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Rima Irwinda
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia, Depok 16424, Indonesia, rima.irwinda@yahoo.com

Ali Sungkar
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia, Depok 16424, Indonesia

Raymond Surya
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia, Depok 16424, Indonesia, raymond_s130291@yahoo.co.id

Valerie Tiempo Guinto
Maternal-Fetal Medicine Phillipine General Hospital, University of the Philippines, Los Baños 4031, Philippines

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Trace elements in maternal serum and their relationships with preterm birth and fetal growth restriction

Rima Irwinda[1], Ali Sungkar[1], Raymond Surya[1*], Valerie Tiempo Guinto[2]

1. Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia, Depok 16424, Indonesia
2. Maternal-Fetal Medicine Phillipine General Hospital, University of the Philippines, Los Baños 4031, Philippines

[*]*E-mail: raymond_s130291@yahoo.co.id*

Abstract

Background: Preterm birth (PTB) and fetal growth restriction (FGR) contribute to high hospital costs. An imbalance in the concentration of the four trace elements (i.e., copper, zinc, iron, and calcium) was shown to be associated with complications during pregnancy. This study aimed to analyze the role of these trace elements in the occurrence of PTB and FGR. **Methods**: A search was conducted in PubMed, Cochrane Library, and Ovid. The articles were filtered based on the inclusion and exclusion criteria, and further screening was based on the association of articles with the clinical question. The risk of bias in each of the studies was assessed using the Cochrane risk of bias table. Forrest plots were created and analyzed using Review Manager 5.3e. **Results**: Three studies were included in the risk of bias assessment and meta-analysis. Maternal serum levels of copper and iron were lower in the FGR group ($p < 0.05$), while copper, zinc, iron, and calcium were lower in the PTB group ($p < 0.05$). The included studies had a low degree of homogeneity (I2 < 50%). **Conclusion**: Maternal iron deficiency was associated with FGR, while low levels of the trace elements copper, zinc, iron, and calcium were associated with PTB.

Keywords: fetal growth restriction, premature birth, trace elements

Introduction

Preterm birth (PTB), which is defined as delivery prior to 37 weeks of gestation, is one of the leading causes of infant mortality and morbidity.[1,2] Apart from the early morbidities associated with PTB, such as respiratory problems, infection, or brain injury, preterm infants have a higher risk for long-term morbidities, including neurologic and developmental disabilities, compared with full term infants.[3] The incidence of PTB varies from 6.2% in Europe to 11.9% in Africa, with a global average of 9.6%.[4] In Indonesia, specifically in the tertiary health center Dr. Cipto Mangunkusumo Hospital, PTB affects 38.5% of pregnancies.[5]

Furthermore, the Institute of Medicine (IOM) stated that in the USA, PTB costs to society, which included the medical the costs for children who had a history of premature birth until they reached the age of 5 years, maternal delivery costs, and the costs of intervention, were $26 billion in 2005.[6] In addition, the average hospital cost per newborn in Canada from 2005–2006 ranged from 1,000 Canadian Dollar (CAD) for babies who weighed 2,500 grams or more to more than 117,000 CAD for babies who weighed less than 750 grams. Singleton neonates born at extremely preterm gestational ages (< 28 weeks) had the highest average cost (84,235 CAD) and stayed in the hospital 40 times longer than full term singleton neonates.[7]

Another pregnancy outcome contributing to the high medical expenses is fetal growth restriction (FGR), which is defined as poor fetal growth inside the womb during pregnancy. Approximately 80–85% of fetuses identified to have FGR are small but healthy; 10–15% have true FGR; and the remaining 5–10% are affected by chromosomal/structural anomalies or chronic intrauterine infections.[8] The impact of FGR includes stillbirth, delayed neurodevelopment in childhood, a higher risk of degenerative diseases in adulthood, and behavioral and social problems later in life.[9,10] The prevalence of FGR has reached 24% of newborn babies, which are mainly in Asia (75%). Previous study stated that the healthcare cost for small for gestational age (SGA) infants was €2,783 higher than that for appropriate for gestational age (AGA) infants. This observation was attributed to the longer length of stay, more frequent hospital readmissions, and higher complication rates.

A modifiable factor to reduce PTB and FGR is maternal nutritional status, which helps determine fetal growth and development. The trace elements that have been linked to adverse pregnancy outcomes are copper, zinc, calcium, magnesium, iron, and iodine. Some studies concluded that copper deficiency was correlated with preterm delivery, premature rupture of membranes, and fetal nervous system damage.[11,12] Zinc has an important role in late pregnancy in preventing fetal growth restriction, congenital malformations, and fetal death.[13,14] Calcium deficiency was shown to cause gestational hypertension and aggravate postpartum haemorrhage.[15–17] Iron deficiency was linked to fetal chronic hypoxia, premature birth, and perinatal fetal mortality.[18,19]

An imbalance in these four trace elements was associated with complications during pregnancy. Therefore, this study analyzed the role of trace elements in the occurrence of PTB and FGR to minimize the occurrence of adverse pregnancy outcomes.

Methods

Type of studies. Cross-sectional, cohort, and case control studies measuring the maternal serum levels of trace elements in women who delivered preterm infants compared to women who delivered term infants and in pregnancies with FGR compared to pregnancies with fetuses without FGR were included.

Type of participants. Pregnant women who did not receive trace element supplementation and whose maternal serum levels of trace elements were measured comprised the study participants.

Type of comparison. The studies included in our review compared two groups: (1) PTB and term delivery or (2) pregnancies with fetuses with FGR and pregnancies with appropriate for gestational age (AGA) fetuses.

Type of outcome. We assessed the outcomes for PTB when pregnant women delivered before 37+0 weeks of gestation. In addition, FGR was defined as a birthweight below the 10^{th} percentile for gestational age and an abdominal circumference below the 2.5^{th} percentile.[20] Another study defined FGR as birthweight −1.5 standard deviation (SD) below the Japanese standard birthweight curve.[21]

Search strategies to identify studies. We did not impose any language or other restrictions at the beginning of the search. The search was conducted in PubMed and Cochrane Library. In PubMed, the search included the keywords using MeSH (i.e., "Pregnancy" AND ("Fetal Growth Retardation” OR "Premature Birth") AND "Trace Elements").

In Cochrane, the MeSH descriptor consisted of [Trace Elements] AND [Pregnancy] AND ([Fetal Growth Retardation] OR [Premature Birth]). The following search strategy was used in Ovid: pregnancy AND trace elements AND (premature birth OR fetal growth retardation). From the above search strategies performed on February 5, 2019, there were 21, 0, and 15 studies in the PubMed, Cochrane Library, and Ovid databases, respectively. The articles were screened using criteria consisting of abstracts answering the clinical question, articles written in the English language, full-text paper availability, and omission of all duplicate papers.

Data collection and analysis

Study selection. Our search generated a list of abstracts. Two review authors (RS and RI) independently screened these abstracts based on the PICO of this study. P stands for the patient/population/problem discussed in the study (i.e., pregnant women). I refers to the intervention/ prognostic factor/exposure (i.e., trace elements). C refers to the comparison, which was not included in this study, and O stands for the outcome of the study (i.e., FGR or PTB). Studies that were not relevant were excluded at this stage. The full text articles of the relevant studies identified were obtained. If there was any uncertainty on the eligibility of the studies based on title and abstract, the full paper was obtained and reviewed by the same two review authors. The search methods and strategies used for this review are shown in Figure 1.

Assessment of risk of bias in the included studies. The risk of bias in the studies was assessed using the Cochrane risk of bias table. Using the risk of bias form, we assessed for data that should have been collected but were not reported.

Measures of outcomes and heterogeneity. Maternal serum trace element levels were measured in patients with each outcome (i.e., PTB, normal delivery, and FGR). We classified the numerical variables for maternal serum level according to the mean difference and fixed effect between outcomes. Heterogeneity was assessed with the I^2 score, and $I^2 < 50\%$ represented homogeneity among studies.

Results

The best study design to answer the prognostic question was a cohort study. In this review, we found 11 studies that investigated our questions; however, 8 studies were excluded due to several reasons, such as the type of material being a proceeding conference book, measurement of trace elements only in a placental site, and the lack of a comparison with a control or normal group. The flow of literature through the assessment process for the update of this review is shown in Figure 1.

Included studies. The studies included in the meta-analysis are shown in Table 1. Three studies were included in the risk of bias assessment and meta-analysis. The study by Kiilhoma *et al.*[22] was a cross-sectional study that aimed to evaluate the role of calcium,

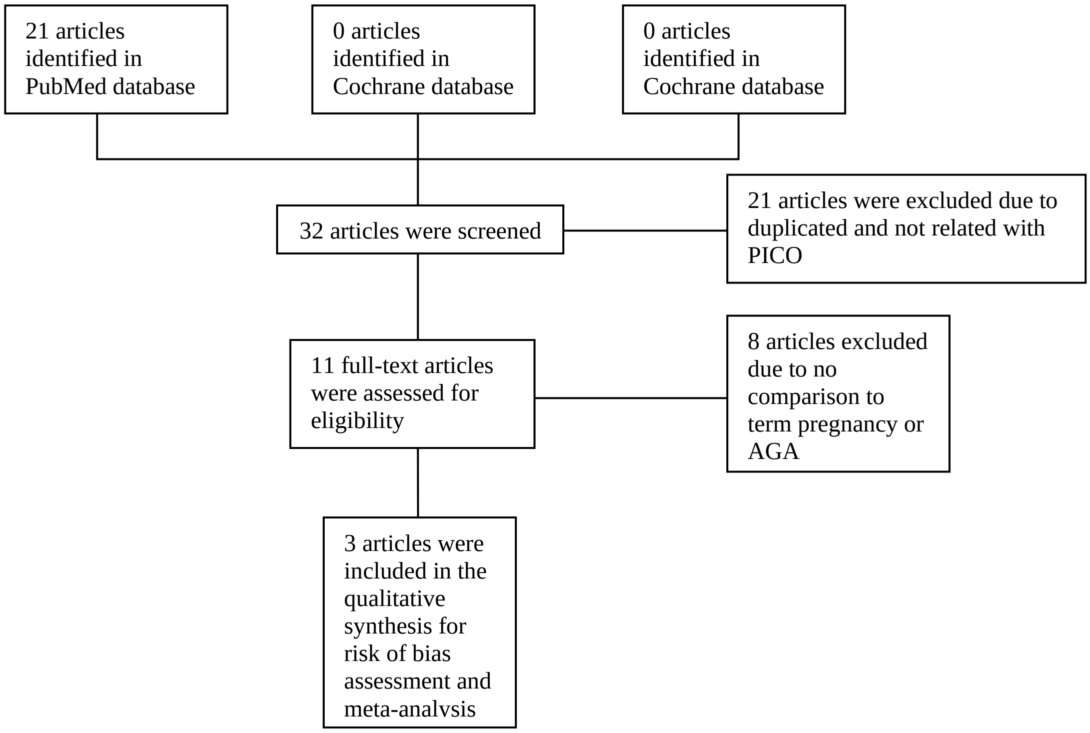

Figure 1. Search strategy in this review. Through Articles were selected from three databases and screened based on the clinical questions. At the end of the selection, three articles were included in the meta-analysis

copper, iron, and zinc in preterm delivery and premature rupture of membranes (PROM). The study involved 60 parturients aged 21–32 years and their newborns. The women were divided into four groups, but this study only analyzed patients from group I and group III. Group I was composed of 20 parturients with normal pregnancy and normal delivery at term (38–40 weeks), while group III was composed of 10 parturients with preterm delivery (29–34 weeks) but normal labor.

After delivery, blood samples were collected from the mother and the umbilical cord. Before analysis, the serum was stored at −20 °C. The results were expressed as mean ± SD. Between the two groups, there were no significant differences in the serum calcium, copper, iron, or zinc levels.

The second study was conducted by Osada *et al*.[21], who examined whether the levels of trace elements in the maternal blood, fetal blood, and placental tissue was associated with fetal growth. This case control study included 21 mothers and their newborns, who were delivered at 34 gestational weeks with FGR but no morphologic or chromosomal abnormalities. In addition, 30 pairs of mothers and AGA infants were recruited for the control group.

Umbilical cord and maternal blood samples were collected immediately after delivery. The serum was separated from the blood samples via centrifugation at 3000 g for 20 min. The serum and placenta samples were freeze-dried at −45 °C pulverized with a polystyrene rod. The determination of the trace element levels was conducted with coupled plasma mass spectrometry and coupled plasma atomic emission spectrometry. The results showed that there were no significant differences in the maternal serum calcium, copper, iron, or zinc levels between the samples of mothers with AGA infants and the samples of mothers with FGR infants.

The aim of a study conducted by Shen *et al*. was to determine the changes in trace element levels in pregnant women and their association with adverse pregnancy outcomes. Approximately 1568 pregnant women were recruited in the beginning of the study, but only 1178 women remained at the end of the study. The maternal serum copper, zinc, calcium, and iron levels were measured during pregnancy in the first trimester, second trimester, and third trimester. The iron and zinc levels were significantly lower in the preterm group, while all the trace elements (i.e., copper, iron, zinc, and calcium) were significantly lower in the FGR group.

Risk of bias in the included studies. Figure 2 shows the risk of bias summary. The risk of bias in each study is shown in Figure 3.

Table 1. Characteristics of the included studies

<table>
<tr><th>Study</th><th>Methods</th><th>Participants</th><th>Assessment</th><th>Outcomes</th></tr>
<tr><td>Kiilholma P, et al.[22]</td><td>Cross sectional study</td><td>60 parturients consisting of 20 parturients with a normal pregnancy and term delivery (group I) and 10 parturients with preterm delivery but normal labor (group III)</td><td>Blood samples were collected from the mother. To determine trace element levels, serum samples were stored at -20°C until analyzed. Serum calcium, copper, iron, and zinc levels were analyzed without preconcentration with the particle-induced X-ray emission (PIXE) method. The determination was made using a beam of 6 MeV H2 ions from a 103-cm AVF cyclotron and an energy dispersive detector with a beam current of 150 µA, beam diameter of 8 mm, and irradiation time of 4 min.</td><td>Serum Maternal serum calcium, copper, iron, and zinc levels (mg/l, mean ± SD) p > 0.05
<table>
<tr><th>Study group</th><th>Calcium</th><th>Copper</th><th>Iron</th><th>Zinc</th></tr>
<tr><td>I</td><td>89±12</td><td>2.37±0.27</td><td>0.86±0.19</td><td>0.63±0.09</td></tr>
<tr><td>III</td><td>88±10</td><td>2.32±0.27</td><td>0.84±0.22</td><td>0.54±0.12</td></tr>
</table></td></tr>
<tr><td>Osada H, et al.[21]</td><td>Case control study</td><td>21 mothers who delivered infants after 34 gestational weeks with FGR but no morphologic or chromosomal anomalies and 30 mothers who delivered appropriate for gestational age (AGA) infants as the controls</td><td>Maternal venous blood samples were collected immediately after delivery. Serum samples were freeze-dried at -45°C and pulverized with a polystyrene rod. Approximately 100 mg of serum was digested with 0.5 ml of 68% ultrapure nitric acid and 0.2 ml of 35% hydrogen peroxide using a microwave digester (MLS-1200, Milestone, Italy). The determination of trace element levels was conducted using coupled plasma mass spectrometry (ICP-MS; HP4500, Yokokawa Electric Co., Japan), and two other trace elements (i.e., Mg and Fe) were determined by inductively coupled plasma atomic emission spectrometry (ICP-AES; SPS-7000, Seiko Electric Industry Co., Japan).</td><td>Maternal serum, copper, iron, and zinc levels (µmol/l, mean ±SD))
<table>
<tr><th>Elements</th><th>AGA (n = 30)</th><th>FGR (n = 21)</th><th>p-value</th></tr>
<tr><td>Copper</td><td>25.3±3.6</td><td>23.0±6.3</td><td>NS</td></tr>
<tr><td>Iron</td><td>15.6±5.0</td><td>17.2±6.3</td><td>NS</td></tr>
<tr><td>Zinc</td><td>3.91±0.75</td><td>3.9±1.5</td><td>NS</td></tr>
</table></td></tr>
<tr><td>Shen PJ, et al.[26]</td><td>Prospective cohort study</td><td>1435 cases of primiparous women and 133 cases of multiparous women in the beginning of the study and 1178 women at the end of the study</td><td>A volume of 5 ml fasting blood was separated in a centrifuge at 1000-2000 r/min for 10 min and measured for trace elements (i.e., copper, zinc, calcium, iron) using a BH-5100 five channel atomic absorption spectrophotometer.</td><td>Maternal serum calcium, copper, iron, and zinc levels (µmol/l, mean±SD)
<table>
<tr><th>Elements</th><th>Preterm</th><th>FGR</th><th>Control</th></tr>
<tr><td>Copper</td><td>29.30±5.80</td><td>23.28±5.27*</td><td>32.74±6.23</td></tr>
<tr><td>Iron</td><td>6.51±1.19*</td><td>6.39±1.01*</td><td>7.09±1.21</td></tr>
<tr><td>Zinc</td><td>73.55±14.09*</td><td>71.28±12.09*</td><td>87.29±14.87</td></tr>
<tr><td>Calcium</td><td>1.53±0.20</td><td>1.45±0.15*</td><td>1.64±0.21</td></tr>
</table>
*p < 0.05; compared with the control group</td></tr>
</table>

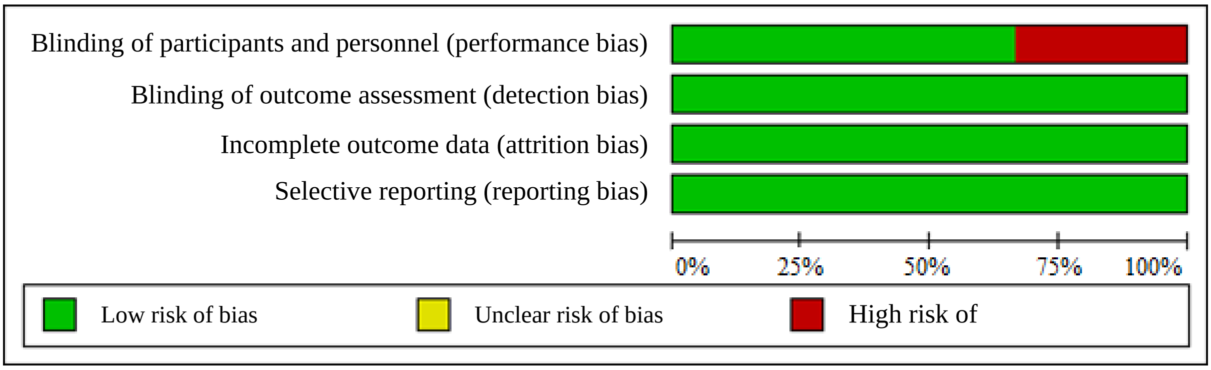

Figure 2. Risk of bias summary for studies included in the meta-analysis

Table 2. Maternal serum of trace elements to IUGR and PTB

Trace elements	Intrauterine Growth Restriction (IUGR)	I^2	Preterm birth (PTB)	I^2
Copper (µmol/L)	-7.09 (-8.81, -5.37)*	93%	-2.76 (-4.37, -1.14)*	52%
Zinc (µmol/L)	-0.32 (-1.03, 0.39)	97%	-14.04 (-18.32, -9.76)*	0%
Iron (mmol/L)	-0.66 (-1.06, -0.26)*	48%	-0.58 (-0.96, -0.20)*	0%
Calcium (mmol/L)	N/A		-0.09 (-0.15, -0.04)*	20%

* $p < 0.05$

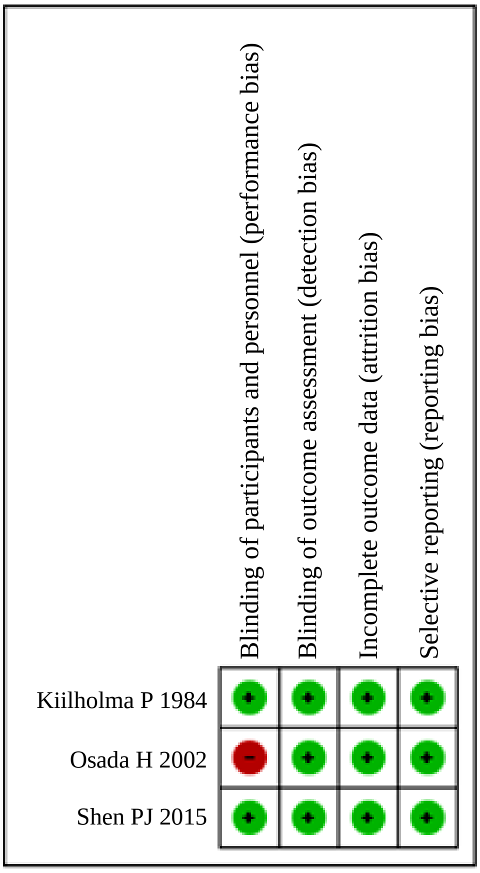

Figure 3. Risk of bias summary for each study

Maternal serum trace elements and outcomes. Table 2 shows the relationship between the maternal serum trace element levels and outcomes (i.e., FGR and PTB) in the studies included in this meta-analysis. The maternal copper and iron levels were lower in the FGR group ($p < 0.05$), while the copper, zinc, iron, and calcium levels were lower in the PTB group ($p < 0.05$). The included studies had a low degree of homogeneity ($I^2 < 50\%$).

Discussion

The limitation of this review was that no proceedings of conferences were included, which could reveal different results. The author only included some of the studies published because this review aimed to compare maternal serum trace element levels' effects between FGR and AGA and between PTB and term birth.

Another study showed that the dietary recommendation for copper was 1 mg/day based on USA, WHO, and European recommendations. Copper has a role to protect body cells from the toxicity of superoxide ions, promoting growth and development, and an important role in the absorption and metabolism of iron.[23] In the maternal serum, 96% of the copper is firmly bound to ceruloplasmin. Ceruloplasmin has a high molecular weight and, therefore, cannot cross the placental barrier. In addition, ceruloplasmin increases due to elevated levels of estrogen during pregnancy.[24] Therefore, it reduces the transfer of copper through the placenta.[22] In the fetus, plasma copper is synthesized by the fetal liver, but the fetal liver has a limited capacity to synthesize ceruloplasmin compared to adults.[24] Copper deficiency is common in premature infants, and it was proven in this review that the copper level in maternal serum samples was lower in those who gave birth prematurely. The low level of copper was due to decreased transfer of free copper from the mother to the fetus in a shorter period of gestation and reduced synthesis of fetal ceruloplasmin. In addition, copper has a role in bone collagen and cytochrome synthesis; therefore, copper deficiency contributes to FGR, which is in accordance with the results of our study.

Zinc is transported through binding to albumin, and the concentration is higher in fetal tissues; the dietary recommendation has been reported as 12 mg (USA) and 7.3–13.3 mg (WHO) per day.[25] Zinc has a role in a variety of enzymes, such as carbonic anhydrase, DNA polymerase, and RNA polymerase, to promote growth and development. This review did not show a significant difference in the zinc level between patients with and without FGR. Another study stated that zinc concentrations in maternal blood were inconsistent (i.e., elevated, reduced, or unchanged)[21]. This inconsistency was because FGR neonates were born to healthy women without complications. This study revealed that the zinc level significantly differed between PTB and FGR ($p < 0.05$). This finding suggests that zinc deficiency might play a role in the initiation of preterm labor, which corresponds to the results in another study.[22]

Iron is intensively transferred through the placenta, particularly during late pregnancy, due to fetal requirements, and the transfer is facilitated by transferrin. Iron requirements increase significantly by more than 80% in the last trimester. Iron deficiency decreases the capacity of hemoglobin to carry oxygen, which results in a chronic lack of oxygen in the mother and fetus. Therefore, iron deficiency directly affects fetal growth and development. It was shown that the iron level is significantly lower in FGR patients.[26] The serum iron levels mothers with PTBs were lower than in mothers with term births, which was consistent with the results in the study previous study.[27–29] They concluded that maternal anemia in the first half of pregnancy, when analyzed as a continuous outcome, was associated with a reduction in gestational age, while maternal anemia in the second half of pregnancy reduced the risk of PTB. In the United States, iron supplementation at lower doses (30 mg/day) is recommended during pregnancy.[25]

The calcium concentration is higher in the fetus than in the mother due to placental transfer, and the dietary reference intake has been reported as 1000–1300 mg (USA) and 1000–1200 mg (WHO).[25] There are physiological variations in the maternal calcium levels. The levels decrease to a nadir level at 32–36 weeks and increase until delivery.[22] Therefore, the maternal calcium serum level is lower in PTB.

Conclusions

Among the four trace elements reviewed in this study, copper and iron influenced the occurrence of FGR with homogeneity among the studies. Likewise, the maternal serum zinc, iron, and calcium levels impacted the occurrence of PTB. Studies that aim to measure the requirements for supplementation of these trace elements are needed.

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Conflict of Interest Statement

No conflict of interest was declared.

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References

1. Purisch SE, Gyamfi-Bannerman C. Epidemiology of preterm birth. *Semin Perinatol.* 2017;41:387–91.
2. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. *Sci.* 2014;345:760–5.
3. Ream MA, Lehwald L. Neurologic Consequences of Preterm Birth. *Curr Neurol Neurosci Rep.* 2018;18:48.
4. Beck S, Wojdyla D, Say L, Bertran AP, Meraldi M, Requejo JH, *et al*. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ.* 2010;88:31–8.
5. Sungkar A, Fattah ANA, Surya R, Santoso BI, Zalud I. High preterm birth at Cipto Mangunkusumo Hospital as a national referral hospital in Indonesia. *Med J Indones.* 2017;26:198–203.
6. Committee on Understanding Premature Birth and Assuring Healthy Outcomes. *Preterm Birth: Causes, Consequences, and Prevention-PubMed-NCBI* [Internet]. [cited 2019 Feb 11]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20669423.
7. Lim G, Tracey J, Boom N, Karmakar S, Wang J, Berthelot J-M, *et al.* CIHI Survey: Hospital Costs for Preterm and Small-for-Gestational Age Babies in Canada. *Healthc Q*. 2009;12:20–4.
8. Manning F. *General principles and applications of ultrasonography*. Matern-Fetal Med 4th Ed Phila WB Saunders Co. 1999;169–206.
9. Taylor HG, Margevicius S, Schluchter M, Andreias L, Hack M. Persisting Behavior Problems in Extremely Low

Birth Weight Adolescents. *J Dev Behav Pediatr JDBP*. 2015;36:178–87.

10. Dahl LB, Kaaresen PI, Tunby J, Handegård BH, Kvernmo S, Rønning JA. Emotional, behavioral, social, and academic outcomes in adolescents born with very low birth weight. *Pediatrics*. 2006;118:e449–59.
11. Ergaz Z, Shoshani-Dror D, Guillemin C, Neeman-azulay M, Fudim L, Weksler-Zangen S, *et al*. The effect of copper deficiency on fetal growth and liver anti-oxidant capacity in the Cohen diabetic rat model. *Toxicol Appl Pharmacol.* 2012;265:209–20.
12. Kashanian M, Hadizadeh H, Faghankhani M, Nazemi M, Sheikhansari N. Evaluating the effects of copper supplement during pregnancy on premature rupture of membranes and pregnancy outcome. *J Matern Fetal Neonatal Med.* 2018;31:39–46.
13. Dickinson N, Gulliver J, MacPherson G, Atkinson J, Rankin J, Cummings M, *et al*. A framework to explore micronutrient deficiency in maternal and child health in Malawi, Southern Africa. *Environ Health Glob Access Sci Source.* 2009;8:S13.
14. Chaffee BW, King JC. Effect of Zinc Supplementation on Pregnancy and Infant Outcomes: A Systematic Review. *Paediatr Perinat Epidemiol.* 2012;26:118–37.
15. Esteban-Vasallo MD, Aragonés N, Pollan M, López-Abente G, Perez-Gomez B. Mercury, cadmium, and lead levels in human placenta: A systematic review. *Environ Health Perspect.* 2012;120:1369–77.
16. Hofmeyr GJ, Lawrie TA, Atallah ÁN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev*. 2018;10:CD001059.
17. Kumar A, Kaur S. Calcium: A Nutrient in pregnancy. *J Obstet Gynaecol India.* 2017;67:313–8.
18. Abu-Ouf NM, Jan MM. The impact of maternal iron deficiency and iron deficiency anemia on child's health. *Saudi Med J.* 2015;36:146–9.
19. Suryanarayana R, Chandrappa M, Santhuram AN, Prathima S, Sheela SR. Prospective study on prevalence of anemia of pregnant women and its outcome: A community based study. *J Fam Med Prim Care.* 2017;6:739–43.
20. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, *et al*. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol.* 2016;48:333–9.
21. Osada H, Watanabe Y, Nishimura Y, Yukawa M, Seki K, Sekiya S. Profile of trace element concentrations in the feto-placental unit in relation to fetal growth. *Acta Obstet Gynecol Scand.* 2002;81:931–7.
22. Kiilholma P, Grönroos M, Erkkola R, Pakarinen P, Näntö V. The role of calcium, copper, iron and zinc in preterm delivery and premature rupture of fetal membranes. *Gynecol Obstet Invest.* 1984;17:194–201.
23. Lewicka I, Kocyłowski R, Grzesiak M, Gaj Z, Oszukowski P, Suliburska J. Selected trace elements concentrations in pregnancy and their possible role-literature review. *Ginekol Pol.* 2017;88:509–14.
24. Goel R, Misra PK. Plasma copper in foetal malnutrition. *Acta Paediatr Scand.* 1982;71:421–3.
25. Plećas D, Plesinac S, Kontić Vucinić O. Nutrition in pregnancy: basic principles and recommendations. *Srp Arh Celok Lek.* 2014;142:125–30.
26. Shen P-J, Gong B, Xu F-Y, Luo Y. Four trace elements in pregnant women and their relationships with adverse pregnancy outcomes. *Eur Rev Med Pharmacol Sci.* 2015;19:4690–7.
27. Alwan NA, Cade JE, McArdle HJ, Greenwood DC, Hayes HE, Simpson NAB. Maternal iron status in early pregnancy and birth outcomes: insights from the Baby's Vascular health and Iron in Pregnancy study. *Br J Nutr.* 2015;113:1985–92.
28. Symington EA, Baumgartner J, Malan L, Wise AJ, Ricci C, Zandberg L, *et al*. Maternal iron-deficiency is associated with premature birth and higher birth weight despite routine antenatal iron supplementation in an urban South African setting: The NuPED prospective study. *PLOS ONE.* 2019;14:e0221299.
29. Rahmati S, Azami M, Badfar G, Parizad N, Sayehmiri K. The relationship between maternal anemia during pregnancy with preterm birth: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med.* 2019:1–11.