ANALYSIS OF THE INCIDENCE OF PREECLAMPSIA IN PREGNANT WOMEN WITH CONSUMPTION OF HERBAL MEDICINE CONTAINING CHOLIN, CITRININ, DIBUTYL PHTHALATE DURING PREGNANCY

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KEYWORDS
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ABSTRACT
Preeclampsia is the second leading cause of maternal death globally each year associated with pregnancy, characterized by elevated blood pressure and proteinuria that usually appear during the second trimester or after 20 weeks. One of the natural medicines in Indonesia is "Jamu" which refers to a traditional drink of the Indonesian people used to prevent and treat diseases. Research on the content of compounds in jamu and their impact on the health of pregnant women, especially preeclampsia, is still limited. The results of LCMS analysis of the types of jamu commonly consumed in Boyolali Regency, namely papaya leaf decoction and sinom jamu, contain compounds such as dibutyl phthlate, citrinin, and cholin, which have the potential to affect sFlt1 levels. This study aims to analyze the differences in cholin, citrinin, and dibutyl phthalate (DBP) levels in the urine of pregnant women with preeclampsia (PE) and without PE, as well as the impact of herbal medicine consumption on the levels of these compounds. Using an analytic observational design and case-control study method, this study involved 110 pregnant women at Waras Wiris Andong Hospital in Boyolali Regency from January to July 2024. The results showed higher levels of choline and critinin in the PE group compared to non-PE, while DBP levels were higher in the non-PE group. Pregnant women who consumed herbal medicine had higher levels of choline and critinin. However, there was no significant correlation between the three compounds and the incidence of PE. These findings suggest significant differences in urinary compound levels based on PE status and herbal medicine consumption, although there is no simultaneous correlation with PE incidence.

INTRODUCTION

Preeclampsia (PE) is one of the most serious complications of pregnancy and a leading cause of maternal and infant morbidity and mortality worldwide. Over the past three decades, the frequency of PE has increased significantly, with approximately 4 million women diagnosed annually, and more than 70,000 maternal deaths and 500,000 infant deaths reported due to the condition.(Poon et al., 2019). The prevalence of PE varies across countries, with higher rates seen in low-income and developing countries, including Indonesia. The incidence of PE deaths in Indonesia remains high, placing the condition as the second leading cause (27.1%) of maternal deaths after hemorrhage (30.3%).(Kementrian Kesehatan, 2014). Data from the Central Java

Provincial Health Office shows that in 2018, hypertension was the leading cause of maternal mortality (MMR) in Boyolali district, with 33.4% of cases caused by eclampsia.(Dinas Kesehatan Provinsi Jawa Tengah, 2022).

The clinical characteristics of PE are characterized by systolic blood pressure ≥ 140 mmHg and diastolic ≥ 90 mmHg after 20 weeks of gestation, as well as the presence of proteinuria, which indicates damage to kidney function and has the potential to cause further complications in the fetus, such as low birth weight, stillbirth, seizures, kidney failure, and endanger the life of the mother and fetus.(Sastrawinata, 2005). Although the pathogenetic mechanisms of PE are not fully understood, an imbalance between angiogenesis and antiangiogenesia factors in the maternal circulation has been identified as the main cause of this condition.(Mayrink et al., 2018).

One of the angiogenesis factors currently associated with PE is sFlt1, which has antiangiogenesis effects. sFlt-1 functions as a decoy receptor for VEGF and PlGF, which when bound reduces the availability of these two factors, thereby disrupting angiogenesis and causing endothelial dysfunction. This mechanism is critical as VEGF and PlGF are required to maintain endothelial integrity and support vascular remodeling during pregnancy.(Palmer et al., 2017)(Maynard et al., 2003)(Vogtmann et al., 2021). Decreased levels of VEGF and free PlGF contribute to clinical symptoms such as hypertension and proteinuria that are hallmarks of preeclampsia. The ratio of sFlt-1 to PlGF has been identified as an effective clinical biomarker to predict the onset of preeclampsia, even before clinical symptoms appear, so it can be used for early diagnosis.(Vogtmann et al., 2021)(Silvani, 2019).

On the other hand, jamu as a traditional Indonesian drink, has been used for generations for the treatment of various diseases. Jamu contains various natural ingredients, such as rhizomes, leaves, and fruit peels, which are believed to provide health benefits for pregnant women, including reducing symptoms of nausea, vomiting, and weakness. However, research on the content of compounds in jamu and their impact on the health of pregnant women, especially in the context of PE, is still limited. The types of jamu commonly consumed in Boyolali Regency include papaya leaf decoction and jamu sinom. The results of LCMS analysis showed that these herbs contain compounds such as dibutyl phthlate, citrinin, and cholin, which could potentially affect sFlt1 levels.

Along with the increasing prevalence of PE and its impact on maternal and infant health, it is important to explore the relationship between herbal medicine consumption in pregnant women and increased levels of compounds that can trigger PE. Therefore, a study entitled "Analysis of Preeclampsia Incidence in Pregnant Women with Herbal Medicine Consumption Containing Cholin, Citrinin, Dibutyl Phthalate during Pregnancy" was conducted. This study aims to investigate the relationship, and compare the levels of dibutyl phthalate, citrinin, and cholin compounds in the urine of pregnant women with and without preeclampsia in Boyolali Regency. Thus, it is hoped that this study can contribute to understanding the factors that contribute to the development of preeclampsia and raise awareness regarding the consumption of herbal medicine in pregnant women.

RESEARCH METHOD

This study used an analytic observational design with a *case-control* study approach to analyze the relationship between preeclampsia (PE) and certain risk factors. The study population was pregnant women with PE at Waras Wiris Hospital, Andong, Boyolali Regency, Central Java, from January to July 2024, with a sample of 110 pregnant women taken by purposive sampling. The criteria for the PE group included an increase in blood pressure ≥ 140/90 mmHg after 20 weeks of pregnancy, accompanied by proteinuria. The control group consisted of pregnant women without PE symptoms. Sampling was conducted at the obstetric polyclinic of Boyolali Regency Hospital, and analysis of choline, citrinin, and DBP levels was conducted at Okta Santika Laboratory in Malang. Data analysis used statistical tests to test normality, homogeneity, validity, reliability, and relationship between variables. The normality test was performed using the Shapiro-Wilk test for samples ≤ 50, where data were normally distributed if the p-value > 0.05, while the homogeneity test used the Levene test to ensure equal variation in the sample. To analyze the relationship between

the independent and dependent variables, logistic regression or linear regression tests were used to assess the effect of choline, citrinin, and DBP in urine samples on the incidence of preeclampsia.

RESULTS AND DISCUSSION

Measurement of the levels of choline, citrinin, Dibutyl Phthalate in the urine of pregnant women who experienced preeclampsia (PE) compared to pregnant women who did not experience preeclampsia (non PE) provides information on differences in biochemical profiles between the two groups. Table 1 presents the results of the analysis which discusses the summary of the results of the difference test between the means of PE and non-PE pregnant women.

Table 1. Mean difference test results of PE and non-PE pregnant women

	Choline (Mean±SD)	**Critinine (Mean±SD)**	**DBP (Mean±SD)**
non PE (n=55)	0.434±0.104	0.263±0.063	0.588±0.038
PE (n=55)	0.762±0.191	0.535±0.126	0.309±0.125
Statistics (p-value)	**Z = -7.691 (0.000)**	**Z = -8.701 (0.000)**	**Z = -8.480 (0.000)**
Table	**$Z_{0.05}$ = 1.960**	**$Z_{0.05}$ = 1.960**	**$Z_{0.05}$ = 1.960**

The average Choline number of the non PE group of 0.434 ± 0.104 was lower than the average Choline number of the PE group of 0.762 ± 0.191. With the Mann Whitney test, the calculated Z value is smaller than -Z table (-7.691 < -1.960), and the p-value is smaller than α (0.000 < 0.050), meaning there is a significant average difference in Choline number between the non PE and PE groups. Critinine of the non PE group of 0.263 ± 0.063 was lower than the average Critinine of the PE group of 0.535 ± 0.126, the calculated Z value was smaller than -Z table (-8.701 < -1.960), and the p-value was smaller than α (0.000 < 0.050), this means there was a significant difference in Critinine between the non PE and PE groups. The Dibutyl Phthalate (DBP) number of the non PE group of 0.588 ± 0.038 is higher than the PE group of 0.309 ± 0.125, the calculated Z value is smaller than -Z table (-8.480 < -1.960), and the p-value is smaller than α (0.000 < 0.050), this means that there is a significant average difference in DBP numbers between the non PE and PE groups.

Choline is an essential nutrient that plays a role in lipid metabolism and neurotransmitter synthesis, and is involved in brain and memory formation as well as protecting the fetus from the environment that causes congenital defects.(Jaiswal et al., 2023). Choline examination in the body uses blood and urine samples. The level of choline in the body of an adult woman ranges from 133 pmol/50 µL.(Sheyn et al., 2018). Research shows that low choline levels in pregnant women may be associated with the risk of preeclampsia. Adequate choline intake may help reduce some of the risk factors associated with preeclampsia. Notably, choline supplementation in pregnant women has been shown to reduce levels of soluble fms-like tyrosine kinase-1 (sFlt1), a protein that is elevated in preeclampsia and contributes to endothelial dysfunction. Decreased levels of sFlt1 may improve placental function and nutrient transfer to the fetus, which is often impaired in preeclampsia.(Jaiswal et al., 2023; King et al., 2017).

Citrinin is a benzopyran compound produced by organisms such as plants and some species of microorganisms. Plants that produce citrinin are grains, nuts, fruits and vegetables. Citrinin is described as a natural compound derived from Penicillium citrinum, which is also formed by other genera of fungi, such as Aspergillus species and Monascus species, which are all molds. In addition, *Penicillium* (P. expansum and P. viridicatum) and *Aspergillus* (A. niveus, A. terreus, A. awentil, A. fumigatus, A. awamori, A. ostianus, and A. parasiticus) are known to be citrinin-producing fungi.(Zhang et al., 2021). Although generally known as a neurologic mycotoxin, citrinin has antimicrobial, antifungal, anticancer and neuroprotector activities in vitro.(Zargar & Wani, 2023). Based on previously conducted studies, citrinin exposure has been shown to negatively impact oocyte maturation and embryo development through mechanisms such as oxidative stress and apoptosis. These effects may lead to poor reproductive outcomes, which may be relevant in the

context of preeclampsia, a condition characterized by hypertension and proteinuria during pregnancy.(Y. Wu et al., 2017).

Dibutyl Phthalate (DBP) is an ester of phthalic acid and butyric acid that is used as a plasticizer, and is also known to have negative effects on health. In the context of pregnancy, research suggests that DBP may contribute to oxidative stress and inflammation, both of which play a role in the pathogenesis of preeclampsia.(H. Wu et al., 2021). Widespread DBP exposure among pregnant women has an effect on thyroid hormone levels, particularly elevated FT4 and TSH. This exposure has the potential to disrupt the endocrine system during pregnancy, which may affect fetal growth and development.(Al-Saleh et al., 2024).

Various studies have found that DBPs are pollutant agents that are harmful to the ecosystem. In addition to polluting the environment, DBPs that enter the body cause various health problems including fetal disorders during pregnancy. At a concentration of 15 ppm embryos exposed to DBP showed various malformations, including edema and craniofacial abnormalities.(Gardner et al., 2016). DBP affects spermatogenesis and reproductive organ weight through endocrine disruption.(Rashad et al., 2018). Recent studies have shown that DBP exposure causes lipid metabolism disorders, affects the structure and composition of the gut microbiota and especially activates the LPS-TLR4-NFκβ pathway that triggers the onset of liver inflammation.(Xiong et al., 2020).

Based on the results of LCMS analysis, the herbal medicine consumed by pregnant women in Boyolali Regency contains compounds such as dibutyl phthlate, citrinin, and cholin, which have the potential to affect sFlt1 levels. Therefore, the average levels of cholin, citrinin and dibutyl phthalate in the group of pregnant women who consumed herbal medicine and did not consume herbal medicine were tested.

Table 2: T-test results of the mean difference between pregnant women consuming herbal medicine and non-hamam medicine

	Choline (Mean±SD)	**Critinine (Mean±SD)**	**DBP (Mean±SD)**
non Jamu (n=66)	0.550±0.219	0.362±0.174	0.516±0.124
Herbal medicine (n=44)	0.671±0.217	0.455±0.145	0.247±0.175
Statistics (p-value)	**Z = -3.225 (0.001)**	**Z = -3.606 (0.000)**	**Z = -4.698 (0.000)**

Based on the table above, it is known that the choline level in the group of pregnant women who do not consume herbal medicine (non herbal medicine) is 0.550 ± 0.219, lower than the herbal medicine group with an average of 0.671 ± 0.217. Mann Whitney test showed the Z value (-3.225) which was smaller than -Z table (-1.960) and p-value (0.001) which was smaller than α (0.050), indicating a significant difference between the two groups. The creatinine level in the non herbal medicine group of 0.362 ± 0.174 was lower than the herbal medicine group which reached 0.455 ± 0.145, with the Mann Whitney test results showing the Z count value (-3.606) and p-value (0.000), which means there is a significant difference. In contrast, the average DBP level in the non-Jamu group was 0.516 ± 0.124, higher than the Jamu group whose average was 0.347 ± 0.175, with Mann Whitney testing showing the Z count value (-4.698) and p-value (0.000), so there was also a significant difference in DBP levels between the two groups.

Therefore, it can be concluded that the urine of pregnant women who consume herbal medicine has higher levels of choline and critinin compared to those who do not consume herbal medicine. Statistical tests showed that this difference was significant, which means that consumption of herbal medicine most likely influenced the increase in choline and critinin levels. In contrast, DBP levels in the group that did not consume herbal medicine were higher than the group that consumed herbal medicine. This also showed a significant difference, meaning that herbal medicine consumption may be associated with lower DBP levels.

Table 3. Simultaneous effect test

		Chi-square	p-value
Step 1	Step	152.475	0.000
	Block	152.475	0.000
	Model	152.475	0.000

Based on table 3, it can be seen that there is a test of the effect of independent variables simultaneously or simultaneously on the dependent variable using the Omnibus test in logistic regression. The Chi square value of the model is 152.475 with a p-value of 0.000, with a p-value smaller than α (5%) so it can be concluded that there is a simultaneous correlation of choline, citrinin, dibutyl phthlate on the incidence of preeclampsia in pregnant women in the Boyolali region, Central Java. In other words, the independent variables namely Choline, Critinine, and Dibutyl Phthalate together have a significant effect on the dependent variable.

Table 4. Hypothesis testing of partial influence

Variables	B	Wald	p-value	Exp(B)	Description
Choline	-185869.915	0.296	0.586	0.000	Not significant
Critinine	307749.808	0.296	0.586	-	Not significant
DBP	-253.341	0.298	0.585	0.000	Not significant
Constant	-336.850				

Choline variable showed a negative and insignificant effect on the PE variable, with a Wald value (0.296) smaller than the chi-square table (3.842) and a p-value (0.586) greater than α (0.050). The negative regression coefficient and exp B of 0.000 indicate that an increase in choline tends to lead to the non PE category, although it is not significant. Similarly, the critinin variable had a positive but insignificant effect on PE, with a Wald value (0.296) and p-value greater than α (0.586 > 0.050). The regression coefficient is positive (and exp B is absent) indicating that an increase in the Critinine variable has no tendency towards any category of PE variable.

Meanwhile, the DBP variable also showed a negative and insignificant effect on PE, with a Wald value (0.298) and p-value (0.585) indicating that an increase in DBP tends to lead to the non-PE category, but the effect is not significant. So it can be concluded that the results showed that each of the variables analyzed, namely choline, critinin, and DBP (dibutyl phthalate) partially had an insignificant effect on the risk of preeclampsia (PE) in pregnant women.

The insignificant effect of choline, citrinin, and DBP on the risk of preeclampsia may be due to other influences that dominate the occurrence of preeclampsia in pregnant women. According to previous research, it is stated that medical history is very influential in the occurrence of preeclampsia. Women with a history of chronic hypertension have a higher risk of developing preeclampsia. Pre-existing high blood pressure can worsen the condition during pregnancy, causing serious complications for both mother and fetus. In addition, both type 1 and type 2 diabetes also significantly increase the risk of preeclampsia. Women with diabetes are two to four times more likely to develop this condition compared to non-diabetic women.(Weissgerber & Mudd, 2015). In addition, paternal genes may also influence the risk of preeclampsia. Genetic factors from both mother and fetus contribute to susceptibility to preeclampsia.(Williams & Broughton Pipkin, 2011).

CONCLUSIONS

Based on the research results, it can be concluded that:

1. There are differences in the levels of choline, citrinin, dibutyl phthalate in the urine of pregnant women who experience preeclampsia with non-preeclampsia in the Boyolali area, Central Java.
2. There are differences in the levels of choline, citrinin, dibutyl phthalate in the urine of pregnant women who consume herbal medicine and do not drink herbal medicine in the Boyolali area, Central Java.
3. There is a significant simultaneous correlation of choline, citrinin, dibutyl phthalate on the incidence of preeclampsia in the Boyolali region of Central Java. However, partially choline, critinin, and DBP have an insignificant influence on the incidence of preeclampsia in the Boyolali region of Central Java.

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