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ORIGINAL RESEARCH

Doppler Evaluation of Uterine Blood Flow in Patients with Unexplained Recurrent Pregnancy Loss

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Objective: This study aimed to analyze uterine artery and spiral artery hemodynamics in patients with unexplained recurrent pregnancy loss (URPL) with varying pregnancy outcomes.

Methods: 174 pregnant women with URPL and 144 pregnant women without adverse pregnancy histories were enrolled in this retrospective study. Based on pregnancy outcomes, these patients were divided into two groups: normal pregnancy outcomes (URPL-N, n=138) and adverse pregnancy outcomes (URPL-A, n=36). Control group participants were categorized into normal pregnancy outcomes (CON-N, n=129) and adverse pregnancy outcomes (CON-A, n=15). We compared uterine artery and spiral artery hemodynamics during different stages of gestation and the predictive value of these parameters for pregnancy outcomes.

Results: URPL-N group had fewer pregnancy losses and lower BMI compared to URPL-A group (P< 0.05). Spiral artery hemodynamics in URPL-N and CON-N groups were lower than those in URPL-A and CON-A groups during the mid-luteal phase, 11–13 weeks, 15–17 weeks, and 19–21 weeks of gestation, respectively. Uterine artery hemodynamics ((Pulsatility index (mPI), resistive index (mRI), and systolic-to-diastolic ratio (mS/D)) in the mid-luteal period were lower in URPL-N group than URPL-A group. Similarly, in CON-N group were lower than CON-A group. The URPL-A and CON-A groups had higher uterine artery and spiral artery hemodynamics when compared to the URPL-N and CON-N groups. Spiral artery hemodynamics exhibited larger areas under the ROC curve compared to uterine artery parameters.

Conclusion: Abnormal hemodynamics in these arteries may contribute to URPL and adverse pregnancy outcomes. Spiral artery hemodynamics are more reliable predictors of pregnancy outcomes than uterine artery parameters.

Keywords: unexplained recurrent pregnancy loss, spiral artery, uterine artery, blood flow, pregnancy outcome

Introduction

Recurrent Pregnancy Loss (RPL), a complex medical condition, refers to a woman experiencing two or more consecutive spontaneous miscarriages during pregnancy.[1] Statistics from the American Society for Reproductive Medicine (ASRM) indicate that approximately 1% to 5% of women of reproductive age suffer from RPL.[2] In cases where routine medical examinations fail to identify the specific causes of the miscarriages, the situation is classified as Unexplained Recurrent Pregnancy Loss (URPL).[3] The diagnosis of URPL presents significant challenges to patients and their families due to the lack of a clear etiology, making it difficult to implement targeted treatment plans. This uncertainty not only increases the physical risks for the patients but also leads to profound psychological and emotional distress.[4]

Miscarriage is a common complication of pregnancy, with about 15%-25% of known pregnancies ending in miscarriage. In women with a history of intrauterine pregnancy, the proportion experiencing two consecutive

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miscarriages is about 5%, and this proportion decreases to approximately 1% for three or more consecutive miscarriages.[2] Despite these figures providing an overview, the actual number of affected women may be higher, as many miscarriages occur early in pregnancy and may go unnoticed by the women themselves. Research on URPL is particularly critical as, in many cases, the causes of these miscarriages remain unknown, posing significant challenges to treatment and prevention strategies.[5]

The pathophysiology of URPL is multifaceted, involving genetic, anatomical, endocrine, and immunological factors. Genetic factors may include parental chromosomal balance translocations or other genetic abnormalities;[6,7] immunological factors, especially autoimmune diseases and embryonic rejection responses, are also considered to play a crucial role in URPL;[8] anatomical abnormalities such as uterine malformations may hinder embryo implantation or increase inflammation within the uterine cavity through mechanical interference;[9] moreover, endocrine factors like luteal phase deficiency could lead to an unfavorable uterine environment for the embryo.[10]

Adequate uterine and placental blood flow is one of the key factors in maintaining a successful pregnancy. Sufficient blood flow not only provides essential oxygen and nutrients but also aids in the elimination of metabolic waste and carbon dioxide.[11] Insufficient or abnormal uterine arterial blood flow could be a significant cause of URPL, as it may lead to placental dysfunction and restricted embryonic growth, potentially resulting in pregnancy failure.[12]

Doppler ultrasound, an imaging technique that assesses blood flow speed and direction, is used during pregnancy to evaluate uterine artery Doppler signals, allowing physicians to observe blood flow dynamics and assess whether the blood flow is normal. In the context of URPL, Doppler ultrasound is employed to evaluate the Resistance Index (RI) and Pulsatility Index (PI) of the uterine arteries, which help in identifying whether the uterine blood supply is adequate.[13]

Data from Doppler ultrasound can help predict pregnancy outcomes such as preterm birth, eclampsia, and fetal growth restriction, and is particularly important for the management of URPL.[14] Early identification of abnormal blood flow may allow for interventions such as the use of aspirin or low molecular weight heparin to improve the uterine blood flow.[15] However, current research on assessing uterine blood flow in URPL patients using Doppler ultrasound is relatively limited. Applying Doppler ultrasound technology to anticipate and intervene in URPL patients early might improve their clinical prognosis.[16–18] This study aims to deeply evaluate the uterine blood flow characteristics of URPL patients using Doppler ultrasound technology, exploring the potential links between these characteristics and recurrent miscarriages. Through the data provided by this study, we hope to offer a more solid scientific basis for the diagnosis and treatment of URPL, improving clinical management and reducing the economic and psychological burden on patients due to URPL.

Previous studies have shown a strong association between increased uterine and spiral artery blood flow resistance and adverse pregnancy outcomes. Habara et al[18] found significantly higher uterine artery resistance index (RI) in patients with unexplained recurrent pregnancy loss (RPL) compared to those with successful pregnancies. Similarly, Ferreira et al[17] observed elevated spiral artery blood flow resistance in RPL patients, emphasizing its role in pregnancy maintenance. However, there is limited research on continuously monitoring these parameters across different stages of pregnancy, particularly in URPL cases. This study aims to address that gap.

Materials and Methods

Study Participants

Study Design

This retrospective study was conducted to evaluate the hemodynamics of the uterine and spiral arteries in women with unexplained recurrent pregnancy loss (URPL).

Study Place

The study was carried out at the outpatient department of the First Affiliated Hospital of Soochow University from January 2020 to January 2022.

Study Participants

All women underwent a full-scale assessment. A total of 174 patients (excluded 30 participants) were in the URPL group with a history of at least two RPLs with unexplained etiology (ie, excluding parental chromosomal aberrations, reproductive abnormalities, autoimmune diseases, and endocrinologic anomalies). 30 participants were excluded due to incomplete collection of uterine artery and spiral artery blood flow parameters during the mid-luteal phase, at 11–13 weeks of pregnancy, in the CON-N group, at 15–17 weeks of pregnancy, and at 19–21 weeks of pregnancy. As a comparison group, we included 144 pregnant women with no history of adverse pregnancies (Figure 1).

Inclusion and Exclusion Criteria

Inclusion Criteria: This retrospective study included women aged between 20 and 40 years, with a history of two or more unexplained recurrent pregnancy losses as defined by the absence of known causes such as parental chromosomal aberrations, anatomical reproductive abnormalities, autoimmune disorders, or endocrine anomalies. All participants had a normal menstrual cycle (25–35 days) and were followed up from January 2020 to January 2022.

Exclusion Criteria: Women were excluded from the study if they had any known reproductive or systemic conditions that could influence pregnancy outcomes, such as polycystic ovarian syndrome, uterine malformations, or thyroid disorders. Participants who had taken any fertility medications or interventions before enrollment were also excluded. Furthermore, those with incomplete medical records or who did not complete the follow-up period were not considered for this study.

Outcome Variable

After careful follow-up until the conclusion of pregnancy, patients meeting any of the subsequent conditions were classified into the Adverse Pregnancy Group:[6–8]

① miscarriage, which is defined as pregnancy loss before the 24th week of gestation;② preterm delivery, characterized by delivery occurring between the 24th and 37th week of gestation; ③ hypertensive disorders during pregnancy, including gestational hypertension, preeclampsia, and eclampsia; ④ fetal growth restriction, identified when the fetal birth weight is below the 10th percentile for the corresponding gestational age; and ⑤ fetal distress or neonatal asphyxia, which is evident from an Apgar score of ≤7 one minute after birth or instances of stillbirth. The Apgar score comprises 5 components: (1) color; (2) heart rate; (3) reflexes; (4) muscle tone; and respiration. Each of these components is given a score of 0, 1, or 2). All other deliveries without these complications were placed in the Normal Pregnancy Group.

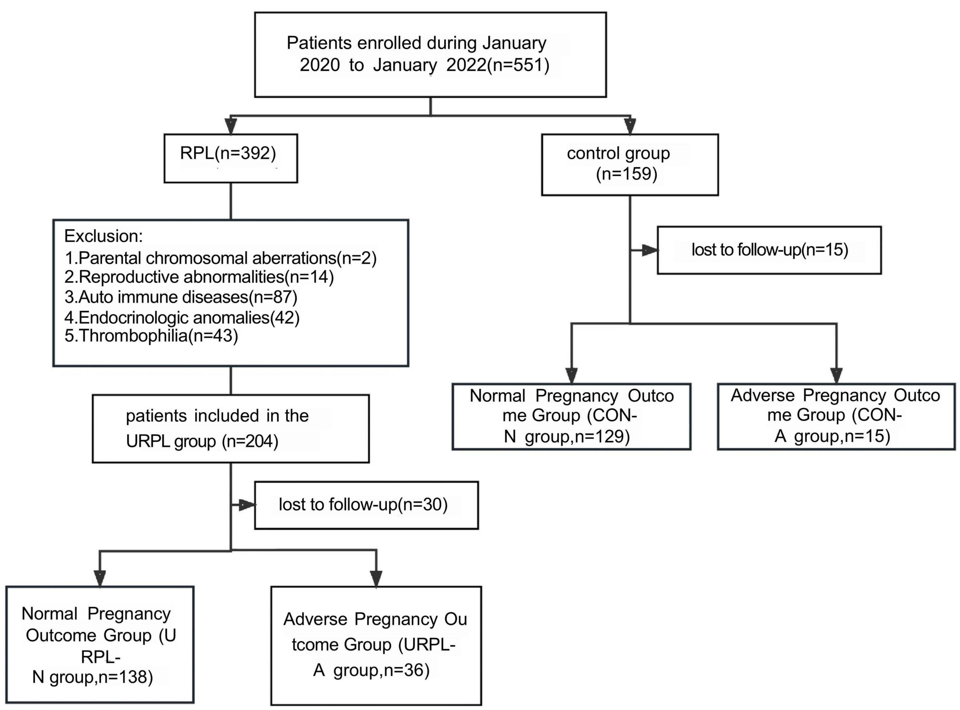

Figure 1 Characteristics of study participants. Abbreviations: RPL, recurrent pregnancy loss; URPL, unexplained recurrent pregnancy loss.

Based on their pregnancy outcomes, URPL patients were categorized into two groups: the Normal Pregnancy Outcome Group (URPL-N group, n=138) and the Adverse Pregnancy Outcome Group (URPL-A group, n=36). Similarly, the control group was divided into the Normal Pregnancy Outcome Group (CON-N group, n=129) and the Adverse Pregnancy Outcome Group (CON-A group, n=15) (Figure 1).

Measurement of Hemodynamics

The uterine artery and spiral artery hemodynamics were measured by color Doppler ultrasonography (GE Voluson E8). These measurements were conducted during the midluteal period (the time of embryo implantation) and at weeks 11–13, 15–17, and 19–21 of pregnancy. The procedures were conducted by a certified sonographer with over 10 years of experience in obstetric ultrasound, specializing in fetal medicine. This ensured high reliability and consistency of the hemodynamic assessments. The sonographer was specifically trained in the standardization of uterine and spiral artery Doppler measurements to minimize inter-operator variability. During these assessments, vaginal measurements were obtained during the middle luteal period, while abdominal measurements were taken between 11 and 21 weeks of gestation.

Uterine artery measurements were performed on both the right and left sides of the uterine artery flow. Spiral artery measurements were taken at the endometrial edge during the middle luteal period and at the junction of the placenta and myometrium during gestation. To optimize the flow image, the best longitudinal scan showing the curved beam was acquired. After blood flow sampling with an θ Angle <30° along the long axis of the vessel, the blood flow spectrum was evaluated once stable blood flow spectrum data was obtained. Each parameter was measured thrice, and their average values were calculated and represented as Pulsatility index (mPI), resistive index (mRI), and systolic-to-diastolic ratio (mS/D). It's noteworthy that all procedures were conducted by a professional examiner for consistency.[16]

Ethical Approval

Ethical approval for this study was granted by the Ethics Committee of the First Affiliated Hospital of Soochow University (Approval No. 121(2022)). Prior to participation in the study, all potential subjects were thoroughly informed about the nature of the research, including the study's aims, the procedures involved, potential risks, and benefits. Written informed consent was obtained from each participant after ensuring they understood the information and had the opportunity to ask questions. This process was conducted in accordance with the ethical guidelines of the Helsinki Declaration and was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University.

Statistical Analysis

For statistical analysis, SPSS version 22.0 was employed. Normally distributed data were expressed as mean ± standard deviation (±SD) and analyzed using a *T*-test, while sample rates were compared using the Chi-square test. A significance level of $p<0.05$ was applied to denote statistical differences. To evaluate the diagnostic value of the disease, a Receiver Operating Characteristic (ROC) curve was utilized. GraphPad Prism 9 was used for data visualization, and MATLAB2020's k-Nearest Neighbor (KNN) classification algorithm was implemented for handling missing data.

Results

Patient Characteristics Comparison

When comparing the basic information of the enrolled patients, no differences were observed in age and BMI between the URPL group and the control group ($P>0.05$). However, the URPL-N group exhibited a lower number of pregnancy losses compared to the URPL-A group ($P<0.05$), and the BMI in the URPL-N group was notably lower than that in the URPL-A group ($P<0.001$). There was no significant difference in age within the URPL groups ($P>0.05$). Similarly, there were no significant differences in age and BMI between the control groups ($P>0.05$) (Table 1).

Comparison of Uterine and Spiral Artery Hemodynamics

Hemodynamics in URPL Groups

In the URPL-N group, the spiral artery hemodynamics (mRI, mPI, and mS/D) were consistently lower than those in the

Table 1 Comparison of Basic Information

Characteristic	URPL group (n=174)	Control group (n=144)	P-value
Age (years)	31 (27–33)	29 (27–33)	0.194
BMI (kg/m^2)	22.55 (21.18–23.47)	22.55 (21.02–23.35)	0.549
Pregnancy Outcome	**URPL-N (n=138)**	**CON-N (n=129)**	
Age (years)	30.34 ± 4.04	29 (27–33)	0.729
BMI (kg/m^2)	22.18 (20.77–23.26)	22.55 (20.94–23.38)	<0.001
No. of losses	2 (2–2)	N/A	0.001
Adverse Pregnancy Outcome	**URPL-A (n=36)**	**CON-A (n=15)**	
Age (years)	30.08 ± 3.59	28 (25–29)	0.052
BMI (kg/m^2)	23.2 (22.81–24.22)	22.67 (22.15–23.26)	0.523

Note: URPL: Unexplained recurrent pregnancy loss; BMI: Body mass index. ($\bar{x}$±SD).

URPL-A group across various gestational phases (P<0.05), while the uterine artery hemodynamics (mRI, mPI, and mS/D) in the URPL-N group were significantly lower than those in the URPL-A group during the middle luteal phase (P<0.05). However, as pregnancy progressed, there were no significant differences in uterine artery hemodynamics (mRI, mPI, and mS/D) between the two groups at 19–21 weeks of gestation (Table 2) and (Figure 2A).

Table 2 Hemodynamics of Uterine Artery and Spiral Artery in URPL Group

A						
TIME (No. URPL-N/ No. URPL-A)	**URPL-N**			**URPL-A**		
	mRI	**mPI**	**mS/D**	**mRI**	**mPI**	**mS/D**
Uterine Artery						
LP(133/36)	0.83(0.79~0.86)▲	2.164±0.411▲	5.913±1.485▲	0.853±0.023	2.56(2.13~2.70)	6.98(6.48~7.53)
12W(130/34)	0.71(0.67~0.75)	1.476±0.281▲	3.47(3.05~4.08)	0.725±0.045	1.508±0.231	3.73(3.28~4.17)
16W(123/30)	0.64(0.57~0.69)	1.20(0.96~1.36)	2.75(2.31~3.22)▲	0.66(0.65~0.71)	1.282±0.243	3.073±0.562
20W(115/25)	0.54(0.48~0.61)	0.89(0.74~1.14)	2.16(1.95~2.56)	0.55(0.54~0.59)	1.00(0.89~1.20)	2.27(2.08~2.45)
Spiral Artery						
L-P(133/36)	0.45(0.42~0.49)▲	0.65(0.56~0.74)▲	1.80(1.67~1.91)▲	0.513±0.052	0.764±0.126	2.085±0.192
12W(130/34)	0.40(0.37~0.43)▲	0.527±0.089▲	1.662±0.131▲	0.42(0.40~0.44)	0.56(0.52~0.61)	1.72(1.65~1.80)
16W(123/30)	0.35(0.31~0.38)▲	0.45(0.39~0.49)▲	1.525±0.128▲	0.38(0.36~0.40)	0.49(0.43~0.53)	1.61(1.54~1.67)
20W(115/25)	0.28(0.23~0.33)▲	0.35(0.28~0.42)▲	1.41(1.29~1.49)▲	0.330±0.044	0.421±0.081	1.49(1.44~1.56)
B						
TIME(No.CON-N/ No. CON-A)	**CON-N**			**CON-A**		
	mRI	**mPI**	**mS/D**	**mRI**	**mPI**	**mS/D**
Uterine Artery						
L-p(125/13)	0.79(0.74~0.82)▲	1.82(1.58~2.08)▲	4.66(4.01~5.52)▲	0.828±0.021	2.191±0.105	5.983±0.606
12W(119/11)	0.70(0.64~0.73)▲	1.48(1.25~1.65)▲	3.65(2.65~4.06)▲	0.726±0.026	1.673±0.216	4.471±0.681
16W(102/9)	0.65(0.55~0.68)	1.18(1.03~1.44)	2.99(2.02~3.2)	0.68(0.63~0.68)	1.34(1.03~1.52)	2.945±0.497
20W(110/10)	0.51(0.48~0.64)	0.86(0.83~1.25)	2.16(2.05~2.56)	0.54(0.51~0.64)	0.91(0.66~1.09)	2.49(1.72~2.61)
Spiral Artery						
L-p(125/13)	0.43(0.38~0.48)▲	0.6(0.52~0.69)▲	1.68(1.62~1.81)▲	0.53(0.50~0.55)	0.773±0.084	1.994±0.195
12W(119/11)	0.41(0.32~0.43)▲	0.55(0.42~0.59)▲	1.64(1.47~1.74)▲	0.445±0.033	0.603±0.055	1.79(1.66~1.87)
16W(102/9)	0.36(0.25~0.38)▲	0.45(0.31~0.49)▲	1.56(1.33~1.61)▲	0.38(0.36~0.38)	0.48(0.45~0.49)	1.595±0.027
20W(110/10)	0.31(0.18~0.33)▲	0.39(0.2~0.41)▲	1.46(1.19~1.49)▲	0.318±0.022	0.419±0.051	1.49(1.39~1.51)

Note: ▲indicates that the hemodynamics of the URPL-N group are significantly greater than the same hemodynamics of the URPL-A group during the same gestation period (P < 0.05); L-p: mid-luteal phase; Data were analyzed using independent sample *T*-test. ($\bar{x}$±SD).
Abbreviation: URPL:unexplained recurrent pregnancy loss.

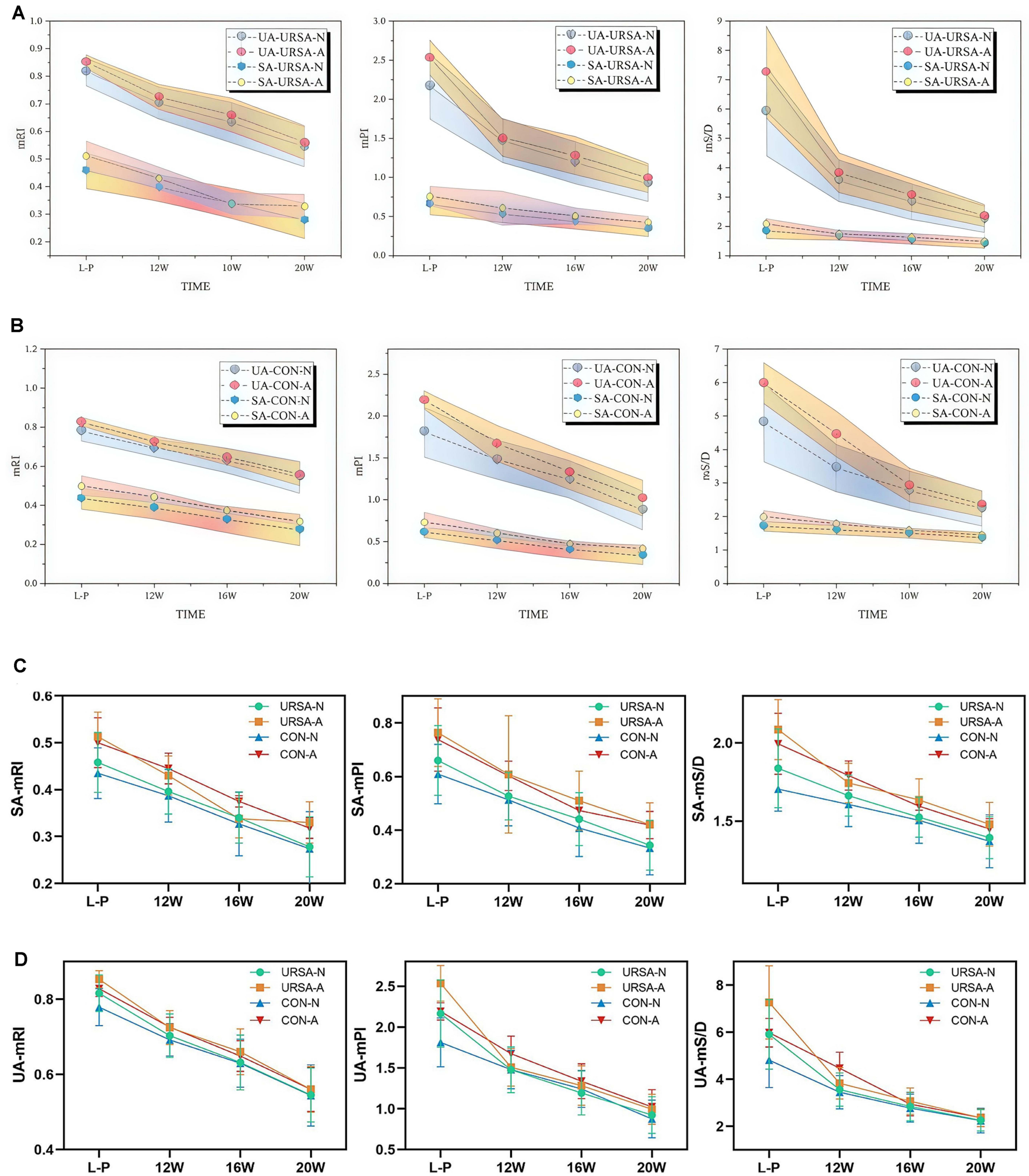

Figure 2 Hemodynamic Comparisons of Uterine and Spiral Arteries in URPL and Control Groups During the Mid-Luteal Phase (**A**) Hemodynamics of uterine artery and spiral artery in URPL-N group and URPL-A group (Modified Resection Index (mRI), Modified Performance Index (mPI) and Modified Stroke/Death ratio (mS/D)). UA-URPL-N: Uterine arteries in the normal pregnancy outcome of the unexplained recurrent pregnancy loss group; UA-URPL-A: Uterine arteries in the adverse pregnancy outcome of the unexplained recurrent pregnancy loss group.SA-URPL-N: Spiral artery in the normal pregnancy outcome of the unexplained recurrent pregnancy loss group; SA-URPL-A: Spiral artery in the adverse pregnancy outcome of the unexplained recurrent pregnancy loss group.L-P: Mid-luteal phase. **(B)** Hemodynamics of uterine artery and spiral artery in CON-N group and CON-A group (Modified Resection Index (mRI), Modified Performance Index (mPI) and Modified Stroke/Death ratio (mS/D)). UA-CON-N:Uterine arteries in the normal pregnancy outcome of the control group; UA-CON-A:Uterine arteries in the adverse pregnancy outcome of the control group. SA-CON-N:Spiral artery in the normal pregnancy outcome of the control group; SA-CON-A:Spiral artery in the adverse pregnancy outcome of the control group.M-LP: Mid-luteal phase. (**C**) Uterine artery hemodynamics (Modified Resection Index (mRI), Modified Performance Index (mPI) and Modified Stroke/Death ratio (mS/D) in URPL-N, URPL-A, CON-N and CON-A groups. URPL-N:Normal pregnancy outcome in the unexplained recurrent pregnancy loss group; URPL-A:Adverse pregnancy outcome in the unexplained recurrent pregnancy loss group; CON-N:Normal pregnancy outcome in the control group; CON-A:Adverse pregnancy outcome in the control group; L-P: Mid-luteal phase. (**D**) Spiral artery hemodynamics (Modified Resection Index (mRI), Modified Performance Index (mPI) and Modified Stroke/Death ratio (mS/D) in URPL-N, URPL-A, CON-N and CON-A groups. URPL-N:Normal pregnancy outcome in the unexplained recurrent pregnancy loss group; URPL-A:Adverse pregnancy outcome in the unexplained recurrent pregnancy loss group; CON-N:Normal pregnancy outcome in the control group; CON-A:Adverse pregnancy outcome in the control group; L-P: Mid-luteal phase.

Hemodynamics in Control Groups

Within the control groups, the spiral artery hemodynamics (mRI, mPI, and mS/D) of the CON-N group were consistently lower than those of the CON-A group across various gestational phases (P<0.05). Additionally, the uterine artery hemodynamics (mRI, mPI, and mS/D) of the CON-N group were lower than those of the CON-A group during the mid-luteal phase and at 11–13 weeks of gestation (P<0.05). However, there were no significant differences in uterine artery hemodynamics (mRI, mPI, and mS/D) between the groups at 15–17 weeks and 19–21 weeks of gestation (Table 2) (Figure 2B).

Overall Comparison

Generally, when comparing hemodynamics (mRI, mPI, and mS/D), the CON-N group exhibited the lowest values, slightly lower than those in the URPL-N group. In contrast, the URPL-A and CON-A groups had higher uterine artery and spiral artery hemodynamics (mRI, mPI, and mS/D) when compared to the URPL-N and CON-N groups (Figures 2C and D).

ROC Curve Analysis of Hemodynamics

URPL Patients

The hemodynamics of the uterine artery and spiral artery in URPL patients were analyzed and compared. Notably, the area under the ROC curve of the spiral artery was consistently larger, signifying its superior predictive value for pregnancy outcomes. Particularly, midluteal spiral artery mS/D emerged as the most valuable parameter for diagnosing pregnancy outcomes. The mS/D ratio of the spiral artery during the midluteal phase emerged as the most valuable parameter for diagnosing pregnancy outcomes, with an AUC of 0.916, indicating high accuracy. Additionally, the spiral artery mRI and mPI showed AUC values of 0.900 and 0.910, respectively, further supporting the predictive strength of spiral artery parameters (Figure 3A).

Control Group

Similarly, within the control group, the area under the ROC curve for the uterine artery (mRI, mPI, and mS/D) during the luteal phase was 0.867, 0.874, and 0.916, respectively. At 11–13 weeks of gestation, the respective values were 0.789, 0.767, and 0.859. Once again, the ROC curve illustrated that the spiral artery outperformed the uterine artery in predicting pregnancy outcomes, with midluteal spiral artery mS/D showing the highest diagnostic value (Figure 3B). All data seen in the Table 3.

Pregnancy Outcomes in URPL Patients

The adverse pregnancy rate was significantly higher in the URPL group (20.69%) compared to the control group (10.42%) ($P < 0.05$) (Figure 4).

Discussion

This study aims to conduct an in-depth analysis of the hemodynamics of the uterine and spiral arteries in patients with Unexplained Recurrent Pregnancy Loss (URPL) and to explore the relationship between these parameters and pregnancy outcomes. Although previous research has investigated Doppler indices for Recurrent Pregnancy Loss (RPL) and recurrent implantation failure, comparative studies on the blood flow indices of uterine and spiral arteries are relatively scarce.[17–21] Moreover, existing studies often lack continuous monitoring and comparison of uterine blood flow indices throughout pregnancy. By conducting detailed Doppler assessments of the uterine and spiral arteries in early and mid-pregnancy, this study aims to fill this research gap.

Our findings reveal that, compared to the control group, the URPL group exhibited higher impedance in the hemodynamics of the uterine and spiral arteries, including mean Resistance Index (mRI), mean Pulsatility Index (mPI), and systolic/diastolic ratio (mS/D). This aligns with existing literature, which correlates elevated hemodynamic indices in the uterine and spiral arteries with adverse pregnancy outcomes. These parameters were significantly higher in the group with adverse pregnancy outcomes than in the group with normal outcomes ($P < 0.05$), further supporting this correlation. Based on these findings, it is recommended that clinicians monitor these hemodynamic indices early in pregnancy for URPL patients to identify those at higher risk of adverse outcomes and apply timely interventions.

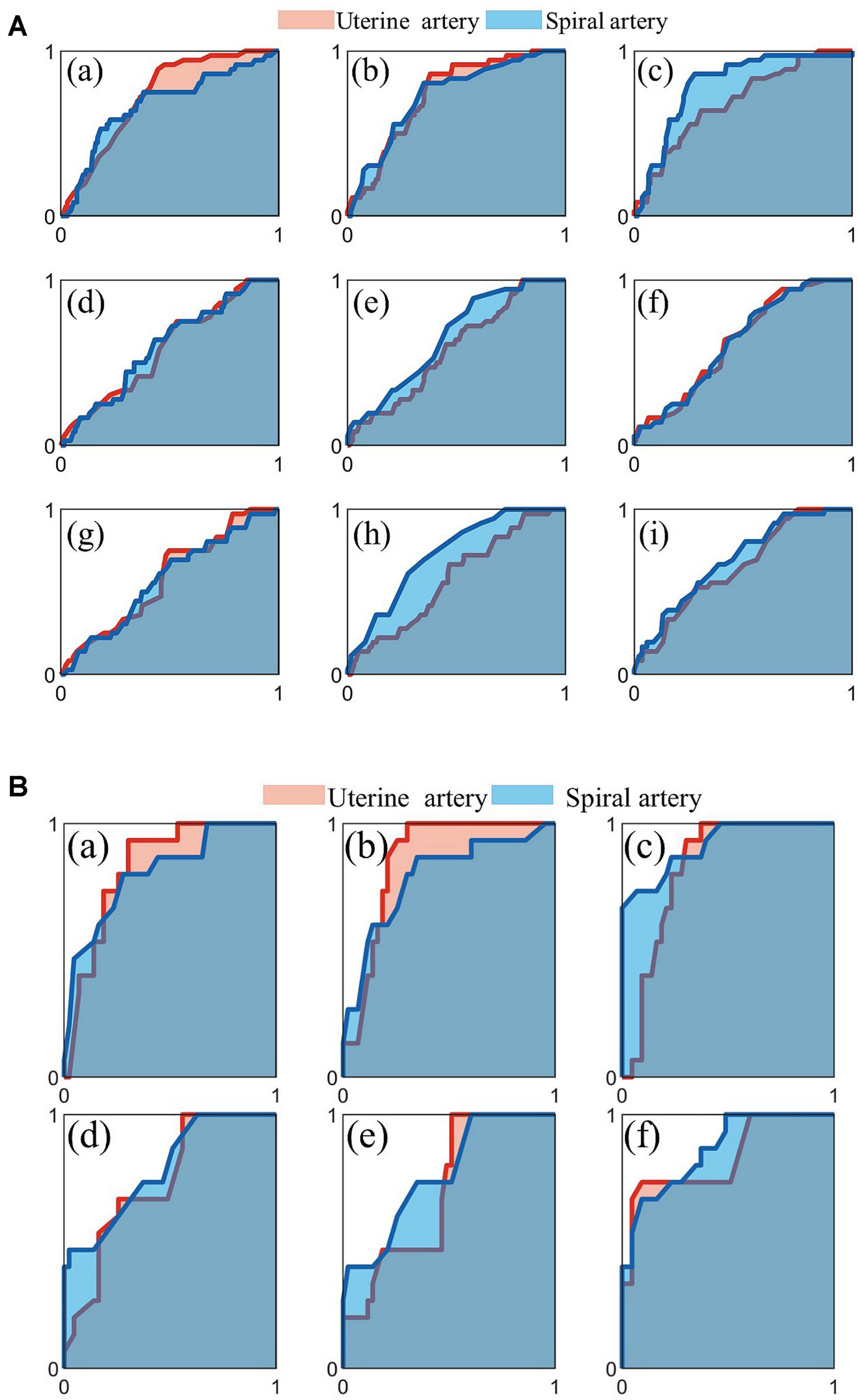

Figure 3 ROC Curve Analysis of Uterine and Spiral Arteries in URPL and Control Groups Across Different Gestational Stages (**A**) The URPL group: (a) The mRI ROC curves of uterine artery and spiral artery in the middle luteal period; (b) The mPI ROC curve of uterine artery and spiral artery in the middle luteal period; (c) The mS/D ROC curve of uterine artery and spiral artery in the middle luteal period; (d) The mRI ROC curves of uterine artery and spiral artery at 12 weeks of gestation; (e) The mPI ROC curve of uterine artery and spiral artery at 12 weeks of gestation; (f) The mS/D ROC curve of uterine artery and spiral artery at 12 weeks of gestation; (g) The mRI ROC curves of uterine artery and spiral artery at 16 weeks of gestation; (h) The mPI ROC curve of uterine artery and spiral artery at 16 weeks of gestation; (i) The mS/D ROC curve of uterine artery and spiral artery at 16 weeks of gestation. **(B)** The control group: (a) The mRI ROC curves of uterine artery and spiral artery in the middle luteal period; (b) The mPI ROC curve of uterine artery and spiral artery in the middle luteal period; (c) The mS/D ROC curve of uterine artery and spiral artery in the middle luteal period; (d) The mRI ROC curves of uterine artery and spiral artery at 12 weeks of gestation; (e) The mPI ROC curve of uterine artery and spiral artery at 12 weeks of gestation; (f) The mS/D ROC curve of uterine artery and spiral artery at 12 weeks of gestation.

Table 3 ROC Curve Analysis of Blood Flow Parameters for URPL Patients

Parameter	Time Point	AUC	Sensitivity	Specificity	P-value
MRI Uterine	Mid-Luteal	0.867	82%	79%	<0.01
MPI Uterine	Mid-Luteal	0.874	85%	77%	<0.01
MS/D Uterine	Mid-Luteal	0.916	88%	81%	<0.01
MRI Spiral	Mid-Luteal	0.900	83%	80%	<0.01
MPI Spiral	Mid-Luteal	0.910	86%	82%	<0.01
MS/D Spiral	Mid-Luteal	0.930	89%	84%	<0.01
MRI Uterine	12 weeks	0.789	75%	70%	<0.05
MPI Uterine	12 weeks	0.767	72%	69%	<0.05
MS/D Uterine	12 weeks	0.859	80%	76%	<0.05
MRI Spiral	12 weeks	0.840	78%	74%	<0.05
MPI Spiral	12 weeks	0.855	81%	75%	<0.05
MS/D Spiral	12 weeks	0.880	83%	79%	<0.05

Note:URPL: unexplained recurrent pregnancy loss; mPI:Pulsatility index, mRI: resistive index, mS/D: systolic-to-diastolic ratio.

In evaluating the predictive value of the Doppler parameters, we found the mS/D of the spiral arteries to be the most accurate predictor of pregnancy outcome risks, with an Area Under the Curve (AUC) of 0.916. This result suggests that the hemodynamic parameters of the spiral arteries, especially mS/D, may be effective tools for predicting pregnancy

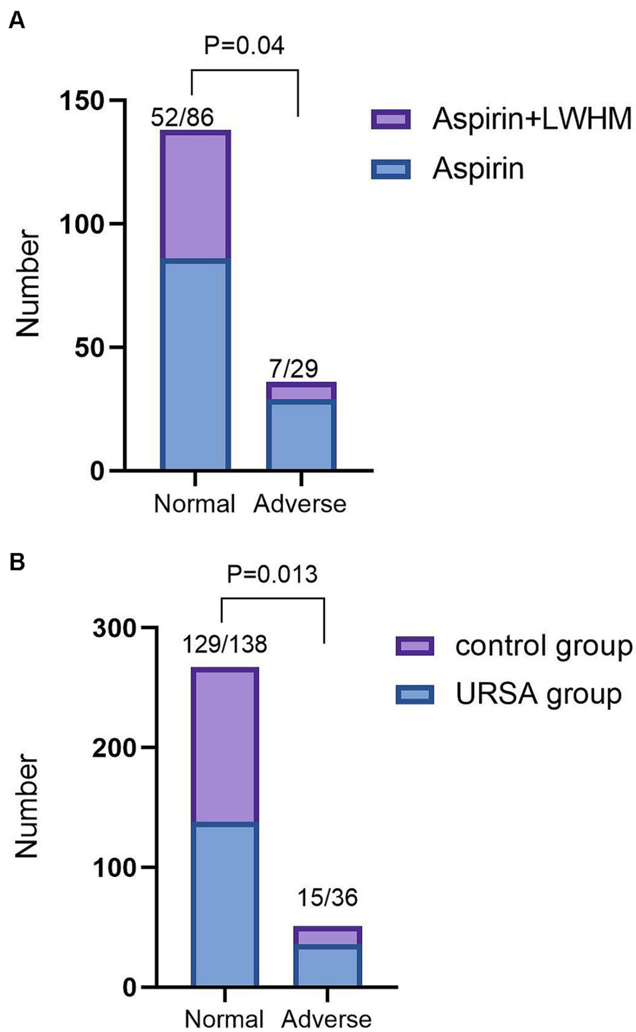

Figure 4 Comparative Analysis of Pregnancy Outcomes Among Aspirin, Aspirin + LWHM, unexplained recurrent pregnancy loss (URPL), and Control Groups **(A)** Comparison of pregnancy outcomes between Aspirin group and Aspirin +LWHM group. (**B**) Comparison of pregnancy outcomes between URPL group and control group.

outcomes in URPL patients. The ROC curve analysis highlighted the mS/D ratio's high sensitivity (89%) and specificity (84%). Sensitivity reflects the test's ability to correctly identify patients with adverse pregnancy outcomes, while specificity measures its ability to identify those without. The balance between these ensures most high-risk patients are detected early, minimizing false negatives, while also avoiding unnecessary interventions in low-risk patients. Besides, to enhance clinical relevance, we propose defining a cut-off value instead of relying solely on the AUC. Using Youden's Index, we determined the optimal cut-off for the mS/D ratio to be approximately 1.49–1.50. When the mS/D exceeds 1.50, the risk of adverse pregnancy outcomes significantly increases. This threshold provides a practical tool for early identification and intervention in high-risk URPL patients. Additionally, the mPI and mRI of the spiral arteries also demonstrated high predictive accuracy, with AUC values of 0.874 and 0.867, respectively. While the predictive value of these parameters slightly decreased between 11–13 weeks of pregnancy, they still showed good predictive performance. (Figure 3B).

The uterine and spiral arteries are primary contributors to the blood supply of the uterus and placenta, directly reflecting the blood perfusion of the placenta and embryo.[22,23] During pregnancy, the remodeling of the spiral arteries is crucial for placental formation. In the mid-luteal phase, when the endometrium is in a receptive state, trophoblastic cells begin to erode the spiral arteries, transforming them from coiled structures into straight, enlarged, low-resistance vessels, thus increasing blood flow. This process is vital for fetal growth and development.[24] However, in pathological conditions such as RPL, this remodeling process may be disrupted, leading to increased blood flow resistance and reduced volume, which can affect embryo development and potentially result in pregnancy loss, preterm birth, and pregnancy-induced hypertension.[25,26]

The strength of this study lies in its longitudinal approach to monitoring both uterine and spiral artery hemodynamics across different stages of pregnancy, offering a detailed understanding of how these parameters evolve and their association with pregnancy outcomes. Furthermore, the use of high-resolution Doppler ultrasound technology ensured that our measurements were highly accurate and reliable, thereby enhancing the robustness of our findings. The large, well-defined cohort and the rigorous matching of controls also contribute to the generalizability of the study's conclusions.

Limitations

The primary limitation of this study is that the factors influencing pregnancy outcomes are often diverse, especially in URPL patients. Due to the limited number of patients, we were unable to comprehensively analyze and statistically account for all potential factors impacting adverse pregnancy outcomes. Moreover, as this study was retrospective, it may be subject to selection and information biases. Future research should employ a prospective design and consider a broader patient cohort to validate our findings and explore other factors that may influence pregnancy outcomes.

Conclusion

This study, through detailed Doppler assessments, highlights the importance of spiral artery hemodynamics in the management of URPL and provides valuable information for future research and clinical practice. By early monitoring and appropriate interventions, we can offer better pregnancy outcomes for URPL patients, alleviating their economic and psychological burdens. We look forward to future studies that can further validate these findings and offer more insights into the diagnosis and treatment of URPL. By defining a cut-off value of 1.49–1.50 for the mS/D ratio using Youden's Index, we provide a practical threshold for early identification of high-risk URPL patients. This cut-off value allows clinicians to better assess pregnancy risks and implement timely interventions, potentially improving outcomes for patients with unexplained recurrent pregnancy loss.

Although this finding is helpful in predicting adverse pregnancy outcomes, further research is needed to explore how they can be integrated into clinical practice for the prevention and management of recurrent pregnancy loss. Future studies should focus on validating these results in larger populations and developing personalized treatment strategies based on hemodynamic monitoring to improve pregnancy outcomes.

Data Sharing Statement

The data that underpins the findings of this study are accessible on request of the corresponding author.

Ethical Statement and Consent to Participate

The authors take full responsibility for the integrity and accuracy of all aspects of this study. All procedures involving human participants conducted in this research comply with the principles laid out in the Declaration of Helsinki, as revised in 2013. This study received approval from the Medical Ethics Committee of the First Affiliated Hospital of Soochow University (Approval No. 121(2022)). Written informed consent was obtained from each participant after ensuring they understood the information and had the opportunity to ask questions.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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