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The Impact Of Maternal Zinc Supplementation On Pregnancy Outcomes And Maternal Serum Zinc : A Systematic Review

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Background: Zinc is one of the important trace elements needed by the human body, because it is present in more than a hundred specific enzymes and functions as an important structural ion in transcription factors. Maternal Zn deficiency during pregnancy is associated with adverse pregnancy outcomes including abortion, preterm delivery, stillbirth, and fetal neural tube defects.Reduced placental zinc transport and fetal zinc supply could be a result of lower plasma zinc levels. Based on these findings, the United Nations Children's Fund (UNICEF) recommends that all pregnant women in impoverished countries take numerous micronutrient supplements, including zinc

Aim: to review journals on nutritional interventions through Zinc Supplementation for pregnant women on Pregnancy Outcomes and maternal serum zinc

Methods: Using an online journal database that provides free articles and journals in PDF form such as: Pubmed, Elsevier, Scinapse, Plos One and Google Scholar in studies published from 2010 to 2021. A total of 11 articles were used in this review.

Results : Nine articles were obtained on the effect of supplementation on pregnancy outcome. Only 3 studies support that there is a positive correlation between zinc supplementation and pregnancy outcome, while 6 studies show no significant effect of zinc supplementation on pregnancy outcome. One study showed that maternal zinc supplementation may increase infant birth weight among malnourished women, and two studies evaluating the effect of zinc intake during pregnancy on neonatal birth length reported that zinc supplementation can increase the length of the baby's birth length. Three articles showed the effect of

zinc supplementation on maternal zinc status, and overall showed that pregnant women who received zinc supplements had significantly higher serum zinc concentrations than those received the placebo.

Conclusion: There was no significant effect of zinc administration during pregnancy on pregnancy outcome but zinc supplementation can increase maternal zinc status.

Key Word : Zinc, Supplementation, Pregnancy.

Introduction

The World Health Organization (WHO) estimates that more than 2 billion people are deficient in key vitamins and minerals, especially vitamin A, iodine, iron and zinc.(1). Zinc is one of the important trace elements required by the human body, because it is present in more than a hundred specific enzymes and functions as an important structural ion in transcription factors. It is widely distributed throughout different tissues including brain, muscle, bone, liver and kidney, with very large amounts in prostate and eye parts, zinc has a key role in reproductive physiology, immune modulation, growth and development (2).

Zinc deficiency is estimated to be responsible for around 0.5 million maternal deaths and disability among children under the age of five in low-income countries, according to the Lancet series on maternal and child malnutrition**.**(3). Reduced placental zinc transport and fetal zinc supply could be a result of lower plasma zinc levels. Based on these findings, the United Nations Children's Fund (UNICEF) recommends that all pregnant women in impoverished countries take numerous micronutrient supplements, including zinc (4)

Around 82 percent of pregnant women around the world have lower zinc intake capacity than the recommended dietary requirement. Developed countries are attempting to reduce the incidence of zinc insufficiency through supplementation, while poor and medium income countries are unable to reduce the magnitude of zinc deficiency, which could be as high as 100%.(5). Premature neonates are more likely to develop zinc deficiency than full-term infants because they have insufficient body stores of zinc and a poor ability to absorb zinc from the gut, despite their high zinc requirements. Acrodermatitis enteropathica is a clinical manifestation of zinc insufficiency, with severity proportional to zinc level.(6). During breastfeeding, the zinc

concentration in human milk decreases from 2.5 μg/ml in the first month to 0.9 μg/ml after three months and 0.7 μg/ml after four months (7).

The World Health Organization (WHO) recommends a zinc intake of 1.1 to 2.0 milligrams per day during pregnancy (7). It is estimated that 100 mg of zinc is retained in the fetus, placental tissue, amniotic fluid, uterine and mammary tissue, and mother blood during pregnancy. (7)Excellent sources of zinc are red meat (especially offal), pumpkin and white beans (8).

Maternal Zn deficiency during pregnancy is associated with adverse pregnancy outcomes including abortion, preterm delivery, stillbirth, and fetal neural tube defects(9). In addition, during pregnancy, zinc deficiency can cause preterm labor, pregnancy-induced hypertension, low birth weight, and preeclampsia..(10). Low zinc consumption can also cause growth failure in the fetus or baby and impaired wound healing in childbirth and prevent the increase in enzyme activity. Zinc deficiency can increase the risk of pregnancy in the form of increased blood pressure and susceptibility to infection, besides the role of zinc in pregnant women is also closely related to the formation of body organs such as the palate, lips, brain, eyes, bones, lungs, and the baby's urogenital system. (11).

Maternal zinc deficiency during pregnancy increases the risk of low birth weight and small gestational age babies (12). However, other studies have also shown that taking daily zinc supplements may be associated with a 14% reduction in the risk of preterm delivery, but there is no convincing evidence that zinc supplementation during pregnancy produces other useful and important benefits.(13). Therefore, the aim of this literature review is to review journals on nutritional interventions through Zinc Supplementation for pregnant women on Pregnancy Outcomes and maternal zinc serum

Method

The study was conducted from January to April 2021. Study selection the systematic review use data base from the PubMed, Google Scholar, Cochcrane library, scinapse, and Proquest. The search criteria in the database, use the word "Zinc supplementation ", "Pregnancy OR Maternal ",and "outcome pregnant", growth with restrictions on articles

published during the last ten years (2010 to 2021), English language articles, open access . The inclusion criteria were (1) full-text articles were selected, (2) Targeting studies of pregnant women (3) This review is RCT study. Exclusion criteria were (1). Editorial, reports, conference proceedings, systematic review/ literature review, study protocol, case series and meta analysis. (2).Studies those participants who are not human.

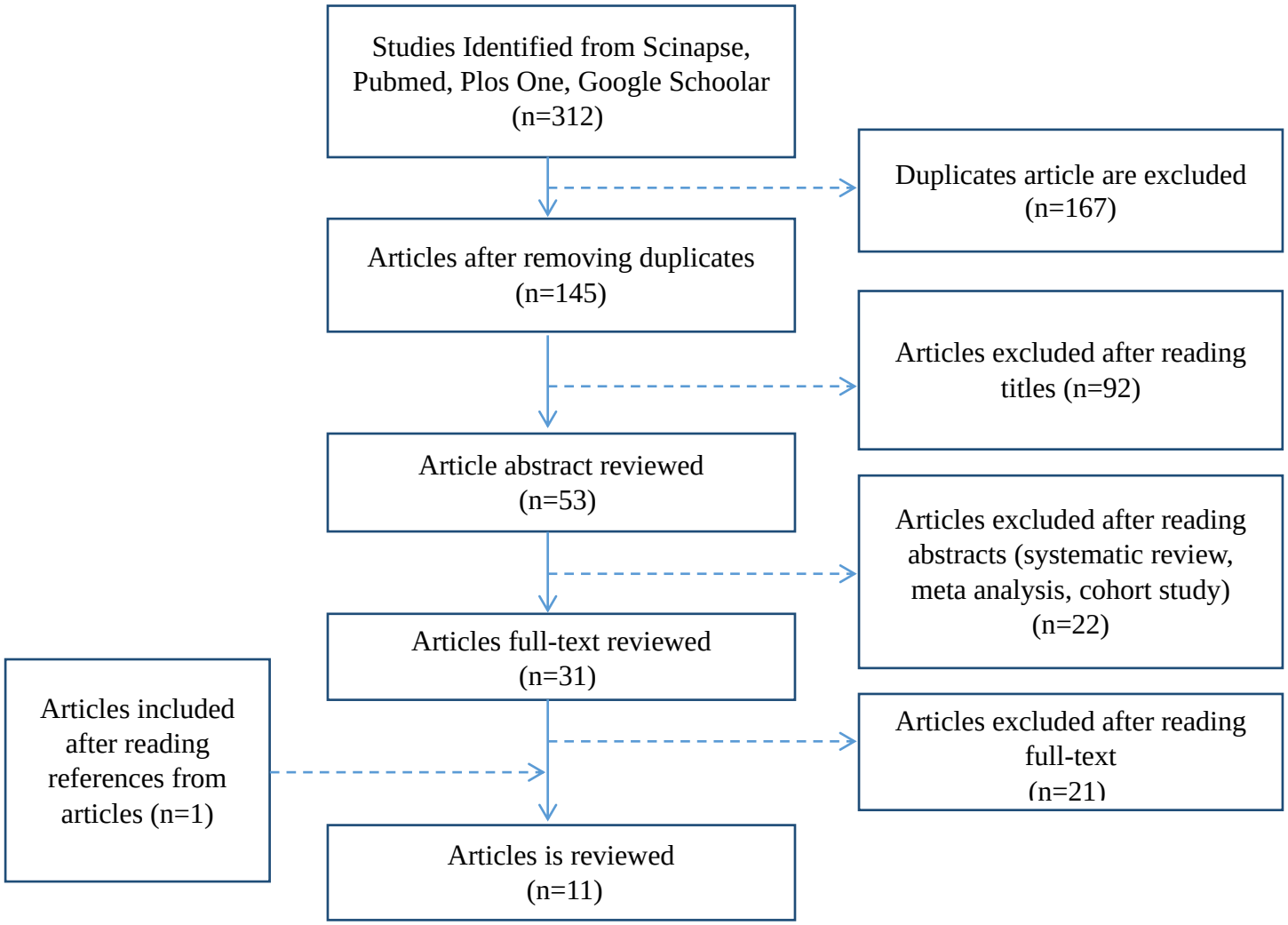

Figure 1. Flow chart for study based on PRISMA 2015 guideline

Result

The results of the literature search are presented in Table 1

No	Author/Place/ Year	Study Objective	Design	Study Outcome
1.	2015. Mesir (14)	To evaluate the effect of two Zn supplementation regimens on pregnancy outcome	a double-blind, randomised controlled trial	Zn supplementation was effective in reducing pregnancy complications and early neonatal infections among women with Zn deficiency in this trial.
2.	Azar Danesh,et al, 2010. Iran (15)	To assess the effect of high-dose zinc (Zn) supplementation during pregnancy on pregnancy outcomes in healthy pregnant women with previous preterm delivery in Isfahan, Iran..	a double-blind randomized, placebo-controlled trial.	Adding Zn supplementation during pregnancy to the routine care of women with previous preterm delivery had no significant effect on gestational age at delivery and birth weight but increased head circumference at birth..
3.	Endy P, et al, 2013. Indonesia(16)	To assess whether vitamin A and/or zinc supplementation given during pregnancy increases birth weight, length of delivery, neonatal morbidity, or infant mortality..	a double-blind, randomised controlled trial	Zn supplementation during pregnancy increases birth length after adjusting for maternal height and pre-pregnancy weight
4.	Mehri, Et al. 2019 Iran. (17)	To determine the effects of magnesium-zinc-calcium-vitamin D co-supplementation on parameters of inflammation and oxidative stress, and pregnancy outcomes among women with GDM	Follow-up of a randomized controlled trial	the findings of this study have demonstrated that magnesium-zinc-calcium-vitamin D cosupplementation for 6 weeks to women with GDM may reduce biomarkers of inflammation and oxidative stress.butGestational age, newborn's birth size and Apgar scores did not significantly change following co-supplementation of magnesium-zinc-calcium-vitamin D.

5.	M. Saaka, 2012, Ghana(18)	To determine the impact of zinc deficiency on indicators of iron status in pregnant women	a double-blind, randomised controlled trial	Combined iron-zinc supplementation is effective in increasing Hb and serum ferritin values in women with iron deficiency in early pregnancy but not in iron-sufficient women..
6.	Zahiri , et al, 2016, Iran(19)	To evaluate the impact of prenatal zinc supplementation on pregnancy outcome.	A randomized controlled trial	zinc supplementation 15 mg daily from 16 weeks of gestation until delivery does not improve pregnancy outcome.
7.	Anne, et al, 2017, Tanzania(20)	to determine whether daily oral supplementation with one or both nutrients starting in the first trimester reduces the risk of placental malaria and adverse pregnancy outcomes	double-blind placebo-controlled trial	there were no other differences in adverse birth outcomes associated with the two supplements. .
8.	Darmstadt, et al. Bangladesh. 2012(21)	to assess the effect of maternal zinc supplementation on skin infections among infants	A randomized double-blind clinical trial	-There was a decrease in the incidence of IUGR and LBW infants by 73% after zinc supplementation. - Zinc supplementation can reduce the risk of premature birth.
9.	Karamali,et al.2016, Iran (22)	to determine the beneficial effects of zinc intake on biomarkers of inflammation, oxidative stress, and pregnancy outcome among pregnant women with gestational diabetes (GDM).	a double-blind, randomised controlled trial	Changes in serum zinc levels after 6 weeks of supplementation were greater in women taking zinc than in the placebo group (+8.5 ± 13.5 vs -3.6 ± 16.2 mg/dL, P = 0.006). Changes in serum high-sensitivity C-reactive protein (hs-CRP) (−110.1 ± 1 475.5 vs. +1 137.8 ± 2 429.2 ng/mL, P = 0.03) and plasma concentration of total antioxidant capacity (TAC) (+ 60.0 ± 129.0) vs. -28.4 ± 81.4 mmol/L, P = 0.006) differed significantly between the women given the supplement and the placebo

				group but there was no significant effect of zinc administration on pregnancy outcome.
10.	Karamali,et . Iran.2015(23)	to determine the effects of zinc supplementation on glucose homeostasis parameters and lipid concentrations in GDM women.		Patients who received zinc supplements had significantly higher serum zinc concentrations (+6.9 ± 13.2 vs. −1.5 ± 16.5 mg/dL, P = 0.03) than those received the placebo.
11	Rohmawati,et al. Indonesia. 2021(24)	To determine the effect of zinc supplementation on pregnant women for stunting prevention through analysis maternal serum zinc, umbilical cord blood osteocalcin and infant birth length.	A randomized double-blind clinical trial	- The mean maternal serum zinc levels after zinc supplementation were significantly higher than those of the placebo group: 55.1±9.9 to 59.1±8.6) µg/dL (p=0.017) and 54.2±7.5 to 50±8.6 µg/dL (p=0.001), - median neonatal birth lengths in the supplementation group was higher than in the placebo group (49.3 (46.5-51.3) vs 48.3 (46-50.8) cm (p=0.004).

Discussion

Over the last ten years, 11 studies in developing nations compared zinc supplementation to placebo in pregnant women. The majority of the research recommended zinc supplementation till after the baby is delivered.

Effect Of Zinc Supplementation on pregnancy Outcome

A total of 9 studies were determined to be eligible to examine the effect of zinc supplementation on maternal and newborn outcomes as a consequence of the supplied search and selection criteria. Only 3 studies have proven that zinc supplementation can improve pregnancy outcomes(16), (21),(24), while the other 6 studies showed the opposite result, (14), (15), , (17), (19), (22), (20).

Regarding low birth weight (LBW), there are only 3 studies RCTs (14), (17), (21)conducted over the last 10 years. Darmstadt, et al (21) found that maternal zinc supplementation may increase infant birth weight among malnourished women. Prenatal zinc supplementation has no influence on newborn birth weight, according to the other study (14), (17). Furthermore, two studies evaluating the effect of zinc intake during pregnancy on neonatal birth length reported that zinc supplementation can increase the length of the baby's birth length.(16), (24).

Based on the scientific literature on the effect of Zn supplementation on birth outcomes, different results were obtained. From the results of the study Nossier et al.(14), found no detectable difference in mean birth weight between the three groups (mean 2.929 · 12 (SD 330 · 28), 2.922 · 22 (SD 324 · 05) and 2.938 · 48 (SD 317 · 39) grfor the placebo group, Zn and Zn plus multivitamins, both single and combined Zn supplements were nearly as effective in reducing second and third stage complications (relative risk (RR) 0 · 43, 95% CI 0 · 31, 0 · 60 for Zn group and RR 0 · 54 , 95% CI 0 · 40, 0 · 73for the combined group). Stillbirth and preterm delivery were significantly lower in the two supplemented groups compared with the placebo group (P = 0.01) Early neonatal morbidity was also significantly lower in the supplemented group (RR0 · 23, 95% CI 0 · 15, 0 · 35 for Zn group and RR 0 · 25, 95% CI 0 · 16, 0 · 37 for the combined) .

This is in line with a study conducted in Iran where this study aimed to evaluate the impact of prenatal zinc supplementation on pregnancy outcomes showing that daily zinc supplementation of 15 mg from 16 weeks of gestation until delivery does not improve pregnancy outcome. (19). This study is consistent with the results of a systematic review reviewing and meta-analysis of randomized controlled trials evaluating the effects of preventive zinc supplementation for 3 months or more during pregnancy or children up to 5 years of age, pregnancy outcome and child growth, finding that maternal zinc supplementation does not significantly increase birth weight (25). This is also reinforced by the results of a systematic review study which found that no impact of zinc supplements on the risk of Low Birth Weight (26)(25).This is in contrast to the research conducted by Lassy et al which showed that the addition of zinc supplementation during pregnancy can reduce the risk ofLow Birth Weight**.** (27)**.**

A double-blind, randomized controlled study conducted in Indonesia showed that Zn supplementation during pregnancy increased birth length after adjusting for maternal height and pre-pregnancy weight.(16)(28).

As a result, three study used a randomized controlled trial to investigate the effects

of zinc supplementation on preterm birth. The majority of studies found no evidence of zinc supplementation having a substantial favorable effect on preterm birth (15), (17). An Iranian study aimed at assessing the effect of high-dose zinc (Zn) supplementation during pregnancy on pregnancy outcomes in healthy pregnant women with previous preterm delivery found that adding Zn supplementation during pregnancy to the routine care of women with previous preterm delivery had no significant effect on age. pregnancy during childbirth(15)**.** However, Darmstadt, et al observed that zinc supplementation reduced preterm birth by such a small but significant amount (21).

Effect Of Zinc Supplementation on Maternal zinc status

The results of three trials revealed that zinc supplementation had a substantial impact on serum zinc concentration (22), (23), (24). When compared to controls, Karamali et al, found a substantial change in serum zinc concentration in pregnant women. After 6 weeks of supplementation, serum zinc levels were higher in the zinc group (+8.5 13.5 vs -3.6 16.2 mg/dL, P = 0.006) than in the placebo group (+8.5 13.5 vs -3.6 16.2 mg/dL, P = 0.006)(22). Similarly, Rohmawati et al found that after zinc supplementation, mean maternal serum zinc levels were considerably higher than those of the placebo group: 55.19.9 to 59.18.1 g/dL (p=0.017) and 54.27.5 to 508.6 g/dL (p=0.001), respectively (24).

Similarly, if zinc was fortified in bread, the absorption of zinc and iron in the group consuming high-zinc bread was significantly greater than in the group receiving low-zinc bread ($p < 0.01$). It was concluded that flour fortification with 50-100 ppm zinc is an effective way to achieve adequate zinc intake and absorption in zinc-deficient people. It seems that eating zinc-fortified bread increases iron absorption (29).

In terms Zinc Supplementation and the Effects on Pregnancy Outcomes in Gestational Diabetesshowed that the change in serum zinc levels after 6 weeks of supplementation was greater in women taking zinc than in the placebo group (+ 8,5 ± 13,5 vs -3,6 ± 16,2 mg / dL, P = 0,006). Changes in serum high-sensitivity C-reactive protein (hs-CRP) (−110.1 ± 1 475.5 vs. +1 137.8 ± 2 429.2 ng / mL, P = 0.03) and plasma concentration of total antioxidant capacity (TAC) (+ 60.0 ± 129.0) vs. -28,4 ± 81,4 mmol / L, P = 0,006) significantly different between the women given the supplement and the placebo group but no significant effect of zinc administration on pregnancy outcome was found. (22). This is in line with a study conducted in Bangladesh which investigated the effect of maternal zinc supplementation on infant immune function in a population at risk for zinc deficiency, which found that maternal zinc supplementation did not have a negative impact on the copper

status of the mother or her baby.Maternal zinc supplementation did not affect infant thymus size, but cord blood IL-7 was found to be positively associated with thymus size at 1 month of age (r = 0.392) and with hepatitis B vaccine response at 6 months of age (r = 0.386).Prenatal and postnatal zinc supplementation slightly enhances T cell-dependent antibody responses in infants along with IL-7, a cytokine involved in human T cell development and maintaining homeostasis. (30)**.**

Moreover, zinc intake was found to have a good influence on other outcomes, such as reducing biomarkers of inflammation and oxidative stress (17), and improving Hb and serum ferritin levels in women with iron deficiency in early pregnancy (18).

Conclusion

There was no significant effect of zinc administration during pregnancy on pregnancy outcome but zinc supplementation can increase maternal zinc status.

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