Physiology International 113 (2026) 2, 250–261
DOI: 10.1556/2060.2026.00920

1828
AKADÉMIAI KIADÓ

Increased circulating heat shock protein 27 (HSPB1), heat shock protein 60 (HSPD1) and heat shock protein 90 (HSPC1) levels in normal pregnancy and preeclampsia

ANDRÁS KECSKEMÉTI and ATTILA MOLVAREC*

Department of Obstetrics and Gynecology, Semmelweis University, Budapest, Hungary

Received: May 9, 2026 • Revised manuscript received: May 15, 2026 • Accepted: May 18, 2026
Published online: June 15, 2026
© 2026 The Author(s)

ABSTRACT

Objective: The aim of this study was to evaluate circulating levels of heat shock protein 27 (HSPB1, Hsp27), heat shock protein 60 (HSPD1, Hsp60) and heat shock protein 90 (HSPC1, Hsp90) in a large cohort of healthy non-pregnant and pregnant women, as well as in patients with preeclampsia. In addition, we investigated whether serum levels of these heat shock proteins are associated with clinical characteristics and routine laboratory parameters of the study population. *Methods:* The study included 60 women with preeclampsia, 60 healthy pregnant women with uncomplicated pregnancies and 59 healthy non-pregnant controls. Serum concentrations of Hsp27, Hsp60 and Hsp90 were measured with ELISA. Standard clinical chemistry parameters were assessed on an automated analyzer. Statistical analyses were performed using nonparametric methods. *Results:* Serum levels of Hsp27, Hsp60 and Hsp90 were significantly higher in healthy pregnant women compared with healthy non-pregnant controls. Moreover, preeclamptic patients exhibited significantly elevated levels of all three heat shock proteins compared with both control groups. In the preeclamptic group, serum Hsp27 levels showed significant positive correlations with serum bilirubin and lactate dehydrogenase activity. Hsp60 levels were positively correlated with blood urea nitrogen, creatinine, aspartate aminotransferase activity and lactate dehydrogenase activity. Hsp90 levels showed a significant positive correlation with aspartate aminotransferase activity. *Conclusions:* Moderately increased circulating levels of Hsp27, Hsp60 and Hsp90 in otherwise healthy pregnancies may reflect adaptive physiological responses. In contrast, markedly elevated levels observed in preeclampsia may be associated with placental ischemia and oxidative stress, as well as maternal systemic inflammation, endothelial dysfunction, and tissue injury in both placental and maternal organs.

* Corresponding author. Baross utca 27, Budapest, H-1088, Hungary. Tel.: +36 20 957 1636, E-mail: molvarec.attila@semmelweis.hu

AKJournals

Brought to you by MTA Könyvtár és Információs Központ olvasók | Unauthenticated | Downloaded 07/14/26 12:55 PM UTC

KEYWORDS

heat shock protein 27, heat shock protein 60, heat shock protein 90, pregnancy, preeclampsia

INTRODUCTION

Preeclampsia is a serious pregnancy complication characterized by new-onset hypertension developing at or beyond 20 weeks of gestation, accompanied by proteinuria and/or other maternal end-organ dysfunction and/or uteroplacental insufficiency, and it is associated with considerable maternal and perinatal morbidity and mortality [1, 2]. Despite extensive investigation, its precise etiology and pathomechanism remain incompletely understood. Accumulating evidence suggests that placental ischemia and oxidative stress, along with an exaggerated maternal systemic inflammatory response, widespread oxidative stress, and generalized endothelial dysfunction, play central roles in the pathogenesis of the disorder [3–5].

Heat shock proteins are widely distributed and evolutionarily conserved molecules, highlighting their essential biological functions [6]. They are primarily recognized as intracellular proteins with molecular chaperone activity and cytoprotective properties [7]. Nevertheless, heat shock protein 27 (HSPB1, Hsp27), heat shock protein 60 (HSPD1, Hsp60), heat shock protein 70 (HSPA1A, Hsp70) and heat shock protein 90 (HSPC1, Hsp90) can also be detected in the peripheral circulation of both healthy non-pregnant and pregnant individuals [8–10]. In our previous studies, we demonstrated that serum Hsp70 levels are elevated in preeclampsia and are associated with systemic inflammation, oxidative stress and hepatocellular damage [11, 12]. We further showed that patients with HELLP syndrome - characterized by hemolysis, elevated liver enzymes and low platelet count - have significantly higher serum Hsp70 levels compared to severely preeclamptic patients without HELLP syndrome [13]. According to our previous findings, increased serum Hsp70 level reflects tissue injury (including hemolysis and hepatocellular damage) as well as disease severity in HELLP syndrome [14]. Additionally, we observed elevated circulating Hsp70 levels in gestational diabetes mellitus and in pregnant women with asthma [15, 16].

The objective of the present study was to assess circulating levels of Hsp27 (HSPB1), Hsp60 (HSPD1) and Hsp90 (HSPC1) in a large cohort of healthy non-pregnant and pregnant women, as well as in patients with preeclampsia. Furthermore, we investigated whether serum levels of these heat shock proteins are associated with clinical characteristics and routine laboratory parameters of the study participants.

MATERIALS AND METHODS

Study population

This case-control study included 60 women with preeclampsia, 60 healthy pregnant women with uncomplicated pregnancies and 59 healthy non-pregnant controls. Participants were recruited at the First Department of Obstetrics and Gynecology and at the Department of Obstetrics and Gynecology of Kútvölgyi Clinical Center, Semmelweis University, Budapest, Hungary.

Brought to you by MTA Könyvtár és Információs Központ olvasók | Unauthenticated | Downloaded 07/14/26 12:55 PM UTC

All participants were Caucasian and lived in the same geographic region of Hungary. Exclusion criteria comprised multiple gestation, chronic hypertension, diabetes mellitus, autoimmune disorders, vascular disease, renal pathology, maternal or fetal infection, and fetal congenital abnormalities. All participants were fasting at the time of blood sampling; none of the pregnant women were in active labor or had rupture of amniotic membranes.

Preeclampsia was defined as new-onset hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic on at least two occasions at least 6 h apart) occurring after 20 weeks of gestation in previously normotensive women, accompanied by proteinuria (≥0.3 g/24 h). Blood pressure normalized within 12 weeks postpartum in all affected patients. Women with eclampsia or HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count) were excluded. Fetal growth restriction (IUGR) was diagnosed when birth weight fell below the 10th percentile for gestational age and sex, according to Hungarian reference standards.

The study protocol was approved by the Regional and Institutional Committee of Science and Research Ethics of Semmelweis University, and written informed consent was obtained from all participants. The study adhered to the principles of the Declaration of Helsinki.

Measurement of circulating heat shock proteins

Venous blood samples were collected from the antecubital vein into plain tubes and centrifuged at room temperature with a relative centrifugal force of 3,000 *g* for 10 min. Serum aliquots were stored at −80 °C until the analysis. Circulating levels of Hsp27 (HSPB1), Hsp60 (HSPD1) and Hsp90 (HSPC1) were determined with commercially available ELISA kits (Enzo Life Sciences, Farmingdale, NY, USA; Cat. No.: ADI-EKS-500, ADI-EKS-600, ADI-EKS-895, respectively) on an automated ELISA analyzer (Elisys UNO, Human GmbH, Wiesbaden, Germany), following the manufacturer's protocols. Routine clinical chemistry parameters were measured using an automated analyzer (Cobas Integra 800, Roche, Mannheim, Germany) with the corresponding reagents.

Statistical analysis

The distribution of continuous variables was evaluated using the Shapiro-Wilk's *W* test. As the data were not normally distributed, nonparametric methods were applied. Differences between two groups were assessed using the Mann-Whitney *U* test, while comparisons across multiple groups were performed using the Kruskal-Wallis analysis of variance by ranks test, followed by post hoc multiple comparisons of mean ranks. Categorical variables were examined using the Fisher's exact test and the Pearson's χ^2 test. The Spearman rank order correlation was employed to calculate correlation coefficients.

Statistical analyses were carried out using STATISTICA (version 14.2; Cloud Software Group, Inc., Fort Lauderdale, FL, USA) and IBM SPSS Statistics for Windows (version 31.0; IBM Corp., Armonk, NY, USA). A *P*-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

The clinical features of the study population are summarized in Table 1. No significant differences in age were observed among the three groups. Similarly, gestational age at blood sampling

Brought to you by MTA Könyvtár és Információs Központ olvasók | Unauthenticated | Downloaded 07/14/26 12:55 PM UTC

Table 1. Clinical features of healthy non-pregnant women, healthy pregnant women and patients with preeclampsia

	Healthy non-pregnant women (n = 59)	Healthy pregnant women (n = 60)	Patients with preeclampsia (n = 60)
Age (years)	28 (23–35)	30 (28–32)	29 (26–32)
BMI at blood sampling (kg m^{-2})	20.8 (19.6–22.9)	25.8 (24.3–27.9)[b]	29.9 (26.9–33.3)[b,d]
Smoking status	14 (23.7%)	0 (0%)[b]	3 (5.0%)[a]
Primiparity	n.a.	37 (61.7%)	38 (63.3%)
Systolic blood pressure (mmHg)	115 (110–120)	110 (107–120)	162 (155–180)[b,d]
Diastolic blood pressure (mmHg)	80 (70–80)	70 (60–80)[b]	100 (97–110)[b,d]
Gestational age at blood sampling (weeks)	n.a.	36 (36–37)	37 (36–39)
Gestational age at delivery (weeks)	n.a.	39 (38–40)	38 (37–39)[d]
Birth weight (grams)	n.a.	3,450 (3,150–3,700)	3,125 (2,450–3,475)[d]
Fetal growth restriction	n.a.	0 (0%)	11 (18.3%)[d]

Data are shown as median (25th-75th percentile) for continuous variables and as number (%) for categorical variables.
n.a.: not applicable; BMI: body mass index.
[a] $P < 0.05$ versus healthy non-pregnant women.
[b] $P < 0.001$ versus healthy non-pregnant women.
[c] $P < 0.05$ for patients with preeclampsia versus healthy pregnant women.
[d] $P < 0.001$ for patients with preeclampsia versus healthy pregnant women.

and the proportion of primiparous women did not differ significantly between preeclamptic patients and healthy pregnant controls. In contrast, all other clinical parameters listed in Table 1 showed significant differences across the groups. Fetal growth restriction was not observed in healthy pregnancies, whereas it occurred in 18.3% of preeclamptic cases. Among the preeclamptic patients, 21 were classified as having severe disease, and early-onset preeclampsia was identified in 5 cases.

Routine clinical chemistry parameters and circulating heat shock protein levels

The laboratory findings of the participants are presented in Table 2. Significant differences were found in most measured laboratory parameters among the three groups, with the exception of serum aspartate aminotransferase (AST) activity. Serum levels of Hsp27 (HSPB1), Hsp60 (HSPD1) and Hsp90 (HSPC1) were significantly elevated in healthy pregnant women compared to healthy non-pregnant controls. Moreover, patients with preeclampsia exhibited significantly higher levels of all three heat shock proteins than both control groups (Figs 1–3).

Within the preeclamptic cohort, serum levels of Hsp27, Hsp60 and Hsp90 did not differ significantly between mild and severe cases, between early- and late-onset disease, or between patients with and without fetal growth restriction (data not shown).

Brought to you by MTA Könyvtár és Információs Központ olvasók | Unauthenticated | Downloaded 07/14/26 12:55 PM UTC

Table 2. Laboratory findings of healthy non-pregnant women, healthy pregnant women and patients with preeclampsia

	Healthy non-pregnant women (n = 59)	Healthy pregnant women (n = 60)	Patients with preeclampsia (n = 60)
Blood urea nitrogen (mmol l^{-1})	4.1 (3.5–4.8)	2.8 (2.0–3.3)[b]	3.5 (2.7–4.2)[a,c]
Creatinine (μmol l^{-1})	66 (61–72)	49 (42–56)[b]	63 (55–71)[d]
Bilirubin (μmol l^{-1})	9.3 (6.6–12.4)	5.4 (4.0–6.8)[b]	7.3 (5.7–8.9)[a,c]
Aspartate aminotransferase (U/l)	17 (15–20)	19 (17–21)	19 (15–25)
Alanine aminotransferase (U/l)	14 (12–17)	12 (10–15)[a]	16 (11–23)[c]
Lactate dehydrogenase (U/l)	154 (128–170)	158 (138–169)	192 (153–225)[b,d]
Heat shock protein 27 (ng ml^{-1})	4.44 (2.57–8.51)	17.50 (11.37–37.40)[b]	39.10 (17.80–67.10)[b,d]
Heat shock protein 60 (ng ml^{-1})	0.55 (0.38–0.77)	4.09 (3.80–4.57)[b]	4.42 (4.21–4.68)[b,c]
Heat shock protein 90 (ng ml^{-1})	8.02 (5.95–11.09)	11.76 (9.60–18.63)[b]	17.93 (10.07–24.66)[b,c]

Data are shown as median (25th-75th percentile).
[a] $P < 0.05$ versus healthy non-pregnant women.
[b] $P < 0.001$ versus healthy non-pregnant women.
[c] $P < 0.05$ for patients with preeclampsia versus healthy pregnant women.
[d] $P < 0.001$ for patients with preeclampsia versus healthy pregnant women.

Associations between heat shock protein levels and clinical/laboratory parameters

We further evaluated potential associations between serum heat shock protein levels and clinical as well as laboratory variables using Spearman rank correlation (for continuous variables) and the Mann–Whitney U test (for categorical variables). In preeclamptic patients, serum Hsp27 levels showed significant positive correlations with serum bilirubin ($R = 0.26$, $P < 0.05$) and lactate dehydrogenase activity ($R = 0.42$, $P < 0.05$). Serum Hsp60 levels of preeclamptic patients were positively correlated with blood urea nitrogen ($R = 0.32$, $P < 0.05$), creatinine ($R = 0.28$, $P < 0.05$), aspartate aminotransferase activity ($R = 0.36$, $P < 0.05$) and lactate dehydrogenase activity ($R = 0.33$, $P < 0.05$). Serum Hsp90 levels showed a significant positive correlation with aspartate aminotransferase activity ($R = 0.32$, $P < 0.05$) in the preeclamptic group. No additional significant associations were identified between serum heat shock protein levels and the examined clinical or laboratory parameters in any of the study groups.

DISCUSSION

In this study, we found significantly higher serum Hsp27 (HSPB1), Hsp60 (HSPD1) and Hsp90 (HSPC1) levels in healthy pregnant women than in healthy non-pregnant women. There was a

Brought to you by MTA Könyvtár és Információs Központ olvasók | Unauthenticated | Downloaded 07/14/26 12:55 PM UTC

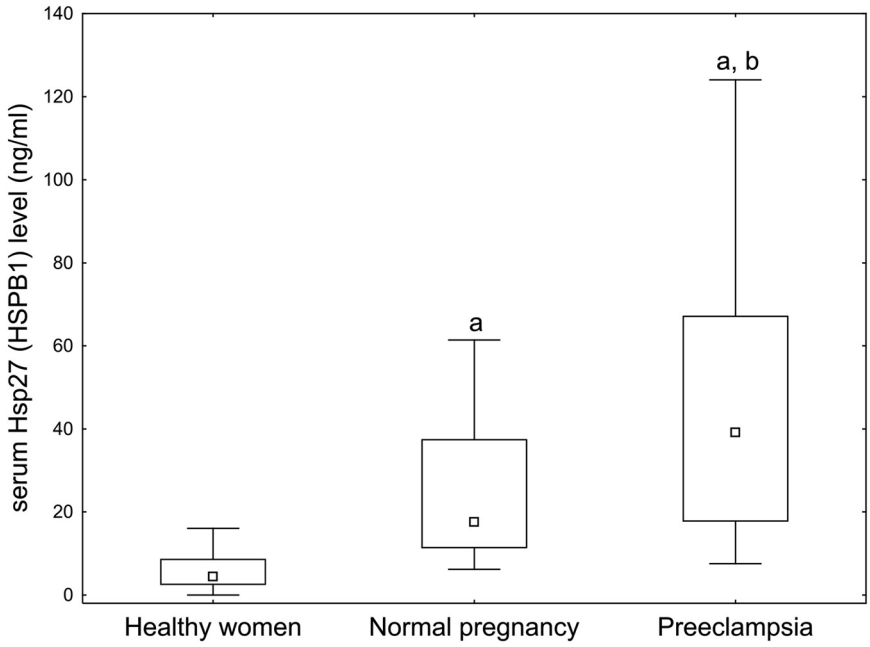

Fig. 1. Serum heat shock protein 27 (HSPB1, Hsp27) levels in healthy non-pregnant women, healthy pregnant women and patients with preeclampsia
Center point: median; Box: interquartile range (25th–75th percentile); Whiskers: range excluding outliers
[a] $P < 0.001$ versus healthy non-pregnant women
[b] $P < 0.001$ for patients with preeclampsia versus healthy pregnant women

further significant increase in circulating Hsp27, Hsp60 and Hsp90 levels in preeclampsia. Previous reports on circulating Hsp27, Hsp60 and Hsp90 protein/mRNA levels in preeclampsia determined by ELISA, Western blot, mass spectrometry or real-time reverse-transcriptase polymerase chain reaction (RT-PCR) are controversial [17–24]. In addition, previous studies lacked a healthy non-pregnant control group.

Normal pregnancy is a physiological controlled stress state involving major hormonal, haemodynamic, immunologic and metabolic changes. The elevated circulating levels of Hsp27, Hsp60 and Hsp90 in normal pregnancy observed in our study may reflect this adaptive response, serving to maintain cellular homeostasis and protect maternal tissues from stress-induced damage. Endometrial and uterine cells show abundant Hsp27, Hsp60 and Hsp90 expression, with involvement in decidualization, implantation, placentation and modulation of endoplasmic reticulum (ER) stress, all critical for a successful pregnancy [10]. Placental cells also express Hsp27, Hsp60 and Hsp90 [25]. These proteins may enter the maternal circulation through syncytiotrophoblast shedding, apoptosis, and extracellular vesicle release. Heat shock proteins, especially Hsp90, act as chaperones for steroid hormone receptors, including those for estrogen and progesterone. The marked elevation of these hormones during normal pregnancy may stimulate heat shock protein expression, thereby contributing to their increased circulating levels. Heat shock proteins have also been implicated in immune modulation, functioning as

Brought to you by MTA Könyvtár és Információs Központ olvasók | Unauthenticated | Downloaded 07/14/26 12:55 PM UTC

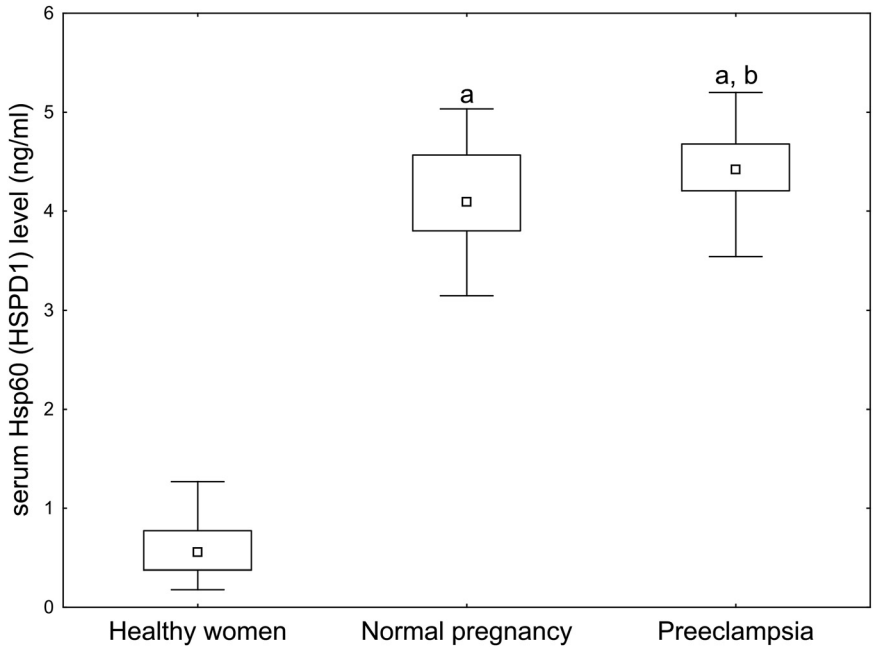

Fig. 2. Serum heat shock protein 60 (HSPD1, Hsp60) levels in healthy non-pregnant women, healthy pregnant women and patients with preeclampsia
Center point: median; Box: interquartile range (25th–75th percentile); Whiskers: range excluding outliers
[a] $P < 0.001$ versus healthy non-pregnant women
[b] $P < 0.05$ for patients with preeclampsia versus healthy pregnant women

mediators of antigen presentation and cytokine signaling [26, 27]. Their increased presence in maternal circulation may contribute to the fine balance between immune activation and tolerance that characterizes normal pregnancy.

Preeclampsia is a multifactorial disorder driven by placental ischemia, oxidative stress, systemic inflammation and widespread endothelial dysfunction. The present findings demonstrating elevated circulating Hsp27, Hsp60 and Hsp90 levels in preeclamptic patients can be explained by these multiple converging stresses. These stressors can activate intracellular protective pathways and simultaneously trigger the extracellular release of heat shock proteins, leading to their increased circulating levels.

A central feature of preeclampsia is placental hypoxia-reperfusion injury, which generates excessive oxidative stress and disrupts protein homeostasis. Under such conditions, the accumulation of unfolded or misfolded proteins induces the expression of stress-responsive chaperones, including Hsp27, Hsp60 and Hsp90 [28]. Placental studies show up-regulation and post-translational modification of heat shock proteins in preeclampsia. Hsp27 is overexpressed in preeclamptic placentas and localized mainly to trophoblasts [29–33]. Hsp60 undergoes aberrant lactylation in preeclamptic placentas, particularly under hypoxic conditions. Hsp60 lactylation promotes mitochondrial dysfunction, increases mitochondrial reactive oxygen

Brought to you by MTA Könyvtár és Információs Központ olvasók | Unauthenticated | Downloaded 07/14/26 12:55 PM UTC

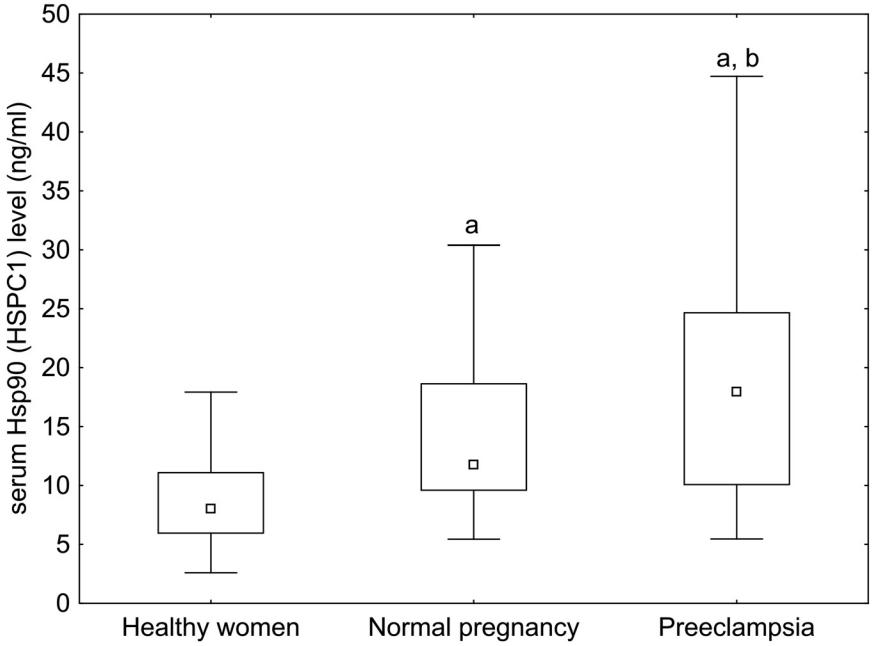

Fig. 3. Serum heat shock protein 90 (HSPC1, Hsp90) levels in healthy non-pregnant women, healthy pregnant women and patients with preeclampsia
Center point: median; Box: interquartile range (25th–75th percentile); Whiskers: range excluding outliers
[a] $P < 0.001$ versus healthy non-pregnant women
[b] $P < 0.05$ for patients with preeclampsia versus healthy pregnant women

species (ROS) production and sensitizes trophoblasts to apoptosis [34]. Such trophoblast stress/damage provides a plausible source of elevated circulating Hsp27 and Hsp60 and links heat shock protein changes directly to defective placentation and the pathophysiology of preeclampsia.

We previously reported that increased serum Hsp70 levels correlate with oxidative stress marker malondialdehyde and indices of tissue damage in women with preeclampsia and HELLP syndrome [12, 14]. Given the conserved chaperone functions of heat shock proteins, similar mechanisms may be responsible for the observed increases in circulating Hsp27, Hsp60 and Hsp90 levels, suggesting their role as biomarkers of cellular stress and damage in preeclampsia. Indeed, in the present study, serum Hsp27, Hsp60 and Hsp90 concentrations of preeclamptic patients showed significant positive correlations with renal and liver function parameters.

Systemic endothelial dysfunction plays a crucial role in the development of the maternal syndrome of preeclampsia. In a recent study, serum Hsp90 alpha level showed positive correlation with both systolic and diastolic arterial blood pressure in preeclamptic patients, suggesting its potential role as an indicator of endothelial stress [24]. Hsp27 expression is increased in preeclamptic placentas and serum Hsp27 level is elevated in the first and second trimester before clinical onset of preeclampsia, especially in early-onset disease [22, 29–33]. These observations are consistent with the role of Hsp27 in cytoskeletal stability and stress protection in vascular

Brought to you by MTA Könyvtár és Információs Központ olvasók | Unauthenticated | Downloaded 07/14/26 12:55 PM UTC

and trophoblast cells. Taken together, these findings suggest that elevated extracellular Hsp27 and Hsp90 are not only bystanders but also components of a compensatory response to vascular and trophoblast injury.

Beyond their intracellular roles, extracellular heat shock proteins derived from stressed and damaged, necrotic cells function as danger-associated molecular patterns (DAMPs), capable of activating innate and adaptive pro-inflammatory immune responses [26, 35, 36]. We previously demonstrated that increased serum Hsp70 concentrations in women with preeclampsia are associated with pro-inflammatory changes in circulating cytokine profile [37]. In another study, the concentrations of extracellular Hsp60 and Hsp70 correlated positively with IL-1β and TNF-α levels in patients with preeclampsia [38]. By extension, the elevated circulating Hsp27, Hsp60 and Hsp90 levels observed in this study might contribute to the development of the excessive systemic inflammatory response and generalized endothelial dysfunction characteristics of the maternal syndrome of the disease. This dual role - as markers of cellular injury and mediators of inflammation - positions heat shock proteins at a critical interface between placental pathology and maternal systemic response.

A limitation of our study is its cross-sectional design. Therefore, this study cannot establish a mechanistic role of the investigated heat shock proteins in the pathogenesis of preeclampsia. Additionally, we cannot draw firm conclusions from the subgroup analyses (mild vs. severe preeclampsia, early- vs. late-onset disease, with vs. without fetal growth restriction) because of the relatively small subgroup sample sizes.

In conclusion, moderately increased circulating levels of Hsp27, Hsp60 and Hsp90 in otherwise healthy pregnancies may reflect adaptive physiological responses. In contrast, markedly elevated levels observed in preeclampsia may be associated with placental ischemia and oxidative stress, as well as maternal systemic inflammation, endothelial dysfunction, and tissue injury in both placental and maternal organs. Further studies are required to determine their mechanistic contributions and to evaluate their potential as predictive biomarkers or therapeutic targets in preeclampsia.

Conflict of interest: AM is related to a member of the editorial board, however, this relation had no impact on the peer review process; the manuscript was reviewed by external reviewers.

REFERENCES

1. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The 2021 International society for the study of hypertension in pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens 2022; 27: 148–69. https://doi.org/10.1016/j.preghy.2021.09.008
2. Mancia G, Kreutz R, Brunstrom M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European society of hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens 2023; 41(12): 1874–2071. https://doi.org/10.1097/HJH.0000000000003480
3. Redman CW. Preeclampsia: a multi-stress disorder. Rev Med Interne 2011; 32(Suppl 1): S41–4. https://doi.org/10.1016/j.revmed.2011.03.331

Brought to you by MTA Könyvtár és Információs Központ olvasók | Unauthenticated | Downloaded 07/14/26 12:55 PM UTC

4. Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. BMJ 2019; 366: l2381. https://doi.org/10.1136/bmj.l2381
5. Redman CWG, Staff AC, Roberts JM. Syncytiotrophoblast stress in preeclampsia: the convergence point for multiple pathways. Am J Obstet Gynecol 2022; 226(2S): S907–27. https://doi.org/10.1016/j.ajog.2020.09.047
6. Kampinga HH, Hageman J, Vos MJ, Kubota H, Tanguay RM, Bruford EA, et al. Guidelines for the nomenclature of the human heat shock proteins. Cell Stress Chaperones 2009; 14(1): 105–11. https://doi.org/10.1007/s12192-008-0068-7
7. Hightower LE. Heat shock, stress proteins, chaperones, and proteotoxicity. Cell 1991; 66(2): 191–7. https://doi.org/10.1016/0092-8674(91)90611-2
8. Molvarec A, Tamasi L, Losonczy G, Madach K, Prohaszka Z, Rigo J Jr. Circulating heat shock protein 70 (HSPA1A) in normal and pathological pregnancies. Cell Stress Chaperones 2010; 15(3): 237–47. https://doi.org/10.1007/s12192-009-0146-5
9. De Maio A, Vazquez D. Extracellular heat shock proteins: a new location, a new function. Shock 2013; 40(4): 239–46. https://doi.org/10.1097/SHK.0b013e3182a185ab
10. Jee B, Dhar R, Singh S, Karmakar S. Heat shock proteins and their role in pregnancy: redefining the function of 'Old rum in a new bottle'. Front Cell Dev Biol 2021; 9: 648463. https://doi.org/10.3389/fcell.2021.648463
11. Molvarec A, Prohaszka Z, Nagy B, Szalay J, Fust G, Karadi I, et al. Association of elevated serum heat-shock protein 70 concentration with transient hypertension of pregnancy, preeclampsia and superimposed pre-eclampsia: a case-control study. J Hum Hypertens 2006; 20(10): 780–6. https://doi.org/10.1038/sj.jhh.1002060
12. Molvarec A, Rigo J Jr, Lazar L, Balogh K, Mako V, Cervenak L, et al. Increased serum heat-shock protein 70 levels reflect systemic inflammation, oxidative stress and hepatocellular injury in preeclampsia. Cell Stress Chaperones 2009; 14(2): 151–9. https://doi.org/10.1007/s12192-008-0067-8
13. Molvarec A, Prohaszka Z, Nagy B, Kalabay L, Szalay J, Fust G, et al. Association of increased serum heat shock protein 70 and C-reactive protein concentrations and decreased serum alpha(2)-HS glycoprotein concentration with the syndrome of hemolysis, elevated liver enzymes, and low platelet count. J Reprod Immunol 2007; 73(2): 172–9. https://doi.org/10.1016/j.jri.2006.07.002
14. Madach K, Molvarec A, Rigo J Jr, Nagy B, Penzes I, Karadi I, et al. Elevated serum 70 kDa heat shock protein level reflects tissue damage and disease severity in the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Eur J Obstet Gynecol Reprod Biol 2008; 139(2): 133–8. https://doi.org/10.1016/j.ejogrb.2007.12.012
15. Garamvolgyi Z, Prohaszka Z, Rigo J Jr, Kecskemeti A, Molvarec A. Increased circulating heat shock protein 70 (HSPA1A) levels in gestational diabetes mellitus: a pilot study. Cell Stress Chaperones 2015; 20(4): 575–81. https://doi.org/10.1007/s12192-015-0579-y
16. Tamasi L, Bohacs A, Tamasi V, Stenczer B, Prohaszka Z, Rigo J Jr, et al. Increased circulating heat shock protein 70 levels in pregnant asthmatics. Cell Stress Chaperones 2010; 15(3): 295–300. https://doi.org/10.1007/s12192-009-0143-8
17. Peracoli JC, Bannwart-Castro CF, Romao M, Weel IC, Ribeiro VR, Borges VT, et al. High levels of heat shock protein 70 are associated with pro-inflammatory cytokines and may differentiate early- from late-onset preeclampsia. J Reprod Immunol 2013; 100(2): 129–34. https://doi.org/10.1016/j.jri.2013.08.003
18. Hromadnikova I, Dvorakova L, Kotlabova K, Kestlerova A, Hympanova L, Novotna V, et al. Assessment of placental and maternal stress responses in patients with pregnancy related complications via monitoring of heat shock protein mRNA levels. Mol Biol Rep 2015; 42(3): 625–37. https://doi.org/10.1007/s11033-014-3808-z
19. Sahin H, Gunel T, Benian A, Onay Ucar E, Guralp O, Kilic A. Genomic and proteomic investigation of preeclampsia. Exp Ther Med 2015; 10(2): 711–6. https://doi.org/10.3892/etm.2015.2509

Brought to you by MTA Könyvtár és Információs Központ olvasók | Unauthenticated | Downloaded 07/14/26 12:55 PM UTC

20. Hromadnikova I, Dvorakova L, Kotlabova K, Kestlerova A, Hympanova L, Novotna V, et al. Circulating heat shock protein mRNA profile in gestational hypertension, pre-eclampsia & foetal growth restriction. Indian J Med Res 2016; 144(2): 229–37. https://doi.org/10.4103/0971-5916.195037
21. Guzel C, van den Berg CB, Duvekot JJ, Stingl C, van den Bosch TPP, van der Weiden M, et al. Quantification of calcyclin and heat shock protein 90 in sera from women with and without preeclampsia by mass spectrometry. Proteomics Clin Appl 2019; 13(3): e1800181. https://doi.org/10.1002/prca.201800181
22. Martin RL, Sottile ML, Redondo AL, Gomez LC, Gauna GV, Flamini MI, et al. Circulating heat shock protein 27 (HSPB1) levels in prediction of pre-eclampsia: a pilot study. Int J Gynaecol Obstet 2022; 158(1): 93–100. https://doi.org/10.1002/ijgo.13982
23. Robellada-Zarate CM, Luna-Palacios JE, Caballero CAZ, Acuna-Gonzalez JP, Lara-Pereyra I, Gonzalez-Azpeitia DI, et al. First-trimester plasma extracellular heat shock proteins levels and risk of preeclampsia. J Cell Mol Med 2023; 27(9): 1206–13. https://doi.org/10.1111/jcmm.17674
24. Canbolat KH, Acikgoz AS, Gok K, Tuten A, Kaya B, Gayretli TK, et al. Serum heat shock protein 90 alpha levels in mild and severe preeclampsia. Rev Assoc Med Bras (1992) 2025; 71(6): e20241990. https://doi.org/10.1590/1806-9282.20241990
25. Kandil B. Immunohistochemical distribution of heat shock proteins 27, 60, 70 and 90 in the placenta of goats in the second and third trimester of pregnancy. Anat Histol Embryol 2025; 54(2): e70027. https://doi.org/10.1111/ahe.70027
26. Pockley AG. Heat shock proteins as regulators of the immune response. Lancet 2003; 362(9382): 469–76. https://doi.org/10.1016/S0140-6736(03)14075-5
27. Pockley AG, Muthana M, Calderwood SK. The dual immunoregulatory roles of stress proteins. Trends Biochem Sci 2008; 33(2): 71–9. https://doi.org/10.1016/j.tibs.2007.10.005
28. Samara AA, Lafioniatis A, Ioannou M, Tsiapakidou S, Gerede A, Anastasakis E, et al. The role of heat shock proteins in placental ischemic disease: a narrative review of the current literature. Int J Gynaecol Obstet 2025; 169(3): 960–7. https://doi.org/10.1002/ijgo.70039
29. Geisler JP, Manahan KJ, Geisler HE, Tammela JE, Rose SL, Hiett AK, et al. Heat shock protein 27 in the placentas of women with and without severe preeclampsia. Clin Exp Obstet Gynecol 2004; 31(1): 12–4.
30. Webster RP, Pitzer BA, Roberts VH, Brockman D, Myatt L. Differences in the proteome profile in placenta from normal term and preeclamptic preterm pregnancies. Proteomics Clin Appl 2007; 1(5): 446–56. https://doi.org/10.1002/prca.200600745
31. Jin H, Ma KD, Hu R, Chen Y, Yang F, Yao J, et al. Analysis of expression and comparative profile of normal placental tissue proteins and those in preeclampsia patients using proteomic approaches. Anal Chim Acta 2008; 629(1–2): 158–64. https://doi.org/10.1016/j.aca.2008.09.015
32. Shin JK, Jeong YT, Jo HC, Kang MY, Chang IS, Baek JC, et al. Increased interaction between heat shock protein 27 and mitogen-activated protein kinase (p38 and extracellular signal-regulated kinase) in preeclamptic placentas. J Obstet Gynaecol Res 2009; 35(5): 888–94. https://doi.org/10.1111/j.1447-0756.2009.01053.x
33. Shin JK, Baek JC, Kang MY, Park JK, Lee SA, Lee JH, et al. Proteomic analysis reveals an elevated expression of heat shock protein 27 in preeclamptic placentas. Gynecol Obstet Invest 2011; 71(3): 151–7. https://doi.org/10.1159/000315162
34. Xu J, Wang X, Qin Z, Liu J, Chen J, Li Q, et al. Hsp60 lactylation promotes mitochondrial dysfunction and trophoblast apoptosis in preeclampsia. Biochem Biophys Res Commun 2025; 778: 152379. https://doi.org/10.1016/j.bbrc.2025.152379
35. Asea A. Stress proteins and initiation of immune response: chaperokine activity of hsp72. Exerc Immunol Rev 2005; 11: 34–45.

Brought to you by MTA Könyvtár és Információs Központ olvasók | Unauthenticated | Downloaded 07/14/26 12:55 PM UTC

36. Pockley AG, Henderson B. Extracellular cell stress (heat shock) proteins-immune responses and disease: an overview. Philos Trans R Soc Lond B Biol Sci 2018; 373(1738). https://doi.org/10.1098/rstb.2016.0522
37. Molvarec A, Szarka A, Walentin S, Beko G, Karadi I, Prohaszka Z, et al. Serum heat shock protein 70 levels in relation to circulating cytokines, chemokines, adhesion molecules and angiogenic factors in women with preeclampsia. Clin Chim Acta 2011; 412(21–22): 1957–62. https://doi.org/10.1016/j.cca.2011.06.042
38. Alvarez-Cabrera MC, Barrientos-Galeana E, Barrera-Garcia A, Osorio-Caballero M, Acevedo JF, Flores-Herrera O, et al. Secretion of heat shock -60, -70 kD protein, IL-1beta and TNFalpha levels in serum of a term normal pregnancy and patients with pre-eclampsia development. J Cell Mol Med 2018; 22(11): 5748–52. https://doi.org/10.1111/jcmm.13824

Open Access statement. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited, a link to the CC License is provided, and changes – if any – are indicated. (SID_1)

Brought to you by MTA Könyvtár és Információs Központ olvasók | Unauthenticated | Downloaded 07/14/26 12:55 PM UTC