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Original Research

Peripartum Changes in Neuroendocrine, Angiogenic, and Inflammatory Biomarkers in Gestational Hypertension

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Abstract

Background: Hypertensive disorders in pregnancy, such as gestational hypertension (GH), pose significant risks to maternal and fetal health, affecting a substantial proportion of pregnancies worldwide. Despite their prevalence, the dynamics of various biomarkers across the peripartum period remain poorly understood, limiting comprehensive insight into their pathophysiology. This study aimed to evaluate changes in neuroendocrine, angiogenic, and inflammatory biomarkers before and after delivery in women with GH and to compare these profiles with those of normotensive controls. **Methods**: This prospective study included women with singleton vaginal deliveries, assigned to GH and control groups (n = 20 per group). Clinical data were collected, and blood samples (pre- and 2 hours post-delivery) were analyzed for chromogranin A (CgA), catestatin (CST), soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), interleukin-6 (IL-6), and C-reactive protein (CRP). Peripartum changes were evaluated using rank-based repeated-measures analysis. **Results**: CgA concentrations decreased significantly after delivery in both groups ($p_{Time} < 0.001$), with comparable peripartum kinetics ($p_{Group \times Time} = 0.718$; median difference [MD]: 2.3 ng/mL; 95% confidence interval [CI]: –5.4 to 7.8). PlGF concentrations were significantly lower in the GH group ($p_{Group} = 0.002$) and declined after birth ($p_{Time} < 0.001$), with a clinically meaningful trend toward a greater decline in the GH group (MD: 78 pg/mL; 95% CI: 30 to 220). IL-6 increased 10-fold after delivery ($p_{Time} < 0.001$), with a comparable shift between groups ($p_{Group \times Time} = 0.456$; MD: 6.9 pg/mL; 95% CI: –9.1 to 21.2). CRP concentrations increased after delivery ($p_{Time} < 0.001$), with no difference in peripartum kinetics between groups ($p_{Group \times Time} = 0.257$). Pre-delivery CgA and sFlt-1 were strongly correlated in the control group (rs = 0.636, $p = 0.003$). Sex-stratified analyses revealed significantly lower IL-6 concentrations in female fetuses within the control group (1.9 *vs.* 3.6 pg/mL; $p = 0.037$), and significantly lower PlGF concentrations in female fetuses within the GH group (73 *vs.* 153 pg/mL; $p = 0.039$). **Conclusions**: Our results align with established patterns for angiogenic and inflammatory markers, but these novel neuroendocrine findings require validation in larger groups. Incorporating neuroendocrine regulation into models of GH is a key area for future study. **Study Registration**: The study has been registered on https://zenodo.org/ (registration number: zenodo. 18958924; registration link: https://zenodo.org/records/18958924).

Keywords: gestational hypertension; peripartum changes; neuroendocrine biomarkers; angiogenic biomarkers; inflammatory biomarkers

1. Introduction

Hypertensive disorders in pregnancy represent a spectrum of conditions characterized by elevated blood pressure during pregnancy, including gestational hypertension (GH), preeclampsia, eclampsia, and chronic hypertension with superimposed preeclampsia. These disorders affect approximately 5–8% of pregnancies worldwide and are a significant cause of maternal and perinatal morbidity and mortality [1,2]. GH is the most common hypertensive disorder of pregnancy. Although its complications are generally less severe compared with preeclampsia, it is not without risk, as GH can progress to preeclampsia, and it is associated with adverse maternal and fetal outcomes. The severity of blood pressure elevation and the gestational age at presentation influence the risk of complications [1,2]. Despite extensive research, the precise etiology remains unclear, although placental dysfunction is widely recognized as a key pathogenic event, alongside angiogenic imbalance, systemic inflammation, and neuroendocrine dysregulation [3]. This complex interplay of factors contributes to the full clinical presentation of the disorder. Beyond hypertensive disorders, dysregulation of neuroendocrine, inflammatory, and angiogenic signaling pathways is frequently associated with other pregnancy complications, such as intrauterine growth restriction (IUGR), gestational diabetes mellitus (GDM), and premature membrane rupture (PROM) [4–6].

Neuroendocrine dysregulation also contributes to these disease pathogeneses, with evidence indicating changes in maternal autonomic function and increased sympathetic nervous system activity in hypertensive disorders of pregnancy [3]. Chromogranin A (CgA) is a glycoprotein widely expressed in neuroendocrine cells and serves as a precursor for multiple biologically active peptides. CgA and its peptides are involved in a range of biological processes, including the maintenance of cardiovascular homeostasis and the regulation of the immune system [7]. Catestatin (CST), a peptide derived from CgA, exhibits immunomodulatory properties and has been linked to various inflammatory conditions [8,9]. It displays vasodilatory and anti-adrenergic effects, reducing catecholamine release. Altered CST levels have been associated with blood pressure regulation in nonpregnant populations, with evidence suggesting a protective role against hypertension. Both CgA and CST are produced by the placenta and show promising theoretical potential based on their functions in vascular regulation. However, clinical evidence remains limited and inconsistent across studies [10].

Angiogenic factors, including soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), provide the strongest clinical evidence for diagnosing and monitoring hypertensive disorders in pregnancy. An imbalance between the antiangiogenic factor sFlt-1 and the proangiogenic factor PlGF results in a higher sFlt-1/PlGF ratio in pregnancies with hypertension [2]. Elevated sFlt-1 enhances inflammation by increasing endothelial sensitivity to proinflammatory factors [11], whereas PlGF deficiency impairs immunomodulatory responses and angiogenesis, further exacerbating endothelial dysfunction [12, 13].

Inflammatory markers are consistently elevated in hypertensive pregnancies and correlate with disease severity. However, their nonspecific nature limits their diagnostic utility as standalone markers [14]. The proinflammatory cytokine interleukin-6 (IL-6), produced by several cell types, including trophoblasts, mediates the acute-phase response and promotes endothelial activation [15]. C-reactive protein (CRP), an acute-phase protein synthesized by the liver, is a nonspecific marker of inflammation that may reflect systemic inflammation. This inflammatory condition contributes to widespread endothelial dysfunction throughout the maternal vasculature [14].

The process of labor and delivery induces significant physiological changes that influence circulating biomarker levels through mechanisms such as placental separation, tissue injury, and acute inflammation. Neuroendocrine markers are not well characterized during the peripartum period. Although CgA and CST have been examined in pregnancy complications data on their peripartum kinetics remain limited. Angiogenic markers change rapidly after delivery, with sFlt-1 decreasing sharply and PlGF declining more gradually [16]. Inflammatory markers also show notable fluctuations during the peripartum period. IL-6 levels increase substantially with the onset and progression of labor [17], and CRP levels exhibit an early postpartum spike that correlates with labor duration, the number of vaginal examinations, and intrapartum interventions [18].

This study investigates six biomarkers representing distinct pathophysiological pathways: neuroendocrine markers (CgA, CST), angiogenic factors (sFlt-1, PlGF), and inflammatory markers (IL-6, CRP), along with their potential interconnections and temporal patterns before and after delivery in GH. The primary aim of this study was to compare the peripartum kinetic shifts of the neuroendocrine markers CgA and CST between normotensive pregnant women and those with GH. Secondary and exploratory objectives included assessing peripartum changes in angiogenic and inflammatory biomarkers, analyzing relationships among biomarkers, and investigating the potential influence of fetal sex on these profiles. To our knowledge, this is the first study to characterize the immediate peripartum kinetics of neuroendocrine markers in GH.

2. Materials and Methods

2.1 Subjects

The study was conducted at the Department of Gynecology and Obstetrics at Sestre Milosrdnice University Hospital Center, Zagreb, Croatia, from January 2023 to March 2025. The hospital's Ethics Review Board (ERB) approved the study. Written informed consent was obtained from all participants. The study included multiparous women with singleton pregnancies undergoing vaginal delivery. Exclusion criteria included preexisting autoimmune, coronary, and renal diseases; use of proton pump inhibitors; known fetal anomalies; and IUGR. To exclude Hemolysis, Elevated Liver enzymes, Low Platelets (HELLP) syndrome, pregnancies with creatinine levels $>$100 µmol/L, uric acid $>$310 µmol/L, aminotransferase levels $>$70 IU/L, lactate dehydrogenase $>$600 IU/L, and platelet counts $<100 \times 10^9$/L were not included. Labor was induced by amniotomy and oxytocin between 39 and 41 weeks of gestation without the use of epidural analgesia. Fig. 1 summarizes the study design.

Women were divided into either the GH group (n = 20) or the control group (n = 20). GH was defined according to the American College of Obstetricians and Gynecologists criteria [1] as systolic blood pressure (sBP) $\geq$140 mmHg and/or diastolic blood pressure (dBP) $\geq$90 mmHg on two separate occasions at least 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure.

2.2 Clinical and Anthropometrical Assessments

Maternal, pregnancy, and neonatal characteristics were recorded, including age, blood pressure, height, weight, gestational weight gain, smoking status, gestational age at delivery, birth weight and length, and the neonatal sex. Birth weight centiles were calculated according to

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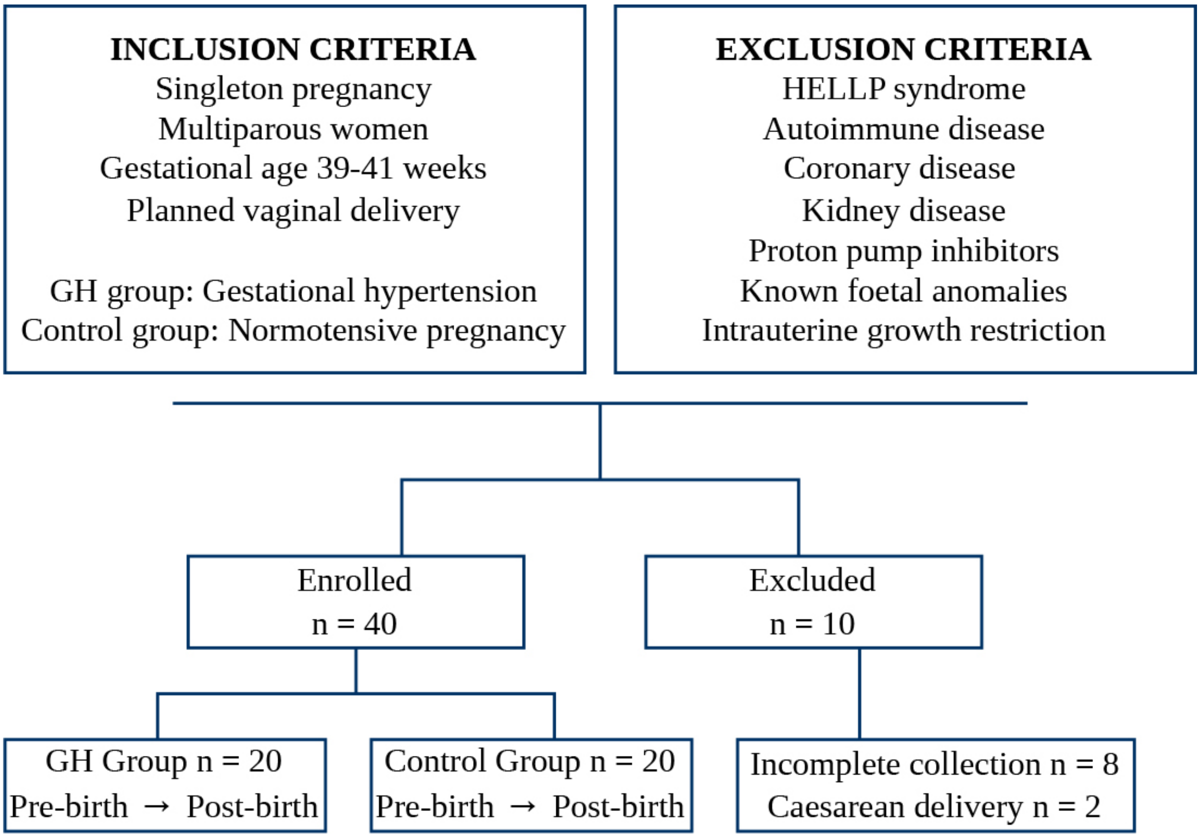

Fig. 1. Study flowchart showing initial inclusion and exclusion criteria, the number of participants enrolled with peripartum sample collection, and the number of participants subsequently excluded. GH, gestational hypertension; HELLP, Hemolysis, Elevated Liver enzymes, Low Platelets.

Nicolaides *et al*. [19]. Body mass index (BMI) was calculated as body mass (kg) divided by the square of height (m^2).

2.3 Laboratory Assessments

Blood samples were collected before labor (pre-birth) and 2 hours postpartum after expulsion of the placenta (post-birth). Samples were obtained by venipuncture into tubes containing a clot activator (7 mL Vacuette, Greiner Bio-One GmbH, Kremsmünster, Austria). After clot formation, samples were centrifuged at 2200 $\times$g for 10 minutes, and the serum was stored at –80 °C until analysis.

In all samples, concentrations of CgA, CST, sFlt-1, PlGF, IL-6, and CRP were measured. CgA and CST concentrations were measured using enzyme-linked immunosorbent assay (ELISA). The manufacturer of the CgA assay (cat. no. TM E-9000, LDN Labor Diagnostika Nord GmbH & Co. KG, Nordhorn, Germany) reports a measurement range of 2.3–900 ng/mL, with an intra-assay coefficient of variation (CV) $<$6.3% and an inter-assay CV $<$5.3%. The manufacturer of the CST assay (cat. no. EK-053-27CE, Phoenix Pharmaceuticals Inc., Burlingame, CA, USA) reports a measurement range of 0–100 ng/mL, with an intra-assay CV $<$10% and an inter-assay CV $<$15%. Measurements for sFlt-1, PlGF, and IL-6 were performed on a Roche cobas analyzer (Roche Diagnostics GmbH, Mannheim, Germany) using an electrochemiluminescent immunoassay with the Elecsys sFlt-1, PlGF, and IL-6 reagents (cat. no. 07027818190, 07027648190, and 09015612190, respectively; Roche Diagnostics, Mannheim, Germany). CRP concentrations were measured with an Abbott Alinity analyzer (Alinity, Abbott, Chicago, IL, USA) using the Abbott CRP reagent kit (cat. no. 07P5620, Abbott, Chicago, IL, USA).

2.4 Statistics

Results were analyzed using MedCalc (v22.014, MedCalc Software Ltd., Ostend, Belgium) and RStudio (v2025.09.02, Posit Software, PBC, Boston, MA, USA). Sample size was determined based on peripartum CgA concentrations to achieve 80% statistical power (β = 0.2) at a 5% significance level (α = 0.05) [20]. Due to the small sample size (n = 20 per group), nonparametric statistical methods were applied without testing for normality. Continuous variables were expressed as medians with interquartile ranges (Q1; Q3), whereas categorical variables were presented as frequencies and percentages.

For baseline maternal and neonatal characteristics, as well as fetal sex effects, differences between independent groups were assessed using the Mann-Whitney U test, and

Table 1. Maternal and neonatal characteristics.

	Control	GH	MD (95% CI)	*p*-value
Maternal characteristics				
Age (years)	35 (30; 38)	32 (30; 38)	–1 (–4; 3)	0.786
BMI (kg/m^2)	27.1 (26.4; 28.2)	32.0 (29.7; 37.4)	4.9 (2.7; 8.5)	<0.001
Weight gain (kg)	13 (9; 17)	12 (11; 14)	–1 (–4; 2)	0.694
sBP (mmHg)	110 (110; 120)	143 (135; 157)	30 (25; 40)	<0.001
dBP (mmHg)	70 (65; 80)	88 (80; 90)	15 (10; 20)	<0.001
Smoking	1 (5%)	0 (0%)	–	1.000
Neonatal characteristics				
Sex (male)	11 (55%)	12 (60%)	–	1.000
Birth weight (g)	3645 (3320; 3990)	3375 (3210; 3835)	–190 (–460; 80)	0.164
Birth length (cm)	51 (50; 52)	50 (49; 52)	–1 (–2; 1)	0.352
Birth weight (centile)	69 (48; 88)	72 (52; 92)	2 (–15; 18)	0.655

The values presented as median (Q1; Q3) were tested using the Mann-Whitney U test, and the values presented as frequency (percentage) were tested using Fisher's exact test. Effect size is expressed as the Hodges-Lehmann MD for continuous variables with 95% CI. Effect size is not applicable for categorical variables. n = 20 per group. CI, confidence interval; BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure; MD, median difference.

categorical data were analyzed using Fisher's exact test. A *p*-value of 0.05 was considered statistically significant. To evaluate peripartum biomarker dynamics, a unified rank-based longitudinal model was applied using the Wald-type statistic to simultaneously assess the main effects of group (control *vs.* GH) and time (pre-birth *vs.* post-birth), as well as their interaction (Group × Time). Multiplicity control was maintained using the Bonferroni adjustment. For the primary neuroendocrine endpoints (CgA and CST), the primary comparison was the Group × Time interaction, with a Bonferroni-adjusted significance threshold of α = 0.025 (0.05/2). Secondary endpoints were analyzed as exploratory outcomes without a Bonferroni adjustment. Effect size was estimated by calculating the Hodges-Lehmann median difference (MD) with corresponding 95% confidence interval using the Mann-Whitney U test applied to measured values for group comparisons, and to per-subject peripartum changes (Δ = post − pre) for the Group × Time interaction effect.

To determine correlations between CgA and CST and clinical and laboratory variables, Spearman's rank correlation test was used. Bonferroni correction was applied separately for each neuroendocrine marker, with an adjusted significance threshold of α = 0.007 (0.05/7). Results were reported as the Spearman rank correlation coefficient (rs) and its 95% CI.

3. Results

3.1 General Characteristics of the Study Population

The study included 20 pregnant women in the control group and 20 in the GH group, all with full-term deliveries between 39 and 41 weeks of gestation. Maternal and neonatal characteristics are summarized in Table 1. The GH group demonstrated significantly higher sBP and dBP, as expected by the study design (both $p < 0.001$). Furthermore, women in the GH group had a significantly higher BMI, with a MD of 4.9 kg/m^2 (95% CI: 2.7 to 8.5). Gestational weight gain did not differ between groups, with a MD of –1 kg (95% CI: –4 to 2), suggesting that BMI differences preceded pregnancy. No other maternal characteristics, such as age and smoking status, differed significantly between groups. Similarly, neonatal outcomes, including birth length, birth weight, and birth weight centiles, showed no significant differences between the groups.

3.2 Peripartum Changes and Interaction Analysis

Fig. 2 presents box plots for CgA (A), CST (B), sFlt-1 (C), PlGF (D), IL-6 (E), and CRP (F) in the control and GH groups before and after birth. Table 2 presents medians with interquartile ranges for each biomarker at the pre- and post-birth time points for both groups, as well as the results for the main effects and time-by-group interaction. To evaluate peripartum changes in biomarkers, an integrated rank-based longitudinal model was employed to assess the main effects of group (p_{Group}) and time (p_{Time}), as well as their interaction ($p_{Group \times Time}$), using Wald-type statistics. The interaction effect size is expressed as the Hodges-Lehmann MD in peripartum changes between the GH and control groups, with 95% CIs.

For the primary neuroendocrine endpoints, CgA and CST, trends toward lower concentrations in the GH group were observed (CgA p_{Group} = 0.072; CST p_{Group} = 0.088), but these did not reach statistical significance. A significant main effect of group was identified for PlGF (p_{Group} = 0.002), with markedly lower concentrations in the GH group at both pre- and post-birth time points compared with controls. A highly significant main effect of time was observed for most biomarkers ($p_{Time} < 0.001$), including CgA,

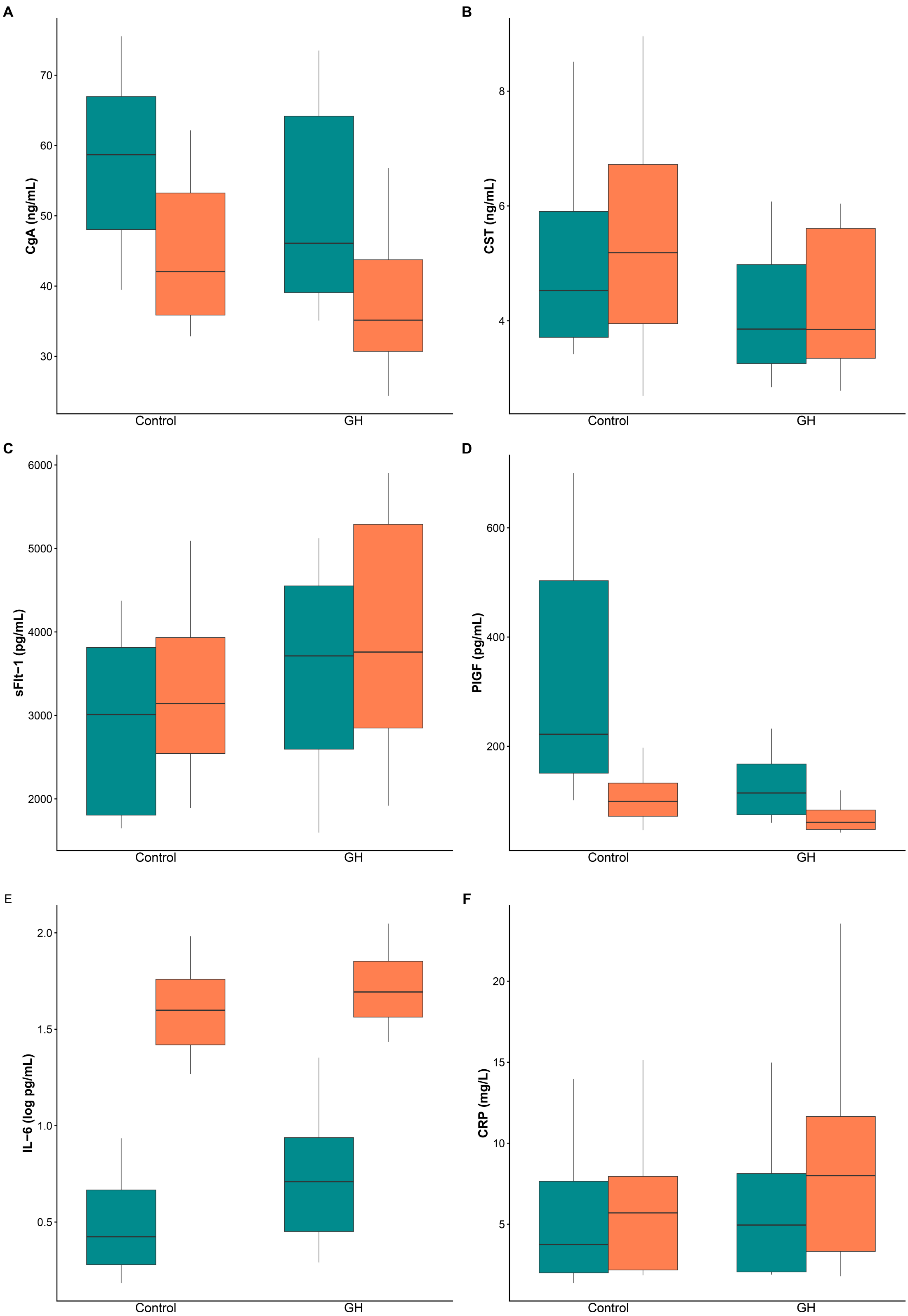

Fig. 2. Biomarker levels before and after birth in control and GH groups. Box plots display the median (central line), the interquartile range (box), and whiskers that extend to the 10th and 90th percentiles. (A) CgA. (B) CST. (C) sFlt-1. (D) PlGF. (E) IL-6 (log scale). (F) CRP. Pre-birth results are shown in green, while post-birth samples are in orange. n = 20 per group. CgA, chromogranin A; CST, catestatin; sFlt-1, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor; IL-6, interleukin-6; CRP, C-reactive protein.

PlGF, IL-6, and CRP. Specifically, CgA and PlGF concentrations declined significantly from pre-birth to 2 h post-birth, whereas inflammatory markers IL-6 and CRP exhibited a substantial increase in both groups.

No significant interaction effects ($p_{Group \times Time}$) were detected for any of the analyzed biomarkers, indicating that peripartum changes were similar between the control and GH groups. For PlGF, although the interaction was not statistically significant ($p_{Group \times Time}$ = 0.312), the GH group showed a greater peripartum decline than controls (MD: 78 pg/mL; 95% CI: 30 to 220).

3.3 Biomarker Correlation Analyses

Due to multiple comparisons, Bonferroni correction was applied, with an adjusted significance threshold of $p < 0.007$ (0.05/7; 7 pairwise correlations per marker within each group). All results are presented in **Supplementary Table 1**. Since CgA and CST are less well characterized, we examined the relationship between their pre-birth concentrations and sFlt-1, PlGF, IL-6, and CRP. No correlation was found between CgA and CST in either group. A strong positive correlation was identified in the control group between CgA and sFlt-1 (rs = 0.636, 95% CI: 0.269 to 0.842; p = 0.003). No other statistically significant associations were found between CgA or CST and the remaining biomarkers.

Additionally, pre-birth neuroendocrine markers were tested in relation to sBP and dBP. In the control group, CST was positively correlated with both sBP (rs = 0.536, 95% CI: 0.122 to 0.791; p = 0.015) and dBP (rs = 0.470, 95% CI: 0.035 to 0.756; p = 0.036). However, these associations did not remain statistically significant after Bonferroni corrections for multiple comparisons. No other correlations were found in the GH group, nor for CgA in either group.

3.4 Influence of Fetal Sex

As some studies suggest that fetal sex may influence concentrations, we analyzed potential sex-related variations within each group in pre-birth samples. Sex-stratified analyses were conducted using Mann-Whitney U tests within each group, and the results are presented in Table 3, together with Hodges-Lehmann MDs and 95% CIs. In the control group, IL-6 concentrations were significantly lower in women carrying female fetuses (MD: –1.2 pg/mL; 95% CI: –4.96 to –0.02; p = 0.037), whereas PlGF concentrations showed a trend toward higher levels in the female subgroup (MD: 246 pg/mL; 95% CI: –9 to 542; p = 0.067). In the GH group, PlGF concentrations were significantly lower in cases with female fetuses (MD: –63 pg/mL; 95% CI: –112 to –11; p = 0.039). Furthermore, trends toward lower neuroendocrine marker concentrations in female fetuses were observed within the GH group for CgA (MD: –11.6 ng/mL; 95% CI: –25.3 to 0.5; p = 0.054) and CST (MD: –1.0 ng/mL; 95% CI: –2.7 to 0.2; p = 0.083). No other sex-related differences were observed for the remaining biomarkers in either the control or GH groups. Given the limited sample size of these subgroups and the exploratory nature of this analysis, these findings are reported at the nominal significance level ($p < 0.05$) and should be interpreted as hypothesis-generating.

4. Discussion

This study offers insights into the interrelationships among biomarkers across various pathophysiological pathways in GH. Our analysis of six biomarkers representing neuroendocrine, angiogenic, and inflammatory pathways demonstrated distinct patterns of expression and regulation in GH pregnancies compared with normotensive pregnancies, both before and after delivery. The current findings align with existing literature in some areas while also providing new information, especially regarding neuroendocrine markers and their relationships with other biomarker systems. To our knowledge, this is the first study to characterize immediate peripartum changes of neuroendocrine markers (CgA and CST) in GH, as well as to examine their potential interactions with angiogenic and inflammatory factors. While previous research has documented altered CgA and CST concentrations in preeclampsia [10,21,22], the acute peripartum changes of these markers in GH, and their relationship with angiogenic dysregulation, have not yet been investigated.

4.1 Neuroendocrine Markers

The similar decrease in CgA observed in both groups suggests that this decline reflects universal physiological changes during delivery. As the placenta is a major contributor to CgA production, a sharp decline in CgA following placental expulsion likely reflects the removal of this primary source [22]. The consistent magnitude of decline in both groups suggests that placental CgA production is not differentially affected by GH, despite other aspects of placental dysfunction. The literature on peripartum CgA kinetics in hypertensive disorders remains limited, making direct comparisons challenging.

Recent literature has begun to establish the relevance of CST in preeclampsia, with some studies reporting reduced [21,23] and others reporting increased concentrations [24]. Our finding of unchanged CST in GH, with no significant interaction between group and time, does not clarify these discrepancies. However, CST concentrations may differ across hypertensive phenotypes, potentially reflecting disease severity or the timing of sample collection. The lack of significant CST changes during birth in either group suggests that CST concentrations are relatively stable across the peripartum transition, at least within the 2-hour timeframe examined. Current literature provides insufficient data on CST half-life and clearance mechanisms; therefore, the similar postpartum concentrations observed may reflect insufficient time for clearance to reach non-pregnant values.

Table 2. Biomarker changes between control and GH group with interaction across time.

	Control		GH		Main effect		Interaction	
	Pre-birth	Post-birth	Pre-birth	Post-birth	p_{Group}	p_{Time}	$p_{Group \times Time}$	MD (95% CI)
CgA (ng/mL)	58.7 (47.0; 67.8)	42.1 (35.8; 53.4)	46.1 (40.0; 65.1)	35.2 (30.5; 45.5)	0.072	<0.001	0.718[1]	2.3 (–5.4; 7.8)
CST (ng/mL)	4.5 (3.7; 6.1)	5.2 (3.9; 6.7)	3.9 (3.2; 5.1)	3.9 (3.3; 5.7)	0.088	0.560	0.815[1]	–0.2 (–1.3; 0.8)
sFlt-1 (pg/mL)	3010 (1804; 3840)	3142 (2450; 4101)	3713 (2412; 4565)	3758 (2675; 5381)	0.106	0.077	0.672	–139 (–755; 402)
PlGF (pg/mL)	222 (146; 507)	99 (70; 136)	115 (73; 171)	61 (48; 85)	0.002	<0.001	0.312	78 (30; 220)
IL-6 (pg/mL)	2.6 (1.9; 5.3)	39.7 (24.4; 57.6)	5.1 (2.8; 8.8)	49.4 (36.0; 72.6)	0.091	<0.001	0.456	6.9 (–9.1; 21.2)
CRP (mg/L)	3.8 (2.0; 8.4)	5.7 (2.2; 8.5)	5.0 (2.0; 8.2)	8.0 (3.0; 11.7)	0.330	<0.001	0.257	0.7 (–0.8; 2.8)

Data for pre- and post-birth groups are presented as median (Q1; Q3). p-values for main effects (Group and Time) and the interaction (Group $\times$ Time) were derived from a rank-based longitudinal model using the Wald-type statistic. Interaction effect size is expressed as the Hodges-Lehmann MD with 95% CI, using the Mann-Whitney U test applied to per-subject peripartum changes (Δ = post – pre). [1] Primary endpoints (Group $\times$ Time interaction for CgA and CST) evaluated with Bonferroni-adjusted $\alpha = 0.025$ (0.05/2). All other main effects and interactions are exploratory and not adjusted for multiple comparisons ($p < 0.05$). n = 20 per group.

Table 3. Pre-birth results based on fetal sex.

	Control				GH			
	Male	Female	MD (95% CI)	p-values	Male	Female	MD (95% CI)	p-values
CgA (ng/mL)	55.0 (40.9; 65.7)	59.1 (55.1; 69.9)	5.1 (–14.6; 19.9)	0.370	51.7 (44.9; 65.1)	38.8 (34.3; 56.5)	–11.6 (–25.3; 0.5)	0.054
CST (ng/mL)	4.5 (3.8; 5.6)	4.6 (3.5; 7.6)	0.6 (–1.1; 3.1)	0.648	4.0 (3.7; 5.8)	3.3 (2.6; 4.6)	–1.0 (–2.7; 0.2)	0.083
sFlt-1 (pg/mL)	3038 (2329; 3897)	2458 (1673; 3227)	–691 (–1545; 470)	0.261	3345 (1763; 4763)	3891 (3316; 4514)	658 (–840; 2224)	0.427
PlGF (pg/mL)	185 (127; 289)	500 (218; 751)	246 (–9; 542)	0.067	153 (106; 180)	73 (65; 113)	–63 (–112; –11)	0.039
IL-6 (pg/mL)	3.6 (2.1; 7.2)	1.9 (1.5; 2.6)	–1.24 (–4.96; –0.02)	0.037	4.5 (2.3; 7.3)	7.7 (3; 16)	2.6 (–1.7; 11.4)	0.231
CRP (mg/L)	4.0 (2.3; 12.0)	2.1 (1.6; 6.7)	–1.8 (–6.5; 1.5)	0.223	3.7 (2.0; 7.6)	7.9 (3.1; 8.7)	–1.1 (–3.8; 6.0)	0.354

Data presented as median (Q1; Q3). p-values were derived using the Mann-Whitney and were not adjusted for multiple comparisons (exploratory analysis). Effect size is expressed as the Hodges-Lehmann MD with 95% CI. Control group (male: n = 11, female: n = 9); GH group (male: n = 12, female: n = 8).

In summary, the absence of significant differences in CgA and CST between the control and GH groups at either time point suggests that these markers are not specific for distinguishing GH from normal pregnancy in our cohort.

4.2 Angiogenic Biomarkers

The absence of elevated sFlt-1 in GH aligns with established literature indicating that this disorder represents a milder placental dysfunction compared with preeclampsia [25,26]. Severe preeclampsia is characterized by marked elevations in sFlt-1 and markedly elevated sFlt-1/PlGF ratios that predict adverse outcomes [27,28], whereas GH typically shows minimal or absent sFlt-1 elevation [25,26,29,30]. This distinction reflects fundamental differences in placental pathology between these conditions.

Our finding of significantly lower PlGF concentrations in the GH group at both time points supports PlGF as a marker of placental dysfunction in GH. This is consistent with extensive literature establishing PlGF as a key biomarker in hypertensive disorders of pregnancy [27]. Lower PlGF concentrations observed are consistent with studies across the spectrum of hypertensive pregnancy disorders, although the reductions are typically more pronounced in severe preeclampsia than in GH. These variations in biomarker concentrations likely indicate a generalized placental response that is not exclusive to a single hypertensive condition, aligning with the evidence that specific signaling pathways are fundamental for maintaining overall placental function and health throughout gestation [31].

Literature reports an sFlt-1 half-life of approximately 1.4 days, with concentrations falling to less than 1% of pre-delivery values within the first week, while PlGF has a longer half-life of approximately 3.7 days and stabilizes at approximately 30% of pre-delivery values within the first week [16]. Our sampling at 2 hours post-birth likely captures only the earliest phase of this clearance. For sFlt-1, this timeframe may be too early to detect a significant decline, as initial release from the separating placenta may maintain circulating concentrations before clearance mechanisms predominate, resulting in no significant difference in peripartum kinetics between groups. In contrast, our measurements at the 2-hour time point captured the early decline in PlGF concentrations, with substantially lower levels in the GH group. Although the Group × Time interaction for PlGF did not reach statistical significance, the MD suggests a clinically meaningful trend toward a greater decline in PlGF in the GH group.

In clinical practice, the sFlt-1/PlGF ratio is used as a diagnostic tool for short-term prediction of preeclampsia after 20 weeks of gestation [27,28]. However, the present analysis focused on behavior of individual biomarkers during the peripartum period to characterize their specific kinetic patterns and responses to delivery without introducing additional analytical complexity.

4.3 Inflammatory Markers

The higher pre-birth IL-6 concentrations in the GH group suggest chronic low-grade inflammatory activation in GH, consistent with extensive literature linking proinflammatory cytokines to hypertensive pregnancy disorders [14]. Although the group effect did not reach statistical significance, the magnitude of baseline difference suggests that systemic inflammation is an intrinsic feature of the pathophysiology of GH, rather than simply a consequence of clinical complications or interventions. The pre-existing elevation of IL-6 may contribute to the hypertensive phenotype through IL-6-mediated endothelial activation and vascular dysfunction [14,15].

The marked post-birth increase in IL-6 in both groups (approximately 10-fold) likely reflects the combined inflammatory stimuli of delivery, tissue injury, and placental separation [17,32]. The absence of a between-group difference in the magnitude of this increase suggests that the labor and delivery process produces a stimulus that overrides baseline differences between groups, resulting in a parallel inflammatory response in both normotensive and GH pregnancies.

The non-significant differences in CRP between groups are consistent with the literature reporting heterogeneous CRP responses across hypertensive disorder phenotypes. Although CRP is often elevated in preeclampsia, variability across studies likely reflects differences in disease severity, timing, and cohort characteristics [14]. The modest post-delivery CRP increase aligns with the literature, which shows that CRP typically peaks at 24 hours postpartum [18]. Our 2-hour sampling precedes this peak, explaining the modest magnitude of change compared with IL-6. As a downstream acute-phase reactant produced in response to IL-6 stimulation, CRP response is delayed, and this pattern appears unaffected by GH during the immediate peripartum period.

4.4 Relationships Among Biomarkers

The absence of a correlation between CgA and CST at any time point or across groups is a significant negative finding. Since CST is a cleavage product of CgA, a correlation between their concentrations might be expected. The lack of correlation suggests that CST levels are not solely determined by CgA availability but may instead depend on specific proteolytic processing, clearance rates, or tissue-specific regulation. Bralewska *et al.* [21] similarly reported no correlation between CgA and CST in both control and preeclamptic placentas.

The strong positive correlation between CgA and sFlt-1 in the control group, which was absent in the GH group, represents a novel and potentially important finding. CgA and its derived peptides are involved in cardiovascular homeostasis and have been linked to blood pressure regulation [7], whereas sFlt-1 modulates angiogenic balance and

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vascular permeability [27]. The positive correlation, which remained significant after Bonferroni correction for multiple comparisons, suggests that in normal pregnancy these systems may work together to maintain appropriate vascular adaptation and placental function. While CgA and sFlt-1 showed a positive association in the control group, the GH group exhibited a contrasting pattern, with lower CgA and higher sFlt-1 concentrations, although these differences did not reach statistical significance. As shared regulatory pathways between CgA and sFlt-1 remain unknown, this dissociation likely reflects a disruption of a previously synchronized physiological state rather than a direct influence of one marker on the other.

Although diminished CST concentrations have been linked to hypertension, data on the relationship between CST and blood pressure in pregnancy remain limited. Recent studies in nonpregnant populations have shown a negative correlation between CST and blood pressure [33,34], consistent with CST's vasodilatory properties and its proposed protective role against hypertension [35]. However, other studies report opposite findings, indicating a positive correlation between CST and blood pressure [24,36,37]. Our analysis identified positive correlations between CST and both sBP and dBP in the control group only, although these associations did not remain significant after Bonferroni correction for multiple comparisons. Further, larger studies are needed to clarify these inconsistencies in both the published literature and our findings.

4.5 Influence of Fetal Sex

Fetal sex may influence the concentrations of both CgA and CST in preeclamptic placental cells. CST protein concentrations were significantly lower, while *CHGA* gene expression was higher in preeclamptic pregnancies with female fetuses compared with controls [21]. In the general population, healthy female subjects typically exhibit higher CST concentrations than males, which may reflect enhanced CgA processing into CST. On the other hand, males generally have higher plasma CgA concentrations [35]. Our results showed a downward trend in both maternal CgA and CST concentrations in the GH group in pregnancies with female fetuses. However, data on sex-related differences in neuroendocrine markers remain limited.

Fetal sex also appears to influence concentrations of angiogenic markers. Male fetal sex has been associated with lower sFlt-1 concentrations [38]. In our study, no such differences were observed, consistent with Rahman *et al.* [39]. Women carrying male infants exhibit higher PlGF concentrations than those carrying female infants [39,40]. Our results show sex-specific differences in PlGF, with a trend toward higher concentrations in pregnancies with female fetuses within the control group and significantly lower concentrations in the GH group. This opposing pattern suggests that fetal sex may differently modulate maternal angiogenic balance in normal versus pathological pregnancies.

Current evidence suggests that fetal sex influences the maternal immune response, although data remain inconsistent and limited [40–42]. One study indicates that pregnant women carrying a female fetus exhibit greater stimulated cytokine production throughout pregnancy [41], whereas another shows that carrying a male fetus is associated with higher concentrations of inflammatory cytokines during pregnancy, with these differences subsiding postpartum [40]. Our study shows a lower IL-6 concentration in pregnancies with female fetuses, albeit only in the control group. This difference was not maintained in the GH group, suggesting that the systemic inflammation characteristic of GH may override baseline sex-specific immune profiles.

However, given the small subgroup sizes and the exploratory nature of sex-stratified analyses, all findings related to fetal sex should be interpreted with caution. While these findings suggest potentially relevant maternal-fetal interactions, they should be considered preliminary. Larger studies are needed to confirm these patterns before drawing definitive conclusions about how fetal sex influences the biology of hypertensive disorders.

4.6 Limitations

This mechanistic study was designed as a hypothesis-generating investigation to explore potential biomarker interactions in GH. Several limitations should be acknowledged when interpreting these findings. The sample size (n = 20 per group), while sufficient for the primary neuroendocrine endpoints, restricts the statistical power to detect subtle effects in secondary and exploratory analyses. Therefore, findings related to angiogenic and inflammatory markers, biomarker correlations, and sex-stratified analyses should be considered exploratory and hypothesis-generating rather than confirmatory. These observations regarding peripartum biomarker dynamics require external validation in larger, preferably multicenter, and adequately powered cohorts. The timing of postpartum sampling (2 hours after placental expulsion) captures acute peripartum changes but may not reflect longer-term recovery patterns.

5. Conclusions

This study demonstrates that the neuroendocrine marker CgA and inflammatory markers (IL-6, CRP) showed consistent peripartum changes, whereas CST concentrations remained stable, regardless of hypertensive status. Although no significant Group $\times$ Time interactions were detected for any biomarker, the angiogenic marker PlGF showed significantly lower concentrations in GH at both time points, consistent with impaired placental function. The loss of correlation between CgA and sFlt-1 in GH, which was observed in normotensive controls, suggests disrupted synchronization between neuroendocrine and angiogenic systems. Sex-stratified analyses revealed patterns requiring validation in larger cohorts.

These findings highlight the potential importance of neuroendocrine pathways in the pathophysiology of hypertensive pregnancy disorders. Future research should integrate neuroendocrine regulation into comprehensive models of GH, alongside established angiogenic and inflammatory mechanisms.

Availability of Data and Materials

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request and have been publicly deposited in Zenodo (https://zenodo.org/records/18958924).

Author Contributions

AB: Methodology, writing—original draft, writing—review & editing, visualisation; DB: Methodology, writing—original draft, writing—review & editing; ID: Writing—original draft, writing—review & editing, analysis; MČ: Writing—original draft, writing—review & editing, acquisition of data; SS: Writing—original draft, writing—review & editing, acquisition of data; MGR: Writing—original draft, writing—review & editing, analysis, supervision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the Ethics Committee of Sestre Milosrdnice University Hospital Center (Ethics Approval Number: 003-06/20-03/004), and all of the participants provided signed informed consent.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used Grammarly v 1.2 in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG50841.

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