ISSN (Online) 2456 -1304

International Journal of Science, Engineering and Management (IJSEM)

Vol 9, Issue 9, September 2022

Current Concept and Research Progress of Pre-Eclampsia (Early-Onset and Late-Onset Pre-Eclampsia)

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Abstract*— Pre-eclampsia is a syndrome that belongs to the group of hypertensive disorders of pregnancy. It is a multi-organ disease and can affect the kidney, liver, brain and the blood clotting system [1,2]. Pre-eclampsia is one of the most common causes of maternal and fetal morbidity and mortality [3]. Pre-eclampsia is defined as new-onset hypertension developed after 20 weeks of gestation (systolic or diastolic blood pressure ≥140 and/or ≥90 mmHg, respectively, measured at least two occasions, 4 hour to 1 week apart) and proteinuria(≥300 mg in a 24- hour urine collection, or two random urine specimens obtained 4 hours to 1 week apart containing≥1+ by dip stick or one dipstick demonstrated ≥2+ protein)[22,23]. Mild pre-eclampsia was diagnosed as pre-eclampsia was systolic blood pressure <160 mmHg, diastolic blood pressure <110 mmHg, platelet count≥100,000 per mm3, non-elevated liver enzymes, absence of renal insufficiency, pulmonary edema, cyanosis, new-onset cerebral/visual disturbances, and/or right upper quadrant or epigastric pain[24,25]. Severe pre-eclampsia is diagnosed as pre-eclampsia with systolic blood pressure ≥160 mmHg, or diastolic blood pressure ≥110 mmHg, platelet count <100,000 per mm 3, elevated liver enzymes, renal insufficiency, pulmonary edema or cyanosis, new-onset cerebral/visual disturbances, and/or right upper quadrant or epigastric pain [24,25].

A major advance in the classification of pre-eclampsia is its subdivision into early-onset and late-onset pre-eclampsia[26,27]. Especially, early-onset and late-onset pre-eclampsia have a serious threat to the maternal and neonatal lives, and in the clinical practice, it is of great difficulties and challenging in its treatment. Therefore, it is of great importance to pay enough attention to early-onset and late-onset pre-eclampsia.

According to the statistics of recent years in China, the prevalence of pre-eclampsia has become less due to increase in attention paid to the pregnant women with the hypertensive disorder and in the maternity examination during their period of antenatal check-up.

***Index Terms*— Early-onset, late-onset preeclampsia**

I. INTRODUCTION

Pre-eclampsia is the frequent complication of Hypertensive disorders during pregnancy that affects 5%- 8% of all gestations [4,6]. Worldwide, it is the leading cause of maternal and perinatal morbidity and mortality.[8-22]After several types of research and advancement in this field, now it has become clear over the last decade that pre-eclampsia is not only a single disorder but a syndrome with many etiologies [24,41]. Major etiologies of pre-eclampsia are: 1) Abnormal placentation;2) Utero-placental ischemia;3) Endothelial dysfunction;4) Vascular disorders of the placenta;5) Systemic maternal inflammation;6) Insulin resistance.

The concept of early-onset and late-onset pre-eclampsia was put forward in the 1980s by the scholars. Several research and discussions are going on in this concept of early-onset and late-onset pre-eclampsia around the world among the medical circles. In recent years, as a result of a major advance in the classification of pre-eclampsia, it is subdivided according to the time of onset, as early-onset and late-onset pre-eclampsia [28,29].

Early-onset preeclampsia is defined as pre-eclampsia diagnosed before 34 weeks [22]. Late-onset preeclampsia is defined as pre-eclampsia diagnosed at or after 34 weeks of gestation. Among these two variants of onset, late-onset pre-eclampsia is more common than early-onset pre-eclampsia and it accounts for 90% of the cases and also it shows the substantial fraction of maternal complications [15, 22, 30]. In a study, done in South Africa, late-onset pre-eclampsia accounted for 30% of severe maternal complications, 13% of eclampsia and 1.9% of fetal deaths [30]. For early-onset pre-eclampsia, as the patient is not full term the maternal and fetal conditions are serious but in the case of late-onset pre-eclampsia as its onset is after 34 weeks of gestation, the rate of neonatal morbidity declines and comparatively less effect on the maternal health.

The relationship between vitamin E as an antioxidant and the early-onset and late-onset Pre-eclampsia:

Vitamin E, as a potent antioxidant can inhibit lipid peroxidation and can prevent endothelial cell damage and protect blood vessels. It is an important intramembrane antioxidant and membrane stabilizer

Vitamin E also plays an important role as free radicals during pregnancy. Pregnancy is the state in which there is a vigorous increase in the metabolism, which enhances the lipid peroxidation reaction resulting in the increase of free radicals. If not managed in the time, may lead to an increase in the risk of pregnancy-induced hypertension, placental aging and even in the adverse effect on the pregnancy

ISSN (Online) 2456 -1304
International Journal of Science, Engineering and Management (IJSEM)
Vol 9, Issue 9, September 2022

outcomes. The deficiency of vitamin E can cause accumulation of lipid peroxidation products, which, in turn, can cause vasoconstriction.

Vitamin E is a potent antioxidant. Oxidative stress has been proposed as a key factor involved in the development of pre-eclampsia. Lack of vitamin E lead to an imbalance between the oxidation system and antioxidant system.

Supplementation with vitamin E during pregnancy may help to counteract oxidative stress and thereby prevent or delay the onset of pre-eclampsia.

1.1.Causes of early-onset and late-onset pre-eclampsia:

Early-onset preeclampsia is likely caused by a disorder of deep placentation in which there is a failure of physiologic transformation of the spiral arteries, a small placenta with histologic features of maternal vascular underperfusion[31,32,33,34], fetal growth restriction or small for gestational age [35,36,37,38], and abnormal Doppler velocimetry of umbilical and uterine arteries[39,40]. It frequently requires preterm delivery for maternal and/or fetal indications [15]. But on the contrary, late-onset pre-eclampsia seems to be the manifestation of a mismatch between the metabolic demands of the growing fetus close to terms and maternal supply [28, 41] as a result of which the placenta has fewer lesions of maternal vascular under perfusion and abnormalities of umbilical/uterine artery Doppler velocimetry [41]. So, in most cases of late-onset pre-eclampsia, neonates are found out to be appropriate or large for gestational age [42, 43, 44].

1.2.The severity of disease in early-onset and late-onset preeclampsia:

In case of Early-onset pre-eclampsia, as the onset is earlier and far away from the maturation of the fetus, severe degree of intrauterine fetal organs development abnormalities (heart, lungs, liver, brain, kidneys and other vital organs) occurs. In early-onset pre-eclampsia, as the patient is not full-term so the maternal and fetal conditions are serious. As the severity of the disease is more serious in the case of early-onset pre-eclampsia in comparison to late-onset preeclampsia. It is a serious threat to the life of pregnant woman and fetus and plays an important role in maternal mortality and perinatal infections and mortality. Maternal morbidity is defined as any potentially life-threatening condition. Early-onset pre-eclampsia conferred a substantially higher risk of the cardiovascular, respiratory, central nervous system, renal, hepatic and other morbidities [45]. So, the maternal and perinatal mortality rate in case of early-onset pre-eclampsia is higher [46].

1.3.Risk factors for early and late-onset pre-eclampsia:

The risk factors differ between early-onset and late-onset pre-eclampsia. The risk factors between early and late-onset pre-eclampsia were mainly based on the h/o chronic hypertension and the family h/o chronic HTN. History of Chronic hypertension was associated with increased risk for only early-onset pre-eclampsia, while a family history of chronic hypertension was associated with increased risk for only late-onset pre-eclampsia [65].

1.4.Pathological condition in early-onset and late-onset pre-eclampsia: Decidual vascular disease, placental infarction, abruption placenta, and placental villi dysplasia were seen in both the groups of pre-eclampsia. But the incidence of decidual vascular disease and placental villi dysplasia in early-onset pre-eclampsia is higher than those in late-onset pre-eclampsia [47,51].

1.5.Clinical observations and indicators in early-onset and late-onset pre-eclampsia:

Early antenatal follow-up and warning clinical factors of early-onset and late-onset preeclampsia women:

Prenatal examination of pregnant women with severe pre-eclampsia which should be strictly observed are: 1) Prenatal examination time;2) Whether patient is under high salt diet, high fats, high sugar ;3) Whether their weight changes, edema changes, blood pressure fluctuates and urinary protein changes and hypoproteinemia and 4) whether vitamin A, D, E is deficient because these are the warning signs of early-onset and late-onset preeclampsia.

Observation and recording were done in pregnant women who are at risk for early-onset and late-onset pre-eclampsia are :

Demographic characteristic like age, parity, family history, past history of eclampsia.

Continuous ambulatory blood pressure at admission, prenatal examination, general edema.

Auxillary examination: Blood routine examination (platelets count), Urine routine examination,(24-hour urine protein), Electrolytes, LFT, (serum HDL, serum Total bilirubin, indirect bilirubin, direct bilirubin)RFT(uric acid, urea, creatinine), 24hour urinary protein every 2 days, TSH, free T3, freeT4, Fundal examination, CVS, Color Doppler USG, and abdominal viscera, Urinary System Color Doppler USG, Thoracic and Ascitic USG, ECHOCARDIOGRAPHY, Evaluation of pericardial and pleural effusion, Umbilical artery , S/D value.

Clinical Indicators and observations of neonatal outcome:

The parameters that are observed daily during the antenatal visit in the pregnant women who are at risk of early-onset and late-onset pre-eclampsia are fetal heart rate, the number of fetal movements and the changes in S/D ratio. Amniotic fluid volume, fetal growth, placental maturity, placental abruption, Intrauterine fetal death was observed by B-mode USG every week.

Observation of the maternal complications:

Pregnant women should be assessed for placental abruption, heart, liver and kidney failure, pulmonary edema, cerebral hemorrhage, persistent headache, severe visual loss or retinal exfoliation, upper abdominal pain, decrease in platelets count, hemolysis, which can lead to the occurrence of common clinical complications such as HELLP Syndrome,

ISSN (Online) 2456 -1304
International Journal of Science, Engineering and Management (IJSEM)
Vol 9, Issue 9, September 2022

eclampsia, DIC, and PPH.

Observation of neonatal records:

In the clinical practice, it is very important to observe the birth weight, Apgar Score and birth rate of early-onset neonates after delivery, neonatal ventricular breath, premature birth, neonatal respiratory distress syndrome, neonatal hypoxic-ischemic encephalopathy, neonatal death, whether to carry out neonatal rescue, whether to transfer to neonatal department and so on.

II. TREATMENT METHODS

Conventional interventions in the treatment of severe pre-eclampsia include:

Restriction of activity, encouragement of rest in the lateral position, restriction of sodium intake, vitamin supplementation, appropriate high protein diet, sedation if necessary and so on.

The basic loading dose of MgSO4 injection is given. 25% MgSO4 16 ml, loading dose was added to the 100ml of 5% glucose solution for intravenous drip within 30 min and then 60 ml concentration is given for micro-pumping at the rate of 2g/hr and 25g MgSO4 was used daily for 48 hours.

Blood pressure of the patient should be observed during the treatment. The patient is treated orally by Labetalol 100mg TDS+ Nifedipine 30 mg QID and the dosage of drugs is adjusted according to the blood pressure.

The target range of the blood pressure control according to the Obstetrics and Gynecologist Journal is as follows;

1) Systolic BP is controlled at 130-155 mmHg and Diastolic BP is controlled at 80-105 mmHg if there is no organ dysfunction in pregnant women.

2) If clinical complications of organ dysfunction occur in pregnant women, Systolic BP should be controlled between 130-139 mmHg and Diastolic BP should be controlled between 80-89 mmHg.

3) The process of BP reduction should be stable and not less than 120/80 mmHg.

2.1. Management of early-onset and late-onset preeclampsia:

For late-onset pre-eclampsia, it is very important to evaluate the maturity or near maturity of fetal lungs. If the blood pressure is not stable or fetus has reached full term, terminating a pregnancy as soon as possible is a very effective treatment. Conservative management of delayed childbirth or timely terminations of pregnancy are the difficult problems in the clinical practice.

Expectant management of early-onset pre-eclampsia and careful neonatal monitoring has led to high perinatal and neonatal survival rates [58]. Several research data shows that almost half of the women presenting with early-onset pre-eclampsia was qualified for expectant management. Early fetal distress was the most frequent reason for preventing expectant management [59]. In the tertiary center, careful non-invasive management can diminish and limit the impact of serious maternal complications. In this way, time in the prolongation of pregnancy can be gained and along with this neonatal outcomes can be improved [60].

After delivery, severe complications occur in pregnant women. At the same time due to premature birth, there is an increased rate of immature fetal lungs development, poor Apgar score, abnormal respiratory function, pediatric consultation for neonatal rescue. Therefore, attention should be paid towards early detection, prevention, and treatment to reduce pre-eclampsia in pregnant women and its related complications to improve the survival rate of pregnant women and perinatal infants.

2.2. Prognosis of early-onset and late-onset pre-eclampsia:

In the modern days, after the several types of research and with the advancement and continuous improvement in the treatment of hypertensive disorders in pregnancy, the improvement rate of pre-eclampsia in pregnant women is increasing and postpartum recovery is better. However, in the case of early-onset pre-eclampsia, postpartum hypertension in severe pre-eclampsia patient continuous to rise to 12 weeks or even longer. The time of proteinuria turning negative is longer than that of late-onset preeclampsia. So, the prognosis of early-onset pre-eclampsia is worse than the late-onset pre-eclampsia [55].

III. INDICATION FOR TERMINATION OF PREGNANCY

1. If blood pressure is not controlled and is fluctuating greatly.
2. If the patient has proteinuria and massive pleural and pericardial effusion.
3. If there is a continuous decrease in amniotic fluid accompanied by frequent late deceleration of fetal heart rate.
4. If the patient has the condition of heart failure, abnormalities in liver function and kidney failure.
5. If there is a continuous decrease in platelets, intravascular hemolysis, the clinical appearance of jaundice, hemoglobinuria and anemia leading to HELLP Syndrome.
6. Severe fundus hemorrhage with an increase in ICP.
7. If the patient has the occurrence of Eclampsia, convulsions [48].

3.1. Comparison of the indication of pregnancy termination in early-onset and late-onset pre-eclampsia:

The early-onset indicates to terminate the pregnancy were mainly fetal-related, while late-onset pre-eclampsia were mainly maternal-related. Postpartum neonatal morbidity and mortality were significantly higher, mean gestational age-onset and delivery was significantly longer, admission 24-hour proteinuria was significantly higher than in late-onset preeclampsia. Early-onset preeclampsia is a distinct and more severe clinical entity with earlier gestational age-onset and delivery. Early-onset pre-eclampsia

might be fetal-related disease complicated by severe placental and perinatal injuries. On the contrary, late-onset pre-eclampsia might be a maternal-related derived disease condition [49,50].

3.2. Choice of delivery mode for early-onset and late-onset pre-eclampsia:

Pre-eclampsia is a disease that is unique to human pregnancy and only known cure for this complication is delivery. So, termination pf pregnancy is the most effective method for the treatment of pre-eclampsia. The choice of delivery mode depends on the condition of the mother and the infant, gestational age and the condition of the cervix in response to dilatation and effacement. Cesarean section is the common choice of treatment.

Relevant research data done in China shows that the mode of termination of pregnancy in severe pre-eclampsia has changed significantly from 1977 to 2010[50]. The rate of cesarean section in early-onset pre-eclampsia is higher than that in late-onset preeclampsia.

At the end of the 20th century, the main way of termination of pregnancy in early-onset pre-eclampsia was induced labor. The main reason behind this was the lack of attention in the prenatal examination consciousness of the pregnant women and also the treatment for pre-eclampsia was not sufficient. So the survival rate of perinatal babies delivered before 32 weeks was low. With the development of medical researches, sufficient knowledge and expectations and treatment modalities of early-onset pre-eclampsia, it was found that the survival rate of infants delivered after 34 weeks was increased significantly and Cesarean section has become the main mode of delivery.

It does not matter which mode of delivery is chosen, but when the gestational age is earlier, the condition is more serious and worse. So according to the situation of the pregnant women, appropriate means for the prolongation of gestational age is chosen, and appropriate ways for termination of pregnancy is done [54].

3.3. Fetal monitoring in early-onset and late-onset pre-eclampsia:

Fetal monitoring is very important to reduce the rate of fetal mortality. The common clinical mainly monitors the fetal umbilical blood circulation, so that there is more blood flow to the fetal umbilical artery. Analysis of the blood circulation of the placenta-fetus indirectly reflects the condition of the fetus in the uterus under the condition of fetal hypoxia. The umbilical artery blood flow is most sensitive in monitoring fetal umbilical blood circulation.

When there is early or late-onset pre-eclampsia, the umbilical artery and the umbilical vein contracts obviously, which eventually leads to increase the resistance of feto-placental circulation increasing in S/D ratio and resulting in serious fetal intrauterine hypoxia.

Relevant research data shows that Fetal Growth Restriction occurs when S/D≥4 in Fetal Umbilical Artery Doppler flow detection and there is also the increased incidence of fetal distress, neonatal ventricular breath, whereas when the S/D ≤4, the Disorder of these risks decreases [53]. Hence, routine monitoring of fetal umbilical blood flow using Doppler USG is used to assist diagnosis and reflect the intrauterine fetal condition in early and late-onset pre-eclampsia. In addition, early detection and early treatment of fetal ischemia, hypoxia, and fetal distress can greatly improve the pregnant women and perinatal babies survival rate.

3.4. Prediction of early-onset and late-onset pre-eclampsia:

Maternal serum copeptin concentration: According to several types of research it is clear that early-onset pre-eclampsia is primarily associated with placental dysfunction whereas late-onset pre-eclampsia is associated with maternal constitutional disorders. As a protein co-synthesized with vasopressin, copeptin is a potential marker of metabolic syndrome and insulin resistance, which is known to share similar risk factors with pre-eclampsia [56].

Expression of Complement System's Activation factors in plasma of patients with early/late-onset severe pre-eclampsia. Abnormal activation of the complement system exists in the maternal circulation of patients with early-onset and late-onset severe pre-eclampsia. In case, when the patients were complicated with late-onset pre-eclampsia, the complement system was activated through both the classical and alternative pathways, while in case of early-onset pre-eclampsia, the complement system was activated mainly through the alternative pathway [57]. Pre-eclampsia has been proposed to be an antiangiogenic state that may be detected by the determination of the concentration of the soluble vascular endothelial growth factor receptor-1(Svegfr-1) and placental growth factor(PIGF) in maternal blood even before the clinical development of diseases. The combination of abnormal Uterine Artery Doppler Velocimetry (UADV) and maternal plasma PIGF concentration of <280 pg/ml in the second trimester is associated with a high risk for pre-eclampsia and early-onset and/or severe pre-eclampsia in a low-risk population. Among with abnormal UADV, a maternal plasma concentration of PIGF of <280 pg/ml identifies most patients who will experience early-onset and/or severe pre-eclampsia [61].

Circulating angiogenic factors have been shown to be important in the pathophysiology of pre-eclampsia. The soluble forms-like tyrosinase-1(sFlt -1)/ Placental growth factors (PIGF) ratio in early-onset pre-eclampsia was higher than that in late-onset preeclampsia. So, the high ratio of sFlt-1 to PIGF can be suggested as a strong predictive marker for early-onset preeclampsia[62,63].

Only a few biomarkers for the diagnosis of late-onset preeclampsia have been reported. Matrilysin, also known as matrix metalloproteinase-7(MMP-7), uterine metalloproteinase is an enzyme in humans that is encoded by the MMP7 gene. Elevated MMP-7 early in gestation (8-22)

weeks and low PIGF later in gestation (after 22 weeks) are the strongest predictors for the subsequent development of late-onset preeclampsia suggesting that the optimal identification of patients at risk may involve a two-step diagnostic process [64].

IV. CONCLUSION

Early-onset and late-onset pre-eclampsia are the two different variants of onset of pre-eclampsia. Both the variants have a serious threat to the maternal and neonatal lives and in the clinical practice, it is of great difficulties and challenging in its treatment. Among these two variants of onset of pre-eclampsia, late-onset pre-eclampsia is more common than early-onset pre-eclampsia. Early-onset preeclampsia has a serious threat to the life of pregnant woman and fetus and plays an important role in maternal mortality and perinatal infections and mortality compared to late-onset preeclampsia. As the severity of the disease is more serious in the case of early-onset pre-eclampsia in comparison to late-onset preeclampsia. Hence, the prognosis of early-onset pre-eclampsia is worse than the late-onset preeclampsia.

Vitamin E is a potent antioxidant. Oxidative stress has been proposed as a key factor involved in the development of early-onset and late-onset pre-eclampsia. Lack of vitamin E lead to an imbalance between the oxidation system and antioxidant system.

In the modern days, after the several types of research and with the advancement and continuous improvement in the treatment of hypertensive disorders in pregnancy, the improvement rate of pre-eclampsia in pregnant women is increasing and postpartum recovery is better. There are only a few biomarkers namely MMP-7, PIGF for the diagnosis of these variants of preeclampsia from one another. The high ratio of sFlt-1 to PIGF is suggested as a strong predictive marker for early-onset preeclampsia. If the early or late-onset pre-eclampsia is diagnosed in the earlier stages with the help of these predictive markers than the patient can be strictly observed during the antenatal period.

Further with the regular clinical checkup of the patient and strict observation and clinical recording of these patients and along with strict monitoring of the fetus during the antenatal checkup, restriction activity, appropriate diets, appropriate management and treatment methods, the maternal morbidity and mortality can be reduced and fatal outcomes can be improved.

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