Heliyon 7 (2021) e07540

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

# Effect of maternal zinc supplementation or zinc status on pregnancy complications and perinatal outcomes: An umbrella review of meta-analyses

Sehar Iqbal [a,b], Inayat Ali [c,*]

[a] Department of Environmental Health, Centre for Public Health, Medical University of Vienna, Kinderspitalgasse 15, 1090, Vienna, Austria
[b] National University of Medical Sciences, PWD Campus, Islamabad, Pakistan
[c] Department of Social and Cultural Anthropology, University of Vienna, Universitätsstrasse 7, 1010 Vienna, Austria

ARTICLE INFO

*Keywords:*
Zinc
Pregnancy
Complications
Perinatal outcomes
Meta-analyses
Umbrella review

ABSTRACT

Zinc is an essential trace element involved in different physiological functions. During pregnancy, it plays a crucial role in healthy embryogenesis. This umbrella review, therefore, aimed to summarize the existing literature of meta-analyses evaluating the effect of maternal zinc supplementation or zinc status on maternal and neonatal outcomes. Two databases, PubMed and Scopus, were selected to search the available literature without any temporal restriction. The literature search was performed during October 2020 and a total of 192 records were identified through the literature search. After screening the titles and applying the inclusion/exclusion criteria, finally, 15 articles were included in this umbrella review. This umbrella review showed that maternal zinc supplements reduce the risk of preterm birth. Although no substantial effect of zinc supplements was found for other feto-maternal outcomes. Also, we found a significant relationship between low maternal zinc status and risk of pregnancy complications. Zinc supplements reduce the risk of preterm birth. Long-term interventions and cohort studies are needed for future research directions. Further studies and a thorough investigation will help to decide the recommended zinc dose or intake during pregnancy.

## 1. Introduction

"Zinc," a vital trace element, is present in all tissues and body fluids. As an integral physiological constituent of the oxidant defense system, it plays a significant role in cellular signaling [1]. Zinc is involved in regulating more than 300 metalloenzymes and plays a vital role in signal transduction, cellular proliferation, apoptosis, gene expression, and infant neurological development [2]. Being a part of numerous proteins, zinc is essential for different anabolic processes, protein synthesis, and nucleic acid metabolism [3].

During pregnancy, zinc plays a significant role in healthy embryogenesis. The transfer of zinc to the fetus is mainly dependent on adequate maternal zinc status [4]. Thus, premature infants are at high risk of deficiency due to limited zinc transfer from mother to a fetus [5]. The World Health Organization (WHO) suggested the standard zinc requirement during pregnancy from 1.1 to 2.0 mg/day [6], though, the requirements increase in the later stages of pregnancy up to 3 mg/day [7]. Zinc is stored in the liver as zinc-binding protein (metallothionein), to meet the fetal demands and to protect the fetus from zinc deficiency during the immediate postnatal period [8]. In the initial pregnancy stages, zinc is required for cell multiplication and differentiation and fetal organ formation [9]. Its deficiency, mainly in later pregnancy, adversely affects the normal neuronal replication, migration, synaptogenesis, and gene expressions [9]. Zinc deficiency during pregnancy impairs cell cycle progression, cell migration, intracellular signaling, and normal functioning of zinc enzymes leading to chromosomal and oxidative damage [10].

Despite its crucial role in normal reproduction and fetal development, zinc deficiency is widespread around the world. The global estimate shows that 17.3% of the world population have inadequate zinc intake, with the highest risk reported in Africa and Asia [11]. A recent study reported an alarming zinc deficiency situation in pregnant and reproductive-age women of Ethiopia, Kenya, Nigeria, and South Africa [12]. Similarly, global zinc deficiency is the 11th highest risk factor for disease mortality and morbidity with nearly 20% of perinatal mortalities on the global level are attributed to zinc deficiency [13].

Given that, the effects of maternal zinc supplements are well-known to reduce the magnitude of maternal zinc deficiency and to prevent adverse perinatal outcomes [14]. Also, different studies and randomized control trials have currently evaluated the effects of maternal zinc

* Corresponding author.
*E-mail address:* inayat_qau@yahoo.com (I. Ali).

https://doi.org/10.1016/j.heliyon.2021.e07540
Received 9 December 2020; Received in revised form 30 May 2021; Accepted 7 July 2021

supplements on fetal and maternal complications [15]. Yet, the literature of conflicting studies reflects uncertainty in the evidence linking maternal zinc status and pregnancy complications [16]. However, due to an increase of available studies, systematic reviews, and meta-analyses, conducting an umbrella review is a novel and preferred approach to providing comprehensive, systematic, diverse, and reliable research evidence available for a specific research topic [17]. Therefore, this umbrella review of meta-analyses aimed to summarize the existing meta-analyses regarding the effect of maternal zinc supplementation on maternal and neonatal outcomes. Furthermore, we summarized the available data of meta-analytical studies showing the association between zinc status during pregnancy and perinatal outcomes.

## 2. Methods

### 2.1. Data sources and search criteria

A bibliographic search was carried out in October (27/10/20 to 29/10/20) using PubMed and Scopus databases. Two reviewers independently searched the literature by entering the search term ("zinc" or "Zn") and ("pregnant" or "gestation" or "maternal" or "perinatal" or "neonatal" or "preterm" or "birthweight" or "miscarriage" or "preeclampsia") and ("metaanalysis" or "meta-analysis") with no temporal restriction. A database-specific search syntax file regarding complete search terms and strategies for each database are provided (Supp. file 1).

Given that, a total of 192 records were identified through search. At the first screening step, 129 irrelevant titles were excluded not meeting the study objective, leaving 63 articles to scan for abstracts (Figure 1). After reviewing the abstracts, further 29 articles were excluded providing a total of 34 articles for full-text perusal. Finally, 15 meta-analytical articles were included in this umbrella review according to inclusion/exclusion criteria to evaluate the association of maternal zinc supplements or status and its effects on feto-maternal outcomes.

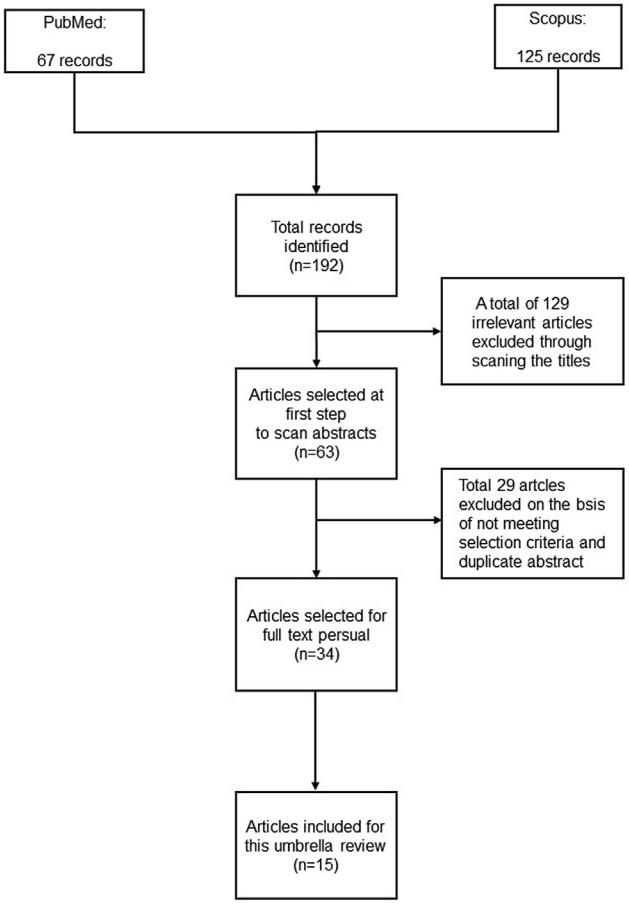


**Figure 1.** Flow diagram of screening process.

### 2.2. Inclusion/exclusion criteria

In this umbrella review, the study design i.e. meta-analysis of randomized controlled trials (RCTs) and quasi-randomized trials, interventional studies, or cohort studies, were included to assess the primary outcomes. Focusing on perinatal outcomes, the effects of zinc supplementation on preterm birth, small for gestational age (SGA), low birth weight (LBW), pre-eclampsia, head circumference, premature rupture of membrane, stillbirth child mental and psycho-motor development index, 5-minute APGAR (appearance, pulse, grimace, activity, and respiration) score and childhood wheeze were taken as primary outcomes. While, meta-analyses evaluating the association of maternal zinc status and its effects on pregnancy complication were considered as secondary outcomes and included the previous meta-analyses comprising case-control, cross-sectional and observational studies.

The availability of odds ratios (OR), ß-coefficients, risk ratios (RR), effect size (ES), mean difference, and confidence intervals, was considered as a prerequisite for all included meta-analyses of randomized controlled and interventional trials. Furthermore, the studies excluded on the basis of (a) duplicate, (b) no meta-analysis conducted, and (c) meta-analysis which combined zinc supplements with other multi-micronutrients including trace elements and minerals to analyze the main effect of zinc supplements.

### 2.3. Quality assessment

Both reviewers assessed the methodological quality of each included meta-analyses. In this regard, reviewers followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. Also, the process for selecting studies including screening, determining eligibility, citation details, study aim and objective of the included meta-analysis, participant details, setting and context, number of databases sourced and searched, number and type of studies, and reported result outcomes were assessed by using the Aromataris and colleagues study guidelines [17]. While the tools for assessing quality and susceptibility to bias in observational studies were assessed by using the study protocols as describes in proposed by [19].

### 2.4. Maternal and child outcomes

Maternal and child outcomes such as preterm birth, low birth weight, change in birth weight, small for gestational age, head circumference, Psycho-motor Development Index (PDI), Mental Development Index (MDI), Stillbirth or neonatal death, low 5-minute APGAR score (<5), childhood wheeze, premature rupture of membrane and preeclampsia were categorized as primary result outcomes to evaluate the effects of maternal zinc supplementation on pregnancy complications and perinatal outcomes. All discrepancies regarding exclusion/exclusion criteria, a full-text perusal of studies, and selection of included studies were resolved through discussion and consensus of both reviewers.

### 2.5. Data extraction

A qualitative methodological approach used for organizing and reporting the findings. In this regard, we extracted data and reviewed each meta-analysis according to (1) availability of odds ratio (OR), relative risk (RR), mean difference (MD), effect size (ES), or ß coefficient, (2) test for heterogeneity (p-value), (3) $I^2$ value (%), and (4), and whether fixed or random-effects models were used in the pooling of results. The number of trials, type of the included studies, zinc interventions and dose, and information about the number of interventional and control group participants were extracted from the selected meta-analyses.

Finally, the concluding remarks from the paper were included to better understand the result outcomes.

In addition, we summarized the previous metanalyses showing the association of maternal zinc status and perinatal outcomes. On the same lines, we extracted the available information regarding study reference, year, outcomes, study aim, number of trials, analysis model, test for heterogeneity (p-value), $I^2$ value, and extraction of MD or RR, and concluding study remarks.

## 3. Results

### 3.1. Effect of zinc supplementation on pregnancy outcomes

As a result of the given search and selection criteria, total 10 papers were found eligible to evaluate the effect of zinc supplementation on maternal and neonatal outcomes [20, 21, 22, 23, 24, 25, 26, 27, 28, 29]. The studies included RCTs (n = 6), RCTS and quasi-randomized trials (n = 2), interventional studies (n = 1) and cohort studies (n = 1).

The available number of participants treated with zinc supplements were inclusive of 35,115 pregnant women in the zinc supplemented group and 34,482 in the control group. However, the participants' detailed descriptions of both groups were not provided in the remaining 8 study trials (Table 1). The number of trials in the selected meta-analyses varied from 1 up to 24 and the provided dose of zinc supplements during pregnancy was 1mg/day to 62 mg/day. Almost all studies used a test for heterogeneity (p-value) and $I^2$ (%) to validate the pooled estimates. The $I^2$ value in the selected studies ranged from 0% to 96%, whereas the p-value varied from <0.00001 to 0.97. Most of the study trials used the fixed-effect model (n = 20) compared to the random effect model (n = 9).

### 3.2. Preterm birth

In total, 12 feto-maternal outcomes, i.e., preterm birth, small for gestational age, low birth weight, change in birth weight, preeclampsia, head circumference, psychomotor development, mental development, stillbirth, premature rupture of membrane, low APGAR score (<5) and childhood wheezing were identified from the selected papers.

Given that, five studies conducted meta-analyses to determine the effects of zinc supplements on preterm birth [20, 21, 22, 23, 24]. Most of the studies indicated that zinc supplements reduce the risk of preterm birth. Likewise, Mahomed and colleagues [24] found that zinc supplementation resulted in a small but significant reduction in preterm birth [RR: 0.86 (0.76–0.98)]. Correspondingly, the meta-analyses of Ota et al [22] and Chaffee and King [23] included the studies of pregnant women treated with zinc supplements ranging from 5-50 mg/day and found that maternal zinc supplementation lowers the risk of preterm birth respectively [RR: 0.86 (0.76–0.97)] and [RR: 0.86 (0.75–0.99)]. While meta-analysis of Lassi and allies [21] included the studies with a lower range of zinc supplements (14–20 mg/day) and reported that pregnant adolescent women supplemented with even smaller zinc dose can reduce the risk of preterm births. However, only the study of Oh and colleagues did not observe any significant positive effect of zinc supplementation on preterm birth [20].

### 3.3. Small for gestational age

Furthermore, four studies evaluating the effect of zinc intake during pregnancy on small for gestational age (SGA) infants found no association between maternal zinc supplementation and SGA [20, 22, 23, 24]. Such as a study by Oh and Colleagues [20] found little or no effect of zinc supplements on reducing the risk of SGA infants [RR: 1.05 (0.97–1.13)]. Similarly, meta-analyses of Chaffee and King [23] in 2012 and Ota and colleagues [22] in 2015 did not find any effect of zinc supplementation on SGA infants [RR: 1.03 (0.91–1.17)] and [RR: 1.02 (0.94–1.11)] respectively. Likewise, a previous Cochrane Database Systematic Review determined the effects of zinc supplements vs no zinc (with or without placebo) in 2007 and did not report any significant effects on SGA [24].

### 3.4. Low birth weight

Regarding low birth weight (LBW), eight meta-analyses including RCTs and quasi-randomized trials were conducted from 2007 to 2020. Only the study of Lassi and colleagues [21] reported that zinc supplements reduce the risk of LBW [RR: 0.39 (0.15–0.98)], while the other seven meta-analyses found no effect of prenatal zinc supplementation on infant birth weight [20, 22, 23, 24, 25, 26, 27]. For instance, the meta-analysis of Oh [20] and Mahomed [24] with their colleagues determined the effects of zinc supplementation versus placebo and found no impact of zinc supplements on the risk of LBW [RR:1.08 (0.94–1.25] and [RR: 1.03 (0.94–1.13)] respectively. Similarly, Petry and colleagues [26] included the studies of pregnant women treated with <21 mg/day zinc and also found no effects of maternal zinc supplementation on LBW [RR: 0.96 (0.67–1.37)]. On the same lines, the study of Ota and colleagues [22], Chaffee and King [23], and Liu and colleagues [25] included studies of zinc supplementation ranging from 5-50 mg/day and reported no effects on LBW. Considerably, Gebreselassie and Gashe [27], in their meta-analysis included RCTs with even higher zinc doses (ranged from 15-62 mg/day) and found no significant association between prenatal zinc supplementation and infant birth weight [ES: 0.0268 [0.0764 – (-0.0229)].

### 3.5. Mental and psychomotor development index

To evaluate the effects on mental and psychomotor development index, we found only two meta-analyses. The study of Ota and colleagues [22] found that zinc supplemented group (ranged from 5-44 mg/day) had significantly low psychomotor development index (PDI) and mental development index (MDI) scores respectively as compared to no-zinc group [PDI = Mean difference: -7.00 (-11.92 to -2.08)] [MDI = Mean difference: -3.30 (-6.51 to -0.09)]. In contrast, the study from Nissensohn et al. [28] in 2013 found no association between zinc intake and MDI and PDI scores in infants.

### 3.6. Other outcomes

Also, no positive effect of zinc intake was identified on other outcomes such as infant head circumference [22, 23, 24], 5-minute APGAR score [22], stillbirth, or neonatal death [22], preeclampsia [20, 22], and premature rupture of the membrane [22]. Though, Beckhaus and colleagues [29] in their cohort study, showed the protective effect of maternal zinc intake against childhood wheeze.

### 3.7. Maternal zinc status and its relation to pregnancy complications or child outcomes

In total, five meta-analyses evaluated the association between maternal zinc status and pregnancy complications and child outcomes [30, 31, 32, 33, 34]. For all outcomes, the meta-analyses included 4 to 29 no of trials and used the random-effect model (Table 2). A high heterogeneity with $I^2$ values reported between 62.34% and 96%—the mean difference for different outcomes varied from -0.59 to -15.91.

All studies showed that low maternal zinc status increases the risk of pregnancy complications. For example, a recent meta-analysis from Akdas and Yazihan [30] found low maternal zinc status and low cord blood zinc levels in pregnant women with complications than healthy controls. Similarly, two meta-analytical studies [31, 32] stated that women with preeclampsia had a lower zinc status than healthy control pregnant women. Likewise, He and colleagues [33] reported a high incidence of Pregnancy-induced hypertension in pregnant women with low serum zinc status [MD: -1.14 [-1.69 – (-0.59)]. Moreover, Molina-Solana and collaborators [34] found an association between a

**Table 1.** Effect of maternal zinc supplementation on pregnancy complications and perinatal outcomes: A summary of meta-analyses.

| Study outcome | Reference/year | Studies included | No. of trials | No. of participants | Analysis model | Zinc interventions or dose | Risk estimates [RR/OR/ES/ MD/ß (95%CI)] | $I^2$ value (%) | Test for heterogeneity (p value) | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Preterm birth | Oh et al [20] 2020 | Randomized controlled trials (RCTs) and quasi-randomized trials | 11 | Total (n) = 5017 zinc group/controls (2524/2493) | Random effect model | Zinc supplementation versus placebo* | RR: 0.97 (0.80–1.17) | 22% | p = 0.73 | The results showed no significant effect of zinc supplements on reducing the risk of preterm birth. |
| | Lassi et al [21] 2017 | Interventional trials (zinc supplementation versus placebo) | 2 | N/A[a] | Random effect model | 14–20 mg/day | RR: 0.57 (0.46–0.69) | 0% | p = <0.00001 | The studies on pregnant adolescents reported that zinc supplements reduce the risk of preterm births. |
| | Ota et al [22] 2015 | RCTs | 16 | Total (n) = 7637 zinc group/controls (3851/3786) | Fixed effect model | 5–44 mg/day | RR: 0.86 (0.76–0.97) | 17% | p = 0.012 | Zinc supplementation helps to reduce the risk of preterm birth. |
| | Chaffee and King [23] 2012 | RCTs | 16 | Total (n) = 7818 | Fixed effect model | 5–50 mg/day | RR: 0.86 (0.75–0.99) | 26% | p = 0.162 | The study results found that maternal zinc supplementation lowers the risk of preterm birth, however, no evidence of zinc supplements on other fetal outcomes was reported. |
| | Mahomed et al [24] 2007 | RCTs | 13 | Total (n) = 6854 zinc group/controls 3421/3433 | Fixed effect model | Zinc supplements vs no zinc (with or without placebo) | RR: 0.86 (0.76–0.98) | 22% | p = 0.021 | Zinc supplementation resulted in a small but significant reduction in preterm birth. |
| Small for Gestational Age (SGA) | Oh et al [20] 2020 | RCTs and quasi-randomized trials | 3 | Total (n) = 2174 zinc group/controls (1094/1080) | Random effect model | Zinc supplementation versus placebo* | RR: 1.05 (0.97–1.13) | 0% | p = 0.24 | The study found little or no effect of zinc supplements on reducing the risk of SGA infants. |
| | Ota et al [22] 2015 | RCTs | 8 | Total = 4252 zinc group/controls (2161/2091) | Fixed effect model | 5–44 mg/day | RR: 1.02 (0.94–1.11) | 28% | p = 0.58 | No effect of zinc supplementation was seen on SGA infants |
| | Chaffee and King [23] 2012 | RCT | 5 | Total (n) = 3441 | Fixed effect model | 25–45 mg/day | RR: 1.03 (0.91–1.17) | 59% | p = 0.04 | No effect of zinc supplements was reported on SGA |
| | Mahomed et al [24] 2007 | RCTs | 5 | Total = 3469 zinc group/controls 1731/1738 | Fixed effect model | Zinc supplements vs no zinc (with or without placebo) | RR: 1.04 (0.96–1.13) | 22% | p = 0.30 | No significant effect of zinc supplements was observed on SGA infants |

(*continued on next page*)

**Table 1** (*continued*)

| Study outcome | Reference/year | Studies included | No. of trials | No. of participants | Analysis model | Zinc interventions or dose | Risk estimates [RR/OR/ES/ MD/ß (95%CI)] | $I^2$ value (%) | Test for heterogeneity (p value) | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Low Birth Weight (LBW) | Oh et al [20] 2020 | RCTs and quasi-randomized trials | 10 | Total (n) = 4633 zinc group/controls (2327/2306) | Random effect model | zinc supplementation versus placebo* | RR:1.08 (0.94–1.25 | 14% | p = 0.26 | The results found no impact of zinc supplements on the risk of LBW. |
| | Liu et al [25] 2018 | RCTs | 24 | Total (n) = 13,167 | N/A | 10–50 mg/day | RR: 0.76 (0.52–1.11) | 91.1% | p = 0.000 | Maternal zinc supplementation has no effects on LBW |
| | Lassi et al [21] 2017 | RCTs | 6 | Total (n) = 507 zinc group/controls (249/258) | Fixed effect model | 14–20 mg/day | RR: 0.39 (0.15–0.98) | N/A[a] | p = 0.04 | The studies on pregnant adolescent reported that zinc supplements reduce the risk of low birth weight |
| | Petry et al [26] 2016 | RCTs and quasi-randomized trials | 7 | Total (n) = 6,2518 | Random effect model | ≤21 mg/day | RR: 0.96 (0.67–1.37) | 0% | p = 0.83 | The results found that 21 mg/day of zinc during pregnancy has no significant effect on the prevalence of LBW. |
| | Ota et al [22] 2015 | RCTs | 14 | Total (n) = 5643 zinc group/controls (2884/2759) | Random effect model | 5–44 mg/day | RR: 0.93 (0.78–1.12) | 38% | p = 0.46 | No clear differences were seen between the zinc and no zinc groups for the reduction of LBW. |
| | Chaffee and King [23] 2012 | RCT | 11 | Total (n) = 5614 | Fixed effect model | 5–50 mg/day | RR: 1.06 (0.91–1.23) | 37.5% | p = 0.100 | No effect of zinc supplements was reported on LBW. |
| | Mahomed et al [24] 2007 | RCTs | 11 | Total (n) = 4860 zinc group/controls 2454/2406 | Fixed effect model | Zinc supplements vs no zinc (with or without placebo) | RR: 1.03 (0.94–1.13) | 17% | p = 0.51 | The results showed no effect of zinc supplements on LBW infants |
| | Gebreselassie and Gashe [27] 2011s | RCTs | 17 | Total (n) = 6209 | Fixed effect model | 15–62 mg/day | ES: 0.0268 [0.0764 – (-0.0229)] | N/A[a] | p = 0.09 | The results found no association between prenatal zinc supplementation and infant birth weight. |
| Pre-eclampsia | Oh et al [20] 2020 | RCTs and quasi-randomized trials | 3 | Total (n) = 1226 zinc group/controls (608/618) | Random effect model | zinc supplementation versus placebo* | RR: 1.01 (0.53–1.93) | 0% | p = 0.97 | The results showed no effect of zinc supplements on reducing the risk of preeclampsia/eclampsia. |
| | Ota et al [22] 2015 | RCTs | 7 | Total (n) = 2975 1483/1492 | Fixed effect model | 5–44 mg/day | RR:0.83 (0.64–1.08) | 26% | p = 0.17 | The study reported no effect of zinc intake on preeclampsia. |
| Head circumference (cm) | Ota et al [22] 2015 | RCTs | 7 | Total (n) = 3991 zinc group/controls 2014/1977 | Fixed effect model | 5–44 mg/day | Mean difference: -0.03 (-0.17 – 0.11) | 45% | p = 0.67 | The study reported no effect of zinc intake on infant head circumference |
| | Chaffee and King [23] 2012 | RCT | 11 | Total births (n) = 5065 | Fixed effect model | 5–50 mg/day | Mean difference: 0.3 (-0.3 – 0.9) | 52.3% | p = 0.021 | There was no evidence to support a meaningful zinc supplementation effect on change in head circumference. |
| | Mahomed et al [24] 2007 | RCTs | 7 | Total (n) = 3991 zinc group/controls 2014/1977 | Fixed effect model | Zinc supplements vs no zinc (with or without placebo) | Mean difference: -0.06 (-0.15 – 0.04) | 45% | p = 0.24 | The study reported no effect of zinc intake on infant head circumference. |

(*continued on next page*)

**Table 1** (*continued*)

| Study outcome | Reference/year | Studies included | No. of trials | No. of participants | Analysis model | Zinc interventions or dose | Risk estimates [RR/OR/ES/ MD/ß (95%CI)] | $I^2$ value (%) | Test for heterogeneity (p value) | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Psycho- motor Development Index (PDI) | Ota et al [22] 2015 | RCTs | 1 | 83/85 | Fixed effect model | 5–44 mg/day | Mean difference:-7.00 (-11.92 – -2.08) | N/A[a] | p = 0.0053 | The zinc group had significantly worse psychomotor development index scores than the no-zinc group. |
| | Nissensohn et al [28] 2013 | RCTs | 11 | Total (n) = 1775 Intervention/control group (917/858) | Random effect model | 1–10 mg/day | β: 0.00 (-0.03 – -0.02) | 96% | p = 0.83 | The study found no association between zinc intake and PDI scores in infants |
| Mental Development Index (MDI) | Ota et al [22] 2015 | RCTs | 1 | Total (n) = 168 zinc group/controls 83/85 | Fixed effect model | 5–44 mg/day | Mean difference:-3.30 (-6.51 – -0.09) | N/A[a] | p = 0.044 | The zinc group had significantly worse mental development index scores than the no-zinc group. |
| | Nissensohn et al [28] 2013 | RCTs | 11 | Total (n) = 1775 Intervention/control group (917/858) | Random effect model | 1–10 mg/day | β: -0.01 (-0.02 – 0.00) | 82% | p = 0.17 | The study found no association between zinc intake and MDI scores in infants. |
| Stillbirth or neonatal death | Ota et al [22] 2015 | RCTs | 8 | Total = 5100 zinc group/controls (2646/2454) | Fixed effect model | 5–44 mg/day | RR: 1.12 (0.86–1.46) | 0.0% | p = 0.38 | No effect of zinc supplementation was seen on stillbirth or neonatal deaths. |
| Premature rupture of membrane | Ota et al [22] 2015 | RCTs | 2 | Total (n) = 1691 zinc group/controls 827/864 | Fixed effect model | Zinc supplements vs no zinc (with or without placebo) | RR: 0.93 (0.78–1.11) | 0% | p = 0.43 | The study reported no effect of zinc intake on the premature rupture of the membrane. |
| 5-minute APGAR score (<5) | Ota et al [22] 2015 | RCTs | 2 | Total (n) = 1691 zinc group/controls 827/864 | Fixed effect model | 5–44 mg/day | RR: 1.02 (0.26–4.03) | 0% | p = 0.96 | Zinc intake has no effect on APGAR score |
| Childhood wheeze | Beckhaus et al [29] 2015 | Cohort studies | 3 | Total (n) = 3315 | Fixed effect model | N/A | OR: 0.57 (0.40–0.81) | 0% | p = 0.002 | Maternal zinc intake has a protective effect against childhood wheeze |

[*] Dose of zinc supplementation is not available.
[a] N/A = not available or applicable.

**Table 2.** Maternal zinc status and pregnancy complications or child outcomes: A summary of meta-analyses.

| Reference/year | Study aim | Studies included | No. of trials | Analysis model | MD or RR (95%CI) | $I^2$ value (%) | Test for heterogeneity p-value |
|---|---|---|---|---|---|---|---|
| Akdas and Yazihan [30] 2020 | The study aimed to evaluate the association between cord blood zinc level and pregnancy complications | Case-control and cross-sectional studies | 29 | Random effect model | Cord blood zinc level vs pregnancy outcome MD: -7.9 [- 12.48 – (-3.31)] | 96% | p = 0.0007 |
| | The study aimed to evaluate the association between maternal serum zinc levels and all pregnancy complications | Case-control and cross-sectional studies | 18 | Random effect model | Maternal blood zinc level vs pregnancy outcomes MD: -15.91 [- 27.74 – (-4.08)] | 93% | p = 0.008 |
| Zhu et al [31] 2016 | The study evaluated the association between zinc level and the risk of preeclampsia | Case-control and cross-sectional studies | 13 | Random effect model | MD: -0.61 [-0.74 – (-0.48)] | 88.5 % | p = 0.000 |
| Ma et al [32] 2015 | The study evaluated the association between serum zinc level and preeclampsia | Observational studies | 14 | Random effect model | Maternal zinc status vs preeclampsia MD: -0.59 [-0.96 – (-0.21)] | 88.4% | p = 0.000 |
| He et al [33] 2016 | The study evaluated the relationship between serum zinc, magnesium, and calcium levels and PIH | NA | 8 | Random effect model | MD: -1.14 [-1.69 – (-0.59)] | 89% | p = <0.0001 |
| Molina-Solana et al [34] 2013 | The study aimed to evaluate the effect of environmental factors, such as tobacco, alcohol stressful events, low zinc status and fever during pregnancy on the incidence of cleft lip and/or palate | Case-control, cohort and cross-sectional studies | 4 | Random effect model | RR: 1.82 (0.88–3.79) | 62.34% | p = 0.734 |

low maternal zinc level and risk of cleft lip and/or palate in children [RR: 1.82 (0.88–3.79)].

## 4. Discussion

In summary, we described the summary of 15 meta-analyses meeting our selection criteria to determine the effect of maternal zinc supplements and zinc status during pregnancy. Most of the studies discovered the effects of zinc supplementation on feto-maternal outcomes. Yet, very few meta-analyses were available, showing the association between maternal zinc status and perinatal outcomes.

The findings of this umbrella review suggested that zinc supplements during pregnancy significantly reduce the risk of preterm infants, though weak or no substantial evidence was found for other maternal and neonatal outcomes. A reduced risk of preterm births has been found previously in the zinc supplemented pregnant group [35]. Villar and colleagues suggested that zinc supplements might help decline neonatal mortality and preterm births [36]. Similarly, another study found that low maternal serum zinc concentration is associated with a high risk of preterm births [37].

Hypertensive disorders, hemorrhage, and intrauterine growth restriction are few common diagnoses associated with preterm births. Moreover, cigarette smoking, short cervix, history of previous preterm birth, and low serum levels of micronutrients, including zinc, have been suggested to increase the risk of preterm births [38]. In the period of early fetal development, zinc deficiency might have adverse effects on embryogenesis and the duration of pregnancy due to a reduced amount of hepatic stores [39]. Different physiological changes during pregnancy, such as alterations in tissue zinc distribution, an increase of zinc absorption, reduced endogenous zinc losses, and changes in the exchangeable zinc pools kinetics, appear to influence the maternal zinc status [40]. Also, the percentage of total serum zinc bound to albumin, and the affinity of zinc for serum albumin, are found lower during pregnancy, which might decrease the total circulating zinc concentrations during pregnancy [40].

Regarding SGA, this umbrella review of previous meta-analyses showed no association between maternal zinc supplementation and SGA. However, the impact of zinc in inflammatory processes on fetal outcomes is well-reviewed [41, 42]. Previously, an association between placental inflammation and the incidence of SGA infants was found during pregnancy due to activation of placental NF-κ B signaling and elevation of serum inflammatory cytokines [43].

Furthermore, most of the included meta-analyses did not find any effect of zinc supplements during pregnancy to reduce the risks of LBW. The bioavailability of zinc supplement might be the major reason suggested in previous studies to explain the insignificant zinc supplements effect on birth weight [35, 44].

Additionally, in agreement with previous studies [35, 45], we found a weak or no clear benefit of maternal zinc supplements on different other perinatal outcomes, including head circumference, and stillbirth or neonatal death. The study on pregnant women in Iran found no effect of zinc supplements on prematurity, preeclampsia, premature rupture of membrane, stillbirth, small for gestational age, and head circumference [46]. Yet, our results identified that zinc supplements negatively affect PDI and MDI scores. In contrast, a previous study by Caulfield and colleagues found no effect of prenatal zinc supplementation on children's cognitive, social, or behavioral development [47]. Nonetheless, the availability of very few studies, the difference in population groups, high heterogeneity, small effect magnitude, publication bias, and duration of intervention necessitated further research in this regard.

Moreover, our results showed that low maternal zinc status increases the risk of different perinatal and child complications. Simultaneously, few previous studies found no association between maternal zinc status and feto-maternal outcomes [16, 48]. A positive association between low maternal zinc status and etiology of preeclampsia and pregnancy-induced hypertension has been found in pregnant women due to a decline in

antioxidant activities [49, 50, 51]. Moreover, the beneficial effects of zinc to improve the immune system, cellular functions, signal transduction, and its anti-inflammatory activities are well known during the gestational period [40, 42].

Different factors including (a) low maternal body stores due to reduced time for placental transfer of zinc, (b) an increase of endogenous zinc losses, and (c) low/marginal zinc intake can increase the risk of zinc-related perinatal complications [39]. Also, an excessive amount of supplemental iron, any gastrointestinal disease could interfere with zinc absorption during pregnancy [4]. High phytate content and cereal-based diets can also have a negative effect on zinc absorption during pregnancy [52]. Moreover, maternal zinc deficiency due to a drug-mineral interaction might induce tissue damage, cytokine release, increased synthesis of metallothionein, sequestration of zinc in the maternal liver, and reduction of feto-maternal zinc concentration [53]. Other factors, such as smoking, alcohol abuse, and acute stress response to infection or trauma, may alter maternal plasma zinc concentrations and its transport to the fetus [4].

Ingestion of zinc supplements up to 40 mg elemental zinc per day in adults is mostly considered safe; however, prolonged exposure more than the tolerable upper intake level may suppress immunity, decrease high-density lipoprotein levels, and may cause hypochromic microcytic, i.e., red cells [54]. During normal conditions, the uptake from the gastrointestinal tract is approximately 20–30% of ingested dose [13]. Under certain deficiency conditions, zinc uptake may increase to more than 90%; however, the uptake may decrease to below 10% under conditions of excess exposure [13].

During pregnancy, zinc as a zinc-binding protein (metallothionein) accumulates in the liver and helps to protect the fetus from zinc deficiency during the immediate postnatal period [8]. Therefore, the requirement for zinc intake has been recommended from 1.1 to 2.0 mg/day in normative pregnant women [6]. Nonetheless, the absorption of at least 3 mg elemental zinc/day is recommended during the last two trimesters of pregnancy, which accounts for a dietary intake of 15 mg zinc/day, assuming a bioavailability of 20% [7].

## 5. Study limitations

This summary of meta-analyses determines the effect of maternal zinc supplements and zinc status on feto-maternal outcomes. However, our study also has limitations. Due to the varying doses of zinc supplementation, we were unable to determine the ideal dose-response relationship between zinc supplementation and feto-maternal outcomes, however, World Health Organization (WHO) and International Zinc Nutrition Consultative Group provided the gestational zinc requirement of 2.27 (mg/day) and 2.68 (mg/day) respectively [55]. Also, not prior registration on PROSPERO could be taken is another limitation. Our findings are based on available meta-analyses studies and their results. Due to the limited accessibility of databases, we selected PubMed and Scopus databases. These databases were selected because the PubMed database contains multi-disciplinary peer-reviewed literature, while Scopus also contains non-peer-reviewed literature. Whilst, this could be taken as a limitation. Nonetheless, few previous studies included only these 2 databases showing the effects of iron supplementation or iron status on maternal and neonatal outcomes [56]. Further studies for more extensive and more rigorous prospective placebo control trials are needed to confirm the relation between maternal zinc status and perinatal outcomes.

## 6. Conclusion and recommendations

This summary of meta-analyses showed that maternal zinc supplements could help to reduce preterm birth and low maternal zinc status that is associated with an increased risk of pregnancy complications. However, the effect of perinatal zinc supplements on children's mental development needs a thorough investigation due to limited available literature.

Several confounders such as duration, dose, and pregnancy stage of the start of the zinc supplementation might be a contributing factor for less consistent results. Moreover, different study designs and various confounders may limit the interpretation of aggregated data. Thus, the need for multisite studies based on a common protocol, minimizing the effects of confounders might help to endorse concrete zinc supplementation effects during pregnancy.

Long-term interventions and cohort studies might help with future research directions. Moreover, by combining the data of available meta-analyses, this umbrella review will provide a better understanding and further insights on maternal zinc supplantation programs to reduce the risk of adverse feto-maternal outcomes. A comprehensive approach and guidelines on zinc and multi-micronutrient supplements are needed to best address the issue.

## Declarations

### *Author contribution statement*

Sehar Iqbal and Inayat Ali: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

### *Funding statement*

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### *Data availability statement*

Data included in article/supplementary material/referenced in article.

### *Declaration of interests statement*

The authors declare no conflict of interest.

### *Additional information*

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2021.e07540.

## References

[1] P.I. Oteiza, G.G. Mackenzie, Zinc, oxidant-triggered cell signaling, and human health, Mol. Aspect. Med. 26 (2005) 245–255.
[2] M. Nissensohn, A. Sánchez-Villegas, D. Fuentes Lugo, P. Henríquez Sánchez, J. Doreste Alonso, L. Peña Quintana, C. Ruano, N.L. Lowe, V. Hall Moran, A.L. Skinner, M. Warthon-Medina, L. Serra-Majem, Effect of zinc intake on growth in infants: a meta-analysis, Crit. Rev. Food Sci. Nutr. 56 (2016) 350–363.
[3] M. Favier, I. Hininger-Favier, Zinc and pregnancy, Gynecol. Obstet. Fertil. 33 (2005) 253–258.
[4] J.C. King, Determinants of maternal zinc status during pregnancy, Am. J. Clin. Nutr. 71 (Suppl) (2000) 1334S–1343S.
[5] C. Livingstone, Zinc: physiology, deficiency, and parenteral nutrition, Nutr. Clin. Pract. 30 (2015) 371–382.
[6] World Health Organization (WHO), Trace Elements in Human Nutrition and Health, 1996.
[7] S.J.M. Osendarp, C.E. West, R.E. Black, Public health importance of maternal zinc deficiency the need for maternal zinc supplementation in developing Countries : an unresolved issue, J. Nutr. 133 (2003) 817–827.
[8] L.A. Scheplyagina, Impact of the mother's zinc deficiency on the woman's and newborn's health status, J. Trace Elem. Med. Biol. 19 (2005) 29–35.
[9] H.H. Sandstead, Zinc is essential for brain development and function, J. Trace Elem. Exp. Med. 16 (2003) 165–173.
[10] J.Y. Uriu-Adams, C.L. Keen, Zinc and reproduction: effects of zinc deficiency on prenatal and early postnatal development, Birth Defects Res. 89 (2010) 313–325.
[11] R.L. Bailey, K.P. West, R.E. Black, The epidemiology of global micronutrient deficiencies, Ann. Nutr. Metab. 66 (2015) 22–33.
[12] R. Harika, M. Faber, F. Samuel, J. Kimiywe, A. Mulugeta, A. Eilander, Micronutrient status and dietary intake of iron, Vitamin A, iodine, folate and zinc in women of

reproductive age and pregnant women in Ethiopia, Kenya, Nigeria and South Africa: a systematic review of data from 2005 to 2015, Nutrients 9 (2017).
[13] J. Nriagu, Zinc deficiency in human health, Encycl. Environ. Heal. (2011) 789–800.
[14] E. Ota, R. Mori, P. Middleton, R. Tobe-Gai, K. Mahomed, C. Miyazaki, Z.A. Bhutta, Zinc supplementation for improving pregnancy and infant outcome, Cochrane Database Syst. Rev. 2015 (2015).
[15] E. Mesdaghinia, F. Naderi, F. Bahmani, M. Chamani, A. Ghaderi, Z. Asemi, The effects of zinc supplementation on clinical response and metabolic profiles in pregnant women at risk for intrauterine growth restriction: a randomized, double-blind, placebo-controlled trial, J. Matern. Neonatal Med. (2019) 1–7.
[16] S. Iqbal, I. Ali, P. Rust, M. Kundi, C. Ekmekcioglu, Selenium, zinc, and manganese status in pregnant women and its relation to maternal and child complications, Nutrients 12 (2020) 725.
[17] E. Aromataris, R. Fernandez, C.M. Godfrey, C. Holly, H. Khalil, P. Tungpunkom, Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach, Int. J. Evid. Base. Healthc. 13 (2015) 132–140.
[18] L. Shamseer, D. Moher, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle, L.A. Stewart, D.G. Altman, A. Booth, A.W. Chan, S. Chang, T. Clifford, K. Dickersin, M. Egger, P.C. Gøtzsche, J.M. Grimshaw, T. Groves, M. Helfand, J. Higgins, T. Lasserson, J. Lau, K. Lohr, J. McGowan, C. Mulrow, M. Norton, M. Page, M. Sampson, H. Schünemann, I. Simera, W. Summerskill, J. Tetzlaff, T.A. Trikalinos, D. Tovey, L. Turner, E. Whitlock, Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: elaboration and explanation, BMJ 349 (2015) 1–25.
[19] S. Sanderson, I.D. Tatt, J.P.T. Higgins, Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography, Int. J. Epidemiol. 36 (2007) 666–676.
[20] C. Oh, E.C. Keats, Z.A. Bhutta, Vitamin and mineral supplementation during pregnancy on maternal, birth, child health and development outcomes in low- and middle-income countries: a systematic review and meta-analysis, Nutrients 12 (2020) 491.
[21] Z.S. Lassi, A. Moin, J.K. Das, R.A. Salam, Z.A. Bhutta, Systematic review on evidence-based adolescent nutrition interventions, Ann. N. Y. Acad. Sci. 1393 (2017) 34–50.
[22] E. Ota, R. Mori, P. Middleton, R. Tobe-Gai, K. Mahomed, C. Miyazaki, Z.A. Bhutta, Zinc supplementation for improving pregnancy and infant outcome, Cochrane Database Syst. Rev. 2015 (2015) CD000230.
[23] B.W. Chaffee, J.C. King, Effect of zinc supplementation on pregnancy and infant outcomes: a systematic review, Paediatr. Perinat. Epidemiol. 26 (2012) 118–137.
[24] K. Mahomed, Z.A. Bhutta, P. Middleton, Zinc supplementation for improving pregnancy and infant outcome, Cochrane Database Syst. Rev. (2007) CD000230.
[25] E. Liu, L. Pimpin, M. Shulkin, S. Kranz, C.P. Duggan, D. Mozaffarian, W.W. Fawzi, Effect of zinc supplementation on growth outcomes in children under 5 years of age, Nutrients 10 (2018) 1–20.
[26] N. Petry, I. Olofin, E. Boy, M.D. Angel, F. Rohner, The effect of low dose Iron and zinc intake on child micronutrient status and development during the first 1000 days of life: a systematic review and meta-analysis, Nutrients 8 (2016) 1–22.
[27] S.G. Gebreselassie, F.E. Gashe, A systematic review of effect of prenatal zinc supplementation on birthweight, meta-analysis of 17 randomized controlled trials, J. Health Popul. Nutr. 29 (2011) 134–140.
[28] M. Nissensohn, A. Sánchez-Villegas, D.F. Lugo, P.H. Sánchez, J.D. Alonso, A.L. Skinner, M.W. Medina, N.M. Lowe, V.H. Moran, L. Serra-Majem, Effect of zinc intake on mental and motor development in infants: a meta-analysis, Int. J. Vitam. Nutr. Res. 83 (2013) 203–215.
[29] A.A. Beckhaus, L. Garcia-Marcos, E. Forno, R.M. Pacheco-Gonzalez, J.C. Celedōn, J.A. Castro-Rodriguez, Maternal nutrition during pregnancy and risk of asthma, wheeze, and atopic diseases during childhood: a systematic review and meta-analysis, Allergy Eur. J. Allergy Clin. Immunol. 70 (2015) 1588–1604.
[30] S. Akdas, N. Yazihan, Cord blood zinc status effects on pregnancy outcomes and its relation with maternal serum zinc levels: a systematic review and meta-analysis, World J. Pediatr. 16 (2020) 366–376.
[31] Q. Zhu, L. Zhang, X. Chen, J. Zhou, J. Liu, J. Chen, Association between zinc level and the risk of preeclampsia: a meta-analysis, Arch. Gynecol. Obstet. 293 (2016) 377–382.
[32] Y. Ma, X. Shen, D. Zhang, The relationship between serum zinc level and preeclampsia: a meta-analysis, Nutrients 7 (2015) 7806–7820.
[33] L. He, L. Lang, Y. Li, Q. Liu, Y. Yao, Comparison of serum zinc, calcium, and magnesium concentrations in women with pregnancy-induced hypertension and healthy pregnant women: a meta-analysis, Hypertens. Pregnancy 35 (2016) 202–209.
[34] R. Molina-Solana, R.M. Yáñez-Vico, A. Iglesias-Linares, A. Mendoza-Mendoza, E. Solano-Reina, Current concepts on the effect of environmental factors on cleft lip and palate, Int. J. Oral Maxillofac. Surg. 42 (2013) 177–184.
[35] S.A. Nossier, N.E. Naeim, N.A. El-Sayed, A.A. Abu Zeid, The effect of zinc supplementation on pregnancy outcomes: a double-blind, randomised controlled trial, Egypt, Br. J. Nutr. 114 (2015) 274–285.
[36] J. Villar, M. Merialdi, A.M. Gülmezoglu, E. Abalos, G. Carroli, R. Kulier, M. De Oni, Nutritional interventions during pregnancy for the prevention or treatment of maternal morbidity and preterm delivery: an overview of randomized controlled trials, J. Nutr. 133 (2003) 1606S–1625S.
[37] H. Wang, Y.F. Hu, J.H. Hao, Y.H. Chen, P.Y. Su, Z. Yu, L. Fu, F.B. Tao, D.X. Xu, Maternal serum zinc concentration during pregnancy is inversely associated with risk of preterm birth in a Chinese population, J. Nutr. 146 (2016) 509–515.
[38] K. Flood, F.D. Malone, Prevention of preterm birth, Semin. Fetal Neonatal Med. 17 (2012) 58–63.
[39] G. Terrin, R.B. Canani, M. Di Chiara, A. Pietravalle, V. Aleandri, F. Conte, M. De Curtis, Zinc in early life: a key element in the fetus and preterm neonate, Nutrients 7 (2015) 10427–10446.
[40] C.M. Donangelo, J.C. King, Maternal zinc intakes and homeostatic adjustments during pregnancy and lactation, Nutrients 4 (2012) 782–798.
[41] K. Gruber, L. Rink, The Role of Zinc in Immunity and Inflammation, Woodhead Publishing Limited, 2013.
[42] D. Shah, H.P.S. Sachdev, Zinc deficiency in pregnancy and fetal outcome, Nutr. Rev. 64 (2006) 15–30.
[43] H. Wang, Y. Hu, J. Hao, Y. Chen, P. Su, Y. Wang, Maternal zinc deficiency during pregnancy elevates the risks of fetal growth restriction : a population-based birth cohort study, Sci. Rep. 5 (2015) 11262.
[44] R.S. Gibson, The role of diet- and host-related factors in nutrient bioavailability and thus in nutrient-based dietary requirement estimates, Food Nutr. Bull. 28 (2007) 77–100.
[45] Z. Zahiri Sorouri, H. Sadeghi, D. Pourmarzi, The effect of zinc supplementation on pregnancy outcome: a randomized controlled trial, J. Matern. Neonatal Med. 29 (2016) 2194–2198.
[46] N. Aminisani, F. Ehdaivand, S.M. Shamshirgaran, M. Mohajery, F. Pourfarzi, M.D. Sadeghiyeh Ahari, Zinc supplementation during pregnancy: a randomized controlled trial, Iran, J. Pharmacol. Ther. 8 (2009) 67–71.
[47] L.E. Caulfield, D.L. Putnick, N. Zavaleta, F. Lazarte, C. Albornoz, P. Chen, J.A. DiPietro, M.H. Bornstein, Maternal gestational zinc supplementation does not influence multiple aspects of child development at 54 mo of age in Peru, Am. J. Clin. Nutr. 92 (2010) 130–136.
[48] F. Aydemir, A.O. Çavdar, F. Söylemez, B. Cengiz, Plasma zinc levels during pregnancy and its relationship to maternal and neonatal characteristics A longitudinal study, Biol. Trace Elem. Res. 91 (2003) 193–202.
[49] R. Negi, D. Pande, K. Karki, A. Kumar, R.S. Khanna, H.D. Khanna, Trace elements and antioxidant enzymes associated with oxidative stress in the pre-eclamptic/eclamptic mothers during fetal circulation, Clin. Nutr. 31 (2012) 946–950.
[50] S. Biswas, A. Roy, S. Biswas, Comparative study of copper, zinc, iron, ferritin, calcium and magnesium levels in pregnancy induced hypertension and normotensive primigravida mothers, Int. J. Res. Med. Sci. 4 (2016) 1879–1883.
[51] S. Jain, P. Sharma, S. Kulshreshtha, G. Mohan, S. Singh, The role of calcium, magnesium, and zinc in pre-eclampsia, Biol. Trace Elem. Res. 133 (2010) 162–170.
[52] B. Lonnerdal, Dietary factors influencing zinc absorption, J. Nutr. 130 (2000) 1344S–1349S.
[53] C.L. Keen, M.S. Clegg, L.A. Hanna, L. Lanoue, J.M. Rogers, G.P. Daston, P. Oteiza, J.Y. Uriu-Adams, The plausibility of micronutrient deficiencies being a significant contributing factor to the occurrence of pregnancy complications, J. Nutr. 133 (2003) 1597S–1605S.
[54] R.B. Saper, R. Rash, Zinc: an essential micronutrient, Am. Fam. Physician 79 (2009) 768–772.
[55] C. Hotz, K.H. Brown, Contents international zinc nutrition consultative group (IZiNCG ) technical document # 1, Food Nutr. Bull. 25 (2004) S94–S200.
[56] S. Iqbal, C. Ekmekcioglu, Maternal and neonatal outcomes related to iron supplementation or iron status: a summary of meta-analyses, J. Matern. Neonatal Med. 32 (2019) 1528–1540.