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# Preeclampsia management: different insight from hospital to hospital approach in Indonesia



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## ABSTRACT

**Introduction:** The incidence of preeclampsia quite high and can cause high morbidity and mortality rates for pregnant women thereby preeclampsia is still a problem experienced worldwide. Preeclampsia in Indonesia still gives a frightening impression for both the mother and the fetus. The key to success in the treatment of preeclampsia is prevention and adequate therapy to reduce morbidity and mortality. Indonesia itself, which is an archipelagic country resulting in far apart geographical location between one central hospital to another central hospital that will cause some differences related to the treatment of preeclampsia itself.

**Aim:** The purpose of this review is to give an overview of the different approaches to handling preeclampsia in hospitals in Indonesia, especially Sanglah General Hospital Denpasar and Kandou General Hospital Manado.

**Conclusion:** There are several differences in the treatment of severe preeclampsia at Sanglah General Hospital Denpasar Bali and Prof. Dr. R.D. Kandou Hospital Manado. The differences found were ways to induce labor, use of corticosteroids, detail of MGS04 administration, and the selection of antihypertensive drugs.

**Keywords:** preeclampsia, management, hospital, different.

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## INTRODUCTION

Preeclampsia remains a major problem in the world because preeclampsia affects many systems in the body. Preeclampsia occurs when hypertension or blood pressure is found more than or equal to 140/90 mmHg and proteinuria is found at 300 mg / 24 hours or +1 dipstick test, occurs in women with a gestational age of 20 weeks or more. Preeclampsia is difficult to detect at the beginning of pregnancy so that pregnant women are advised to conduct routine antenatal care for detection of preeclampsia routinely. In pregnant women, high blood pressure is found but no proteinuria is found, diagnosis of preeclampsia cannot be made. In this situation we still have to be vigilant, because proteinuria usually appears after high blood pressure is found.

The incidence of preeclampsia in the world varies in each country. It is estimated that the prevalence of preeclampsia in the world is around 2-10% of pregnancies. American countries account for 5-8% of all births occurring preeclampsia and hypertension in pregnancy. Preeclampsia in Saudi Arabia was found to be 13,876 of the population of 25,795,938. As much as 4-18% are found severe preeclampsia and eclampsia in developing countries. The incidence of preeclampsia in the UK is found in around 15% of all maternal deaths. This disease is a major cause of maternal and perinatal morbidity and mortality.<sup>1,2</sup>

In 2015 the World Health Organization (WHO) reported that there were 830 mothers dying every day in the world, or there were 303,000 mothers die each year due to complications from pregnancy such as bleeding, hypertension, and infection. Indonesia recorded the mortality rate due to preeclampsia in pregnant women was 4.91% or 8,739-170,725 pregnant women. Preeclampsia harms pregnant women and fetuses in the womb. Pregnant women can give birth fewer months while the fetus can be born with low birth weight and fetal growth is disrupted. This poor condition causes detecting pregnant women who have a high risk of preeclampsia must be done immediately.<sup>3,4</sup>

The cause of preeclampsia still unknown, but many pathophysiology theories have been stated. The theory that is often associated with the cause of the incidence of preeclampsia is the failure of trophoblast invasion to the spiral arteries, this condition causes the spiral arteries do not dilate. Spiral arteries which cannot dilate cause uteroplacental blood flow to decrease, hypoxia and placental ischemia occur. In further pregnancy the need for placenta for blood supply will increase, causing oxidative stress. The ischemic placenta stimulates the formation of free radicals such as hydroxyl radicals. Hydroxyl radicals into toxins cause damage to cell membranes, nuclei, and endothelial cell proteins.<sup>5,6</sup>

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Preeclampsia can cause major complications such as kidney failure, liver damage, systemic heart disease, disseminated intravascular coagulation to brain hemorrhage.<sup>7,8</sup>

Prevention of preeclampsia is always a top priority, current recommendation low-dose aspirin is recommended for pregnant women who are at high risk for preeclampsia. Research that has been conducted by Park et al. reports that the use of low-dose aspirin can be a preventive drug for the occurrence of preeclampsia if the administration starts at <16 weeks of gestation. The use of aspirin has been shown to reduce the incidence of preeclampsia and is associated with a decrease in the prevalence of death and illness.<sup>9</sup>

Research conducted by Juliantari et al. in 2015, in Sanglah General Hospital Denpasar, Bali, found 108 cases of preeclampsia. There are 53 nulliparous, 30 primiparous, and 24 multiparous, and 1 grande multiparous. In age grouping, there were 10 mothers (9.26%) with ages <20 years, 76 mothers (70.37%) with ages 20-35 years, and 22 mothers (20.37%) with age > 35 years.<sup>10</sup>

Research conducted by Warouw et al. in 2014 in Prof. Dr. R.D. Kandou General Hospital, Manado, North Sulawesi, found 201 cases of preeclampsia. Divided into 3 groups, 60 women with mild preeclampsia, 109 women with severe preeclampsia, and 32 mothers with superimposed preeclampsia.<sup>11</sup>

The description above gives an illustration that preeclampsia is still a disease that is a problem and can cause mortality and morbidity of the mother. This review will provide an overview of the different approaches to preeclampsia in hospitals in Indonesia, especially Sanglah General Hospital Denpasar and Kandou General Hospital Manado.

### **Management of severe preeclampsia in Sanglah General Hospital Denpasar, Bali-Indonesia**

Diagnosis of severe preeclampsia made based on clinical and laboratory criteria such as gestational age of 20 weeks or more, systolic blood pressure  $\geq 160$  mmHg and diastolic  $\geq 110$  mmHg, proteinuria more than five gram in 24 hours or qualitative +4, and obtained one or more of the symptoms of severe preeclampsia as below:

1. Oliguria, the amount of urine production is less than 500 cc in 24 hours
2. The existence of subjective complaints: blurred vision, headache, epigastric pain, and hyperreflexia.
3. Increase in serum creatinine > 1.2 mg / dl
4. Pulmonary edema and cyanosis
5. Epigastric pain and right upper quadrant pain caused by stretching of capsule glisoni.

6. Impaired liver function: increased alanine or aspartate aminotransferase
7. Microangiopathic hemolysis
8. HELLP syndrome
9. Intra-Uterine Growth Retardation (IUGR)

### **The basic concept of preeclampsia management**

In any pregnancy with complications, basic management is carried out. Therapy for complications, therapy with medication for complications. Attitudes towards her pregnancy are divided into expectative and active. Expectative if the gestational age is <35 weeks, which means that pregnancy is maintained as long as possible while providing medical therapy. Active if the gestational age is  $\geq 35$  weeks, meaning that the pregnancy is terminated after receiving medical therapy for maternal stabilization.

### **Medication approach for preeclampsia**

Immediately into the hospital, bed rest with left side position intermittently and given a ringer lactate infusion or 5% ringer dextrose. Giving anti-seizure MgSO<sub>4</sub> as a prevention and seizure therapy. The administration of MgSO<sub>4</sub> is divided into initial doses and advanced doses. The initial dose of 4% MgSO<sub>4</sub> was dissolved in normal saline intravenously (i.v) for 10-15 minutes and maintenance dose was 1 g MgSO<sub>4</sub>/hour/i.v in 24 hours. Requirements for MgSO<sub>4</sub> administration are normal patellar reflexes, respiration >16 times per minutes, urine production in the previous 4 hours >100 cc (0.5 cc/kg BW/hour), and 10% Calcium Gluconate ampoule is available.

Antihypertension is given if blood pressure is  $\geq 180/110$  mmHg or mean arterial pressure (MAP)  $\geq 126$ . The use of nifedipine is an option with a dose of 10-20 mg orally, repeated after 30 minutes, a maximum of 120 mg in 24 hours. Also, it can be considered using labetalol, bolus 50 mg labetalol (10 ml labetalol 5 mg/ml) in 5 minutes, repeat bolus if blood pressure has not dropped <160/105 mmHg. Can be repeated every 10 minutes to a maximum of 300 mg. Labetalol infusion 20 mg i.v / hr droplet dose is increased twice every 30 minutes to a maximum of 160 mg/hour, until the blood pressure drops as desired and stable. If difficult for giving intravenous, can also be given orally with an initial dose of 200 mg. Can be repeated if within 30 minutes the blood pressure has not dropped.

Other antihypertensive agents that can be used are nicardipine with a dose of 10 mg in 100 or 250 cc normal saline or ringer lactate given i.v for 5 minutes, if it fails within 1 hour it can be repeated with a dose of 12.5 mg for 5 minutes. If it still fails within 1 hour, it can be repeated once more

at a dose of 15 mg for 5 minutes. Blood pressure is gradually reduced, an initial decrease of 25% from systolic pressure. Blood pressure is lowered to <160/105 and MAP <125. Maintenance therapy can use methyldopa 500-3000 mg orally divided by 2-4 doses and nifedipine 3x10 mg.

The use of diuretic drugs is only used if there is pulmonary edema, congestive heart disease, and generalized edema.

### Conservative Management

Conservative therapy is an approach that is chosen if the fetus is still less than 35 weeks old without any signs of impending eclampsia. This approach focuses on the use of medical therapies, corticosteroids for fetal lung maturation, close hospital monitoring, regular measurements of laboratory parameters (especially urine protein), and ensuring fetal well-being by periodic ultrasound.

### Active Management

The choice of active treatment is aimed at two indications, such as maternal indications and fetal indications. Maternal indications include failure of medical therapy, signs and symptoms of impending eclampsia, impaired liver function, impaired renal function, suspected placental abruption, onset of parturition, premature rupture of membranes, bleeding.

Whereas indications for the fetus include gestational age  $\geq$  35 weeks, severe intrauterine growth retardation (IUGR) based on ultrasound examination, nonreactive nonstress test (NST) and abnormal biophysical profile, oligohydramnios.

There are also indications of active treatment apart from the two indications that have been described, namely laboratory indications of progressive thrombocytopenia, which leads to HELLP syndrome.

### Management of severe preeclampsia in Prof. Dr. R. D. Kandou, Manado-Indonesia

Severe preeclampsia is a condition where there is an increase in systolic >160 mmHg and diastolic >110 mmHg with proteinuria (+3 or +4 qualitative examinations) or >5 gramam/24 hours, oliguria, hyperreflexia, frontal headache, visual impairment, epigastric pain and pregnancy > 20 weeks.

Tell the patient/family of the patient about the procedure to be performed. Medical treatment for the use of MgSO<sub>4</sub> with an initial dose of 4 g MgSO<sub>4</sub> 40% i.v (10 cc) for 5 minutes. Immediately followed by 6 g (15 ml) was put in a solution of 500 cc of ringer acetate or lactated ringer gave for 6 hours (1 g MgSO<sub>4</sub>/hour). If the seizure recurs after 15 minutes, give MgSO<sub>4</sub> (40%) 2 g (5cc) i.v

for 5 minutes. Maintenance dose of 1 g / hr MgSO<sub>4</sub> through infusion of acetic ringer or lactate ringer gave up to 24 hours postpartum. Dose of 15 cc of 40% MgSO<sub>4</sub> is included in 500 cc of ringer acetate or ringer lactate. The diuretic is not given unless there is pulmonary edema, congestive heart failure, and general edema. Antihypertension is given if systolic blood pressure is > 180 mmHg, diastolic > 110 mmHg.

The use of antihypertensive drugs that can be used is nifedipine 10-20 mg / oral observed every 1/2 hour, a maximum dose of 120 mg. Nifedipine should not be given sublingually because of the very fast vasodilation effect. Diastole blood pressure should not be less than 90 mmHg, a reduction in blood pressure is a maximum of 30%. Clonidine can be used as an antihypertensive in a dose of 1 ampoule / 0.15 mg/cc dissolved in 10cc of saline solution for injection (Careful risk of rebound effects after treatment). Another option is to use methyldopa at a dose of 3 x 125 mg / day to 3 x 500 mg / day. Given cardiotoxic drugs, given if there are signs of heart failure the type of cardiotoxic given is cedilanid - D. Treatment is carried out together with a heart installation. If HELLP syndrome is found, dexamethasone 10 mg / 12 hours can be given, 2 times before labor, followed by delivery at a dose of 10 mg, 10 mg, 5 mg, 5 mg i.v with a 6-hour interval.

Attitudes toward pregnancy, if pregnancy >37 weeks of pregnancy termination. If not already done, labor induction is performed with amniotomy and oxytocin drips with the condition that the bishop score >5. Cesarean section if oxytocin drips are not met or if there is contraindication of oxytocin drips, 12 hours after the start of oxytocin drips has not entered the active phase, more directed to primigravida termination with cesarean section.

If it is already in the first stage of the latent phase, amniotomy and oxytocin drips are carried out at least 15 minutes after medical treatment. If 5 hours after amniotomy there is no complete opening, cesarean section is performed. If labor has entered stage II, it is resolved by artificial labor. Information on contraindications to cesarean section if, HELLP syndrome with severe thrombocytopenia < 50,000 and stroke.

### Recommendation of preeclampsia management based on World Health Organization Guide

The diagnosis of preeclampsia is made based on the onset of a new episode of persistent hypertension during pregnancy with diastolic blood pressure  $\geq$  90 mmHg and substantial proteinuria >0.3g/24 hours. Pregnant women with severe hypertension during pregnancy must receive treatment

with anti-hypertensive drugs. WHO recommends the administration of anti-hypertensive drugs in patients with severe preeclampsia. The selection and administration of an anti-hypertensive drug during pregnancy is not explained in detail. WHO explained that the administration of certain anti-hypertensive drugs is based primarily on the experience of the doctor in selecting and administering a particular anti-hypertensive drug used, the cost of the drug, and the availability of the drug in the area. Administration of diuretics, especially thiazides, is not recommended as prevention of preeclampsia and its complications. Giving MgSO<sub>4</sub> is an anti-seizure medication recommended for patients with severe preeclampsia and eclampsia, then immediately referred to a hospital that has more complete facilities for further treatment.

If labor induction cannot be performed due to maternal or fetal conditions, it is advisable to do cesarean section. In preeclampsia patients it is not recommended to rest at home, but to be hospitalized. Hospital treatment aims to intervene in primary prevention of preeclampsia and pregnancy hypertension disorders in women who are considered at risk of developing the condition. Pregnant women with preeclampsia or hypertension in pregnancy are not advised to have too much bed rest. WHO describes restrictions on dietary salt intake during pregnancy with the aim of preventing the development of preeclampsia and its complications. Calcium supplementation during pregnancy is recommended for prevention of preeclampsia in all women with a dose of 1.5–2.0 g of calcium/day, especially in those at high risk of developing pre-eclampsia and in areas with less calcium intake.

Giving vitamin D supplementation during pregnancy as a preventive development of preeclampsia and its complications is not recommended. As well as giving vitamin C combined with vitamin E supplementation during pregnancy is not recommended to prevent the development of preeclampsia and its complications. Low dose acetylsalicylic acid, 75 mg/day is recommended for prevention of preeclampsia in high-risk women and administration begins before 20 weeks gestation.

## DISCUSSION

In severe preeclampsia the evaluation of labor is carried out immediately. Standard procedure of Sanglah hospital and Kandou hospital has several differences, but not much different from one another. Evaluating a severe preeclampsia patient by considering whether the pregnancy can be maintained until the onset of normal labor or artificial labor. If pregnancy can still be maintained until a normal birth occurs, treatment is given, namely

the administration of antihypertensive drug therapy, anti-seizure medication, corticosteroids for fetal lung maturation, close monitoring of maternal conditions and fetal well-being. Conversely, there are circumstances in which artificial labor is considered, such conditions as failure of medical therapy, onset of parturition, premature rupture of membranes, bleeding, suspected placental abruption, gestational age  $\geq 35$  weeks (at Sanglah hospital), gestational age  $\geq 37$  weeks (in Kandou hospital), severe fetal developmental disorders based on ultrasound examination, non-reactivated non-stress test (NST) results, and abnormal biophysical profiles.<sup>13,14</sup>

Pregnancy that is maintained until a normal birth occurs is given medical therapy. Anti-hypertensive treatment in severe preeclampsia is done if blood pressure is  $\geq 180/110$  mmHg, type of antihypertensive medication at Sanglah hospital is 10-20 mg of nifedipine orally, labetalol by bolus 50 mg, and nicardipine 10 mg in 100 or 250 cc of normal saline or ringer lactate. Anti-hypertensive treatment at Kandou General Hospital is nifedipine 10-20 mg per oral, clonidine one ampoule /0.15 mg/cc dissolved in 10cc normal saline solution, and methyldopa 3 x 125 mg/day.<sup>13,14</sup> Based on Royal College of Obstetrics and Gynecologist (RCOG) guidelines, recommending the use of labetalol, nifedipine, and hydralazine as the antihypertensive treatment of choice among other drugs. Severe preeclampsia patients who have a history of asthma are not recommended to use labetalol. Nifedipine is given orally and cannot be given sublingually. Whereas according to Roberts et al. recommend labetalol 10-20 mg i.v followed by 20-80 mg every 20-30 minutes to a maximum dose of 300 mg, nifedipine 10-20 mg orally, and methyldopa 0.5-3 gram orally daily as an anti-hypertensive drug of choice among other drugs.<sup>15,16</sup>

The recommendation of the World Health Organization (WHO) patients with severe preeclampsia is given anti-hypertensive drugs but there isn't specific type of drugs described in detail. WHO explains the selection of antihypertensive drugs based on the experience of the doctor on an antihypertensive drug used, costs, and availability of drugs in the area. Based on the explanation from WHO, both in Sanglah hospital and Kandou hospital each had an election in the administration of antihypertensive drugs in each region. In Sanglah hospital methyldopa drugs are used as antihypertensive maintenance drugs while in Kandou hospitals use methyldopa as one of the options in the initial treatment of antihypertension.<sup>12-14,17</sup>

WHO recommends giving MgSO<sub>4</sub> as the preferred anti-seizure medication for severe preeclampsia patients among other anti-seizure

medications. The provision of anti-seizures to patients with severe preeclampsia is intended to avoid the occurrence of eclampsia. Based on Magee et al., MgSO<sub>4</sub> is the first choice anti-seizure medication among other anticonvulsant drugs. The use of MgSO<sub>4</sub> is not used as an anti-hypertensive agent. In Sanglah hospital and Kandou hospital also recommends the administration of MgSO<sub>4</sub> in severe preeclampsia.<sup>17,18</sup>

Giving MgSO<sub>4</sub> in Kandou Manado Hospital or Sanglah Bali Hospital is divided into two doses, the initial dose and maintenance dose. However, there is a slight difference between the two hospitals, at Kandou hospital 4 g of 40% i.v MgSO<sub>4</sub> for 5 minutes followed by 6 g was put in a solution of 500 cc of ringer acetate or ringer lactate given for 6 hours or 1 gram of MgSO<sub>4</sub> / hour. While at Sanglah Hospital the initial dose of 50% MgSO<sub>4</sub> was dissolved in normal saline i.v for 10-15 minutes.<sup>13,14</sup> Based on Lu and Nightingale study in 2000 explained the initial dose of using 4 g of MgSO<sub>4</sub> 40% magnesium plasma i.v for 5-10 minutes. Based on the explanation of Tuffnell et al. in the Royal College Of Obstetric And Gynecologist (RCOG) guidelines describe the same thing in the treatment of the administration of MgSO<sub>4</sub> in the prevention of severe seizures of preeclampsia patients.<sup>15,19</sup>

Based on the standard procedures of both hospitals both Sanglah Bali Hospital and Kandou Manado Hospital, explained that diuretic medication is not recommended but in certain circumstances diuretic treatment is needed. Certain conditions such as if there is pulmonary edema, congestive heart failure, and generalized edema in patients with severe preeclampsia.<sup>13,14</sup> Based on RCOG guidelines for diuretic use should be avoided, unless pulmonary edema is found in patients with severe preeclampsia. Explanation of Roberts et al. in 2013 describes diuretic drugs can be used as a second choice treatment, by regulating doses that are appropriate for the patient's needs. Excessive use of diuretics can cause hypokalemia and impaired growth of the fetus due to lack of blood flow that supplies nutrients to the fetus. Based on WHO guide, administration of diuretic drugs is not recommended for pregnant women with severe preeclampsia.<sup>15-17</sup>

Both hospitals (Sanglah hospital and Kandou Hospital) provides corticosteroids in patients with severe preeclampsia, this is intended for fetal lung maturation before birth. In the Sanglah hospital corticosteroids are given at 23-34 weeks of gestation for 48 hours. In the treatment procedure for severe preeclampsia at Kandou hospital, it does not explain how many gestational ages to be given corticosteroids. Roberts et al. in 2013 advocated the use of corticosteroid for 48 hours at 34 weeks gestation. The use of steroid is intended for fetal

lung maturation before birth and its use also in certain conditions such as thrombocytopenia (<100,000/mL), severe oligohydramnios, and fetal growth disorders.<sup>13,14,16</sup>

Management of preeclampsia at the Kandou Manado hospital recommends giving cardiotoxic drugs if low cardiac output is found in patients with severe preeclampsia. The type of cardiotoxic drug used is cedilanid-D, as well as treatment along with heart installation. This treatment is intended to prevent the occurrence of heart complications due to severe preeclampsia. Whereas in Sanglah hospital Bali described the administration of cardiotoxic drugs as needed in patients who had eclampsia and did not give any cardiotoxic drugs to patients with severe preeclampsia. Based on a description from Roberts et al. in 2013, patients with severe preeclampsia with cardiovascular disorders must be identified early, so that prevention and treatment of cardiovascular complications can be carried out. Handling in these patients is carried out together with cardiologists so that complications of cardiovascular disorders can be resolved properly.<sup>13,14,16</sup>

Labour induction in severe preeclampsia patients in both hospitals will be done with the condition of the bishop score >5. At Sanglah hospital, it was explained that induction could be performed with cervical ripening using misoprostol, while in Kandou hospital did not use misoprostol. Labor induction must have reached stage II phase of labor within 24 hours. In a prospective cohort study by Nahar et al. in 2014, the use of misoprostol can accelerate labor induction to the birth of the fetus, can reduce the rate of cesarean section, and there are no adverse effects in the use of misoprostol in labor. This study also explained that the use of misoprostol given through the vagina has the same effectiveness as conventional methods of labor induction.<sup>13,14,20,21</sup>

Indications of cesarean section in both hospitals were severe preeclampsia patients who did not qualify for vaginal delivery, labor induction failed, and fetal distress occurred. Kandou hospital recommends that primigravida with severe preeclampsia be performed cesarean section. However, contraindications for cesarean section are severe thrombocytopenia <50,000/mL. If the patient is already partnered, the Sanglah hospital procedure will try to make normal labor with a Friedman curve guidance, monitors blood pressure every 30 minutes, cesarean section is performed if there is maternal emergency, fetal distress, and obstetric indications. Whereas in Kandou hospital in patients who are already partnered, drip amniotomy and oxytocin are performed, if after 5 hours after amniotomy there is no complete opening, cesarean section is performed.<sup>13,14</sup>

The important thing that was evaluated in severe preeclampsia patients from both hospitals is that if there is a contraindication to induction of labor, there is an emergency in the mother and fetus, then the pregnancy must be terminated immediately with cesarean section.<sup>13,14</sup> WHO explained that if labor induction cannot be done because of the condition of the mother or fetus, then it is recommended to do cesarian section. Magee et al. also stated the same opinion to terminate pregnancy with cesarean section in patients with severe preeclampsia who did not fit for labor induction.<sup>17,18</sup>

## CONCLUSION

There are several differences in the treatment of patients with severe preeclampsia at Sanglah Hospital, Bali and Prof. Dr. R.D. Kandou Manado. Nifedipine is the first choice antihypertensive drug to treat severe preeclampsia patients between the two hospitals. MgSO<sub>4</sub> is the best anti-seizure medication among other anti-seizure drugs in pregnant women with severe preeclampsia or eclampsia. The use of diuretic drugs cannot be given to patients with severe preeclampsia except for certain circumstances. Administration of corticosteroid drugs is given at gestational age  $\leq$  34 weeks. Cesarean section is performed in patients who cannot be labor-induced, there is an emergency in the mother and fetus.

## CONFLICT OF INTEREST

Author declares there is no conflict of interest regarding all aspect of this study

## REFERENCES

1. Khader YS, Batieha A, Al-njadat RA, Hijazi SS. Preeclampsia in Jordan: incidence, risk factors, and its associated maternal and neonatal outcomes. *The journal of maternal-fetal & neonatal medicine*. 2017;31(6):770-776.
2. Jameil NA, Tabassum H, Ali MN, Qadeer MA, Khan FA, Rashed MA. Correlation between serum trace elements and risk of preeclampsia: A case controlled study in Riyadh, Saudi Arabia. *Saudi Journal of Biological Sciences*. 2017;24:1142-1148.
3. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi JM. Preeclampsia: pathophysiology, diagnosis, and management. *Vascular Health and Risk Management*. 2011;7:467-474.
4. Vata PK, Chauhan NM, Nallathambi A, Hussein F. Assessment of prevalence of Preeclampsia from Dilla region of Ethiopia. *Bio Med Central Res Notes*. 2015;8:816-822.
5. Bej P, Chhabra P, Sharma AK, Guleria K. Determination of Risk Factors for Pre-eclampsia and Eclampsia in a Tertiary Hospital of India: A Case Control Study. *Journal of Family Medicine and Primary Care*. 2013; 2(4): 371-375.
6. Wong TY, Gramoen H, Faas MM, Pampus MG. Clinical Risk Factors for Gestational Hypertensive Disorders in Pregnant Women at High Risk for Developing Preeclampsia. *International Journal of Women's Cardiovascular Health*. 2013;3:248-253.
7. English FA, Kenny LC, McCarthy FP. Risk factors and effective management of preeclampsia. *Integrated Blood Pressure Control*. 2015;8:7-12.
8. Kamravamanesh M, Kohan S, Rezavand S, Farajzadegan Z. A comprehensive postpartum follow-up care program for women with history of preeclampsia: protocol for mix method research. *Reproductive Health*. 2018;15:81-88.
9. Park HJ, Shim SS, Cha DH. Combined Screening for Early Detection of Pre-Eclampsia. *Int. J. Mol. Sci*. 2015;16:17952-17974.
10. Juliantari KB, Sanjaya INH. Characteristics of preeclampsia mother in Sanglah General Hospital 2015. *E-Jurnal Medika*. 2017;6(4):1-9.
11. Warouw PC, Suparman E, Wagey FW. Characteristics of preeclampsia in Prof. Dr. R. D. Kandou General Hospital Manado. *Jurnal e-Clinic (eCl)*. 2016;4(1):375-379.
12. World Health Organisation. Trends in maternal mortality:1990 to 2015. Geneva: WHO Library Cataloguing. 2015. p. 1-4.
13. Surya IGP, Karkata MK, Kusuma AANJ, Suwardewa TGA, Negara IKS. Operational Standard Protocol Fetomaternal. Department Obstetrics and Gynaecology of Udayana University. 2012.
14. Warouw NN, Wagey F, Sanger OM, Suparman E, Loho MFT, Sondakh J, et al. Operational Standard Protocol in Obstetric and Gynaecology Departement Prof. Dr. RD. Kandou Hospital Manado. Department Obstetrics and Gynaecology of Sam Ratulangi University. 2013.
15. Tuffnell DJ, Shennan AH, Waugh JJS, Walker JJ. *The Royal College of Obstetricians and Gynaecologists Guideline*. England. 2010.
16. Roberts JM, Druzin M, August PA, Gaiser RR, Bakris, G, Gramanger JP, et al. Hypertension in pregnancy. America: library of congress cataloging. 2013.
17. Mbizvo M (Director department of reproductive health and research). WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia. Switzerland: WHO Library Cataloguing. 2011.
18. Magee LA, Helewa M, Moutquin JM, Dadelszen PV, Cardew S, Cote AM, et al. Diagnosis, Evaluation, and Management of the Hypertensive Disorders of Pregnancy. *Journal of Obstetrics and Gynaecology Canada*. 2008; 30(3): s1-s48.
19. Lu JF and Nightingale CH. Magnesium Sulfate in Eclampsia and Pre-Eclampsia Pharmacokinetic Principles. *Clin Pharmacokinet*. 2000; 38(4): 305-314.
20. Nahar A, Sultana R, Akter FM, Ferdousi M, Yusuf MA, Nahar K. Use Of Misoprostol in Term pregnant women for Good Delivery Outcome: Experience at a tertiary care Hospital in Dhaka. *Journal of Science Foundation*. 2014; 12(2): 22-26.
21. Manuaba AP. Prosedur Penggunaan Alat Perlindungan Diri Dan Biosafety Level 1 Dan 2. *Intisari Sains Medis*. 2016 Jun 11;6(1):117-23. DOI: 10.15562/ism.v6i1.27



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