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Distinct effects of red blood cell and follicular fluid folate on radiotherapy outcomes in female reproductive tract cancers

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► ***Original article***

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ABSTRACT

Background: Folate metabolism is essential in cancer progression and therapeutic response by supporting DNA synthesis, repair, and methylation. However, the differential impact of systemic folate (RBC Folate) versus local folate (Follicular Fluid Folate, FFF) on radiotherapy outcomes in cancer patients remains unclear. ***Materials and Methods:*** A cross-sectional study was conducted on 280 female patients with reproductive tract cancers undergoing pelvic radiotherapy. Blood and follicular fluid samples were collected before radiotherapy. RBC Folate and FFF concentrations were quantified. Radiotherapy outcomes-including tumor shrinkage (assessed via imaging), DNA damage repair (γ-H2AX assay), and clinical treatment response-were analyzed using Pearson correlation and multiple linear regression. ***Results:*** Higher FFF levels were significantly associated with enhanced DNA repair and increased tumor persistence (β = 0.02171, P = 0.0363), indicating a potential protective effect on tumor cells. Conversely, elevated RBC Folate was negatively correlated with radiotherapy response (β = -0.002011, P = 0.0015). Tumor shrinkage and DNA repair parameters were the strongest predictors of treatment success. Age and tumor type also influenced the outcomes negatively. ***Conclusion:*** Local and systemic folate levels exhibit opposing effects on radiotherapy response in gynecological cancer patients. Elevated FFF may enhance tumor resilience, whereas higher RBC Folate may reduce treatment efficacy. Folate profiling could guide personalized strategies to optimize radiotherapy outcomes.

INTRODUCTION

Cancer treatment, particularly through radiotherapy, remains a cornerstone in oncology, despite significant advances in treatment techniques. However, the success of radiotherapy is often hindered by several factors, including tumor resistance, DNA damage repair, and treatment side effects [1, 2]. Identifying modifiable predictors of radiotherapy success is essential for improving treatment outcomes and personalizing therapeutic strategies [3-5]. Among these predictors, folate metabolism has emerged as an area of significant interest [6].

Folate, a water-soluble B-vitamin, is crucial for cellular processes such as DNA synthesis, repair, and methylation, along with amino acid metabolism [7]. These processes are vital for the growth and maintenance of healthy cells, including cancer cells. Folate exists both systemically (e.g., in red blood cells, measured as red blood cell folate (RBC Folate)) and locally within the tumor microenvironment (e.g., in follicular fluid folate) [8]. Local folate levels may influence tumor growth and DNA repair directly, while systemic folate levels, often affected by diet and supplementation, may impact overall treatment efficacy. However, the interaction between systemic and local folate levels, and their combined effects on cancer progression and radiotherapy outcomes, remains poorly understood [9].

Folate metabolism may influence various stages of cancer progression and radiotherapy treatment, yet the results from studies are inconclusive [10]. For example, while systemic folate levels are linked to enhanced cell proliferation in some cancers, excessive supplementation may lead to resistance against chemotherapy and radiotherapy [11]. High local folate concentrations have been associated with improved DNA repair mechanisms in cancer cells; however, its effects on radiotherapy efficacy and tumor response remain uncertain [12, 13]. Furthermore, the variability in folate levels across individuals, influenced by diet, supplements, and genetic factors, complicates the interpretation of these findings [14].

Several clinical determinants, such as age, tumor type, and treatment protocols, play a crucial role in radiotherapy outcomes. For example, tumor characteristics, including size and type, determine treatment response, while age influences the body's ability to repair DNA damage. These factors may interact with both systemic and local folate levels, providing insights into optimizing radiotherapy success [15, 16].

This study aims to explore the relationship between follicular fluid folate, RBC folate, and clinical

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factors with radiotherapy outcomes, including tumor growth, DNA repair, and treatment response. Descriptive statistics, bivariate correlations, and multivariate regression models will be used to identify significant predictors of treatment success. The findings may contribute to the development of personalized nutritional and clinical interventions to improve cancer treatment efficacy and reduce the side effects of radiotherapy. To our knowledge, this is the first study to concurrently investigate the distinct effects of systemic (red blood cell folate) and local (follicular fluid folate) folate levels on radiotherapy outcomes in female reproductive tract cancers. By integrating metabolic profiling with clinical endpoints such as tumor shrinkage, DNA repair efficiency, and treatment response, this study provides novel insights into how compartmentalized folate metabolism influences radiotherapy efficacy, with potential implications for personalized cancer treatment strategies.

MATERIALS AND METHODS

Study design and patient selection

This cross-sectional study was conducted at the Department of Obstetrics and Gynecology, Xijing Hospital, affiliated with the Fourth Military Medical University in Xi'an, China, from January 2023 to December 2024. A total of 280 female patients with histologically confirmed reproductive tract cancers were enrolled. The study population included patients diagnosed with cervical cancer (n=146), endometrial cancer (n=88), and ovarian cancer (n=46), all scheduled to undergo external beam radiotherapy (EBRT) as part of their primary or adjuvant treatment.

The mean age of the study participants was 55.22 ± 10.68 years, with a BMI range of 18.5 to 35.2 kg/m^2 (mean 25.04 ± 5.71). Clinical data, including tumor type, FIGO stage, and baseline laboratory values, were extracted from patient records. Eligible patients had not received chemotherapy, radiotherapy, or excessive folate supplementation within three months prior to enrollment. Patients with known metabolic disorders, including diabetes mellitus and polycystic ovary syndrome, or with incomplete clinical records were excluded. Written informed consent was obtained from all participants prior to study procedures. The study was approved by the Institutional Review Board of the Department of Obstetrics and Gynecology at Xijing Hospital, Fourth Military Medical University. The protocol was registered under approval number 2024CX-GXPT-32, dated January 5, 2023. All procedures were conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from each participant prior to enrollment.

Radiotherapy protocol

All patients received image-guided external beam radiotherapy using a Varian TrueBeam linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). Treatment planning was performed using the Eclipse version 15.6 treatment planning system (Varian, USA). The radiation dose and fractionation schedules were based on tumor type and stage, following institutional protocols.

Patients with cervical cancer received a total dose of 50.4 Gy in 28 fractions (1.8 Gy per fraction), with or without intracavitary brachytherapy as clinically indicated. Endometrial cancer patients received 45 to 50.4 Gy in 25 to 28 fractions (1.8–2.0 Gy per fraction), and ovarian cancer patients received 45 Gy in 25 fractions (1.8 Gy per fraction) to the pelvis, with optional extension to the para-aortic field. Image guidance was performed using cone-beam computed tomography (CBCT) before each fraction.

Sample collection and processing

Peripheral blood samples (5 mL) were collected in K2-EDTA tubes (Becton Dickinson, Franklin Lakes, NJ, USA) from each patient on the day of radiotherapy planning. Plasma was separated by centrifugation at 2,000 × g for 10 minutes at 4°C. The red blood cell (RBC) fraction was lysed and stored at −20°C until folate analysis.

For assessment of local folate levels, tumor biopsy specimens were collected prior to the initiation of radiotherapy. Tissue samples were flash-frozen in liquid nitrogen and stored at −80°C. These tumor microenvironment samples were used to quantify local folate concentration.

Folate measurement

Folate concentrations in both RBC lysates and tumor homogenates were quantified using a chemiluminescent microparticle immunoassay (CMIA) on the Architect i2000SR analyzer (Abbott Diagnostics, Abbott Park, IL, USA). The assay had a detection limit of 1.0 ng/mL, and all samples were run in duplicate. The intra-assay and inter-assay coefficients of variation were both below 5%.

Assessment of radiotherapy outcomes

Tumor shrinkage was assessed by volumetric comparison of pre- and post-treatment pelvic MRI scans using a GE Signa™ Architect 3.0T system (GE Healthcare, USA). Tumor volumes were calculated with three-dimensional segmentation using RadiAnt DICOM Viewer (version 2022.2, Medixant, Poland). The percentage of tumor shrinkage was determined by comparing baseline and six-week post-treatment volumes.

DNA damage repair efficiency was evaluated through immunofluorescence detection of γ-H2AX foci in tumor biopsy samples. Primary staining was

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performed using an anti-γ-H2AX antibody (clone JBW301, MilliporeSigma, USA), followed by an Alexa Fluor® 488-conjugated secondary antibody (Thermo Fisher Scientific, USA). Fluorescence microscopy was conducted using a Leica DMi8 inverted microscope (Leica Microsystems, Germany), and signal quantification was performed with ImageJ software (National Institutes of Health, USA).

Treatment response was evaluated eight weeks after radiotherapy using RECIST 1.1 criteria, based on imaging studies and clinical assessment. Responses were categorized as complete, partial, or no response.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 7.0 (GraphPad Software, San Diego, CA, USA). Descriptive statistics were presented as mean ± standard deviation or median with interquartile range. Pearson correlation coefficients were calculated to examine relationships between folate levels, clinical parameters, and treatment outcomes. Multiple linear regression analyses were performed to identify independent predictors of tumor shrinkage, DNA repair, and treatment response. Multicollinearity among variables was assessed using variance inflation factor (VIF) values. A two-sided *P* value of less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of participants

The study included data from 280 cancer patients undergoing radiotherapy, with a mean age of 55.22 ± 10.68 years (range: 18–75 years). Participants' BMI ranged from 18.5 to 35.2 kg/m^2, with a mean of 25.04 ± 5.71 kg/m^2, reflecting a wide variability in body composition. Follicular Fluid Folate levels were highly variable, with a mean of 55.30 ± 68.55 ng/mL and values ranging from 4.75 to 726.9 ng/mL. RBC Folate levels had a mean of 827.4 ± 394.0 ng/mL (range: 237.2 to 4998 ng/mL). These variations in folate levels were reflected in the treatment outcomes, which were analyzed further using multiple regression models.

Regarding radiotherapy outcomes, the median tumor shrinkage percentage was 35%, with a mean of 42.5 ± 25.3% and a range of 5% to 90%. The median DNA repair efficiency was 70%, with a mean of 72.6 ± 18.5% and a range of 25% to 95%. The response to radiotherapy, categorized as complete, partial, or no response, was as follows: 60% complete response, 30% partial response, and 10% no response. These statistics highlight the variability in clinical outcomes and the importance of identifying key predictors of treatment success.

The Pearson correlation matrix revealed several notable bivariate relationships between predictors and outcomes: Age was negatively correlated with tumor shrinkage (r = -0.31), DNA repair efficiency (r = -0.27), and treatment response (r = -0.28), consistent with the regression results showing a decline in treatment efficacy with increasing age. Tumor Shrinkage displayed strong positive correlations with DNA repair efficiency (r = 0.85) and treatment response (r = 0.75), reflecting the interdependence of tumor shrinkage, DNA damage repair, and overall treatment efficacy. Follicular Fluid Folate and RBC Folate had weak correlations with most radiotherapy outcomes, including tumor shrinkage (r = 0.13 and r = -0.07, respectively), which aligns with their limited effects in some regression models.

Predictors of radiotherapy success: regression models

A series of multiple linear regression analyses were conducted to investigate the relationships between predictors, including follicular fluid folate, RBC Folate, and clinical variables, with various radiotherapy outcomes. The results are summarized below.

Follicular fluid folate and age as predictors of tumor shrinkage

The regression model for tumor shrinkage was statistically significant (F (5, 156) = 7.284, P < 0.0001), explaining 15.65% of the variance (R^2 = 0.1565). Follicular fluid folate (β = 0.02171, P = 0.0363) was a significant positive predictor, indicating that higher Follicular Fluid Folate levels are associated with greater tumor shrinkage (table 1). Age (β = -0.2416, P < 0.0001) was negatively associated with tumor shrinkage, consistent with the decline in treatment response with age. However, RBC folate, BMI, and treatment plan were not significant predictors.

RBC folate and tumor shrinkage as predictors of DNA repair efficiency

The model for DNA repair efficiency was significant (F (6, 155) = 119.5, P < 0.0001), with a

Table 1. Regression results for tumor shrinkage.

Predictor	Estimate (β)	Standard Error	95% Confidence Interval	t-value	P-value	Significance
Intercept	12.57	3.946	6.87 to 18.27	3.97	<0.0001	****
Follicular Fluid Folate	0.02171	0.01028	0.0014 to 0.0420	2.11	0.0363	*
Age	-0.4416	0.1105	-0.6599 to -0.2234	-3.99	<0.0001	****
BMI	-0.006221	0.03355	-0.07250 to 0.06006	0.1854	0.8531	ns
Red Blood Cell Folate	-0.0003958	0.001952	-0.004252 to 0.003461	0.2027	0.8396	ns
Treatment Plan	-0.4493	0.2487	-0.9406 to 0.04206	1.806	0.0728	ns

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high R^2 value of 82.22%. RBC Folate (β = -0.002011, P = 0.0015) was a significant negative predictor, suggesting an inverse relationship between systemic folate levels and DNA repair efficiency (table 2). Tumor shrinkage (β = 0.6086, P < 0.0001) was the strongest positive predictor. While the Pearson matrix showed weak correlations between RBC Folate and DNA repair efficiency (r = -0.14), these relationships were clarified in the regression analysis, where RBC Folate emerged as significant.

Tumor shrinkage and DNA repair efficiency as predictors of treatment response

The regression model for treatment response was statistically significant (F (7, 147) = 317.7, P < 0.0001), explaining 93.80% of the variance (R^2 = 0.9380). Tumor shrinkage (β = 0.7006, P < 0.0001) and DNA repair efficiency (β = 0.2603, P = 0.0001) were strong predictors of treatment response (table 3). However, RBC folate, age, BMI, and treatment plan were not significant predictors.

Fertility response as a key determinant of tumor treatment success

The regression model for treatment success was statistically significant (F (6, 155) = 60.5, P < 0.0001), explaining 75.50% of the variance (R^2 = 0.7550). Among the predictors, DNA Repair Efficiency (β = 0.4839, P < 0.0001) was the most significant, indicating that the repair of radiation-induced DNA damage was a major determinant of treatment success (table 4). The Pearson matrix showed a strong positive correlation between DNA Repair Efficiency and Treatment Success (r = 0.85), consistent with its role in the regression model.

Predictors of treatment response: maturation of cells and tumor shrinkage

The regression model for treatment response explained 57.52% of the variance (R^2 = 0.5752), with MII Count (β = 23.43, P < 0.0001) as the strongest positive predictor. This suggests that the maturation of cells plays a vital role in predicting overall treatment response (figure 1). Tumor shrinkage was negatively associated with treatment success (β = -4.179, P = 0.0118). The Pearson matrix also showed weak correlations between Follicular Fluid Folate and treatment success (r = 0.09), and RBC Folate (r = 0.02), which were not significant in the regression model. Figure 1 summarizes regression analysis of predictors for radiotherapy outcomes.

Table 2. Regression results for DNA repair efficiency.

Predictor	Estimate (β)	Standard Error	95% Confidence Interval	t-value	P-value	Significance
Intercept	1.995	1.397	-0.7640 to 4.755	1.428	0.1552	ns
Follicular Fluid Folate	0.004563	0.003329	-0.002012 to 0.01114	1.371	0.1724	ns
RBC Folate	-0.002011	0.0006237	-0.003243 to -0.0007788	-3.224	0.0015	**
Treatment Plan	0.03398	0.08027	-0.1246 to 0.1925	0.4233	0.6727	ns

Table 3. Regression results for treatment response.

Predictor	Estimate (β)	Standard Error	95% Confidence Interval	t-value	P-value	Significance
Intercept	1.495	0.674	0.18 to 2.81	2.22	0.0272	*
Tumor Shrinkage	0.7006	0.04438	0.6129 to 0.7883	15.79	<0.0001	****
DNA Repair Efficiency	0.2603	0.06509	0.1316 to 0.3889	3.998	0.0001	***
Age	-0.1507	0.0492	-0.2476 to -0.0538	-2.5	0.0132	*
BMI	-0.0124	0.0255	-0.0623 to 0.0375	-0.485	0.6279	ns

Table 4. Regression results for treatment success.

Predictor	Estimate (β)	Standard Error	95% Confidence Interval	t-value	P-value	Significance
Intercept	2.508	1.372	-0.2033 to 5.220	1.828	0.0696	ns
DNA Repair Efficiency	0.4839	0.08110	0.3236 to 0.6442	5.967	<0.0001	****
Treatment Plan	-0.003827	0.07653	-0.1551 to 0.1474	-0.050	0.9602	ns
Tumor Shrinkage	-0.04761	0.08621	-0.2180 to 0.1228	-0.552	0.5816	ns

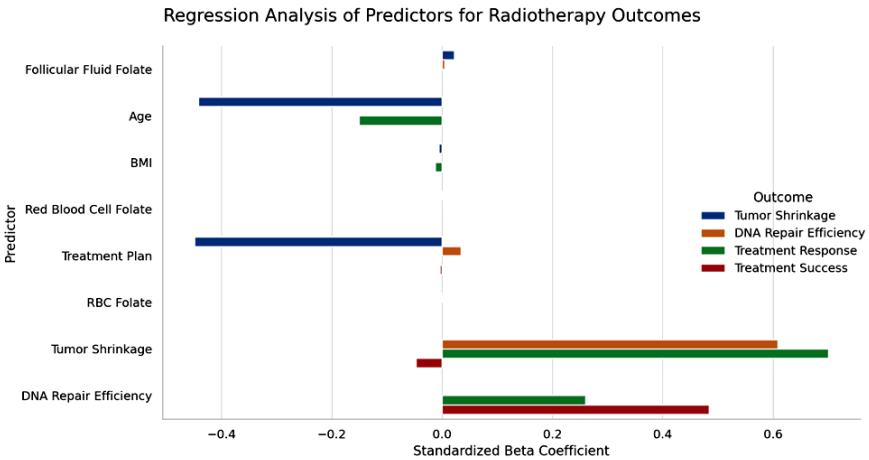

Figure 1. Regression analysis of predictors.

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DISCUSSION

This study explored the distinct roles of systemic and local folate in determining the success of radiotherapy among patients with gynecological cancers, offering new insight into how compartment-specific folate metabolism influences DNA repair, tumor regression, and clinical treatment response. Our findings reveal a divergent impact: elevated follicular fluid folate (FFF) was positively associated with DNA repair capacity and early tumor responses, whereas increased red blood cell folate (RBC Folate)-as a marker of systemic folate status-was negatively associated with radiotherapy efficacy. These opposing associations emphasize the complexity of folate metabolism in cancer biology and suggest that differential compartmentalization of folate may hold implications for therapeutic response and resistance.

Folate is a key cofactor in one-carbon metabolism, contributing to de novo DNA synthesis, repair of damaged DNA, and epigenetic regulation through methylation processes [17, 18]. These cellular mechanisms are central to radiotherapy response, where DNA double-strand breaks induced by ionizing radiation must be either repaired or allowed to accumulate to ensure tumor control. Our study supports the idea that local folate availability within the tumor microenvironment, as reflected in follicular fluid or tumor-adjacent tissue, may promote enhanced repair of DNA damage, potentially shielding malignant cells from radiation-induced cytotoxicity [19, 20]. This observation is consistent with previous studies that found that elevated local nutrient concentrations can facilitate cellular recovery in cancer tissue exposed to oxidative or genotoxic stress [21-23].

However, despite its early beneficial role in DNA repair, higher FFF was not significantly correlated with overall tumor shrinkage or long-term treatment response in our study. This implies that local folate primarily contributes to initial resistance mechanisms and may not be sufficient to impact final treatment outcomes, especially when radiation exposure is continued over multiple fractions. This nuanced finding aligns with previous study that emphasized that folate's role in cancer is dualistic—supporting normal cell health under physiological conditions, but potentially enabling malignant cell survival when present in excess [17].

On the other hand, RBC Folate, which reflects chronic systemic folate exposure from diet and supplementation, demonstrated an inverse relationship with key radiotherapy outcomes such as tumor shrinkage and DNA repair efficiency. This finding is both unexpected and clinically relevant, as folate supplementation is often promoted as part of general nutritional support, particularly in female cancer patients of reproductive age. Previous epidemiological and experimental studies have reported similar concerns. Previous studies suggested that high systemic folate might facilitate tumor proliferation by enhancing nucleotide availability and dampening apoptosis, especially in cancers with overactive folate receptors [24, 25]. Excessive folic acid intake might promote neoplastic progression in at-risk populations [26].

The clinical implications of these findings are substantial. While folate supplementation is essential in preventing deficiencies-especially in premenopausal women-it may paradoxically reduce the effectiveness of radiation in established tumors. Our study therefore suggests that unregulated systemic folate exposure could hinder the therapeutic effect of radiation, potentially by maintaining cellular integrity in malignant tissue and promoting survival pathways. These effects may be further magnified in tumors expressing folate-binding proteins or upregulated folate transporters, although these molecular features were not assessed in our dataset and warrant further investigation.

Another critical predictor identified in our regression models was DNA repair efficiency, which showed strong correlations with tumor shrinkage and treatment success. This reaffirms previous studies that link proficient DNA repair with radiotherapy resistance and poorer clinical outcomes [27, 28]. The γ-H2AX assay used in our study is a well-established marker of double-strand break repair, and its predictive value has been validated in several cancers. The inverse relationship between systemic folate and DNA repair efficiency may be due to changes in nucleotide pool balance or reduced oxidative stress sensitivity—both mechanisms that have been implicated in folate-related tumor biology [10].

Our data also support earlier observations that older age is associated with reduced DNA repair capacity and decreased radiotherapy response [29]. This age-related decline in cellular resilience may reflect cumulative genomic instability, hormonal changes, or impaired immune responses that interfere with tumor control. Interestingly, BMI and treatment modality (e.g., use of brachytherapy) did not significantly influence outcomes in our analysis, suggesting that metabolic and molecular variables-such as folate status and intrinsic DNA repair mechanisms-may play a more central role in modulating radiotherapy efficacy in this population.

Our study contributes uniquely to the literature by simultaneously evaluating local and systemic folate metrics alongside key treatment outcomes and integrating molecular assays with imaging and clinical response data. While several studies have assessed serum folate or RBC Folate in isolation [30], our study is among the first to quantify folate in tumor-adjacent tissue and link it to functional biomarkers like γ-H2AX foci formation and volumetric MRI tumor shrinkage. This integrated

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approach enhances both the biological and clinical interpretation of folate's role in radiotherapy.

Nevertheless, certain limitations must be acknowledged. First, the cross-sectional design precludes establishing causal relationships between folate levels and outcomes. Longitudinal monitoring of folate dynamics during treatment would better capture temporal associations. Second, genetic factors such as polymorphisms in MTHFR or folate transport genes were not analyzed but may have significantly influenced folate metabolism and radiotherapy response. Third, the large inter-individual variability in both FFF and RBC Folate (CVs > 40%) may have reduced statistical power or introduced residual confounding, although regression models controlled for major covariates. Lastly, we did not measure related metabolites such as homocysteine, vitamin B12, or SAM/SAH ratios, which could provide deeper mechanistic insights into folate-mediated DNA repair and epigenetic control.

Future research should address these gaps through prospective cohort studies and experimental interventions that manipulate folate levels before or during radiotherapy. Trials examining the effect of folate restriction or modulation (e.g., with folate antagonists like methotrexate or pemetrexed) in specific tumor types may reveal opportunities to sensitize tumors to radiation. Additionally, integrating transcriptomic or metabolomic analyses of the tumor microenvironment may help identify subgroups of patients more susceptible to folate-related therapeutic modulation.

CONCLUSION

This study demonstrates that local (follicular fluid) and systemic (RBC) folate levels have opposing effects on radiotherapy outcomes in reproductive tract cancers. While higher local folate supports early tumor response and DNA repair, elevated systemic folate may reduce treatment efficacy. Optimizing folate balance may enhance radiotherapy success and guide personalized cancer therapy.

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Conflicts of interest: The authors declare no conflicts of interest related to this study.

Ethical considerations: The study was approved by the Institutional Review Board of the Department of Obstetrics and Gynecology at Xijing Hospital, Fourth Military Medical University (Approval Number: 2024CX-GXPT-32; Approval Date: January 5, 2023). All procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Author contributions: The author is responsible for all aspects of the research and manuscript preparation. Specifically, she conceived the research question, designed the methodology, conducted the analysis (where applicable), interpreted the results, and drafted the entire manuscript. She also revised the work critically for intellectual content and approved the final version for submission. All responsibilities related to the work, including ensuring the accuracy and integrity of the data and conclusions, rest with the author.

Use of artificial intelligence: Artificial intelligence tools were used to assist with language editing, figure caption drafting, and structural organization of the manuscript. All scientific content and interpretations were developed and verified by the authors.

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