Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.63, No.6(2023). p.443-9; DOI: https://doi.org/10.14238/pi63.6.2023.443-9

Original Article

Zinc supplementation in preterm infants and growth indicators in a developing country

Risma Kerina Kaban[1], Ahmad Kautsar[1], Henri Azis[2], Titis Prawitasari[1], Setya Dewi Lusyati[3], Nadia Dwi Insani[4]

Abstract

Background Zinc is one of the micronutrients that is found deficient in preterm infants. To date, no parenteral zinc supplements are available in Indonesia and there is no recommendation established for routine zinc supplementation in preterm infants.

Objective To evaluate the impact of zinc supplementation on growth indicators and morbidity in preterm infants.

Methods This double-blind, randomized controlled trial included preterm infants aged 28-32 weeks who were assigned to one of two groups: the first group received a 10 mg zinc supplementation, while the second (control) group received a placebo. At discharge or at a maximum of 40 weeks post-menstrual age (PMA, calculated from the first day of the mother's last menstrual period), the following were evaluated : growth indicators (weight, length, and head circumference), serum zinc level, zinc supplementation side effects, and morbidity rate (intraventricular hemorrhage/IVH, necrotizing enterocolitis/NEC, btonchopulmonary dysplasia/BPD). Data were analyzed with independent T-test using *SPSS version 22 software*.

Results Seventy-eight subjects were assigned to the zinc supplementation group and 76 subjects were assigned to the placebo group. Serum zinc level and mean body weight increment were significantly higher in the zinc group compared to the placebo group (P=0.00 and P=0.02, respectively). There were no significant differences between groups in mean body length or head circumference increment, nor in morbidity rate.

Conclusion Preterm infants who received zinc supplementation have higher serum zinc level and mean body weight increment compared to the placebo group. No side effects are observed to have been caused by zinc supplementation. **[Paediatr Indones. 2023;63:443-9; DOI: https://doi.org/10.14238/pi63.4.2023.443-9**].

Keywords: *zinc; preterm infant; growth indicators*

Zinc is a chemical element that is found abundantly in the human body; it plays a role in several protein activities.[1,2] Zinc functions in cell division and growth, electrolyte gut absorption, neurotransmission, immune response, thymus activity, and eyesight.[3-5] Severe zinc deficiency may result in growth failure, dermatitis, diarrhea, neurological disorder, infection, and delayed healing following an injury.[1,6] In preterm infants, transplacental zinc transfer ceases, causing low zinc storage, and, along with improper gut absorption, increases the risk of zinc deficiency.[7,8]

Zinc level can decrease to as little as 20% when infants are 48 to 72-hours-old. The serum zinc level in preterm infants measured in placental blood at birth is higher than the zinc level in full term infants. However, the serum zinc level in preterm infants

From the Department of Child Health, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General Hospital, Jakarta and Bunda Women and Children Hospital Jakarta, Jakarta[1], HM Rabain Hospital, Muara Enim Regency, South Sumatra[2], National Center for Women and Children's Health Harapan Kita[3], and Fatmawati Central General Hospital[4], Jakarta, Indonesia.

Corresponding author: Ahmad Kautsar. Department of Child Health Faculty of Medicine UI Kiara Building Level 11, Jl. Pangeran Diponegoro No.71, Senen, Central Jakarta, Special Capital Region of Jakarta 10320. Email: dr.ahmad.kautsar@gmail.com.

Submitted September 7, 2022. Accepted November 20, 2023.

rapidly decreases in the first month of life, and by the age of 40 weeks post-conception, it drops to lower than that of full term infants.[7] A Jakarta study showed that 28% of preterm infants had zinc deficiency, with growth disorders as the most common symptoms.[9] A normal serum zinc concentration typically falls within the range of 65-110 μg/dL. Mild hypozincemia (>60 to <65 μg/dL) can result in mild growth disorders. Moderate hypozincemia (40-60 μg/dL) may lead to growth and developmental disorders, T-cell dysfunction, and edema. Severe hypozincemia (<40 μg/dL) can cause growth arrest, skin and acro-orificial lesions, stomatitis, glossitis, behavioral disorders, diarrhea, and alopecia.[10] However, it's important to note that a universally accepted benchmark for infant zinc levels has not yet been established.[11]

Zinc may be administered in the form of parenteral nutrition support, fortified breast milk, zinc-fortified formula for preterm infants, or specific products containing zinc.[11] Enteral feeding recommended for zinc is within the range of 0.6 to 3 mg/kgBW/day. The zinc requirement for term infants is around 0.8 mg/kgBW/day, while preterm infants may need 2 to 3 mg/kgBW/day to achieve adequate zinc retention. Parenteral supplementation of zinc may be given at a dose of 350 mcg/kgBW/day. Higher doses of zinc supplementation may be considered for preterm infants, particularly during the final trimester of pregnancy, as during this period, the fetus receives approximately 1 mg zinc/kgBW/day from the mother through the placenta.[10,11]

We aimed to evaluate the effect of zinc supplementation on growth indicator increments (body length, body weight, and head circumference) as well as morbidity rate in preterm infants.

Methods

This study was a double-blind, randomized, controlled trial involving preterm newborns in the Perinatology Ward of Dr. Cipto Mangunkusumo General Hospital, Harapan Kita Women and Children's Hospital, Bunda Mother and Children Hospital, and Fatmawati General Hospital, all located in Jakarta from May 2019 until December 2020. The inclusion criteria were preterm infants with gestational age of 28-32 weeks; the exclusion criteria were severe congenital malformation, digestive tract disorder (partial or total obstruction, and/or atresia), severe hemodynamic disorder, early onset sepsis, maternal history of routine alcohol consumption (twice/month), and infants receiving zinc supplementation. The subjects were assigned to one of two groups: the intervention group received 10 mg of oral zinc supplementation and the control group received placebo. Evaluation was conducted on growth indicator differences (body weight, body length, and head circumference), serum zinc level before and after intervention, medication side effects occurring during study period, and morbidities in preterm infants (IVH, NEC, retinopathy of prematurity/ROP, and BPD) for both groups. Weight gain was assessed using post-natal growth velocity with an exponential model formula[12]:

$$GV = 1000 \times \ln\left(\frac{W_n}{W_l}\right) / (D_n - D_l)$$

[W=weight in grams, D=day, l=beginning of time interval, n=end of time interval in days]

Subjects were selected by consecutive sampling, with block randomization and concealment. Random allocation sequencing was done using randomization software. A third party was delegated to enroll and assign participants to interventions. Participants, care providers, and researchers were all blinded to the each subject's group identity. In the intervention group, 10 mg of oral zinc supplementation was given once daily at the time the subject received oral nutrition of ≥20 mL/kgBW/day and continued during hospital care until the time of discharge or at a maximum of 40 weeks post-menstrual age (PMA was the baby's age calculated from the first day of the mother's last menstrual period), if hospital care was still required beyond that point.

Growth indicators were monitored once per week, consisting of body weight, body length, and head circumference measurements. Body weight and length were measured using a *SECA 334* baby scale. The morbidity rate (NEC, ROP, BPD and IVH) and blood zinc level were evaluated before (age 48-72 hours) and after intervention (at time of discharge or at 40 weeks PMA). Evaluation of blood zinc level was conducted with a wet heat method using an atomic absorption spectrophotometer (AAS) type *933 AA* (manufactured by *AGBC Scientific Equipment Ltd.*,

Australia) at *SEAMEO RECFON Laboratory*, Jakarta.

To demonstrate differences between the intervention and control groups with 90% research power and a type 1 error=0.05 (2-tailed test), the minimum required sample size was determined to be 76 subjects per group. Data were collected and analyzed by *Statistical Package for Social Sciences (SPSS) version 22* (*IBM*, New York) software to calculate mean, standard deviation, and P value for quantitative variables.

The protocols of this study were approved by Health Research Ethics Commitees of the Universitas Indonesia and Dr. Cipto Mangunkusumo Hospital (HREC-FMUI/CMH), Harapan Kita Women and Children Hospital Hospital, Bunda Mother and Children Hospital Jakarta and Fatmawati General Hospital Jakarta. Written informed consent was obtained from all participants' parents.

Results

A total of 154 subjects were included, with 78 in the intervention (zinc) group and 76 in the control (placebo) group. The mean gestational age at birth was 31 (SD 1.24) weeks for the zinc group and 30.8 (SD 1.14) weeks for the placebo group. The mean PMA of 35.38 weeks (SD 2.39) for the zinc supplementation group and 36.17 weeks (SD 2.66) for the placebo group. Subject enrollment was discontinued when sufficient data was collected. The study subject flow chart is shown in **Figure 1** and subjects' characteristics are shown in **Table 1**.

The mean body weight increment in the zinc group was significantly higher than that of the placebo group (P=0.023), as shown in **Table 2**. However, the mean body length and head circumference increment were not significantly different between groups (P=0.909 and P=0.847, respectively).

Serum zinc level following supplementation is shown in **Table 3**. After supplementation, mean serum zinc level in the zinc group [75.27 (SD 24.79) ug/dL] was significantly higher than in the placebo group [57.09 (SD 18.77) ug/dL]; (P<0.0001).

There were no severe side effects (hypersensitivity incidents or anaphylactic shock) and no mild side effects (drug allergy, skin rashes, urticaria, vomiting, or diarrhea) due to zinc supplementation or placebo use in our subjects.

There were no statistically significant differences in terms of three morbidity types between the zinc and placebo groups (**Table 4**). Neither harms nor unintended effects were found in either group.-

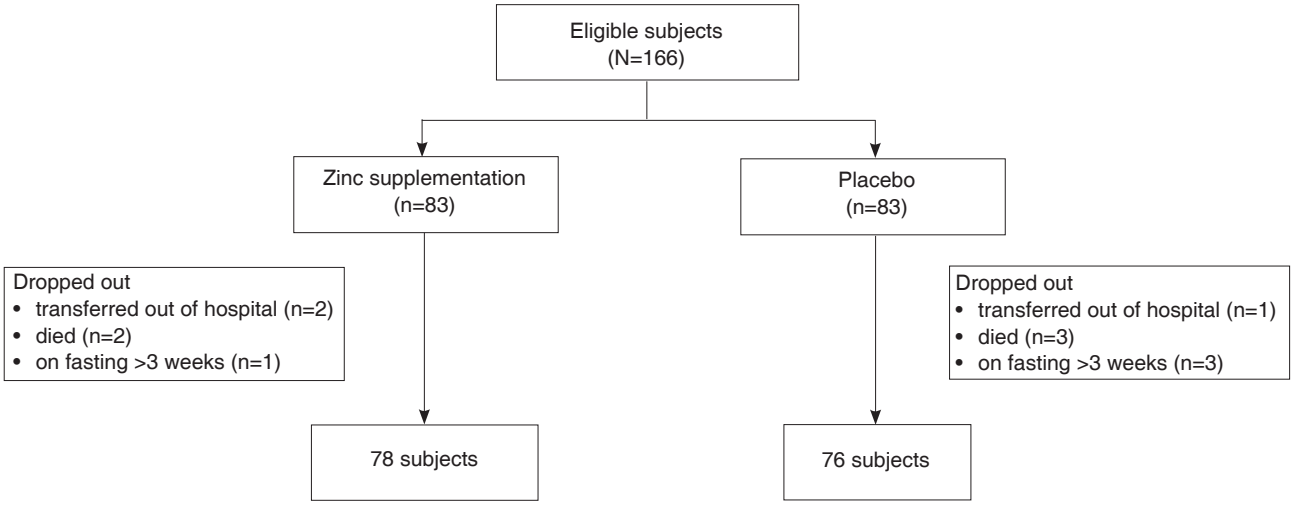

Figure 1. Study subjects' allocation algorithm

Table 1. Subjects' characteristics

Characteristics	Zinc group (n=78)	Placebo group (n=76)
Mean birth weight (SD), g	1,416 (290)	1,372 (281)
Mean birth length (SD), cm	38.55 (3.30)	38.15 (2.90)
Mean head circumference (SD), cm	27.61 (1.96)	27.26 (2.16)
Mean gestational age (SD), weeks	31.00 (1.24)	30.8 (1.14)
Mode of delivery, n (%)		
Vaginal	14 (17.9)	16 (21.1)
Caesarean section	64 (82.1)	60 (78.9)
Sex, n (%)		
Male	34 (43.6)	34 (44.7)
Female	44 (56.4)	42 (55.3)
Mean Apgar at 1 minute (SD)	6 (2)	6 (2)
Mean Apgar at 5 minutes (SD)	8 (1)	8 (1)
Resuscitation, n (%)		
No resuscitation	14 (17.9)	7 (9.2)
CPAP	51 (65,4)	48 (63.2)
PPV	13 (16.7)	21 (27.6)
Body weight status, n (%)		
Small for gestational age	15 (19.2)	9 (11.8)
Appropriate for gestational age	63 (80.8)	67 (88.2)
Large for gestational age	-	-
Mean age when feeding was started (SD), days	3.7 (2.4)	4.3 (3.5)
Mean PMA at discharge (SD), weeks	35.38 (2.39)	36.17 (2.66)
Mean time to reach full feeding (SD), days	12.9 (6.7)	5.3 (9.3)
Mean length of stay (SD), days	35.24 (13.9)	42.13 (17.4)

Table 2. Growth indicators

Variables	Zinc group	Placebo group	P value
Mean daily body weight increment/growth velocity (SD), g/day	9.06 (4.52)	7.01 (6.44)	0.023
Mean body length increment (SD), cm/week	0.80 (0.58)	0.79 (0.41)	0.909
Mean head circumference increment (SD), cm/week	0.67 (0.52)	0.66 (0.48)	0.847

Table 3. Mean serum zinc level before and after supplementation

Mean serum zinc (SD), ug/dL	Zinc group	Placebo group	P value
Before supplementation	79.39 (26.68)	74.75 (24.79)	0.271
After supplementation	75.27 (24.79)	57.09 (18.77)	0.000

Table 4. Morbidities

Morbidities	Zinc group (n=78)	Placebo group (n=76)	P value
BPD, n (%)	7 (8.9)	12 (15.8)	0.199
NEC, n (%)	2 (2.6)	7 (9.2)	0.079
ROP, n (%)	-	1 (1.3)	0.92
IVH, n (%)	7 (8.9)	7 (9.2)	0.959
Dermatitis, n (%)	-	-	

Discussion

In our study, zinc supplementation in preterm infants was observed to improve body weight increment (growth velocity) compared to preterm infants who received a placebo. However, we found no statistically significant difference in body length or head circumference increments, nor in 3 types of morbidities between infants supplemented with oral zinc and infants given placebo.

The recommended zinc supplementation for preterm infants based on the *The European Society for Paediatrics Gastroenterology Hepatology and Nutrition* (EPSGHAN) guidelines is 1.2-2 mg/kgBWper day.[13] We used a daily oral zinc supplementation of 10 mg, without considering body weight. This dose was adopted from two previous studies. A study administered both enteral and parenteral zinc at a total of 9.7-10.7 mg per day, and showed good results for all growth velocity, namely, body weight, body length, and head circumference. The dose also lowered the morbidity and mortality rate in preterm infants.[6] Another study administered oral zinc at 10 mg per day to 134 infants who weighed < 1,500 grams for 8 weeks, and yielded good results.[14]

An advantage of our study was that subjects were at gestational age of 28-32 weeks, which is the time when zinc transfer via placenta increases, yet it is abruptly disrupted by premature birth. At gestational age <28 weeks, the survival rate is very low in Indonesia, while zinc transfer via placenta partially occurs in infants with gestational age >32 weeks.[7]

The initial mean serum zinc levels were 79.39 (SD 26.68) ug/dL in the zinc group and 74.75 (SD 24.79) ug/dL in the placebo group, similar to a study reported a mean serum zinc level of 83.45 (SD 16.74) μg/dL in preterm infants. They evaluated for an association between the serum zinc level in premature infants and their mothers. The mean serum zinc level in the zinc group maintained a normal level of 75.27 (SD 24.79) ug/dL and was significantly higher than that of the placebo group.[15] Similarly, other studies administered zinc supplementation in preterm infants and found that after three months of supplementation, serum zinc level significantly increased, was maintained until discharge, and was subsequently higher compared to a non-supplemented group.[16-17]

In our study, body weight increment velocity was significantly higher in the zinc group than in the placebo group. Mean head circumference and body length increment differences were not significantly different between the two groups. This result was in agreement with several previous studies.[6,14,18] In contrast, a study found no significant differences in body weight increment velocity and head circumference in their study.[17] These variations were attributed to the limited small sample size available for analysis at the end of the study (36 out of 52 infants; 69%). In their study, zinc supplements were administered through fortified formula to 52 premature infants weighing under 1,500 grams. However, the absorption of zinc from the formula was less efficient when compared to that from breast milk or direct administration in the form of medication.[11] Furthermore, a study administered zinc to 36 infants born weighing 1,000-2,500 grams. They noted a significant difference in body length, but not in body weight increment.[16] The differing results may have been due to the fact that supplementation was not started early in life, as zinc supplementation is most needed in preterm infants.

We also found no significant differences in terms of mean weekly head circumference increment between study groups, similar to previous studies.[16,18,19,20] In contrast, a previous study administered zinc supplementation at a dose of 10 mg per day to infants weighing <1,500 grams at birth and found a significant difference in HC increment.[14] Differing results may have been due to different timing of the observations and interventions in their study, as they were conducted up to 52 weeks PMA. In their study, the observation at 40 weeks PMA revealed an non-significant mean head circumference increment between groups. Our results also differed from other studies in which zinc supplementation was given at a dose of 2 mg/kgBW/day and subjects were observed for 4 and 8 weeks, respectively.[22,23] The different zinc dosage and observation times may have led to varying results.

Morbidities related to IVH, NEC, ROP and BPD were found in either group, however, the statistical differences were not significant. In contrast, a study concluded that zinc supplement administration could lower the rate of morbidity (NEC) in premature infants. This may have been due to their larger sample size, which exceeded 100 subjects per group.[6]

No side effects from zinc supplementation were

observed in our subjects, including severe side effects, such as anaphylactic shock, as well as mild side effects, such as urticaria, vomiting, or diarrhea. Previous studies also reported that enteral zinc supplementation did not result in significant side effects.[17-20] Moreover, another study reported incidents of vomiting occurring 15 minutes after the administration of zinc and placebo, in as many as 2% of cases.[6] The rate, however, was not significant for either group. Our trial commenced during hospitalization, and no further follow up was done after discharge. There was no potential bias since we applied the double-blind randomized controlled trial (RCT) method.

In conclusion, preterm infants receiving zinc supplementation during hospitalization or up to 40 weeks PMA have significantly higher increment in body weight and serum zinc level compared to infants who received a placebo. However, body length and head circumference increment as well as morbidities are not significantly different between the zinc and placebo groups. No side effects were observed due to zinc supplementation.

Conflict of interest

None declared.

Funding acknowledgment

The study described in this paper was partially funded by PT Combiphar.

References

1. King JC. Zinc: an essential but elusive nutrient. Am J Clin Nutr. 2011;94:679S-84S. DOI: https://doi.org/10.3945/ajcn.110.005744.
2. Vallee BL, Auld DS. Zinc coordination, function, and structure of zinc enzymes and other proteins. Biochemistry. 1990;29:5647-59. DOI: https://doi.org/10.1021/BI00476A001.
3. MacDonald RS. The role of zinc in growth and cell proliferation. J Nutr. 2000;130:1500S-8S. DOI: https://doi.org/ 10.1093/JN/130.5.1500S.
4. Prasad AS. Zinc in human health: effect of zinc on immune cells. Mol Med. 2008;14:353-7. DOI: https://doi.org/10.2119/2008-00033.Prasad.
5. Fukada T, Yamasaki S, Nishida K, Murakami M, Hirano T. Zinc homeostasis and signaling in health and diseases: zinc signaling. J Biol Inorg Chem. 2011;16:1123-34. DOI: https://doi.org/ 10.1007/S00775-011-0797-4.
6. Terrin G, Berni Canani R, Passariello A, Messina F, Conti MG, Caoci S, *et al*. Zinc supplementation reduces morbidity and mortality in very-low-birth-weight preterm neonates: a hospital-based randomized, placebo-controlled trial in an industrialized country. Am J Clin Nutr. 2013;98:1468-74. DOI: https://doi.org/10.3945/AJCN.112.054478.
7. Wastney ME, Angelus PA, Barnes RM, Subramanian KN. Zinc absorption, distribution, excretion, and retention by healthy preterm infants. Pediatr Res. 1999;45:191-6. DOI: https://doi.org/ 10.1203/00006450-199902000-00006.
8. Uriu-Adams JY, Keen CL. Zinc and reproduction: effects of zinc deficiency on prenatal and early postnatal development. Birth Defects Res B Dev Reprod Toxicol. 2010;89:313-25. DOI: https://doi.org/10.1002/bdrb.20264.
9. Kaban RK, Dharmasetiawani N, Siswanto JE. Prevalens dan faktor risiko terjadinya hipozincemia bayi berat lahir rendah pada usia koreksi mendekati cukup bulan atau cukup bulan. Sari Pediatr. 2016;13:207-14. https://dx.doi.org/10.14238/sp13.3.2011.207-14.
10. Hambidge KM, Casey CE, Krebs NF. Zinc. In: Mertz W. Trace elements in human and animal nutrition. 5th Edition. New York: Academic Press, Inc.; 1986. p.1-137.
11. Hambidge KM, Krebs NF. Zinc in the fetus and neonate. In: Polin RA, Abman SH, Rowitch DH, Benitz WE, Fox WW, eds. Fetal Neonatal Physiol. 5th ed. Philadelphia: Elsevier; 2017. p.313-6. ISBN: 978-0-323-35214-7. DOI: https://doi.org/10.1016/B978-0-323-35214-7.00177-3.
12. Patel AL, Engstrom JL, Meier PP, Jegier BJ, Kimura RE. Calculating postnatal growth velocity in very low birth weight (VLBW) premature infants. J Perinatol. 2009;29:618-22. DOI: https://doi.org/10.1038/jp.2009.55.
13. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, *et al.*; ESPGHAN Committee on Nutrition. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010;50:85-91. DOI: https://doi.org/10.1097/MPG.0b013e3181adaee0.
14. Ram Kumar TV, Ramji S. Effect of zinc supplementation on growth in very low birth weight infants. J Trop Pediatr. 2012;58:50-4. DOI: https://doi.org/10.1093/tropej/fmr036.
15. Jyotsna S, Amit A, Kumar A. Study of serum zinc in low birth

weight neonates and its relation with maternal zinc. J Clin Diagn Res. 2015;9:SC01-3. DOI: https://doi.org/ 10.7860/JCDR/2015/10449.5402.

16. Díaz-Gómez NM, Doménech E, Barroso F, Castells S, Cortabarria C, Jiménez A. The effect of zinc supplementation on linear growth, body composition, and growth factors in preterm infants. Pediatrics. 2003;111:1002-9. DOI: https://doi.org/10.1542/peds.111.5.1002.
17. Friel JK, Andrews WL, Matthew JD, Long DR, Cornel AM, Cox M, et al. Zinc supplementation in very-low-birth-weight infants. J Pediatr Gastroenterol. Nutr. 1993;17:97-104. DOI: https://doi.org/10.1097/00005176-199307000-00015.
18. Islam MN, Chowdhury MA, Siddika M, Qurishi SB, Bhuiyan MK, Hoque MM, et al. Effect of oral zinc supplementation on the growth of preterm infants. Indian Pediatr. 2010;47:845-9. DOI: https://doi.org/10.1007/s13312-010-0145-8.
19. Lira PI, Ashworth A, Morris SS. Effect of zinc supplementation on the morbidity, immune function, and growth of low-birth-weight, full-term infants in northeast Brazil. Am J Clin Nutr. 1998;68:418S-24S. DOI: https://doi.org/10.1093/ajcn/68.2.418S.
20. Ragab SM, Hegran HH, Kassem SA. The effect of zinc supplementation on growth and development in preterm neonates. Menoufia Med J. 2014;27:524-8. DOI: https://doi.org/ 10.4103/1110-2098.145500.
21. El Mashad GM, El Sayed HM, Shawky Elghorab AM. Effect of zinc supplementation on growth of preterm infants. Menoufia Med J. 2016;29:1112-5. DOI: https://doi.org/ 10.4103/1110-2098.202496.
22. Al-Bahadily AKJM, Al-Omrani AAM, Abdul-Zahraa A. The effect of zinc on the growth of preterm baby in Baghdad, Iraq. Int J Pediatr Res. 2016;3:143-7. DOI: https://doi.org/10.17511/ijpr.2016.i03.02
23. Sonawane R, Patil S, Gulati L, Sonawane S. To study the role of zinc supplementation on growth of low birth weight infants. MVP Journal of Med Sci. 2014;1:25-9. DOI: https://doi.org/10.15306/mvpjms/2014/v1i1/46887.