BMC Endocrine Disorders

RESEARCH

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Predictive value of growth hormone and insulin-like growth factor-1 axis for gestational diabetes mellitus: a prospective cohort study

Lingling Cui[1], Yibo Wang[1], Zhiqian Li[1], Xiaoli Yang[1], Huijun Zhou[1], Zhengya Zhang[1], Yuting Gao[1], Linpu Ji[1], Ruijie Sun[1] and Luying Qin[2*]

Abstract

Objective This study aimed to explore the role of growth hormone/insulin-like growth factor-1 risk factor axis in gestational diabetes mellitus, as well as to rank independently risk factors.

Methods This was a prospective cohort study conducted between April 2019 and April 2022. The baseline data and serum samples were collected and analyzed from 241 pregnant women during the second trimester. Logistic regression and restricted cubic spline analyses were conducted to assess the relationship between GH and IGF-1 correlated with risk of GDM. Back-propagation artificial neural network (BPNN) and Receiver operating characteristic (ROC) curve analysis were performed to identify the predictive ability of the GH/IGF-1 axis for GDM.

Results The present study found that the higher serum levels of IGF-1 and the lower serum levels of GH in pregnant women were significantly correlated with risk of GDM. GH and IGF-1 were different in both case and control groups($P < 0.05$). BPNN analysis identified IGF-1 as accounting for the highest proportion in the ranking of GDM risk prediction weights (up to 25.4%). Furthermore, the area under ROC curve (AUC) value of the GH and IGF-1 combinations reached 0.770 (95%*CI*:0.707, 0.83).

Conclusions GH (growth hormone) and IGF-1 (insulin-like growth factor 1) are intricately linked to the development of gestational diabetes mellitus (GDM). Disruptions in the GH/IGF-1 axis can trigger insulin resistance, thereby elevating the risk of GDM.

Trial registration Current Controlled Trials: ChiCTR2000028811. Registration Date:20,200,104.

Keywords Gestational diabetes mellitus, Insulin resistance, Growth hormone, Insulin-like growth factor-I risk factor, Serum

*Correspondence:
Luying Qin
qinluying761@126.com
[1]College of Public Health, Zhengzhou University, Zhengzhou 450001, Henan, China
[2]School of Nursing and Health , Zhengzhou University, Zhengzhou 450001, Henan, China

Introduction

Gestational diabetes mellitus (GDM) is the initial manifestation of diabetes mellitus resulting from aberrant glucose metabolism during pregnancy, representing a prevalent complication of gestation [1]. According to the International Diabetes Federation (IDF), GDM affects approximately 6–15% of pregnant individuals globally, with an estimated 21.1 million live births in 2021 demonstrating a prevalence of about 16.7% among pregnant women. Furthermore, individuals with a prior diagnosis of GDM are at a higher risk of developing metabolic disorders and type 2 diabetes later in life [2]. The main risk factors for GDM include genetic background, pre-pregnancy BMI, excessive weight gain, advanced maternal age, environmental factors, family history of diabetes and polycystic disease, as well as hormonal metabolism and disorders [3, 4]. However, the connection between hormone metabolism and GDM is still unclear.

During pregnancy, a natural occurrence involves the interference of hormones secreted by the placenta with the body's capacity to efficiently utilize insulin, a phenomenon referred to as insulin resistance, which is a characteristic aspect of the gestational process. However, in specific instances among women, insulin resistance may surpass a healthy threshold, ultimately resulting in the development of GDM [2]. A longitudinal study showed that healthy adolescents developed insulin resistance when growth hormone (GH) and insulin-like growth factor-I (IGF-1) increased during the period of rapid longitudinal growth, suggesting that the effects of GH were not balanced by the insulin-like effects of IGF-1 [5]. Therefore, the GH/IGF-1 axis might play a role in the development of insulin resistance.

GH, a glucose counterregulatory hormone, significantly surges in response to hypoglycemia, thereby inducing hyperglycemic effects and fostering insulin resistance [6]. The previous research showed that increased GH secretion had been well documented, suggesting that increased plasma GH concentrations might have been an important risk factor in the development of complications in diabetic patients [7]. IGF-1, a polypeptide hormone structurally resembling insulin, is primarily produced by the liver under the influence of GH stimulation. This hormone exerts its effects on peripheral target organs, mimicking insulin-like actions, enhancing insulin sensitivity, suppressing insulin resistance, and ultimately stabilizing blood glucose levels [8].

The GH/IGF-1 axis occupies a pivotal role in metabolic regulation, reproduction, and aging processes, overseeing the modulation of carbohydrate and lipid metabolism, and stimulating bodily growth [9, 10]. The GH/IGF-1 axis is likely to maintain glucose homeostasis by insulin synergy [11]. Rui Jiao et al. found a lack of GH/IGF-1 might increase risk of GDM in patients with acromegaly [12]. However, the diagnostic effect and significance of the combined effects for GDM patients remain unclear. Therefore, we collected and analyzed the basic data and serum samples from 241 Chinese women including 113 GDM cases and 128 controls in the second trimester of pregnancy to comprehensively evaluate the relationship between GH/IGF-1 axis and the risk of GDM. We hope the present study result could provide new evidence for the prevention and treatment of GDM.

Methods

Study design and population

A prospective study was conducted at the Third Affiliated Hospital of Zhengzhou University. Pregnant women who met the inclusion and exclusion criteria were recruited. Inclusion criteria: (a) the blood system function was normal (b) conception naturally (c) the clinical data were complete and traceable; Exclusion criteria: (a) a history of smoking and drinking, (b) pregnant complication or miscarried, (c) a family history of thyroid disorders, (d) took the medicine influencing hormone secretion and glucometabolism, (e) with diabetes mellitus, hypertension, disease of heart, or renal disease in pre-pregnancy. A total of 113 patients and 128 controls were recruited and written informed consent was obtained from each patient. The study was approved by the Ethics Committee of Zhengzhou University.

Measurements

Physical examination

Researchers were trained to collect data on demographic characteristics and details of the subject's pregnancy history. The weight of participants was measured using the InBody J30 (Biospace, Seoul, South Korea) and heir height was determined using a stadiometer.Participants were requested to take off their shoes and wear non-bulky clothing for standardized assessments.The pregnancy body mass index (BMI) was calculated by weight (kg)/height^2 (m^2).Following standardized protocols, two consecutive blood pressure measurements were obtained using an arm circumference-appropriate cuff, and the average of both measurements was calculated for final analysis. We calculated the waist-to-hip ratio using the formula: waist circumference (m) divided by hip circumference (m).

Laboratory testing

Maternal serum was collected at 24–28 weeks, centrifuged and stored in -80℃ refrigerator for later use. The reagents used were as follows: Concentrations of serum fasting insulin (Wuhan Elabcience Company, China), GH (Wuhan Elabcience Company, China), and IGF-1(Wuhan CUSABIO Company, China) were determined

Table 1 Baseline characteristics of the study population($N=241$)

Characteristic	GDM($n=113$)	Non-GDM($n=128$)	t /χ^2	P_{value}
Age	31(29, 34)	29(27,31)	-5.215	<0.001
BMI	22.03(20.14,22.03)	21.23(20.09,23.50)	-1.391	0.164
Education level, n%			5.181	0.070
1	3(2.7%)	6(4.7%)		
2	38(33.6%)	59(46.1%)		
3	72(63.7%)	63(49.2%)		
Residential, n%			3.518	0.061
1	49(47.1%)	71(59.2%)		
2	64(52.9%)	57(40.8%)		
Pregnancy times, n%			5.516	0.190
1	62(54.9%)	89(69.5%)		
≥ 2	51(45.1%)	39(30.5%)		
parity, n%			6.574	0.010
0	44(44.5)	71(55.5)		
1	69(61.1)	57(38.9)		
History of poor pregnancy outcome, n%			8.997	0.003
0	101(89.4%)	126(98.4%)		
1	12(10.6%)	2(1.6%)		
Family history of chronic diseases, n%			1.785	0.182
0	95(84.1%)	115(89.8%)		
1	18(15.9%)	13(10.2%)		
History of chronic disease, n%			4.008	0.045
0	3	125		
1	9	104		
Waist–hip ratio	0.89 ± 0.05	0.88 ± 0.05	1.359	0.175
SBP (mmHg)	110.95 ± 10.6	111.54 ± 10.12	0.440	0.660
DBP (mmHg)	65.43 ± 7.57	66.02 ± 8.61	0.561	0.575

Continuous data are expressed as median (P25, P75) or mean ± SD and categorical variables as number (%)

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

by enzyme-linked immunosorbent assay (ELISA) following the manufacturer's protocol. The steps are as follows:

GH and IGF-1levels were analysed by indirect Simple Step Human ELISA kits GH (Wuhan Elabcience Company, China) and IGF-1(Wuhan CUSABIO Company, China) following the manufacturer's instructions. Briefly, serum samples and standards were reacted with specific antibodies coated in the microplates for each protein under investigation and incubated at room temperature (18–25 °C) for 1 h on a plate shaker. Next, the cocktail of antibodies (capture and detector antibodies) was added and incubated as before. One hundred microliters of TMB substrate was added to the microplate and incubated as previously described. The reactions were stopped by adding 100 µl stop solution to each well, and the absorbance was read by a microplate reader at 450 nm.

Table 2 Biochemical characteristics of the study population($N=241$)

Characteristic	GDM($n=113$)	Non-GDM($n=128$)	t /χ^2	P_{value}
FBG	4.96 ± 0.46	4.48 ± 0.30	-9.680	<0.001
OGTT 1hPG (mmol/L)	9.05 ± 1.71	6.98 ± 1.14	-10.877	<0.001
OGTT 2hPG (mmol/L)	8.36 ± 1.22	6.50 ± 0.94	-13.125	<0.001
Fasting insulin	21.98 ± 14.77	21.51 ± 12.04	0.278	0.781
HOMA-IR	4.55(3.54,4.55)	3.61(2.95,3.61)	-2.809	0.005
$AUC_{Glucose}$	15.71 ± 2.03	12.47 ± 1.41	-14.206	<0.001
IGF-1	7.33 ± 6.09	3.66 ± 3.44	-5.658	<0.001
GH	0.60 ± 0 0.73	0.91 ± 1.33	2.278	0.024

Continuous data are expressed as median (P25, P75) or mean ± SD

FPG fasting plasma glucose, OGTT oral glucose tolerance test, 1hPG 1-h plasma glucose, 2hPG 2-h plasma glucose, HOMA-IR homeostasis model assessment of insulin resistance, IGF insulin-like growth factor, GH growth hormone

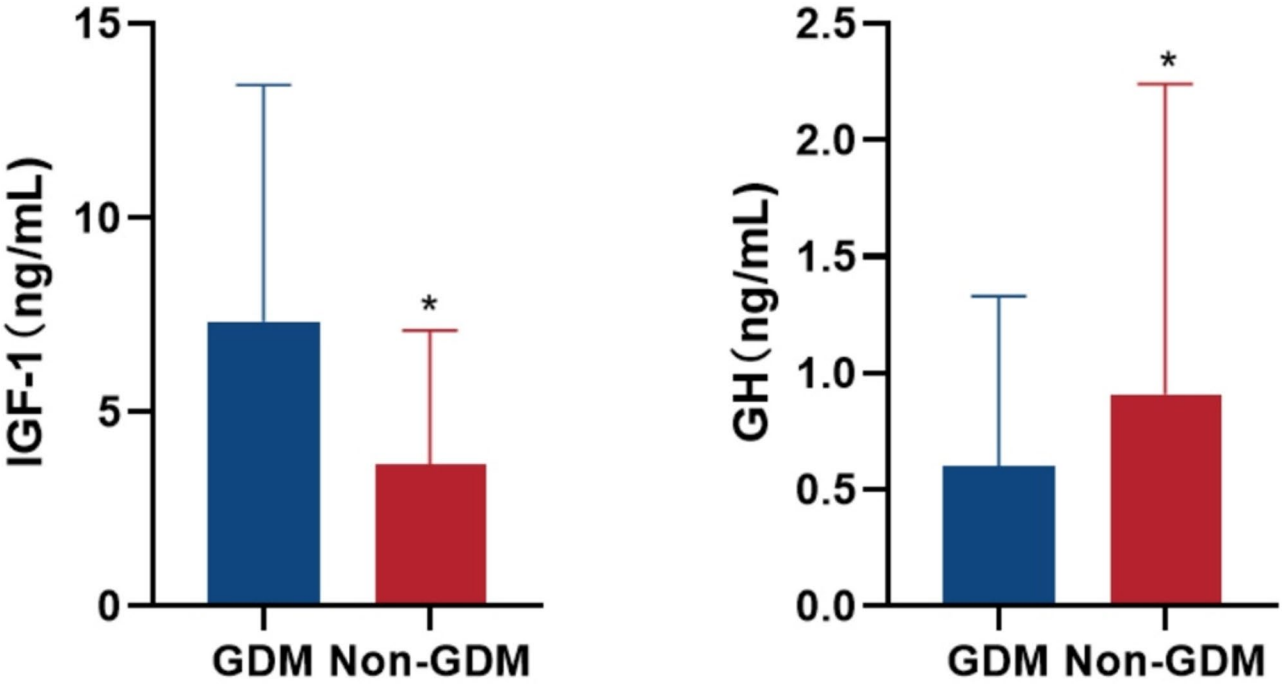

Fig. 1 Blood IGF-1and GH levels in GDM and Non-GDM pregnant women. Data were expressed as mean ± S.D. *$p < 0.05$, considered as statistically significant

Outcome assessment

At 24–28 gestational weeks, all participants underwent a standardized 2-hour 75 g oral glucose tolerance test (OGTT) for gestational diabetes mellitus (GDM) screening. Diagnostic criteria adhered to guidelines from the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and the World Health Organization (WHO).

Assessment of covariates

Basic information of pregnant women was collected as a covariate, including maternal age, height, ethnicity, pre-pregnancy weight, systolic blood pressure, diastolic blood pressure, family history of diabetes, gravida, education level, residence, and history of abortion.Educational levels were classified as follows: ≤9 years (basic education), 10–12 years (secondary education), and ≥ 13 years (post-secondary education). Maternal pre-pregnancy BMI was calculated from self-reported weight prior to conception and measured height, applying the standard formula (weight/height^2).

Definitions

Participants underwent a 75 g OGTT to measure plasma glucose levels. GDM diagnosis was based on IADPSG-recommended cutoffs: fasting ≥ 5.1 mmol/L, 1-hour ≥ 10.0 mmol/L, or 2-hour ≥ 8.5 mmol/L.The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR = fasting plasma insulin (μIU/L) × fasting plasma glucose (FPG) (mmol/L)/22.5. The area under the curve of glucose (AUC Glucose) was using the following formula: AUC Glucose = fasting plasma glucose (FPG) (mmol/L) + (OGTT 1 h + OGTT 2 h)/2.

Statistical analyses

Data were expressed as mean ± standard deviation (SD) for continuous variables.We performed analysis of variance (ANOVA) test (Dunnett method was used for pairwise comparisons) for continuous variables and chi-square test for categorical variables, respectively. If the data did not exhibit normal distribution, continuous variables were described as the median (interquartile range, IQR), and comparisons between groups were performed by the Wilcoxon rank-sum test. Binary logistic regression was used to test the association between GDM and IGF-1 /GH, and the results were presented as adjusted odds ratios *(ORs)* (95% confidence intervals *[CIs]*). Statistical analysis was performed by IBM SPSS 25.0 and R software (version 4.2.1).

Results

Table 1 showed the characteristics of all participants involved in this study. The median (IQR) maternal age of GDM and non-GDM in the cohort were 31 (29–34) years and 29 (27–31) years, respectively. Differences in age, parity, history of previous poor pregnancy outcome, and history of chronic diseases between the case

Table 3 Subgroup analyses of the relationship between IGF-I and GDM

Variables(ng/mL)	Model1	*P*	Model2	*P*	Model3	*P*
	OR (95%CI)		OR (95%CI)		OR (95%CI)	
IGF-1						
Q1(< 2.57)	Ref	0.000	Ref	0.000	Ref	0.000
Q2(2.57 ~ 3.88)	1.11(0.493 ~ 2.524)	0.794	0.07(0.027 ~ 0.178)	0.000	1.11(0.448 ~ 2.744)	0.822
Q3(3.88 ~ 6.05)	4.01(1.848 ~ 8.703)	0.000	0.08(0.030 ~ 0.195)	0.000	5.71(2.398 ~ 13.574)	0.000
Q4(≥ 6.05)	12.26(5.190 ~ 28.99)	0.000	0.335(0.141 ~ 0.794)	0.013	15.92(6.119 ~ 41.426)	0.000
P for trend	0.000		0.000		0.000	
GH						
Q1(< 0.12)	Ref	0.000	Ref	0.001	Ref	0.001
Q2(0.12 ~ 0.38)	3.42(1.615 ~ 7.253)	0.001	3.99(1.771 ~ 8.992)	0.001	3.40(1.560 ~ 7.403)	0.002
Q3(0.38 ~ 0.97)	0.77(0.369 ~ 1.621)	0.497	1.12(0.500 ~ 2.509)	0.782	0.81(0.374 ~ 1.732)	0.579
Q4(≥ 0.97)	0.87(0.419 ~ 1.808)	0.709	0.828(0.380 ~ 1.802)	0.634	0.85(0.398 ~ 1.801)	0.666
P for trend	0.000		0.001		0.001	

Abbreviations: FBG Fasting blood glucose; OR, odds ratio; CI, confidence interval

Model 2, adjusted for age and pre-pregnancy BMI

Model 3: further adjusted for Order of birth, history of chronic diseases and history of previous poor pregnancy outcome based on Model 2

and control groups were statistically significant (all $P < 0.05$). The levels of glucose levels of fasting (4.96 ± 0.46 vs. 4.48 ± 0.30, $P < 0.001$), 1 h (9.05 ± 1.71vs. 6.98 ± 1.14, $P < 0.001$), and 2 h (8.36 ± 1.22 vs. 6.50 ± 0.94, $P < 0.001$), HOMA-IR (4.55(3.54,4.55) vs. 3.61(2.95,3.61), $P = 0.005$), and AUC Glucose (15.71 ± 2.03vs. 12.47 ± 1.41, $P<0.001$) among cases were significantly higher than those among controls. (all $P < 0.05$, Table 2). No significant differences were found in pre-pregnancy BMI, residential area, family history of chronic diseases, SBP, DBP, waist–hip ratio, and Pregnancy times between the GDM patients and controls (all $P > 0.05$). There was no significant difference in fasting insulin level ($P > 0.05$) whereas maternal plasma IGF-1 was significantly higher and GH was significantly lower in GDM women when compared with Non-GDM. ((all $P < 0.05$, Fig. 1).

Logistic regression analysis ORs for GDM risk across quartiles of IGF-1 and GH were shown in Table 3. In model 1, compared to the first quartile of IGF-1, the crude ORs (95% CIs) of GDM risk were 4.01 (1.848, 8.703) for the third quartile and 12.26 (5.190, 28.990) for the fourth quartile, respectively (both $P < 0.05$). Compared to the first quartile of GH, the crude ORs (95% CIs) of GDM risk were 0.77 (0.369, 1.621) for the third quartile and 0.87(0.419, 1.808) for the fourth quartile, respectively (both $P < 0.05$). Adjusted for potential confounders, including maternal age, pre-pregnancy BMI, order of birth, history of chronic diseases and history of previous poor pregnancy outcome, serum IGF-1 level was still associated with a higher risk of GDM and serum GH levels were associated with a lower risk of GDM.

Table 4 Subgroup analyses of the relationship between GH and GDM

Variables(ng/mL)	Model1	*P*	Model2	*P*	Model3	*P*
	OR (95%CI)		OR (95%CI)		OR (95%CI)	
GH < 0.77						
Q1(< 2.63)	Ref	0.000	Ref	0.000	Ref	0.000
Q2(2.63 ~ 3.79)	0.054(0.17 ~ 0.164)	0.000	0.064(0.020 ~ 0.205)	0.000	0.045(0.014 ~ 0.146)	0.000
Q3(3.79 ~ 5.87)	0.069(0.023 ~ 0.205)	0.000	0.055(0.017 ~ 0.180)	0.000	0.067(0.022 ~ 0.205)	0.000
Q4(≥ 5.87)	0.208(0.072 ~ 0.598)	0.004	0.224(0.074 ~ 0.675)	0.008	0.184(0.062 ~ 0.544)	0.002
P for trend	0.000		0.000		0.000	
GH > 0.77						
Q1(< 2.46)	Ref	0.002	Ref	0.001	Ref	0.002
Q2(2.46 ~ 4.28)	0.102(0.023 ~ 0.462)	0.003	0.038(0.005 ~ 0.288)	0.002	0.024(0.003 ~ 0.218)	0.001
Q3(4.28 ~ 7.03)	0.057(0.011 ~ 0.302)	0.001	0.038(0.005 ~ 0.271)	0.001	0.033(0.004 ~ 0.252)	0.001
Q4(≥ 7.03)	0.393(0.093 ~ 1.653)	0.202	0.316(0.058 ~ 1.720)	0.183	0.201(0.033 ~ 1.220)	0.081
P for trend	0.002		0.001		0.002	

Abbreviations: FBG Fasting blood glucose; OR, odds ratio; CI, confidence interval

Model 2, adjusted for age and pre-pregnancy BMI

Model 3: further adjusted for Order of birth, history of chronic diseases and history of previous poor pregnancy outcome based on Model 2

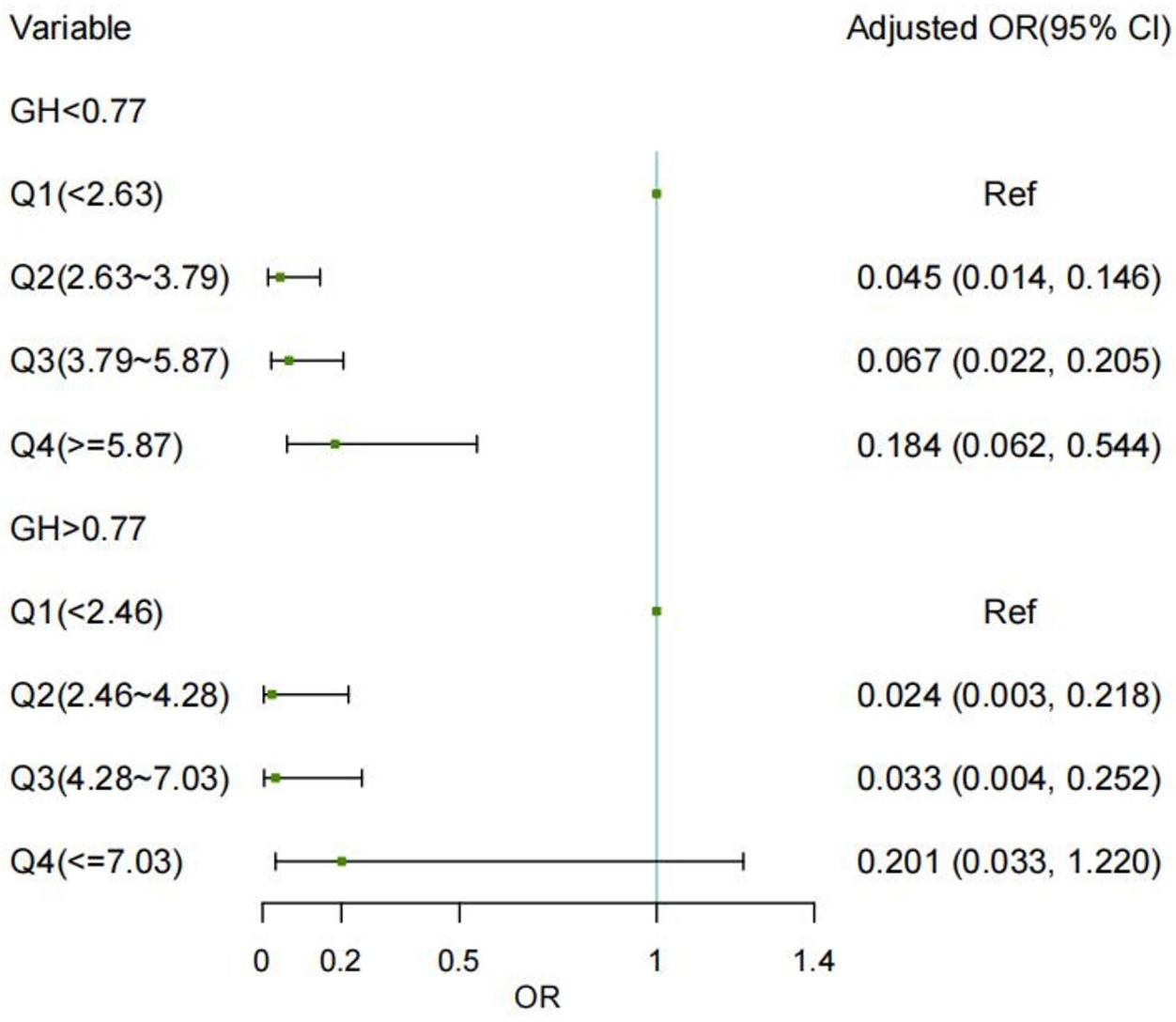

Fig. 2 Odds ratio (ORs) and 95% confidence intervals for the associations of GH with gestational diabetes mellitus (GDM)

Additionally, the linear trend tests of IGF-1 an GDM risk were also statistically significant (all $P_{trend} < 0.001$).

In the subgroup analysis (Table 4; Fig. 2), logistic regression analysis were adjusted for maternal age, pre-pregnancy BMI, order of birth, history of chronic diseases and history of previous poor pregnancy outcome. In the subgroup of GH<0.77, compared to the first quartile of IGF-1, the third quartile and the fourth quartile was negative associated with the risk of GDM[ORs (95% CIs):0.067(0.022, 0.205), 0.184(0.062, 0.544), respectively] (all $P < 0.05$) In the subgroup of GH>0.77, compared to the first quartile of IGF-1, the ORs (95% CIs) of GDM risk were 0.046(0.008, 0.281) for the third quartile and 0.238(0.049, 1.159) for the fourth quartile.

Restricted cubic spline analysis showed that IGF-1 and GH levels showed a non-linear relationship with the occurrence of GDM, respectively (Fig. 3A and B$P_{IGF-1\ trend}$ <0.001, $P_{IGF-1\ non-linear}$<0.001 and $P_{GH\ trend}$ =0.010, $P_{IGF-1\ non-linear}$=0.015). With the adjustment for confounding variables including age and pre-pregnancy BMI in Model 2, a non-linear relationship between IGF-1 and GDM (Fig. 3C, P_{trend} <0.001, $P_{non-linear}$ <0.001). GH and GDM was a non-linear relationship(Fig. 3D, P_{trend} =0.010, $P_{non-linear}$ =0.042). In the Model 3 indicated that after adjusted age, pre-pregnancy BMI, order of birth, history of chronic diseases and history of previous poor pregnancy outcome, IGF-1 and GDM was a non-linear (Fig. 3E, P_{trend} <0.001, P_{linear} <0.001), GH and GDM was a linear (Fig. 3F, P_{trend} =0.023, P_{linear} =0.062).

Receiver operating characteristic analysis showed that area under the curve (AUC) of IGF-1 and GH for predicting the risk of GDM was respectively 0.758 and 0.602(Fig. 4). The IGF-1 combined with GH for predicting the risk of GDM was higher than that of IGF-1 or GH

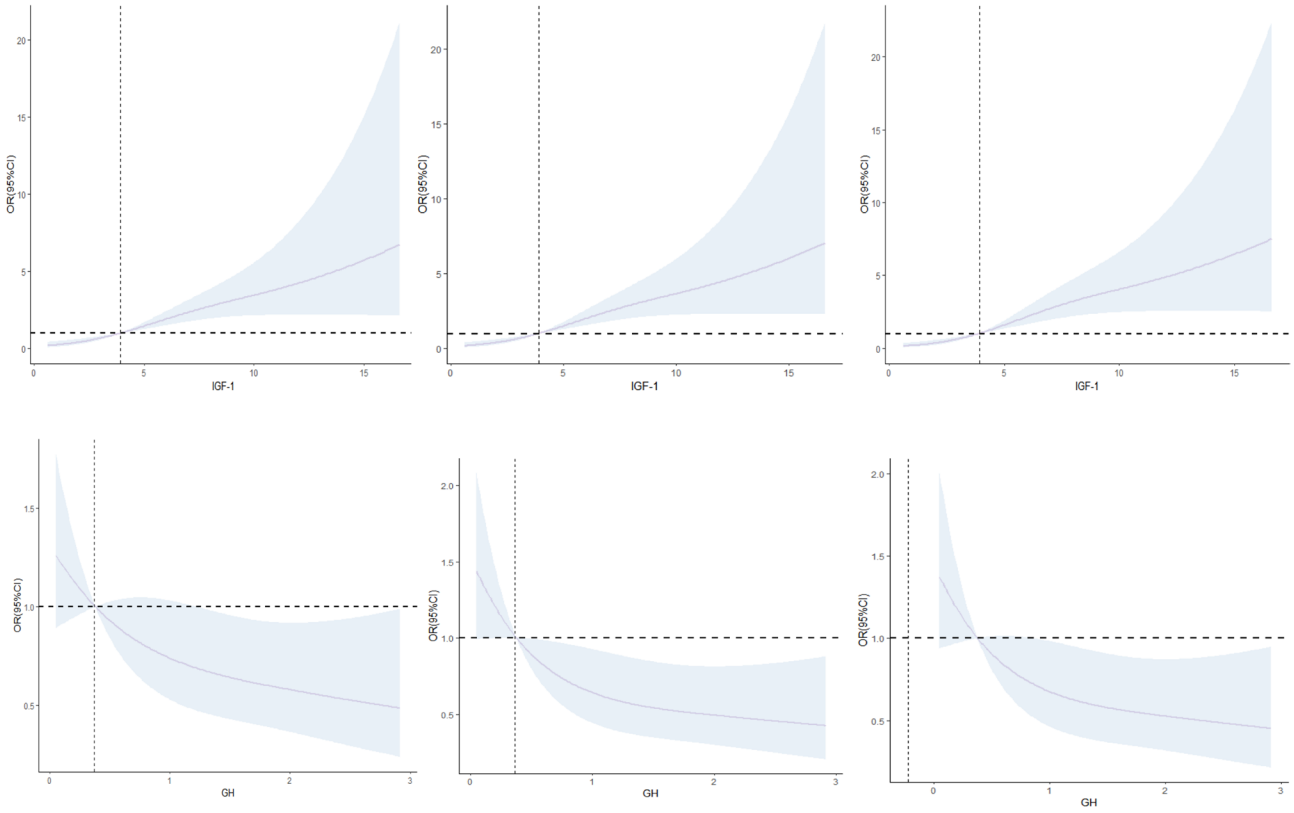

Fig. 3 The restricted cubic spline for the association between IGF-1 and GH concentration and risk of GDM

alone (AUC 0.770, 95% CI 0.707–0.83). Backpropagation artificial neural network was used to rank the weight of variables for GDM risk prediction (Fig. 5). Interestingly, FBG accounted for24.7%, ranking second after IGF-1 at 25.4%.

Discussion

To investigate the role of the GH/IGF-1 axis in GDM, we conducted an exploratory metabolomic analysis on 241 Chinese pregnant women (including 113 GDM cases and 128 normal controls) in the second trimester. By logistic regression results found that the higher serum levels of IGF-1 and the lower serum levels of GH in pregnant women were significantly correlated with an increased risk of GDM. ROC analysis showed We have found that IGF-1 and GH, either singly or in combination, were still associated with an increased risk of GDM. Furthermore, when sorting the prediction weights of GDM risk factors, the IGF-1 was higher than that of FBG.

GH possesses various vital functions, including fostering bone growth, participating in metabolic processes, modulating sexual development, and accelerating tissue repair [13]. Additionally, it plays a pivotal role in inhibiting glucose breakdown, promoting lipolysis, and maintaining a balanced interplay with insulin. A series of studies by multiple groups reported that GH has the potential to induce growth, diabetes, and hyperglycemia in animals [14, 15]. In Spain, a case-control study including 27 noninsulin-dependent diabetes mellitus of patients showed that GH secretion is well documented in insulin dependent diabetes mellitus, and it was suggested that increased plasma concentrations of GH in diabetes may be important for the development of complications [7]. In studies of growth hormone deficiency (GHD), changes in body composition and insulin resistance have been observed during GH treatment as IGF-1 concentrations shift to low- or high-normal levels in GH-deficient adults [16–18]. The binding of GH to the GH receptor (GHR) mediates downstream production of growth promoting IGF-1 and its binding protein (IGFBP-3) [19]. Our stratified analysis revealed that IGF-1 was associated with the risk of GDM when GH levels were less than 0.77 ng/mL, which might indicate that the association between IGF-1 and GDM is influenced by GH levels.

The human GH gene family consists of five tandemly arranged and highly related genes, including pituitary GH (GH-N), placental GH variant (GH-V) and the chorionic somatomammotropins (CSs) CS-A, CS-B and CS-L [20]. Placental growth hormone (PGH) is the product of the GH-V gene, predominantly expressed in the syncytiotrophoblast layer of the human placenta [21]. Its level increases in maternal circulation throughout pregnancy

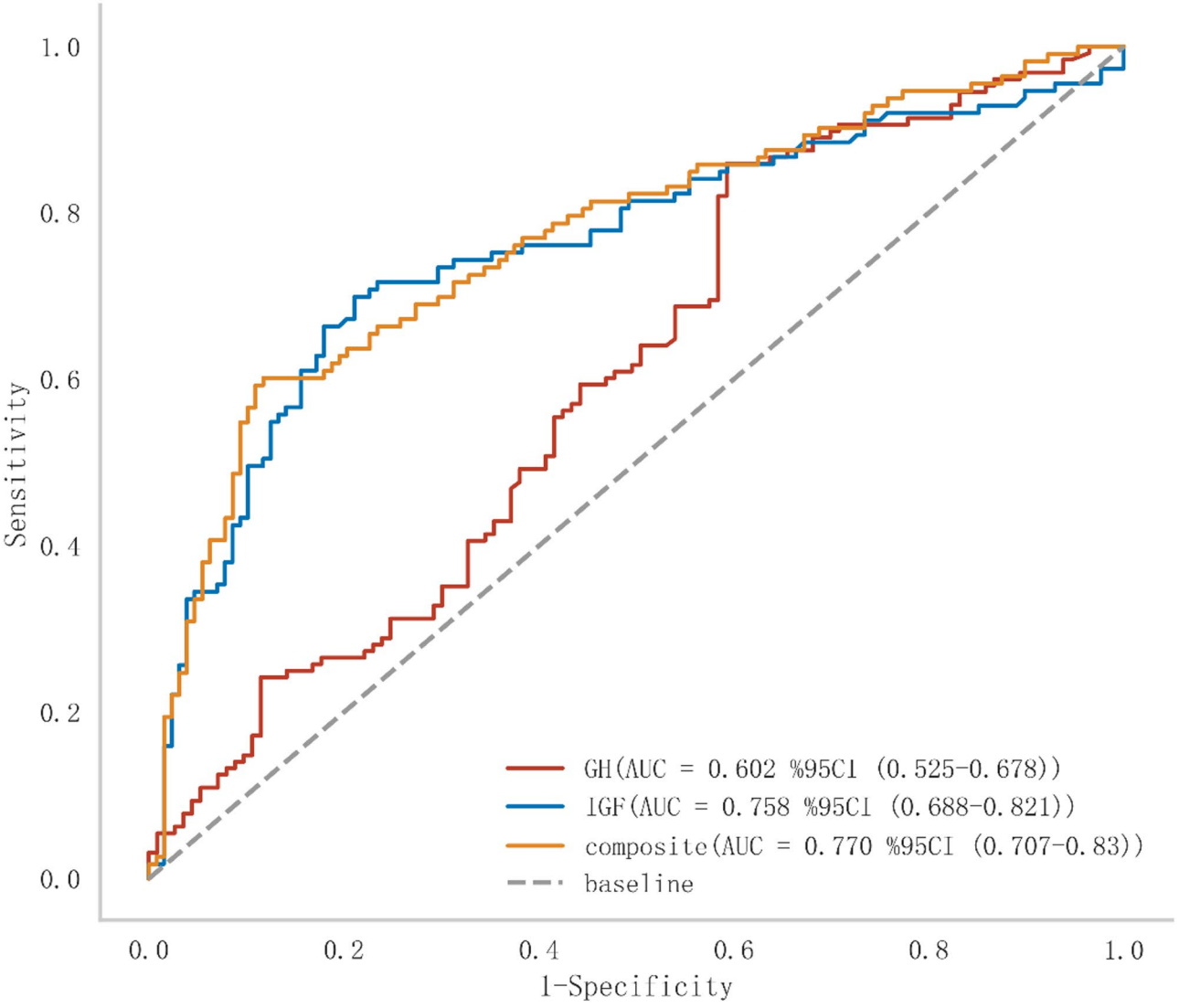

Fig. 4 Receiver operating characteristic (ROC) curves of IGF-1, GH and composite. AUC, area under the ROC curve

from gestational weeks 5 to 7 until term, and gradually after the fifteenth to twentieth week of pregnancy [22]. McIntyre et al.show a strong correlation between PGH and glycemia at 28–30 weeks of gestation and they hypothesized that in long-term regulation, PGH levels in diabetic pregnancy are driving increased glycemia [23]. The syncytiotrophoblast seems to exert partial control of maternal metabolism during pregnancy by replacing pituitary GH with its own product, PGH [24]. The present study measured GH in the serum at 24–28 weeks of gestation, which might represent the GH levels secreted majority from placenta. We found decreased maternal serum GH might increase the risk of GDM, but related mechanisms is still limited to date.

Recently, several studies also investigated the relationship between IGF-1 and GDM. An Indian cross-sectional study is in line with our findings, revealing that IGF-1 concentrations are significantly higher in the gestational diabetes mellitus (GDM) group compared to the control group during pregnancy [25]. Our study demonstrated that the serum level of IGF-1 was the risk factor for GDM in the second trimester. In a longitudinal multiracial study conducted in the United Stat, a total of 2,802 pregnant women participated, has been observed that increased concentrations of IGF-1 and IGF-1/IGFBP-3 molar ratio are related to an increased risk of GDM in early pregnancy (10–14 weeks of gestation) [26, 27]. IGF-1, along with its six binding proteins, IGFBPs, plays an intrinsic role in glucose metabolism and homeostasis within the body [28]. A significant portion of IGF-1 is bound to IGFBP-3, and IGF-1 in circulation is thought to be controlled by rapid alterations in IGFBP-1 concentrations [29]. The production of IGF-1 is dependent on a suitable supply of nutrients, such as glucose, amino

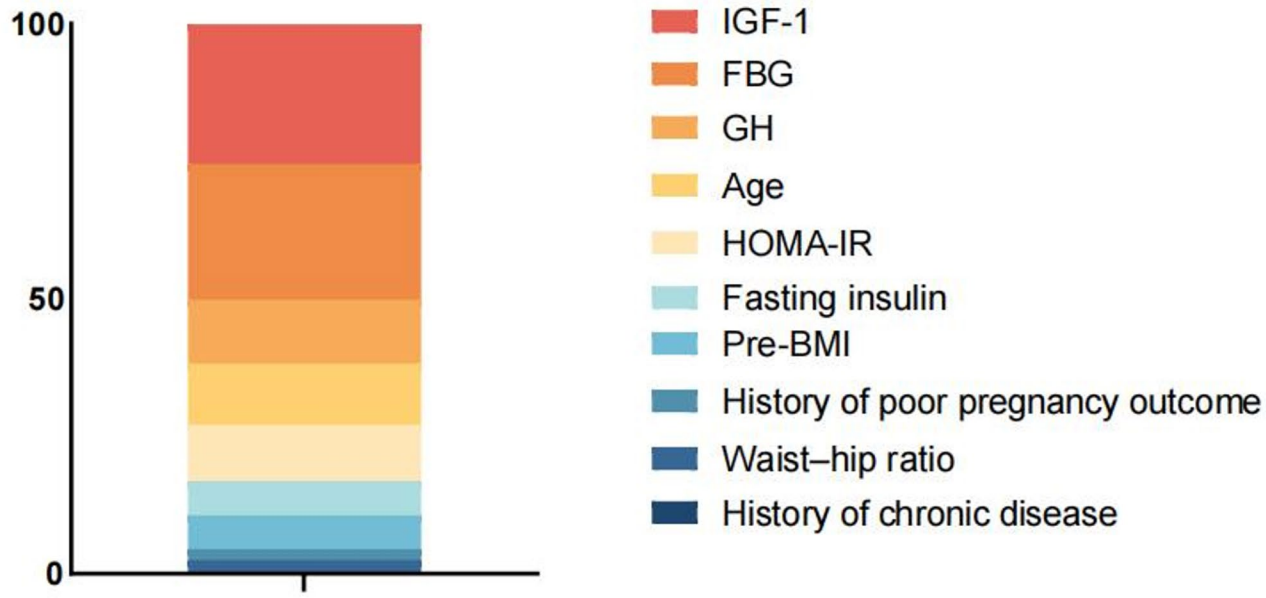

Fig. 5 Weight ranking of independent variables by the importance on the Backpropagation artificial neural network (BPNN) for predicting the risk of gestational diabetes mellitus (GDM). BPNN, Backpropagation artificial neural network

acids and lipids. It is secreted in practically every tissue for autocrine and/or paracrine purposes [30]. Moreover, IGF-1, via IGF1R and INSR downstream signaling pathways, participates in glucose transport to insulin sensitive tissues, such as skeletal muscle, adipose tissue and liver, decreasing glucose levels and improving insulin sensitivity, as IGF-1 levels does not oscillate over time as insulin does [31].

GH stimulates the liver and other tissues to produce IGF-1, which then promotes cell growth and differentiation [32]. IGF-1 provides negative feedback to the pituitary gland and hypothalamus to regulate GH secretion [33]. Although the mechanisms underlying the link of GH/IGF-1 axis to GDM were not well established. By analyzing the biochemical indicators of GDM patients in the second trimester of pregnancy, we found that IGF-1 and GH were risk factors for GDM. In a study on type 1 diabetes mellitus among children, the results indicate that the GH/IGF-1 axis may be associated with the disease process of diabetes [34]. The second trimester of gestation is a period where insulin sensitivity is impaired, in order to limit maternal glucose uptake to maintain a suitable nutrient supply for the growing fetus [35, 36]. This could be due to the effects of placental hormones, e.g., placental lactogen (PL) and GH, which stimulate the liver increasing growth factor levels, including IGF-1 [37]. This is consistent with our findings. We suggest that this may lead to increased IGF-1 levels and decreased GH levels in the second trimester of pregnancy. A meta-analysis showed that GDM was consistently associated with higher IGF-1 concentrations in mid-gestation and late gestation, which might be attributable to elevated insulin secretion [26, 38, 39], and/or enhanced secretion of placental GH the main driver of maternal IGF-1 production in pregnancy [24].

Our study has the several strengths. The GH/IGF-1 axis was used as a potential indicator of hormonal dysregulation in patients with GDM for the first time. In addition. The BPNN model is used to rank the independently related risk factors for predicting GDM. Nevertheless, there are also several limitations should be noted. Firstly, our study focused on exploring the association between GH and IGF-1 levels during the second trimester of pregnancy and the risk of developing GDM. Secondly, the pregnant participants were solely recruited from a city in central China, limiting the sample size and generalizability of the findings. Therefore, we should be cautious when extrapolating the current findings to other populations.

Conclusion

In summary, our investigation confirmed a negative association between the serum level of GH and the risk of GDM and a positive association between the serum level of IGF-1 and the risk of GDM in the second trimester. In women with GDM, dysregulation of the GH/IGF-1 axis might lead to increased IGF-1 synthesis and decreased GH synthesis. The present evidence might provide forceful epidemiological evidence for the pathogenesis and mechanism of GDM. However, more prospective studies across different stages of pregnancy and more in-depth mechanistic research should be conducted in the future

to further confirm validate the correlation between the GH/IGF-1 axis and GDM.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01953-w.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
We would like to thank all participants who accepted to participate in this study and the doctors and research assistants who participated in the study.

Author contributions
Each author is expected to have made substantial contributions to the conception.Lingling Cui design of the work; Yibo Wang the acquisition, Zhiqian Li and Zhengya zhang analysis, Xiaoli Yang and Yuting Gaointerpretation of data; Huijun Zhou and Linpu Ji the creation of new software used in the work; Ruijie Sun and Luying Qin have drafted the work or substantively revised it.AND to have approved the submitted version (and any substantially modified version that involves the author's contribution to the study); AND to have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.Corresponding authors are responsible for ensuring that all listed authors have approved the manuscript before submission, including the names and order of authors, and that all authors receive the submission and all substantive correspondence with editors, as well as the full reviews, verifying that all data, figures, materials (including reagents), and code, even those developed or provided by other authors, comply with the transparency and reproducibility standards of both the field and journal.

Funding
This study was supported by the Henan Province Key Research Project Plan of Higher Education Institutions (22A320058), Henan Province Medical Science and Technology Research (SBGJ202103090 and LHGJ20210426), Henan Province Key Research and Development Project (221111310700), and Henan Environmental and Reproductive Health Engineering Research Center. The funders had no role in the study design, implementation, analysis, decision to publish, or reparation of the manuscript.

Data availability
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Data availability
All authors make sure that all data and materials as well as the software application or custom code support their published claims and comply with feld standards.

Declarations

Ethics approval and consent to participate
The study was approved by the Clinical Trial Ethics Committee of the Third Afliated Hospital of Zhengzhou University, and the study had been registered with the Chinese Clinical Trial Registry (ChiCTR2000028811). The study adhered to the Declaration of Helsinki.

Consent to participate
Informed consent was provided by all participants before they were recruited for the study, and data were analyzed anonymously.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 5 March 2025 / Accepted: 6 May 2025
Published online: 19 May 2025

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