



## A POLYMORPHISM IN HAPTOGLOBIN MAY AFFECT THE LEVEL OF RISKS ASSOCIATED WITH CARDIOVASCULAR DISEASE BIOMARKERS IN PREVIOUSLY HYPERTENSIVE PREGNANT WOMEN

Dr. Bhavya G\*

\*Assistant Professor, Sri lakshminarayana Institute of medical sciences Puducherry, India.

### ABSTRACT

Cardiovascular disease risk is increased when someone suffers from preeclampsia (PE). Inflammatory, anti-oxidant, and angiogenic properties of HP genotype may modulate the risk of PE through Peripheral tissues and hepatocytes, which synthesize HP as a result of oxidative stress. Among 352 women age 2-16, we conducted a prospective study old, of whom 165 had experienced PE in the past. As part of our study, we examined demographic, anthropometric, and hemodynamic markers including as well as liver function tests (AST and ALT), lipid profiles (total LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and apolipoprotein A and B), we also evaluate C-reactive protein (CRP), myeloperoxidase (MPO), nitric oxide metabolites (total and nitrites), and CRP (C-reactive protein) levels. Additionally, we investigate the relationship between All these biomarkers are associated with Hp genetic polymorphisms and their influence on PE and the prognosis of its remote cardiovascular disease. Hp 1/2 variants may modulate the variation of biomarkers associated with preeclamptic events (MPO, nitrites, and ALT), which was observed previously in hypertensive and normotensive women with preeclampsia. Women premenopausal with a Heart disease may be more prevalent in people with PE history when combined with these biomarkers.

**Key words: -**

Access this article online

Home page:

<http://www.mcmed.us/journal/ajomr>

Quick Response code



Received: 14.12.17

Revised: 09.01.18

Accepted: 11.02.18

### INTRODUCTION

The most common pregnancy complication is hypertension in mothers. Hypertension during pregnancy may take several forms, such as preeclampsia, eclampsia, chronic hypertension, or preeclampsia causing chronic hypertension as well as gestational hypertension [1]. A number of diseases can be attributed to inflammation and oxidative stress arterial hypertension. The risk of cardiovascular disease during pregnancy may be affected by preeclampsia and other forms of hypertensive conditions during pregnancy [2, 3].

Preeclampsia is Hypertension in pregnant women is associated with this factor and atherosclerosis, according to a number of authors [2, 3]. In pregnancy-predisposed hypertensive women may develop hypertension in the future due to an association between inflammation and hypertension is detected by biomarkers. As a Hepatocyte and peripheral tissue glycoproteins synthesized in the blood, haptoglobin (Hp) scavenges Modulates cardiovascular risk by increasing free hemoglobin depending on their genotypes by having antioxidant and anti-inflammatory properties [6, 7]. Neutrophils, for instance, are cells involved in inflammatory processes and

Corresponding Author:

Dr. Bhavya G

express the Hp gene predominantly in their bodies [8]. Protein CD163 attaches strongly to circulating monocytes (M2 type), Liver Kupffer cells and resident macrophages (type M2), causing pronounced anti-inflammatory effects [9–11]. CD163, Hp, and HO-1 participate in this pathway, which are strongly induced in cells either This can occur directly or indirectly through the action of cytokines (IL-6, IL-1), tumor necrosis factors, growth factors (M-CSF), and hormones (catecholamines, steroids, etc.). By preventing in endothelial cells, free radicals are formed and accumulate may play a protective During pregnancy, hypertension plays a significant role, preventing further cardiovascular risks [9, 11, 13]. The anti-inflammatory response of HP is greatly influenced by genetic polymorphisms (Hp 1.1, 2.1, and 2.2); namely, Hp 2.2 has a The Hp phenotype with the lowest antioxidant capacity due to its larger Number of molecules in a molecule, which limits its extravascular Dissipation [6, 7, 14]. The HP/HB ratio is 2.2 has also been shown to scavenge the production of nitric oxide (NO) should be increased in the bloodstream A longer half-life makes Hp 1.1/Hb more effective [7, 15, 16]. As a result of their less pronounced the drug inhibits the synthesis of prostaglandins more than Hp 1.1, they are able to exert a Efficacy against inflammation is lower [6, 17, 18]. While both Hp 2.0 and Hp 2.2 can promote collateral vessel formation, Hp 2.2 has the greatest angiogenic potential in chronic inflammatory processes [19, 20]. It appears that the hydrophobic signal peptide that is located on the A B-chain gene of haptoglobin (Hp), located on chromosome 16 near the cluster of Hp, might explain the association between these proteins and lipoprotein particles (HDL) and membranes. Women with histories of hypertension were evaluated This study examined. A study of the Relations between the two pregnancy/preeclampsia and hypertension phenotypes in the future. As a second objective, we evaluated the relationship between circulating cardiovascular risk biomarkers and blood pressure level and the Hp genetic polymorphism.

## Materials and Methods

### Population sampled

352 women aged 35 to 56 years were studied. Of these, 165 had preeclampsia between 2 and 16 years ago, as per their medical records. The International Society for the Study of Hypertension in Pregnancy (ISSHP) classifies preeclampsia as high blood pressure during pregnancy is diagnosed based on ISSHP criteria [22]. Similarly, to the study group, there was also an age matching between the control and experimental groups within the same hospital. They were interviewed over the phone in the beginning. A research center invitation was extended to them at the same phase of their menstrual cycle to provide samples. The questionnaire also identified Post-pregnancy smokers and drinkers, as well as those who had engaged in unhealthy behaviors.

According to Women with preeclamptic pregnancy (PE), ISSHP [22] pregnant women (NBPP), hypertensive women (HTA), and normotensive women (NBP), were stratified into groups based on criteria set forth by Eurohypertension and Eurocardiology Societies [23].

### A method for detecting haptoglobin polymorphisms

In order to detect the presence of A polyacrylamide gel containing HP (1.1, 2.1, and 2.2). electrophoresis (PAGE) was used to separate plasma phenotypes, and peroxidase by detecting haptoglobin-hemoglobin complexes over the color o-dianisidine, activity was determined.

### Determination of cardiac risk biomarkers in the circulation

ELISA tests were used to determine different biomarkers in the blood, including myeloperoxidase (MPO, ng/mL). Using conventionally standardized methods, NOx and nitrite metabolites, as well as ASL and ALA were determined using the transaminase assays AST and ALT, respectively. Assays for serum lipids, HDL cholesterol, and LDL cholesterol, as well as apolipoprotein A and B, Immunoturbidimetric analyses by ABX Diagnostic, were used for measuring LDL and HDL cholesterol, together with total cholesterol (t-cholesterol, mg/dl). Highton and Hessian, 1984 [26] adapted an immunoenzymatic method for The CRP level in the blood is determined by measuring serum CRP, mg/L.

### Anthropometric parameter measurement and blood pressure measurement

An oscillometric method Blood pressure was measured with this device (BP). In the study, classical measurement instruments were used to determine an individual's body mass index (BMI) and waist circumference (CCM) around their hips and thighs.

### A campaign's success can be estimated

A Kolmogorov Smirnov test was used to detect deviations from normality, and Comparison of means was then performed using appropriate parametric or nonparametric tests. Statistically significant results were also obtained by using Chi-squared tests the Mann-Whitney test for pairwise comparisons between groups at 0.05 probability. Our analysis was conducted using version 21 of the SPSS program.

## Results

There are two parts to the results. According to the distribution of Hp phenotypes during pregnancy, women are at increased risk of preeclampsia (Study 1). In women who have had preeclampsia in the past, the second study investigates the possibility of cardiovascular risk an additional subsample was collected over 2 to 16 years, while taking into account A study of biomarkers of

cardiovascular disease and the Hp phenotype in circulating blood (Figure 1).

A study to investigate the relationship between haptoglobin polymorphism and preeclampsia susceptibility. This table shows the distribution of phenotypes for pregnant women with normotensive (NBPP) and hypertensive (PE) blood pressures (n=265). (P=0.011) NT women were significantly younger compared with preeclampsia women (27.93 x 4.91 x S.D) Over 34 weeks is the average gestational age of women pregnant, regardless of A hypertensive state level, but there are significantly in addition, twenty-three percent of preeclamptic women (P=0.011) were found to be obese (not shown).

Table 1 compares the Hp phenotype distributions of 128 normotensive pregnant women (NT) with 137 Two

hundred and seventy-seven Caucasian pregnant women were found to have preeclampsia (PE). (P=0.422).

A significant difference was not found in Table 2 in Hp phenotype distribution among preeclamptic women between 34 weeks and >34 weeks of pregnancy (Table 2). A risk profile analysis of Preeclampsia-prone women and their babies Biomarkers and their impact on long-term cardiovascular risk (2–16 years) showed that There was an association between HP phenotype and susceptibility to cardiovascular risk.

The follow-up population included previously preeclamptic women and normotensive ones adjusted for their age during pregnancy for anthropometric and hemodynamic parameters and biomarkers of cardiovascular risk. The phenotype of Hp also influences circulating biomarkers.

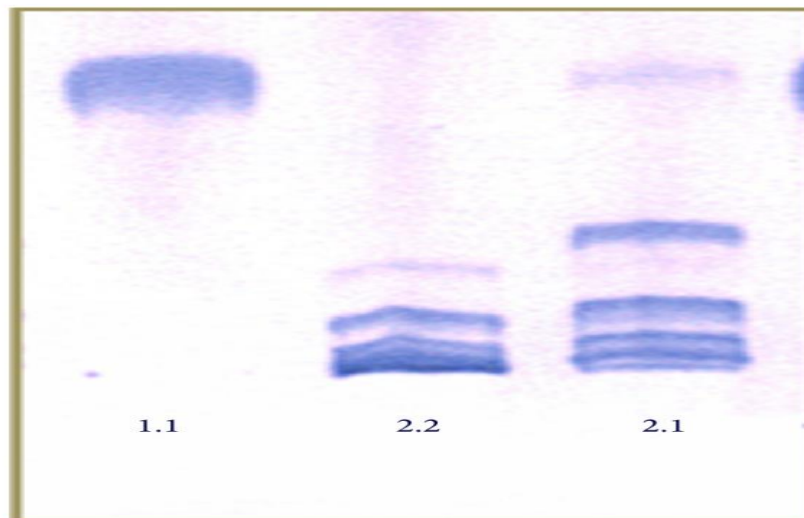
**Table 1: Preeclamptic and The HBPP and PE phenotypes of pregnant women with normal blood pressure distributions are shown.**

Genes and phenotypes	NBPP = 129	PE = 138	value
	(%)	(%)	
Hp 1.1	29 (22.0)	23 (17.2)	0.422
Hp 2.1	67 (52.7)	73 (53.6)	
Hp 2.2	35 (27.6)	44 (32.5)	

**Table 2: An analysis based on the age of gestation at diagnosis of preeclamptic women (PE) shows that distinct phenotypes of HP are found Women with preeclampsia (PE) were included in the study.**

	Hp 1.1	Hp 2.1	Hp 2.2	value
≤Gestation at 34 weeks, (%)	6 (15.7)	24 (57.2)	13 (30.4)	0.792
A gestational age >34 weeks, (%)	14 (16.2)	44 (51.1)	31 (35.0)	

Figure 1: shows a 1.1, 2.1, and 2.2 phenotypic bands are typically arranged in this manner in polyacrylamide gel electrophoresis (PAGE).



## Discussion

An Obesity, dyslipidemia, insulin resistance, and hypertension are among the most common symptoms of metabolic syndrome prevalent causes of morbidity in pre- and postmenopausal women. There has been substantial evidence in the last ten years that preeclampsia High blood pressure contributes to cardiovascular disease development [2, 5]. Under perfusion, hypoxia, and local oxidative stress cause Preeclampsia (PE) is a hypertensive condition associated with pregnancy. Placentas with PE exhibit low levels of proinflammatory activity. Endothelial dysfunction leads to PE symptoms as a secondary consequence. When placenta is ischemia perfused, advanced glycation end products (AGEs) are likely to be formed and released, which The AGE-RAGE receptor is also activated in a secondary manner. A local response in the placenta or systemic response in the liver due to the AGE-RAGE axis will result Through the axis of Hp-CD163-heme oxygenase (HO), acquired immunity switches from Th1 to Th2. Preeclampsia susceptibility and long-term prognosis were not clearly associated with Hp phenotypes in the present study. However, other authors [31–33] observed that There is an Hp allele 1 in the population protected against these outcomes. There is some evidence that the Hp 2.1 phenotype has a great potential for immune tolerance [34, 35]. There is, however, controversy surrounding this topic [36, 37]. The early PE, more characterized by placental dysfunction, is not explained by the Hp polymorphism compared with late

PE, which results from endothelial dysfunction caused by constitutional factors including the metabolic syndrome (BMI) and body mass index (BMI) (Table 2).

A significant increase in BMI, waist circumference, and Blood pressure measurements, systolic and diastolic was observed in our cohort independently of age. Blood concentrations of Nitrites, Apo B, MPO, and ALT also rise when these substances are elevated. Other authors have reached similar conclusions [3, 38]. As compared with Groups 1 and 2, which were previously hypertensive or still normotensive after PE, as well as Group 3 (NBPP > HTA), the difference NBPP > NBP, previously normotensive pregnant women who maintain normotension, are surrogate biomarkers for metabolic syndrome and NO bioavailability.

## Conclusions

In terms of classic cardiovascular risk biomarkers and those Despite becoming normotensive during pregnancy, prior preeclampsia and premenopausal women continued to show significant differences from previous normotensive women due to metabolic syndrome, NO bioavailability, and inflammation. Haptoglobin polymorphism may modulate these biomarker variations to a greater extent in individuals carrying the haptoglobin 1 allele. Women in particular after menopause may be at risk for cardiovascular disease based on their history of hypertensive disease during pregnancy, when combined with these biomarkers including genetic markers.

## REFERENCES:

1. M. Noris, N. Perico, and G. Remuzzi, "Mechanisms of disease: pre-eclampsia," *Nature Clinical Practice: Nephrology*, vol. 1, no. 2, pp. 98–120, 2005.
2. S. Intapad and B. T. Alexander, "Future cardiovascular risk interpreting the importance of increased blood pressure during pregnancy," *Circulation*, vol. 127, no. 6, pp. 668–669, 2013.
3. S. D. McDonald, J. Ray, K. Teo et al., "Measures of cardiovascular risk and subclinical atherosclerosis in a cohort of women with a remote history of preeclampsia," *Atherosclerosis*, vol. 229, no. 1, pp. 234–239, 2013.
4. C. Staff, "Circulating predictive biomarkers in preeclampsia," *Pregnancy Hypertension*, vol. 1, no. 1, pp. 28–42, 2011.
5. W. Chen, I. Z. Jaffe, and S. A. Karumanchi, "Pre-eclampsia and cardiovascular disease," *Cardiovascular Research*, vol. 101, no. 4, pp. 579–586, 2014.
6. M. R. Langlois and J. R. Delanghe, "Biological and clinical significance of haptoglobin polymorphism in humans," *Clinical Chemistry*, vol. 42, no. 10, pp. 1589–1600, 1996.
7. P. Levy, R. Asleh, S. Blum et al., "Haptoglobin: basic and clinical aspects," *Antioxidants and Redox Signaling*, vol. 12, no. 2, pp. 293–304, 2010.
8. K. Theilgaard-Mönch, L. C. Jacobsen, M. J. Nielsen et al., "Haptoglobin is synthesized during granulocyte differentiation, stored in specific granules, and released by neutrophils in response to activation," *Blood*, vol. 108, no. 1, pp. 353–361, 2006.
9. P. Akila, V. Prashant, M. N. Suma, S. N. Prashant, and T. R. Chaitra, "CD163 and its expanding functional repertoire," *Clinica Chimica Acta*, vol. 413, no. 7-8, pp. 669–674, 2012.
10. J. H. Graversen, M. Madsen, and S. K. Moestrup, "CD163: a signal receptor scavenging haptoglobin-hemoglobin complexes from plasma," *International Journal of Biochemistry and Cell Biology*, vol. 34, no. 4, pp. 309–314, 2002.
11. M. J. Nielsen, H. J. Møller, and S. K. Moestrup, "Hemoglobin and heme scavenger receptors," *Antioxidants and Redox Signaling*, vol. 12, no. 2, pp. 261–273, 2010.
12. E. Gruys, M. J. M. Toussaint, T. A. Niewold, and S. J. Koopmans, "Acute phase reaction and acute phase proteins," *Journal of Zhejiang University: Science*, vol. 6, no. 11, pp. 1045–1056, 2005.



13. F. Vallelian, C. A. Schaer, T. Kaempfer et al., "Glucocorticoid treatment skews human monocyte differentiation into a hemoglobin-clearance phenotype with enhanced heme-iron recycling and antioxidant capacity," *Blood*, vol. 116, no. 24, pp. 5347–5356, 2010.
14. H. Van Vlierberghe, M. Langlois, and J. Delanghe, "Haptoglobin polymorphisms and iron homeostasis in health and in disease," *Clinica Chimica Acta*, vol. 345, no. 1-2, pp. 35–42, 2004.
15. Azarov, X. He, A. Jeffers et al., "Rate of nitric oxide scavenging by hemoglobin bound to haptoglobin," *Nitric Oxide—Biology and Chemistry*, vol. 18, no. 4, pp. 296–302, 2008.
16. Alayash, "Haptoglobin: old protein with new functions," *Clinica Chimica Acta*, vol. 412, no. 7-8, pp. 493–498, 2011.
17. P. A. Kendall, S. A. Saeed, and H. O. J. Collier, "Identification of endogenous inhibitor of prostaglandin synthetase with haptoglobin and albumin," *Biochemical Society Transactions*, vol. 7, no. 3, pp. 543–545, 1979.
18. S. A. Saeed, N. Ahmad, and S. Ahmed, "Dual inhibition of cyclooxygenase and lipoxygenase by human haptoglobin: Its polymorphism and relation to hemoglobin binding," *Biochemical and Biophysical Research Communications*, vol. 353, no. 4, pp. 915–920, 2007.
19. M. C. Cid, D. S. Grant, G. S. Hoffman, R. Auerbach, A. S. Fauci, and H. K. Kleinman, "Identification of haptoglobin as an angiogenic factor in sera from patients with systemic vasculitis," *Journal of Clinical Investigation*, vol. 91, no. 3, pp. 977–985, 1993.
20. Guetta, M. Strauss, N. S. Levy, L. Fahoum, and A. P. Levy, "Haptoglobin genotype modulates the balance of Th1/Th2 cytokines produced by macrophages exposed to free hemoglobin," *Atherosclerosis*, vol. 191, no. 1, pp. 48–53, 2007.
21. R. Asleh, R. Miller-Lotan, M. Aviram et al., "Haptoglobin genotype is a regulator of reverse cholesterol transport in diabetes in vitro and in vivo," *Circulation Research*, vol. 99, no. 12, pp. 1419–1425, 2006.
22. M. A. Brown, M. D. Lindheimer, M. de Swiet, A. van Assche, and J.M. Moutquin, "The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP)," *Hypertension in Pregnancy*, vol. 20, no. 1, pp. 9–14, 2001.
23. "2013 Practice guidelines for the management of arterial hypertension of the European society of hypertension (ESH) and the European society of cardiology (ESC): ESH/ESC task force for the management of arterial hypertension," *Journal of Hypertension*, vol. 31, no. 10, pp. 1925–1938, 2013.
24. R. P. Linke, "Typing and subtyping of haptoglobin from native serum using disc gel electrophoresis in alkaline buffer: application to routine screening," *Analytical Biochemistry*, vol. 141, no. 1, pp. 55–61, 1984.
25. Guerra, C. Monteiro, L. Breitenfeld et al., "Genetic and environmental factors regulating blood pressure in childhood: prospective study from 0 to 3 years," *Journal of Human Hypertension*, vol. 11, no. 4, pp. 233–238, 1997.
26. Highton and P. Hessian, "A solid-phase enzyme immunoassay for C-reactive protein: clinical value and the effect of rheumatoid factor," *Journal of Immunological Methods*, vol. 68, no. 1-2, pp. 185–192, 1984.
27. F. J. Valenzuela, A. Pérez-Sepúlveda, M. J. Torres, P. Correa, G. M. Repetto, and S. E. Illanes, "Pathogenesis of preeclampsia: the genetic component," *Journal of Pregnancy*, vol. 2012, Article ID 632732, 8 pages, 2012.
28. C. M. Cooke, J. C. Brockelsby, P. N. Baker, and S. T. Davidge, "The Receptor for Advanced Glycation End Products (RAGE) is elevated in women with preeclampsia," *Hypertension in Pregnancy*, vol. 22, no. 2, pp. 173–184, 2003.
29. Q. T. Huang, M. Zhang, M. Zhong et al., "Advanced glycation end products as an upstream molecule triggers ROS-induced sFlt-1 production in extravillous trophoblasts: a novel bridge between oxidative stress and preeclampsia," *Placenta*, vol. 34, no. 12, pp. 1177–1182, 2013.
30. Bicho, A. P. da Silva, R. Medeiros, and M. Bicho, "The role of haptoglobin and its genetic polymorphism in cancer: a review," in *Acute Phase Proteins*, S. Janciauskiene, Ed., InTech, Rijeka, Croatia, 2013.
31. R. N. Sammour, F. M. Nakhoul, A. P. Levy et al., "Haptoglobin phenotype in women with preeclampsia," *Endocrine*, vol. 38, no. 2, pp. 303–308, 2010.
32. T. L. Weissgerber, R. E. Gandley, P. L. McGee et al., "Haptoglobin phenotype, preeclampsia risk and the efficacy of vitamin C and E supplementation to prevent preeclampsia in a racially diverse population," *PLoS ONE*, vol. 8, no. 4, Article ID e60479, 2013.
33. T. L. Weissgerber, J. M. Roberts, A. Jeyabalan et al., "Haptoglobin phenotype, angiogenic factors, and preeclampsia risk," *The American Journal of Obstetrics and Gynecology*, vol. 206, no. 4, pp. 358.e10–358.e18, 2012.
34. Berkova, A. Lemay, D. W. Dresser, J. Fontaine, J. Kerzitz, and S. Goupil, "Haptoglobin is present in human endometrium and shows elevated levels in the decidua during pregnancy," *Molecular Human Reproduction*, vol. 7, no. 8, pp. 747–754, 2001.
35. F. Gloria-Bottini, N. Bottini, M. La Torre, A. Magrini, A. Bergamaschi, and E. Bottini, "The effects of genetic and seasonal factors on reproductive success," *Fertility and Sterility*, vol. 89, no. 5, pp. 1090–1094, 2008.
36. H. T. Depypere, M. R. Langlois, J. R. Delanghe, M. Temmerman, and M. Dhont, "Haptoglobin polymorphism in patients with preeclampsia," *Clinical Chemistry and Laboratory Medicine*, vol. 44, no. 8, pp. 924–928, 2006.
37. T. Raijmakers, E. M. Roes, R. H. Te Morsche, E. A. Steegers, and W. H. Peters, "Haptoglobin and its association with the HELLP syndrome," *Journal of Medical Genetics*, vol. 40, no. 3, pp. 214–216, 2003.

T. F. McElrath, K. Lim, E. Pare et al., “Longitudinal evaluation of predictive value for preeclampsia of circulating angiogenic factors through pregnancy,” *American Journal of Obstetrics and Gynecology*, vol. 207, no. 5, p. 407.e1, 2012.

**Cite this article:**

Dr. Bhavya G. A Polymorphism in Haptoglobin May Affect the Level of Risks Associated with Cardiovascular Disease Biomarkers in Previously Hypertensive Pregnant Women. *American Journal of Oral Medicine and Radiology*, 2018,5 (2), 48-53.



**Attribution-NonCommercial-NoDerivatives 4.0 International**