

Original article:

Delivery of cesarean section tends to reduce umbilical zinc levels in healthy newborns

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Abstract:

Background: Indonesia is estimated to be among countries with deficiencies in zinc intake. Zinc deficiency increase the risk of immune deficiency, preterm birth, retarded fetal growth, duration of infection healing, and stunting. Umbilical cord zinc levels can reflect zinc levels of newborns. Research on newborn zinc in Indonesia is still limited. **Objective:** Look for factors related to zinc levels of the newborns umbilical cord. The factors studied included maternal/newborn characteristics, and mode of delivery. **Methods:** A Cross sectional study of 88 healthy newborns at term pregnancy with their healthy mothers. Zinc samples were taken from cord blood immediately after birth. Measurement of zinc levels with Atomic Absorption Spectrophotometer. Chi-Square test was used to prove the relationship between low zinc levels ($< 65\mu\text{g/dl}$) with characteristics of both mother and newborn. The Mann-Whitney test was used to prove differences in zinc levels between groups according to characteristics, mode of delivery, and birth weight. Software SPSS-statistic 21. **Results:** There was no significant relationship between mother and newborn characteristics with low umbilical cord zinc levels ($< 65\mu\text{g/dl}$), with a p value > 0.05 . There was a significant difference in mean umbilical cord zinc levels between the two groups ($p=0.015$), that cesarean section delivery had a mean rank of lower zinc levels ($41.5\mu\text{g/dl}$) median 79.8 (min.50.9-max.140.3 $\mu\text{g/dl}$) compared to spontaneous vaginal delivery ($59.3\mu\text{g/dl}$) median 97.7 (min.57.6-max.132.9 $\mu\text{g/dl}$). Umbilical cord zinc levels from 2500 - < 2800 g birth weight group have lower mean rank ($37.7\mu\text{g/dl}$) compared to 2800 - 3900 g birth weight group ($48.2\mu\text{g/dl}$), with a p value = 0.028. **Conclusions:** There is a tendency to decrease zinc levels in healthy newborns from cesarean delivery. Decreased zinc levels in healthy newborns may cause lower birth weight.

Keywords: umbilical cord zinc levels, cesarean section delivery, lower birth weight

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Introduction

Humans need zinc in very small amounts but the presence of zinc is mandatory. Zinc is part of approximately 300 types of metalloenzyme. Enzyme is a protein that serves as a catalyst for almost every part of human body related to the role of zinc. Its role as part of catalysator, the structure and function of protein and cell membranes apart from helping regulating gene expression or cell signally, is thought to influence the release of

hormones and neurotransmitters. Research shows that zinc is related to cell responses to growth regulator hormones (IGF-1), many enzymes and bone growth hormones. Primary zinc deficiency occurs easily in high phytates diet individuals, low sources of zinc (vegetarian). Pregnant and breastfeeding women are one of the high risk group of zinc deficiency because the increasing needs. Indonesia is at a high risk of zinc deficiency according to estimation risk based on

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shunting prevalence data under 5 years of age and inadequate zinc intake (relating to animal protein intake, high content of phytate). Stunting prevalence in Indonesia during 2005-2017 was 36.4% the third largest in South East Asia region. Pregnant women are prone to malnutrition, while the main source of fetal zinc and newborns comes from the mother through the placenta, so the level of maternal blood serum can affect the infant's umbilical cord zinc level.^{1,3} Study in Shenyang showed that there was positive correlations of maternal zinc and umbilical cord. Zinc deficiency is often associated with preterm birth and low birth weight as previously studied in Jakarta, that zinc from placental infants term is significantly higher compared to premature, even though it is not significantly different for umbilical cord zinc levels. Study in Padang stated that the blood zinc of the newborn placenta with normal growth are higher compared to groups with growth disruption. The research supported previous research in Iran where there is relationship between neonatal umbilical zinc weight deficiency with low birth weight situation.

Previous research data supported the importance of umbilical cord zinc status on fetal growth and prematurity, so it is necessary to study the factors associated with neonatal umbilical cord zinc levels. Factors can be classified based on maternal characteristics (age, number of pregnancies, gestational age, nutritional status), infection factors of pregnant women, and mode of delivery (spontaneous, cesarean section). The cesarean section can affect the timing of baby's umbilical cord's clamping. Most of the indications are emergency so the newborns tends to be quickly resuscitated where doctor's reactions were quicker to cut umbilical cord compared to less emergency spontaneous delivery.

WHO recommend for umbilical cord clamping 1-3 minutes after birth to prevent anemia, iron deficiency and other nutrition elements in neonates. Studies on the relationship of neonatal zinc status with mode of delivery are still very limited in Indonesia, in addition to that, the umbilical cord's zinc status can affect the baby's growth. Therefore, it is very important to asses the mode of delivery and other factors on umbilical cord zinc levels to prevent the risk of zinc deficiency in newborns. The aim of the study was to look for association between umbilical cord zinc levels with factors such as maternal/newborns characteristics, mode of delivery, lower birth weight (2500 - < 2800g),

frequent infections of pregnant women and history of pregnant women dietary habit for the last 3 months. .

Materials and methods

Cross sectional study on 88 healthy infants born from healthy mothers, term pregnancy in the labor ward Sultan Agung Islamic Teaching Hospital and Bangetayu Community Health Center in Semarang City, between September to November 2017. This study is part of a prospective cohort study that examines risk factors for allergic infants. Consecutive sampling technique was used to meet the inclusion-exclusion criteria. Exclusion criteria of newborns include birth weight <2500g, infants with moderate to severe asphyxia, neonatal respiratory distress syndrome, severe infections, seizures, critical infant at NICU (Neonatal Intensive Care), and there are congenital defects (suspicious of genetic disorders). Exclusion Criteria for mothers include severe illness treated in the ICU, decreased consciousness and seizures. Umbilical cord blood collection were conducted immediately after birth as much as 3 cc put into sterile vacutainer , inside 2-8 °C cool bag to be taken to the GAKI laboratory University of Diponegoro medical school, then centrifuged to obtain blood serum, then subsequently stored in sub zero temperatures -20 ° C until the zinc analysis time. Techniques for measuring zinc levels with Atomic absorbance Flame Emission Spectrophotometer(AA-6401F Shimadzu, Japan). Data were collected from both maternal and infant medical records and interviews using a questionnaire.

Characteristics factors examined include maternal age, gestational age, number of pregnancies, gender of the baby, and birth weight. Furthermore, to investigate the association of zinc levels with mode of delivery factor, lower birth weight (2500g- <2800g), frequent infection history of the mother and pregnant mothers dietary habit history. The number of pregnancies is the history of how many pregnancies experienced, divided into two groups, primigravida is a mother who is pregnant for the first time and multi gravida is a mother who experienced pregnancy more than once (1-5). Nutritional status of pregnant women is assessed from the measurement notes of Mid-Upper Arm Circumference in pregnat women, measurements using the standard tape Ministry of Health Republic of Indonesia, if <23.5cm are classified as malnourished. Classification of maternal age is based on young reproductive age (17-35 years),

and old reproductive age (> 35 years)).

Classification of zinc levels are considered low if $< 65 \mu\text{g} / \text{dL}$, $65 \mu\text{g}/\text{dL}$ equivalent to $9.95 \mu\text{mol}/\text{l}$ corresponding previous studies. History of frequent infectious mothers is a symptom of fever accompanied by or without symptoms of common cold, cough / runny nose or diarrhea with a frequency of illness $\geq 2x$ over the past 3 months. There is no definitive definition that states the limits of frequent infectious illness in adults, but based on previous literature recurrent respiratory infection associated with abnormal conditions (decreased immunity) in children to limit the frequency of illness $\geq 6x / \text{year}$. It can be concluded that normal adults will rarely get sick if the infection is resilient, if infection sickness (respiratory infections or other infections) is maximal $< 6x/\text{year}$ or $1x/3$ months, then the definition of frequent infectious disease in this study is when infection symptoms appear $\geq 2x / 3$ months means the same as 8 times/ year. Daily dietary habits of pregnant women every day are categorized into two: often consuming a certain food and rarely consuming it. Often consume a food / drink is almost every day or at least within 3 days every week will / drink these foods. Mothers often eat shellfish dishes, if they regularly eat shellfish every day or at least once every two days every week ($\geq 3x / \text{week}$), while pregnant women often drink cow's milk if they drink regularly every day or at least every two days in every week ($\geq 3x / \text{week}$), all the habits are carried out during the last 3 months.

Lower birth weight is determined by the criteria 2500 to $< 2800\text{g}$ based on the minimum ideal birth weight of term infants (37 weeks gestational age) located at the 50 percentile according to Lubchenco's growth curve which is around 2800g. Based on this assessment, this research creates a new category which is lower birth weight newborns ($2500\text{g} - < 2800\text{g}$) and ideal birth weight group $\geq 2800\text{g} - 3900\text{g}$.

Hypothesis testing to find the relationship between maternal / newborn characteristic factors with zinc levels with the chi-square test, for those who do not qualify were tested using Fisher test. Unpaired t-test was used to look for mean differences in umbilical zinc levels between mode of delivery, history of infection of pregnant women, diets of pregnant women, and lower birth weight. Zinc data was not normally distributed, after transformation the results were still abnormal, Nonparametric tests were conducted using Mann-Whitney test.

Software SPSS-statistic 21.

All parents of infants who agreed to be research subjects signed informed consents after understanding the purpose, benefits and possible side effects. The study protocol was approved by the Health and Medical Research Ethics Commission Faculty of Medicine, Diponegoro University, Semarang.

Results

There were 110 mothers and their babies according to the inclusion-exclusion criteria and agreed to take part in the study, 22 were excluded because failed during blood drawing (12), 2 infants were seriously ill, 6 refused to join the research until finished, and 2 moved out of town. Total 88 infants and their mothers become the subject of this research.

Table 1. Relationship between low zinc levels and maternal/newborn characteristics

Group	Low Cord blood zinc levels ($< 65\mu\text{g}/\text{dL}$)		P* value
	Yes n (%)	No n (%)	
Mother's age 17 - 35 years old ≥ 35 years old	16(88.9) 2 (11.1)	59(84.3) 11(15	

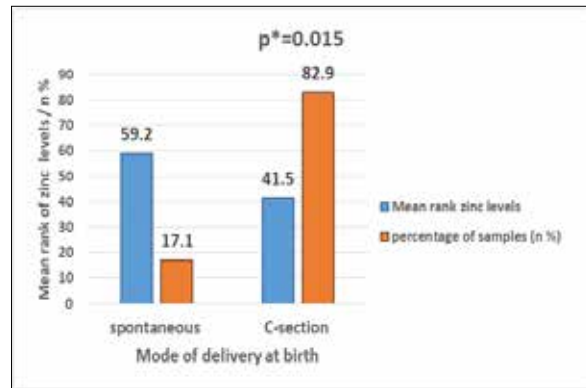
Table. 2. Mean Difference of Zinc Levels between Groups

Group	n	Cord blood zinc levels		p* value
		Mean rank	Median (min-max)	
Frequent infection of Pregnant Women				
Yes	39	46.9	93.4(53.3-140.3)	0.435
No	49	42.6	79.8(50.9-133.4)	
Frequent Milk intake				
Yes	57	43.9	90.2(50.9-140.3)	0.773
No	31	45.6	86.5(53.6-133.4)	
Frequent consumption of shellfish				
Yes	12	41.3	87.4(52.6-126.2)	0.644
No	76	45.0	90.1(50.9-140.3)	
Frequent eggs intake				
Yes	60	46.8	91.3(50.9-140.3)	0.226
No	28	39.7	87.5(53.3-132.9)	

*Mann-Whitney test

Table 2 , displays the mean difference (mean rank)of zinc levels between group of pregnant women according to independent variable the frequent history of infection and the daily dietary habit. There is no significant mean rank difference in umbilical cord zinc level between groups of pregnant women with frequent history of infections and without frequent infections ($p=0.435$), between pregnant women who frequently consuming dairies with infrequent dairy consuming group ($p=0.773$), between pregnant women frequently consuming seashells compared to infrequent seashells consuming ($p=0.644$),and between pregnant woman who frequently consuming eggs and infrequent egg consuming group ($p=0.226$).

The mean rank of umbilical zinc levels in the cesarean section was lower (41.5) compared to the spontaneous birth group (59.2), the median value of the cesarean section group was 79.8(min.50.9 - max.140.3) $\mu\text{g/dL}$, the median value of the spontaneous group was 97.7(min.57.5 - max.132.9) $\mu\text{g/dL}$, with $p=0.015$



metalloenzymes, one of them is RNA Polymerase. Zinc is the enzyme cofactor and influences gene expression through transcription factors. Somatic growth is regulated by growth hormone and Insulin Growth Factor-I(IGF-I). Zinc deficiency can reduce the activity of mitogenic hormone signal pathways which ultimately inhibits proliferation. Zinc deficiency causes growth disruption based on previous research

The opposite results found in studies conducted in Iran that suggests there is an inverse relationship between birthweight of term infants with zinc levels, lower birthweight among groups of mother with normal zinc levels ($> 54\mu\text{g/dL}$). Other study in Iran indicated different results where there is a deficiency of umbilical cord zinc level degree to Low birth weight, severe zinc deficiency is more common in Low birth weight, the research subjects include premature infants. The Jakarta study stated that there was no significant correlation between maternal blood serum zinc levels with birth weight, body length or infant's head circumference.

Premature infants are proven to be more associated with zinc deficiency according to systematic review study of 20 experimental researches on zinc supplementation in pregnant women, there was a significant decrease in preterm births but had no effects on birth weight, said the possibility of zinc reduced the risk of infection of pregnant women so prevented the premature births. Several studies have indicated the positive effect of zinc supplementation on increasing birth weight of infants in the population of undernourished or zinc deficient mothers. This research proves lower umbilical cord zinc levels in infants with lower birth weight groups ($2500\text{g}-<2800\text{g}$) than the more ideal birth weight groups ($> 2800\text{g}$). All term infants, so it is already set aside the prematurity as confounding factor and confirms the result of previous studies that zinc is associated with a tendency to decrease the ideal birth weight (percentile 50) of gestational age > 37 weeks infants. These contradictory results possibly based on specific target population such as maternal zinc status, options of zinc resources, infection prevalence, gestational weeks and prevalence of deficiency of other trace elements (iron, Iodine) which may differ between regions of the country.^{1,17,18}

Although the research on the effect of zinc deficiency on birth weight is still contradictory, zinc remains a very important element in most

normal cell metabolism. The zinc's role in early life is very important starting from the fetal development until birth. Zinc is not only responsible for cell proliferation but also in the early development of immune system. Zinc deficiency can cause thymic atrophy, and normal immunity balance impairment. Zinc in pregnant and nursing women is very influential for their babies. Maternal zinc is positively associated with newborn's umbilical cord zinc level.⁴ Pregnant and nursing mothers have a high risk of zinc deficiency due to the increase need of zinc. The degree of zinc deficiency is mostly mild to moderate, severe zinc deficiency is uncommon.¹⁷ Mild degree of zinc deficiency in infants must not be ignored.

Futhermore, it is necessary to observe all factors that can reduce the zinc transfer from mothers to their babies. We found that there is a tendency for umbilical cord zinc level is lower during caesarian section deliveries than per vaginal spontaneous delivery. There might be tendencies to cut the umbilical cord faster < 3 minutes for several reasons such as cesarean section indications are often associated with emergencies in both mother and baby, so the birth attendants tend to cut the umbilical cord as soon as possible because the baby may need immediate resuscitation or must immediately follow up on mother during stage three. The WHO recommendation of delayed umbilical cord clamping means that the umbilical cord must not be cut faster than 1 minute after the baby is born. The recommendation aims to support the adequate flow of nutrients and also ensuring adequate iron status of the baby until 6 months old. Based on this study, it is proven the tendency to decrease umbilical cord zinc level possibly related to the speed of umbilical cord cutting in cesarean section due to the cutting of umbilical cord < 1 minute not only reduce the iron status of the infants but other trace elements. However, it is necessary to investigate other factors related to maternal blood supplies to the placenta during cesarean section. The side effect of caesarean section which can affect the blood supply to the baby during surgery can be caused by hypotensive effects of anesthetic drugs and other drugs, organs bleeding, decreased blood volume and the effects of uterine contractions.. The decreased of blood pressure were frequently happen in spinal anesthesia group so the vasopressors are needed often.

characteristics because the population tends to be homogenous with distinctive inclusion-exclusion criteria, this research is part of cohort study of risk allergy infants. The limitation of this research is failed to prove the relationship of maternal dietary factor with umbilical cord zinc level, because we did not specifically investigating food recall which associated with the main source of other zincs such as meat, rich in zinc cereals, and others. Further deeper assessments is needed such as erythrocyte metallothionein also placental tissue to explain their effects on birthweight.

Conclusions

Attention is needed during the cutting of umbilical cord due to the tendency of the baby experience decreased umbilical cord blood serum levels. Other factors such as maternal blood supply to the baby during the cesarean section require further study.

There is tendency for decreased birthweight under the ideal 50 weight percentiles of Lubchenco's perinatal growth curves (around 2500 to < 2800g) on lower zinc level mean rank group..

Conflict of Interest

There is no conflict of interest in this study.

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Authors contributions: Idea owner of this study: Sri P,

Data gathering: All Authors

Writing and submitting manuscript: All Authors

Editing and approval of final draft: All Authors

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