxidative cell damage of reactive oxygen species (ROS). The potential antiviral effect of selenium would be attributed to the antioxidant characteristic of selenite (Se4+) that can block the viral protein disulfide isomerase (PDI) and prevention from virus penetration to healthy cells	60 mcg/day
Zinc	Zinc has anti-inflammatory, immunomodulatory, antioxidant, and antiviral properties. The potential antiviral effect of zinc could be attributed to the inhibition of RNA polymerase which is an essential enzyme for the replication RNA viruses such as SARS-CoV-2.	11 mg/day

4. Conclusion

So, according to our clinical practice and previous researches, administration of these essential micronutrients including zinc, selenium, and iron and vitamins including vitamin A, B8 (myo-inositol), C, D, and E with optimum recommended dietary allowances (RDAs) during pregnancy would be promising and suggestive to improve maternal/neonatal complications during COVID-19 infection due to the enhanced immunity system against viral infection and COVID-19 pneumonia (13, 24). The possible mechanism(s) and RDAs of these mentioned micronutrients for COVID-19 management during pregnancy have been summarized in Table 1.

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Conflict of Interest

None declared.

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