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Maternal and neonatal outcomes in women with preeclampsia screening program at primary healthcare centers in Indonesia

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Abstract
Preeclampsia can cause increased neonatal mortality and serious neonatal morbidity. This study aimed to analyze the result of the preeclampsia screening program to the maternal and neonatal outcome at primary healthcare centers. A retrospective study through medical records and ultrasound records. Screening program, including anamnesis, physical examination, were Body Mass Index (BMI), Mean Arterial Pressure (MAP), Roll Over Test (ROT), and use of Doppler ultrasound. We conducted screening to 474/693 women with 308 (64.9%)/219 (36.7%) positive results with positive risk factor of 236 cases (49.8%)/378 (63.3%). In this study, 591 persons were primigravida with 200 obese pregnant women. We found 233 pregnant women with MAP >90 mmHg and as many as 140 pregnant women with ROT >15. For neonatal outcomes, we studied infants with congenital anomalies, Intra-Uterine Fetal Death (IUFD), Intra-Uterine Growth Restriction (IUGR), abortion, preterm birth, and APGAR score <7. IUFD, IUGR and premature events were respectively 1.1%, 0.19%, and 1.7% on normal Doppler Velocimetry Uterine Artery (DVUA) ultrasound compared with increased DVUA ultrasound. There were 19 pregnant women becoming preeclampsia, severe preeclampsia, and eclampsia from pregnant women screening positive preeclampsia with normal DVUA compared to 5 (0.95%) pregnant women becoming preeclampsia screening positive preeclampsia with DVUA.

Keywords: preeclampsia, doppler velocimetry uterine artery, maternal outcome

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INTRODUCTION

Maternal mortality rate (MMR) is one of the benchmarks of achieving the Sustainable Development Goals (SDGs) which shows the degree of public health in Indonesia. There was an increase in MMR of 228 (2007) to 359 (in 2013) even though Indonesia was targeting a decline in MMR to 102 in 2015. East Java had a good achievement of reducing MMR by 93.52 (in 2014) so that it is sufficiently located below the Millennium Developments Goals (MDGs) target in 2015. During 2014 567 maternal deaths were found in East Java. In 2014, the most common cause of maternal mortality in East Java was 29.9% preeclampsia and bleeding by 26.12% (Salam et al. 2015).

The maternal and fetal/neonatal morbidity and mortality of hypreeclampsiartension, including preeclampsia are related. The incidence of pregnancy with hypertension ranges from 3-10%. World Health Organization reports the incidence of hypertension around 16% of all maternal deaths in developing countries. Renal failure, stroke , heart failure, respiratory failure, coagulopathy, and liver failure are severe morbidities associated with preeclampsia and eclampsia. About 12-25% Intra-Uterine Growth Restriction (IUGR) and 15-20% of small infants in preterm labor are associated with preeclampsia which causes an increase in neonatal mortality and serious neonatal morbidity (Jeyabalan 2013; Suparman et al., 2018).

Preeclampsia has a characteristic imbalance between prostacyclin and thromboxane production, such as the failure of trophoblast invasion of the endometrium-myometrial blood vessels with abnormal uteroplacental blood flow (Ebrashy et al. 2005). In Indonesia, with average of 12 preeclampsiarcent,

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preeclampsia-eclampsia contributes considerably to MMR (Molvarec et al. 2011). It was announced in East Java that maternal mortality was 117 (28.2%) out of 414 maternal deaths in 2007 (Adeline et al. 2018). Severe preeclampsia occurs if it has typically developing blood pressure criteria ≥ 160/110, serum creatinine >1.1 mg/dl, liver function improvement (more than twice), platelets <100,000, pulmonary edema, headache, visual disturbances, and epigastric pain. Clinically and according to the latest literature, only the term preeclampsia and severe preeclampsia are used with the aim of not alleviating preeclampsia, especially in primary health facilities (Salaam et al. 2015). The strong adverse effects of preeclampsia and the incomprehensibility of pathophysiology promote early diagnosis of preeclampsia in women who are apregnant; therefore, different treatment strategies can be implemented to postpone preeclampsia (Royani et al. 2019).

The pregnancy itself makes a rising in the bodyweight so that it can lead to more severe interference/damage, which is shown by proteinuria (Kartika et al. 2018). Obesity in pregnancy increases the risk of preeclampsia about 2-3 times (Stewart et al. 2007). With increased BMI, also within the normal range, the risk of preeclampsia increases. This does not only raise the risk of slow or moderate preeclampsia, but also raises perinatal morbidity and mortality, both early and extreme preeclampsia. Several mechanisms are underlying the relationship of obesity with preeclampsia. Placental vasculopathy and endothelial dysfunction are the main mechanisms. Obesity causes chronic hypertriglyceridemia, a risk factor for endothelial dysfunction. Hypertriglyceridemia changes prostaglandin regulation which causes arteriolar constriction including inhibitors of plasminogen activation, leptin and tumor necrosis factor which are high in preeclampsia (Molvarec et al. 2011).

This condition is characterized by an increase in blood pressure accompanied by proteinuria. Although the etiology of preeclampsia remains unclear, it is widely accepted that a defect in placental trophoblast invasion while implantation has a role in the incompletion of spiral artery remodeling process in patients with preeclampsia (Lukas et al. 2019). Factors related to the two stages of preeclampsia can increase activation of blood components, excess syncytiotrophoblast fragments, activation of immune cells and transmission of lipid oxidation or excess inflammatory cytokines. Another possibility is decreased placental perfusion and decreased food delivery, the placental fetal unit releases material to overcome this deficiency (Roberts et al. 2009).

Doppler ultrasound is a non-invasive examination to see uteroplacental perfusion. Uterine artery Doppler at 11-14 weeks' gestation identifies the possibility of preeclampsia and IUGR. 5% of the population with a mean uterine artery PI >2.35 at 11-14 weeks gestation develops preeclampsia by 27% and IUGR in pregnancies without preeclampsia by 12%. In pregnancy, the spiral arteries increase blood supply to the fetoplacental unit in the third trimester 10 times higher than non-pregnant women. This vascular placental change relies on the invasion of the trophoblast spiral artery located in the blood vessel walls. Uterine arterial sensitivity of an average PI >95th percentile can predict preeclampsia, and IUGR is lower at 11-14 weeks' gestation than at 22-24 weeks' gestation. The benefits of early screening are prophylactic interventions, such as the administration of low-dose aspirin which is more effective for the prevention of preeclampsia and IUGR (Martin et al. 2001).

Access to perinatal care, early detection of the disorder, careful monitoring and appropriate management are crucial elements in prevention of preeclampsia related deaths. Efforts to prevent preeclampsia/eclampsia have long been carried out, and there have been many studies conducted to assess the benefits of various groups of non-pharmacological and pharmacological ingredients (Saxena et al. 2016). The purpose of this study was to analyze the effect of preeclampsia screening on maternal and neonatal outcomes, including maternal risk factors (maternal age, history of chronic hypertension, diabetes mellitus, kidney and heart disease), calculation of Body Mass Index (BMI), Mean Arterial Pressure (MAP), Roll Over Test (ROT), and Doppler Velocimetry of Uterine Artery (DVUA) at primary healthcare centers.

MATERIAL AND METHODS

A retrospective study, tracing medical records of pregnant women who were screened at primary healthcare centers in Mulyorejo and Kalijudan Surabaya, Indonesia between 2013-2015 for pregnant women who were screened for preeclampsia (positive and negative results) and DVUA ultrasound examination at Dr. Soetomo Hospital, each group sought maternal and neonatal outcomes.

The inclusion criteria of this study were all pregnant women examined at the Primary healthcare centers in Mulyorejo and Kalijudan, Surabaya who screened positive and negative preeclampsia who gave birth during the 2013-2015 period. Preeclampsia screening was carried out for all pregnant women who controlled at 16-24 weeks gestational age with a history of preeclampsia in a previous pregnancy, chronic hypertension, pregestational diabetes, RPL (Recurrent Pregnancy Loss), age <16 years or >35 years, BMI >30, MAP >90, ROT >15, and ultrasound DVUA (if positive (RI >0.58)). If >2 points above or positive DVUA ultrasound was obtained, the patient received aspirin therapy 100 mg/day for up to 36 weeks (if there were no

Table 1. Subject Characteristics

Variable	Category	Frequency	Preeclampsia Percentage (%)
Mother Age (year)	<20	201	17.22
	20-34	533	45.67
	<35	433	37.10
Gravida	Primipara	591	50.64
	Multipara	576	49.36
Body Mass Index	<18.51	10	0.85
	18.5 – 24.9	917	78.58
	25.0 – 29.9	40	3.42
	>30	200	17.13
Mean Arterial Pressure	<90	934	80.03
	≤90	233	19.97
Rollover Test	<15	1027	88.00
	≥15	140	11.99

signs of preeclampsia or severe preeclampsia in pregnant women) and was stopped if pregnant women had found signs of preeclampsia or severe preeclampsia.

ROT is a method performed by positioning the left lateral recumbent position and then measuring the mother's blood pressure. After that, the mother was in supine position for 2 minutes, then the mother's blood pressure was measured again, said to be positive if there was an increase in diastolic pressure ≥ 15 mmHg from the side sleeping position to be supine. MAP calculation is by systolic added 2 times diastolic and then divided by 3, if >90 is obtained, it is said to be positive.

RESULTS

Some of the characteristics are listed in **Table 1** which are the main risk factors for preeclampsia are maternal age, parity, and body mass index. Age is an important factor for preeclampsia, maternal age over 40 years is said to increase almost 2 times the risk of preeclampsia (1.96 (1.34-2.87)). In this study, the youngest pregnant woman was 15 years old, while the oldest was 43 years old. The first disease of pregnancy (primipara) is long considered preeclampsia (Carty 2012). In this study, 591 people were primigravidae having obesity in pregnancy, increasing the risk of preeclampsia about 2-3 times. 14 In this study, there were 200 pregnant women with obesity. The occurrence of preeclampsia can also be detected early by calculating MAP. This test has a sensitivity of 93% and a specificity of 62%, while the ROT sensitivity and specificity are 93% and 91% 12. Positive MAP (MAP >90 mmHg) has a 3.5 times chance of preeclampsia. In this study, we found 233 pregnant women with MAP >90 mmHg and as many as 140 pregnant women with ROT >15.

Preeclampsia was screened for 2,349 pregnant women with characteristics shown in **Table 2** at the Mulyorejo Healthcare Center in 2013-2015 with 474 with positive results as many as 308 (64.9%), negative results as many as 166 (35%), and positive risk factors as many as 236 (49.8%); BMI results ≥30 were 126 (26.6%); MAP ≥90 as many as 117 (24.7%); and ROT

Table 2. Maternal Outcome

Characteristic	Normal DVAU USG	Increased DVAU USG
Preeclampsia	7	1
Severe Preeclampsia	12	4
Eclampsia	0	0
Deaths	0	0
Caesarean Section (CS)	108	39
Hemorrhagic Post-Partum (HPP)	0	0

≥15 as many as 52 (10.9%); DVUA increased by 8 (1.7%). Of the 474 pregnant women, 4 (0.8%): 2 were preeclampsia positive screening; severe preeclampsia 0, 1 (0.2%) with normal DVUA and 1 (0.2%) with increased DVUA; eclampsia 0; mothers who died as many as 0. Methods of labor were with spontaneous parturition as many as 418 (88.2%); vacuum/forceps extraction as many as 0; cesarean delivery as many as 56 (11.8%); Outcomes of infants with Intra-Uterine Fetal Death (IUFD) as many as 7 (1.5%); and moderate asphyxia as many as 2 (0.4%).

Preeclampsia screening for 2,010 pregnant women with characteristic in **Table 1** at Kalijudan Health Center in 2013-2015 was 693 with positive results of 219 (36.7%), negative results of 474 (79.4%), positive risk factors of 378 (63.3%); the BMI ≥30 results were 65 (10.9%); MAP ≥90 many as 123 (20.6%); ROT ≥15 as many as 88 (14.7%); DVUA increased by 36 (6.03%). Of the 597 pregnant women, 44 (7.4%) of preeclampsia became 13 (2.2%) with positive preeclampsia screening, 9 (1.5%) with negative preeclampsia screening, 18 (3.01%) with normal DVUA, 4 (0.67%) with increased DVUA; severe preeclampsia of 16 (2.68%), 11 with positive preeclampsia screening, 5 with negative preeclampsia screening, 4 with increased DVUA, 12 with normal DVUA; and 0 with eclampsia. Pregnant women who died by 0. Methods of labor were with spontaneous parturition as many as 504 (84.4%), vacuum extraction/forceps as many as 2 (0.34%); and caesarean delivery as many as 91 (15.2%). Outcomes of infants with Intra-Uterine Fetal Death (IUFD) were 6 (1.01%), premature were 9 (1.51%), and asphyxia was 0.

In this study, we found the incidence of preeclampsia (preeclampsia, severe preeclampsia and eclampsia) in pregnant women with positive preeclampsia screening but normal DVUA ultrasound of 10 pregnant women (20.8%) compared to those with increased DVUA ultrasound (**Table 2**).

For neonatal outcomes, we studied infants with congenital anomalies, Intra-Uterine Fetal Death (IUFD), Intra-Uterine Growth Restriction (IUGR), abortion, preterm birth, and APGAR score <7. IUFD, IUGR, and premature events were 1.1%, 0.19%, and 1.7%, respectively, on normal DVUA ultrasound compared with increased DVUA ultrasound (**Table 3**).

Table 3. Neonatal Outcome

Characteristic	Normal DVAU USG	Increased DVAU USG
Congenital Anomalies	0	0
IUFD	6	0
IUGR	1	0
Abortus	7	0
Premature	9	0
Apgar Score <7	2	0

DISCUSSION

In this study, tracing the medical records was performed of pregnant women who were screened at primary healthcare centers in Mulyorejo and Kalijudan Surabaya, Indonesia between 2013-2015 for pregnant women who were screened for preeclampsia (positive and negative results) and DVUA ultrasound examination at Dr. Soetomo Hospital, each group sought maternal and neonatal outcomes. Of the 1167 pregnant women undergoing preeclampsia screening, there were 527 pregnant women with positive preeclampsia screening, which found 44 pregnant women with increased DVUA ultrasound. During this study, we found that the incidence of Preeclampsia (Preeclampsia, Severe Preeclampsia) was more increased in pregnant women with positive preeclampsia screening but normal DVUA ultrasound, so it can be seen that preeclampsia screening can be performed without DVUA ultrasound, especially in areas with equipment and Human Resources (HR) facilities which are is inadequate. We obtained the incidence of preeclampsia, severe preeclampsia, and eclampsia of 15 pregnant women (2.8%) preeclampsia 527 pregnant women with positive preeclampsia screening due to other risk factors for preeclampsia, such as; maternal age >35 years, primigravida, MAP >90 and diabetes even though we had given aspirin11. Another study said that low dose aspirin (125 mg/day) in pregnant women with abnormal DVUA ultrasound in 16-24 weeks of gestation can reduce uterine artery resistance.

Obesity has been highly prevalent and has been shown in several studies to be a risk factor for cancer, hypreeclampsiartension, hypreeclampsiarcholesterolemia, diabetes mellitus, metabolic disorders, and adult disability (Lestari S, Machrina Y 2017). In metabolic syndrome, obesity contributes to hypertension by multiple mechanisms, including reducing nitric oxide in oxidative stress, increasing sympathetic tone, and increasing the release of angiotensinogen by fat tissue. Hypertension can lead to various human body problems. The pathological condition of elevated blood pressure in various organisms such as the heart, lungs, kidney, eye and brain may lead to abnormalities (Anto et al. 2019).

Although the exact cause is unknown, the pathophysiology of preeclampsia is divided into two stages. The first stage includes a reduction in placental perfusion due to placental anomalies due to trophoblast invasion and an inadequate reconstruction of uterine spiral arteries. The second stage characterizes maternal systemic manifestations with inflammation, metabolic and thrombotic reactions which change the function of the vascular and cause multiorgan damage. During the first trimester and just before the failure of vascular remodeling, abnormalities that contribute to reduced placental perfusion may be observed, related to preeclampsia and implantation, abnormalities of morula to trophoblast differentiation or trophoblast differentiation to cytotrophoblast and syncytiotrophoblast. An important difference between the previous placentation and deep trophoblast invasion by vascular remodeling has been shown by the presence of early markers. Early changes cause severe placental dysfunction and Intra-Uterine Growth Restriction (IUGR) with preeclampsia. Stage 1 preeclampsia begins when vascular remodeling occurs before placentation abnormalities. During preeclampsia, a spiral artery invasion by trophoblast takes place at 6-8 weeks of gestation. Early pregnancy placental abnormalities are the primary causes of implantation/placentation abnormalities and abnormal placental vascular remodeling late in pregnancy (Roberts et al. 2009).

The relationship of the placenta to the maternal is a modification factor for maternal metabolism to increase the availability of nutrients and play a role in the placenta as food transfer. Women who cannot tolerate this modification will more easily develop preeclampsia. Although the amino acid transport system decreases in the placenta in pregnancies without preeclampsia with growth disorders, this transport does not decrease in fetuses with impaired growth in pregnancies with preeclampsia. IUGR occurs in preeclampsia when the signal is inadequate to resolve nutritional deficiency (Roberts et al. 2009).

Doppler ultrasound screening at 23 weeks' gestation is better for identifying preeclampsia and IUGR. The sensitivity of screening for preeclampsia with IUGR (69%) is 3 times higher than preeclampsia without IUGR (24%), and IUGR without preeclampsia (13%) increases to 93%, 80% and 56%. Implementation of the uterine artery screening program into routine antenatal examinations will help prevention because an increase in PI complications will increase 6 times compared to a normal PI.11 Screening at 20-24 weeks gestation can detect pregnancies that develop into preeclampsia by 50-70% with false-positive by 5% (Nicolaides et al. 2006).

In abnormal uterine artery velocimetry doppler there are oxidative stress (decreased ascorbate circulation), increased asymmetric dimethylarginine concentration (an endogenous inhibitor of nitric oxide synthesis), and increased prevalence of agonist autoantibodies against angiotensin AT1 receptors. The presence of these

markers is not related to whether the pregnancy undergoes a process that leads to IUGR, preeclampsia or normal pregnancy. There are two causes, namely abnormal vascular remodeling and decreased placental perfusion (Roberts et al. 2009). The presence of diastolic arrest in uterine artery waves at 24 weeks' gestation increases the risk of preeclampsia 68 times. In women who are at great risk for preeclampsia with irregular uterine artery doppler, low-dose aspirin administered at a gestation of 14-16 weeks can decrease the incidence of serious preeclampsia (Salam et al. 2015). Integrated Antenatal Services are comprehensive and quality antenatal services provided to all pregnant women to fulfill the right of every pregnant woman to obtain quality antenatal services so that they are able to have a healthy pregnancy, deliver safely, and deliver healthy babies. It is hoped that proactive prevention efforts (preventive stages) in preeclampsia are needed since early pregnancy and no longer at the curative stage, which is carried out jointly by midwife health workers in the village and pregnant women, husbands and families (Stephenson et al. 2014).

Improve referral access are utilization of maternal health care facilities and facilities following the risk factors through referral plans for mothers and fetuses. Prevention efforts for preeclampsia/eclampsia have long been carried out and many studies have been conducted to assess the benefits of various groups of non-pharmacological ingredients and pharmacological ingredients, such as low salt diet, vitamin C, tocopherol (Vit E), beta carotene, fish oil (eicosapentaenoic acid), zinc, magnesium, diuretics, anti-hypertension, low-dose aspirin, and calcium to prevent the occurrence of preeclampsia and eclampsia (Molvarec et al. 2011). Adding efforts to prevent preeclampsia/eclampsia includes diligently checking the content regularly so that it can be detected early on the presence or absence of preeclampsia/eclampsia in pregnant women. Uterine artery Doppler (UAD) can be of help in predicting preeclampsia in the at-risk population. Doppler ultrasonography of the uterine arteries predicts about 40 preeclampsiarcent of subsequent preeclampsia in 20-24 weeks of gestation in order to detect irregular trophoblast invasion. Examination in pregnant women includes preeclampsia screening (Verma et al. 2016).

The limitation of our study is that we did not analyze adherence to antenatal examination of pregnant women and adherence to taking aspirin. Suggestions need to be carried out in a more detailed review of other factors that influence the results of this study.

CONCLUSION

We found that the incidence of preeclampsia, severe preeclampsia, and eclampsia was found to be higher in pregnant women with positive preeclampsia screening than negative preeclampsia screening and higher in normal DVUA compared to increased DVUA.

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