Volume 4, Nomor 2, Juni 2023 **ISSN : 2774-5848 (Online)**
ISSN : 2774-0524 (Cetak)

BLOOD LEAD LEVELS AS RISK FACTOR FOR PREECLAMPSIA IN ASIAN CONTINENT: A SYSTEMATIC REVIEW

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ABSTRACT
Preeclampsia is a hypertensive disorder in pregnancy which complicates around 2-8% of all pregnancies in the world. Based on estimates from the World Health Organization (WHO), the prevalence of preeclampsia in developing countries is seven times higher than in developed countries. Preeclampsia also causes death of pregnant women in Africa and Asia, around 9%. Increased serum lead levels of pregnant women are associated with an increased risk of preeclampsia. This systematic review study aims to review articles discussing whether blood lead levels are a risk factor for preeclampsia in Asian Continent. This research is a systematic review using PRISMA guidelines. Articles were obtained from several scientific databases, such as Pubmed, Google Scholar, ProQuest, Scopus, and Science Direct (published between 2015 and 2022), using relevant keywords including ("Blood Lead" OR "Lead exposure") AND ("Risk factor") AND ("Preeclampsia") AND ("Pregnant women" OR "Pregnant mother"). Majority of article exposures have the same results regarding the effects of lead exposure in pregnant women with preeclampsia in various countries on the Asian Continent. Results showed that there was significant increase in blood lead levels in the group of pregnant women with preeclampsia compared to pregnant women without complications. We conclude that lead in the blood can be a risk factor for preeclampsia in pregnant women on the Asian Continent. Further research is highly expected to assess the relationship between lead exposure and preeclampsia in pregnant women through experimental studies with larger study samples in the exposed and unexposed groups.

Keywords: *asian continent, preeklampsia, lead*

ABSTRAK
Preeklampsia merupakan gangguan hipertensi dalam kehamilan yang menjadi penyulit sekitar 2-8% dari seluruh kehamilan di dunia. Berdasarkan perkiraan World Health Organization (WHO), prevalensi preeklampsia di negara berkembang tujuh kali lebih tinggi dibandingkan negara maju. Preeklampsia juga menyebabkan kematian ibu hamil di Africa dan Asia sekitar 9%. Meningkatnya level timbal serum ibu hamil dikaitkan dengan peningkatan risiko preeklampsia. Penelitian tinjaun sistematik ini bertujuan untuk memastikan timbal serum sebagai salah satu faktor risiko preeklampsia pada ibu hamil di Benua Asia. Penelitian ini merupakan tinjauan sistematis dengan menggunakan pedoman PRISMA. Artikel diperoleh dari beberapa database ilmiah, seperti Pubmed, Google Scholar, ProQuest, Scopus, dan Science Direct (diterbitkan antara tahun 2015 dan 2022), menggunakan kata kunci yang relevan termasuk ("Blood Lead" OR "Lead exposure") AND ("Risk factor") AND ("Preeclampsia") AND ("Pregnant women" OR "Pregnant mother"). Mayoritas dari tinjauan artikel memiliki hasil yang sama terkait efek paparan timbal pada ibu hamil dengan preeklampsia di berbagai negara di Benua Asia. Hasil menunjukkan bahwa adanya peningkatan kadar timbal dalam darah secara signifikan pada grup ibu hamil dengan preeklampsia dibandingkan dengan ibu hamil tanpa komplikasi. Peneliti menyimpulkan bahwa timbal dalam darah dapat menjadi faktor risiko terjadinya preeklampsia pada ibu hamil di Benua Asia. Penelitian selanjutnya sangat diharapkan untuk menilai hubungan antara paparan timbal dengan preeklamsia pada ibu hamil melalui studi eksperimental dengan sampel penelitian yang lebih besar pada kelompok terpapar dan tidak terpapar.

Kata kunci ***:*** *benua Asia, preeklampsia, timbal*

INTRODUCTION

Preeclampsia based on the criteria of The American College of Obstetricians and Gynecologists (ACOG) is a hypertensive disorder in pregnancy that occurs after 20 weeks of gestation until approaching term of gestation (Gestational Hypertension and Preeclampsia,2021). Currently, preeclampsia is one of the most common health problems in pregnant women, as well as being a major cause of death and morbidity in pregnant women and the high rate of preterm birth worldwide (Yang at al, 2021). Not only that, based on a public health perspective, there are several problems behind the occurrence of preeclampsia, namely the challenges in the detection and prevention of preeclampsia; challenges in managing preeclampsia caused by delays in decisions to seek care, reach health facilities, and provide health services; and the existence of some health policies that are not based on evidence (Osungbade,2011).

Preeclampsia is currently estimated to complicate 2-8% of pregnancies worldwide. Deaths caused by preeclampsia in Latin America and the Caribbean are around 26%, while in Africa and Asia they are as many as 9% (Machano, 2020). The World Health Organization (WHO) estimates that the incidence of preeclampsia in developing countries is seven times higher than in developed countries. Around 70,000 deaths of pregnant women worldwide are caused by preeclampsia based on a report from WHO. In Sub-Saharan Africa, pre-eclampsia remains a major public health problem due to the prevalence of preeclampsia around 1.8 - 16.7%, and this condition contributes to high maternal mortality [4-6]. From the results of a study conducted in Japan, the prevalence of preeclampsia in Asia was 0.2-6.7% (umesewa (2017). The death of pregnant women in Indonesia also increases every year due to preeclampsia. In West Aceh Province, about 33% of the causes of death of pregnant women are preeclampsia (Yushida, 2020).

Several risk factors that have been studied so far are closely related to the increased incidence of preeclampsia (Yushida, 2020). However, several studies have shown that environmental factors are risk factors for preeclampsia that must be considered (Suhartono, 2022). One of the heavy metals indicated to be a risk factor for preeclampsia is lead. Lead exposure can be obtained from industrial activities, transportation, sanding of paint or house dust, cosmetics, eating and drinking utensils, soil, glass pots, drinking water from lead pipes, faucets, plumbing fixtures, battery recycling, contaminated daily food, and agriculture (Suhartono, 2022). Lead in the blood has the main target of toxicity, namely the central nervous system. Increased levels of lead in the blood will increase the blood pressure of pregnant women through the mechanism of oxidative stress. Endothelial dysfunction and increased blood pressure are triggered by an increase in Reactive Oxygen Species (ROS) (Suhartono, 2022). In addition, increased lead exposure can increase the risk of spontaneous abortion and low birth weight babies (American College of Obstetricians and Gynecologists, 2012)

In Brebes Regency, exposure to the heavy metal lead (Pb) is associated with an increased incidence of preeclampsia in pregnant women (Suhartono, 2022). The same thing also happened in Saudi Arabia, from research that has been done, there is a significant relationship between increased blood lead and the risk of preeclampsia in pregnant women)Jameil, 2014). A case control study in Iran showed that there was a significant relationship between blood lead levels and the onset of preeclampsia, where every 1 μg/dL increase in lead levels would increase systolic blood pressure by 0.014 mmHg and diastolic blood pressure by 0.013 mmHg (Bayat, F., Amir, AA., Dabirioskoei, A., Nasiri, M., Mellati, A, 2016).

Several previous review studies stated that lead could be considered as a risk factor for preeclampsia (Kahn, 2018). In addition, a systematic review study conducted by Poropat et al. in 2018 found that every 1 μg/dL increase in blood lead increased the risk of preeclampsia by

1.6% (Poropat at al,2018). However, there has been no systematic research on this matter in the Asian Continent.

Despite the available evidence, the American College of Obstetricians and Gynecologists (ACOG) states that it is still unclear whether lead-induced increases in blood pressure during pregnancy lead to severe hypertension or preeclampsia (Gestational Hypertension and Preeclampsia,2020). In addition, there is a need for identification and further analysis regarding lead as a risk factor for preeclampsia. Systematic review analyzes regarding lead as a risk factor for preeclampsia are still rarely carried out, especially on the Asian Continent. Therefore, a systematic review study regarding lead as a risk factor for preeclampsia in the Asian Continent needs to be carried out to overcome the existing ambiguity and analyze the effect of lead as a risk factor for preeclampsia in the Asian Continent.

METHODS

A systematic review method was used to gain an understanding of lead as a risk factor for preeclampsia on the Asian Continent by summarizing empirical facts obtained from scientific articles. Inclusion criteria in the search for scientific articles, including articles from peer-reviewed journals; published from 2015 to 2022; use English or Indonesian; carried out on the Asian Continent; original research and analytical observational study articles (case-control, cross-sectional, and cohort); full text articles; accessible in open access journals. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Figure 1)

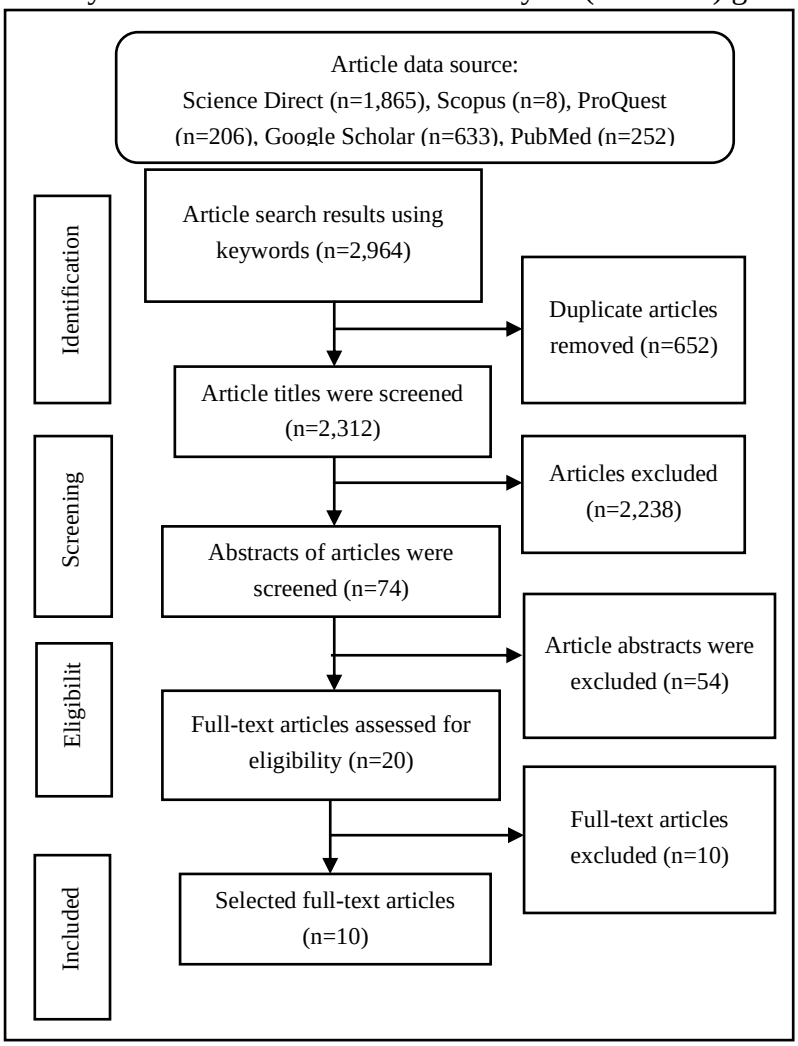

Figure 1. PRISMA Chart (Lead as a Risk Factor for Preeclampsia in Pregnant Women in the Asian Continent)

Were Applied To Determine The Relationship Between Lead As A Risk Factor For Triggering Preeclampsia In Pregnant Women On The Asian Continent. The Data Sources Used Were Obtained From The Pubmed, Google Scholar, ProQuest, Scopus, and Science Direct databases. Keywords for reference search were formulated using the PICOS method [16], including ("Blood Lead" OR "Lead exposure") AND ("Risk factor") AND ("Preeclampsia") AND ("Pregnant women" OR "Pregnant mother"). Article quality is determined by assessing the quality of the methodology, especially for observational studies based on checklist criteria for measuring article quality using Downs and Black's checklists of 17 out of 27 items, namely the following parameters, including hypotheses/objectives/objectives, main results, attributes sample, distribution of important confounders, major findings, estimates of random variability, hard-to-find participant attributes, absolute likelihood values, sample representativeness, recruitment of participants over the same period and from the same population, and statistical analysis fit. A score of zero is given when a study does not meet certain predetermined parameters. Specifically for confounding variables, a score of two is given if it matches the specified parameters, and a score of one when only some of the parameters are met, with the maximum score from this checklist being 28 points. The points of intersection based on the Downs and Black checklists to categorize studies based on quality are divided into four categories, namely very good (26 - 28), good (20 - 25), moderate (15 - 19), and bad (≤14) categories .

RESULTS

A systematic search for original articles was conducted from Science Direct with 1,865 articles, Scopus with 8 articles, ProQuest with 206 articles, Google Scholar with 633 articles, and PubMed with 252 articles based on keywords for reference searches that have been formulated. Thus, the total number of original articles from a systematic search is 2,964 articles. Of the 2,964 articles, there are 652 duplicate articles based on titles and abstracts that have been identified. A total of 2,238 articles were excluded because several titles were part of a book, had topics that were irrelevant to the current research, were meta-analyses and systematic reviews, and used languages other than Indonesian and English. Fifty-four inappropriate abstracts were also excluded. After reading the remaining 20 articles, 10 articles were excluded because they had research locations outside the Asian Continent, outcomes were not in accordance with the topic, and the research year was outside of 2015-2022, so that 10 article manuscripts were selected.

It was found that of the 10 articles that had been selected (Table 1), there were four research articles from Indonesia, and one research each from China, Iraq, Iran, India, Turkey, and Thailand. In addition, there are three case-control study designs [18, 22, 27], six cross-sectional study designs [19-20, 23, 24-25, 26], and one cohort study design [21]. Seven of the 10 articles used samples of pregnant women with preeclampsia and as controls, namely pregnant women with normotension [18-22, 25, 27], and the remaining three articles used samples of pregnant women only [23-24, 26].

Table 1. Journals reviewed

Research Title	Research Title	Researcher /Year of Publication /Country	Sample	Study/Downs Design and Black	Analysis	Research result	Conclusion
Blood lead and calcium levels in pregnant	Blood lead and calcium levels in pregnant women	Areej A. Zabbon/2015/Iraq	15 pregnant women with severe preeclampsia, 15	Case-Control/D&B - 16 (no descriptio	Calculate the mean and standard deviation using the T	Significant increases in systolic and diastolic blood pressure and	The results of this study can be a useful index gauge for

women suffering from severe preeclampsia in Bahdad, Iraq [19]	suffering from severe preeclampsia in Bahdad, Iraq		controls (pregnant women with normal blood pressure). Age range 26-45 years Exclusion: pregnant women with complications (diabetes mellitus, kidney failure, heart failure/ischemic heart disease)	n of drop-out follow-up sample)	test. The p value is significant if ≤ 0.05 Adjusted factors: age (26-45 years), third trimester pregnancy with a diagnosis of preeclampsia	urine albumin at 24 hours (p=0.001) paralleled with significant increase in blood lead levels of pregnant women with severe preeclampsia (p=0.001). Mean ± SD of lead in women with severe preeclampsia (32.58 ± 4.08 µg/dL); Mean ± SD of lead in control (13.06 ± 3.11 µg/dL).	monitoring pathological changes during pregnancy. High blood lead levels in pregnant women in Iran are an important factor in causing preeclampsia
Association of raised blood lead levels in pregnant women with preeclampsia: A study at tertiary centre [20]	Association of raised blood lead levels in pregnant women with preeclampsia: A study at tertiary centre	Disha, Shailja Sharma, Manu Goyal, PVSN Kiran Kumar, Raghumoy Ghosh, Praveen Sharma/2019/India	23 pregnant women with preeclampsia, 44 healthy pregnant women as controls Excludes: history of chronic hypertension, renal impairment, diabetes mellitus	Cross sectional/ D&B - 16 (no description of drop-out follow-up sample)	Analysis using Pearson correlation (significant if p < 0.05) Adjusted factors: mother's age, gestational age, BMI	There was a significant correlation between blood lead levels and systolic blood pressure (r = 0.71, p <0.0001) and diastolic blood pressure (r = 0.57, p = 0.004). Mean ± SD of lead in women with severe preeclampsia (3.42 ± 2.18 µg/dL); Mean ± SD of lead in control (2.38 ± 2.43 µg/dL).	Higher blood lead levels are associated with an increased risk of preeclampsia in pregnant women.
Relationship between blood lead levels and nitrit oxide (NO) levels in preeclampsia [21]	Relationship between blood lead levels and nitrit oxide (NO) levels in preeclampsia	Rina Oktaviana, Yusrawati, Arni Amir/2022/Indonesia	33 normal pregnant women, 33 pregnant women with preeclampsia living within a radius of >10 km from the Semen Padang factory, 33 pregnant women with preeclampsia within a radius of ≤10 km from the Semen Padang Factory.	Cross sectional/ D&B - 16 (no description of drop-out follow-up sample)	Analysis using the Spearman correlation test and logistic regression analysis Adjusted factors: smoking status, distance to housing, and the surrounding environment	There is a strong correlation between blood lead and nitric oxide levels in pregnant women with preeclampsia within a radius of ≤10 km from the Semen Padang factory (r = -0.601; p <0.001). From the results of multivariate analysis, there was a decrease in NO levels in preeclamptic mothers who had high lead levels 2 times compared to	There is a relationship between blood lead and Nitric Oxide levels with preeclampsia in pregnant women.

						preeclamptic mothers with normal lead levels with 95% CI (0.652 - 6.362) after controlling for smoking status, living environment, and distance of residences.	
Association of blood lead levels with preeclampsia: A cohort study in China [22]	Association of blood lead levels with preeclampsia: A cohort study in China	Su Zhen Wu, Huan Ying Xu, Ying Chen, Yu Chen, Qiao Ling Zhu, Min Hua Tan, Miao Miao Zhang/2021/China	2174 pregnant women (2115 normal pregnant women, 59 pregnant women with preeclampsia)	Retrospective cohort/D&B - 16 (no description of drop-out follow-up sample)	Analysis used logistic regression multivariate analysis, and a two-stage linear regression model to determine the dose-effect. Adjusted factors: age at delivery, BMI before pregnancy, educational status, parity, and method of conception	Non-linear relationship between blood lead level and risk of preeclampsia (dose-effect) with a cut-off value of 4.2 □g/dL (the risk of preeclampsia would increase significantly with an increase in blood lead level (OR = 2.05, 95% CI (1.50, 2.81). In multivariate analysis, a 1□g/dL increase in blood lead increased the risk of preeclampsia by 105% (OR = 1.43, 95% CI (1.17, 1.74).	By knowing the dose-effect relationship of preeclampsia with low blood lead levels, the cutoff point can be identified as anticipation of the risk of preeclampsia.
The relationship between blood lead level and preeclampsia [23]	The relationship between blood lead level and preeclampsia	Fatemeh Bayat, Sedigheh Amir Ali Akbari, Atousa Dabirioskoei, Malihe Nasiri, Aliosat Mellati/2016/Iran	158 pregnant women with an age range of 15-40 years	Case control/D&B - 16 (no description of drop-out follow-up sample)	Analysis using Mann-Whitney test, Chi square, independent t test, Pearson correlation, and simple linear regression analysis. Adjusted factors: age, single pregnancy, gestational age above 20 weeks, BMI, mother's education, income	There is a significant relationship between blood lead levels and preeclampsia (p = 0.028), where with an increase of 1 □g/dL of lead in the blood, systolic blood pressure will be increased by 0.014 mmHg and diastolic blood pressure will be increased by 0.013 mmHg (p = 0.004).	There is a significant relationship between lead levels and preeclampsia in pregnant women.
Blood lead levels in	Blood lead levels in	Nova Amalia	86 pregnant women	Cross sectional/	Univariate analysis	The mean lead level in the	Lead levels in pregnant

pregnant women and the source of exposure in northern coastal area of Brebes Regency [24]	pregnant women and the source of exposure in northern coastal area of Brebes Regency	Sakina, Suhartono, Nikie Astorina Yunita Dewanti/2018/Indonesia		D&B - 15 (no description of p-value and drop-out follow-up sample)	(mean, standard deviation, minimum, maximum and proportion) Adjusted factors: second and third trimester gestational age, mother's age, educational status, occupation, BMI	blood of pregnant women is 42.437 + 19.758 µg/dL. Sources of lead exposure in pregnant women include wrapping food using newsprint (80.2%), engaging in agricultural activities (37.2%), the habit of consuming seafood (44.2%), and passive smoking (70.9%).	women at the northern coastal area of Brebes have exceeded the standard set by the CDC, namely 5 µg/dL.
Blood lead levels of pregnant women in agricultural and coastal area: a sdg's indicator for health and pollution in Brebes District [25]	Blood lead levels of pregnant women in agricultural and coastal area: a sdg's indicator for health and pollution in Brebes District	N.A.Sakina/2021/Indonesia	84 pregnant women (42 pregnant women in agricultural areas, 42 pregnant women in coastal areas)	Cross sectional/ D&B - 16 (No follow-up description of participants who dropped out)	Univariate analysis (minimum, maximum, standard deviation, median and mean); Bivariate analysis (independent t test with normality test using Kolmogorov Smirnov) Adjusted factors: mother's age, mother's education	The results showed that the age of pregnant women in agricultural areas was between 20-38 years, while in coastal areas between 19-41 years. Most pregnant women's education is elementary school. There is a significant difference from the average blood lead levels in pregnant women in agricultural and coastal areas in Brebes Regency (p-value = 0.047). The average blood lead level of pregnant women is higher in agricultural areas (46.243 µg/dL) than in coastal areas (37.731 µg/dL).	Lead levels in preeclamptic women in the agricultural and coastal areas of Brebes District exceed the established standards. Lead levels are much higher in agricultural areas due to pesticides that still contain lead.
The Differences in blood lead levels in women with gestational hypertension or pre-eclampsia	The Differences in blood lead levels in women with gestational hypertension or pre-eclampsia and women	Suhartono Suhartono, Apoina Kartini, Budiyono Budiyono, Yusniar Hanani Darundiati/2	64 subjects (18 subjects with gestational hypertension/preeclampsia (case group) and 46 subjects with	Cross sectional/ D&B - 16 (No follow-up description of participants who	Independent t test, Mann-Whitney test, Chi-Square test, multivariate logistic regression test, and Rank-	The median value and range of blood lead values in the case and control groups were 40.20 g/dL (15.50-89.20) and 32.75 g/dL (3.60-42.80)	Blood lead levels in pregnant women with preeclampsia are higher than normal pregnancies.

and women with normal pregnancy (a study in the North Coast of Java, Brebes District) [26]	with normal pregnancy (a study in the North Coast of Java, Brebes District)	022/Indonesia	normotension (control group)	dropped out)	Spearman correlation test. Risk estimation is calculated using Odds-Ratio (OR) and 95% Confidence Interval (CI). Adjusted factors: mother's age, gestational age >20 weeks, single pregnancy	respectively (p = 0.011). Pregnant women with BLL ≥ 35.15 g/dL have eight times the risk of experiencing GH/PE (Adj-OR = 8.1; 95% CI = 1.7-39.0). Lead exposure will increase the production of Reactive Oxygen Species (ROS).	
Blood lead levels among non-occupationally exposed pregnant women in Southern Thailand [27]	Blood lead levels among non-occupationally exposed pregnant women in Southern Thailand	Donrawee Waeyeng, Tanaporn Khamphaya, Phisit Pouyfung, Udomratana Vattanasit, Supabhorn Yimthiang/2022/Thailand	80 pregnant women	Cross sectional/ D&B - 16 (No follow-up description of participants who dropped out)	Bivariate analysis (independent t test or One Way Anova with 95% confidence interval (CI); Pearson correlation); Multivariate analysis (logistic regression analysis). Adjusted factors: mother's age, parity, gestational age, BMI	The mean lead levels was 4.68 ± 1.55 µg/dL (95% CI 4.33–5.02) and 42.50% pregnant women had blood lead levels ≥ 5 µg/dL. The only demographic factors associated with lead levels ≥ 5 µg/dL (aOR 0.16, 95% CI 0.03–0.80, p = 0.027) were higher education and systolic blood pressure (aOR 5.00, 95% CI 1.23–17.16, p = 0.023). However, even a low BLL had little effect on systolic blood pressure.	Lead can be detected in pregnant women who were working with lead exposure. High lead levels are associated with high systolic blood pressure in pregnant women.
Analyses of maternal plasma cadmium, lead, and vanadium levels in the diagnosis and severity of late-onset preeclampsia: a prospective and	Analyses of maternal plasma cadmium, lead, and vanadium levels in the diagnosis and severity of late-onset preeclampsia: a prospective and comparative study	Ali Ovayolu, Vugar Ali Turksoy, Ismet Gun, Erbil Karaman, Ilkay Dogan & Abdulkadir Turgut/2021/Turkey	46 pregnant women with late-onset preeclampsia (cases) and 46 pregnant women with normal blood pressure (controls)	Case control/ D&B - 16 (No follow-up description of participants who dropped out)	Independent analysis t test if normally distributed, Mann-Whitney test if not normally distributed, Receiver operating characteristic (ROC), Spearman Correlation test	Case and control groups were matched for maternal age, gestational age, and gravidity (p ≥ 0.05). There was no difference between lead metal concentrations in patients with preeclampsia (p ≥ 0.05).	There is no significant relationship between blood lead levels and preeclampsia.

comparative study [28]		Adjusted factors: gestational age, BMI, maternal age, parity, gravida

The relationship between lead exposure and the development of preeclampsia is discussed in 10 selected articles. Further specifications in the discussion, namely regarding lead exposure in preeclamptic women are contained in seven articles [18-22, 25, 27], exposure and sources of lead in pregnant women are contained in one article [23], and lead exposure associated with residence and employment of pregnant women are found in two articles [24,26]. The strong relationship between lead exposure and blood pressure in pregnant women with preeclampsia was clearly discussed in nine articles ($p<0.05$) [18-22, 25-26] whereas one article stated that there was no significant relationship between lead exposure and preeclampsia [27].

Blood lead levels can be determined by several methods using a blood sample. The lead inspection methods used by several articles discussed in this study include the atomic absorption spectrophotometer (AAS) method [18-21, 23-26]; potentiometric method with PSA Ion3 (Steroglass-Italy) [22]; and coupled plasma-mass spectrometry [27]. Repeat analyzes are usually performed to produce precise lead levels (Zabbon, AA, 2015).

Most of the manuscripts reviewed have sufficient scores according to the D&B criteria. However, one article scored low because no p-value was reported, and follow-up losses were not explained [23]. Each study has different confounding factors. These factors revealed the most favorable relationship between preeclampsia and lead. BMI, maternal age, education, method of conception, and household income are significantly associated with preeclampsia [19, 21-22, 25-26]. However, based on research by Ovayolu, et al in 2021, it stated that there was no significant relationship between the factors of maternal age, gestational age, gravida, parity with pregnancy and lead (Ovayolu , at al, 2021).

DISCUSSIONS

Blood lead levels in Asian populations are described as much higher than in developed countries. This is supported by research conducted by Li, et al in 2021, that lead levels in the blood of adults in China in 1980-2018 increased continuously in 1980-2000, and then decreased since 2002, influenced by air pollution and land in China (Li, Y , 2021). Then, research conducted in 2016 by Hore et al, stated that around 20% of South Asian adults living in New York City have blood lead levels $\geq$ 5 µg/dL. This condition is influenced by home renovation work, Bangladeshi and Indian ethnicity, cannot speak English, and jobs with a high risk of lead exposure (Hore, 2017).

The mechanism of lead in causing preeclampsia can be concluded from several previous studies. Several previous studies stated that lead would trigger oxidative stress by reducing antioxidants and increasing reactive oxygen species (ROS) concentrations, especially hydroperoxides and lipoperoxides (Nosratola, D., Vaziri, XQ., Wang, FO., Behdad, R, 2000) Lyn, PND, 2006). Through their activity, ROS elicit changes in cell and tissue membranes, resulting in damage to blood vessels, nerves, and genes [31-32]. Not only that, lead will also allow dysregulation of the renin-angiotensin-aldosterone system, together with effects on the endothelium and vascular smooth muscle, and stimulation of the sympathetic nervous system due to increased catecholamine production (Lyn, PND, 2006). Lead also promotes the release of endothelin from the endothelium; increased thromboxane, serum norepinephrine, and

angiotensin converting enzyme levels; and causes decreased production of prostacyclin which favors vasoconstriction (Solenkova, at al, 2014).

Ikechukwu et al in 2012 in their study have noted that lead increases levels of circulating endothelin (Ikechukwu, at al, 2012). Endothelin is a vasoactive which constricts the diameter of blood vessels so that it can affect blood pressure. This mechanism would lead to preeclampsia either by inducing vasoconstriction and placental ischemia or direct toxicity to endothelial cells and renal function causing proteinuria, which is a common feature of preeclampsia (Solenkova, 2014). Lead also reduces serum levels of vasodilators such as nitric oxide (NO) and endothelial-derived relaxing factor (EDRF) due to lead-mediated increases in reactive oxygen species. Lead can also inhibit membrane adenosine triphosphatase (ATPase) which works to increase intracellular calcium ions and vasoconstriction (Moreau,1988).

Several other studies do not support the concept that lead exposure will affect the occurrence of preeclampsia in pregnant women. This is illustrated in a study conducted by Ovayolu et al in 2021 which concluded that there was no difference between lead metal concentrations in patients with preeclampsia ($p \geq 0.05$) (Ovayolu, 2021). Liu et al in their 2019 study also support this, that there is not enough evidence to suggest that lead is related to the occurrence of preeclampsia. This might have happened because the blood lead levels in the sample in Liu et al's study were lower than in previous studies (Liu,, 2019). However, even low blood lead levels can pose health risks for women (wells at al. 2011).

Lead exposure can come from the environment around humans. Various studies have shown that lead exposure in pregnant women can be through the air (Chen, XK, at al, 2006), through water (Troesken, W, 2006), and through soil (Zahran, 2014). Prolonged environmental exposure may be associated with long-term presence of lead in bone and this in turn may be associated with a much greater risk of proteinuria among pregnant women (Rothenberg , at al, 200). In addition, living within a radius of <10 km from a cement factory also significantly affects pregnant women exposed to lead so that they suffer from preeclampsia. This condition can occur because the cement produced can contain lead which can be spread by wind and rain (Oktaviana, R , at al, 2022). Evidence linking lead exposure to preeclampsia shows that lead exposure can also come from several sources, such as seafood contaminated with lead, food wrappers using newspapers or magazines, engaging in agricultural activities, painting houses less than one year old, using cosmetics, having spouses with occupational risks with high levels of lead, and secondhand smokers (Mielke, HW, 2011)

There are some limitations of evidence that may exist in the articles that have been reviewed, particularly regarding the relationship between lead exposure and the incidence of preeclampsia in pregnant women. Most of the articles reviewed used observational studies such as cross-sectional, case-control, or cohort approaches. Differences in study design, study sites, timing of lead exposure, number of participants enrolled, outcomes related to preeclampsia in pregnant women, adjustment for confounding variables in data analysis, and type of statistical analysis used could lead to varying results in studies.

CONCLUSION

Lead exposure is a widespread and ongoing problem throughout the world, especially on the Asian Continent. This review of the articles stated that lead in the blood can be a risk factor for preeclampsia in pregnant women on the Asian Continent. This is supported by the existence of sources and pathways of lead exposure in work and the environment which can affect the incidence of preeclampsia in pregnant women. Not only that, the presence of malnutrition (calcium deficiency) in pregnant women also increases lead exposure in pregnant women with preeclampsia. Therefore, it is important to quickly monitor and intervene in blood lead levels in pregnant women with preeclampsia symptoms so it will not exceed 5 µg/dL through regular

lead level checks when lead exposure is known both from the environment and work. In addition, it is important to consume foods that contain calcium, prevent exposure to lead, and eliminate sources of lead. Further research is highly expected to assess the relationship between lead exposure and preeclampsia in pregnant women through experimental studies with larger study samples in the exposed and unexposed groups.

ACKNOWLEDGEMENTS

Thank you very much to all those who participated in helping to write this journal so that the writer can finish this article well.

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