Comparison of Pregnancy Outcomes of Women with and Without Hypertension at the Latent Phase of Labor Who Were Under Medical Care for Preeclampsia

Resul KARAKUS1, Cetin KILICCI1, Enis OZKAYA1, Ezgi DARICI1, Onder TOSUN1, Sultan Seren KARAKUS1, Ali ARAS1
İstanbul, Turkey

ABSTRACT

OBJECTIVE: We explored the association between hypertension (>140/90) at the latent phase of labor (resistant hypertension) and the subsequent development of major maternal complications or adverse infant outcomes in women with preeclampsia under medical care.

STUDY DESIGN: We drew data from 824 women who were under follow-up at the Department of Perinatology of Health Sciences University Zeynep Kamil Women and Children's Health Training and Research Hospital with a diagnosis of preeclampsia. Women with and without resistant hypertension were compared in terms of major maternal complications and adverse infant outcomes.

RESULTS: Mean age and body mass index were similar between the two groups (p>0.05). The rate of preeclamptic complaints was significantly higher in groups with resistant hypertension (90.1% vs. 67.2%, p<0.05). Proteinuria was more frequent in the resistant hypertension group (78.7% vs. 66.8%, p<0.001). The newborn intensive care unit admission rate was significantly higher in the group with resistant hypertension (65.6% vs. 45.9%, p<0.001). Gestational age at delivery was significantly lower in the group with resistant hypertension compared to the normotensive group (34.6 vs. 32.9 weeks, p<0.001). There was a significant difference between the two groups in terms of the rate of preterm delivery (78.5% vs. 66.7%, p=0.04).

CONCLUSION: Resistant hypertension is associated with a higher rate of preeclamptic symptoms during labor and newborn intensive care unit admission.

Keywords: Hypertension, Pregnancy, Labor

Gynecol Obstet Reprod Med 2021; (Article In Press)

Introduction

Hypertensive complications of pregnancy have a wide range of presentations; therefore, it is accepted as a clinical syndrome (1). Clinical presentations include hypertension, proteinuria, platelet consumption, peripheral vasoconstriction, and hypovolemia, which have been considered to be secondary to placental insufficiency and generalized endothelial dysfunction (2,3). The main goal of managing preeclampsia is to keep the woman's blood pressure within the normal range with anti-hypertensive and to prevent the development of complications such as eclampsia. Delivery of the fetus and placenta is the only definitive treatment for preeclampsia. Treatment is largely symptomatic with monitoring of the development of complications. When blood pressure rises above a certain level, it can directly lead to vascular damage, which may result in life-threatening complications such as renal failure, stroke, and fetal distress (4). The primary goal of preeclampsia treatment should always be the safety of the mother. Although birth is always appropriate for the mother,
it may not be suitable for the fetus due to extreme prematurity. The decision between delivery and conservative management depends on fetal gestational age, maternal and fetal status during the initial evaluation, presence of labor or fetal membrane rupture, and the level of newborn and maternal services available. It is important to emphasize that hypertension is directly related to one of the most serious consequences for the mother, which may lead to focal neurological events including convulsions, cortical blindness, and even cerebral involvement such as cerebral hemorrhage, therefore the benefits of acute pharmacological control of severe hypertension before delivery are generally accepted (5). On the other hand, the significance of uncontrolled hypertension and strict blood pressure control during labor is still controversial.

We explored the association between hypertension at the latent phase of labor (resistant hypertension) and the subsequent development of major maternal complications or adverse infant outcomes in women with hypertensive complications of pregnancy under medical care.

### Material and method

We drew data from 824 women who were under follow-up at the Department of Health Sciences University Zeynep Kamil Women and Children’s Health Training and Research Hospital with a diagnosis of preeclampsia. Women with and without resistant hypertension were compared in terms of major maternal complications and adverse infant outcomes. The study protocol was approved by the institutional ethics committee (2017/30) and the study was conducted under the Declaration of Helsinki.

Inclusion criteria were as follows; hypertension with or without proteinuria of ≥300 mg per 24 h or thrombocytopenia and if there is Hypertension plus proteinuria (i.e. in renal disease or class F Diabetes), worsening severe hypertension plus proteinuria and either new onset of symptoms, thrombocytopenia, or elevated liver enzymes. Singleton pregnancy with no previous cesarean delivery, age 18 years or older.

Exclusion criteria were as follows; eclampsia complicated by acute renal failure, HELLP syndrome (hemolysis, high liver enzymes, and low platelet count) or pulmonary edema, concomitant maternal diagnosis of renal disease and/or seizure disorder before labor starts, contraindication to Magnesium sulfate (MgSO4 (e.g. drug hypersensitivity, myasthenia gravis, anuria or oliguria), any other anticonvulsant intake, age <17 years.

Participants were divided into two groups as a group with hypertension ≥140/90 mmHg (resistant hypertension) and a group with blood pressure <140/90 mmHg at the latent phase of labor.

Preeclampsia was diagnosed in women with a new-onset
was more frequent in the resistant hypertension group (78.7% vs. 66.8%, p<0.001). The liver enzymes were found to be significantly increased in the persistent hypertensive group when compared to control (Table II).

**Table I.** Comparison of some demographic characteristics of groups with and without hypertension at the latent phase of labor

|          | N  | Mean  | Std. Deviation | p     |
|----------|----|-------|----------------|-------|
| Age (Years) | NT  | 542   | 30.057         | 6.3   | 0.109 |
|          | HT  | 282   | 29.330         | 5.9   |        |
| BMI (Kg/m²) | NT  | 542   | 30.788         | 5.5   | 0.614 |
|          | HT  | 282   | 30.996         | 5.8   |        |

NT: Normotensive, HT: Hypertensive, BMI: Body mass index

**Table II.** Comparison of some serum biochemical analysis results of groups with and without hypertension at the latent phase of labor

|          | Mean | Std. Deviation | p     |
|----------|------|----------------|-------|
| BUN (mg/dL) | NT  | 10.04          | 3.8   |       |
|          | HT  | 10.5           | 3.9   | 0.239 |
| Creatinine (mg/dL) | NT  | 1.5            | 0.9   |       |
|          | HT  | 1.6            | 0.9   | 0.861 |
| ALT (mg/dL) | NT  | 34.4           | 4.2   |       |
|          | HT  | 44.5           | 5.1   | 0.003 |
| AST (mg/dL) | NT  | 37.5           | 4.2   |       |
|          | HT  | 46.1           | 5.3   | 0.013 |
| LDH (U/L) | NT  | 256.1          | 19.7  |       |
|          | HT  | 274.2          | 24.7  | 0.253 |

NT: Normotensive, HT: Hypertensive, BUN: Blood urea nitrogen, ALT: Alanine transferase, AST: Aspartate transferase, LDH: Lactate dehydrogenase

Approximately half of the pregnant women were required to undergo labor induction (54.2% vs. 48.9%, p=0.148). Eclamptic seizures were observed in 3.5% of cases in the groups with resistant hypertension; whereas there were 12 (2.2%) cases in the group with normotension (p=0.260). Antihypertensive medication was needed in 94% of cases in the hypertensive groups; whereas 58.9% cases in the group with normotension (p<0.001) before labor. MgSO4 infusion was indicated in 95.4% of cases in the group with hypertension; whereas 70.1% of cases in the group with normotension (p=0.001) during labor. The newborn intensive care unit admission rate was significantly higher in the group with resistant hypertension compared to the normotensive (65.6% vs. 45.9%, p<0.001). Gestational age at delivery was significantly lower in the group with persistent hypertension (2467g vs. 2104g, p<0.001). The multivariate regression model MgSO4 therapy, preterm delivery, presence of preeclamptic symptoms, proteinuria, and resistant hypertension at the latent phase of labor were included in the model, prematurity was found to be a significant factor for newborn intensive care unit admission after adjustment for other confounders [OR:19.5, 95%CI (6.5-58), p<0.001]. No significant difference was determined in terms of the duration of hospital stay between the two groups (3.8 vs. 3.9 days, p=0.525). Again no difference was found between the two groups in terms of first and fifth minutes APGAR scores (p=0.374 and p=0.340, respectively). Cesarean delivery rates were similar between the two groups (79.2% vs. 84.4%, p=0.07).

**Discussion**

In this study, we aimed to explore the association between hypertension at the latent phase of labor and the subsequent development of major maternal complications or adverse infant outcomes in women with hypertensive complications of pregnancy under medical care. Our data analysis revealed that hypertension at the latent phase of labor is associated with a higher rate of preeclamptic symptoms during labor, a higher rate of premature delivery, and newborn intensive care unit admission.

Hypertension in pregnancy is associated with high perinatal morbidity and mortality, especially premature delivery, fetal growth restriction, and hypoxemia due to placental insufficiency. Mortality and morbidity increased on the maternal side and the incidence of cardio and cerebrovascular events and long-term complications have been reported. Most complications are associated with severe preeclampsia (7). Additionally, the previous meta-analysis showed that the presence of chronic hypertension was also associated with a risk of preeclampsia, cesarean delivery, preterm birth, low birth weight, neonatal intensive care admission, and perinatal mortality (8).

Maternal complications are related to the severity of the disease. On the other hand, periodic events are associated with placental insufficiency and prematurity. Therapeutic pregnancy terminations in cases of severe hypertension or fetal distress are the main cause of preterm delivery. On the other hand, in an uncontrolled hypertension scenario, delivery delays put both mother and fetus at risk. Treatment of hypertension in pregnancy has been associated with worse fetal outcomes, such as intrauterine growth restriction and preterm labor (9,10). In these cases, it is not clear whether this poor outcome following antihypertensive medication is related to teratogenicity or decreased blood pressure and following impaired placental perfusion. On the other hand, the hypertensive disease itself may be responsible for placental and fetal deterioration, especially when preeclampsia is present (11,12).
Most guidelines recommend pharmacological treatment in patients with severe hypertension (13-16). In the case of mild or moderate hypertension, treatment targets, as well as treatment, have been questioned (11). In patients with chronic hypertension, the ACOG statement recommends the preservation of drugs initiated before pregnancy to keep systolic blood pressure and diastolic blood pressure between 120/160 mmHg and 80/105 mmHg respectively (13).

More recently, the CHIPS study (17) compared “strict control (target DPB 85 mmHg) versus less strict control (target DPB 100 mmHg)” of blood pressure for perinatal and maternal events. The primary outcome was a loss of a pregnancy or a high level of neonatal survival longer than 48 hours in the first 28 days, and a secondary outcome was severe maternal complications until hospital discharge or the end of the puerperium. It was reported that there was no significant difference in perinatal events between the two groups. Another entity has been introduced in the literature, which is defined to be labor onset hypertension, however, the pathophysiology of labor onset hypertension is still unclear.

Lao et al. suggested that labor onset hypertension represents a late manifestation of the preeclampsia process (18). They reasoned that labor onset hypertension patients had lower blood pressure in pregnancy and were not identified until the intrapartum elevation of blood pressure. However, although the pathophysiology of labor onset hypertension is still unknown, preeclampsia is currently considered to arise from endothelial dysfunction during pregnancy (19-21). This disorder, preeclampsia itself causes fetal disturbances including fetal growth restriction, immaturity of organs, and non-reasurring fetal status via placental dysfunction (21).

In addition to hypertension, another clinical finding that is frequently encountered in cases with preeclampsia is proteinuria, according to the previous studies, 8–10% of eclamptic patients had proteinuria without hypertension, additionally, 50% of women with new-onset proteinuria were shown to develop preeclampsia within 3 weeks (22). Several different related outcomes have been introduced for both proteinuria and hypertension separately, for example; the major threat of hypertension during labor is stroke, which is associated with extremely significant risks for both the mother and child (23). Pregnancy-related strokes were shown to be encountered in 20–25/100,000 deliveries (24) which resulted in a 9–38% maternal mortality rate (23). This subject is further complicated by the labor itself because some significant impacts of labor on systemic tension have been shown. Hypertension was not observed before labor onset in 53% (10/19 cases) of cases of eclampsia during labor (25). Additionally, in another study, it was reported that three out of eight eclamptic episodes occurred during labor (26). Furthermore 27% of eclamptic episodes involved patients who displayed elevated blood pressure at delivery without any prior symptoms of hypertension or proteinuria (27). Several other studies considered hypertension that initially develops during labor to be a physiological change and reported this change to have positive outcomes (28). Further studies suggested that the greater fetal demand and reduced placental blood flow during labor might be the main underlying mechanism of labor onset hypertension (29), which may be accepted to be a compensatory mechanism. Therefore, tension control during labor may deteriorate placental perfusion by interfering with this compensatory mechanism.

All these aforementioned data showed us that both approaches, controlling hypertension or not strictly controlled hypertension during labor, may lead to an unfavorable outcome for the mother or the fetus. Therefore, further clinical assessments seem to be mandatory while determining the target tension during labor.

Acknowledgment: NA
Funding: NA
Conflict of interest: Nothing to declare
Ethic approval: 2017/30
Data availability: Yes
Authors’ contributions: RK: Data collection. CK: Data collection. OT: Data collection. ED: Manuscript preparation. SSK: Data collection. EO: Manuscript preparation, data analysis. AA: Data collection

References
1. Sibai BM. Prevention of preeclampsia: a big disappointment. Am J Obstet Gynecol. 1998;179(5):1275-8. Doi: 10.1016/s0002-9378(98)70146-2.
2. Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol. 1999;180(2 Pt 1):499-506. Doi: 10.1016/s0002-9378(99)70239-5.
3. Harlow FH, Brown MA. The diversity of diagnoses of preeclampsia. Semin Perinatol. 2009;33(3):130-7. Doi: 10.1053/j.semperi.2009.02.010.
4. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33(3):130-7. Doi: 10.1053/j.semperi.2009.02.010.
5. Dekker GA. Management of preeclampsia. Pregnancy Hypertens. 2014;4(3):246-7. Doi: 10.1016/j.preghy.2014.04.021.
6. Mandel HC. Duration of oxytocin and rupture of the membranes before diagnosing a failed induction of labor. Obstet Gynecol. 2016;128(5):1183. Doi: 10.1097/AOG.0000000000001729.
7. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG. 2014;121 Suppl
8. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ. 2014;348:g2301. Doi: 10.1136/bmj.g2301.

9. Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. Hypertension. 2012;60(2):444-50. Doi: 10.1161/Hypertensionaha.112.196352.

10. Bateman BT, Huybrechts KF, Fischer MA, Seely EW, Ecker JL, Oberg AS, Franklin JM, Mogun H, Hernandez-Diaz S. Chronic hypertension in pregnancy and the risk of congenital malformations: a cohort study. Am J Obstet Gynecol. 2015;212(3):337.e1-14. Doi: 10.1016/j.ajog.2014.09.031.

11. Brown CM, Garovic VD. Drug treatment of hypertension in pregnancy. Drugs. 2014;74(3):283-96. Doi: 10.1007/s40265-014-0187-7.

12. Moser M, Brown CM, Rose CH, Garovic VD. Hypertension in pregnancy: is it time for a new approach to treatment? J Hypertens. 2012;30(6):1092-100. Doi: 10.1097/HJH.0b013e3283536319.

13. ACOG. 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.

14. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA, et al. The SOMANZ Guidelines for the Management of Hypertensive Disorders of Pregnancy 2014. Aust N Z J Obstet Gynaecol. 2015;55(1):11-6. Doi: 10.1111/ajo.12253.

15. 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. 2014;4(2):97-104. Doi: 10.1016/j.preghy.2014.02.001.

16. Royal College of Obstetricians and Gynaecologists, The Royal College of Midwives. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. NICE Clin Guidel. 2011;1-295.

17. Magee LA, Singer J, von Dadelszen P; CHIPS Study Group. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med. 2015;372(24):2367-8. Doi: 10.1056/NEJMc1503870.

18. Lao TT, Chin RK. Pregnancy outcome in women with labor-onset hypertension. Similar outcome between labor-onset hypertension and preeclampsia. Gynecol Obstet Invest. 1990;29(3):173-6. Doi: 10.1159/000293370.

19. Eiland E, Nzerue C, Faulkner M. Preeclampsia 2012. J Pregnancy. 2012;2012:586578. Doi: 10.1155/2012/586578.

20. Wolfe DS, Williams SF, Ross MG, Beall MH, Apuzzo JJ. Does preeclampsia predict the risk of late postpartum eclampsia? AJP Rep. 2013;3(1):13-6. Doi: 10.1055/s-0032-1329127.

21. Al-Jameil N, Aziz Khan F, Fareed Khan M, Tabassum H. A brief overview of preeclampsia. J Clin Med Res. 2014;6(1):1-7. Doi: 10.4021/jocmr1682w.

22. Morikawa M, Yamada T, Yamada T, Cho K, Yamada H, Sakuragi N, et al. Pregnancy outcome of women who developed proteinuria in the absence of hypertension after mid-gestation. J Perinat Med. 2008;36(5):419-24. Doi: 10.1515/JPM.2008.062.

23. Di Carlo A, Lamassa M, Consoli D, Inzitari D, Gall SL, Donnan G, et al. Sex differences in presentation, severity, and management of stroke in a population-based study. Neurology. 2010;75(7):670-1; author reply 671. Doi: 10.1212/WNL.0b013e3181ec68b5.

24. Kittner SJ, Stern BJ, Feesser BR, Hebel R, Nagey DA, Buchholz DW, et al. Pregnancy and the risk of stroke. N Engl J Med. 1996;335(11):768-74. Doi: 10.1056/NEJM199609123351102.

25. Lao TT, Chin RK, Leung BF. Labour-related eclampsia. Eur J Obstet Gynecol Reprod Biol. 1987;26(2):97-104. Doi: 10.1016/0028-2243(87)90003-8.

26. Kojima R, Matsuura A, Yamamoto T, Watanabe K, Suzuki Y. Characteristic changes in systolic blood pressure in eclampsia. Hypertens Res Preg. 2014;2:1-5.

27. Zhang J, Klebanoff MA, Roberts JM. Prediction of adverse outcomes by common definitions of hypertension in pregnancy. Obstet Gynecol. 2001;97(2):261-7. Doi: 10.1016/s0029-7844(00)01125-x.

28. Long PA, Oats JN, Beischer NA. Labour-onset preeclampsia. Aust N Z J Obstet Gynaecol. 1981;21(1):16-9. Doi: 10.1111/j.1479-828x.1981.tb00117.x.