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FETOMATERNAL OUTCOMES IN PREEKLAMPSIA PATIENTS WITH PROTEINURIA AND WITHOUT PROTEINURIA

KEY WORDS:

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ABSTRACT

BACKGROUND AND OBJECTIVES : The high maternal mortality rate is still found mainly in Southeast Asia including Indonesia. Maternal deaths that occur are caused by various things. High blood pressure during pregnancy (preeclampsia and eclampsia) is one of the major causes of maternal death in the world besides heavy bleeding (usually postpartum) and infection. The relationship between proteinuria and poor fetal outcomes has been investigated by experts, increasing protein excretion in women with preeclampsia (PE) is generally associated with poor maternal and fetal (fetomaternal) outcomes, proteinuria levels in women with PE are poor predictors of outcomes fetomaternal. But another opinion says that proteinuria is not an absolute criterion that must be found to diagnose PE, where multiorgan dysfunction in PE patients with or without proteinuria does not have a significant difference. From these results the researchers wanted to know the fetomaternal outcomes of PE patients with proteinuria (+ 1, + 2, + 3, + 4) and preeclampsia without proteinuria.

METHODS : This research is a descriptive study with a retrospective design, carried out using secondary data analysis of patients diagnosed with PE with or without proteinuria and have been terminated. This research was conducted at the General Hospital. H. Adam Malik Medan. The time of the study is from October 2017 to February 2018. The study population is PE patients treated and terminated from February 2013 to May 2017. PE patients in this study will henceforth be assessed based on protein levels in the urine (proteinuria). The sample size in this study uses the Lemeshow formula which aims to find a large proportion in a population.

RESULTS: A total of 62 PE women with proteinuria and 21 PE women without proteinuria. Of all the samples, maternal and fetal outcomes were assessed. Based on Proteinuria, research subjects who were diagnosed with PE with proteinuria were 62 people. The highest number was 36.1% in PE with proteinuria + 3, followed by 18.1% in PE with proteinuria +1, then as much as 15.7% in PE with proteinuria +4, and with the smallest amount of 4.8% in PE with proteinuria +2. Research subjects diagnosed with PE without proteinuria totaled 21 people, as many as 25.3% of the total sample.

CONCLUSION : Most research subjects ranged age 21-30 years with gestational age, ≥ 37 weeks, multipara. Subjects were diagnosed with PE with proteinuria more than PE without proteinuria. The most maternal outcome is ICU treatment followed by HELLP syndrome, eclampsia and pulmonary edema then maternal death. The highest fetal death rate for babies with birth weight is LBW, with more normal APGAR scores.

INTRODUCTION

Maternal death, according to WHO, is death during pregnancy or in the 42-day period after the end of pregnancy, due to all causes related to or exacerbated by pregnancy or treatment, but not caused by accident / injury.1,2 The global maternal mortality rate is found to be a number 385 per 100,000 live births in 1990. This value then decreased in 2015 to 216 per 100,000 live births.[2]

Southeast Asia is one of the regions that has a high maternal mortality rate. In 1990 the maternal mortality rate was 525 per 100,000 live births, then decreased to 352 in 2000, and 164 in 2015.3 Data from WHO shows that Indonesia, which is included in the Southeast Asia region, had a maternal mortality rate of 446 per 100,000 live births in 1990 and dropped dramatically to 126 in 2015.[4]

Maternal deaths that occur are caused by various things. High blood pressure during pregnancy (preeclampsia and eclampsia) is one of the major causes of maternal death in the world in addition to heavy bleeding (usually postpartum) and infection.5 WHO noted Preeclampsia (PE) occurs with an incidence of 3-10% of all pregnancies.6 For Indonesia itself, found that high blood pressure contributed 21.5% of maternal deaths in 2010. However, that number increased to 27.1% in 2013.[1]

In North Sumatra there were 30 cases of PE reported, particularly in H. Adam Malik General Hospital Medan in 2005-2006.7 In addition, PE cases were reported as many as 3,560 cases out of 251,449 pregnancies during 2010. Meanwhile, reported maternal mortality rates of PE patients in RSUD dr. Pirngadi Medan City in 2007-2008 was 3.45%, in 2008-2009 it was 2.1%, and in 2009-2010 it was 4.65% .[8]

The American College of Obstetricians and Gynecologists (ACOG) in 2013 defined PE as a syndrome that primarily includes the occurrence of new-onset hypertension in the second trimester of pregnancy. The diagnosis is made with systolic blood pressure ≥ 140 mmHg or 160 mmHg or diastolic blood pressure ≥ 90 mmHg or 110 mmHg on two examinations (a minimum of 4 hours apart) after gestational age past 20 weeks in women who previously had normal blood pressure, plus proteinuria or thrombocytopenia, impaired liver function, pulmonary edema, or visual or cerebral symptoms if no proteinuria is found.[9]

The relationship between proteinuria and poor fetal outcomes was first highlighted by Page and Christianson. Since then, increased protein excretion in women with PE has generally been associated with poor maternal and fetal outcomes.[11]

Over time, research on proteinuria and its relation to fetomaternal outcomes is growing. Review conducted by Thangaratinam et al. showing proteinuria levels in women with PE is a poor predictor of fetomaternal outcomes.[11]

Nischintha et al. conduct research that assesses proteinuria

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with fetomaternal outcome criteria that include infant birth weight, APGAR score (Appearance, Pulse, Grimace, Activity, Respiration), NICU (Neonatal Intensive Care Unit) treatment, fetal complications namely fetal growth retardation and neonatal sepsis, and maternal complications in the form of placental ablation, eclampsia, post-saline bleeding, Disseminated Intravascular Coagulation (DIC), and Hemolysis, Elevated Liver Enzymes, and Low Platelets (HELLP) syndrome, and other complications. The results obtained showed no statistical significance between proteinuria and fetomaternal outcomes in PE.[10]

In a 2016 study in Medan, Lumbanraja SN found that proteinuria is not an absolute criterion that must be found to diagnose PE, where multiorgan dysfunction in PE patients with or without proteinuria does not have a significant difference.[28]

However, research conducted by Homer et al. showed that PE women with proteinuria had worse fetomaternal outcomes, especially preterm births and perinatal deaths greater than those without proteinuria.[12]

Researchers are interested in examining how the fetomaternal outcomes of PE patients with proteinuria and without proteinuria in RSUP.H. Adam Malik Medan. It is hoped that this research can be a reference in the management of PE and increase alertness when receiving patients with a diagnosis of PE so that the maternal and infant prognosis can be better going forward.

METHODS

This research is a descriptive study with a retrospective design, carried out using secondary data analysis of patients diagnosed with PE with or without proteinuria and have been terminated. This research was conducted at the General Hospital. H. Adam Malik Medan. The time of the study is from October 2017 to February 2018. The study population was PE patients treated and terminated from February 2013 to May 2017. PE patients in this study will henceforth be assessed based on protein levels in the urine (proteinuria). The sample size in this study uses the Lemeshow formula which aims to find a large proportion in a population.

Inclusion criteria in the form of subjects treated with a diagnosis of PE in H. Adam Malik General Hospital Medan in February 2013 - May 2017, where medical record data meet the data needed to be examined. The exclusion criteria are patients with a diagnosis of PE but have a history of previous illness (eg renal failure, malignancy, heart disease).

RESULTS

The sample of this research was 62 women with proteinuria and 21 women without proteinuria. Of all the samples, maternal and fetal outcomes were assessed.

Table 1. **Frequency distribution based on characteristics of maternal age, gestational age, parity, proteinuria, delivery methods**

Characteristics	N (%) = 83
Maternal age	
<20 ages	4 (4,8)
21-30 ages	35 (42,2)
31-35 ages	20 (24,1)
>35 ages	24 (28,9)
Gestational age	
≤28 weeks	17 (20,5)
29-32 weeks	18 (21,7)
33-36 weeks	23 (27,7)
≥37 weeks	25 (30,1)
Parity	
Nulipara	27 (32,5)
Primipara	19 (22,9)
Multipara	37 (44,6)
Proteinuria	
Wihout proteinuria	21 (25,3)
+	15 (18,1)
++	4 (4,8)
+++	30 (36,1)
++++	13 (15,7)
Metode of Labor	
Spontaneous of Delivery	12 (14,4)
Vacum Extraction	2 (2,4)
Sectio Caesarea	69(83,1)

In the table, research subjects aged <20 years were 4 people (4.8%), 21-30 years were 35 people (42.2), 31-35 years were 20 people (24.1%), and age> 35 year as many as 24 people (28.9%). According to gestational age, subjects with gestational age ≤ 28 weeks were 17 people (20.5%), gestational age 29-32 weeks were 18 people (21.7%), 33-36 weeks were 23 people (27.7%) , and ≥ 37 weeks were 25 people (30.1%). The subjects of the study were mostly multipara parity as many as 37 people (44.6%) then nulliparous parity as many as 27 people (32.5%) and primipara as many as 19 people (22.9%).

Based on Proteinuria, research subjects who were diagnosed with PE with proteinuria were 62 people. The highest number was 36.1% in PE with proteinuria + 3, followed by 18.1% in PE with proteinuria +1, then as much as 15.7% in PE with proteinuria +4, and with the smallest amount of 4.8% in PE with proteinuria +2. Research subjects diagnosed with PE without proteinuria totaled 21 people, as many as 25.3% of the total sample.

Method of delivery, as many as 69 people (83.1%) underwent saesarea section, 12 people (14.4%) had spontaneous vaginal delivery, and 2 people (2.4%) gave birth by vacuum extraction.

Maternal Outcomes of PE Patients based on Proteinuria

From the table below it is found that fetal outcomes in infant mortality were found in 25 people, with proteinuria (-) 2 people, proteinuria (+1) 4 people, proteinuria (+3) 14 people, proteinuria (+4) 5 people. Outcome of birth weight for infants, as many as 27 people, in proteinuria (-) as many as 11 people, proteinuria (+1) 8 people, proteinuria (+2) 50 people, proteinuria (+3) 4 people, proteinuria (+4) 2 person. LBW as many as 29 people, in proteinuria (-) as many as 8 people, proteinuria (+1) 2 people, proteinuria (+2) 1 person, proteinuria (+3) 12 people, proteinuria (+4) 6 people. BBLSR as many as 17 people, in proteinuria (-) 1 person, proteinuria (+1) 4 people, proteinuria (+2) 1 person, proteinuria (+3) 8 people, proteinuria (+4) 3 people. BBLASR as many as 10 people, in proteinuria (-) 1 person, proteinuria (+1) 1 person, proteinuria (+3) 6 people, proteinuria (+4) 2 people.

Table 2. **Maternal Outcomes of PE Patients based on Proteinuria**

	Proteinuria with Preeclampsia					Total
	-	+	++	+++	++++	
Maternal Outcomes						
Maternal death						
Yes	1(4,8)	0 (0.0)	0 (0.0)	2 (6,7)	0 (0.0)	3(3,61)
No	20(95,2)	15 (100)	4 (100)	28 (93.3)	13 (100)	80(96,39)
Eclampsia						

Yes	2(9.5)	0 (0.0)	0 (0.0)	2 (6.7)	0 (0.0)	4(4.82)
No	19 (90.5)	15 (100)	4 (100)	28 (93.3)	13 (100)	79(95.18)
ICU care						
Yes	4 (19)	3 (20)	0 (0.0)	4 (13.3)	1 (7.7)	12(14.46)
No	17(81)	12 (80)	4 (100)	26 (86.7)	12 (92.3)	71(85.54)
HELLP Syndrome						
Yes	0 (0.0)	0 (0.0)	1 (25)	5 (16.7)	1 (7.7)	7 (8.43)
No	21(100)	15 (100)	3 (75)	25 (83.3)	12 (92.3)	76(91.57)
Lung Edema						
Yes	1 (4.8)	1 (6.7)	0 (0.0)	1 (3.3)	1 (7.7)	4 (4.82)
No	20(95.2)	14 (93.3)	4 (100)	29 (96.7)	12 (92.3)	79(95.18)

From the table above it was found that maternal mortality of PE maternal mortality was found in 3 people, with proteinuria (+1) 1 person and proteinuria (+3) 2 people. Maternal output of Eclampsia was found in 4 people, with proteinuria (-) 2 people, proteinuria (+3) 2 people. ICU maternal care outcomes are 12 people, with proteinuria (-) 4 people, proteinuria (+1) 3 people, proteinuria (+3) 4 people, proteinuria (+4) 1 person. For maternal *HELLP Syndrome* outcomes, as many as 7 people, with proteinuria (+2) 1 person, proteinuria (+3) 5

people, proteinuria (+4) 1 person. Maternal output Lung edema, as many as 4 people, with proteinuria (-) 1 person, proteinuria (+1) 1 person, proteinuria (+3) 1 person, proteinuria (+4) 1 person.

Fetal Outcomes of PE Patients based on Proteinuria

Table 3. **Fetal Outcomes of PE Patients based on Protei nur ia**

			Proteinuria			**Total**
	-	+	++	+++	++++	
Fetal Outcomes Infant death						
Yes	2 (9.5)	4(26.7)	0(0.0)	14 (46.7)	5(38.5)	25(24)
No	19(90.5)	11(73.3)	4 (100)	16 (53.3)	8 (61.5)	58(76)
Birth weight						
Normal	11(52.4)	8 (53.3)	2 (50)	4 (13.3)	2 (15.4)	27(37)
BBLR	8 (38.1)	2 (13.3)	1 (25)	12 (40)	6 (46.2)	29(33)
BBLSR	1 (4.8)	4 (26.7)	1 (25)	8 (26.7)	3 (23.1)	17(21)
BBLASR	1(4.8)	1 (6.7)	0 (0.0)	6(20)	2 (15.4)	10(9)
APGAR						
Normal (7-10)	18(85.7)	10(66.7)	4 (100)	16(53.3)	7 (53.8)	55(72)
Moderate (4-6)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	2 (2)
Low (0-3)	2 (9.5)	5 (33.3)	0 (0.0)	14(46.7)	5 (38.5)	26(26)

From the table above it was found that fetal outcomes in infant mortality were found to be 25 people, with proteinuria (-) 2 people, proteinuria (+1) 4 people, proteinuria (+3) 14 people, proteinuria (+4) 5 people. Outcome of birth weight for infants, as many as 27 people, in proteinuria (-) as many as 11 people, proteinuria (+1) 8 people, proteinuria (+2) 50 people, proteinuria (+3) 4 people, proteinuria (+4) 2 person. LBW as many as 29 people, in proteinuria (-) as many as 8 people, proteinuria (+1) 2 people, proteinuria (+2) 1 person, proteinuria (+3) 12 people, proteinuria (+4) 6 people. BBLSR as many as 17 people, in proteinuria (-) 1 person, proteinuria (+1) 4 people, proteinuria (+2) 1 person, proteinuria (+3) 8 people, proteinuria (+4) 3 people. BBLASR as many as 10 people, in proteinuria (-) 1 person, proteinuria (+1) 1 person, proteinuria (+3) 6 people, proteinuria (+4) 2 people.

DISCUSSION

In this study found that the most research subjects at the age of 21-30 years were 35 people. In a retrospective study in 2017 in which fetomaternal PE outcomes were severe and eclampsia was studied with the most subjects being 26-30 years old as many as 47 cases out of 110 cases studied. Age has an important influence on the incidence of PE. Young primigravidas <20 years old and all patients > 30 years old have an increased risk of developing PE.[30] The same findings suggest that PE is more common in patients younger than 21 years and older than 35 years.[31]

Pregnant women with age <20 years 3.87 times the risk of experiencing PE compared to those aged > 20 years.[32] Similar observations have also been reported, observed that teenage pregnancy is one of the risk factors for PE & eclampsia.[33] The highest incidence of hypertension in pregnant women occurs in groups age 18-22 years (41.3%).[34] Factors affecting the development of PE before age 20 may be due to the initial trophoblast invasion and how the mother reacts to it. The failure of normal invasion of trophoblast cells leads to adaptation of the spiral arteriolar mall, which is related to the cause of PE.35 hence, it can be concluded that the adolescent and> 30 years age groups are more susceptible to the occurrence of PE.

Most gestational age subjects were 33 to 37 weeks of pregnancy. In one study it was found that the majority of 44 (40%) PE patients were acquired at 33 to 36 weeks' gestation. From the research of Jose Paolo et al regarding fetomaternal outcomes in PE patients based on proteinuria, the average age of pregnancy at delivery was 33 weeks (± 3.8) and the majority were diagnosed with PE with ballast symptoms.[36] In the results of one study, PE occurred earlier in the proteinuria group massive than mild proteinuria groups. Early onset PE has been described as occurring before 32-34 weeks' gestation and tends to have more severe maternal and fetal outcomes than slow onset PE because of the risk of maternal multi-organ dysfunction and fetal death. Gestational age in each group was also lower in the massive proteinuria group than in the mild proteinuria group.

Based on parity explained that most of the PE research subjects with multipara parity were as much as 44.6%. Nulliparity is one of the risk factors for PE, in this study 32.5% subjects were nulliparities. Of the 110 cases of severe PE and eclampsia in one study, 67 primigravidas and 18 people were less than 20 years old. The highest number of cases is the 26-30 years age group. Severe PE is more common in primigravidas. Other studies by Sibai and Cunningham also support this finding.[39]

Nulliparity patients are known to suffer from severe PE compared to those who have recurrence or superimposed PE.22 Based on Proteinuria, it can be seen that the study subjects diagnosed with proteinuria were 62 people. The highest number is 36.1% in PE with proteinuria + 3.

Chan et al reported that increased proteinuria in PE increased the risk of fetomaternal severity. They concluded that a protein / creatinine ratio greater than 900 mg / mmol in patients aged less than 35 years, and a protein / creatinine ratio greater than 500 mg / mmol in patients aged > 35 years will increase the severity of maternal outcomes that can occur.[22] Homer et al divided patients in gestational hypertension, PE proteinuria and non-proteinuria. In all groups systolic blood pressure ≥ 140 mm Hg and diastolic blood pressure ≥ 90 mm Hg, appear after 20 weeks of pregnancy. PE patients with proteinuria have heart or kidney disease plus evidence of involvement of other organs such as liver disease, neurological problems, haematological disorders or stunted fetal growth. The study reported that PE women with proteinuria had worse pregnancy outcomes, especially greater perinatal mortality, compared to women with PE without proteinuria. Women with clinical PE including organ involvement without proteinuria have worse pregnancy outcomes when compared with women with gestational hypertension.[22]

However, from the study of Lumbanraja SN et al, it was found that proteinuria is not an absolute criterion that must be found to diagnose PE, where multiorgan dysfunction in PE patients with or without proteinuria does not have a significant difference.[28] PE women with massive proteinuria do not show maternal morbidity compared to with PE women with severe and mild proteinuria. Massive proteinuria can be a marker of early onset disease and progression to severe PE, but not to maternal adverse outcomes. Neonatal morbidity arises limited to prematurity and is not related to the state of massive proteinuria.[32]

The amount of proteinuria does not correlate with severe PE, when proteinuria is detected, but it is related to the severity of the PE itself, especially at the initial onset of PE. The amount of proteinuria correlates with the time of PE, but the time between PE onset and delivery is not related to the amount of proteinuria. Poor fetal outcomes occur due to prematurity.[38]

Based on the delivery method 83.1% underwent saesarea section. The results of one study stated that cesarean delivery was the most frequent route of delivery (84%) and the average gestational age at 33 weeks of delivery.[7] The most common mode of delivery was cesarean section section in 64.5% of cases and the most indicative general is a history of previous saessar operations. The mode of delivery is determined by the severity of the mother's condition, Bishop's score, gestational age, fetal condition, ultrasound, and laboratory examination. From one study related to preeclampsia, caesarean section was found in 33%.[13,14] The high rate of cesarean section is due to more than 36% of cases undergoing previous cesarean section and also because of the emergency labor approach taken to prevent further maternal and fetal complications due to severe PE or eclampsia especially in cases where the cervix is unfavorable for induction.[39]

There were 3 maternal deaths of maternal mortality. In a ten-year study conducted by Igberase et al. An important cause of maternal death in severe PE was acute renal failure, disseminated intravascular coagulopathy (DIC), cardiac arrest, pulmonary edema and cerebrovascular accidents.[18] Maternal eclampsia was found in 4 people. ICU maternal care outcomes are 12 people. In one study of fetomaternal outcomes in PE patients, it was found that PE with proteinuria required more ICU care (9.3 vs. 16.3%), but it was still considered insignificant.

A positive result was found to be weak but there was a significant correlation between the amount of protein in the urine and ICU treatment. Hypertension in pregnancy is the most common cause of ICU treatment in obstetric patients.[22] For maternal outcomes of HELLP syndrome, as many as 7 people. Various studies have reported placental abruption and HELLP syndrome as more common complications. A study by Farid M et al. Had 11% incidence of HELLP syndrome and 10% incidence of placental abruption.[17] Maternal outcomes Pulmonary edema, 4 people. In this study, fetal output with PE mothers based on proteinuria, infant mortality was found in 25 people, with proteinuria (-) 2 people, proteinuria (+1) 4 people, proteinuria (+3) 14 people, proteinuria (4) 5 people. Almost all babies born with body weight <1500 gr. Fetal birth weight, 27 people were normal, LBW 29 people, LBW 17 people, LBW 10 people. Prematurity is the most common complication among neonates seen in 64.5% of cases. 65.3% of the incidence of prematurity from research that has been done.[11] The high incidence of preterm birth can be attributed to early intervention and induction of labor or LSCS which is done to prevent further maternal and perinatal complications.

The main factors affecting perinatal mortality and morbidity are prematurity, IUGR and irregular antenatal visits. The perinatal mortality rate in one study was 18%, 7 of which were intrauterine fetal deaths, 3 stillbirths and 10 neonatal deaths all due to prematurity and respiratory distress syndrome. A perinatal mortality rate of 22.7% was reported from southeastern Nigeria. Pakistan reports perinatal deaths as high as 41.6% of one study related to preeclampsia.[39]

APGAR normal scores were found in 55 babies, moderate (4-6) as many as 2 babies, and low (0-3) as many as 26 babies. Neonates with massive proteinuria are more likely to treat NICU and have neonatal respiratory distress syndrome. Neonates with massive proteinuria were also found to be born at lower weights.[32] PE women with proteinuria were more likely to have 2.7 children with IUGR compared with controls.[22] With increased proteinuria, the risk of severity of fetal output also increased. However, the amount of proteinuria mentioned is uncertain. One study found that there was a relationship between fetal output and massive proteinuria (> 5 g / L in 24 hours) .[38]

CONCLUSION

The most research subjects ranged age 21-30 years, namely 35 people (42.2%), with gestational age, ≥ 37 weeks of pregnancy 25 people (30.1%). multipara, as many as 37 people (44.6%). Subjects diagnosed with PE with proteinuria were 62 people. PE with proteinuria +3 was 36.1%. PE without proteinuria totaled 21 people or 25.3% of the total sample. For the delivery method, 69 people (83.1%) underwent saesarea section. Most maternal outcomes were in ICU care at 14.4%, followed by Hellp syndrome 8.4%, eclampsia and pulmonary edema each at 4.8% then maternal mortality at 3.61%. Fetal output of infant mortality is 24%, the highest birth weight of babies is LBW 37% followed by APGAR normal score of 72%.

REFERENCES

1. Pusat Data dan Informasi Kementerian Kesehatan RI.Situasi Kesehatan Ibu. InfoDATIN.Kementerian Kesehatan RI. 2014.
2. Alkema L, Chou D, Hogan D, Zhang S, Moller AB, Gemmill A, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. The Lancet. Nov 2015;387(10017):462-74.
3. Global Health Observatory Data Repository. Maternal Mortality Data by WHO region. World Health Organization. 2015. Available from: http://apps.who.int/gho/data/view.main.1370?lang=en.
4. Global Health Observatory Data Repository. Maternal Mortality Data by Country. World Health Organization. 2015. Available from: http://apps.who.int/gho/data/view.main.1390?lang=en.
5. World Health Organization Media Centre. Maternal Mortality Fact Sheet. World Health Organization. 2016. Available from: http://www.who.int/mediacentre/factsheets/fs348/en/.
6. Jeyabalan A. Epidemiology of preeclampsia: Impact of obesity. Nutr Rev. Oct 2013;71(01).

7. Rossa. 2006. In: Resmi AS. Faktor yang Berhubungan dengan PE pada Kehamilan di RSU Muhammadiyah Sumatera Utara Medan Tahun 2011-2012. Medan: Repository Universitas Sumatera Utara. 2014. Available from: http://repository.usu.ac.id/bitstream/handle/123456789/39621/Chapter%20I.pdf?sequence=5&isAllowed=y. [cited 20th Oct 2017]
8. Dinas Kesehatan Provinsi Sumatera Utara. 2011. In: Resmi AS. Faktor yang Berhubungan dengan PE pada Kehamilan di RSU Muhammadiyah Sumatera Utara Medan Tahun 2011-2012. Medan: Repository Universitas Sumatera Utara. 2014. Available from: http://repository.usu.ac.id/ bitstream/handle/123456789/39621/Chapter%20I.pdf?sequence=5&isAllowed=y. [cited 20th Oct 2017]
9. Task Force on Hypertension and Pregnancy. Hypertension in Pregnancy. The American College of Obstetricians and Gynecologists. 2013.
10. Nischintha S, Pallavee P, Ghose S. Correlation between 24-h urine protein, spot urine protein/creatinine ration, and serum uric acid and their association with fetomaternal outcomes in preeclamptic women. J Nat Sc Biol Med. 2014;5:255-60.
11. Thangaratinam S, Coomarasamy A, O'Mahony F, Sharp S, Zamora J, Khan KS, et al. Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review. BMC Med. 2009;7:10.
12. Homer CS, Brown MA, Mangos G, Davis GK. Non-proteinuric pre-eclampsia: a novel risk indicator in women with gestational hypertension. J Hypertens. 2008;26:295-302.
13. Cunningham FG, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, et al.Chapter 40. Hypertensive Disorders. In: Williams Obstetrics. 24th ed. United States: McGraw-Hill Education; 2014.
14. Dutta DC. Hypertensive Disorders. In: DC Dutta's Textbook of Obstetrics. 7th ed. New Delhi: Jaypee Brothers Medical Publishers Ltd; 2014.
15. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi JM. Preeclampsia: pathophysiology, diagnosis, and management. Vasc Health Risk Manag. 2011;7:467-74.
16. Keiser SD, Boyd KW, Rehberg JF, Elkins S, Owens MY, Sunesara I, et al. A high LDH to AST ratio helps to differentiate pregnancy-associated thrombotic thrombocytopenic purpura (TTP) from HELLP syndrome. J Matern Fetal Neonatal Med. 2012;25(7):1059-63.
17. Sheikh S, Haq G, Kazi S. Frequency of pereterm delivery in proteinuric verses non proteinuric pregnancy induced hypertension. J Pak Med Assoc. 2015; 65(11):1178-81.
18. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA, et al. The SOMANZ Guideline for the Management of Hypertensive Disorders of Pregnancy. Society of Obstetric Medicine of Australia and New Zealand. 2014.
19. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP.Pregnancy Hypertens. Apr 2014;4(2):97-104.
20. NICE. Hypertension in Pregnancy: The Management of Hypertensivie Disorders During Pregnancy. National Instititue for Health and Clinical Excellence. 2012.
21. World Health Organization Regional Office for South-East Asia. WHO South-East Asia Journal of Public Health. Volume 1, Issue 3, July-September 2012, 227-358.
22. Parlakgumus HA, Simsek E, Cok T, Tarim E. The Relationship Between, Proteinuria in Severe Preeclampsia and Maternal and Fetal Outcomes. Gynecol Obstet Reprod Med. 2012;18:7-11.
23. Demirci O, Kumru P, Arinkan A, Ardic C, Arisoy R, Tozkir E, et al. Spot Protein/Creatinine Ratio in Preeclampsia as an Alternative for 24-Hour Urine Protein. Balkan Med J. Jan 2015;32(1):51-55.
24. Cote AM, Brown MA, Lam E, von Dadelszen P, Firoz T, Liston RM, et al. Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review. BMJ. May 2008;336(7651):1003-6.
25. Sachan R, Patel ML, Sachan P, Gauray A, Singh M, Bansal B. Outcomes in hypertensive disorders of pregnancy in the North Indian population. Int J Womens Health. 2013;5:101-108.
26. Brown MA & Buddie ML. The Importance of Nonproteinuric Hypertension in Pregnancy. Hypertens Pregnancy. 2009;14(1):57-65.
27. Newman MG, Robichaux AG, Stedman CM, Jaekle RK, Fontenot MT, Dotson T, et al. Perinatal outcomes in preeclampsia that is complicated by massice proteinuria. Am J Obstet Gynecol. Jan2003;188(1):264-68.
28. Lumbanraja SN. Proteinuria is not a Prequisite Criteria for Preeclampsia Diagnosis. Research Journal of Medical Sciences. 2016; 10 (Special Issue 1): 755-758.
29. Lumbanraja SN. Determining the Maternal Characteristics that Predicts the Adverse Outcomes for Patients with Preeclampsia. JUMMIC. 2013;16(1).
30. Diagnosis and management of preeclampsia and eclampsia. ACOG Practice Bulletin. Number 33, January 2002.
31. Chen YY, Wu ML, Kao MH, Su TH, Chen CP. Perinatal outcome of recurrent pre-eclampsia versus pre-eclampsia in nulliparas. J Obstet Gynaecol Res. 2009;35:1042-6.
32. Newman M, Robichaux A, Stedman C, et al. Perinatal outcomes in pre eclampsia that is complicated by massive proteinuria. Am J Obstet Gynecol 2003;188:264-8.
33. Chan P, Brown M, Simpson JM, Davis G. Proteinuria in preeclampsia: how much matters? BJOG March 2005;112:280-5
34. Selo-Ojeme DO, Omosaiye M, Battacharjee P, Kadir RA. Risk factors for obstetric admissions to the intensive care unit in a tertiary hospital: a case-control study. Arch Gynecol Obstet. 2005;272:207-10. Epub 2005 Feb 3.
35. Schiff E, Friedman S, Kao L, Sibai B. The importance of urinary protein excretion during conservative management of severe preeclampsia. Am J Obstet Gynecol 1996;175(5):1313-6.
36. Paolo J, et al. Maternal and perinatal outcomes in preeclampsia according to the magnitude of proteinuria: Results from a high risk referral center in Brazil. Pregnancy
37. Kim MJ, et al. is masive proteinuria associated with maternal and fetal morbidities in preeclampsia?. Obstet Gynecol Sci 2017;60(3):260-265.
38. Dong X, et al. Proteinuria in preeclampsia: Not essential to diagnosis but related To disease severity and fetal outcomes. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 8 (2017) 60–64
39. Pillai SS. Fetomaternal outcome in severe preeclampsia and eclampsia: a retrospective study in a tertiary care centre. Int J Reprod Contracept Obstet Gynecol. 2017 Sep;6(9):3937-3941