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SERUM SOLUBLE HEMOGLOBIN SCAVENGER RECEPTOR (SCD163), HEME OXYGENASE-1 (HO-1) AND SESTRIN 2 (SESN2) IN FETAL HYPOXIA OF PREGNANT WOMEN WITH GESTATIONAL HYPERTENSION

SERUMSKI RASTVORLJIV RECEPTOR ZA VEZIVANJE HEMOGLOBINA (sCD163), HEM OKSIGENAZA 1 (HO-1) I SESTRIN 2 (SESN2) U FETALNOJ HIPOKSIJI KOD TRUDNICA SA GESTACIONOM HIPERTENZIJOM

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Summary

Background: To assess the value of the serum levels of sestrin 2 (SESN2), heme oxidase 1 (HO-1), and soluble haemoglobin scavenger receptor (sCD163) for the prediction of intrauterine fetal hypoxia in pregnant women with gestational hypertension disorder (HDCP).
Methods: A total of 230 pregnant women with HDCP who were diagnosed and treated at this hospital from January 2023 to December 2024 were selected as the HDCP group, and 75 pregnant women with normal pregnancies who underwent prenatal examination at this hospital were included in the control group. Changes in the levels of serum SESN2, HO-1, and sCD163 were observed in the two groups. The levels of each index in pregnant women with HDCP of different severities were compared, and patients were divided into two groups based on whether intrauterine fetal hypoxia occurred: those with intrauterine hypoxia and those without. The factors influencing intrauterine fetal hypoxia in pregnant women with HDCP, and the predictive efficacy of serum SESN2, HO-1, and sCD163 levels for intrauterine fetal hypoxia in pregnant women with HDCP, were analysed.

Kratak sadržaj

Uvod: Procena vrednosti serumskih nivoa sestrina 2 (SESN2), hem oksigenaze 1 (HO-1) i rastvorljivog receptora za vezivanje hemoglobina (sCD163) u predviđanju intrauterine fetalne hipoksije kod trudnica sa hipertenzivnim poremećajima u trudnoći (HDCP).
Metode: U HDCP grupu je uključeno ukupno 230 trudnica sa ovim poremećajem, koje su dobile dijagnozu i koje su lečene u našoj ustanovi od januara 2023. do decembra 2024. godine, dok je kontrolnu grupu činilo 75 trudnica sa urednom trudnoćom koje su obavile prenatalni pregled u istoj ustanovi. Praćene su promene serumskih nivoa SESN2, HO-1 i sCD163 u obe grupe. Upoređivani su nivoi ovih parametara kod trudnica sa HDCP – različite težine oboljenja, a ispitanice su potom podeljene na one kod kojih je došlo do intrauterine hipoksije i one bez hipoksije. Analizirani su faktori koji utiču na intrauterinu hipoksiju kod trudnica sa HDCP, kao i prediktivna vrednost serumskih nivoa SESN2, HO-1 i sCD163 za razvoj intrauterine hipoksije.
Rezultati: Trudnice sa HDCP su imale značajno više vrednosti serumskih SESN2 i sCD163 u poređenju sa grupom

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Results: The HDCP group had significantly higher levels of serum SESN2 and sCD163 than the normal pregnancy group (P<0.01), while the normal pregnancy group had significantly lower levels of serum HO-1 (P<0.01). Serum SESN2 and sCD163 levels were substantially greater in the severe preeclampsia group than in the moderate preeclampsia and gestational hypertension groups (P<0.01), while the mild preeclampsia and gestational hypertension groups had significantly lower serum HO-1 levels (P<0.01). Serum HO-1 levels in the mild preeclampsia group were significantly lower than those in the gestational hypertension group (P<0.01), while serum SESN2 and sCD163 levels were significantly higher than those in the latter group (P<0.01). While the intrauterine hypoxia group's prothrombin time and HO-1 levels were significantly lower than those of the nonintrauterine hypoxia group (P<0.01), the intrauterine hypoxia group's levels of serum D-dimer, fibrinogen (FIB), SESN2, and sCD163 were significantly higher. Multivariate logistic regression analysis revealed that elevated D-dimer, FIB, SESN2, and sCD163 levels were risk factors for intrauterine hypoxia in pregnant women with HDCP (P<0.05), whereas elevated prothrombin time and HO-1 levels were protective factors (P<0.05). The AUCs of individual and combined detection of serum SESN2, HO-1, and sCD163 for predicting intrauterine fetal hypoxia in pregnant women with HDCP were 0.823 (95% CI: 0.768–0.870), 0.868 (95% CI: 0.817–0.909), and 0.848 (95% CI: 0.795–0.8), respectively 92), 0.960 (95% CI: 0.926–0.981), and the AUC of the combined detection was significantly greater than that of SESN2 (Z=4.665, P<0.001), HO-1 (Z=4.876, P<0.001), and sCD163 (Z=4.228, P<0.001) single detection.

Conclusions: SESN2, HO-1, and sCD163 are involved in the occurrence and progression of HDCP and are closely associated with its severity. The combined detection of these three indicators helps determine a fetus's intrauterine hypoxic status.

Keywords: sestrin 2, heme oxidase 1, soluble haemoglobin scavenger receptor, hypertensive disorders in pregnancy, intrauterine hypoxia

Zaključak: SESN2, HO-1 i sCD163 učestvuju u nastanku i progresiji HDCP i blisko su povezani sa težinom oboljenja. Kombinovano određivanje ovih pokazatelja doprinosi pravovremenom prepoznavanju intrauterine hipoksije fetusa.

Ključne reči: sestrin 2, hem oksigenaza 1, rastvorljivi receptor za vezivanje hemoglobina, hipertenzivni poremećaji u trudnoći, intrauterina hipoksija

Introduction

Hypertensive disorder in pregnancy (HDCP) is a specific complication during pregnancy, with an incidence rate of approximately 10% (1–3). Its pathogenesis remains unknown to date, posing a certain threat to both pregnant women and children, and it is one of the essential reasons for adverse pregnancy outcomes (4). The common impact of HDCP on the fetus is a reduction in placental blood perfusion, which leads to relative hypoxia in the fetus, thereby affecting the normal development of the fetus and even causing complications. Therefore, early detection of fetal intrauterine hypoxia and intervention measures are the keys to preventing adverse pregnancy outcomes (5). Sestrin 2 (SESN2) is an antioxidant protein that can be activated under various conditions, such as DNA damage and hypoxia. Studies have shown that elevated serum SESN2 levels are a predictor of poor prognosis in newborns and can indicate intrauterine growth restriction (6–8). Heme oxygenase-1 (HO-1) is a protein expressed under stress, and its level is significantly decreased in HDCP, which is associated with the severity of preeclampsia and pregnancy outcomes (9). Mononuclear macrophages produce the soluble haemoglobin scavenger receptor (sCD163), a haemoglobin-specific receptor in the body (10). It can specifically bind to HO-1, thereby regulating the body's inflammatory response (11–13).

Gestational hypertension (GH) is a common complication during pregnancy that seriously threatens the health of both mothers and babies (14). Among them, GH-induced intrauterine hypoxia of the fetus is one of its most serious consequences. It can lead to adverse pregnancy outcomes, such as fetal growth restriction, premature birth, and even stillbirth (15). At present, there are still challenges in the early identification and pathological mechanism of intrauterine hypoxia in pregnant women with GH, and there is a lack of sufficiently sensitive and specific predictive and diagnostic indicators. Oxidative stress and the inflammatory response are widely regarded as the

core pathophysiological links between GH and concurrent fetal hypoxia. Exploring key biomarkers that can reflect the body's response to hypoxia, oxidative damage and inflammatory reactions is highly valuable (16). The soluble haemoglobin scavenger receptor (sCD163) is a marker of macrophage activation and is involved in haemoglobin clearance and in inflammatory regulation. Heme oxygenase-1 (HO-1) is an important antioxidant and anti-inflammatory enzyme that plays a core role in degrading free heme and reducing oxidative stress. Sestrin 2 (SESN2) is a stress-induced protein that regulates redox homeostasis and anti-apoptotic and autophagic processes. All three are closely related to hypoxia, oxidative stress and the inflammatory response (17). However, in the specific clinical situation of GH complicated with fetal hypoxia, how the levels of sCD163, HO-1 and SESN2 in the maternal circulation change, whether there is an intrinsic correlation among the three, and whether these levels can be used as new serological indicators for evaluating the state of fetal hypoxia, systematic research and clear conclusions are lacking (18–20).

Clarifying the dynamic changes and interrelationships of sCD163, HO-1 and SESN2 in the serum of pregnant women with GH during fetal hypoxia not only helps to elucidate the pathological mechanism of GH-related fetal hypoxia, especially revealing its occurrence and development process from the perspective of oxidation/inflammation but also, more importantly, provides a set of potential and easily accessible serological biomarker combinations for clinical practice, assisting in the early warning of fetal hypoxia risk in pregnant women with GH, disease assessment, and exploration of possible intervention targets. This study aims to fill the research gap in this field, evaluate the significance and application prospects of these three key molecules in GH complicated with fetal hypoxia, and provide a new scientific basis for improving the prognosis of mothers and infants.

Materials and Methods

General information

A total of 230 pregnant women with HDCP who were diagnosed and treated in our hospital from January 2023 to December 2024 were selected as the HDCP group, and all met the diagnostic criteria of HDCP. The age of the pregnant women in the HDCP group ranged from 23 to 40 years, with an average age of 32.90±5.02 years. The gestational weeks ranged from 36 to 41, with an average of 38.55±1.33 weeks. HDCP severity was classified into 93 cases of gestational hypertension, 75 cases of mild preeclampsia and 62 cases of severe preeclampsia. Seventy-five normal pregnant women who received prenatal examinations in our hospital during the same period were selected as the normal pregnancy group. Their ages ranged from 23 to 40 years, with an average of 32.52±5.66 years. The gestational age ranged from 36 to 41 weeks, with an average of 38.48±1.38 weeks. The number of pregnancies ranged from 0 to 3, with an average of 1.43±0.39. The exclusion criteria were as follows: preexisting hypertension before pregnancy; obstetric complications such as fetal malformation combined with diabetes and liver and kidney dysfunction; multiple pregnancies for which the clinical data were incomplete; and mental disability or mental illness. There was no statistically significant difference in age, gestational age, or number of pregnancies between the two groups ($P>0.05$), and the groups were comparable.

Blood sample collection and testing

After the pregnant woman was admitted to the hospital, approximately 5 mL of fasting venous blood was drawn in the early morning. The activated partial thromboplastin time, prothrombin time, thrombin time and fibrinogen (FIB) levels were determined via a hemagglutinometer. Serum D-dimer levels were determined by immunoturbidimetry. The levels of serum SESN2, HO-1 and sCD163 were determined via enzyme-linked immunosorbent assay. All the kits were purchased from R&D Company in the United States and were operated in strict accordance with the kit instructions.

Experimental methods

Five to six mL of SST tubes were collected intravenously from the subjects. After being left to stand at room temperature for 30 minutes to coagulate completely, the serum was separated by centrifugation at 4 °C and 1500–2000 × g for 10–15 minutes. Aliquot in small volumes (0.3–0.5 mL per tube), marked with number and time. Store at -80 °C and avoid repeated freezing and thawing (no more than twice).

Determination of serum sCD163, HO-1 and SESN2 (ELISA):

Addition of standard and samples: 100 μL per well (or as per the instructions), and load in parallel with two wells. Blank holes/zero standard holes are set synchronously.

Incubation: Incubate at room temperature or 37 °C (usually 1–2 hours, as per the instructions), gently shake to avoid edge effects.

Washing: Wash the plate with a washing machine 3 to 5 times. Ensure that each well is filled with and suctioned to avoid residual liquid.

Addition of the detection antibody/enzyme conjugate: 100 μL per well. Incubate as per the instructions, then wash the plate 3–5 times.

Colour development: TMB substrate colour development (10–20 min, away from light); terminate the reaction with the stop solution.

Reading: Read at 450 nm with a microplate reader, and use 570/630 nm as reference wavelengths for correction.

Experimental reagents

(1) sCD163 (Soluble CD163) ELISA Kit (Human): RayBiotech, Human CD163 ELISA Kit; item no. ELH-CD163 Specification: 96T.

(2) HO-1 (HMOX1, Heme Oxygenase-1) ELISA Kit (Human): StressMarq Biosciences, Human Heme Oxygenase 1 (HO-1) ELISA Kit; item no. SKT-109-96 Specification: 96T.

(3) SESN2 (Sestrin 2) ELISA Kit (Human): RayBiotech, Human Sestrin 2 (SESN2) ELISA Kit; item no. ELH-SESN2 Specification: 96T.

Diagnosis of fetal intrauterine hypoxia

If any of the following circumstances are true, a diagnosis can be made: More than 160 beats per minute or fewer than 120 beats per minute is the fetal heart rate; there is no variation in the baseline fetal heart rate, but late deceleration or variant deceleration occurs repeatedly. Fetal heart rate monitoring: Positive uterine contraction stress test or oxytocin irritation test; the Apgar score of the fetus 1 minute after birth is 7 points. Scalp blood gas analysis revealed acidosis. The patients were divided into the intrauterine hypoxia group and the nonintrauterine hypoxia group according to whether intrauterine hypoxia occurred.

Observation indicators

Changes in serum levels of SESN2, HO-1, and sCD163 were observed in the two groups, and the levels of these markers were compared among pregnant women with HDCP of different severities.

Statistical methods

SPSS 19.0 software was used to analyse the data. Normally distributed data are expressed as $\bar{x}\pm s$. Independent-samples t-tests were used for comparisons between two groups, analysis of variance for comparisons among multiple groups, and least significant difference (LSD) tests for pairwise comparisons among multiple groups. The χ^2 test was utilised for comparisons, and count statistics are presented as percentages and the number of cases. Multivariate logistic regression was used to analyse the factors influencing fetal intrauterine hypoxia in pregnant women with HDCP. Serum SESN2, HO-1, and sCD163 levels were examined for their predictive value of fetal intrauterine hypoxia in pregnant women with HDCP using receiver operating characteristic (ROC) curves. A P value <0.05 was considered to indicate statistical significance.

Results

Comparison of serum SESN2, HO-1 and sCD163 levels between the two groups

Serum SESN2 and sCD163 levels in the HDCP group were substantially higher than those in the group with a normal pregnancy ($P<0.01$), whereas the level of serum HO-1 was significantly lower than that in the normal pregnancy group ($P<0.01$), see *Table I*.

Comparison of serum SESN2, HO-1 and sCD163 levels in pregnant women with HDCP of different severities

Both the moderate preeclampsia and gestational hypertension groups exhibited significantly lower serum SESN2 and sCD163 levels than the severe preeclampsia group ($P<0.01$), while the mild preeclampsia and gestational hypertension groups had significantly lower serum HO-1 levels ($P<0.01$). The moderate preeclampsia group had considerably higher serum SESN2 and sCD163 levels than the gestational hypertension group ($P<0.01$), whereas the mild preeclampsia group had significantly lower serum HO-1 levels than the gestational hypertension group ($P<0.01$; see *Table II*).

Table I Comparison of serum SESN2, HO-1, and sCD163 levels between two groups ($\bar{x}\pm s$).

Group	n	SESN2 (ng/mL)	HO-1 (ng/mL)	sCD163 (mg/mL)
HDCP group	230	22.53±5.85	380.40±51.55	44.90±9.22
Normal pregnancy group	75	14.07±2.45	502.53±76.40	19.49±4.00
t		17.710	12.919	33.292
P		<0.001	<0.001	<0.001

Table II Comparison of serum SESN2, HO-1, and sCD163 levels in pregnant women with HDCP of different severity levels.

Group	n	SESN2 (ng/mL)	HO-1 (ng/mL)	sCD163 (mg/mL)
Pregnancy-induced hypertension group	93	17.47±2.96	430.38±28.27	36.97±4.66
Mild preeclampsia group	75	23.49±3.45	363.17±22.27#	45.99±4.37#
Severe preeclampsia group	62	29.96±4.29	326.28±31.91	55.47±7.22
F		202.265	287.208	221.379
P		<0.001	<0.001	<0.001

Table III Comparison of clinical data between intrauterine hypoxia group and nonintrauterine hypoxia group ($\bar{x}\pm s$).

Group	n	Age (years)	Gestational age (week)	Pregnancy times (times)	BMI (kg/m^2)	D-dimer (mg/mL)	Prothrombin time (s)
Intrauterine hypoxia group	74	33.08±4.05	38.72±1.41	1.46±0.55	29.29±2.29	875.49±146.97	20.16±4.02
No intrauterine hypoxia group	156	32.81±5.43	38.47±1.29	1.41±0.52	29.78±2.22	788.17±115.78	21.82±3.14
t		0.416	1.322	0.657	-1.768	4.492	-3.114
P		0.678	0.188	0.512	0.078	<0.001	0.002
Group	n	Thrombin time (s)	Activated partial thromboplastin time (s)	FIB (g/L)	SESN2 (ng/mL)	HO-1 (ng/mL)	sCD163 (mg/mL)
Intrauterine hypoxia group	74	23.53±4.46	49.12±6.12	4.59±0.70	27.14±5.81	336.21±37.47	52.85±8.99
No intrauterine hypoxia group	156	24.67±4.51	49.02±7.25	4.23±0.61	20.34±4.43	401.36±43.47	41.13±6.55
t		-1.806	0.106	3.894	8.918	-11.081	10.023
P		0.072	0.916	<0.001	<0.001	<0.001	<0.001

Comparison of clinical data between the intrauterine hypoxia group and the nonintrauterine hypoxia group

The patients were divided into an intrauterine hypoxia group (74 patients) and a nonintrauterine hypoxia group (156 patients) according to whether fetal intrauterine hypoxia occurred. While the intrauterine hypoxia group's prothrombin time and HO-1 levels were significantly lower than those of the nonintrauterine hypoxia group ($P<0.01$), the intrauterine hypoxia group's levels of serum D-dimer, FIB, SESN2, and sCD163 were significantly higher ($P<0.01$). Age, gestational age, number of pregnancies, BMI, thrombin time, and activated partial thromboplastin time did not differ significantly between the two groups ($P>0.05$; see *Table III*).

Multivariate logistic regression analysis was conducted to analyse the factors influencing fetal intrauterine hypoxia in pregnant women with HDCP

To determine whether intrauterine hypoxia occurred in pregnant women with HDCP as the dependent variable (occurrence =1, nonoccurrence =0) and D-dimer ($P<0.05$), prothrombin time, FIB, SESN2, HO-1, and sCD163 (*Table III*) were the independent variables (all indicators were input as original values), and multivariate logistic regression analysis was conducted. The results revealed that elevated levels of D-dimer, FIB, SESN2 and sCD163 were risk factors for intrauterine fetal hypoxia in pregnant women with HDCP ($P<0.05$), whereas elevated levels of prothrombin time and HO-1 were protective factors for intrauterine fetal hypoxia in pregnant women with HDCP ($P<0.05$), see *Table IV*.

Table IV Multivariate logistic regression analysis of factors affecting intrauterine hypoxia in HDCP pregnant women.

Indicator		SE	Wald x^2	P	OR	OR (95%CI)
D-dimer	0.006	0.002	5.574	0.018	1.006	1.001~1.010
Prothrombin time	-0.286	0.100	8.186	0.004	0.751	0.618~0.914
FIB	1.538	0.479	10.302	0.001	4.653	1.820~11.900
SESN2	0.311	0.071	19.099	<0.001	1.364	1.187~1.568
HO-1	-0.042	0.010	19.098	<0.001	0.959	0.941~0.977
sCD163	0.221	0.051	18.539	<0.001	1.248	1.128~1.380
constant term	-7.698	5.169	2.218	0.136	0.000	-

Table V Prediction efficacy of single and combined detection of serum SESN2, HO-1, and sCD163 for intrauterine hypoxia in HDCP pregnant women.

Item	Best Truncation Value	Sensitivity (%)	Specificity (%)	Youden index	P	AUC	AUC 95%CI
SESN2	24.67 ng/mL	73.0	82.7	0.557	<0.001	0.823	0.768~0.870
HO-1	382.91 ng/mL	93.2	64.7	0.579	<0.001	0.868	0.817~0.909
sCD163	47.21μg/mL	75.7	82.1	0.578	<0.001	0.848	0.795~0.892
SESN2+HO-1+sCD163		83.8	95.5	0.793	<0.001	0.960	0.926~0.981

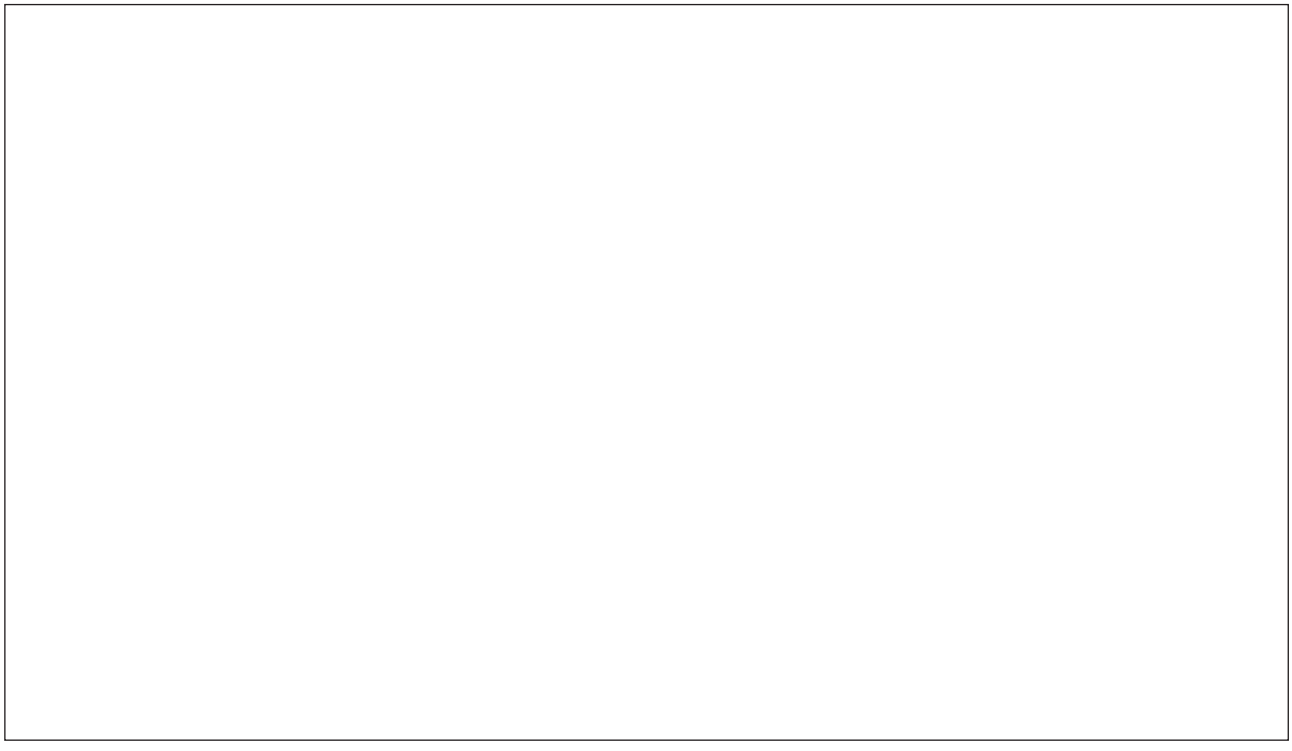

Figure 1 1 ROC curves of individual and combined detection of serum SESN2, HO-1 and sCD163 for predicting intrauterine fetal hypoxia in pregnant women with HDCP.

Predictive efficacy of serum SESN2, HO-1 and sCD163 levels for intrauterine fetal hypoxia in pregnant women with HDCP

The positive specimen was taken as the intrauterine hypoxia of the fetus in pregnant women with HDCP, and the negative specimen was taken as the absence of intrauterine hypoxia of the fetus. According to the equation Y=0.311×XSESN2-0.042×XHO-1+0.221×XsCD163 obtained from the 2.4 multivariate logistic regression analysis, the combined detection model was used. The AUCs of individual and combined detection of serum SESN2, HO-1, and sCD163 for predicting intrauterine fetal hypoxia in pregnant women with HDCP were 0.823 (95% CI: 0.768–0.870), 0.868 (95% CI: 0.817–0.909), 0.848 (95% CI: 0.795–0.8), 92), and 0.960 (95% CI: 0.926–0.981), respectively, and the AUC of the combined detection was significantly greater than that of SESN2 (Z=4.665, P<0.001), HO-1 (Z=4.876, P<0.001), and sCD163 (Z=4.228, P<0.001) single detection (*Table V* and *Figure 1*).

Discussion

The pathological features of pregnant women with HDCP are microcirculation disorders, which cause spasm of small arteries throughout the body, a significant reduction in blood perfusion to organs, and an increase in vascular permeability, leading to a decrease in placental blood flow and insufficient oxygen supply to the fetus, resulting in various complications during pregnancy, among which the most common is intrauterine hypoxia of the fetus (21–23). How to detect intrauterine hypoxia in the fetus at an early stage has important clinical significance for improving the prognosis of both the mother and the baby. This study revealed that serum D-dimer, FIB, SESN2, and sCD163 levels were significantly higher in the intrauterine hypoxia group than in the nonintrauterine hypoxia group. The intrauterine hypoxia group's HO-1 levels and prothrombin time were noticeably lower than those in the nonintrauterine hypoxia group (24). Multivariate logistic regression analysis revealed that elevated D-dimer, FIB, SESN2 and sCD163 levels are risk factors for intrauterine fetal hypoxia in pregnant women with HDCP, whereas elevated prothrombin time and HO-1 levels are protective factors for intrauterine fetal hypoxia in pregnant women with HDCP. Therefore, in this study, the levels of SESN2, HO-1, and sCD163 in the serum of pregnant women with HDCP were measured to assess their ability to predict fetal intrauterine hypoxia (25–27).

The serum SESN2 level is a marker of HDCP severity. SESN2 is an inducible protein produced during stress responses (28). Its main function is to reduce the accumulation of reactive oxygen species and participate in the pathophysiological processes of immune regulation, cell growth and autophagy. Multivariate logistic regression analysis revealed that elevated serum SESN2 levels are a risk factor for fetal intrauterine hypoxia in pregnant women with HDCP. Studies (29–31) have shown that Serum SESN2 levels are substantially higher in preeclamptic pregnant women than in healthy pregnant women, and they are linked to unfavourable pregnancy outcomes. One possible explanation is that pregnant women with preeclampsia may have ischemia-reperfusion injury in their placentas, which causes the body to release a lot of SESN2. The latter can reduce oxidative stress damage to the vascular endothelium caused by ischemia reperfusion injury (32). Moreover, SESN2 can affect the pathophysiological processes of preeclampsia by participating in autophagy, oxidative stress and other processes in the body, thereby leading to adverse pregnancy outcomes. This study revealed that when the serum SESN2 level is 24.67 ng/mL, the sensitivity for predicting intrauterine fetal hypoxia in pregnant women with HDCP is 73.0%, the specificity is 82.7%, and the AUC is 0.823, indicating that SESN2 has high predictive efficacy for intrauterine fetal hypoxia in pregnant women with HDCP (33). Pregnant women with elevated SESN2 levels are at risk of intrauterine hypoxia of the fetus (34).

Compared to the normal pregnancy group, the HDCP group's serum HO-1 level was substantially lower. As HDCP severity increased, serum HO-1 levels decreased, suggesting that HO-1 levels are related to HDCP severity (35). The main function of HO-1 is to degrade haemoglobin and produce carbon monoxide, which can alleviate the toxic effects of hypoxia and inflammatory mediators. Pregnancy-related placental development and uterine blood vessel integrity are significantly aided by its anti-inflammatory, anti-apoptotic, and antioxidant properties. Additionally, it is thought to be connected to the development of gestational hypertension. Compared to the nonintrauterine hypoxia group, the intrauterine hypoxia group's serum HO-1 level was noticeably higher. Multivariate logistic regression analysis indicated that elevated HO-1 levels were a protective factor against fetal intrauterine hypoxia in pregnant women with HDCP. The decrease in the serum HO-1 level of pregnant women caused by intrauterine hypoxia of the fetus may be due to placental ischemia and hypoxia in pregnant women with HDCP, which in turn leads to destruction of the microenvironment of the placenta and massive dissolution of trophoblast cells, resulting in a significant decrease in the HO-1 level. This study revealed that when the serum HO-1 level is 382.91 ng/mL, the sensitivity for predicting intrauterine fetal hypoxia in pregnant women with HDCP is 93.2%, the specificity is 64.7%, and the AUC is 0.868, indicating that the serum HO-1 level has high predictive efficacy for intrauterine fetal hypoxia in pregnant women with HDCP. Whether further intervention measures are warranted for pregnant women with decreased HO-1 levels remains unclear (36).

By detecting the levels of sCD163, HO-1 and SESN2 in the serum of pregnant women with gestational hypertension, the activation characteristics of maternal oxidative stress and inflammatory response under fetal hypoxia were revealed. This systemic stress state may have a potential impact on the recovery of postpartum reproductive endocrine in parturients. Oxidative damage induced by chronic hypoxia and the persistent low-grade inflammatory microenvironment may indirectly affect the reconstruction of the postpartum menstrual cycle by interfering with the functional regulation of the hypothalamic-pituitary-ovarian axis. HO-1, as the ring-limiting enzyme for heme degradation, although its continuous high expression enhances the antioxidant capacity of cells, it may alter local tissue iron homeostasis, and iron overload is associated with ovarian dysfunction. Meanwhile, the persistently activated state of macrophages, as indicated by sCD163, may prolong the postpartum inflammation-resolution cycle and interfere with endometrial repair. Although the SESN2-mediated stress protection mechanism helps to alleviate cellular damage, its long-term activation may reflect that the body is in a continuous compensatory state. The above-mentioned multi-dimensional physiological changes collectively constitute potential risk factors, which may make the patient group more prone to reproductive endocrine disorders such as delayed resumption of menstruation, cycle disorders or n

Compared to the typical pregnancy group, the HDCP group's serum sCD163 level was noticeably higher, and it increased with increasing severity of HDCP, indicating that the expression of sCD163 is related to the occurrence and development of HDCP. CD163 is a member of the scavenger receptor superfamily and regulates the expression of anti-inflammatory factors such as HO-1. Compared to the nonintrauterine hypoxia group, the intrauterine hypoxia group's serum sCD163 level was noticeably higher. An increased blood sCD163 level is a risk factor for fetal intrauterine hypoxia in pregnant women with HDCP, according to multivariate logistic regression analysis (37). The serum sCD163 level of pregnant women with gestational diabetes is significantly greater than that of normal pregnant women, and the sCD163 level is an important indicator for predicting renal function impairment. When the serum sCD163 concentration is 47.21 μg/mL, the sensitivity for predicting intrauterine hypoxia in pregnant women with HDCP is 75.7%, the specificity is 82.1%, and the AUC is 0.848, indicating that sCD163 has high predictive efficacy for intrauterine hypoxia in pregnant women with HDCP. This study also revealed that the combined detection of SESN2, HO-1 and sCD163 levels has greater predictive efficacy for intrauterine fetal hypoxia in pregnant women with HDCP. Its sensitivity was 83.8%, specificity was 95.5%, and AUC was 0.960, which was significantly greater than that of a single indicator.

Conclusion

SESN2, HO-1, and sCD163 are involved in the occurrence and development of HDCP and are associated with its severity. The combined detection of SESN2, HO-1, and sCD163 helps determine the fetal intrauterine hypoxia status.

Authors' contribution

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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