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Maternal serum heparan sulfate in preeclampsia pathophysiology: Insights from a systematic review and meta-analysis

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ABSTRACT

Preeclampsia (PE) is a hypertensive disorder that generally occurs after the first half of pregnancy, at delivery or even postpartum; it is associated with maternal organ dysfunction and significantly increases maternal, fetal, and newborn morbidity and mortality. During PE, the syncytiotrophoblast and endothelial cells are damaged, and molecules from the extracellular matrix, such as heparan sulfate (HS), can be released into the blood. Therefore, this study aimed to perform a systematic review and meta-analysis to assess the HS levels in serum from women with preeclampsia and normal pregnancy. To perform this systematic review and meta-analysis study, we comprehensively searched PubMed, ScienceDirect and LILACS and collected published studies about HS and preeclampsia. The risk of bias was assessed using the Newcastle-Ottawa Scale score. Upon search completion, 568 studies were identified, and 4 studies were retrieved for the present analysis. The forest plot showed an increase in serum HS in women with preeclampsia relative to non-preeclamptic women, standardized mean difference -SMD-with 95 % CI 1.2 (−0.41 to 2.81), and this relationship is maintained in early PE group (SMD 1.05; 95 % CI (0.22–2.32)). In conclusión, we presented here that HS possibly plays a vital role in the pathogenesis of preeclampsia since the results showed an increase in this molecule's levels in serum from women with preeclampsia.

1. Introduction

Preeclampsia (PE) is a maternal multisystemic disorder affecting 2–8 % of pregnant women worldwide that causes approximately 50,000 maternal deaths worldwide due to complications such as eclampsia, HELLP syndrome, stroke, pulmonary edema, renal failure, or coagulation disorders [1]. In addition, it is related to around 500,000 fetal deaths associated with intrauterine growth restriction, leading to low birth weight or premature birth that increases the likelihood of birth complications [1,2]. In the Latin America and Caribbean region, determining the total prevalence of PE has been challenging due to the limited studies available. However, the Panamerican Health Association (PAHO) estimates a PE prevalence of 6.6 % (IC 95 %: 4.9 %–8.6 %) and highlights the heterogeneity of that estimation that reflects the diversity in the region [3].

Although the pathophysiological changes of PE occur early in pregnancy, the signs and symptoms become evident after the 20th week of gestation, often close to term, which delays its diagnosis. It is widely accepted that those changes are related to an abnormal placentation process. PE is part of a group of alterations defined as hypertensive disorders of pregnancy. The main diagnostic criteria for PE consist of the presence of systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, and associated with organ dysfunction such as kidney damage, thrombocytopenia, liver damage, pulmonary edema, neurological impairment, and endothelial dysfunction [4].

Establishing early markers would allow for appropriate clinical management with a focus on preventing the development of the disease and its complications. Biomarkers such as angiogenic/antiangiogenic

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factors have been extensively explored such as vascular endothelial growth factor (VEGF), placental growth factor (PlGF), and the splice variant of the VEGF receptor, fms-like tyrosin kinase 1 (sFlt1) since both clinical and experimental approaches suggested the imbalance among those factors [5]. In the case of PlGF, it is known that it is implicated in angiogenesis and extravillous trophoblast invasion into maternal spiral arteries and it reaches at maximum level around 30 weeks of gestation. It could be complexed with SFlt1 during pregnancy and the second and third trimester PlGF/SFlt1 ratios determine a detection rate of 87.5 % for early prediction of early-onset preeclampsia [6]. Thus, PlGF-based biomarker testing has been an adjunct to improve the prediction of preeclampsia in the standard clinical assessment in high-income countries. A cost-utility analysis of various biomarkers has not been conducted due to the uncertainty surrounding their effects on maternal and neonatal outcomes in low- and middle-income countries. This is particularly relevant given the high prevalence of hypertensive disorders of pregnancy in certain regions, such as Latin America, compared to other parts of the world [7].

By the other hand, Heparan sulfate (HS) is an important extracellular matrix (ECM) component. It is a linear polysaccharide that can be chemically or enzymatically broken down into disaccharides, each consisting of an amino sugar or hexosamine and a uronic acid. The amino sugar is glucosamine (GlcN), which can be N-acetylated (GlcNAc) or N-sulfated (GlcNS), and the uronic acid can be either glucuronic acid (GlcA) or iduronic acid (IdoA), it can also be sulfate [8,9]. HS is bound to proteins of the families of glypicans, syndecans, or perlecan, forming the molecules known as HS proteoglycans (HSPGs) [10,11]. Interestingly, these HSPGs facilitate interactions with a wide range of extracellular ligands, such as growth factors, adhesion molecules, chemokines, and metalloproteinases, regulating proliferation, morphogenesis, adhesion, differentiation, cellular migration, cytoskeleton organization, vascular permeability, shear stress mechanosensation and mechanotransduction, infiltration and inflammation [12,13], as we illustrated in Fig. 1.

HSPGs can be cleaved by matrix metalloproteinases, leading to the release of the protein ectodomain and the HS [14]. On the other hand, HS domains can also undergo endoglycosidic cleavage by heparanases, thus releasing extracellular HS fragments [15]. In both cases, the protein ectodomain attached to HS and HS fragments keeps their biological potential, which means the ability to bind to different ligands [14]. In PE

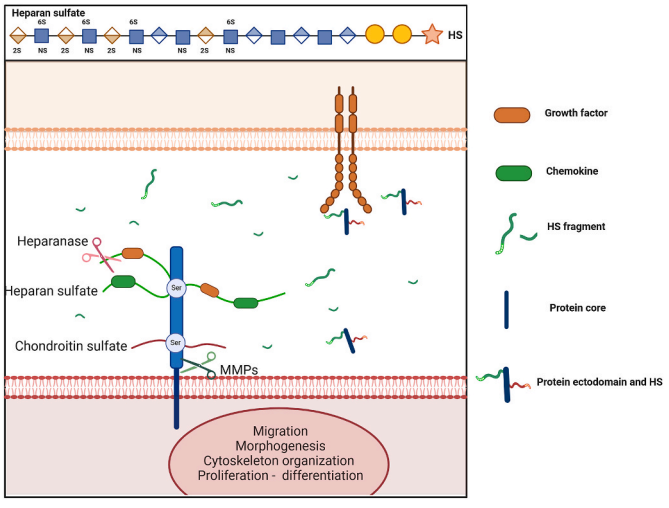

Fig. 1. HS covalently attached to proteins like glypicans, syndecans, or perlecan, and forming proteoglycans (HSPGs), which helps in interaction with diverse extracellular ligands, regulating different processes and responses of the cell [12,13]. HSPGs are broken down by matrix metalloproteinases, and HS domains are also endoglycosidically cleaved by heparanases. The soluble protein ectodomain bound to HS and free HS fragments still have the ability to bind to different ligands in other cells [14].

women have reported increased activity of heparanase [16] and also an altered expression of matrix metalloproteinases (MMP) 2 and 9 [17–19], which is associated with an inflammatory status observed in these patients. This could impact the amount of HS molecules released into the blood and offer a possible marker for this disorder. Therefore, this study aimed to perform a systematic review and meta-analysis to determine the HS levels in serum from women with PE and healthy pregnancies.

2. Materials and methods

2.1. Search strategy

Searches were conducted of the PubMed, ScienceDirect and LILACS (Literatura Latinoamericana y del Caribe en Ciencias de la Salud) databases through January 9, 2025. The search terms included, Preeclampsia and ("Heparan sulfate proteoglycans" OR "Heparan sulfate" OR "Heparitin sulfate" OR Syndecan OR glypican).

2.2. Inclusion and exclusion criteria

Articles were selected according to the following criteria: *i*) preeclamptic and health pregnancy women were investigated, and *ii*) the levels of HS was examined. Reviews, duplicate studies, case reports, abstracts, or studies with insufficient data to investigate the relationship between HS and PE were excluded. The study protocol was registered with the Prospero International Prospective Register of Systematic Reviews (CRD42023421512).

2.3. Data extraction

Three researchers (Gómez-Gutiérrez, Álvarez Gómez and Cardona Maya) independently judged study eligibility while screening the citations and extracting characteristics of eligible studies. Disagreements were resolved by consensus. The main relevant information recorded included the author's surname, year of publication, number of patients, methodology, and HS levels. To compare studies, the reported mean or median, was converted to the same units (ng/mL).

This work was reported following the preferred items for systematic reviews and meta-analysis (PRISMA) reporting guidelines [20]. The PRISMA protocol for systematic review has four stages: identification, screening, eligibility, and inclusion (Fig. 2).

To evaluate the quality of the included studies, Newcastle-Ottawa Scale (NOS) criteria was applied (http://www.ohri.ca/programs/clini

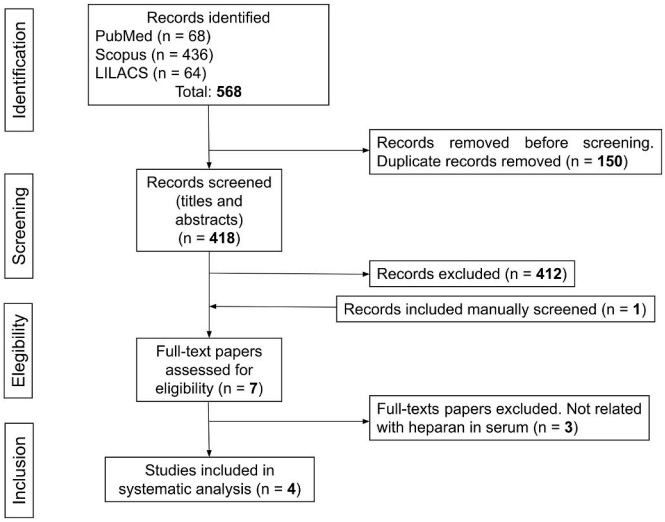

Fig. 2. Flow diagram of the studies selection process. PRISMA flow chart summarizing the process of literature search and selection of studies.

cal_epidemiology/oxford.asp) using a scale for cross-sectional studies (adapted version). We further assessed the risk of bias for each study in the three main domains: selection of the study groups, comparability, and ascertainment of the outcome of interest. Study bias was scaled as inferior quality (0–3 stars), medium quality (4–6 stars), and superior quality (7–9 stars). Disparities and disagreements were resolved by consensus (Table 1).

2.4. Statistical analysis

Mean and standard deviation were used when reported in selected studies. When median with interquartile range or range were reported, we derived the data to mean ± standard deviation from the sample size, and median, IQR, minimum, and maximum values according to the formula published by Wan et al., [21]. In addition, in two articles [22, 23], using the results in the figure, the mean and SD were calculated. Finally, we chose the standardized mean difference (SMD) as the effect size for statistical comparison between cases and controls, which allows the comparison even between those studies.

3. Results

Literature searches identified 568 documents, after excluding duplicate studies, irrelevant literature, and review articles adhering strictly to the inclusion and exclusion criteria, 4 articles [22–25] were finally included (Fig. 2). The included trials were published between 2014 and 2022. In total 347 women, including 138 PE women and 160 health women were involved in those studies; 49 women with other complications were evaluated in separate groups. The studies were performed in obstetric units from Spain, Netherlands, USA and England. Maternal age was among 23–37 years. Table 2 shows general characteristics of the selected studies.

Most of the studies analyzed showed a trend towards increased HS in the serum of women with PE [22,23,25], (Fig. 3A). In contrast, Palomo et al., [24] showed a reduction of HS in the serum of women with both early and late PE. Control groups in all studies were normotensive pregnant women, but several studies included other comparison groups: Al-ofi et al., [22] included a group of non-pregnant women, Weissgerber et al., [25] included women who developed gestational diabetes, and Palomo et al., [24] included pregnant women with SARS-CoV-2. Studies from Al-ofi et al., [22], and Hassani Lahsinoui et al., [23], did not find any statistical difference in serum HS levels between women with PE and the control group. Palomo et al., [24] showed a statistical difference for the severe SARS-CoV-2 and PE groups, while Weissgerber et al., [25] achieved a statistical difference for the early PE group. Interestingly, Al-ofi et al., [22] and Hassani Lahsinoui et al., [23] reported the age of delivery into the group of normotensive women at 32 and 34 weeks respectively, gestational age at which a delivery is considered preterm, although they did not report any complication among the women (Table 2).

As shown in Fig. 3A, the main of the analyzed studies showed an increased levels of serum HS in PE women, which allowed to reach a summary measure indicating higher HS in PE women compared with normal pregnancy women (SMD with 95 % CI 1.2 (−0.41 to 2.81)). In addition, when the groups were analyzed in relation to the onset of PE, it was observed that similar results was maintained in early PE group (SMD 1.05; 95 % CI 0.22 to 2.32) as show in Fig. 3B. The small number of articles that reported data for late PE did not allow the analysis to be carried out in this group.

Table 2
Summary of the studies included in the meta-analysis.

Study	Study population - Groups	Maternal age (years)	Gestational age at delivery (weeks)	HS levels (ng/mL)
Al-ofi, E et al., 2014 [20].	Np - 17	Np 29.3 ± 4.9	Np 32.0 ± 3.7	2090 ± 180[a]
	Early PE - 17	PE 31.4 ± 5.6	PE 32.9 ± 3.7	2450 ± 200[a]
Weissgerber, T. L. et al., 2019 [21].	Np - 73	Np 29.8 ± 4.5	Np 41	2,07 ± 0,22
	Early - 14	Early 29.6 ± 5.7	Early 33	2,91 ± 0,44
	Late - 29	Late 28.9 ± 4.8	Late 38	3,11 ± 0,44
Hassani Lahsinoui, H. et al., 2021 [22].	Np - 60	Np 29 ± 6	Np 34.1 ± 3.8	1390 ± 750[a]
	Early PE - 65	PE 31 ± 5	PE 33.7 ± 3.8	1700 ± 800[a]
Palomo, M et al., 2022 [24].	Np - 10	Np 36.9 (31.6–38.7)	Np 40.2 (38.9–41)	2506 ± 544, 18
	Early PE - 4	PE 29 (26–35.9)	PE 39.1 (35.1–39.6)	1900,35 ± 393,33
	Late PE - 9			1872,48 ± 1056,35

Normal pregnant (Np), Preeclampsia (PE), Heparan sulfate (HS), Early onset preeclampsia (early), Late onset preeclampsia (late).
[a] Data calculated based on article figure.

4. Discussion

PE is part of a group of alterations defined as hypertensive disorders of pregnancy, including gestational hypertension and chronic hypertension with superimposed PE. Currently, diagnosis is based on the presence of arterial hypertension associated with maternal organ dysfunction [26].

At present, it is known that the origin of PE occurs in two stages: stage one or placental, which occurs during the first trimester and is characterized by shallow trophoblast invasion, leading to deficient remodeling of the spiral arterioles [27]. This event generates abnormally narrow vessels of high resistance, followed by high pressure and low flow, leading to poor placental perfusion [28], accompanied by an increase in the production and release of anti-angiogenic factors, such as the placental growth factor (PlGF) soluble receptor (soluble fms-like tyrosin kinase-1, sFlt-1) and soluble endoglin (sENG), and also pro-inflammatory molecules like tumor necrosis factor-alpha (TNF-α) [29]. The combination of those previous events leads to the second stage of the disorder. Stage two is the symptomatic stage, where endothelial dysfunction and systemic vascular injury occur, leading to multi-organ damage and the onset of maternal hypertension [29].

Therefore, it is widely accepted that placental disease precedes

Table 1
Newcastle-Ottawa Scale (NOS) score for included studies.

Reference	Preeclampsia	Selection	Comparability	Outcome	Total x/9
Al-ofi, E et al., 2014 [20]	Early	****	*	***	8
Weissgerber, T. L. et al., 2019 [21]	Early	*****	*	***	9
	Late	*****	*	***	9
Hassani Lahsinoui, H. et al., 2021 [22]	Early	*****	*	***	9
Palomo, M et al., 2022 [24]	Early	****	*	***	8
	Late	****	*	***	8

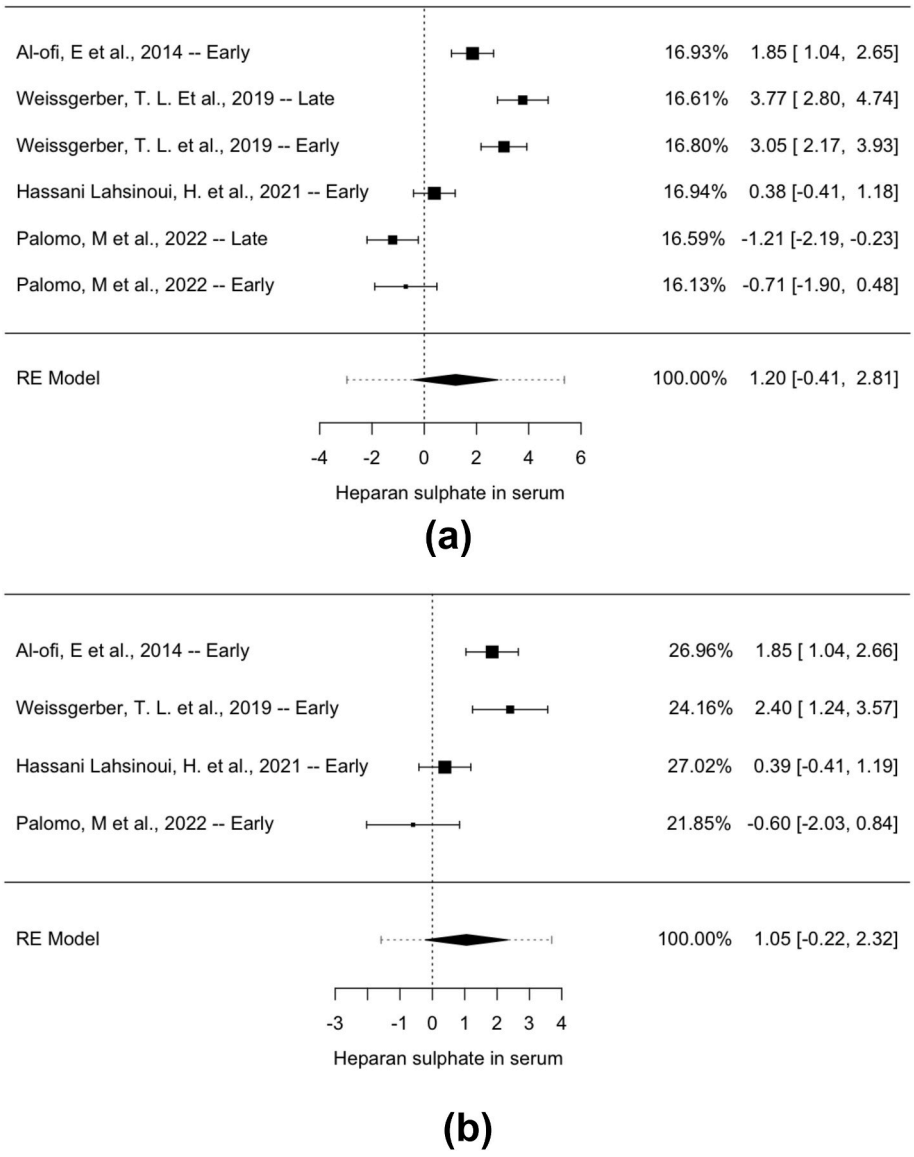

Fig. 3. Forest plot comparing HS serum levels. 3A All studies included. 3B Early PE women group studies.

maternal endothelial dysfunction in the pathogenesis of PE. Molecules released from the placenta (e.g., HS) likely show changes from early stages in gestation, even during placental development. Evidence showed that HS from the syncytiotrophoblast (STB) and the proteoglycans (PGs) to which it is attached binds growth factors (VEGF, FGF-2, BMP), and cytokines, consequently regulating processes such as cell proliferation, differentiation of cytotrophoblasts (CTB) into STB, anticoagulation, and angiogenesis [30]. Since HS is highly expressed in the ECM of the STB, it is possible to find soluble fragments of this molecule in the plasma due to enzymatic detachment caused by heparanases, which are necessary during invasion processes [31]. Given their structural diversity and ability to carry information, these macromolecules are increasingly recognized as valuable tools for identifying future biomarkers that can enhance the diagnosis and prognosis of specific pathophysiological events. This is particularly relevant for easily accessible biological fluids such as blood and urine [32].

HS binds syndecans, a family of PGs that are expressed in the cell membrane of different cell types. It has been established that syndecan 1 (Sdc-1) has a role in the differentiation of CTB cells to STB, since it shows the highest positive regulation among all PGs during syncytialization, and the placenta is considered to be the primary source of this molecule during gestation [33]. That evidence allows us to hypothesize about a modulation in HS levels too, with physiological and pathological changes involved in placental development. Several studies have shown a reduction of Sdc-1 in the serum of women with PE. Gandley et al., evaluated soluble Sdc-1 in uncomplicated and PE pregnancies at mid-pregnancy (20 weeks). They found that, in uncomplicated pregnancies, soluble Sdc-1 increased significantly in the first trimester, reaching an approximately 50-fold increase at pregnancy term. Soluble Sdc-1 was lower in mid-pregnancy in women who later developed PE [34]. Kuessel et al., evaluated maternal serum Sdc-1 levels in pregnant women throughout gestation and compared the results between women who remained healthy and those who later developed PE. Serum Sdc-1 levels were lower, with a statistically significant difference, from 18 weeks of gestation onward in women who developed PE compared to pregnancies without the disease [35]. Some authors have attributed the reduction in the amount of Sdc-1 in the serum of women with PE to an increase in the retention of the protein inside the cell as a consequence of the alteration of cytoskeletal proteins [36]. Therefore, this reduction in Sdc-1 may bring some light on the observed increased levels of HS in PE women since a reduction in the Sdc-1 transport to the cell membrane may result in the secretion of free HS molecules into the serum.

Several studies have identified an abnormal distribution of HS in the placenta of women with preeclampsia. This alteration may be attributed to the action of endoglycosidases, such as heparanases [16,37,38]. This kind of enzymes plays a crucial role in facilitating the placentation process, as it is expressed in the villous trophoblast, STB, and the endothelium of fetal capillaries. Increased heparanase activity has been observed in women with preeclampsia [39], leading to an elevated release of HS into the maternal circulation. Given that HS is known to regulate inflammation [40], this modification in HS content and release into the plasma could contribute to the pathogenesis of preeclampsia.

Early research by Wrenshall et al. demonstrated that HS released from cell surfaces and extracellular matrices during inflammatory states influences T cell-mediated cytotoxicity through the function of antigen-presenting cells and enhances the production of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α by macrophages. Additionally, various immune cells, including macrophages and activated T cells, express enzymes that can cleave HS, which may lead to the activation of endothelial cells [41]. Furthermore, soluble HS has been shown to bind to Toll-like receptors, amplifying the inflammatory response via NF-κB signaling. It can also regulate the diffusion and sequestration of chemokines, thereby participating in the formation and stabilization of chemotactic gradients that provide directional cues for migrating leukocytes [42].

The available body of evidence allows us to propose that early localized inflammatory events in the preeclamptic placenta, leading to an early increased release of HS, are linked with the later systemic inflammatory response observed in women with diagnosed preeclampsia." In this case, the HS released from the placenta can stimulate maternal immune cells to release endothelial HS. That release is accompanied by endothelial activation and damage from multiple maternal vascular beds that lead to organ damages, as pregnancy progresses. To the extent that this is the case, we propose that in the late stage of the PE, serum HS may originate from sources other than the placenta. In accordance with these factors, the research work of Weissgerber TL et al. [25] explored the effect of PE on the vascular endothelial glycocalyx. It quantified glycocalyx degradation with a sidestream dark field imaging camera that makes red blood cells visible while they travel through the microvessels beneath the tongue. The glycocalyx degradation enables red blood cells to penetrate into its deeper layers, as indicated by an elevated perfused boundary region (PBR) value. Besides, the researchers quantified some proteoglycans (PGs) like syndecan-1 (Sdc-1), heparan sulfate proteoglycan (HSPG), and hyaluronic acid concentrations in the blood using ELISA techniques. Though there was no difference in the serum Sdc-1 level between the groups, women with late-onset preeclampsia had increased HSPG concentration.

The studies analyzed in this review explored another mechanisms besides de HS production in PE development. In fact, in some studies, HS was not the primary objective. Data presented by Al-ofi et al., [22] suggest that HS as a ligand of toll-like receptor 4 might play an important role in maintaining the exaggerated inflammation of PE, and fibrinogen instead of HS might function as a biomarker in women with PE. Hassani Lahsinoui et al., [23], attempted to prove that the interaction between soluble Sdc-1 and its association with GAGs contributed to sFLT1-induced high blood pressure in PE. They reported a similar level of HS among PE and normotensive women, while dermatan sulfate (DS) was significantly higher in PE and inversely correlated with soluble Sdc-1 and blood pressure, suggesting that the association of soluble Sdc-1 with BP in preeclampsia could be mediated by DS and not by HS. Contrary to these results, Palomo et al., [24] found a reduction of HS in the serum of women with PE. In this work, the investigators set out to study biomarkers of endothelial damage, coagulation, innate immune response and angiogenesis in preeclampsia and COVID-19 in pregnancy. They observed that most of the biomarker results in medium severity COVID-19 and controls were similar, and also HS was increased in women with severe COVID-19 but not in women with PE.

5. Conclusion

This systematic review and meta-analysis investigating the relationship between antepartum levels of soluble HS in pregnant women with preeclampsia is pioneering. We found statistically significant differences in serum HS levels between normotensive women and those with PE, suggesting that HS plays a vital role in the pathogenesis of PE, given its importance in cellular proliferation, differentiation, and migration processes.

These findings open several avenues for elucidating the mechanisms behind the elevated HS levels in women with PE. However, this raises another question: Do these findings align with the urine excretion rate of HS? It would be intriguing to explore the correlation between serum and urine levels of HS to investigate the potential of urine as a more accessible biological fluid for biomarker identification.

CRediT authorship contribution statement

Alejandra María Gómez-Gutiérrez: Writing – review & editing, Formal analysis, Data curation, Supervision, Methodology, Conceptualization. **Angela María Alvarez-Gómez:** Writing – review & editing, Formal analysis, Data curation, Supervision, Methodology, Conceptualization. **Juan Carlos Quintana-Castillo:** Writing – review & editing, Supervision, Project administration, Methodology. **Julio Cesar Bueno-Sánchez:** Writing – review & editing, Writing – original draft, Resources, Project administration, Formal analysis, Conceptualization. **Walter D. Cardona Maya:** Writing – review & editing, Formal analysis, Data curation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] S.A. Karrar, P.L. Hong, Preeclampsia, in: StatPearls, StatPearls Publishing, 2022 [Internet].
[2] K. Pankiewicz, E. Szczerba, T. Maciejewski, A. Fijałkowska, Non-obstetric complications in preeclampsia, Menopause Review/Przegląd Menopauzalny 18 (2) (2019) 99–109.
[3] E. Blanco, M. Marin, L. Nuñez, E. Retamal, X. Ossa, K.E. Woolley, T. Oludotun, S. E. Bartington, J.M. Delgado-Saborit, R.M. Harrison, Adverse pregnancy and perinatal outcomes in Latin America and the Caribbean: systematic review and meta-analysis, Rev. Panam. Salud Públic 46 (2023) e21.
[4] Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222, Obstet. Gynecol. 135 (6) (2020) e237–e260.
[5] S. Rana, S.D. Burke, S.A. Karumanchi, Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders, Am. J. Obstet. Gynecol. 226 (2S) (2022) S1019–S1034.
[6] H. Zeisler, E. Llurba, F. Chantraine, M. Vatish, A.C. Staff, M. Sennstrom, M. Olovsson, S.P. Brennecke, H. Stepan, D. Allegranza, P. Dilba, M. Schoedl, M. Hund, S. Verlohren, Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia, N. Engl. J. Med. 374 (1) (2016) 13–22.
[7] V.L. Bilano, E. Ota, T. Ganchimeg, R. Mori, J.P. Souza, Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis, PLoS One 9 (3) (2014) e91198.

[8] X. Ai, A.-T. Do, O. Lozynska, M. Kusche-Gullberg, U. Lindahl, C.P. Emerson Jr., QSulf1 remodels the 6-O sulfation states of cell surface heparan sulfate proteoglycans to promote Wnt signaling, J. Cell Biol. 162 (2) (2003) 341–351.
[9] H. Sodhi, A. Panitch, Glycosaminoglycans in tissue engineering: a review, Biomolecules 11 (1) (2020) 29.
[10] C.L.R. Merry, U. Lindahl, J. Couchman, J.D. Esko, Proteoglycans and sulfated glycosaminoglycans. Essentials of Glycobiology, fourth ed., 2022 [Internet].
[11] J.M. Tarbell, L.M. Cancel, The glycocalyx and its significance in human medicine, J. Intern. Med. 280 (1) (2016) 97–113.
[12] M.A. Nugent, J. Zaia, J.L. Spencer, Heparan sulfate-protein binding specificity, Biochemistry (Mosc.) 78 (2013) 726–735.
[13] C.A. Foote, R.N. Soares, F.I. Ramirez-Perez, T. Ghiarone, A. Aroor, C. Manrique-Acevedo, J. Padilla, L. Martinez-Lemus, Endothelial glycocalyx, Compr. Physiol. 12 (4) (2022) 3781–3811.
[14] M.M. Ziganshina, E.L. Yarotskaya, N.V. Bovin, G.T. Sukhikh, Endothelial dysfunction as a consequence of endothelial glycocalyx damage: a role in the pathogenesis of preeclampsia, in: H. Lenasi (Ed.), Endothelial Dysfunction—Old Concepts and New Challenges, 2018, pp. 113–146.
[15] I. Vlodavsky, Y. Friedmann, M. Elkin, H. Aingorn, R. Atzmon, R. Ishai-Michaeli, M. Bitan, O. Pappo, T. Peretz, I. Michal, Mammalian heparanase: gene cloning, expression and function in tumor progression and metastasis, Nat. Med. 5 (7) (1999) 793–802.
[16] E.A. Fama, R.S. Souza, C.M. Melo, L. Melo Pompei, M.A. Pinhal, Evaluation of glycosaminoglycans and heparanase in placentas of women with preeclampsia, Clin. Chim. Acta 437 (2014) 155–160.
[17] A.C. Palei, V.C. Sandrim, L.M. Amaral, J.S. Machado, R.C. Cavalli, G. Duarte, J. E. Tanus-Santos, Association between matrix metalloproteinase (MMP)-2 polymorphisms and MMP-2 levels in hypertensive disorders of pregnancy, Exp. Mol. Pathol. 92 (2) (2012) 217–221.
[18] M. Montagnana, G. Lippi, A. Albiero, S. Scevarolli, G.L. Salvagno, M. Franchi, G. C. Guidi, Evaluation of metalloproteinases 2 and 9 and their inhibitors in physiologic and pre-eclamptic pregnancy, J. Clin. Lab. Anal. 23 (2) (2009) 88–92.
[19] J.E. Myers, S.J. Merchant, M. Macleod, G.J. Mires, P.N. Baker, S.T. Davidge, MMP-2 levels are elevated in the plasma of women who subsequently develop preeclampsia, Hypertens. Pregnancy 24 (2) (2005) 103–115.
[20] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 372 (2021) n71.
[21] X. Wan, W. Wang, J. Liu, T. Tong, Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range, BMC Med. Res. Methodol. 14 (2014) 1–13.
[22] E. Al-Ofi, S.B. Coffelt, D.O. Anumba, Fibrinogen, an endogenous ligand of Toll-like receptor 4, activates monocytes in pre-eclamptic patients, J. Reprod. Immunol. 103 (2014) 23–28.
[23] H. Hassani Lahsinoui, F. Amraoui, L.J.A. Spijkers, G.J.M. Veenboer, S.L.M. Peters, N. van Vlies, L. Vogt, C. Ris-Stalpers, B.J.H. van den Born, G.B. Afink, Soluble syndecan-1 and glycosaminoglycans in preeclamptic and normotensive pregnancies, Sci. Rep. 11 (1) (2021) 1–10.
[24] M. Palomo, L. Youssef, A. Ramos, S. Torramade-Moix, A.B. Moreno-Castaño, J. Martinez-Sanchez, L. Bonastre, M. Pino, P. Gomez-Ramirez, L. Martin, Differences and similarities in endothelial and angiogenic profiles of preeclampsia and COVID-19 in pregnancy, Am. J. Obstet. Gynecol. 227 (2) (2022) 277, e1.
[25] T.L. Weissgerber, O. Garcia-Valencia, N.M. Milic, E. Codsi, H. Cubro, M.C. Nath, W. M. White, K.A. Nath, V.D. Garovic, Early onset preeclampsia is associated with glycocalyx degradation and reduced microvascular perfusion, J. Am. Heart Assoc. 8 (4) (2019) e010647.
[26] A.C.o. Obstetricians, Gynecologists, gestational hypertension and preeclampsia: ACOG practice bulletin, Obstet. Gynecol. 133 (1) (2019) e1–e25.
[27] B.D. LaMarca, J. Gilbert, J.P. Granger, Recent progress toward the understanding of the pathophysiology of hypertension during preeclampsia, Hypertension 51 (4) (2008) 982–988.
[28] C.S. Roland, J. Hu, C.-E. Ren, H. Chen, J. Li, M.S. Varvoutis, L.W. Leaphart, D. B. Byck, X. Zhu, S.-W. Jiang, Morphological changes of placental syncytium and their implications for the pathogenesis of preeclampsia, Cell. Mol. Life Sci. 73 (2016) 365–376.
[29] I. Carrasco-Wong, M. Aguilera-Olguín, R. Escalona-Rivano, D.I. Chiarello, L. J. Barragán-Zúñiga, M. Sosa-Macías, C. Galaviz-Hernandez, S. San Martín, J. Gutiérrez, Syncytiotrophoblast stress in early onset preeclampsia: the issues perpetuating the syndrome, Placenta 113 (2021) 57–66.
[30] C.B. Kirn-Safran, S.S. D'Souza, D.D. Carson, Heparan Sulfate Proteoglycans and Their Binding Proteins in Embryo Implantation and Placentation, Elsevier, pp. 187-193.
[31] Y.-Y. Wang, R. Zhou, B. Zhou, T. Wang, L. Zhang, D. Luo, Overexpression of heparanase is associated with preeclampsia by inhibiting invasion of trophocytes, Int. J. Clin. Exp. Med. 8 (10) (2015) 18107.
[32] D.S. Alonzi, Y.H. Su, T.D. Butters, Urinary glycan markers for disease, Biochem. Soc. Trans. 39 (1) (2011) 393–398.
[33] O. Oravecz, A. Balogh, R. Romero, Y. Xu, K. Juhasz, Z. Gelencser, Z. Xu, G. Bhatti, R. Pique-Regi, B. Peterfia, P. Hupuczi, I. Kovalszky, P. Murthi, A.L. Tarca, Z. Papp, J. Matko, N.G. Than, Proteoglycans: Systems-level insight into their expression in healthy and diseased placentas, Int. J. Mol. Sci. 23 (10) (2022).
[34] R.E. Gandley, A. Althouse, A. Jeyabalan, J.M. Bregand-White, S. McGonigal, A. C. Myerski, M. Gallaher, R.W. Powers, C.A. Hubel, Low soluble syndecan-1 precedes preeclampsia, PLoS One 11 (6) (2016) e0157608.
[35] L. Kuessel, H. Husslein, E. Montanari, M. Kundi, G. Himmler, J. Binder, J. Schiefer, H. Zeisler, Dynamics of soluble syndecan-1 in maternal serum during and after pregnancies complicated by preeclampsia: a nested case control study, Clin. Chem. Lab. Med. 58 (1) (2019) 50–58.
[36] J.H. Kang, H. Song, J.A. Yoon, D.Y. Park, S.H. Kim, K.J. Lee, A. Farina, Y.K. Cho, Y. N. Kim, S.W. Park, G.J. Kim, S.H. Shim, D.H. Cha, Preeclampsia leads to dysregulation of various signaling pathways in placenta, J. Hypertens. 29 (5) (2011) 928–936.
[37] N. Heyer-Chauhan, I.J. Ovbude, A.A. Hills, M.H. Sullivan, F.A. Hills, Placental syndecan-1 and sulphated glycosaminoglycans are decreased in preeclampsia, J. Perinat. Med. 42 (3) (2014) 329–338.
[38] M. Warda, F. Zhang, M. Radwan, Z. Zhang, N. Kim, Y.N. Kim, R.J. Linhardt, J. Han, Is human placenta proteoglycan remodeling involved in pre-eclampsia? Glycoconj. J. 25 (5) (2008) 441–450.
[39] R. Haimov-Kochman, Y. Friedmann, D. Prus, D.S. Goldman-Wohl, C. Greenfield, E. Y. Anteby, A. Aviv, I. Vlodavsky, S. Yagel, Localization of heparanase in normal and pathological human placenta, Mol. Hum. Reprod. 8 (6) (2002) 566–573.
[40] R. El Masri, Y. Cretinon, E. Gout, R.R. Vives, HS and inflammation: a potential playground for the sulfs? Front. Immunol. 11 (2020) 570.
[41] L.E. Wrenshall, R.B. Stevens, F.B. Cerra, J.L. Platt, Modulation of macrophage and B cell function by glycosaminoglycans, J. Leukoc. Biol. 66 (3) (1999) 391–400.
[42] A.R. Pessentheiner, G.M. Ducasa, P. Gordts, Proteoglycans in obesity-associated metabolic dysfunction and meta-inflammation, Front. Immunol. 11 (2020) 769.