

The Obstetric Outcomes in Women with Preeclampsia and Superimposed Preeclampsia

Preeklampsi ve Süperimpoze Preeklampsi Olgularında Obstetrik Sonuçlar

Arife ŞİMŞEK,^a
Seyfettin ULUDAĞ,^a
Abdullah TÜTEN,^a
Sezin ULUDAĞ^a

^aDepartment of Obstetric and Gynecology,
İstanbul University
Cerrahpaşa Faculty of Medicine,
İstanbul

Geliş Tarihi/Received: 04.11.2016
Kabul Tarihi/Accepted: 07.02.2017

Yazışma Adresi/Correspondence:
Arife ŞİMŞEK
İstanbul University
Cerrahpaşa Faculty of Medicine,
Department of Obstetric and Gynecology,
İstanbul,
TURKEY/TÜRKİYE
draksimsek@yahoo.com.tr

*This manuscript has been presented in the form
of an abstract for the 15th World Congress in
Fetal Medicine, 26-30 June 2016, Spain.*

ABSTRACT Objective: This study was performed to compare the obstetric outcomes between preeclampsia and superimposed preeclampsia cases. **Material and Methods:** This retrospective study included 500 women with preeclampsia and 101 women with superimposed preeclampsia who delivered in a tertiary care center. Clinical findings, maternal and perinatal outcomes were compared between the two groups. **Results:** In cases of preeclampsia, antenatal, perinatal, neonatal mortality rates were 13.4%, 17.9%, 5.1% respectively. The rate of cases which mother's life at risk was 30.2%. The antenatal, perinatal and neonatal mortality rates were 12.9%, 19.8%, and 8.9%, respectively, in cases of superimposed preeclampsia and the rate of cases where mother's life was at risk was 25.7%. There was no significant difference between the two groups in terms of time of onset of the symptoms ($p = 0.669$), mean birth week ($p = 0.410$) and birth weight ($p = 0.340$). Rates of intrauterine growth retardation ($p = 0.434$), early and late neonatal loss ($p = 0.111$, $p = 0.848$) and stillbirth ($p = 0.887$) did not differ between the groups. Although maternal deaths and maternal near miss cases were not significantly different between the two groups ($p = 0.370$), the rate of complication with eclampsia in preeclampsia cases was higher than that of superimposed preeclampsia cases ($p = 0.001$). **Conclusion:** Preeclampsia and superimposed preeclampsia have similar obstetric outcomes. Further research is needed to elucidate the mechanisms underlying eclampsia in preeclampsia cases.

Keywords: Pre-eclampsia; perinatal mortality; maternal mortality; pregnancy outcome

ÖZET Amaç: Bu çalışma preeklampsi ve süperimpoze preeklampsi olgularının obstetrik sonuçlarını karşılaştırmak amacıyla gerçekleştirilmiştir. **Gereç ve Yöntemler:** Bu çalışmaya üçüncü basamak bir sağlık biriminde doğumları gerçekleştirilen 500 preeklampsi ve 101 süperimpoze preeklampsi gebeleri dahil edildi. Hasta dosyaları geriye dönük olarak incelendi. İki grup arasında klinik bulgular, maternal ve perinatal sonuçlar karşılaştırıldı. **Bulgular:** Preeklampsi olgularında antenatal, perinatal ve neonatal mortalite oranları sırasıyla %13.4, %17.9, %5.1, anne hayatının risk altında olduğu olguların oranı %30.2 idi. Süperimpoze preeklampsi olgularında antenatal, perinatal ve neonatal mortalite oranları sırasıyla %12.9, %19.8, %8.9, anne hayatının risk altında olduğu olguların oranı %25.7 idi. Semptomların ortaya çıkış zamanı ($p = 0.669$), ortalama doğum haftası ($p = 0.410$) ve doğum kilosu ($p = 0.340$) açısından iki grup arasında anlamlı fark saptanmadı. İntrauterin büyüme geriliği ($p = 0.434$), erken ve geç neonatal kayıp ($p = 0.111$, $p = 0.848$) ve ölü doğum ($p = 0.887$) oranları gruplar arasında farklı değildi. Annenin öldüğü ya da ölümden döndüğü olgular her iki grup arasında anlamlı fark göstermemekle birlikte ($p = 0.370$), preeklampsi olgularında eklampsi ile komplike olma oranı süperimpoze preeklampsi olgularına göre daha yüksek idi ($p = 0.001$). **Sonuç:** Preeklampsi ve süperimpoze preeklampsi olguları benzer obstetrik sonuçlara sahiptir. Eklampsinin preeklampsi olgularda daha fazla görülmesinin altında yatan mekanizmaları aydınlatmak için ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Pre-eklampsi; perinatal mortalite; anne ölümü; gebelik sonucu

There is an increasing tendency towards delayed childbearing. The risk of hypertensive disorders in pregnancy increases gradually with age.¹ The hypothesis that superimposed preeclampsia results in worse

pregnancy outcomes than preeclampsia continues to be the subject of debate.² Superimposed preeclampsia is a severe form of the disease. Besides, aggressive management of superimposed preeclampsia has been thought to cause increased risks of intervention-related events.²

This study was performed to identify and compare the maternal and fetal outcomes of the patients having preeclampsia and superimposed preeclampsia diagnosis.

MATERIAL AND METHODS

This retrospective study included 601 women with preeclampsia who delivered in a tertiary care center over a ten year-period. Of 601 women, 500 had preeclampsia and 101 had superimposed preeclampsia. Clinical findings, maternal and perinatal outcomes were compared between the two groups.

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, and an approval was obtained from the Human Ethics Committee of the Institution. Preeclampsia and features of severity were defined according to criteria provided by American College of Obstetricians and Gynecologists (ACOG) in 2013; blood pressure elevation after 20 weeks of gestation with proteinuria or any of the severe features of preeclampsia.³ Chronic hypertension was defined as systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg that antedates pregnancy or is present before the 20th week of pregnancy (on at least two occasions). Patients with both primary and secondary hypertension were included. Superimposed preeclampsia was defined by the new onset of either proteinuria or end-organ dysfunction after 20 weeks of gestation in a woman with chronic hypertension. For women with chronic hypertension who have proteinuria prior to or in early pregnancy, superimposed preeclampsia was defined by worsening or resistant hypertension (especially acutely) in the last half of pregnancy or development of signs/symptoms of the severe spectrum of the disease. Diagnostic criteria for severe preeclampsia were: 1-Hypertension: systolic >160 mmHg or diastolic >110 mmHg on two occasions at least 4 hours apart while the

patient is on bed rest (unless antihypertensive therapy is initiated before this time). 2- Thrombocytopenia (platelet count $<100,000$ /microliter). 3- Impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for alternative diagnosis, or both. 4- New development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dl, or doubling of serum creatinine in the absence of other renal diseases). 5- Pulmonary edema. 6- New-onset cerebral or visual disturbances.³

Gestational age was determined according to the last menstrual period and/or to the crown-rump length at first trimester ultrasound. Intrauterine growth restriction (IUGR) was defined as a birth weight $<10^{\text{th}}$ percentile for gestational age. Perinatal mortality was defined as the number of stillbirths and deaths in the first week of life. Maternal deaths and maternal near-miss cases were defined in respect of World Health Organization/ International Classification of Diseases-10 (WHO/ICD-10) definitions.⁴ Only maternal deaths and maternal near-miss cases caused by hypertension were accepted as maternal deaths and maternal near miss cases. The demographic and clinical characteristics of the study groups were recorded at hospital admission and presented in Table 1.

All women with severe symptoms were hospitalized. Women without severe symptoms were also hospitalized if they had fetal indications such as non-reassuring fetal status according to cardiotocography and umbilical artery Doppler assessment with an absent or reversed end-diastolic flow, IUGR/oligohydramnios, fetal demise, etc. Magnesium sulfate for eclamptic seizure prophylaxis and acute antihypertensive therapy were administered to women with severe preeclampsia when it is deemed necessary within the indications. Antenatal steroid was administered for fetal lung maturity to all pregnancies less than 34 weeks of gestational age. Indications for delivery were severe preeclampsia, uncontrollable blood pressure, diagnosis of HELLP (Hemolysis, elevated liver enzymes, and low platelets) syndrome, eclamptic

TABLE 1: Demographic and clinical characteristics of the women with preeclampsia and superimposed preeclampsia.

	Preeclampsia n= 500 (%)	Superimposed preeclampsia n= 101 (%)	p value
Maternal age (year)	28.3 ± 6	32.1 ± 6.5	0.000
Nulliparity	279 (55.8)	36 (35.6)	0.000
Prior term delivery	196 (39.2)	58 (57.4)	0.001
History of preterm delivery	28 (5.6)	13 (12.9)	0.008
History of immature delivery	13 (2.6)	3 (3)	0.833
History of stillbirth	26 (5.2)	9 (8.9)	0.146
History of abortion			0.232
Before the 12 th week of gestation	80 (16)	21 (20.8)	0.240
After the 12 th week of gestation	13 (2.6)	3 (3)	0.833
History of elective abortion	58 (11.6)	19 (18.8)	0.048
History of preeclampsia/eclampsia	21 (4.2)	9 (8.9)	0.047
History of cesarean delivery	37 (7.4)	16 (15.8)	0.006
Smoking	33 (6.6)	5 (5)	0.534
Systemic disease			
Diabetes Mellitus	17 (3.4)	12 (11.9)	0.000
Antenatal care	354 (70.8)	84 (83.2)	0.011
Gender of fetus			0.044
Male	257 (51.4)	63 (62.4)	
Female	243 (48.6)	38 (37.6)	
Highest systolic pressure	167 ± 23.23	172 ± 27.7	0.784
Highest diastolic pressure	106.3 ± 14.3	106.6 ± 16	0.922
Mean arterial pressure	126.6 ± 16.1	128.6 ± 18.9	0.876
Beginning of the symptoms			0.669
Before the 34 th week of gestation	226(45.2)	48 (47.5)	
After the 34 th week of gestation	274(54.8)	53 (52.5)	

For those variables not distributed normally, two groups were compared with Mann–Whitney U Test. Chi-square test for independence was used for the analysis of categorical variables.

seizures or non-reassuring fetal status according to cardiotocography and umbilical artery Doppler assessment with an absent or reversed end-diastolic flow, fetal demise. Spontaneous labor was also an indication for delivery.

Statistical Package of the Social Sciences (SPSS) 17.0 software (SPSS Inc., Chicago, USA) was used for the statistical analyses. Data were expressed as n (%) and mean with standard deviation. Quantitative variables were tested for normal distribution (by Kolmogorov–Smirnov Test) and homogeneity (by One-Way Anova Test). For those variables not distributed normally, two groups were compared with Mann–Whitney U Test. Chi-square test for independence was used for the analysis of categorical variables. A p value <0.05 was considered as significant.

RESULTS

In preeclampsia cases, the mean maternal age was 28.3 ± 6 years, mean gestational week at delivery was 33.9 ± 3.9 weeks, mean birth weight was 1971 ± 893 g. Rates of antenatal, perinatal, neonatal mortality were, 13.4%, 17.9% and 5.1% respectively. Maternal life threatening conditions (maternal mortality + maternal near miss) were existing in 30.2% of the cases. In superimposed preeclampsia cases, the mean maternal age was 32.1 ± 6.5 years, mean gestational week at delivery was 33.4 ± 4.2 weeks, mean birth weight was 1891 ± 951 g. Rates of antenatal, perinatal, neonatal mortality were, 12.9%, 19.8% and 8.9% respectively. Maternal life threatening conditions were existing in 25.7% of the patients (Table 1 and Table 2).

TABLE 2: The obstetric outcomes in women with preeclampsia and superimposed preeclampsia.

	Preeclampsia n= 500 (%)	Superimposed preeclampsia n= 101 (%)	p value
Gestational week at delivery	33.9 ± 3.9	33.4 ± 4.2	0.410
Birth before the 34 th week of gestation	226 (45.2)	46 (45.5)	0.949
Birth before the 37 th week of gestation	357 (71.4)	71 (70.3)	0.823
Birth weight (g)	1971 ± 893	1891 ± 951	0.340
Stillbirth	67 (13.4)	13 (12.9)	0.887
Early neonatal death	21 (4.3)	8 (7.9)	0.111
Perinatal mortality	88 (17.9)	20 (19.8)	0.599
Late neonatal death	4 (0.8)	1 (1)	0.848
Neonatal mortality	25 (5.1)	9 (8.9)	0.121
IUGR	194 (38.8)	35 (34.7)	0.434
Maternal mortality and maternal near-miss cases	151 (30.2)	26 (25.7)	0.370
Eclampsia	71 (14.2)	2 (2)	0.001
HELLP syndrome	72 (14.4)	16 (15.8)	0.709
Severe symptoms	384 (76.8)	74 (73.3)	0.447
Cesarean section rate	353 (70.6)	63 (62.4)	0.102

For those variables not distributed normally, two groups were compared with Mann–Whitney U Test. Chi-square test for independence was used for the analysis of categorical variables. IUGR: Intrauterine growth retardation; HELLP: Hemolysis, elevated liver enzymes, and low platelets.

There were 5 maternal deaths. Deaths were occurred due to intraventricular hemorrhage (IVH) in 2 women with eclampsia, multiple organ failure (MOF) in a woman with HELLP syndrome, sub-arachnoid hemorrhage (SAH) and MOF in a woman with HELLP syndrome and eclampsia, hypertensive encephalopathy and acute renal failure (ARF) in a woman with HELLP syndrome and eclampsia.

Incidence of nulliparity was significantly higher in women with preeclampsia compared to ones with superimposed preeclampsia ($p=0.000$). The mean maternal age ($p=0.000$), previous term and preterm birth rates ($p=0.001$, $p=0.008$), history of elective abortion ($p=0.048$), history of cesarean delivery ($p=0.006$), history of preeclampsia/eclampsia ($p=0.047$), accompanying systemic diseases such as diabetes mellitus ($p=0.000$), patients with antenatal care ($p=0.011$) were significantly higher in women with superimposed preeclampsia. Male predominance was also seen in women with superimposed preeclampsia ($p=0.044$) (Table 1). The onset of the symptoms of the disease ($p=0.669$), severity of the symptoms ($p=0.447$), cesarean section rate ($p=0.102$), mean gestational week at delivery ($p=0.410$) and birth weight ($p=0.340$) were

not significantly different between the two groups (Table 1 and Table 2). There were not significant differences in incidences of IUGR ($p=0.434$), stillbirths ($p=0.887$), early and late neonatal deaths ($p=0.111$, $p=0.848$). Although maternal deaths and maternal near miss cases were not significantly different between the two groups ($p=0.370$), complication of eclampsia was significantly higher in women with preeclampsia ($p=0.001$) (Table 2).

DISCUSSION

The risk of hypertensive disorders in pregnancy increases gradually with advancing maternal age and underlying diseases. As expected, in superimposed preeclampsia group, maternal age, parity and systemic diseases such as diabetes mellitus were more frequent when compared with preeclampsia group. These results were similar to the findings of Tuuli et al. Unlike Tuuli et al, we did not find a significant difference between the two groups in terms of smoking.² There are conflicting reports in the literature concerning the relationship between smoking and risk of preeclampsia in chronic hypertension. Chappell et al. found that smoking was an independent risk factor for superimposed preeclampsia, while others did not find any relation.⁵⁻⁷

Although Tuuli et al. did not find significant difference between the groups in terms of fetal gender, we found male predominance in women with superimposed preeclampsia.² We don't know whether that's a coincidence. Further research is needed to identify the role of fetal gender in women with superimposed preeclampsia.

Tuuli et al. revealed that women with superimposed preeclampsia have significantly higher risk of preterm delivery at 34 weeks of gestation (17.3% vs 8.7%), preterm delivery at 37 weeks of gestation (43.8% vs 27.8%) and cesarean delivery (46.2% vs 36.3%), when compared with preeclamptic women.² Roberts et al. also found increased risk of cesarean delivery in women with superimposed preeclampsia compared with preeclampsia group.⁸ Those two studies did not declare any difference in IUGR and stillbirth rates between the two groups.^{2,8} Similar to these studies, we did not find any difference in IUGR and stillbirth rates between the two groups. As well as, no statistically significant difference was shown in rates of cesarean section, preterm delivery at 34 weeks of gestation and preterm delivery at 37 weeks of gestation in our cases. Tuuli et al. reported that superimposed preeclampsia have increased risks of intervention-related events compared to women with preeclampsia. Although there was not conclusive evidence, they concluded that superimposed preeclampsia tends to occur earlier in pregnancy and was a more severe condition.² However, we found that onset of the symptoms and incidence of severity was not different between the two groups. Furthermore, eclampsia was more common in women with preeclampsia (2% vs 14.2%) in contrast to study conducted by Tuuli et al. (0.34% vs 0.30%). These differences can be attributed partially to the inclusion criteria and partially to the differences in the management regarding the timing of delivery. Vigil-De Gracia et al. stated that eclampsia was not detected in women with superimposed preeclampsia suggesting different pathophysiological abnormalities leading to development of eclampsia in women with or without chronic hypertension.⁹ The results of this study reinforced the hypothesis of Vigil-De Gracia et al.

Similar to our results; Vigil-De Gracia et al. did not find any difference in preterm delivery at 37 weeks of gestation between the groups. They also suggested that perinatal outcomes after expectant management were not different in women with superimposed preeclampsia compared to severe preeclampsia.¹⁰ In addition to these findings, we did not find significant differences in frequencies of neonatal and maternal deaths and maternal near miss cases between the two groups.

The timing of delivery is the most important management decision in both preeclampsia and superimposed preeclampsia. ACOG stated that previous studies focusing on the expectant management of preeclampsia typically excluded the subgroup of women with superimposed preeclampsia. ACOG concluded that there were higher risk of intervention-related events and morbidity among women with superimposed preeclampsia, thus raising the issue of potentially unnecessary iatrogenic preterm births with superimposed preeclampsia.³ They did not state any data to specifically address the management of superimposed preeclampsia, therefore evidence from the preeclampsia literature have to be used to guide management. According to ACOG guidelines, superimposed preeclampsia with severe features should be managed in a manner similar to severe preeclampsia and superimposed preeclampsia without severe features should be managed in a manner similar to preeclampsia without severe features.³

This study has some limitations. Because its retrospective nature it was limited by the records of patients. In cases without antenatal care, gestational ages at the onset of the disease were estimated based on hospital admission. We were not able to know exact onset time of the disease, especially in women with severe symptoms, if they were not admitted before. Because inadequate postpartum follow-up, women with chronic hypertension defined according to the persisting hypertension longer than 12 weeks postpartum mistakenly might be classified as preeclampsia instead of superimposed preeclampsia.

As a conclusion, despite initial fears to the contrary, superimposed preeclampsia does not re-

sult in worse outcomes than preeclampsia, if it is managed in a manner similar to preeclampsia. This article reported outcomes of preeclampsia and superimposed preeclampsia separately. It supports ACOG's recommendations. We hope it will encourage researchers to identify why eclampsia develops more commonly in preeclampsia.

Acknowledgements

Authors declare no any acknowledgement.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

All authors planned to produce this study, analyzed the data, reviewed the literature to design it and revised it for final approval of the version to be published.

REFERENCES

1. Liu X, Ruan Y, Liu Y, Zhang W. [Relationship between maternal age and hypertensive disorders in pregnancy]. *Zhonghua Yi Xue Za Zhi* 2015;95(1):19-22.
2. Tuuli MG, Rampersad R, Stamilio D, Macones G, Odibo AO. Perinatal outcomes in women with preeclampsia and superimposed preeclampsia: do they differ? *Am J Obstet Gynecol* 2011;204(6):508.e1-7.
3. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013; 122(5):1122-31.
4. Report on the World Health Organization Working Group on the Classification of Maternal Deaths and Severe Maternal Morbidities. Geneva: World Health Organization; 2009; 87: 733-804.
5. Chappell LC, Enye S, Seed P, Briley AL, Poston L, Shennan AH. Adverse perinatal outcomes and risk factors for preeclampsia in women with chronic hypertension: a prospective study. *Hypertension* 2008;51(4): 1002-9.
6. Lecarpentier E, Tsatsaris V, Goffinet F, Cabrol D, Sibai B, Haddad B. Risk factors of superimposed preeclampsia in women with essential chronic hypertension treated before pregnancy. *PLoS One* 2013;8(5): e62140.
7. Sibai BM, Koch MA, Freire S, Pinto e Silva JL, Rudge MV, Martins-Costa S, et al. The impact of prior preeclampsia on the risk of superimposed preeclampsia and other adverse pregnancy outcomes in patients with chronic hypertension. *Am J Obstet Gynecol* 2011; 204(4):345.e1-6.
8. Roberts CL, Algert CS, Morris JM, Ford JB, Henderson-Smart DJ. Hypertensive disorders in pregnancy: a population-based study. *Med J Aust* 2005;182(7):332-5.
9. Vigil-De Gracia P, Montufar-Rueda C, Smith A. Pregnancy and severe chronic hypertension: maternal outcome. *Hypertens Pregnancy* 2004;23(3):285-93.
10. Vigil-De Gracia P, Montufar-Rueda C, Ruiz J. Expectant management of severe preeclampsia and preeclampsia superimposed on chronic hypertension between 24 and 34 weeks' gestation. *Eur J Obstet Gynecol Reprod Biol* 2003;107(1):24-7.