

# The frequency and fetomaternal outcomes of early-and late-onset preeclampsia: The experience of a single tertiary health center in the bustling metropolis of Turkey; Istanbul

## Erken ve geç preeklampsinin sıklığı ve feto-maternal sonuçları: Türkiye'nin kalabalık metropol kenti İstanbul'da bir üçüncü düzey sağlık merkezinin deneyimleri

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### ABSTRACT

The purpose of the study is to determine the prevalence preeclampsia and to evaluate the maternal and the fetal adverse outcomes in the severe and the early-onset preeclampsia subgroups. Hundred and sixteen pregnant women with preeclampsia who gave birth in an academic tertiary health centre were included in this study. The preeclampsia rate was 1.4 per 100 singleton births for three years (1.5/100 in 2012 and 1.3/100 in both 2013 and 2014 in this study). The rates of severe and early-onset preeclampsia were found as 0.5 and 0.4 per 100 singleton births in this three years period. Adverse maternal outcomes occurred in 18 cases. Maternal mortality occurred in 1 case. In severe preeclampsia (PE), the mean gestational age (33. week), birth weight (1935 g) and Apgar score at 5th minute at delivery (6.8 points) were calculated. In severe PE, the admission rate to Neonatal Intensive Care Unit (NICU) and neonatal mortality rate were 67% and 24%, respectively. In the early-onset preeclampsia, the mean birth weight and 5th min- Apgar score at delivery were found as 1454 g and 5.4 points, respectively. The admission rate to NICU and neonatal mortality rate were 91% and %30 in early-onset PE, respectively. The rate of severe PE in the early-onset PE was 59%. The women with severe preeclampsia had the highest antihypertensive drug prescribing rate (41%) at discharge. Preeclampsia, particularly early-onset and severe preeclampsia require special attention of the healthcare providers.

**Key words:** Preeclampsia, early onset preeclampsia, severe preeclampsia, maternal outcome, neonatal outcome

### ÖZ

Çalışmanın amacı, preeklampsili kadınların prevalansını saptamak ve erken, ciddi preeklampsia alt gruplarında olumsuz sonuçları değerlendirmektir. Bu çalışma retrospektif tanımlayıcı kesitsel bir çalışma olarak gerçekleştirildi. Akademik 3. basamak bir merkezde doğum yapan 116 preeklampsili gebe kadın bu çalışmaya alındı. Çalışma sonuçları preeklampsia oranlarını üç yıl için 100 tekil doğumda 1.4, 2012 için 1,5, hem 2013 hem de 2014 için 1.3 olarak göstermektedir. Bu üç yıllık süreçte şiddetli ve erken başlangıçlı preeklampsia oranları 100 canlı tekil doğum başına 0,5 ve 0,4 olarak bulundu. Bir olguda ölüm ve 18 olguda anneye ait olumsuz sonuç gelişti. Ciddi preeklampside, ortalama gebelik yaşı, doğum kilosu ve doğumda 5. dk. apgar skoru sırasıyla 33 hafta, 1935 g ve 6,8 puan bulundu. Ciddi preeklampside, yenidoğan yoğun bakıma kabul oranı %67 ve yenidoğan ölüm oranları %24'tür. Ortalama doğum ağırlığı ve doğumda 5. dk. apgar skoru, erken başlangıçlı preeklampside 1454 g ve 5,4 puan olarak bulundu. Yenidoğan yoğun bakıma kabul ve yenidoğan ölüm oranları erken başlangıçlı preeklampside %91 ve %30'dur. Erken başlangıçlı preeklampsideki ciddi preeklampsia oranı %59'dur. Ciddi preeklampsili kadınlar %41 ile taburculukta en yüksek anti hipertansif ilaç önerilme oranına sahiptir. Preeklampsili kadınlar, özellikle erken başlangıçlı ve ciddi preeklampsia sağlık sunucularının ayrıcalıklı dikkatine gereksinim duyarlar.

**Anahtar kelimeler:** Preeklampsia, erken başlangıçlı preeklampsia, ciddi preeklampsia, anneye ait sonuçlar, yenidoğana ait sonuçlar

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## INTRODUCTION

Hypertensive Disorders in Pregnancy are categorized as chronic hypertension, gestational hypertension, preeclampsia and eclampsia<sup>1</sup>. The third global leading cause of major complications in childbirth was preeclampsia or eclampsia. World Health Organization reported that "There were 529 000 annual maternal deaths worldwide. Hypertensive disorders of pregnancy were responsible for the death of 63 000 and were the cause of 12% of maternal deaths."<sup>2</sup> The prevalence of pre-eclampsia was reported as 2-8% of all pregnancies varying between countries, even between different ethnic groups living in same country<sup>3,4</sup>. According to a latest study, "the prevalence of preeclampsia changed over three decades (between 1980 and 2010), and preeclampsia had a tendency to shift from the mild to the severe preeclampsia"<sup>5</sup>.

Preeclampsia is described as a multisystem syndrome specific to human pregnancy and occurs as hypertension with new or worsening proteinuria after 20 weeks of gestation<sup>6,7</sup>. The inflammatory agents produced during the inadequate interactions are released to maternal systemic circulation and lead to systemic maternal inflammatory responses characterized by the activation of the coagulation cascade, and the injury of the vascular and the glomerular endothelial cells<sup>8,9</sup>.

The clinical symptoms occur as hypertension, proteinuria, neurologic disturbances, pulmonary oedema, hepatic dysfunction and thrombocytopenia. Preeclampsia is also a major threat for newborns as it leads to several problems related with intrauterine growth restriction, oligohydramnios, abnormal oxygenation and prematurity. Preeclamptic environment affects the women and their offsprings during pregnancy and maintains its influence on their health after birth. Several studies have reported that the women with preeclampsia can face with the increased risk of cardiovascular complications later in life<sup>10,11</sup>.

On the basis of this information, the women who have experienced preeclampsia in pregnancy are

converted to a special group by the long- and short-term consequences of preeclampsia. Particular attention should be paid to the needs of these women by healthcare providers. By knowing the incidence and clinical properties of preeclampsias, they can easily perform their outpatient follow-up when providing them preventive health care. We aimed to find out the rate of preeclampsia in our clinic and to analyze maternal and neonatal consequences as well as the clinical and laboratory characteristics of women with preeclampsia.

## MATERIAL and METHOD

The study was carried out as retrospective, descriptive and cross-sectional trial by evaluating medical records. The patients with preeclampsia admitted to Istanbul Medeniyet University Göztepe Teaching and Research Hospital, Department of Obstetrics and Gynaecology between January 2012 and December 2014 were enrolled in the study. Local Ethics Committee approval was obtained for this study.

The diagnosis of preeclampsia (PE) and the definition of subgroups were based on the report of the American Congress of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy issued in 2013<sup>12</sup>. High blood pressure was defined as systolic blood pressure (SBP) of  $\geq 140$  mmHg and/or diastolic blood pressure (DBP) of  $\geq 90$  mmHg at at least two measurements with a minimal interval of 4 hours. Pregnant women who had high blood pressure at the admission of prenatal care or emergency unit were hospitalized for surveillance with the initial diagnosis of preeclampsia in the obstetric ward. The definition of preeclampsia was established as SBP of  $\geq 140$  mmHg or DBP of  $\geq 90$  mmHg, after 20 weeks of pregnancy in previously normotensive pregnant women together with new-onset proteinuria or any severe features of preeclampsia such as "thrombocytopenia (platelet count less than 100.000/microliter)", "renal insufficiency (serum creatinine concentration greater than 1.1 mg/dL)", "impaired liver function (elevated liver enzymes to twice normal concentration, associated with epigastric or right upper-quadrant pain)", "pul-

monary oedema, new-onset cerebral or visual disturbance" according to ACOG 2013 parameters<sup>12</sup>. Proteinuria was defined dipstick reading of  $\geq 1$  (+) protein in urine.

All the PE cases were divided into two groups, based on the severity of the clinical symptoms; severe PE and preeclampsia without severe features. For all the PE cases there was another division which could be stated as early-onset and late-onset preeclampsia, based on the disease onset. The severe form of preeclampsia was defined as SBP  $\geq 160$  mmHg or DBP  $\geq 110$  mmHg along with the presence of other severe features of preeclampsia that were mentioned above. If the clinical symptoms and the delivery occur before 34 weeks of pregnancy, it was identified as early-onset PE. The definition of late-onset PE was made when manifestations occur after 34 weeks.

Information about maternal age, parity, laboratory parameters such as serum creatinine, platelet count, aspartate transaminase (AST), alanine transaminase (ALT), level of urinary protein with dipstick reading at the time of admission, clinical symptoms and demographic properties of preeclamptic patients were obtained from their medical records. The information about previous chronic diseases such as, chronic hypertension, renal disease and diabetes mellitus were also collected and recorded.

Furthermore, maternal adverse outcomes were defined as abruption of placenta, disseminated coagulopathy, eclampsia, need for blood transfusion due to obstetric haemorrhage, longevity of hospital stay, and maternal mortality.

When the patient had high blood pressure at discharge, antihypertensive drugs such as methyl-dopa, nifedipine, metoprolol tablet or drug combination were prescribed. Drug combination consisted of methyl-dopa and nifedipine tablet or methyl-dopa and metoprolol tablet. Drugs prescribed at discharge was also included in the evaluation.

The gestational age was estimated with the last

menstrual period (LMP) and was confirmed by the first trimester sonogram. Small for gestational age (SGA) was defined as the newborn who had a lower birth weight within 10<sup>th</sup> percentile of the weight adjusted for its gestational age. Intrauterine growth restriction (IUGR) is entitled to a foetus with an estimated foetal weight <10<sup>th</sup> percentile of its gestational age -adjusted weight as detected on ultrasound. Low Apgar scores were defined as less than 7 points estimated at the 5<sup>th</sup> minute of life. Apgar scores at the 5<sup>th</sup> minute were recorded. Neonatal mortality was defined as death occurred during the neonatal period, that is up to 28 days after live birth at or after 22 completed weeks of gestation. Information about foetal outcomes such as Apgar scores at birth, need for neonatal intensive care unit (NICU), birth weight, neonatal death were obtained and recorded. The presence of any signs of maternal or foetal adverse outcomes were accepted as poor obstetric outcome.

The data were analyzed using SAS software. The categorical data were presented as n (%), whereas continuous variables as mean ( $\pm$ standard deviation). The associations between two or more categorical variables were tested using the chi-square test with appropriate correction. If the data were normally distributed, the two-sample t-test was used to determine the differences between the mean of two different groups; otherwise, Mann-Whitney U test was used to test the significance between two variables. A difference between two values was considered as significant if p-value was <0.05.

## RESULTS

In three years period from January 2012 to December 2014, the number of all births in the hospital was 8.205 of which 178 of them were admitted to obstetric ward with initial diagnosis of preeclampsia but only 116 fulfilled the predefined criteria of preeclampsia. The data of the patients with preeclampsia in this 3-year-period were evaluated in this hospital-based study. We found that the preeclampsia rate was 1.4 per 100 singleton births in three years and varied as 1.5/100 in 2012, 1.3/100 in 2013, and 1.3/100 in 2014.

Forty-three pregnant women had properties of severe preeclampsia (37%) and 73 cases (62%) did not have symptoms of severe preeclampsia. Early-onset preeclampsia was diagnosed in 34 cases (29%), while 82 patients (71%) had late-onset PE. The frequency of severe PE and early-onset PE were found as 0.5 and 0.4 per 100 singleton births in three years period. The proportion of severe PE in early-onset disease was documented for 20 of 34 cases (59%) and severe PE in late-onset PE was seen in 23 of the 82 cases (28%).

**Table 1. General characteristics of study group (n:116).**

	Mean ( $\pm$ SD)	Min-Max
Age (year)	29.33 (6.04)	16-46
Gestational age at diagnosis (wk)	35.32 (3.94)	23-41
Gestational age at delivery (wk)	35.36 (3.90)	23-41
Maximal SBP <sup>1</sup> at admission (mm/Hg)	160.42 (21.84)	125-220
Maximal DBP <sup>2</sup> at admission (mm/Hg)	100.95 (12.70)	80-150
	n	%
Primiparity	65	56
Multiparity	51	44
Previous history of preeclampsia	6	5
Prescribing antihypertensive drug at discharge	40	34
Methyl-dopa tablet	16	40
Nifedipine tablet	7	17.5
Metoprolol tablet	7	17.5
Drug combination	10	10
Maternal complications	18	14
Perinatal outcome		
	Mean ( $\pm$ SD)	Min-Max
Birthweight g	2387 (893)	510-4400
	n	%
IUGR <sup>3</sup>	11	9
SGA <sup>4</sup>	12	10
Admission to NICU <sup>5</sup>	59	51
Low apgar score	26	22
Death	13	11
Poor obstetric outcome	80	69

<sup>1</sup>systolic blood pressure, <sup>2</sup>diastolic blood pressure, <sup>3</sup>Intrauterine growth restriction, <sup>4</sup>Small for gestational age, <sup>5</sup>Neonatal Intensive Care Unit

Demographic and clinical data of the study population are presented in Table 1. The mean age of all cases was 29 years and 55% of them were primipara.

Maternal adverse outcomes occurred in 18 cases,

while 6 of them were diagnosed as placental abruption and 2 had seizures of eclampsia. The need for blood transfusion (n:9) was the most common maternal obstetric adverse outcome. Maternal mortality occurred in one case diagnosed as disseminated intravascular coagulation and haemolysis/elevated liver enzymes/low platelets (HELLP) syndrome.

Antihypertensive drugs were prescribed for 40% of the patients at discharge (Table 1). Antihypertensive drugs were prescribed for 35% of the whole study population [early-onset preeclampsia (12/34) and the early-onset with severe preeclampsia group (7/20)]. Most frequently (41%; 18/43) women with severe preeclampsia were prescribed antihypertensive drug.

The most common adverse foetal outcomes were the requirement of NICU, low Apgar score and neonatal death. The mean birth weight was 2387 g and SGA and IUGR were found in 9% (n:11) and 10% (n:12) of the newborns, respectively. Neonatal mortality rate in three years period was documented as 1.58 in 1.000 live births (Number of neonatal deaths x 1000/ Total number of live births).

The preeclampsia group with serious symptoms had higher SBP and DBP than the group without severe preeclampsia. In terms of blood pressure, there were no statistical differences between late-onset and early-onset preeclampsia groups.

Liver enzymes such as AST, ALT and proteinuria were significantly higher in the early-onset and serious preeclampsia group when compared with the late-onset and the preeclampsia group without severe manifestations.

The mean gestational age at diagnosis was demonstrated as 33 weeks in the severe preeclampsia group and was significantly lower than the group with preeclampsia without severe symptoms.

In view of the interval between the diagnosis and the delivery, there were significant differences between the early-onset preeclampsia (1.79 day) and the late-

**Table 2. Maternal and neonatal outcome in the preeclampsia subgroups.**

	Early-onset preeclampsia N:34	Late-onset preeclampsia N:82	p-value	Severe preeclampsia N:43	Without severe features preeclampsia N:73	p-value
<b>At diagnosis of PreEclampsia</b>						
SBP <sup>1</sup> mm Hg (±SD)	159.27 (23.87)	157.71 (32.31)	0.60	167.09 (22.76)	152.97 (32.532)	0.02
DBP <sup>2</sup> mm Hg (±SD)	131.32 (12.51)	131.75 (15.55)	0.93	104.77 (14.31)	98.85 (11.15)	0.03
ALT <sup>3</sup> Level U/L (±SD)	38.21 (46.77)	20.12 (31.16)	0.003	40.47 (54.28)	16.61 (16.74)	0.03
AST <sup>4</sup> U/L Level(±SD)	62.14 (92.68)	31.77 (43.62)	0.01	64.54 (97.09)	26.69 (19.19)	0.01
Proteinuria dipstick (±SD)	3 (2.20)	2.51 (1.88)	0.27	3.51 (2.14)	2.15 (1.71)	0.002
Gestational age week (±SD)	30.32 (2.56)	37.45 (1.95)	0.001	33.84 (4.15)	36.27 (3.44)	0.001
Time from diagnosis to delivery/day (±SD)	1.79 (4.10)	0.52 (1.19)	0.001	1.30 (3.73)	0.65 (1.27)	0.81
Time to discharge from delivery/day (±SD)	4.56 (1.37)	3.58 (1.70)	0.0001	4.39 (2.01)	3.55 (1.36)	0.007
<b>Fetal outcome</b>						
APGAR 5 <sup>th</sup> min (±SD)	5.4 (2,9)	8.9 (1,9)	0.0001	6.8 (3,2)	8.6 (2,3)	0.0003
Birthweight g (±SD)	1454 (537.68)	2776 (701.78)	0.0001	1935 (814.13)	2667.29 (828.16)	0.001
Need NICU <sup>5</sup> n(%)	31 (91%)	28 (34%)	0.0001	29 (67%)	30 (40%)	0.009
Death n(%)	10 (30%)	3 (4%)	0.0001	9 (24%)	4 (5%)	0.01

<sup>1</sup>systolic blood pressure, <sup>2</sup>diastolic blood pressure, <sup>3</sup>Alanine transaminase, <sup>4</sup>Aspartate transaminase, <sup>5</sup>Neonatal Intensive Care Unit  
Continuous variables are tabulated as mean (±SD) and categorical variables are tabulated as n(%).

Continuous variables were compared by ANOVA or Kruskal-Wallis, and categorical variables by chi-square.

onset preeclampsia group (0.52 day). The duration of hospital stay was found longer in the early-onset group than the late-onset group. Also this period was longer in the severe preeclampsia group when compared with preeclampsia group without severe features.

In terms of perinatal outcomes, the birth weight and the Apgar score at the 5<sup>th</sup> minute were significantly lower in neonate who were born to a mother with early-onset and with severe preeclampsia. Also the rate of neonatal death was 30% (n:10) in women with early-onset and 24% (n:9) in severe preeclampsia.

In comparison with the late-onset PE group and the PE group without severe features, the rate of neonatal death was appeared to be significantly higher in the early-onset PE group and in the severe PE group.

Ninety-one percent of women with early-onset preeclampsia needed NICU which was significantly higher when compared with women with late-onset preeclampsia. The frequency of need for NICU was 67% for severe preeclampsia group and was 40% for the group with preeclampsia without severe features. There was a statistically significant difference between these two groups.

The data of the study groups related with maternal clinical outcomes and neonatal outcomes are presented in Table 2.

## DISCUSSION

The prevalence of preeclampsia continues to be one of the unresolved questions in the epidemiology. The overall prevalence of preeclampsia ranges between 5-10% globally<sup>2</sup>. In industrialized countries, it was reported between 3 to 5%<sup>13,14</sup>. Although the exact prevalence of preeclampsia in low- and middle- income countries is unknown, it is reported as 9.1% in both Africa and Asia, 25.7% in both Latin America and the Caribbean Countries while it is 2.13% in Southern Iran, respectively<sup>15,16</sup>. In United States, between 1980 and 2010 the rate of preeclampsia was 3.4%<sup>5</sup>. Researchers also reported that “the rate of severe pre-eclampsia in 1980 increased from 0.3% to 1.4% in 2010, in contrast, mild pre-eclampsia in 1980 declined from 3.1% to 2.5% in 2010”. In view of severe and early pre-eclampsia, the prevalence of severe pre-eclampsia was reported as 1.7% in Nova Scotia and as 29.3 per 10.000 deliveries in Singapore<sup>17,18</sup>. In another study, the rates of early and late preeclampsia were reported as 0.3% and 2.7%, respectively (preeclampsia rate was 3.0 per 100 singleton births)<sup>18</sup>.

Compared with the results reported by other centres, a lower rate of preeclampsia obtained in our academic tertiary health centres was unexpected. But the rate of severe and early preeclampsia in this study was consistent with the data reported in other studies. It was explained that especially high risk group of patients were referred to our tertiary health centres. The disease had a lower incidence but the proportion of high risk group patients were high.

Nulliparity is a risk factor for preeclampsia and is based on the primipaternity hypothesis. We found that over half of the cases (55%) were primipara women as it was recorded in other studies, and the mean age of the study population was 29 years<sup>21,22</sup>.

The maternal or perinatal outcomes were affected significantly by preeclampsia. The women with preeclampsia had higher risk of severe maternal morbidity and mortality, by comparison with pregnant women without preeclampsia<sup>20,21</sup>. Also obstetrical adverse outcomes depend on gestational age at diagnosis, severity of preeclampsia, suitable management of the disease and the preexisting medical diseases<sup>18,22,24</sup>. When the gestational age at diagnosis was less than 32 weeks, the disease was associated with 20-fold increased risk of maternal mortality, compared with that at  $\geq 37$  weeks<sup>19,25</sup>. Women with severe disease were more likely to deliver premature and lower birth weight babies<sup>22</sup>.

The average of gestational age of severe preeclampsia in our study was 33 weeks. The vast majority of early-onset preeclampsia had properties of severe preeclampsia, so the proportion of severe preeclampsia in early-onset preeclampsia was found to be high. Therefore, management of preeclampsia far from term comes up as a challenging issue for us and also for other clinicians. Meta-analyses demonstrated that "Expectant management of women with early-onset preeclampsia is associated with a lower incidence of some neonatal morbidity, without significant differences in maternal outcomes."<sup>26</sup> In the absence of worsening maternal condition, we have preferred to use expectant approach for preeclampsia far from

term. The results obtained in this study verified the assumption which states that "the duration from diagnosis to delivery was longer in early-onset preeclampsia". This result demonstrated that early and severe preeclampsia groups were in need of medical support for much longer time because of the severity of their clinical condition. The rate of prescribing antihypertensive drugs at discharge were found as 35% and 41% in these two groups. What we inferred from these results was that these patients were in need of a long and a continuing medical support.

The presence of preeclampsia has been linked with poor perinatal outcomes such as IUGR, low birth weight, low Apgar score at 5<sup>th</sup> min, increased requirement for NICU stay, and neonatal deaths. Latest studies have reported higher rates of admission to NICU had among babies born to women with preeclampsia. Increasing number of premature deliveries in preeclampsia is the most important reason for the requirement for hospitalization in NICU. But, adverse neonatal outcomes are not limited to preterm delivery in preeclampsia. Neonatal thrombocytopenia, neutropenia and bronchopulmonary dysplasia could be accompanied by maternal preeclampsia as well as others that are mentioned above<sup>20,27-29</sup>. In this study, admission to NICU has the highest percentage among. Also IUGR, low birth weight babies and neonatal mortality were more frequently seen among preeclamptic women with adverse perinatal outcomes as emphasized in several studies<sup>30-32</sup>.

Preeclampsia, particularly early-onset preeclampsia and severe preeclampsia are associated with adverse maternal and neonatal outcomes. Also, in the light of previous studies; preeclampsia, and early-onset and severe preeclampsia subgroups are associated with long term cardiovascular risk. To identify the population of women with preeclampsia in secondary or tertiary health centres and to provide their integration with primary healthcare providers are necessary issues for the early detection of cardiovascular diseases.

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