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International Journal of Pharmaceutical Research & Allied Sciences, 2016, 5(3): 365-370

Research Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

A comparative Assessment of Pregnancy Outcomes in Patients with Early and Late Pregnancy Hypertension Disorders

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ABSTRACT

Preeclampsia syndrome is pregnancy-specific and one of the most dangerous types of hypertension whether added to chronic hypertension or with no previous history. The present study aimed to investigate the differences in the fetal and maternal outcomes between the early and late-onset preeclampsia. This was a prospective observational study conducted on 120 pregnant women with preeclampsia referred to the emergency centers and women's clinics of Ahvaz Imam and Razi Hospitals during March 2015 to 2016. Sixty patients with early-onset and 60 patients with the late-onset severe preeclampsia were selected. The inclusion criteria included singleton pregnancy and no previous experience or risk factor of hypertension. The exclusion criteria included any previous experience of cardiovascular, hepatic, renal, pulmonary, and cerebral diseases, diabetes, primary hypertension, multiple pregnancies, any history of previous preeclampsia, eclampsia, stillbirth, placental abruption, oligohydramnios, intrauterine fetal growth restriction, Doppler disorder, abnormal biometry sonography, experience of the newborn with low Apgar and low birth weight. In this study, the clinical maternal, obstetrical, fetal, and neonatal outcomes of the two groups were compared. There were no significant differences in the age and body mass index (BMI) between both groups. The most significant differences of clinical maternal outcomes between the two groups were the frequency of hepatic, hematological, pulmonary, and cerebral diseases, necessity to mother hospitalization in ICU, and maternal death. However, the largest differences in obstetrical and fetal outcomes between the two groups were observed in the amount of preterm delivery, stillbirth, and abnormal middle cerebral artery in Doppler assessment. Finally, the greatest differences in newborn outcomes between the two groups were observed in the low birth weight, fifth- minute Apgar, and the necessity for hospitalization in the NICU. The preeclampsia syndrome is a multi-factorial disease. According to the observed differences in pregnancy outcomes, the division of this syndrome into two subgroups of late and early-onset preeclampsia can play crucial role in the diagnosis and treatment of the complications.

Keywords: Early-onset preeclampsia, Late-onset preeclampsia, Prenatal outcome, Severe preeclampsia

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INTRODUCTION

Hypertension disorders with the prevalence of 5-10 percent worldwide. Preeclampsia syndrome is one of the most dangerous types of hypertension disorders whether added to chronic hypertension or with no previous history (1). In addition, preeclampsia is one of the outcomes of pregnancy so that affecting 3.9 percent of pregnant women (2).

More than half of the maternal deaths related to hypertension can be predicted (3). The preeclampsia syndrome as a pregnancy-specific syndrome affects different organs, however, the precise pathogenesis of this syndrome has not been identified and is most probably multi-factorial (4-8). It has increasingly been identified that the pathologic processes in the blood flow of mother and placenta cause some disorders in endothelial and muscular cells of the vessels leading to a series of diseases (9, 10). It seems that preeclampsia syndrome is clinically the spectral of the gradual increasing disease (11). Preeclampsia is divided by the age of pregnancy into the early-onset preeclampsia (EOP) which occurs before the 34th pregnancy week and late-onset preeclampsia (LOP) which occurs in the 34th pregnancy week or after (9, 10). Most preeclampsia cases which are close to end of pregnancy (pregnancy week ≥ 34) are associated with mild clinical symptoms. Only a few number of patients show severe clinical symptoms (12, 13), while the early-onset preeclampsia can cause serious outcomes due to the earlier involvement of the mother and the fetus (14). On the other hand, the categorization of preeclampsia into early- and late-onset preeclampsia has brought about two relatively different distinguished clinical forms with unique pathophysiologic specifications for each (13). The present study aimed to identify the differences in the fetal and maternal outcomes between the early and late-onset preeclampsia.

MATERIALS AND METHODS

This was a prospective observational study was performed on 120 pregnant women with preeclampsia referred to the emergency centers or women's clinic of the academic centers of Imam and Razi Hospitals of Ahvaz during March 2015 to March 2016. Sixty patients with early-onset and 60 patients with the late-onset preeclampsia were selected based on simple sampling method. The experimental procedures of this study were approved by ethical committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (code: IR.AGUMS.IR.1394.582). Written consent from was obtained from all of patients. The patients were studied from the time of preeclampsia diagnosis followed up for three months after delivery. The 3-month follow up period was selected to achieve the following objectives: tracing the the infancy outcomes (28 days after birth); identification of the chronic hypertension cases (continuity of the blood pressure after 3 months from delivery); and omitting the patients from the study. The including criteria were singleton pregnancy and having no risk factor or hypertension experience. The excluding criteria were the previous experiences of cardiovascular, hepatic, renal, pulmonary and cerebral diseases, diabetes, primary hypertension, multiple pregnancy as well as suffering from any kind of preeclampsia, eclampsia, stillbirth, placental abruption, oligohydramnios, intrauterine fetal growth restriction, Doppler disorder, biometry sonography, experience of the newborn with Apgar, and low birth weight.

The severe preeclampsia was defined as having a blood pressure equal or more than 160/110 mmHg along with 2 g proteinuria per 24 hrs of urine, or one of the following conditions: 1) Platelets fewer than 100,000 per microliter, 2) The level of creatinine more than 1.1 mg/dl or doubling its level compared to the basal level, 3) Twice serum transaminase level compared to the normal level, 4) Headache, visual disturbances, convulsion attacks, 5) Pulmonary edema and 6) Intrauterine fetal growth restriction (1). If the preeclampsia occurs before the 34th week of the pregnancy, it is called early-onset preeclampsia and if it occurs in the 34th week of the pregnancy and after, it is called late-onset preeclampsia (13). The gestational age was calculated from the first trimester ultrasound.

The variables of the study were investigated in four categories including the maternal, obstetrical, fetal, and neonatal medical outcomes. The maternal medical outcomes included hepatic involvement (elevated liver enzymes to twice the normal rate and sub-capsular hematoma), renal disorders (increased serum creatinine to more than 1.1 mg/dl and oliguria: 24 urine volume less than 400 cc), blood disorders (Thrombocytopenia less than 100,000 per microliter), pulmonary disorders (pulmonary edema, plural effusion) and brain disorders (convulsion, visual impairment, persistent headache, cerebral hemorrhage). Meanwhile, the obstetrical outcomes were considered to be placental abruption, oligohydramnios (AFI less or equal to 5 cm) and postpartum hemorrhage. The fetal outcomes, however, included the intrauterine fetal growth restriction (fetal weight below the tenth percentile and fetal abdominal circumference below the tenth percentile), stillborn, abnormal Doppler of the umbilical artery Pulsatility Index (PI) more than 95th percentile, abnormal Doppler of the middle cerebral artery (PI less than 5th percentile). Finally, the neonatal outcomes were considered to be the 5th minute Apgar score less than 7, the birth weight less than 2500 g, the level of cerebral hemorrhage in infants at birth, and the hospitalization cases in NICU.

The statistical analysis was performed with statistical package SPSS (version 22 SPSS Inc., Chicago, Illinois, USA). The qualitative and quantitative variables were analyzed using Chi square test and the independent t student test, respectively. The continuous variables were presented as mean ± standard deviation, and the rating variables with frequency (relative percent). The P value less than 0.05 were considered as the statistical significance.

RESULTS

Sixty patients with the early-onset preeclampsia (starting before the 34th week of pregnancy) and 60 patients with the late-onset preeclampsia (starting at the 34th week of pregnancy and after) were analyzed. Specifications of the mothers and a comparison between the two groups of EOP and LOP have been presented in Table 1. The average age of the mothers with early-onset preeclampsia was 26.77 ± 6.26 and that of mothers with late-onset preeclampsia was 27.80 ± 6.34, which showed no significant difference (P= 0.3). The number of the nulliparity cases in the EOP group (51.7%) was significantly more than the LOP group (33.3%) (P= 0.042). The BMI in the EOP group (25.76 ± 4.73) was less than the LOP group (27.79 ± 6.17) but was not significantly different (P= 0.11) while BMI more than 30 kg/m^2 was significantly observed in the LOP group (P= 0.03).

Table 1. Comparison of maternal characteristics between patients with early and late onset severe preeclampsia

Characteristics		All severe PE(n=120)	Early-onset PE (n=60)	Late-onset PE (n=60)	P-value
Age(years)	Mean ± SD	27.28 ± 6.29	26.77 ± 6.26	27.80 ± 6.34	0.3
	max-min	13 - 44	13 - 44	17- 40	
Parity (nullipara)		51 (42.5)	31 (51.7)	20 (33.3)	0.042
BMI(kg/m^2)	Mean ± SD	26.7 ± 5.57	25.76 ± 4.73	27.79 ± 6.17	0.11
	max-min	18.3-53	18.3-42	19- 49	
BMI>30 kg/m^2		24 (20)	9 (15.1)	15 (25)	0.03
Gestational week at diagnosis , mean ± SD(range)		32 ± 2 (20-42)	28 ± 2 (20-33)	36 ± 1 (34-42)	0.02
Delivery week, mean ± SD (range)		34 ± 2 (22-42)	32 ± 2 (22- 38)	37 ± 0.5 (34 - 42)	0.036

In Table 2, the results of clinical and obstetrical outcomes have been presented for all the patients and for both groups separately. Most of the women participating in this study had hepatic involvement (69 patients, 57.5%), and hepatic involvement in the EOP group was significantly more than the LOP group (45 vs. 24 patients, P< 0.0001). The rate of hematological disorder in EOP was significantly higher than LOP (P= 0.03). Renal complication was observed in 13 patients in the EOP group (21.6%) and 2 patients in the LOP group (11.6%), which represented no significant difference (P= 0.1). The amount of pulmonary involvement in the EOP group (13.3%) was significantly more than that in the LOP group (1.7%) (P= 0.016). In addition, 33 patients (55%) of the 60 patients of the EOP group and 16 patients (26.7%) of the 60 patients of the LOP group had cerebral involvement, showing a significant difference (P= 0.001). The number of ICU hospitalized cases were 28 patients in the EOP group and 12 patients in the LOP group, again indicating a significant difference (P= 0.001). Four cases in the EOP group and one case in the LOP group died and this showed a significant difference (p= 0.04). Nine cases including 7 patients in the EOP group (11.7%) and 2 patients in the LOP group (3.3%) had placental abruption representing no significant difference (p= 0.08). Meanwhile, 22 out of 120 patients had oligohydramnios, 9 of which (15%) were in the EOP group and 13 (21.7%) were in the LOP group indicating no significant difference (p= 0.2). In addition, there was no significant difference in postpartum hemorrhage rate between the EOP group (13.3%) and the LOP groups (11.7%) (p= 0.5).

Table 2: Comparison of clinical and obstetrics outcomes between patients with early and late onset severe preeclampsia

Characteristics	All severe PE(n=120)	Early-onset PE(n=60)	late-onset PE(n=60)	P-value
Liver involvement	69 (57.5)	45 (75)	24 (40)	<0.0001
Hematological involvement	21 (17.5)	15 (25)	6 (10)	0.03
Renal involvement	20 (33.3)	13 (21.6)	7 (11.6)	0.1
Pulmonary involvement	9 (7.5)	8 (13.3)	1 (1.7)	0.016
Cerebral involvement	49 (40.8)	33 (55)	16 (26.7)	0.001
ICU admission	40 (33.3)	28 (46.6)	12 (20)	0.001
Maternal death	5 (4.16)	4 (6.6)	1 (1.6)	0.04
Placenta abruption	9 (7.5)	7 (11.7)	2 (3.3)	0.08
Oligohydramnios	22 (18.3)	9 (15)	13 (21.7)	0.2
Postpartum hemorrhage	15 (12.5)	8 (13.3)	7 (11.7)	0.5
Preterm delivery	75 (62.5)	51 (85)	24 (40)	<0.0001

Table 3 compares the fetal and neonatal outcomes between patients with early and late onset preeclampsia. The rate of stillbirth in the EOP group and the LOP group were 9 and 1 cases, respectively, which indicated a significant difference (p= 0.008). Seventy one of 120 fetuses had growth retardation 34 cases of which (56.7%) were in the EOP group and 37 cases (61.7%) were in the LOP group indicating no significant different (p= 0.3). In the Doppler assessment, 8 cases in the EOP group had umbilical artery above the 95th percentile while 5 cases in the LOP group

demonstrated this disorder (p= 0.2). In addition, the PI of the middle cerebral artery of 19 cases (31.6%) and 6 cases (10%) were less than the 5th percentile, showing a statistically significant difference in the two groups (p= 0.002).

Based on this comparison, the previous studies inficated that the 5th minute Apgar scores in 20 newborns of 120 in the studied sample was less than 7 (33.3%) of which were in the EOP group and only one case in the LOP group. This difference was statistically significant (p< 0.0001). There was 1 case of cerebral hemorrhage in the LOP group and 7 cases (11.6%) in the EOP group, showing no significant difference for the finding (p= 0.061). The number of NICU hospitalized newborns in the EOP group was significantly more than those in the LOP group (63.3% vs.16.7%, p< 0.0001).

Table 3: Comparisons of fetal and neonatal outcomes between patients with early and late onset severe preeclampsia

Characteristics	All severe PE(n= 120)	Early-onset PE(n= 60)	Late-onset PE(n= 60)	P-value
Stillbirth	10 (8.3%)	9 (15%)	1 (1.6%)	0.008
Biometry disorder	71 (59.2%)	34 (56.7%)	37 (61.7%)	0.3
Abnormal Doppler of Umbilical artery	13 (10.8%)	8 (13.3%)	5 (8.3%)	0.2
Abnormal Doppler of cerebral artery	25 (41.6%)	19 (31.6%)	6 (10%)	0.002
Low 5-minute Apgar score	21 (17.5%)	20 (33.3%)	1 (1.6%)	<0.0001
Birth weight ≤ 2500 gr	56 (46.75%)	44 (73.3%)	12 (20%)	<0.0001
Cerebral hemorrhage	7 (5.8%)	7 (11.6%)	1 (1.6%)	0.061
NICU hospitalization	47 (45%)	38 (63.3%)	10 (16.7%)	<0.0001

DISCUSSION

Although the cause of preeclampsia has not yet been definitely identified, any disorder in both the maternal and placental factors affects its pathogenesis. In this study, only the cases of preeclampsia were considered with its further division into the two groups of early-onset preeclampsia (gestational age less than 34th week of pregnancy) and late–onset preeclampsia (the 34th week of pregnancy and after). It is believed that these two groups are different regarding their pathogenesis. While the early-onset is mostly associated with inherent placental factors (Abnormal trophoblast invasion to the uterine spiral vessels), the late-onset is mostly identifiable with maternal factors such as high BMI, diabetes, and others. Based on our results, some of the investigated outcomes are significantly different between the groups and this is in agreement with some other study (14, 15). Dividing the preeclampsia into the early-onset and late-onset is a relatively new concept and seems more logical than dividing the preeclampsia into sever and non-sever groups (16). It is approved that the complications of pregnancy in early-onset preeclampsia are clearly more than those in late-onset preeclampsia (14) and the findings of the present study support these findings.
In the present study, there was no significant difference between the average maternal age between the two groups of early-onset and late–onset. These finding have been approved in the study of Li et al. (17). Although in their study the age more than 35 was considered a main factor in the development of preeclampsia, the lack of difference between the average age of mothers in both groups of early-onset and late–onset has been mentioned in their research (17). In this study, there was a significant difference in parity so that the number of nulliparity areas in the early-onset group was obviously more than the late-onset group clearly (51.7% vs.33.3%). In some studies, findings are in disagreement with our results (9, 14, 17, 18). In our study, the average BMI in the two groups was the same while the number of cases with BMI more than 30 kg/m^2 in the late-onset group was significantly more than those in the early–onset group. These findings are in accordance with the findings of previous studies (17, 18).

In our study, the largest difference between the two groups in clinical maternal outcomes was respectively the amount of hepatic, pulmonary, and cerebral diseases, the necessity for mother hospitalization in the ICU, and the maternal death. Meanwhile, the greatest difference in obstetrical and fetal outcomes between the two groups was observed in the amount of preterm delivery, stillbirth, and abnormal middle cerebral artery Doppler. Finally, the biggest difference in newborn outcomes between the two groups was observed in the low birth weight, the fifth-minute Apgar, and the necessity for hospitalization in the NICU.

In this study, the rate of oligohydramnios in late-onset was more than early-onset but it was no significantly different. It might be because the disease is far from the term in the early-onset preeclampsia and we cannot keep the patient until proximity of the term, we have to terminate the pregnancy in which case we do not realize the loss of amniotic fluid either. On the other hand, in the late-onset preeclampsia, because of the proximity of the disease to the time of term and keeping the pregnancy until then, the probability of identifying the loss of amniotic fluid is

higher than the previous one. These findings are support the findings of the Ebeigble et al.'s study (14). However, the results of Madazli et al. are contrary to these results (9).

According to most studies, the rate of morbidity and mortality of the prenatal has been the highest in rank in early-onset preeclampsia (1, 9, 14, 17, 18). In this study, the rate of stillbirth in early-onset preeclampsia was more than that in late-onset (15% vs. 1.6%). One of the reasons for the stillbirth in this disease is the abnormal and insufficient invasion of the trophoblasts to the uterine spiral vessels, resulting in the lack of sufficient blood supply to the fetus and finally distressing the fetus. This abnormal and insufficient invasion and the lack of ability for reconstructing the uterine spiral vessels seems to have occurred mostly in the early-onset preeclampsia.

In this study, the number of PI of the middle cerebral artery less than the 5^{th} percentile in early-onset preeclampsia was significantly higher than those in late-onset preeclampsia. It can be one of the likely causes for more occurrence of stillbirth in the early-onset preeclampsia. Perhaps, the necessity for precise investigation of Doppler velocimetry in this group of patients should be taken into the consideration.

Although the abnormal and insufficient invasion of the trophoblasts in preeclampsia can cause fetal growth restriction (FGR), this relation is not specific only to preeclampsia since the insufficient invasion of the placenta, even without preeclampsia, can cause fetal growth restriction (1). In the present study, there was no significant difference between the occurrence of the fetal growth restriction in both groups of early-onset and late-onset, which is in accordance with the results of the previous studies (14, 17).

CONCLUSION

The preeclampsia syndrome is a multi-factorial disease. According to the observed differences in pregnancy outcomes, the division of this syndrome into two subgroups of late and early-onset preeclampsia can be very important in the diagnosis and treatment of the complications. The early-onset preeclampsia, especially with the abnormal Doppler findings, demonstrates the disorder in the placental invasion to the uterine spiral vessels and causes more pregnancy complications.

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