REVIEW ARTICLE

Micronutrient Intervention during Pregnancy to Incidence of Preeclampsia: Literature Review

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ABSTRACT

Background: **Every year, around 50.000 mothers die worldwide because of preeclampsia. Several studies and researches show that mineral and nutritional factors play a role as one of the etiologies of preeclampsia.**

Objective: **This study aimed to analyze the effect of giving micronutrient intervention during pregnancy on the incidence of preeclampsia.**

Methods: **The article found in data sources is through the National Library of Indonesia e-resources database, PubMed, EBSCO, ProQuest and Google scholar (2015-2020) to retrieve relevant articles published in English and Indonesian. Related subject searches used keywords and phrases related to micronutrients in pregnancy and preeclampsia. The total article in this study is 9 articles.**

Results: **There are differences in calcium, potassium, magnesium and zinc in normal and preeclamptic pregnant women. Several references have a significant effect of vitamin D on the incidence of preeclampsia; one study results that vitamin D has no impact on the incidence of preeclampsia.**

Conclusion: **Micronutrients in supplements related to the incidence of preeclampsia.**

KEY WORDS

micronutrients, pregnancy, preeclampsia

INTRODUCTION

During pregnancy, good quality and quantity of food are needed to supply the mother's and her baby's nutritional needs. The low nutritional status of pregnant women during pregnancy could result in various adverse effects for both mother and baby, including babies born with low birth weight (LBW)[1,2)]. Malnutrition harms the mother, increasing the risk of gestational anaemia, hypertension, miscarriage and fetal death during pregnancy, premature delivery and maternal death. For newborns, it can lead to low birth weight and intrauterine growth retardation of the fetus, which may have long-life consequences on newborn development, quality of life and health care costs. Malnutrition also harms the development of the newborn's immune system[3)].

The Indonesian Demographic Health Survey in 2015 shows the Maternal Mortality Rate (MMR) was 305/100.000 live births; this figure decreased compared to 2012 with 359/100.000 live births. This figure decreased slightly, although it did not meet the total target of the 5th Millennium Development Goals (MDGs), namely reducing MMR to 102/100.000 live births in 2015. Referring to this condition, the potential to achieve the 5th MDGs to reduce MMR requires hard and earnest work to attain it. Maternal mortality in Indonesia is still dominated by the three leading causes of maternal death, or the primary triad of maternal death, namely bleeding, hypertension in pregnancy, and infection.[4, 5)] The Health Development Program in Indonesia prioritized efforts to improve the health status of mothers and children, especially for vulnerable health groups, namely pregnant women, mothers in childbirth and babies in the perinatal period. Preeclampsia is a disease of hypertension, proteinuria and oedema arising from pregnancy.

The maternal mortality rate in Indonesia is still very high, at 225/100,000 deliveries, where preeclampsia and eclampsia are the most likely causes. During the five years from 2005 to 2009, many studies have demonstrated an association of eclampsia with typical relay cases and maternal mortality. Pulmonary oedema is a complication of eclampsia, a determining factor causing increased maternal mortality[6)]. Preeclampsia is the second-highest cause of maternal death in Indonesia. The incidence of preeclampsia in Indonesia is very high at 24%. West Java is a province in Indonesia with a high preeclampsia rate of 25%. Preeclampsia is a multi-factorial disorder[7)].

Several studies and researches show that mineral and nutritional factors have a role as one of the etiologies of preeclampsia. After being explored in depth, there are potential benefits to be gained from taking calcium supplements during pregnancy which reduce preeclampsia. Vascular function changes are essential in controlling vascular resistance and blood pressure. In addition, calcium supplements prevent hypertension in pregnancy by maintaining calcium ion levels within a physiological range which is very important in synthesizing vasoactive substances such as prostacyclin and nitric oxide in the endothelium in supporting normal endothelial function and reducing blood pressure[8)]. This study aims to analyze the relationship between micronutrient intervention during pregnancy and the incidence of preeclampsia.

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METHODS

1. Study Design

The researcher used a literature review based on research related to micronutrients during pregnancy on the incidence of preeclampsia.

2. Search Strategy and Study Selection

This review includes research results or articles with mixed methods study designs, experimental studies, survey studies, cross-sectional studies, correlation analysis, comparative analysis, and qualitative studies that discuss interventions or the effect of micronutrients during pregnancy on the incidence of preeclampsia. We searched the following database covering from 2015-2020: Google Scholar, PubMed, EBSCO and Proquest—the selected keywords: micronutrients in pregnancy and micronutrients in preeclampsia. Articles or journals that meet the inclusion and exclusion criteria are analyzed further. The requirements for the journals reviewed were research journal articles in Indonesian and English with adult human subjects, full text in pdf format, and peer review articles.

3. Data Extraction

Research journals that match the inclusion criteria are then collected. A journal summary is made, including the name of the researcher, year of publication of the journal, country of research, the title of study, method and summary of results or findings. The outline of the research journal be included in the table sorted alphabetically, and the year of publication of the journal will be according to the format.

To further clarify, the analysis of the abstract and full text of the journal has been read and scrutinized. The summary of the journal is then carried out by analyzing the contents contained in the research objectives and research results/findings. The analysis used the journal's contents, then coding the journal contents and the review using the psychospiritual category. The data that had been collected was then looked for similarities and differences and then discussed to be concluded. The researchers found 2536 journals that matched these keywords. A total of 453 journals found according to the search keywords were then screened; 187 journals were excluded because full-text articles were unavailable. The feasibility assessment of 266 full-text journals was carried out; journals duplicated and did not follow the inclusion criteria were excluded, as many as 230. Therefore, nine full-text journals were reviewed.

RESULTS

Based on the results of a review analysis of the research results related to micronutrients and the incidence of preeclampsia, from 13 research results both published in research journals and the effects of unpublished undergraduate theses and postgraduate theses, it was found that the types of micronutrients studied included micronutrients contained in supplementation, which consists of more than three types of nutrients, nutrients (micro and macro nutrients), Calcium, Potassium, Magnesium, Vitamin D and Zinc.

Based on the documents reviewed, the results were that not all micronutrients affected the incidence of preeclampsia. The average micronutrients of calcium, potassium, magnesium and zinc affect the incidence of preeclampsia, meaning there are differences in the levels of calcium, potassium, magnesium and zinc in average pregnant women and preeclamptic pregnant women. In the micronutrient vitamin D, several references significantly affect the incidence of preeclampsia. Still, there is one study result where Vitamin D does not affect the incidence of preeclampsia.

DISCUSSION

Deficiencies of nutrients occur during pregnancy, especially in early pregnancy, and increase the risk of pregnancy complications, such as abortion, eclampsia/preeclampsia, and prematurity[18,19]. In early pregnancy, a deficiency of micronutrients such as vitamins and minerals will interfere with the implantation process. Implantation failure will lead to abortion or miscarriage, while interference with placentation and remodelling of the spiral arteries will lead to eclampsia/preeclampsia[20,21]. Several studies have proved that providing multi-vitamin-mineral supplements during the preconception or preconception period can lessen the risk of prematurity, preeclampsia, congenital disabilities, and abortion[22,23].

Micronutrients have a role in the implantation mechanism and fetal growth and development. Selenium has a vital role in stimulating the production of the hormone progesterone[24]. Vitamin D, which is synthesized by the decidual cells of the placenta, plays a significant role in the success of the implantation and placentation processes. Vitamin D 1,25(OH)2D also helps transform endometrial cells into decidual cells and increases the expression of the HOXA10 gene, which is crucial for embryo implantation in early pregnancy. In normal pregnancy, there is an increase in vitamin D levels starting from the beginning of pregnancy and will continue to grow as the pregnancy progresses. There will even be a two-fold rise in the third trimester. Increased vitamin D levels have function for bone metabolism, immunomodulation, blood pressure regulation[25] and maintenance of insulin secretion by insulin-producing pancreatic beta cells[26-28].

Zinc (Zn) has a role in the implantation process because it is part of the matrix metalloproteinase (MMP) enzyme, which plays an interest in the arterial remodelling process. In addition, Zn stimulates the expression of IFNγ. Then IFNγ secreted by uNK cells could initiate the modification of the uterine blood vessels and form the integrity of the decidual tissue. All the cellular events involving this fundamental role of micronutrients occur from conception to the second week of gestation[29,30].

The role of calcium in the increased risk of preeclampsia during pregnancy could be explained by low calcium levels or other factors resulting in enhanced blood pressure. Pregnant women with high calcium intake have stable blood pressure levels, which will prevent hypertension, thereby reducing the risk of developing preeclampsia[31-33]. The lack of calcium intake will cause an increase in parathyroid hormone (PTH), thereby causing an increase in intracellular calcium. An enhancement in intracellular calcium will cause the smooth muscle of blood vessels to experience vasoconstriction, increasing blood pressure. The rise of blood pressure during pregnancy is a risk of developing preeclampsia[34].

Nutrition and environmental factors as necessary risk factors for preeclampsia, malnutrition that generally occurs during pregnancy in developing countries is relatively low in mineral and vitamin intake, such as low calcium intake. When calcium intake is low, the body uses a series of mechanisms to maintain serum calcium ion levels. The concentration of ionized serum calcium depends on adequate calcium intake. In preeclampsia, there is a decrease in extracellular calcium concentration with a low level of ionized serum calcium. Extracellular calcium concentration is very substantial for synthesis in the endothelium, such as prostacyclin and NO, because this calcium deficiency is not only a mineral deficiency but also related to physiological effects caused by oxidative stress[35].

Magnesium shows a significant role in eclampsia to prevent recurrent seizures[36]. Magnesium acts as a cerebral vasodilator and membrane stabilizer, reducing ischemia and possible neuronal damage. This drug could also work as a central anticonvulsant that blocks N-methyl-D-aspartat receptors[37]. Magnesium has a wide therapeutic range, and clinical monitoring is sufficient to observe respiratory rate, PO_2 saturation (pulse oximetry) and peripheral reflexes. Magnesium levels play a crucial part in controlling blood pressure and have a positive effect on preventing preeclampsia. In addition, magnesium also plays a role in heart muscle contraction; if the concentration of magnesium in the blood decreases, the heart muscle cannot work optimally, thus affecting blood pressure. Less than optimal function of magnesium levels from food in lowering blood pressure could be caused by a lack of fibre which inhibits magnesium levels in the small intestine[38,39].

CONCLUSION

The types of micronutrients studied included micronutrients contained in supplementation, which consists of more than three types of nutrients, nutrients (micro and macro nutrients), Calcium, Potassium, Magnesium, Vitamin D and Zinc. The average micronutrients of calcium, potassium, magnesium and zinc affect the incidence of preeclampsia, meaning that there are differences in the amount of calcium, potassium, magnesium and zinc in ordinary pregnant women and preeclamp-

Table 1: Characteristics of the Structured Studies Included (N = 9)

No	Author	Year	Reference	Title	Methods	Result
1	Sri Sumarmi(9)	2017	Nutrition and Food Research, June 2017 Vol 40 (1) : 17-28	A critical review of multi-micronutrient interventions in the first 1000 days of life (a review on multi micronutrients intervention during the first 1000 days of life)	D: Literature review S: - V: - I: - A: -	- Prospective cohort studies in several countries have proven that pregnant women who took multivitamin supplements during the preconception period had a 50% reduced risk of preterm birth (RR = 0.50) compared to women who did not take multivitamins. - Taking multivitamins during preconception could reduce the risk of preeclampsia by 45-71% (OR = 0.029-0.55) and reduce the risk of small for gestational age (SGA) by 36%. - A recent randomized trial study conducted in Probolinggo District, East Java, proved that multi-micronutrient supplementation 2-6 months before pregnancy has a better effect on the maternal immune response, as well as the production of the hormone human placental lactogen (hPL), which ultimately increases the weight of the placenta and the weight of the baby born, as well as a reduced risk of abortion and prematurity. - Various empirical shreds of evidence confirm the plausibility of supplementing micronutrients since the preconception period is imperative, not only during pregnancy.
2	Ria Gustirini(10)	2019	*Jurnal Kebidanan* Muhammadiyah University of Semarang, Vol 8 (2), 2019	Calcium Supplementation in Pregnant Women to Reduce the Incidence of Preeclampsia in Developing Countries	D : literature review S : V : I : A :	- Calcium level plays a significant part in the pathogenesis of preeclampsia; pregnant women with preeclampsia have lower serum calcium levels than the normotensive group. - Calcium is generally well tolerated; the most effective dose for calcium supplementation during pregnancy is 2g/day starting from 20 weeks of gestation. - Pregnant women in developing countries should be encouraged to consume foods with substances in calcium; if the intake is less than the recommended dose, then calcium supplementation must be given.
3	Kartika Adyani(11)	2020	*Embrio : Jurnal Kebidanan* (May 2020) Vol 12 No 1	Calcium Diet in Pregnant Women	D : literature review S : V : I : A :	- Pregnant women need calcium for the growth and development of the fetus in the womb. - According to recommendations (± 1300 mg/day), calcium intake could significantly reduce the risk of preterm birth.
4	Siti Marfu'ah, Nopri Padma Nudesti(12)	2021	*Jurnal ilmu dan Teknologi Kesehatan* Vol 12 No 2	Analysis of Magnesium, Calcium and Potassium Levels in Pregnant Women with Preeclampsia as a Result of Sunbathe	D: quasi-experimental research with a one-group pretest-posttest research design S: 20 V: Calcium, magnesium, potassium and preeclampsia I: Results of blood tests A: Wilcoxson test	- The study's results revealed significant differences in the levels of potassium, calcium and magnesium in pregnant women before and after exposure to the sun. - This indicates that the sunbathing intervention significantly increased the levels of potassium, calcium and magnesium in pregnant women with preeclampsia.

5	Ekadewi Retnosari, Wiryawan Permadi, Elsa Pudji Setiawati, Farid Husin(13)	2015	Jurnal Pendidikan dan Pelayanan Kebidanan Indonesia, Volume 2 No 4, December 2015	Correlation between Vitamin D Levels and the Incidence of Preeclampsia	D: analytic, which is done by cross-sectional S: 38 Pregnant Women V: Vitamin D and Preeclampsia I: Results of examination of blood levels of Vitamin D A: Biseral point test analysis	- The study's results using the Point Biserial correlation test showed no relation between vitamin D levels and the incidence of preeclampsia with a p-value of 0.052. - This study concludes that there is no correlation between vitamin D levels and the incidence of early-onset preeclampsia. - Vitamin D levels are related to the late onset of preeclampsia, which is part of maternal factors; the incidence of preeclampsia has been influenced by complex etiopathogenesis.
6	Juhi M. Purswani Abstract, Pooja Gala, Pratibha Dwarkanath, Heather M. Larkin, Anura Kurpad(14)	2017	BMC Pregnancy and Childbirth (2017) 17 : 231	The Role of Vitamin D in Preeclampsia: A Systematic Review	D : Literature Review S : V : I : A :	- Several case-control studies and cross-sectional studies have shown an association between vitamin D status and PE, although evidence has been inconsistent. - Clinical trials to date have been unable to show an independent effect of vitamin D supplementation in preventing preeclampsia.
7	Ira Suryanis *et al*(15)	2020	*Jurnal Kebidanan* Vol 6 No 1	Predictors of Severe Preeclampsia in the view from Hair Zinc Levels, Blood Pressure, Urine Protein and Body Weight	D : Cohorts S : 30 V : Zinc, blood pressure, urine protein and weight, preeclampsia I : A :	- Preeclamptic pregnant women's average Hair Zinc level was 210.317 ± 66.7ng/ml. The average maternal weight was 1.7 ± 0.78, the mean Protein 1 score was 1.00 ± 0.00, the mean Systolic was 131 ± 3.05, and the Diastolic was 90.0 ± 0.00. - There is a correlation between urine protein, body weight, and diastolic blood pressure in severe preeclampsia.
8	Hendri Devita, Vitri Yuli Afni(16)	2016	JKMA, Vol 10 No 2	The Relation between Magnesium Levels and the Incidence of Preeclampsia in Third Trimester Pregnant Women at Dr.M. Djamil Padang in 2015	D : Case control S : 265 V : Magnesium levels, preeclampsia I: Results of examination of magnesium levels A : Different test	- There is a correlation between magnesium levels and the incidence of preeclampsia (p = 0.002). - In this study, it can be concluded that magnesium levels are associated with the incidence of preeclampsia. - Accordingly, it is hoped that health workers can carry out early detection of preeclampsia events by conducting magnesium examinations and providing magnesium therapy.
9	Ella Febriana, M.Zen(17)	2017	JKM, Vol 5 No 4	Correlation among Sodium, Calcium and Magnesium Intake with Blood Pressure in Pregnant Women in the Second and Third Trimesters	D : Analytic survey with cross sectional approach S : 114 pregnant women V : sodium intake, blood pressure, I : Questionnaire - A : sperman range	- This research showed that sodium, calcium and magnesium intake were low. - There was no correlation between the nutritional intake with pregnant women's blood pressure in Bulu Health Center. - This research recommends pregnant women increase their nutritional intake. In consequence, the nutritional needs of the body and fetus could be fulfilled.

A = Analysis; D = Design; I = Instruments; S = Sample; V = Variables

tic pregnant women. In the micronutrient vitamin D, several references significantly affect the incidence of preeclampsia. Still, there is one study result where vitamin D does not affect the incidence of pre-eclampsia.

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CONFLICT OF INTEREST

There was no conflict of interest in this study.

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