Research Article

Assessment Serum Zinc Level in Pregnancy with Covid-19 Compare with Normal Pregnancy

Penilaian Kadar Seng Serum pada Kehamilan dengan Covid-19 Dibandingkan dengan Kehamilan Normal

Freddy.W.Wagey, Vivi Mamangkey, Frank.M.M.Wagey

*Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Sam Ratulangi
Prof. Dr. R. D. Kandou General Hospital
Manado*

Abstract

Objective: The objective of this study was to assess serum zinc levels in pregancy with COVID-19 compared with normal pregnancy.

Methods: The sampling method used was consecutive sampling. All subjects enrolled must meet eligibility inclusion and exclusion criteria with signed informed consent. The study was conducted from March 2021 to June 2021 in Manado. Pregnant women with COVID-19 and normal pregnant women serum zinc levels were measured.

Results: Sixteen pregnant patients with COVID-19 and 16 normal pregnant patients' serum zinc levels were measured. All pregnant women with COVID-19 have low serum zinc levels (100%), whereas in the normal pregnancy group only 8 subjects (50%) have low serum zinc levels and 8 subjects (50%) have normal serum zinc levels. In the pregnancy with COVID-19 group, the mean±SD value was 40.75±10.440, whereas in the normal pregnancy group the mean±SD value was 60.25±17.407. The analysis using an independent T-test shows a significant difference in serum zinc levels between pregnancies with COVID-19 and normal pregnancies (p=0.001).

Conclusion: There is a significant difference in serum zinc levels in pregnancies with COVID-19 and normal pregnancies.

Keywords: COVID-19, pregnancy with COVID-19, zinc in pregnancy.

Abstrak

Tujuan: *Untuk mengetahui kadar seng pada kehamilan dengan COVID-19 dibandingkan pada kehamilan normal.*

Metode: *Pengambilan sampel metode consecutive sampling setiap subjek yang sesuai dengan kriteria inklusi dan eksklusi penelitian dan telah menandatangani surat persetujuan. Penelitian dilakukan bulan Maret 2021 sampai Juni 2021 di Manado. Dilakukan pemeriksaan kadar seng dalam serum pasien hamil dengan COVID-19 dan pasien hamil normal.*

Hasil: *Enam belas pasien hamil dengan COVID-19 dan 16 pasien hamil normal dilakukan pemeriksaan kadar seng. Kelompok kehamilan dengan COVID-19, semuanya memiliki kadar seng rendah (100%). Sedangkan pada kehamilan normal kelompok kadar zinc rendah sebanyak 8 orang (50%) dan kadar seng normal sebanyak 8 orang (50%). Pada kelompok kehamilan dengan COVID-19 didapatkan nilai mean±SD sebesar 40,75±10,440, sedangkan pada kelompok kehamilan normal nilai mean±SD sebesar 60,25±17,407. Pada analisis uji beda independen menunjukkan bahwa terdapat perbedaan bermakna kadar zinc pada kehamilan dengan COVID-19 dan kehamilan normal (p=0.001).*

Kesimpulan: *Terdapat perbedaan bermakna kadar seng pada kehamilan dengan COVID-19 dan kehamilan normal.*

Kata kunci: *COVID-19, kehamilan dengan COVID-19, seng pada kehamilan.*

Correspondence author. Vivi Mamangkey. Department of Obstetrics and Gynecology Faculty of Medicine Universitas Sam Ratulangi. Prof.Dr. R.D. Kandou General Hospital Manado. Email;vivimamangkey@gmail.com

INTRODUCTION

Zinc is an essential micronutrient that plays a role in cell proliferation, differentiation, DNA and RNA synthesis, and cell membrane and structure stabilization.[1,2] Zinc plays an important role in modulating pro-inflammatory response by regulating inflammatory cytokines and controlling oxidative stress.[3] According to the study by Sonja et al. in pregnancy and fetal development, zinc supplementation may reduce the incidence of premature birth by 14%.

Novel coronavirus 2019 (SARS-CoV) is a new type of virus emerging from the coronavirus family, which causes the COVID-19 pandemic.[4] COVID-19 enters the host cell and triggers an immune response, including pro-inflammatory cytokines production, CD4 and CD8+ T-cell activation.[5] The general signs and symptoms of COVID-19 infection include acute respiratory distress such as fever, cough, and dyspnea. Acute respiratory distress syndrome is the severe symptom of this disease. Excessive cytokine production, termed cytokine storm, plays an important role in causing acute respiratory distress syndrome.[6]

Many studies had been done to control the pandemic, including the topic of vaccine and treatment. However, many things are still unknown such as the potential protective effect against the virus, and the effect of micronutrients such as vitamin D, vitamin B12, and zinc in 44 pregnant women with COVID-19.[7] The study found that reduced micronutrient levels affected the immune response of pregnant women with COVID-19. Studies regarding the role of zinc in pregnancies in Indonesia are mainly done in preeclampsia condition, or in the birthweight, mortality, and morbidity.[8,9] However, studies regarding the role of zinc in pregnancies with COVID-19 have never been reported. Therefore, the author wanted to investigate the zinc levels in pregnant women with COVID-19 compared with a normal pregnancy to provide crucial information regarding the role of zinc in pregnancy during the COVID-19 pandemic.

METHODS

This study was a cross-sectional study. The study population was pregnant women who presented to the RSUP Prof. dr. R. D. Kandou Manado and RS Pancaran Kasih Manado from March 2021 until June 2021, with a total subject of 32 patients. The subjects consisted of 16 pregnant women with COVID-19 and 16 normal pregnant women. All subjects met the inclusion and exclusion criteria and signed informed consent. The inclusion criteria were all pregnancies with a confirmed COVID-19 and normal pregnancy who presented to the emergency ward and Obstetrics and Gynecology outpatient polyclinic of RSUP Prof. dr. R. D. Kandou Manado and RS Pancaran Kasih Manado; and agreed to participate in the study with signed informed consent. The exclusion criteria were women suffering from autoimmune disease and HIV; women currently in immunosuppressive therapy; currently using zinc supplementation; refused to participate in the study. Data analysis was done by using the statistical data processing software program SPSS version 23.0. The study was conducted after obtaining the approval and recommendation from the Health Research Ethics Committee, Faculty of Medicine Universitas Sam Ratulangi RSUP Prof RD Kandou Manado.

RESULTS

The study was conducted in RSUP Prof. dr. R. D. Kandou Manado and RS Pancaran Kasih Manado from March 2021 until June 2021 with a total subject of 32 patients. The subjects consisted of 16 pregnant women with COVID-19 and 16 normal pregnant women who met the inclusion and exclusion criteria and had signed informed consent. The subjects' characteristics are shown in Table.

Table 1. Subjects' Characteristics

Characteristics	Pregnancy with COVID-19		Normal Pregnancy	
	N	%	N	%
Maternal age (y o)				
≤20	2	12.5	0	0
21-34	13	81.25	13	81.25
≥35	1	6.25	3	18.75
Parity status				
Primigravida	4	25	4	25
Multigravida	12	75	12	75
Trimester				
I	1	6.25	2	12.5
II	0	0	1	6.25
III	15	93.75	13	81.25

The data above showed that most pregnancies with COVID-19 occurred in the age range of 21-34 years, namely 13 subjects (81.25%). The age group of ≤ 20 consisted of 2 subjects (12.5%), and age group of ≥ 35 consisted of 1 subject

(6.25%). In the normal pregnancies, most subjects were in the age range of 21-34 years old, namely 13 subjects (81.25%), with the age ≥ 35 years consisting of 3 subjects (18.75%).

Table 2. Zinc level in Pregnancy with COVID-19 and Normal Pregnancy

Characteristics	Pregnancy with COVID-19		Normal Pregnancy	
	N	%	N	%
Zinc Levels (ug/dL)				
Low (<60)	16	100	8	50
Normal (60-130)	0	0	8	50
High (>130)	0	0	0	0

Based on the zinc level, all subjects of the pregnancies with COVID-19 group had low zinc levels (100%). In the normal pregnancies group, 8 subjects (50%) had low zinc levels, and 8 (50%) had normal levels.

Table 3. Zinc Levels Distribution in Pregnancy with COVID-19 and Normal Pregnancy

Variable	Pregnancy with COVID-19(n=16)		Normal Pregnancy (n=16)	
Zinc Levels	Mean	40.75	Mean	60.25
	Median	41.50	Median	56.00
	Std deviation	10.440	Std deviation	17.407
	Minimum	19	Minimum	42
	Maximum	57	Maximum	100

Table 3 showed a distribution of zinc levels in the pregnancies with COVID-19 and in normal pregnancies. In the pregnancies with COVID-19 group, the mean±SD value was 40.75±10.440. In the normal pregnancies group, the mean±SD value was 60.25±17.407. Mean zinc levels were lower in the pregnancy with COVID-19 group than that in normal pregnancy.

Table 4. Independent T-test of Zinc Levels in Pregnancy with COVID-19 and In Normal Pregnancy

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	Upper
Zinc	Equal variances assumed	3.449	.073	3.843	30	.001	19.500	5.074	9.137	29.863
	Equal variances not assumed			3.843	24.556	.001	19.500	5.074	9.039	29.961

Based on the Shapiro-Wilk normality test, the zinc levels in pregnancy with COVID-19 and in normal pregnancy data were normally distributed (p = 0.074 and 0.0955). Therefore, we conducted the independent samples T-test (T-test) (Table 4). Table 4 showed a significant difference in zinc levels in pregnancy with COVID-19 and in normal pregnancy (p=0.001).

DISCUSSION

SARS-CoV-2 infection is still uncontrollable; thus, it is still a global issue. As of July 12th, 2021, COVID-19 cases had reached 186.762.453 cases and 4.030.918 death cases globally. Approximately 2.527.203 cases and 66.464 death cases had been reported in Indonesia.8 In our study, we found that the age range of 21-34 years had the most subjects of pregnancy with COVID-19, namely 13 subjects (81.25%). The ≤20 years age group consisted of 2 subjects (12.5%), and the ≥35 years age group consisted of 1 subject (6.25%). In the normal pregnancy group, most subjects were in the 21-34 years age range group, namely 13 subjects (81.25%), whereas the ≥35 years age group consisted of 3 subjects (18.75%). This result is in line with the data from the predominant age group of infected patients in Indonesia, which is the 25-34 years age group.[8]

Based on the parity status in the pregnancy with COVID-19 group, the multigravida group had the most subjects, namely 12 subjects (75%), whereas the primigravida had 4 subjects (25%). While in the normal pregnancy group, the multigravida group also had the most subjects, namely 12 subjects (75%), whereas primigravida also had 4 subjects (25%). Based on the gestational age in the pregnancy with the COVID-19 group, the trimester III group had the most subjects, namely 15 subjects (93.75%), whereas trimester

I had 1 subject (6.25%). In the normal pregnancy group, trimester III also had the most, namely 13 subjects (81.25%), whereas trimester I had 2 subjects (12.5%), and trimester II had 1 subject (6.25%).

Previous studies of COVID-19 infection showed that patients with low zinc levels are strongly associated with the rate of severe complications, longer hospital stays, corticosteroid usage, and increased mortality rate.[9]

Zinc deficiency is strongly associated with the rate of severe respiratory viral infection.[10] Zinc has also been used as nutritional supplementation, both as single or combined supplementation, for the prophylaxis or therapy of COVID-19 infection.[11] Zinc has also been documented to play a role in preventing cellular damage. It has an antiviral effect that underlies the potential of zinc in the management of COVID-19.[12] Multiorgan damage and dysfunction that occurs in COVID-19 infections can also occur based on zinc deficiency, which affects the nerve, cardiovascular, immune, and endocrine systems.[13]

In our study, we found that all subjects in the pregnancy with COVID-19 group had low zinc levels (100%). In the normal pregnancy group, 8 subjects had low zinc levels (50%), and 8 subjects had normal zinc levels (50%). The mean±SD value in the pregnancy with COVID-19 group was 40.75±10.440, while the normal pregnancy group had 60.25±17.407. The independent t-test analysis in our study revealed a significant difference in zinc levels in pregnancy with COVID-19 and the normal pregnancy group ($p=0.001$). The mean zinc levels were lower in the pregnancy with COVID-19 group compared to the normal pregnancy group. Studied 100 pregnant women with COVID-19 and 100 normal pregnant women.[14] The study showed that zinc levels in the pregnancy with COVID-19 group were lower compared to the normal pregnancy in the first trimester (67.19±13.87 vs 55.97±16.57, $p=0.004$), in the second trimester (52.84±12.57 vs 46.38±12.66, $p=0.005$), and in the third trimester (54.37±13.57 vs 46.82±12.51, $p=0.02$). The study also concluded an association between zinc and magnesium on the acute phase reactant, especially in the first trimester.

A similar result was also found in the group of 44 pregnant women with COVID-19, which showed lower zinc levels in pregnancy with COVID-19 group compared to the normal pregnancy group (62.58±2.63, $p<0.001$).[7] They concluded a positive correlation of zinc levels with better immune response in pregnant women by reducing inflammation, increasing mucociliary clearance, preventing lung injury in ventilator usage, and modulating antiviral and antibacterial effects.

Forty-seven pregnant women with COVID-19 also showed lower zinc levels compared to the levels of 45 normal pregnant women, with a median of 74,5 µg/dL vs. 105,8 µg/dL ($p<0.001$).[9] Of 47 pregnancies with COVID-19, 27 subjects (57.4%) had zinc deficiency. There was a higher risk of complication in this group ($p=0.02$), including acute respiratory distress syndrome (18.5% vs 0%, $p=0.06$), increased corticosteroid usage ($p=0.02$), longer hospital stays ($p=0.05$) and increased mortality rate (18.5% vs 0%, $p=0.06$). The limitation of our study is that it is still unclear whether zinc supplementation can lower the severity of the infection. The Spike protein of the SARS-CoV-2 along with its receptors (ACE2) in the lung alveoli is the entry of the virus into the cell. Low zinc plasma levels would cause increased interactions between the viral protein and its receptor, and vice versa; increased zinc levels would cause reduced interactions.[15] Zinc also has an antiviral effect by obstructing RNA synthesis, viral replication, DNA polymerase, reverse transcriptase, and viral protease.[16] Zinc can provide an anti-inflammatory effect by inhibiting the NF-KB signal and modulating the regulation of T-cell function; therefore, reducing the aggravation of cytokine storm. Increased zinc levels can also lower the risk of secondary bacterial co-infections by increasing mucociliary clearance and barrier function of the respiratory epithelial, also with a direct antibacterial effect against S. pneumonia. Zinc status is known to be closely related to the risk factors of severe COVID-19 infections, such as older age, immune deficiencies, obesity, diabetes mellitus, and atherosclerosis.[17]

Based on the previous studies, the author did not find a study that connects zinc supplementation with the incidence of COVID-19 infection risk factors, the effect of zinc levels and zinc supplementation on clinical symptoms severity of COVID-19, and complications related to COVID-19 infection. COVID-19 infection is still a new infection; however, the impact of the pandemic would have a large effect globally. Therefore, further and profound studies regarding the role of zinc in COVID-19 infection are necessary.

CONCLUSIONS

Zinc levels in the pregnancy with COVID-19 group are lower with a mean ± SD value of 40.75±10.440 compared to the normal pregnancy group with a mean ± SD value of 60.25±17.407. Independent t-test showed a significant difference in zinc levels in pregnancy with COVID-19 and normal pregnancy (p=0.001).

SUGGESTIONS

Various factors strongly influence zinc levels in pregnancy with COVID-19. Therefore, more inclusion and exclusion criteria are necessary to be more selective on the study subjects. Moreover, further studies should include a larger sample size. Finally, studies on the effect of zinc levels and supplementation on the clinical severity, risk factors, and complications related to COVID-19 in pregnancy should be conducted.

REFERENCES

1. Rink L, Gabriel P: Zinc and the immune system. Proc Nutr Soc. 2020;59:541-52.
2. Maret W, Li Y: Coordination dynamics of zinc in proteins. Chem Rev. 2019;109:4682-4707.
3. Maret W: Zinc and human disease . Interrelations between Essential Metal Ions and Human Diseases. Sigel A, Sigel H, Sigel RK (ed): Springer, Dordrecht,. The Netherlands. 2013;13:389-414.
4. Li H, Liu SM, Yu XH, Tang SL, Tang CK: Coronavirus disease 2019 (COVID- 19): current status and future perspectives. Int J Antimicrob Agents. 2020;55:105951.
5. Tufan A, Avanoğlu Güler A, Matucci-Cerinic M: COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci. 2020;50:620-32.
6. Ye Q, Wang B, Mao J. The Pathogenesis and Treatment of the Cytokine Storm in COVID-19 . J Infect. 2020;80:607-13.
7. Bahat YP, Talmac MA, Bestel A, Selcuki NF, Aydin Z, Polat I. Micronutrients in COVID-19 Positive Pregnancies. Cureus 12(9):e10609. DOI 10.7759/cureus.10609.
8. Gugus Tugas Percepatan Penanganan COVID-19. Peta sebaran. 2020. www.covid19.go.id/peta-sebar.
9. Jothimani D, Kailasam E, Danielraj S, et al,. COVID-19: poor outcomes in patients with Zinc deficiency. Int J Infect Dis. 2020;100:343–9.
10. Elshafeey F, Magdi R, Hindi N, Elshebiny M. A systematic scoping review of COVID-19 during pregnancy and childbirth. Int J Gynecol Obstet. 2020;150(1):47-52.
11. Roth DE, Richard SA, Black RE. Zinc supplementation for the prevention of acute lower respiratory infection in children in developing countries: meta-analysis and meta-regression of randomized trials. Int J Epidemiol. 2010;39:795–808.
12. Wessels I, Rolles B, Rink L. The potential impact of zinc supplementation on COVID-19 pathogenesis. Front Immunol. 2020;11:1712.
13. Prasad AS. Zinc: an antioxidant and anti-inflammatory agent: role of zinc in degenerative disorders of aging. J. Trace Elem. Med. Biol. 2014;28:364–71.
14. Anuk AT, Polat N, Akdas SS, Erol SA. The Relation Between Trace Element Status (Zinc, Copper, Magnesium) and Clinical Outcomes in COVID-19 Infection During Pregnancy. Biol Trace Elem Res. 2020 ;2:1-10.
15. Devaux CA, Roalin JM, Raoult D. ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure and COVID-19 disease outcome. J. Microbiol. 2020;53:425-35.
16. Read SA, Obeid S, Ashlenstiel C. The role of zinc in antiviral immunity. Adv Nutr. 2019;10(4):696-710.
17. Skalny AV, Rink L, Ajsuvakova OP, Aschner M, Gritsenko VA, Alekseenko SI, et al. Zinc and respiratory tract infections: Perspectives for COVID-19 (Review). Int. J. Mol. Med. 2020;46:17-26.