Heliyon 10 (2024) e30605

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Comparison of zinc levels in mothers with and without abortion: A systematic review and meta-analysiss

Sepideh Tousizadeh [a,b], Fazel Mohammadi-Moghadam [b,c], Abdollah Mohammadian-Hafshejani [d], Ramezan Sadeghi [b,*]

[a] *Student Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Iran*
[b] *Department of Environmental Health Engineering, School of Health, Shahrekord University of Medical Sciences, Shahrekord, Iran*
[c] *Social Determinants of Health Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran*
[d] *Modeling in Health Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran*

ARTICLE INFO

Keywords:
Zn
Abortion
Systematic review
Meta-analysis

ABSTRACT

Introduction: Zinc is an essential trace element involved in different physiological functions. During pregnancy, it plays a crucial role in healthy embryogenesis. Abortion is the most severe problem associated with early pregnancy complications. This study aims to compare the levels of Zn in mothers with and without abortion.
Methods: This study is a systematic review and meta-analysis of studies published between 1980 and 2022 in PubMed, Science Direct, Pro Quest, Wiley, Web of Science, and Scopus databases. The search was conducted using both main and Mesh keywords, specifically targeting terms related to abortion, pregnancy loss, and zinc. Heterogeneity in the studies included in the meta-analysis was evaluated using statistical tests such as the chi-square test, I2, and forest plots. Publication bias was assessed using Begg's and Egger's tests. All analyses were conducted using Stata 15, and statistical significance was considered at $p < 0.05$.
Results: In general, nine studies were included in this analysis. Based on the results of the meta-analysis, the mean difference in the Zn level between mothers with and without abortion is equal to 193.18 (95 % CI; 107.11 to 279.25, $P \leq 0.001$). In other words, the level of Zn in the group of mothers without abortion is 193 units higher than the group of mothers with abortion. The investigation into the comparison of Zn levels in mothers with and without abortion did not reveal any indication of publication bias according to both Begg's test (P-value = 0.858) and Egger's test (P-value = 0.270).
Conclusion: the study findings indicate a significant association between lower levels of Zn in mothers with abortion compared to mothers without abortion. This suggests that a higher level of Zn may have a preventive effect on the occurrence of abortion in pregnant women. The data also highlights the positive role of trace metals, particularly Zn, in influencing pregnancy outcomes and suggests that maintaining adequate levels of Zn may reduce the likelihood of abortion occurrence, along with other contributing factors. It is important to note that further research, including prospective cohort and experimental studies, is needed to provide more substantial evidence and strengthen these findings.

* Corresponding author.
E-mail address: sadeghi.r@skums.ac.ir (R. Sadeghi).

https://doi.org/10.1016/j.heliyon.2024.e30605
Received 28 August 2023; Received in revised form 30 April 2024; Accepted 30 April 2024
Available online 6 May 2024

1. Introduction

Trace elements are involved in numerous biochemical pathways and play an important role in fetal growth and development during pregnancy [1,2]. Due to the needs of the developing baby and changes in the mother's physiology, the concentration of certain trace elements changes throughout pregnancy. Changes in the concentrations and homeostasis of these micronutrients during pregnancy may be closely related to several disorders, such as abortion, preterm labor, stillbirth, intrauterine growth restriction, fetal malformations, premature membrane rupture, and other unfavorable pregnancy outcomes [3–5]. Zinc (Zn) is a crucial trace element in almost all physiological fluids and tissues. It is a vital physiological component of the oxidant defense system and is important for cellular signaling [6,7]. Zn plays a crucial role during pregnancy, especially during the embryonic stage. This is because of its involvement in continuous cellular multiplication, differentiation, organogenesis, apoptosis, and gene expression, all essential for the healthy development of embryos, fetuses, and infant neurological function. Zn is required by over 300 enzymes involved in carbohydrate and protein metabolism, nucleic acid synthesis, and antioxidant functions [7–9]. The transfer of Zn to the fetus is primarily determined by the maternal Zn status [7,10]. Limited Zn transfer from mother to fetus puts premature infants at a high risk of deficiency [11,12]. The World Health Organization (WHO) recommended a Zn requirement of 1.1–2.0 mg/day during pregnancy [13], but the requirements increase to 3 mg/day in the later stages of pregnancy [13,14]. To meet fetal demands and protect the fetus from Zn deficiency during the immediate postnatal period, Zn is stored in the liver as a Zn-binding protein (metallothionein [15,16]. Its absence, particularly in later pregnancy, hurts normal neuronal replication, migration, synaptogenesis, and gene expression [17,18]. Zn deficiency during pregnancy impairs cell cycle progression, cell migration, intracellular signaling, and normal Zn enzyme function, leading to chromosomal and oxidative damage [19,20]. Despite its crucial role in normal reproduction and fetal development, zinc (Zn) deficiency is a prevalent issue worldwide. Approximately 17.3 % of the global population is estimated to lack adequate levels of Zn, with Africa and Asia being the regions at highest risk [19,21]. According to a recent study, pregnant and reproductive-age women are severely Zn deficient [22,23]. Moreover, global Zn deficiency is ranked as the 11th highest risk factor for disease mortality and morbidity, contributing to nearly 20 % of perinatal mortalities worldwide [21,24]. Furthermore, the lack of Zn in late pregnancy can result in fetal growth retardation, congenital malformations, abortion, and fetal death [25,26]. Abortion, preterm delivery, stillbirth,

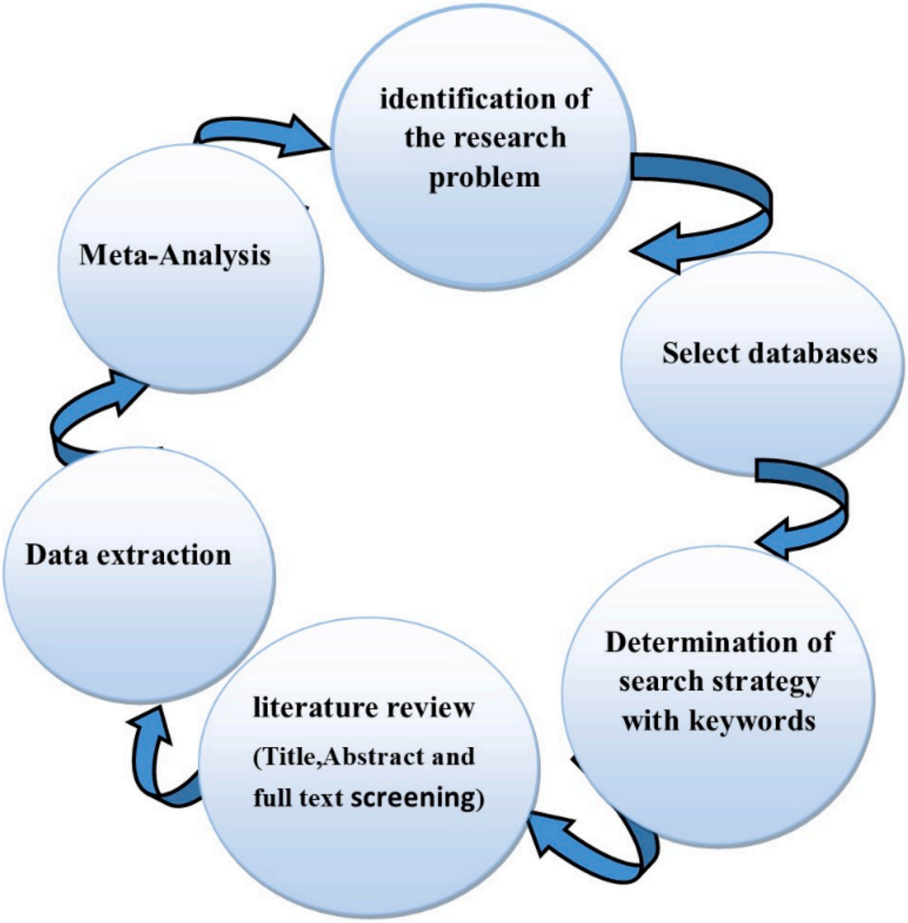

Fig. 1. Methodological flow diagram of the systematic review and meta-analysis.

intrauterine growth restriction, fetal malformations, premature rupture of membranes, and other adverse pregnancy outcomes may be linked to an imbalance of trace elements such as Zn. Spontaneous abortion, the most serious early pregnancy problem, occurs in 17 %–32 % of all known pregnancies [27–30]. Numerous factors, including genetic, immunological, environmental (embryo chromosome abnormalities), maternal endocrine disorders (PCOS, luteal dysfunction, hyper prolactinoma), uterine anomalies, advanced maternal age, inadequate maternal diet, and infections, can result in spontaneous abortions [31,32]. The impact of maternal Zn supplements is well-known to reduce the magnitude of maternal Zn deficiency and to prevent adverse perinatal outcomes [33,34]. Also, different studies have evaluated maternal Zn supplements' effects on fetal and maternal complications [35]. Nonetheless, contradictory research reflects uncertainty in the evidence linking maternal Zn status and pregnancy complications [21]. However, changes in these trace elements during pregnancy in women are poorly understood due to demographics and lifestyles [36]. Several studies have indicated that insufficiencies in trace metals, including copper (Cu), Zinc (Zn), and magnesium (Mg), may increase the likelihood of unfavorable pregnancy outcomes. However, the administration of various micronutrient supplements without proper justification for their inadequacy and potential harm to the fetus has been observed [37]. The results of previous studies were conflicting, but this study shows a definite and noticeable result. So far, it should be noted that no such study has been conducted with these goals. Therefore, by using the results of the present study, we can use it in human societies. While significant studies have been conducted on trace elements and heavy metals in normal pregnancies, few studies have looked at how trace elements and heavy metal concentrations affect problematic pregnancies, such as abortion threats [38]. Even though various investigations have revealed correlations between deficiency of trace elements and adverse outcomes, including abortion, this meta-analysis aims to provide more substantial evidence on the role of Zn in preventing abortion as well as its concentration and future actions regarding the usage of metal ions.

2. Material and methods

2.1. Data sources and search strategy

A systematic review was performed utilizing various databases, including PubMed, Web of Science (ISI), Scopus, Google Scholar, Pro Quest, and Wiley. The search was conducted using both main and Mesh keywords, specifically targeting terms related to abortion, pregnancy loss, and zinc. The search was conducted using the main and Mesh keywords:((abortion*) OR (abortion*) OR (pregnancy* AND loss*)) AND ((Zn*) OR ("Zn")). Two investigators independently evaluated article titles and abstracts using PRISMA principles to select relevant research. The identified articles were collected, and duplicates were removed. The methodological flow diagram for the systematic review and meta-analysis is presented in Fig. 1.

2.2. Eligibility criteria and study selection

The chi-squared test and I^2 are statistical tests utilized to assess heterogeneity. The I^2 index quantifies the extent of heterogeneity through a ratio. Typically, the I^2 index ranges from 0 to 100 %, with negative values considered zero. A zero value for this index signifies homogeneity in the results, while a higher value indicates more significant heterogeneity. The majority of research studies yield these results. The chi-score test determines whether the observed differences among various studies are due to chance or are statistically significant. Additionally, the chi-score test aids in selecting the appropriate models for analysis, namely the fixed or random models. If the P-value is significant, the random meta-analysis model should be employed; conversely, the fixed meta-analysis model is preferred if the P-value is not significant. The forest diagram is the most commonly used in meta-analysis, visually representing individual study information and their final findings. The square size in the diagram corresponds to the weight assigned to each study in the meta-analysis [39].

The peer-reviewed publications were imported into EndNote X9 to identify and remove duplicate publications. Two researchers independently evaluated the titles and abstracts of the studies based on predetermined inclusion and exclusion criteria. The search was not limited by time, encompassing publications from January 1975 to July 2022. The inclusion criteria for the selected articles were as follows: (a) Studies that provided sufficient and quantitative data on Zn concentration for statistical analysis, (b) Studies that reported one, two, or more cases of spontaneous abortions, and (c) Studies published in the English language. Review papers, systematic reviews, theses, letters to the editor, and books were excluded from consideration. Additionally, papers lacking full text or containing insufficient abstract or full-text data, studies focusing on cases other than spontaneous abortions, and publications not available in English were also excluded. The full texts of all eligible publications were independently reviewed. In the event of any discrepancies during the review process, a consensus was reached by engaging in discussions with a third member of the research team.

2.3. Evaluating the quality of the studies

The quality of the articles was reviewed and evaluated based on the Newcastle-Ottawa Scale (NOS) (Supplementary Table 1).

2.4. Data extraction

Data were extracted independently by two individuals. The corresponding author made the final choice when there was a disagreement between the two researchers over whether to include or exclude a particular article. The following information was extracted from the included studies: the year of publication, the name of the first author, the country of study, the number of control samples, the number of case samples, the mean concentration of control samples, and the mean concentration of case samples.

2.5. Statistical analysis

The analysis calculated and considered the overall mean difference and their 95 % confidence intervals (CI) in study groups. The SD of the mean difference was estimated using the formula: SD2 = [(SD cases2 + SD controls2) − (2 × R × SD cases × SD controls)] where correlation coefficient (R) [40]. Heterogeneity in the studies included in the meta-analysis was evaluated using statistical tests such as the chi-square test and I^2, as well as graphical methods like forest plots. The chi-square test was used to investigate differences in results among studies and determine the type of model (fixed or random). Publication bias was assessed using funnel diagrams and Begg's and Egger's tests. All analyses were conducted using Stata statistical software (version 15.0, Stata Corp, College Station, TX), and statistical significance was considered at $p < 0.05$.

3. Result

3.1. Included studies

The included studies (1556 articles) were found on the Web of Science, PubMed, Scopus, Science Direct, and Google Scholar during the systematic and preliminary literature search. Meta-analyses were performed for comparison of Zn levels in mothers with and without abortion with systematic review and meta-analysis design based on nine studies. Study investigation, data collection, and results analysis were done independently [4,38,41–47]. Fig. 2 shows the PRISMA flowchart of the search strategy.

A total of 1556 titles and abstracts were identified during the initial electronic search. However, after removing duplicate titles, a total of 453 articles were excluded from the retrieved pool. Consequently, the meta-analysis incorporated nine studies [4,38,41–49].

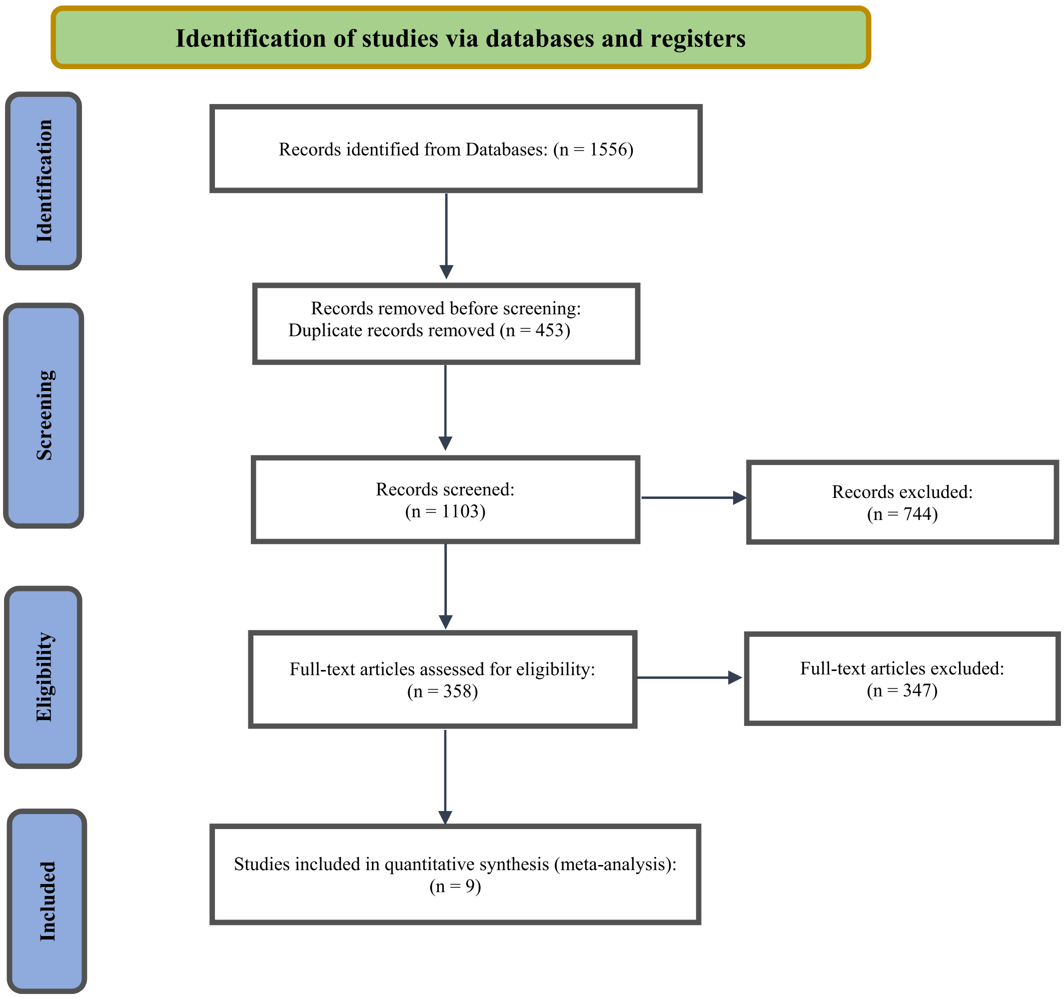

Fig. 2. Flow diagram of included and excluded studies.

3.2. Characteristics of the selected studies

The analysis encompassed studies published from 1975 to 2021. Table 1 presents a comprehensive overview of pertinent details such as sample size, participants in both intervention and control groups, year of publication, study location, and quality assessment based on the Newcastle-Ottawa Scale (NOS).

3.3. Comparison of Zn levels in mothers with and without abortion

In general, nine studies were included in this analysis. Based on the results of the meta-analysis, the mean difference in the Zn level between mothers with and without abortion is equal to 193.18 (95 % CI; 107.11 to 279.25, $P \leq 0.001$). In other words, the level of Zn in the group of mothers without abortion is 193 units higher than the group of mothers with abortion (Fig. 3).

3.4. Publication bias

The investigation into the comparison of Zn levels in mothers with and without abortion did not reveal any indication of publication bias according to both Begg's test (P-value = 0.858) and Egger's test (P-value = 0.270). The corresponding funnel plot is presented in Fig. 4.

3.5. Sensitivity analysis

Sensitivity analysis was performed to evaluate the effect of omitting each study on the final result. A sensitivity analysis was conducted, but the final mean difference estimate remained unchanged, indicating the robustness of the meta-analysis results (Table 2 and Fig. 5).

4. Discussion

There is an increasing concern regarding the negative impact of heavy metals on normal pregnancies due to the extensive human exposure and bioaccumulation of these substances. The potential association between exposure to toxic metals or insufficient essential metals and the occurrence of abortion has been a subject of suspicion for a considerable period. There is limited research on the relationship between Zn and abortion. However, some studies suggest that Zn deficiency may be associated with an increased risk of spontaneous abortion. The consistency of previous research findings regarding the association between blood concentrations of zinc (Zn) and other trace elements and abortion has been inconclusive [50–52]. In order to provide more robust evidence on this important clinical matter, we conducted a meta-analysis that specifically focused on Zn [53]. The purpose of this meta-analysis was to investigate the effect of Zn levels on the abortion risk. In summary, we discussed the findings of nine studies that met our criteria for determining

Table 1
Characteristics of included studies investigating the relationship between the level of Zn and the risk of abortion.

No.	Author and year	Country	Number of subjects		Metal concentration (μg/L)[d]		Analytical method	Reference
			Cases	Controls	Cases	Controls		
1	Ikeh-Tawari EP et al. (2013)	Nigeria	125	35	738.794 ± 176.526	764.946 ± 281.134	AAS	[41]
2	Turan K et al. (2019)	Turkey	45	40	879 ± 95.9	1528.4 ± 33.4	AAS	[42]
3	Thaker R et al. (2019)	India	159	118	1430 ± 30	1463 ± 50	AAS	[43]
4	Lu Y et al. (2022)	China	92	103	5082.32 ± 1030.13	5243.88 ± 960.87	ICP	[44]
5	Shen P et al. (2015)	China	58	1389	4751.1646 ± 783.2524	5442.885 ± 836.2102	AAS	[4]
6	Borella P et al. (1990)	Italy	12	41	891.7832 ± 153.643	858.4394 ± 154.9506	AAS	[46]
7	Ajayi O et al. (2012)	Nigeria	35	34	692.6 ± 6.9	992.5 ± 21.4	AAS	[45]
8	Sami AS et al. (2021)	Turkey	39	39	411.894 ± 46.4198	569.4598 ± 56.2268	ICP	[38]
9[a]	Ghneim HK et al. (2016)	Kingdom of Saudi Arabia	25	25	239.9446 ± 25.4982	268.7118 ± 32.0362	ICP	[47]
10[b]	Ghneim HK et al. (2016)	Kingdom of Saudi Arabia	25	25	228.83 ± 30.0748	352.3982 ± 45.766	ICP	[47],[c]

AAS: atomic absorption spectrometry.
ICP: inductively coupled plasma mass spectrometry.
[a] whole blood.
[b] plasma.
[c] Since this paper (ref.34) investigated plasma and whole blood, it has been presented twice separately.
[d] The unit conversion from 'μmol/L' to 'μg/L' was performed by multiplying the values by the molar mass of zinc, which is 65.38 g/mol, to ensure that all values are expressed in a consistent unit, micrograms per liter (μg/L).

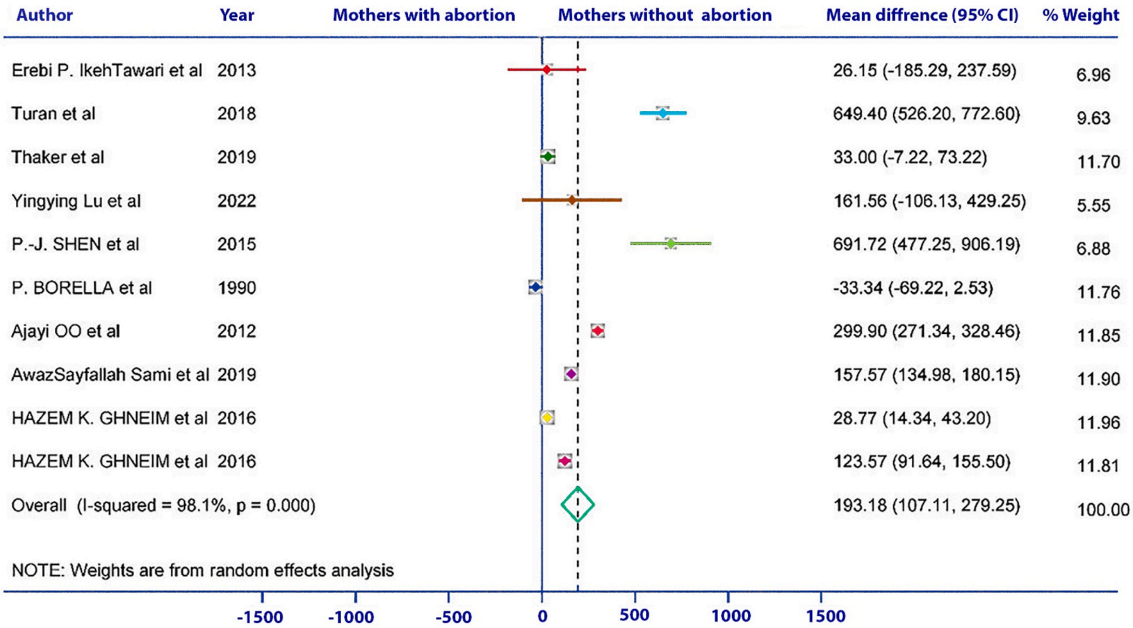

Fig. 3. Comparison of Zn levels in mothers with and without abortion.

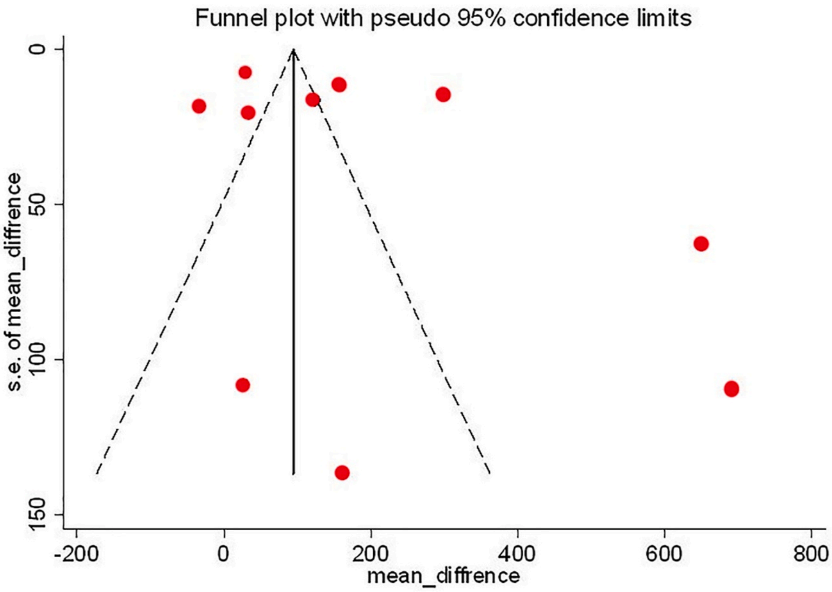

Fig. 4. Evaluation of publication bias in studies included in the meta-analysis.

the relationship between maternal Zn status and abortion. This study represents the first investigation into the overall relationship between blood Zn concentrations and abortion. Our findings indicate that deficiencies in Zn are associated with an increased prevalence of abortion in women. It is worth noting that only one relevant meta-analysis, conducted in 2021, has been published thus far, which demonstrated that exposure to Cd and Pb is linked to a higher incidence of abortion, including undistinguished threatened abortion and recurrent pregnancy loss [32]. In the present study, we recruited more studies to reinforce the association between the concentration of Zn and the reduced risk of abortion. We performed an analysis based on abortion to investigate the effect of Zn on women with and without abortion. In addition, the exploration of Zn in women with abortion provides a basis for clinicians who tend to intervene early against recurrent pregnancy loss and abortion in women with Zn deficiencies. The precise pathways responsible for the initiation of abortion due to exposure to pb and Cd, as well as deficiency of Zn and Cu, remain elusive. It has been established that heavy metals frequently encounter environmental endocrine disruptors. Prior research has indicated that exposure to toxic metals and

Table 2
Sensitivity analysis of the comparison of Zn levels in mothers with and without abortion.

Author	Mean difference (95 % confidence interval)
Ikeh-Tawari, Anetor et al. [41]	205.784(116.352–295.215)
Turan, Arslan et al. [42]	142.137(58.164–226.110)
Thaker, Oza et al. [43]	215.781(120.643–310.920)
Lu, Zhang et al. [44]	195.110(106.390–283.831)
Shen, Gong et al. [4]	156.0299(69.223–242.836)
Borella, Szilagyi et al. [46]	223.608(131.336–315.880)
Ajayi, Charles-Davies et al. [45]	168.786(92.854–244.718)
Sami, Suat et al. [38]	202.274(99.637–304.912)
Ghneim, Al-Sheikh et al. [47]	218.077(119.215–316.938)
Ghneim, Al-Sheikh et al. [47]	205.214(106.803–303.626)

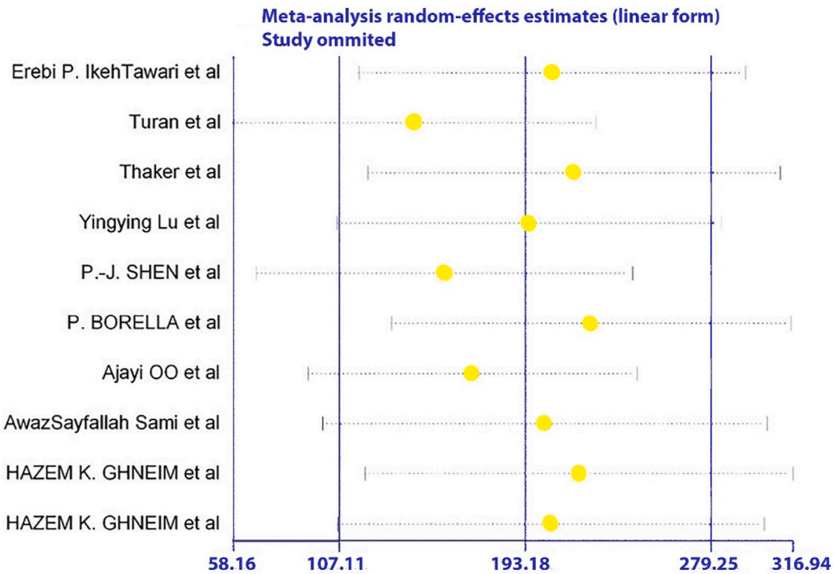

Fig. 5. Sensitivity analysis of the comparison of Zn levels in mothers with and without abortion.

insufficiency of vital metals such as Zn result in miscarriage primarily due to endocrine malfunction, including but not limited to insulin resistance, inadequate vitamin D levels, and abnormal concentrations of thyroid and sex hormones. Zinc (Zn) deficiency has been observed to disrupt the synthesis of sex hormones, leading to recurrent pregnancy loss (RPL) and abortion. Zn can influence the production and function of sex hormones, including progesterone and prolactin, by modulating the levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), as well as inducing oxidative stress [54]. Additionally, Zn may facilitate the release of estrogen by forming ligand bonds with metal-binding sites on the estrogen receptor (ER) [55]. Inadequate secretion of sex hormones, such as progesterone, testosterone, estrogen, and prolactin, can diminish the receptivity of the endometrium and compromise oocyte quality in women, both of which are associated with abortion [56–58]. Most of the research focused on the impact of Zn on pregnancy outcomes such as abortion. Several common problems, such as hypertensive disorders, bleeding, and intrauterine growth restriction, are associated with abortion. Additionally, low levels of micronutrients, like Zn, short cervixes, a history of prior preterm births, and smoking have been linked to an increased risk of abortion [7,59,60]. Maternal Zn status appears to be influenced by various physiological changes during pregnancy, including modifications in tissue Zn distribution, an increase in Zn absorption, a decrease in endogenous Zn losses, and modifications in the exchangeable Zn pool kinetics [61,62]. Additionally, it has been found that Zn's affinity for serum albumin and the percentage of total blood Zn bound to albumin are lower during pregnancy, suggesting a decline in total circulating Zn concentrations [62]. This review of studies demonstrated an association between maternal Zn status and abortion. Furthermore, consistent with previous research, our findings indicate that low Zn levels in women are associated with a higher risk of abortion. Trace elements are critical for fetal growth and development. Certain elements are transferred across the placenta during pregnancy to provide adequate nutrient stores for early infancy. Nutrient deficiencies during pregnancy have been linked to pregnancy complications, adverse birth outcomes, and compromised newborn nutrient storage [63–65]. Zn is one of the elements found at the highest concentrations [66], especially during pregnancy and lactation [61]. Zn deficiency may hurt growth [67], brain development, birth weight, and embryonic development and can harm the amniotic sac [68–70]. Moreover, it should be noted that Zn deficiency in developing nations is responsible for more than 500,000 infant and young child deaths [71]. The meta-analysis findings indicate that the presence of Zn in the body serves as a preventive measure against abortions ($SMD = -2.61$, 95 % $CI = -3.51$ to -1.70, $P \leq 0.001$).

Multiple factors can lead to developmental abnormalities; however, there is a growing body of evidence suggesting that inadequate maternal nutrition plays a significant role in the occurrence of preventable birth defects and has a profound impact on the outcome of human pregnancies [72]. Hua Wang et al. (2015) proposed that maternal zinc (Zn) deficiency during pregnancy increases the likelihood of low birth weight (LBW) and small for gestational age (SGA) infants. Moreover, maternal serum or plasma Zn concentrations decreased as the pregnancy progressed [73–75]. According to the study conducted by Ghneim et al. (2016), plasma and whole blood levels of Zn, copper (Cu), and manganese (Mn) in healthy pregnant (HP) women and recurrent abortion (RM) patients are lower compared to non-pregnant (NP) women [47]. A study performed by Sami et al. (2019) found that the serum concentrations of Se, Zn, Cu, Mg, K, and Na were considerably lower in the habitual abortion (HA) group than those in the healthy controls [38]. The research of Thaker et al. (2019) showed that trace metals like Zn and Cu can have a beneficial influence on pregnancy outcomes, and at the right amounts, they may even be able to reduce the risk of spontaneous abortion. The Cu/Zn ratio positively affects the success of reproduction outcomes [43]. Also, another study conducted by Shen et al. (2015) demonstrated that trace element (Zn, Cu, Ca, and Fe) deficiency is a real problem in pregnant Chinese women. They concluded that the women should be given trace elements, depending on their individual circumstances, especially in late pregnancy. When pregnant women receive enough trace elements, their fetuses stay healthy and develop normally. As a result, pregnant women should maintain nutritional balance. Serum trace elements should also be investigated to reduce adverse pregnancy outcomes [4]. Additionally, it is well-documented that Zn exerts positive effects on the immune system, cellular processes, and signal transduction, and possesses anti-inflammatory properties during pregnancy [62,76]. Turan et al. (2019) reported that the significant diagnostic and prognostic indicators for abortion may include changes in the balance of some vital trace elements (Fe and Zn) and elevated levels of some toxic heavy metals in the blood [42]. Furthermore, maternal Zn insufficiency caused by a drug-mineral interaction may lead to tissue injury, cytokine release, increased metallothionein synthesis, Zn sequestration in the maternal liver, and decreased feto-maternal Zn concentration [77]. Other variables, such as smoking, alcohol misuse, and the acute stress reaction to infection or trauma, may affect maternal Zn concentrations and fetal Zn transport [10]. Another study performed by Iqbal et al. (2021) showed that maternal Zn supplements can decrease the risk of preterm birth. Moreover, there is a significant relationship between the risk of pregnancy complications and low maternal Zn status [21]. This study had some limitations, including limited data access and unpublished reports. Despite the fact that trace elements and heavy metals have been extensively studied in normal pregnancies, very few studies have investigated the relationship between trace element quantities, such as Zn, and abortion. To the best of our knowledge, this research is the first global systematic review and meta-analysis of the association between level Zn and the risk of abortion. Considering that SMD >0.5 was obtained, we conclude that the size of the standardized mean difference was huge and significant. The systematic review and meta-analysis findings suggest that women who have undergone abortion have lower levels of Zn in their blood, serum, or plasma compared to women without a history of abortion. Consequently, maternal Zn supplements can potentially mitigate pregnancy complications, including preterm birth, low maternal Zn status, and the risk of abortion. It is crucial to acknowledge that excessive consumption of Zn can have adverse effects and potentially increase the likelihood of abortion. Generally, supplemental zinc doses of up to 40 mg per day are considered safe for individuals. However, prolonged exposure beyond the recommended upper intake limit may compromise immune function and pose risks to human health [78]. Under typical circumstances, the gastrointestinal tract absorbs approximately 20–30 % of the ingested dose. In instances of deficiency, the uptake of Zn may decline to less than 10 %, while in cases of excessive exposure, Zn uptake may also decrease [79,80]. Throughout pregnancy, Zn accumulates in the liver through its binding to proteins known as metallothionein, which safeguards the fetus against Zn deficiency during the immediate postpartum period [14]. Consequently, the Zn requirement for pregnant women of normal health has been elevated from 1.1 to 2.0 mg/day [13]. This study is subject to certain limitations. First, a subgroup analysis based on abortion type was not performed, and several outdated documents that seemingly satisfied our inclusion criteria were excluded due to our inability to establish contact with the respective authors. Second, the potential sources of heterogeneity in the study were taken into account, including the age of the study population and the specific time at which the samples (whole blood, plasma, or serum) were collected. This consideration was important due to the possibility of heavy metals and trace elements accumulating in the human body over time, potentially resulting in higher blood metal concentrations in older adults. Moreover, it was recognized that metal concentrations can vary during different trimesters, and the timing of blood collection may introduce heterogeneity in the data. Third, the inclusion of only English literature posed significant challenges in terms of language and multiple publication biases. Our study is notable for its comprehensive examination of the associations between Zn concentrations in whole blood, plasma, or serum and rates of abortion. Furthermore, we conducted a systematic review of previous publications on Zn concentrations and abortion, ensuring a thorough analysis of the existing literature. The included studies demonstrated satisfactory definitions of cases and controls, as well as consistent selection of controls and assessment of exposure. The current investigation expands our comprehension of the impact of crucial metallic elements, such as zinc (Zn), on the occurrence of abortion. To enhance our knowledge, it would be advantageous to screen the levels of Zn and other elements including copper (Cu), lead (Pb), and cadmium (Cd) in the bloodstream of women. Nevertheless, it is imperative to conduct meticulously planned prospective cohort studies to elucidate the causal association between abortions induced by trace metals.

5. Conclusions and future perspectives

The present investigation represents a pioneering and all-encompassing endeavor to explore the correlation between the level of Zn and the likelihood of abortion. Prior research endeavors were predominantly confined to case-control studies and the examination of abortion occurrences. This comprehensive review diligently compiled and conducted a meta-analysis of all available publications that documented the impact of Zn on abortion. This study revealed a significant finding that the blood levels of Zn in mothers who had abortions were considerably lower than in women who did not experience abortions. Therefore, higher Zn levels are associated with a lower risk of abortion in pregnant women. In other words, this summary of meta-analyses showed that low-level zinc in mothers with abortion is associated with an increased risk of abortion. Also, zinc has a preventive role during pregnancy and reduces abortion in mothers without abortion. However, the effect of zinc supplements and other environmental risk factors on abortion needs a thorough investigation due to the limited available literature. The study findings demonstrate a significant correlation between decreased levels of Zn in mothers who experienced abortion compared to those who did not. This implies that a higher concentration of Zn might possess a preventive impact on the incidence of abortion in pregnant women. The results of this study and future research with more precise evidence and more accurate data and techniques could increase clinicians' awareness of the advantages and Zn's involvement in preventing adverse pregnancy complications, such as the likelihood of abortion.

Funding sources

This study was funded by the Shahrekord University of Medical Sciences' research deputy [Grant Number: 6412,IR.SKUMS. REC.1401.088].

CRediT authorship contribution statement

Sepideh Tousizadeh: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Fazel Mohammadi-Moghadam:** Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Abdollah Mohammadian-Hafshejani:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Methodology, Formal analysis, Data curation. **Ramezan Sadeghi:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30605.

References

[1] R.E. Black, Micronutrients in pregnancy, Br. J. Nutr. 85 (S2) (2001) S193–S197.
[2] Z. Nie, et al., Associations of maternal exposure to multiple plasma trace elements with the prevalence of fetal congenital heart defects: a nested case-control study, Sci. Total Environ. 912 (2024) 169409.
[3] J.C. King, Physiology of pregnancy and nutrient metabolism, Am. J. Clin. Nutr. 71 (5) (2000) 1218S–1225S.
[4] P. Shen, et al., Four trace elements in pregnant women and their relationships with adverse pregnancy outcomes, Eur. Rev. Med. Pharmacol. Sci. 19 (24) (2015) 4690–4697.
[5] J. Li, et al., Development and internal validation of a clinical prediction model for spontaneous abortion risk in early pregnancy, Clinics 79 (2024) 100318.
[6] P.I. Oteiza, G.G. Mackenzie, Zinc, oxidant-triggered cell signaling, and human health, Mol. Aspect. Med. 26 (4–5) (2005) 245–255.
[7] S. Tousizadeh, et al., Investigation of the levels of essential and non-essential metals in women with and without abortion history: a study based on the Persian population of the Shahrekord cohort, Chemosphere 329 (2023) 138434.
[8] M. Nissensohn, et al., Effect of zinc intake on growth in infants: a meta-analysis, Crit. Rev. Food Sci. Nutr. 56 (3) (2016) 350–363.
[9] M. Favier, I. Hininger-Favier, *Zinc and pregnancy.* Gynecologie, obstetrique & fertilite 33 (4) (2005) 253–258.
[10] J.C. King, Determinants of maternal zinc status during pregnancy, Am. J. Clin. Nutr. 71 (5) (2000) 1334S–1343S.
[11] C. Livingstone, Zinc: physiology, deficiency, and parenteral nutrition, Nutr. Clin. Pract. 30 (3) (2015) 371–382.
[12] P. Babu, et al., Exploring the association between air pollution and spontaneous abortion through systematic review and bibliometric analysis, Air Quality, Atmosphere & Health (2024) 1–27.
[13] W.H. Organization, Trace Elements in Human Nutrition and Health, World Health Organization, 1996.
[14] S.J. Osendarp, C.E. West, R.E. Black, The need for maternal zinc supplementation in developing countries: an unresolved issue, J. Nutr. 133 (3) (2003) 817S–827S.
[15] 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 (1) (2005) 29–35.
[16] H. Koyama, T. Kamogashira, T. Yamasoba, Heavy metal exposure: molecular pathways, clinical implications, and protective strategies, Antioxidants 13 (1) (2024) 76.
[17] H.H. Sandstead, Zinc is essential for brain development and function, J. Trace Elem. Exp. Med.: The Official Publication of the International Society for Trace Element Research in Humans 16 (4) (2003) 165–173.
[18] A.F. Mosaad, et al., Effect of ambient lead on progesterone and pregnancy-associated glycoprotein 1 and their relationship with abortion in Zaraibi goats: a field study, Trop. Anim. Health Prod. 56 (1) (2024) 40.
[19] C. Keen, L.S. Hurley, Zinc and reproduction: effects of deficiency on foetal and postnatal development, in: Zinc in Human Biology, Springer, 1989, pp. 183–220.
[20] M. Kaur, et al., Assessment of Serum Essential/non-Essential Elements, Biochemical Variables and its Association with Semen Parameters and the Risk of Male Infertility, 2024.
[21] S. Iqbal, I. Ali, Effect of maternal zinc supplementation or zinc status on pregnancy complications and perinatal outcomes: an umbrella review of meta-analyses, Heliyon 7 (7) (2021) e07540.

[22] R. Harika, et al., 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 (10) (2017) 1096.
[23] Y. Lawson, K.B. Comerford, E.P. Mitchell, A review of dairy food intake for improving health for black women in the US during pregnancy, fetal development, and lactation, Journal of the National Medical Association 116 (2) (2024) 219–227.
[24] D. Weinstein, D.A. Shah, Wilson disease and pregnancy, Clinical Liver Disease 23 (1) (2024) e0110.
[25] N. Dickinson, et al., A framework to explore micronutrient deficiency in maternal and child health in Malawi, Southern Africa, Environ. Health 8 (1) (2009) 1–7.
[26] P. Ayala-Ramírez, et al., Risk factors and fetal outcomes for preeclampsia in a Colombian cohort, Heliyon 6 (9) (2020) e05079.
[27] A. Garcıa-Enguıdanos, et al., Risk factors in miscarriage: a review, Eur. J. Obstet. Gynecol. Reprod. Biol. 102 (2) (2002) 111–119.
[28] M. Ren, X. Shi, Association between female circulating heavy metal concentration and abortion: a systematic review and meta-analysis, Front. Endocrinol. 14 (2023) 1216507.
[29] Y. Li, et al., Potential pathological mechanisms and pharmacological interventions for cadmium-induced miscarriage, Ecotoxicol. Environ. Saf. 273 (2024) 116118.
[30] D. Yin, et al., Association of plasma metal levels with outcomes of assisted reproduction in polycystic ovary syndrome, Biol. Trace Elem. Res. (2024) 1–17.
[31] C. Bulletti, C. Flamigni, E. Giacomucci, Reproductive failure due to spontaneous abortion and recurrent miscarriage, Hum. Reprod. Update 2 (2) (1996) 118–136.
[32] M. Kaur, et al., Increased incidence of spontaneous abortions on exposure to cadmium and lead: a systematic review and meta-analysis, Gynecol. Endocrinol. 38 (1) (2022) 16–21.
[33] E. Ota, et al., Zinc supplementation for improving pregnancy and infant outcome, Cochrane Database Syst. Rev. (2) (2015).
[34] D. Anvesh, et al., Study of cord blood zinc levels in low and normal birth weight neonates and correlate with their mother's serum zinc levels, Journal of Population Therapeutics and Clinical Pharmacology 30 (16) (2023) 78–83.
[35] E. Mesdaghinia, et al., 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. Fetal Neonatal Med. 34 (9) (2021) 1382–1388.
[36] E. Aromataris, et al., Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach, JBI Evidence Implementation 13 (3) (2015) 132–140.
[37] K. Prabhu, et al., Maternal serum zinc, copper, magnesium, and iron in spontaneous abortions, Indian J. Clin. Biochem. (2022) 1–4.
[38] A.S. Sami, et al., The role of trace element, mineral, vitamin and total antioxidant status in women with habitual abortion, J. Matern. Fetal Neonatal Med. 34 (7) (2021) 1055–1062.
[39] K. Kishore, V. Jaswal, Statistics corner: chi-squared test, J. Postgrad. Med. Educ. Res. 57 (1) (2023) 40–44.
[40] G.A. Kelley, K.S. Kelley, Statistical models for meta-analysis: a brief tutorial, World J. Methodol. 2 (4) (2012) 27.
[41] E.P. Ikeh-Tawari, J.I. Anetor, M. Charles-Davies, Cadmium level in pregnancy, influence on neonatal birth weight and possible amelioration by some essential trace elements, Toxicol. Int. 20 (1) (2013) 108.
[42] K. Turan, et al., Change of the levels of trace elements and heavy metals in threatened abortion, J. Chin. Med. Assoc. 82 (7) (2019) 554–557.
[43] R. Thaker, et al., Correlation of copper and zinc in spontaneous abortion, International Journal of Fertility & Sterility 13 (2) (2019) 97.
[44] Y. Lu, et al., Exposure to multiple trace elements and miscarriage during early pregnancy: a mixtures approach, Environ. Int. 162 (2022) 107161.
[45] O. Ajayi, M. Charles-Davies, O. Arinola, Progesterone, selected heavy metals and micronutrients in pregnant Nigerian women with a history of recurrent spontaneous abortion, Afr. Health Sci. 12 (2) (2012) 153–159.
[46] P. Borella, et al., Maternal plasma concentrations of magnesium, calcium, zinc and copper in normal and pathological pregnancies, Sci. Total Environ. 99 (1–2) (1990) 67–76.
[47] H.K. Ghneim, et al., Superoxide dismutase activity and gene expression levels in Saudi women with recurrent miscarriage, Mol. Med. Rep. 13 (3) (2016) 2606–2612.
[48] W.J. Omeljaniuk, et al., Antioxidant status in women who have had a miscarriage, Adv. Med. Sci. 60 (2) (2015) 329–334.
[49] H.E. Tolunay, et al., Heavy metal and trace element concentrations in blood and follicular fluid affect ART outcome, Eur. J. Obstet. Gynecol. Reprod. Biol. 198 (2016) 73–77.
[50] M. Ren, et al., Association between female circulating heavy metal concentration and abortion: a systematic review and meta-analysis, Front. Endocrinol. 14 (2023).
[51] K. Kazama, K. Sugita, K. Onda, Characterization of Trace Element Concentrations in Blood Samples of Dairy Cows with Uterine Torsion and Their Neonatal Calves, 2023.
[52] W.J. Omeljaniuk, et al., Cadmium and Lead in Women Who Miscarried, vol. 64, Clinical Laboratory, 2018.
[53] G.K. Schwalfenberg, S.J. Genuis, Vitamin D, essential minerals, and toxic elements: exploring interactions between nutrients and toxicants in clinical medicine, Sci. World J. (2015) 2015.
[54] K. Paksy, B. Varga, P. Lazar, Zinc protection against cadmium-induced infertility in female rats. Effect of zinc and cadmium on the progesterone production of cultured granulosa cells, Biometals 10 (1997) 27–36.
[55] A. Humeny, D. Bökenkamp, H.H. Thole, The HDQVH-motif in domain E of the estradiol receptor α is responsible for zinc-binding and zinc-induced hormone release, Mol. Cell. Endocrinol. 153 (1–2) (1999) 71–78.
[56] W.-L. Lee, C.-C. Yeh, P.-H. Wang, Risk to increase threatened abortion: deficiency of some essential trace elements and exposure of toxic heavy metals, J. Chin. Med. Assoc. 82 (8) (2019) 607–608.
[57] J. Li, Research advances in the relationship between prolactin and spontaneous abortion, Zhong xi yi jie he xue bao= Journal of Chinese Integrative Medicine 10 (1) (2012) 7–12.
[58] L.M. Semeniuk, et al., Risk markers of reproductive loss in women with hyperandrogenism, Wiad. Lek. 71 (8) (2018) 1550–1553.
[59] K. Flood, F.D. Malone, Prevention of preterm birth, in: Seminars in Fetal and Neonatal Medicine, Elsevier, 2012.
[60] O.B. Christiansen, et al., ESHRE guideline: recurrent pregnancy loss, Hum. Reprod. Open 2018 (2018), 004.
[61] G. Terrin, et al., Zinc in early life: a key element in the fetus and preterm neonate, Nutrients 7 (12) (2015) 10427–10446.
[62] C.M. Donangelo, J.C. King, Maternal zinc intakes and homeostatic adjustments during pregnancy and lactation, Nutrients 4 (7) (2012) 782–798.
[63] S. Khayat, H. Fanaei, A. Ghanbarzehi, Minerals in pregnancy and lactation: a review article, J. Clin. Diagn. Res.: J. Clin. Diagn. Res. 11 (9) (2017) QE01.
[64] F.E. Viteri, Iron endowment at birth: maternal iron status and other influences, Nutr. Rev. 69 (suppl_1) (2011) S3–S16.
[65] K. Abu-Saad, D. Fraser, Maternal nutrition and birth outcomes, Epidemiol. Rev. 32 (1) (2010) 5–25.
[66] J.C. King, Zinc: an essential but elusive nutrient, Am. J. Clin. Nutr. 94 (2) (2011) 679S–684S.
[67] P. Christian, K.P. West Jr., Interactions between zinc and vitamin A: an update, Am. J. Clin. Nutr. 68 (2) (1998) 435S–441S.
[68] D. Szostak-Węgierek, A. Cichocka, *Żywienie Kobiet Ciężarnych.* Wyd. II, PZWL, Warszawa, 2012.
[69] M. Bolesta, D. Szostak-Wegierek, Żywienie kobiety podczas ciąży. Cz II. Witaminy i składniki mineralne, Żywienie Człowieka i Metabolizm 4 (36) (2009) 656–664.
[70] M.E. Wastney, et al., Zinc absorption, distribution, excretion, and retention by healthy preterm infants, Pediatr. Res. 45 (2) (1999) 191–196.
[71] N. Tomska, et al., Relationship between concentrations of elements and geographic location in Poland, Ann. Agric. Environ. Med. 28 (2) (2021) 283.
[72] C.L. Keen, et al., The plausibility of maternal nutritional status being a contributing factor to the risk for fetal alcohol spectrum disorders: the potential influence of zinc status as an example, Biofactors 36 (2) (2010) 125–135.
[73] C. Hotz, J.M. Peerson, K.H. Brown, Suggested lower cutoffs of serum zinc concentrations for assessing zinc status: reanalysis of the second National Health and Nutrition Examination Survey data (1976–1980), Am. J. Clin. Nutr. 78 (4) (2003) 756–764.
[74] T. Tamura, et al., Maternal plasma zinc concentrations and pregnancy outcome, Am. J. Clin. Nutr. 71 (1) (2000) 109–113.

[75] R.S. Gibson, J.-M. Huddle, Suboptimal zinc status in pregnant Malawian women: its association with low intakes of poorly available zinc, frequent reproductive cycling, and malaria, Am. J. Clin. Nutr. 67 (4) (1998) 702–709.
[76] D. Shah, H. Sachdev, Zinc deficiency in pregnancy and fetal outcome, Nutr. Rev. 64 (1) (2006) 15–30.
[77] C.L. Keen, et al., The plausibility of micronutrient deficiencies being a significant contributing factor to the occurrence of pregnancy complications, J. Nutr. 133 (5) (2003) 1597S–1605S.
[78] R.B. Saper, R. Rash, Zinc: an essential micronutrient, Am. Fam. Physician 79 (9) (2009) 768.
[79] J. Nriagu, Zinc Deficiency in Human Health, 2011.
[80] M. Karajibani, et al., Association of serum zinc levels and some risk factors with gestational diabetes mellitus in women referred to the diabetes clinic of Bu-Ali hospital of Zahedan in 2021, Zahedan Journal of Research in Medical Sciences 25 (2) (2023).