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Original Article

Diagnostic value of serum human chorionic gonadotropin and uterine artery Doppler indices in missed abortion

Wenjuan Li[1], Tian Zhang[1], Panpan Zhuo[1], Xiangyang Zhao[2], Yanhua Wang[2], Yanan Wei[2]

[1]*Department of Ultrasound Medicine, Baoji High-Tech Hospital, No. 19 Gaoxin Fourth Road, Baoji 721013, Shaanxi, China;* [2]*Department of Gynaecology and Obstetrics, Hanzhong People's Hospital, No. 251 North Tuanjie Street, Hantai District, Hanzhong 723000, Shaanxi, China*

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Abstract: Objective: To evaluate the combined diagnostic value of serum human chorionic gonadotropin (HCG) levels and uterine artery Doppler indices - including pulsatility index (PI), resistance index (RI), peak systolic velocity (PSV), and end-diastolic velocity (EDV) - for identifying missed abortion. Methods: This retrospective cohort study included 160 patients diagnosed with missed abortion and 200 women with normal pregnancies between January 2019 and December 2023. Serum HCG levels were measured using electrochemical immunoassay, and uterine artery Doppler indices were obtained by transvaginal ultrasound. Statistical analyses included independent t-tests, Pearson correlation, receiver operating characteristic (ROC) curve analysis, and Akaike information criterion (AIC)-based model selection to assess diagnostic performance. Results: Compared to normal pregnancies, patients with missed abortion had significantly lower HCG levels and significantly higher PI, RI, and EDV values (all $P < 0.001$). Serum HCG levels were negatively correlated with PI ($r = -0.33$), RI ($r = -0.24$), PDV ($r = -0.25$), and EDV ($r = -0.26$). The combined diagnostic model incorporating HCG, PI, RI, PSV, and EDV demonstrated the highest diagnostic accuracy, with an area under the curve (AUC) of 0.941 (95% CI: 0.918-0.964), sensitivity of 86.25%, and specificity of 87.00%. Conclusion: Combining serum HCG levels with uterine artery Doppler indices markedly enhanced the diagnostic accuracy for missed abortion compared to single biomarkers. This multimodal approach offers high sensitivity and specificity, and may be useful in clinical practice.

Keywords: Missed abortion, human chorionic gonadotropin (HCG), uterine artery Doppler

Introduction

Missed abortion is a common complication of early pregnancy, characterized by embryonic or fetal demise without immediate expulsion, resulting in prolonged retention within the uterine cavity [1]. Despite halted development, placental trophoblast cells may continue secreting hormones such as human chorionic gonadotropin (HCG), posing significant physical and psychological risks to patients. Complications may include uterine bleeding, infection, intrauterine adhesions, and, in severe cases, disseminated intravascular coagulation (DIC), which can be life-threatening [2-4]. Therefore, early and accurate diagnosis is crucial. However, diagnosis can be challenging due to subtle and nonspecific early symptoms - some patients may present only with amenorrhea, without noticeable abdominal pain or vaginal bleeding [5]. Conventional diagnostic tools such as ultrasonography and serum HCG testing each have limitations [6], underscoring the need for more accurate and efficient diagnostic approaches.

Recent advances in ultrasonography, particularly transvaginal imaging, have significantly improved the diagnosis of abnormal pregnancies [7, 8]. Transvaginal ultrasound offers high resolution without requiring bladder filling, enabling detailed visualization of embryonic and uterine structures - an advantage for detecting early missed abortion [7, 9]. Doppler ultrasonography, in particular, allows for the assessment of uterine artery blood flow, providing key insight into uteroplacental circulation

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and pregnancy outcomes [10]. Measurements such as pulsatility index (PI), resistance index (RI), and systolic/diastolic velocity ratio (S/D) directly reflect uteroplacental hemodynamic status [11]. Abnormal alterations in these indices have been associated with missed abortion and may serve as diagnostic markers [12].

HCG, a critical biochemical marker in early pregnancy, reflects embryonic viability through its dynamic fluctuations [13]. In normal pregnancies, HCG levels increase exponentially during early gestation, peak at 8-10 weeks, and then gradually decline. In cases of missed abortion, HCG levels are often significantly lower than those of normal pregnancies, suggesting its use as an early screening marker [14]. However, the diagnostic value of either HCG or uterine artery Doppler indices alone remains limited. Their combined application may enhance diagnostic accuracy.

Despite this potential, limited research has explored the combined use of serum HCG levels and uterine artery Doppler indices for diagnosing missed abortion. Most existing studies have focused on single indicators, with insufficient attention to their correlation or combined diagnostic performance [12]. The present study aimed to investigate the diagnostic use of combined HCG levels with uterine artery blood flow indices. Specifically, we compared patients with missed abortion and those with normal early pregnancies, to assess correlations between HCG and Doppler indices (PI, RI, S/D, etc.), and develop a combined diagnostic model. The model's diagnostic performance was evaluated in terms of sensitivity, specificity, and overall accuracy. Therefore, the interplay between HCG levels and uteroplacental hemodynamics, may provide a new perspective on the early diagnosis of missed abortion and the mechanisms of uteroplacental circulatory abnormalities. The findingsmay support the development of personalized management strategies, optimizing clinical outcomes and minimizing associated complications.

Materials and methods

Sample size calculation and clinical data collection

Sample size estimation was based on data from Zhang et al. [15], assuming a 15% incidence of missed abortion (P = 0.15). Using the formula $N = Z^2 \times [P \times (1 - P)]/E^2$, with a 95% confidence level (Z = 1.96) and a 5% margin of error (E = 0.05), the calculated minimum sample size was $N = (1.96)^2 \times [0.15 \times (1 - 0.15)]/(0.05)^2 = 195.92$, rounded up to 196 participants. To enhance statistical robustness and account for potential dropouts (e.g., loss to follow-up or incomplete data), the final sample size was increased to 360 participants.

From January 2019 to December 2023, 160 patients with clinically confirmed missed abortion and 200 women with normal early pregnancies were recruited from our hospital. Ethical approval was obtained from the Ethics Committee of Baoji High-Tech Hospital.

Clinical data collected included maternal age, gestational age at diagnosis, serum HCG levels, uterine artery Doppler indices (PI, RI, peak systolic velocity (PSV), and EDV), and relevant clinical information such as medical history and pregnancy-related complications. These data were used to explore associations between serum HCG levels and uterine artery hemodynamics in missed abortion.

Inclusion and exclusion criteria

Inclusion criteria: Age 18-40 years; 5-12 weeks of amenorrhea with ultrasound-confirmed missed abortion or normal intrauterine pregnancy; absence of major systemic or obstetric diseases; complete clinical records.

Exclusion criteria: Pregnancy complicated by infection or immune/metabolic disorders; use of drugs affecting placental development; uterine structural anomalies; abnormal pregnancies (e.g., ectopic); incomplete clinical or laboratory data.

Clinical data collection and testing

Clinical and laboratory data were obtained through the hospital's electronic medical records and follow-up system. Variables included: age (years), gestational age (based on last menstrual period), amenorrhea duration (≥ 2 months or < 2 months), gravidity (≥ 2 or < 2), parity (nulliparous or multiparous), BMI (kg/m^2), marital status (married/unmarried), employment status (employed/unemployed), conception method (natural or assisted reproduction), smoking history (yes/no), and alcohol consumption (yes/no). Binary variables were categorized accordingly. Serum HCG levels and vaginal ultrasound data were recorded at 8-9 weeks of gestation.

Ultrasound examination

Transvaginal Doppler ultrasound was performed by two experienced physicians using a Philips EPIQ 7 system (Eindhoven, Netherlands). Uterine artery indices measured included PI, RI, EDV, PSV, and S/D ratio. Each measurement was taken three times, and the average was used for analysis.

Outcome measures

Primary outcomes: Differences in serum HCG and uterine artery Doppler indices (PI, RI, EDV, PSV, S/D) between groups; correlation between HCG levels and Doppler indices.

Secondary outcomes: Sensitivity and specificity of individual and combined markers for diagnosing missed abortion; ROC curve analysis including AUC and optimal cutoff values.

Statistical analysis

Data were analyzed using SPSS (v26.0) and R (v4.3.3). Continuous variables were expressed as mean ± standard deviation (Mean ± SD) and compared using the independent samples t-test, depending on normality (Shapiro-Wilk test) and homogeneity of variance (Levene's test). Non-normally distributed variables were analyzed using the Mann-Whitney U test. Categorical variables were presented as frequency (%) and compared using the χ^2 test. A P value < 0.05 was considered significant.

Pearson correlation analysis was used to evaluate associations between HCG levels and uterine artery indices. Diagnostic performance was assessed using ROC curve analysis (pROC package in R), calculating AUC, sensitivity, specificity, and the Youden index. The Delong test was used to compare AUCs between ROC curves. Visualization was performed using ggplot2 and cowplot packages. All statistical tests were two-tailed, with significance set at P < 0.05.

Results

Comparison of baseline data

Baseline characteristics between the missed abortion and normal pregnancy groups showed no significant differences in age, gestational age, BMI, marital status, employment status, parity, gravidity, duration of amenorrhea, mode of conception, smoking history, or alcohol consumption (all P > 0.05) (**Table 1**).

Differences in uterine artery hemodynamic indices and serum HCG levels

Significant differences were observed in serum HCG levels and uterine artery hemodynamic indices between the two groups (all P < 0.001). Compared to the normal pregnancy group, the missed abortion group exhibited significantly lower serum HCG levels (P < 0.001, **Figure 1A**), and significantly higher PI, RI, PDV, and EDV values (P < 0.001, **Figure 1B-E**). No significant difference was found in S/D ratio between the groups (P > 0.05, **Figure 1F**).

Correlation between serum HCG levels and uterine artery hemodynamic indices

As shown in **Figure 2**, serum HCG levels were significantly negatively correlated with PI (r = -0.33, P < 0.001, **Figure 2A**), RI (r = -0.24, P < 0.001, **Figure 2B**), PDV (r = -0.25, P < 0.001, **Figure 2C**), and EDV (r = -0.26, P < 0.001, **Figure 2D**). However, there was no significant correlation between serum HCG levels and the S/D ratio (r = 0.08, P = 0.058, **Figure 2E**).

ROC curve analysis of serum HCG and uterine artery hemodynamic indices for diagnosing missed abortion

The diagnostic use of uterine artery hemodynamic indices and serum HCG levels was confirmed by this study. Among individual markers, PI showed the highest diagnostic efficacy (AUC = 0.803, 95% CI: 0.750-0.856), with a sensitivity of 66.88%, specificity of 95.00%, Youden index of 61.87%, and an optimal cutoff value of 2.295. Serum HCG also demonstrated strong diagnostic performance (AUC = 0.757, 95% CI: 0.706-0.807), with 68.12% sensitivity, 73.00% specificity, a Youden index of 41.12%, and a cutoff value of 34,214.5 mIU/mL. RI had an

Table 1. Comparison of baseline characteristics between groups

Variable	Total	Missed Abortion Group (n = 160)	Normal Group (n = 200)	Statistic Value	*P*-Value
Age (years)	29.74±4.08	30.08±4.18	29.48±3.98	-1.386	0.166
Gestational Weeks (weeks)	8.49±0.51	8.49±0.54	8.50±0.48	0.157	0.875
BMI (kg/m^2)	22.40±3.49	22.61±3.30	22.24±3.63	-1.005	0.315
Marital Status					
Married	347 (96.39%)	157 (98.12%)	190 (95.00%)	2.494	0.114
Unmarried	13 (3.61%)	3 (1.88%)	10 (5.00%)		
Employment Status					
Employed	246 (68.33%)	104 (65.00%)	142 (71.00%)	1.479	0.224
Unemployed	114 (31.67%)	56 (35.00%)	58 (29.00%)		
Parity					
Multiparous	208 (57.78%)	98 (61.25%)	110 (55.00%)	1.423	0.233
Primiparous	152 (42.22%)	62 (38.75%)	90 (45.00%)		
Gravidity					
≥ 2	178 (49.44%)	86 (53.75%)	92 (46.00%)	2.136	0.144
< 2	182 (50.56%)	74 (46.25%)	108 (54.00%)		
Amenorrhea Duration					
≥ 2 months	228 (63.33%)	98 (61.25%)	130 (65.00%)	0.538	0.463
< 2 months	132 (36.67%)	62 (38.75%)	70 (35.00%)		
Pregnancy Method					
Natural Conception	296 (82.22%)	126 (78.75%)	170 (85.00%)	2.375	0.123
Assisted Reproductive Technology	64 (17.78%)	34 (21.25%)	30 (15.00%)		
Smoking History					
Yes	115 (31.94%)	45 (28.12%)	70 (35.00%)	1.933	0.164
No	245 (68.06%)	115 (71.88%)	130 (65.00%)		
Alcohol Consumption					
Yes	29 (8.06%)	11 (6.88%)	18 (9.00%)	0.542	0.462
No	331 (91.94%)	149 (93.12%)	182 (91.00%)		

Note: BMI, Body mass index.

AUC of 0.657 (95% CI: 0.585-0.729), with 61.25% sensitivity, 99.50% specificity, and a Youden index of 60.75%. PSV and EDV had moderate diagnostic value (AUC = 0.722 and 0.701, respectively), while the S/D ratio demonstrated the lowest diagnostic performance (AUC = 0.549, 95% CI: 0.489-0.608) (**Figure 3**; **Table 2**).

Diagnostic models based on HCG and uterine artery hemodynamic indices: AIC comparison

A total of 26 diagnostic models were constructed using different combinations of HCG, PI, RI, PSV, and EDV. AIC values were calculated for each model to evaluate model fit (**Figure 4**), with lower values indicating better performance. The five models with the lowest AIC values are shown in **Table 3**. The best-fitting model (Model 1: HCG + PI + RI + PSV + EDV) had the lowest AIC (227.75). Models 2 (HCG + PI + RI + PSV) and 3 (HCG + PI + PSV + EDV) had AIC values of 255.55 and 258.62, respectively. Models 4 and 5 also showed good fit.

The diagnostic performance (AUC) of the top five models was compared against PI alone (**Figure 5**). The combined model (HCG + PI + RI + PSV + EDV) achieved the highest AUC of 0.941 (95% CI: 0.918-0.964), with 86.25% sensitivity, 87.00% specificity, and a Youden index of 73.25%, representing the best diagnostic efficacy. Other models, including HCG + PI + RI + PSV (AUC = 0.935, 95% CI: 0.911-0.958) and HCG + PI + PSV + EDV (AUC = 0.926, 95% CI: 0.899-0.952), also exhibited high diagnostic accuracy. In contrast, PI alone had an AUC of 0.803 (95% CI: 0.750-0.856), which was signifi-

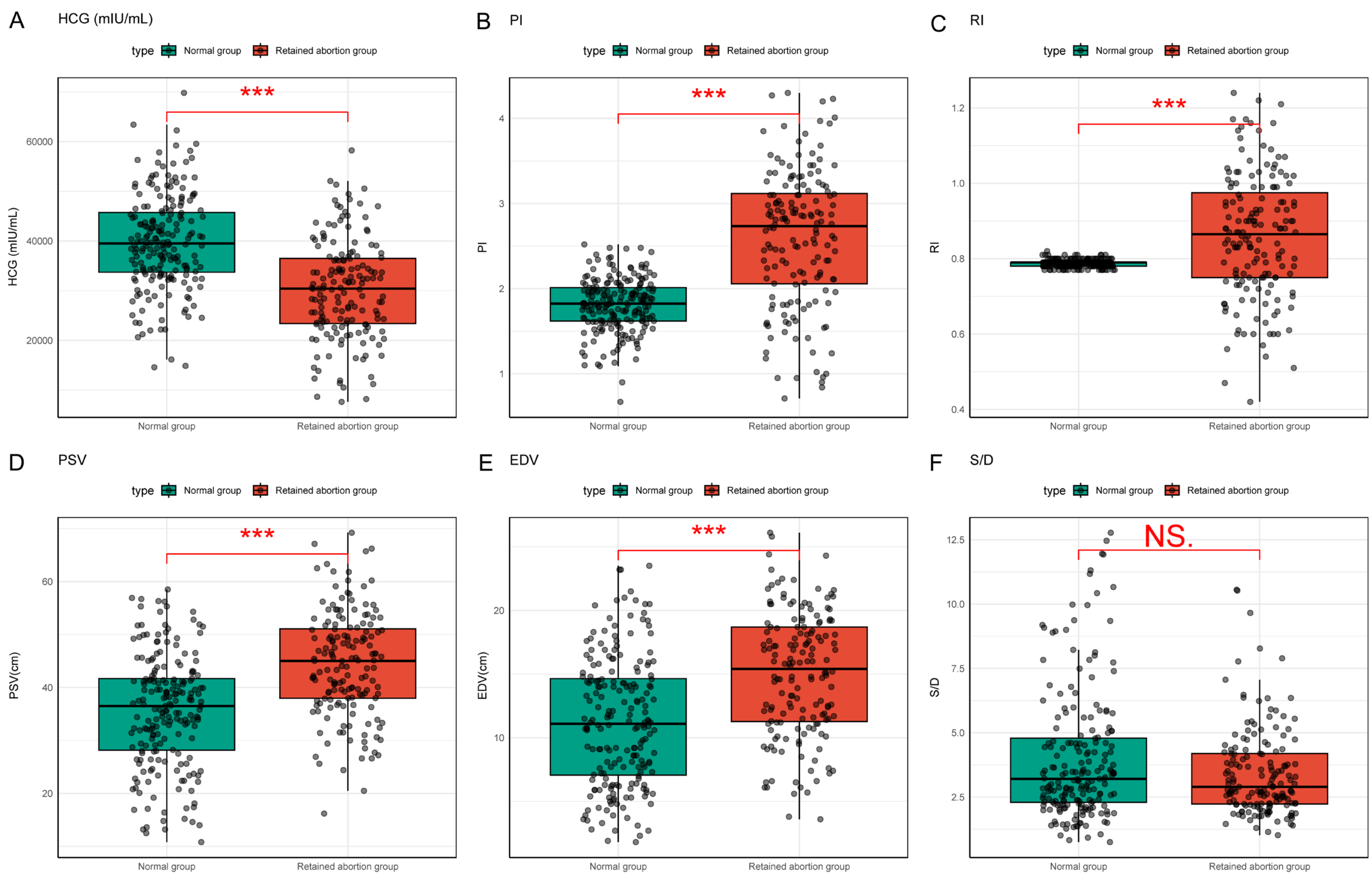

Figure 1. Intergroup differences in uterine artery blood flow indices and serum HCG levels. A: Serum HCG levels (mIU/mL); B: Pulsatility Index (PI); C: Resistance Index (RI); D: Peak Diastolic Velocity (PDV); E: End-Diastolic Velocity (EDV); F: S/D Ratio. Note: HCG, Human Chorionic Gonadotropin; PI, Pulsatility Index; RI, Resistance Index; PDV, Peak Diastolic Velocity; EDV, End-Diastolic Velocity; NS, not statistically significant. P > 0.05, ***: P < 0.001.

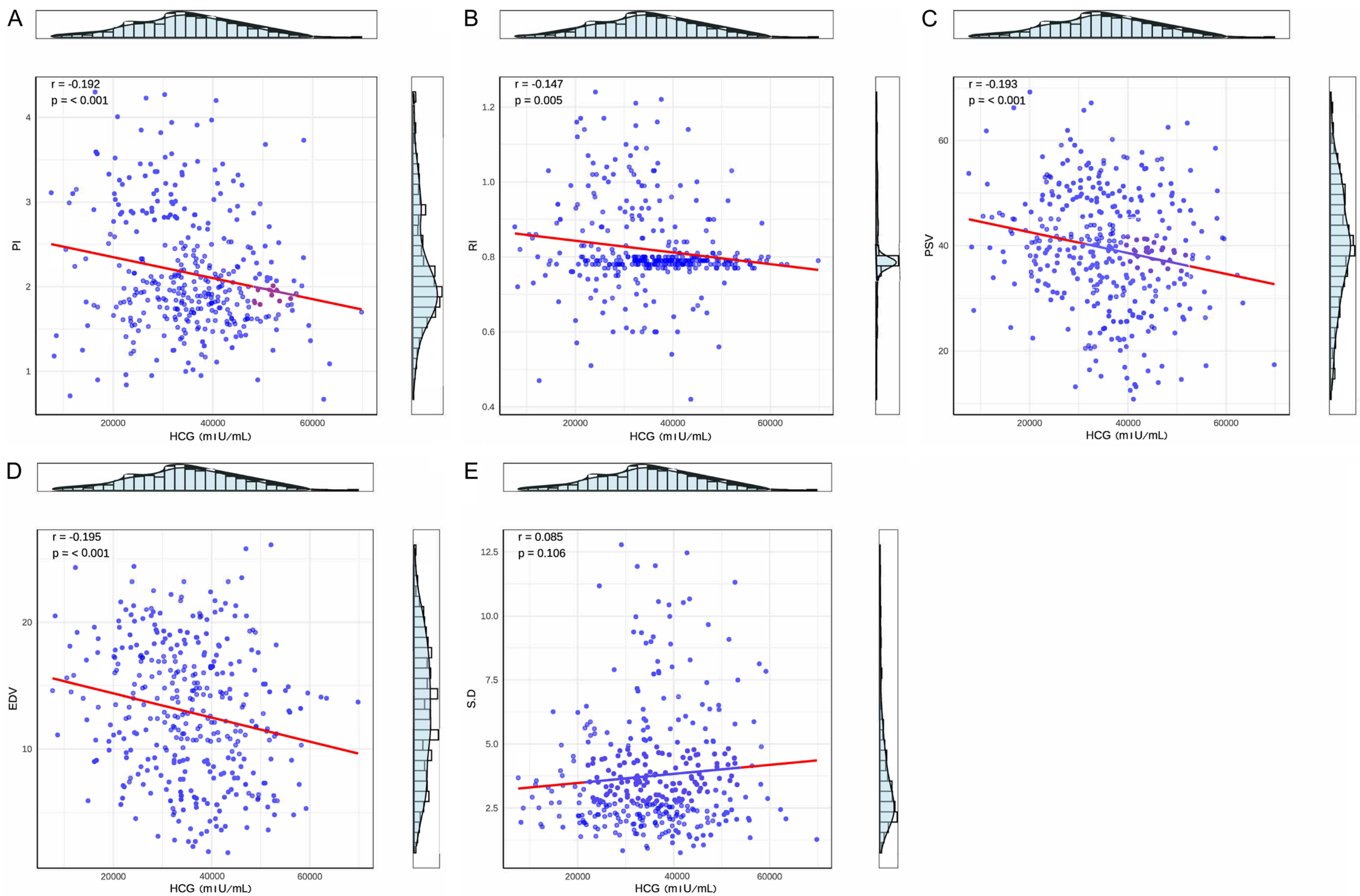

Figure 2. Correlation analysis between uterine artery blood flow indicesand serum HCG levels. A: Serum HCG levels vs. PI; B: Serum HCG levels vs. RI; C: Serum HCG levels vs. PDV; D: Serum HCG levels vs. EDV; E: Serum HCG levels vs. S/D Ratio. Note: HCG, Human Chorionic Gonadotropin; PI, Pulsatility Index; RI, Resistance Index; PDV, Peak Diastolic Velocity; EDV, End-Diastolic Velocity; S/D, Systolic-Diastolic Ratio.

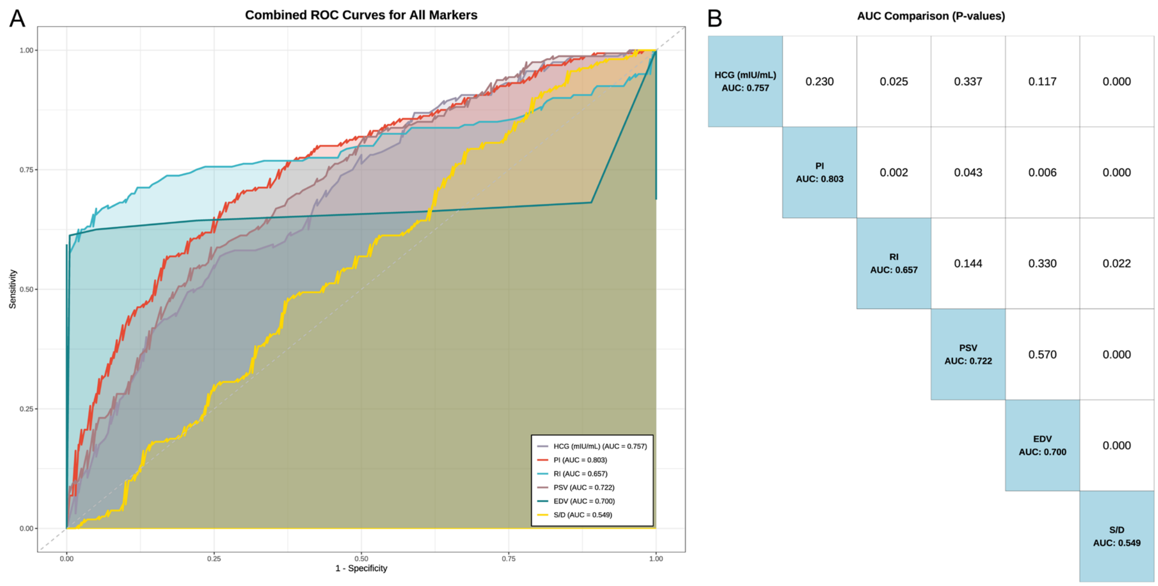

Figure 3. ROC curve analysis of diagnostic value of uterine artery blood flow indices and serum HCG levels for missed abortion. A: ROC curves showing AUC for individual models; B: Comparison of AUC among models. Note: PI, Pulsatility Index; RI, Resistance Index; PSV, Peak Diastolic Velocity; EDV, End-Diastolic Velocity; S/D, Systolic-Diastolic Ratio; AUC, Area Under the Curve.

Table 2. Diagnostic performance of uterine artery blood flow indices and serum HCG levels for missed abortion

Marker	95% CI	Specificity	Sensitivity	Youden_index	Cut_off	Accuracy	Precision	F1_Score
HCG (mIU/mL)	0.706-0.807	73.00%	68.12%	41.12%	34214.5	29.17%	31.87%	28.57%
PI	0.750-0.856	95.00%	66.88%	61.87%	2.295	82.50%	66.88%	77.26%
RI	0.585-0.729	99.50%	61.25%	60.75%	0.815	82.50%	61.25%	75.68%
PSV	0.669-0.774	75.50%	58.75%	34.25%	41.75	68.06%	58.75%	62.05%
EDV	0.647-0.754	74.00%	56.88%	30.87%	14.55	66.39%	56.88%	60.07%
S/D	0.489-0.608	32.00%	79.38%	11.38%	4.425	46.94%	20.62%	25.68%

Note: PI, Pulsatility Index; RI, Resistance Index; PSV, Peak Systolic Velocity; EDV, End-Diastolic Velocity; S/D, Systolic-Diastolic Ratio; AUC, Area Under the Curve.

cantly lower than that of the combined models (P < 0.05) (**Table 4**).

Discussion

Missed abortion, a common complication of early pregnancy, is characterized by embryonic or fetal demise without expulsion from the uterus [16]. Although its etiology remains incompletely understood, contributing factors are believed to include genetic abnormalities, embryonic defects, and uteroplacental insufficiency [17-19]. Traditional diagnosis relies on ultrasound imaging to assess fetal viability and detect uterine abnormalities [20, 21]. However, ultrasonographic findings may be inconclusive, especially during early gestation. Consequently, increasing attention has been directed toward incorporating serum human chorionic gonadotropin (HCG) levels and uterine artery Doppler indices to improve diagnostic accuracy [22-24].

In this study, patients with missed abortion showed significantly lower serum HCG levels and higher PI, RI, and EDV values compared to those with normal pregnancy. These findings suggest that reduced HCG secretion and impaired uteroplacental hemodynamics are core pathologic features of missed abortion. Correlation analysis further revealed significant negative associations between HCG levels and

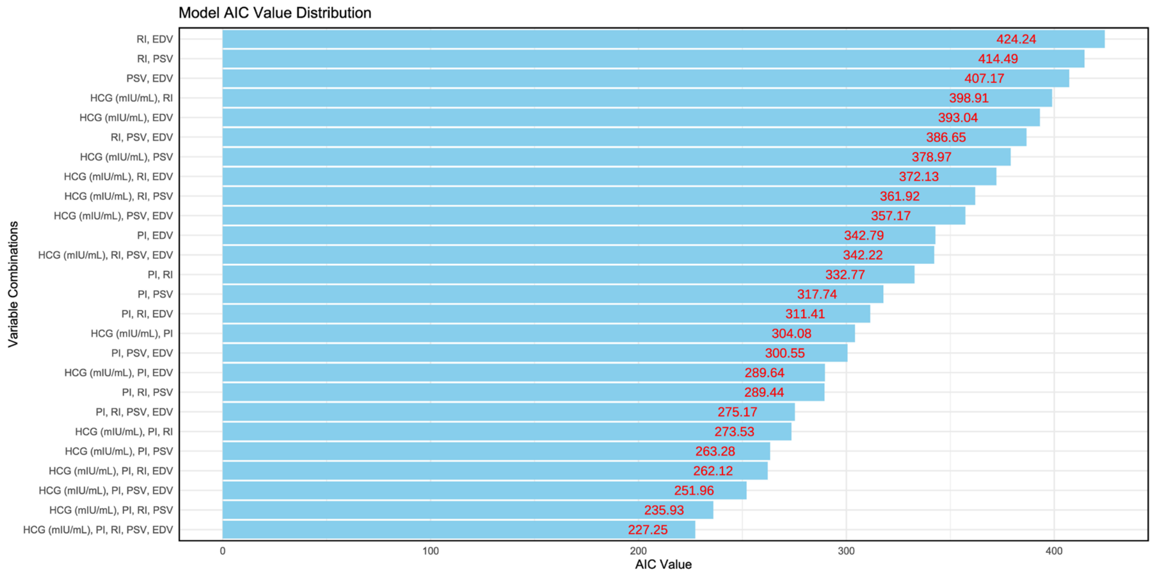

Figure 4. Distribution of AIC values across diagnostic models. Note: AIC, Akaike Information Criterion; HCG, Human Chorionic Gonadotropin; PI, Pulsatility Index; RI, Resistance Index; PSV, Peak Diastolic Velocity; EDV, End-Diastolic Velocity.

Table 3. Diagnostic model formulas with indices having the lowest AIC value

Model	Formula
HCG (mIU/mL) + PI + RI + PSV + EDV	Logit(y) = -0.0001 * HCG (mIU/mL) + 3.0492 * PI + 8.4475 * RI + 0.0994 * PSV + 0.1062 * EDV + -14.5483 (Intercept)
HCG (mIU/mL) + PI + RI + PSV	Logit(y) = -0.0001 * HCG (mIU/mL) + 3.1422 * PI + 8.5771 * RI + 0.1002 * PSV + -13.3940 (Intercept)
HCG (mIU/mL) + PI + PSV + EDV	Logit(y) = -0.0001 * HCG (mIU/mL) + 2.6085 * PI + 0.0978 * PSV + 0.1116 * EDV + -7.1502 (Intercept)
HCG (mIU/mL) + PI + RI + EDV	Logit(y) = -0.0001 * HCG (mIU/mL) + 2.7294 * PI + 8.6954 * RI + 0.1102 * EDV + -10.3506 (Intercept)
HCG (mIU/mL) + PI + PSV	Logit(y) = -0.0001 * HCG (mIU/mL) + 2.6731 * PI + 0.0983 * PSV + -5.7191 (Intercept)

Note: HCG, Human Chorionic Gonadotropin; PI, Pulsatility Index; RI, Resistance Index; PSV, Peak Systolic Velocity; EDV, End-Diastolic Velocity.

Doppler indices, indicating a close relationship between declining trophoblast function and abnormal uterine blood flow [25-27].

HCG, secreted by placental trophoblasts, reflects embryonic and placental viability [28-30]. In cases of missed abortion, embryonic demise results in reduced trophoblastic activity and a corresponding decline in HCG secretion [31-33]. Abnormal uterine artery Doppler indices - specifically elevated PI and RI and reduced EDV - indicate increased vascular resistance and poor placental perfusion, which are commonly attributed to insufficient trophoblast invasion and incomplete spiral artery remodeling [34, 35]. These hemodynamic changes are strongly implicated in early pregnancy failure.

The diagnostic use of Doppler indices has been previously supported by studies such as those of Lian et al. [10], who found that therapeutic modulation of PI and RI could improve pregnancy outcomes. Zhao et al. [36] also confirmed the value of Doppler assessment in early pregnancy complications. Our findings further support the diagnostic relevance of these indices, particularly when used in combination with HCG.

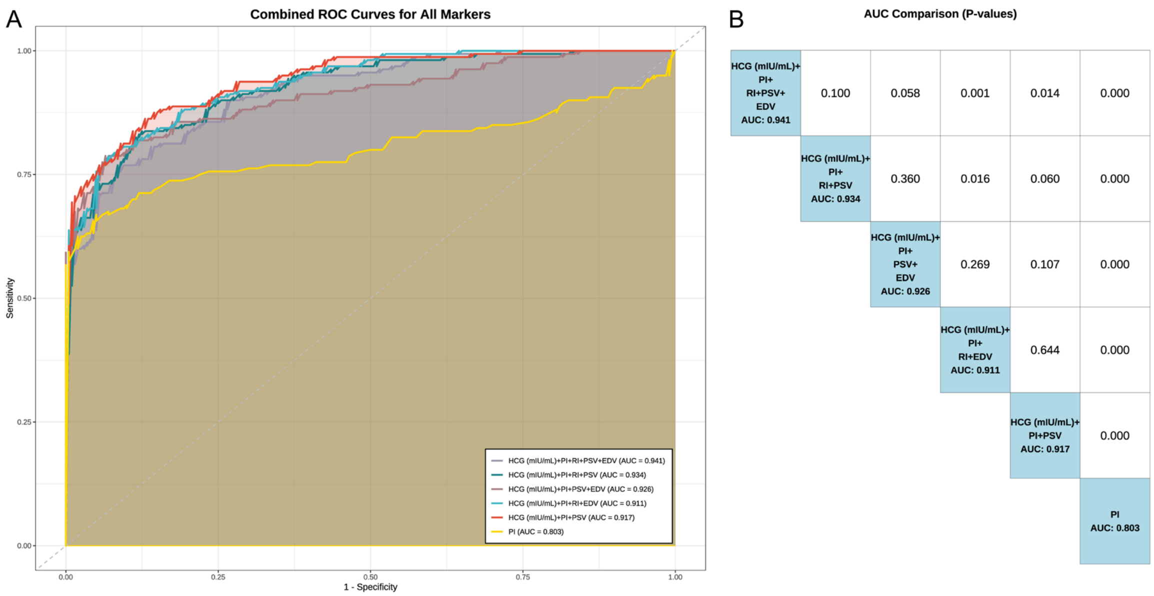

Figure 5. ROC curve analysis and model comparison. A: ROC curves showing AUC for each model; B: Comparison of AUC among models. Note: ROC, Receiver Operating Characteristic Curve; AUC, Area Under the Curve; HCG, Human Chorionic Gonadotropin; PI, Pulsatility Index; RI, Resistance Index; PSV, Peak Diastolic Velocity; EDV, End-Diastolic Velocity.

Table 4. Comparison of ROC curve and diagnostic efficacy between model and univariate

Marker	95% CI	Specificity	Sensitivity	Youden_index	Cut_off	Accuracy	Precision	F1_Score
HCG (mIU/mL) + PI + RI + PSV + EDV	0.918-0.964	87.00%	86.25%	73.25%	0.39	86.67%	86.25%	85.19%
HCG (mIU/mL) + PI + RI + PSV	0.911-0.958	93.00%	78.75%	71.75%	0.562	86.67%	78.75%	84.00%
HCG (mIU/mL) + PI + PSV + EDV	0.899-0.952	87.50%	83.75%	71.25%	0.468	85.83%	83.75%	84.01%
HCG (mIU/mL) + PI + RI + EDV	0.879-0.942	93.50%	78.75%	72.25%	0.567	86.94%	78.75%	84.28%
HCG (mIU/mL) + PI + PSV	0.890-0.945	91.00%	76.88%	67.88%	0.547	84.72%	76.88%	81.73%
PI	0.750-0.856	95.00%	66.88%	61.87%	2.295	82.50%	66.88%	77.26%

Note: PI, Pulsatility Index; RI, Resistance Index; PSV, Peak Systolic Velocity; EDV, End-Diastolic Velocity.

The combined diagnostic model developed by this study, incorporating HCG, PI, RI, EDV, and PSV, demonstrated high sensitivity (86.25%) and specificity (87.00%), significantly outperforming single-measure assessments (AUC = 0.941). This is consistent with previous reports showing that multi-marker models - including uterine Doppler and serum biomarkers such as PLGF and sFlt-1 - can effectively predict pregnancy complications such as hypertensive disorders [12]. Unlike HCG alone, which may be affected by inter-individual variability [8, 31, 37], uterine artery Doppler indices provide objective and reproducible measures of placental function.

Importantly, this multimodal model offers practical clinical advantages. Both Doppler ultrasound and serum HCG testing are non-invasive, accessible, and cost-effective, making them well-suited for routine use. In patients with atypical or asymptomatic presentations - such as those lacking vaginal bleeding or abdominal pain. The model may facilitate earlier and more accurate diagnosis, reducing delays in treatment and preventing complications. Allen et al. [38] further emphasized that ultrasound examination should still be performed even when serum markers are inconclusive or negative, underscoring the value of integrating multiple diagnostic methods.

In addition, Chen et al. [39] reported a hypercoagulable state in women with a history of abortion, which may contribute to placental perfusion abnormalities. This finding complements our results and suggests that a comprehensive diagnostic approach integrating vascular, hormonal, and coagulation markers could further improve early prediction and intervention.

Nevertheless, this study has limitations. It was conducted at a single center with a relatively small sample size, limiting the generalizability of the findings. Possible confounders such as maternal comorbidities or lifestyle factors were not fully assessed. Moreover, the study did not include dynamic monitoring of HCG or Doppler indices over time, nor did it evaluate long-term pregnancy outcomes or complications, which restricts understanding of the model's longitudinal use.

Future research should focus on multi-center studies with larger cohorts, incorporate longitudinal biomarker tracking, and evaluate the inclusion of additional indicators such as PAPP-A and PLGF. Long-term follow-up will also be essential to determine the model's predictive value in clinical practice.

In conclusion, this study demonstrated that combining serum HCG levels with uterine artery hemodynamic indices significantly enhanced diagnostic accuracy for missed abortion. The proposed combined model offers a robust, non-invasive approach for early screening and clinical decision-making for early pregnancy management.

Disclosure of conflict of interest

None.

Address correspondence to: Yanan Wei, Department of Gynaecology and Obstetrics, Hanzhong People's Hospital, No. 251 North Tuanjie Street, Hantai District, Hanzhong 723000, Shaanxi, China. E-mail: wyn15091249306@163.com

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