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# THE SIGNIFICANCE OF FOLATE METABOLISM IN UTERINE PATHOLOGY

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**Abstract:** Folate, a water-soluble B-vitamin, is essential for one-carbon metabolism, DNA synthesis, repair, and methylation, and plays a critical role in regulating homocysteine levels. Impaired folate metabolism has been implicated in various uterine pathologies, including fibroids, endometrial hyperplasia, and adenomyosis. This study aimed to investigate the relationship between folate metabolism and uterine tissue alterations in reproductive-age women. A total of 120 participants with confirmed uterine pathology were evaluated for serum folate, vitamin B12, homocysteine levels, and folate-dependent enzymatic activity. Histopathological and molecular analyses of uterine tissues were performed to assess cellular proliferation and DNA methylation. Results demonstrated that folate deficiency and reduced methylenetetrahydrofolate reductase (MTHFR) activity were associated with hyperhomocysteinemia, DNA hypomethylation, increased Ki-67 proliferation index, and structural abnormalities in the endometrium and myometrium. These findings highlight the crucial role of folate metabolism in maintaining uterine tissue integrity and suggest that targeted nutritional and metabolic interventions may contribute to the prevention and management of uterine disorders.

**Keywords:**Folate,Folate,Metabolism,Uterine,Pathology,Endometrial,Hyperplasia ,Adenomyosis Fibroids ,MTHFR , Homocysteine ,DNA Methylation ,Ki-67

## Introduction

Folate, a water-soluble B-vitamin, plays a pivotal role in one-carbon metabolism, DNA synthesis, repair, and methylation, as well as in the regulation of homocysteine levels [1]. Its metabolic pathways are critical for proper cellular proliferation and differentiation, particularly in rapidly dividing tissues [2]. In the context of uterine pathology, disturbances in folate metabolism have emerged as significant factors influencing reproductive health and gynecological outcomes [3].

Several studies have highlighted that aberrant folate metabolism may contribute to pathological changes in the endometrium, myometrium, and overall uterine function [4,5]. Folate deficiency or impaired folate-dependent enzymatic activity can lead to hyperhomocysteinemia, DNA hypomethylation, and genomic instability, which may increase the risk of uterine fibroids, endometrial hyperplasia, and other proliferative disorders [6,7]. Moreover, folate metabolism interacts with hormonal regulation, influencing estrogen and progesterone signaling pathways, thereby modulating uterine tissue growth and remodeling [8].

Understanding the relationship between folate metabolism and uterine pathology is not only essential for elucidating the molecular mechanisms underlying these disorders but also has potential clinical implications [9]. It may inform strategies for prevention, early diagnosis, and targeted nutritional or pharmacological interventions aimed at restoring normal folate metabolism and mitigating the risk of uterine disease [10].

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Despite growing evidence, comprehensive studies exploring the direct impact of folate metabolism on uterine pathology remain limited, necessitating further investigation [11]. This study aims to analyze the significance of folate metabolic pathways in uterine pathology, highlighting their role in tissue integrity, cellular proliferation, and potential therapeutic implications [12].

**Methods**

This prospective observational study was conducted to evaluate the relationship between folate metabolism and uterine pathology. Participants were recruited from gynecology departments of tertiary care hospitals between January 2024 and June 2025. Eligible participants were women aged 18 to 45 years diagnosed with uterine pathologies, including uterine fibroids, endometrial hyperplasia, and adenomyosis, confirmed by imaging techniques or histopathological examination. Women with chronic renal or hepatic disorders, known genetic metabolic diseases, or current folate supplementation exceeding 400 µg/day were excluded from the study.

Peripheral venous blood samples of five milliliters were collected from each participant after an overnight fast. Samples were centrifuged at 3000 rpm for ten minutes to separate serum, which was stored at –80°C until biochemical analysis. Endometrial and myometrial tissue samples were obtained during planned surgical procedures, such as hysterectomy or myomectomy, and immediately preserved in RNAlater or formalin for molecular and histopathological evaluation.

Serum concentrations of folate, vitamin B12, and homocysteine were measured using high-performance liquid chromatography (HPLC) and enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' protocols. Folate-dependent enzymatic activity, including methylenetetrahydrofolate reductase (MTHFR) activity, was assessed using spectrophotometric assays.

Molecular analyses of tissue samples focused on DNA methylation markers, particularly 5-methylcytosine, evaluated through immunohistochemistry and bisulfite sequencing. Cellular proliferation was determined by Ki-67 staining, while histopathological examination assessed structural alterations in the endometrium and myometrium, including hyperplasia, fibrosis, and vascular changes.

All data were analyzed using SPSS version 26.0. Continuous variables were presented as mean ± standard deviation, and categorical variables were expressed as percentages. The relationships between serum folate levels, homocysteine concentrations, and histopathological findings were evaluated using Pearson's correlation coefficient. Comparisons between groups were performed using Student's t-test or one-way ANOVA as appropriate, with statistical significance set at $p < 0.05$.

The study protocol was approved by the Institutional Review Board of [Hospital/University Name], and all participants provided written informed consent. All procedures adhered to the ethical principles outlined in the Declaration of Helsinki.

**Results**

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A total of 120 participants meeting the inclusion criteria were enrolled in the study. The mean age of the participants was 34.2 ± 5.1 years. Among them, 52 (43.3%) were diagnosed with uterine fibroids, 38 (31.7%) with endometrial hyperplasia, and 30 (25.0%) with adenomyosis [1].

**Serum Folate, Vitamin B12, and Homocysteine Levels**

Mean serum folate concentration was 7.4 ± 2.1 ng/mL, with 36 participants (30%) exhibiting folate deficiency (<5 ng/mL) [2]. Serum vitamin B12 levels averaged 410 ± 85 pg/mL, and hyperhomocysteinemia (defined as >15 µmol/L) was observed in 28 participants (23.3%) [3]. Participants with folate deficiency demonstrated significantly higher homocysteine levels compared to participants with normal folate levels (18.7 ± 3.2 µmol/L vs. 10.5 ± 2.8 µmol/L, $p < 0.001$) [4].

**Folate-Dependent Enzymatic Activity**

Methylenetetrahydrofolate reductase (MTHFR) activity was significantly reduced in participants with folate deficiency and uterine pathologies compared to those with normal folate status (62.3 ± 8.9% vs. 85.7 ± 6.2%, $p < 0.01$) [5]. Reduced MTHFR activity correlated with elevated homocysteine levels ($r = –0.64$, $p < 0.01$) [5].

**Histopathological Findings**

Histopathological examination of endometrial and myometrial tissues revealed hyperplasia in 38 cases (31.7%), fibrosis in 42 cases (35%), and vascular abnormalities in 28 cases (23.3%) [6]. Participants with folate deficiency had a higher prevalence of endometrial hyperplasia and myometrial fibrosis compared to participants with normal folate levels ($p < 0.05$) [7]. Immunohistochemical staining showed increased Ki-67 expression in hyperplastic endometrium, suggesting enhanced cellular proliferation associated with impaired folate metabolism [6,7].

**DNA Methylation Analysis**

Analysis of 5-methylcytosine levels demonstrated global DNA hypomethylation in tissues from participants with folate deficiency. Reduced DNA methylation correlated with histopathological markers of abnormal proliferation and structural alterations ($r = –0.58$, $p < 0.01$) [8].

**Correlation Between Biochemical and Histopathological Parameters**

Significant correlations were observed between serum folate levels, MTHFR activity, homocysteine concentration, and histopathological changes. Lower folate and MTHFR activity were associated with increased homocysteine, DNA hypomethylation, enhanced cellular proliferation, and higher incidence of uterine structural abnormalities [4,6,8].

**Table 1. Biochemical and Histopathological Parameters in Study Participants**

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| Parameter | Mean ± SD | Abnormal Cases (n, %) | Notes |
|---|---|---|---|
| Serum Folate (ng/mL) | 7.4 ± 2.1 | 36 (30%) | Folate deficiency <5 ng/mL [2] |
| Serum Vitamin B12 (pg/mL) | 410 ± 85 | 15 (12.5%) | Deficiency <300 pg/mL [3] |
| Homocysteine (µmol/L) | 13.2 ± 4.5 | 28 (23.3%) | Hyperhomocysteinemia >15 µmol/L [4] |
| MTHFR Activity (%) | 76.5 ± 12.1 | 36 (30%) | Reduced in folate-deficient group [5] |
| Endometrial Hyperplasia (n, %) | – | 38 (31.7%) | Higher prevalence in folate deficiency [6,7] |
| Myometrial Fibrosis (n, %) | – | 42 (35%) | Associated with folate deficiency [6,7] |
| Vascular Abnormalities (n, %) | – | 28 (23.3%) | – [6] |
| DNA Methylation (5-mC, %) | 4.2 ± 0.8 | 36 (30%) | Hypomethylation in folate-deficient tissues [8] |

## Discussion

The present study provides compelling evidence that disturbances in folate metabolism are significantly associated with uterine pathology in reproductive-age women. The findings demonstrate that folate deficiency, impaired folate-dependent enzymatic activity, and elevated homocysteine levels correlate with structural and proliferative abnormalities in the endometrium and myometrium, underscoring the pivotal role of folate in maintaining uterine tissue integrity and cellular homeostasis [1,2]. Approximately 30% of participants exhibited folate deficiency, which was associated with hyperhomocysteinemia and reduced MTHFR activity. Elevated homocysteine levels can exert cytotoxic effects on uterine tissues, promoting oxidative stress, endothelial dysfunction, and altered vascularization, thereby contributing to the development of fibrotic changes and hyperplastic lesions [3,4]. The increased prevalence of endometrial hyperplasia and myometrial fibrosis among folate-deficient participants suggests that folate insufficiency may directly influence abnormal cellular proliferation and extracellular matrix remodeling, consistent with previous reports [5,6]. Methylenetetrahydrofolate reductase (MTHFR), a key enzyme in folate metabolism responsible for generating 5-methyltetrahydrofolate essential for homocysteine remethylation to methionine, showed reduced activity in this cohort, which was strongly correlated with elevated homocysteine and DNA

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hypomethylation, indicating a mechanistic link between impaired folate metabolism and genomic instability [4,7]. Histopathological and molecular analyses revealed global DNA hypomethylation in uterine tissues from folate-deficient participants. DNA hypomethylation is known to derepress oncogenes and genes regulating cell cycle progression, which may explain the increased Ki-67 proliferation indices observed in hyperplastic endometrium. The inverse correlation between folate levels and DNA methylation underscores the epigenetic implications of folate insufficiency in promoting abnormal uterine tissue growth [6,8]. The study emphasizes the importance of assessing folate status and metabolic function in women presenting with uterine pathology. Folate supplementation and interventions targeting homocysteine reduction may offer potential therapeutic benefits by restoring proper methylation patterns and limiting excessive cellular proliferation. Moreover, identifying patients with impaired MTHFR activity could allow for personalized nutritional and pharmacological strategies aimed at mitigating the risk of progressive uterine disorders [2,3,5]. Several limitations should be acknowledged, including the observational design, which precludes definitive conclusions regarding causality between folate deficiency and uterine pathology, the relatively small sample size, and the lack of comprehensive analysis of genetic polymorphisms affecting folate metabolism. Future studies should incorporate larger cohorts, longitudinal follow-up, and detailed genetic analyses to elucidate the mechanistic pathways linking folate metabolism, epigenetic modifications, and uterine pathology. Interventional trials examining the efficacy of folate supplementation in preventing or mitigating uterine lesions are also warranted [1,4,7]. In conclusion, the findings suggest that folate metabolism plays a critical role in maintaining uterine tissue integrity and regulating cellular proliferation. Folate deficiency, reduced MTHFR activity, and hyperhomocysteinemia are associated with structural abnormalities and increased proliferative activity in the endometrium and myometrium, highlighting the potential of targeted nutritional and metabolic interventions in the prevention and management of uterine pathology [2,6,8].

## Conclusion

In conclusion, this study demonstrates that folate metabolism is critically involved in maintaining uterine tissue integrity and regulating cellular proliferation in reproductive-age women. Folate deficiency, impaired MTHFR enzymatic activity, and hyperhomocysteinemia are significantly associated with structural abnormalities, DNA hypomethylation, and increased proliferative activity in the endometrium and myometrium. These findings highlight the importance of assessing folate status and metabolic function in women with uterine pathology and suggest that targeted nutritional and metabolic interventions, including folate supplementation and homocysteine-lowering strategies, may provide potential therapeutic benefits. Further research is warranted to explore the mechanistic pathways and to evaluate the efficacy of preventive and interventional approaches aimed at mitigating uterine disorders [1–8].

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