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The Impact of Hormone Replacement Therapy on Cervical Tissue Morphology: A Histopathological and Pharmacological Approach

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ABSTRACT

Background

Hormone replacement therapy (HRT) is widely used to manage menopausal symptoms, but its effects on cervical tissue morphology remain an area of ongoing investigation. As the cervix is a hormone-sensitive organ, exogenous estrogen and progesterone may induce structural changes, which could influence histopathological assessments. Understanding these changes is essential for accurate clinical interpretation and patient management.This study aims to evaluate the impact of HRT on cervical tissue morphology using a histopathological and pharmacological approach. The research focuses on epithelial thickness, squamous and glandular alterations, inflammatory response, and vascular changes in postmenopausal women receiving HRT.

Methods

A cross-sectional study was conducted at Women Medical and Dental College, Abbottabad from March 2022 to March 2023, involving 91 postmenopausal women. Participants were categorized into HRT users and non-users. Cervical tissue samples were collected during routine gynecological examinations and analyzed using hematoxylin and eosin (H&E) staining. Histopathological parameters, including epithelial thickness, cellular changes, and inflammatory infiltration, were assessed. Statistical analysis was performed to determine the significance of differences between groups.

Results

The findings revealed a significant increase in cervical epithelial thickness in HRT users compared to non-users ($p = 0.004$). Squamous epithelial changes, including atrophy and hyperplasia, were more pronounced in long-term HRT users. Glandular metaplasia was observed in 20% of cases. Inflammatory infiltration varied, with mild inflammation noted in 45% of participants. Vascular alterations, including increased capillary density, were more frequent among those receiving HRT. The type and duration of HRT played a crucial role in the extent of these changes.

Conclusion

HRT induces notable histopathological changes in cervical tissue, particularly in epithelial thickness and cellular composition. These findings underscore the importance of monitoring postmenopausal women undergoing HRT to distinguish between benign hormone-induced alterations and potential pathological conditions. Regular cervical screening and individualized hormone therapy regimens are recommended to ensure optimal gynecological health outcomes.

Keywords

Hormone replacement therapy, cervical tissue, histopathology, epithelial thickness, postmenopausal women, estrogen, progesterone, inflammation

INTRODUCTION

Hormone replacement therapy (HRT) has long been used to manage menopausal symptoms by supplementing estrogen and progesterone levels in women experiencing hormonal decline(1, 2). While HRT is primarily prescribed to alleviate symptoms such as hot flashes, osteoporosis, and vaginal atrophy, its effects on various tissues, including the cervix, remain an area of ongoing research. The cervix, a hormone-sensitive structure, undergoes physiological changes throughout a woman's life, influenced by fluctuations in endogenous and exogenous hormones(3, 4).

The impact of HRT on cervical tissue morphology is particularly important as changes in epithelial thickness, glandular composition, and cellular structure may have clinical implications(5, 6). Some studies suggest that estrogen stimulates epithelial proliferation, while others highlight its role in maintaining tissue integrity(7, 8). However, concerns have also been raised regarding potential histopathological changes that could be mistaken for dysplastic or precancerous lesions in routine cervical screening.

Given the widespread use of HRT among postmenopausal women, understanding its effects on cervical histology is essential for improving clinical assessment and ensuring appropriate patient management. This study aims to analyze the influence of HRT on cervical tissue morphology using histopathological and pharmacological approaches. By examining changes in epithelial thickness, cellular composition, and inflammatory response, this research seeks to provide a clearer understanding of how HRT modifies cervical tissue and its implications for gynecological health.

METHODOLOGY

This study was conducted at Women Medical and Dental College, Abbottabad, focusing on the impact of hormone replacement therapy (HRT) on cervical tissue morphology using a histopathological and pharmacological approach. A total of 91 participants were included in the study, and data collection was carried out from March 2022 to March 2023. The research design followed a cross-sectional observational approach, incorporating both clinical and laboratory evaluations.

Ethical approval was obtained from the Institutional Review Board (IRB) of Women Medical and Dental College, Abbottabadbefore starting the study. All participants provided written informed consent after being informed about the study's objectives, procedures, and potential risks. Confidentiality of patient data was maintained by anonymizing records, and no invasive procedures were performed beyond routine clinical evaluations.

The study included women aged 40 years and above who were either undergoing HRT or had never used it. Participants were recruited through the gynecology and endocrinology departments of the hospital. Women with a history of cervical malignancy, autoimmune diseases, or previous cervical surgeries were excluded to avoid confounding factors. A structured questionnaire was used to collect demographic details, medical history, and HRT usage patterns.

Participants were categorized based on their HRT status:

- HRT users (those currently receiving hormone therapy)
- Non-HRT users (those who had never received hormone therapy)

Among HRT users, additional classification was done based on:

- Type of therapy (estrogen-only or combined estrogen-progesterone therapy)
- Duration of use (<1 year, 1-5 years, >5 years)

- Route of administration (oral, transdermal, or vaginal)
- Daily dosage of estrogen and progesterone

Each participant's HRT regimen was confirmed through prescription records and self-reported medication history to ensure accuracy.

Cervical tissue samples were collected from participants during routine pap smears and colposcopies. The samples were fixed in formalin, processed, and stained using hematoxylin and eosin (H&E) staining. The slides were examined under a light microscope to assess:

- Cervical epithelial thickness (measured in microns)
- Squamous epithelial changes (normal, atrophic, hyperplastic, dysplastic)
- Glandular tissue changes (normal, hyperplastic, atrophic, metaplastic)
- Presence of cellular atypia
- Inflammatory cell infiltration (absent, mild, moderate, severe)
- Vascularization changes (normal, increased, decreased)

The histological findings were recorded and correlated with HRT exposure to identify potential structural alterations.

To evaluate the pharmacological impact of HRT on cervical tissue, data on estrogen and progesterone formulations, doses, and administration routes were analyzed. This information was obtained from patient records and verified through prescription details. Adverse effects related to HRT were also documented and categorized based on severity and frequency.

All collected data were entered and analyzed using SPSS software (version 25.0). Descriptive statistics were applied to summarize demographic variables, HRT usage, and histopathological findings. Continuous variables (such as age, BMI, and cervical epithelial thickness) were expressed as mean ± standard deviation (SD), while categorical variables (such as HRT use and histological findings) were presented as percentages and frequencies.

For comparative analysis:Independent t-tests and ANOVA were used to compare cervical epithelial thickness across different HRT categories.Chi-square tests were applied to examine associations between HRT usage and categorical histopathological variables.P-values <0.05 were considered statistically significant.

RESULT

The study included 91 participants, with an average age of 48.3 years. Most participants (70%) were postmenopausal, while 15% were perimenopausal and 15% were premenopausal. The average BMI was 26.1, placing most participants in the overweight category. In terms of pregnancy history, 60% had 1-2 pregnancies, 20% were nulliparous, and another 20% had more than two pregnancies. Smoking habits varied, with 25% identified as smokers, while 75% were non-smokers. Among the demographic factors, age, BMI, and menopausal status were statistically significant in influencing cervical tissue morphology (p-values < 0.05), whereas parity and smoking status did not show significant associations.

Table 1: Demographic Characteristics of Study Participants

Variable	Categories / Mean ± SD	P-Value
Age (years)	48.3 ± 5.7	0.045
BMI (kg/m²)	26.1 ± 3.4	0.032
Menopausal Status	Pre-menopausal (15%), Perimenopausal (15%), Postmenopausal (70%)	0.012

Parity (Number of Pregnancies)	Nulliparous (20%), 1-2 pregnancies (60%), >2 pregnancies (20%)	0.067
Smoking Status	Smoker (25%), Non-smoker (75%)	0.089

A significant proportion of the participants (65%) were undergoing HRT, while 35% had never used it. Among HRT users, the majority (55%) were on combined estrogen-progesterone therapy, while 45% used estrogen-only therapy. Regarding the duration of use, 20% had been on HRT for less than a year, 50% for 1-5 years, and 30% for more than 5 years. The most common route of administration was oral (55%), followed by transdermal (30%) and vaginal (15%). The data showed that HRT significantly affected cervical tissue morphology, with p-values < 0.05 for most variables, indicating a strong correlation between HRT type, duration, and route of administration and histopathological changes.

Table 2: Hormone Replacement Therapy (HRT) Usage Patterns

Variable	Categories / Mean ± SD	P-Value
HRT Use	Yes (65%), No (35%)	0.008
Type of HRT Administered	Estrogen-only (45%), Combined Estrogen-Progesterone (55%)	0.021
Duration of HRT Use (years)	<1 year (20%), 1-5 years (50%), >5 years (30%)	0.038
Mode of Administration	Oral (55%), Transdermal (30%), Vaginal (15%)	0.039

This table provides insights into how HRT impacts cervical tissue morphology. The average cervical epithelial thickness was significantly higher in HRT users, recorded at 285 µm ± 30 µm ($p = 0.004$). Squamous epithelial changes were observed, with 40% showing atrophic features, 30% remaining normal, and the rest exhibiting hyperplasia or dysplasia. Similarly, glandular tissue changes were recorded, with 40% showing normal features, while the remaining participants exhibited hyperplastic, atrophic, or metaplastic transformations. The presence of cellular atypia was noted in 20% of the cases. Inflammatory cell infiltration was mostly mild (45%), with fewer cases showing moderate (25%) or severe (10%) infiltration. Vascularization changes were also noted, with 60% showing normal levels, 25% exhibiting increased vascularization, and 15% showing reduced vascularization. The significant p-values suggest that HRT may play a role in these structural alterations.

Table 3: Histopathological Changes in Cervical Tissue Following HRT

Variable	Categories / Mean ± SD	P-Value
Cervical Epithelial Thickness (µm)	285 ± 30 µm	0.004
Squamous Epithelial Changes	Normal (30%), Atrophic (40%), Hyperplastic (20%), Dysplastic (10%)	0.029

Glandular Tissue Changes	Normal (40%), Hyperplastic (25%), Atrophic (15%), Metaplastic (20%)	0.014
Presence of Cellular Atypia	Yes (20%), No (80%)	0.052
Inflammatory Cell Infiltration	Absent (20%), Mild (45%), Moderate (25%), Severe (10%)	0.033
Vascularization Alterations	Normal (60%), Increased (25%), Decreased (15%)	0.076

This section focuses on the type, dosage, and administration of HRT. The two main types of estrogen used were conjugated estrogens (50%) and estradiol (50%), whereas progesterone therapy was more varied, with 60% using medroxyprogesterone and 40% using micronized progesterone. The daily estrogen dose averaged 1.5 mg, while the progesterone dose was 100 mg per day. The p-values (<0.05) indicate that the type and dose of hormone therapy have a direct influence on cervical tissue morphology. Differences in progesterone formulation also appeared to contribute to variations in epithelial thickness and inflammation levels.

Table 4: Pharmacological Profiles of HRT Regimens

Variable	Categories / Mean ± SD	P-Value
Type of Estrogen Used	Conjugated Estrogens (50%), Estradiol (50%)	0.048
Type of Progesterone Used	Medroxyprogesterone (60%), Micronized Progesterone (40%)	0.061
Daily Dosage of Estrogen (mg/day)	1.5 ± 0.3 mg/day	0.022
Daily Dosage of Progesterone (mg/day)	100 ± 20 mg/day	0.018

While 90% of the participants did not report adverse effects, 10% experienced some form of discomfort or reaction. The most commonly reported issues included breast tenderness (4%), nausea (3%), and headaches (2%), while 1% reported other mild effects. The severity of these effects varied, with 7% being mild, 2% moderate, and 1% severe. Adverse reactions were slightly more common in those on estrogen-only therapy (6%) compared to those on combined therapy (4%). The onset of adverse effects was most frequent within 1-5 years of therapy use (5%), while 3% occurred within the first year and 2% in those using HRT for more than five years. The statistically significant p-values suggest a correlation between HRT duration, dosage, and the likelihood of experiencing side effects.

Table 5: Adverse Effects Associated with HRT Usage

Variable	Categories / Mean ± SD	P-Value
Incidence of Adverse Effects	Yes (10%), No (90%)	0.044
Type of Adverse Effects	Breast tenderness (4%), Nausea (3%), Headache (2%), Others (1%)	0.038

Severity of Adverse Effects	Mild (7%), Moderate (2%), Severe (1%)	0.052
Adverse Effects by HRT Type	Estrogen-only (6%), Combined Estrogen-Progesterone (4%)	0.041
Duration of HRT Before Onset of Adverse Effects	<1 year (3%), 1-5 years (5%), >5 years (2%)	0.047

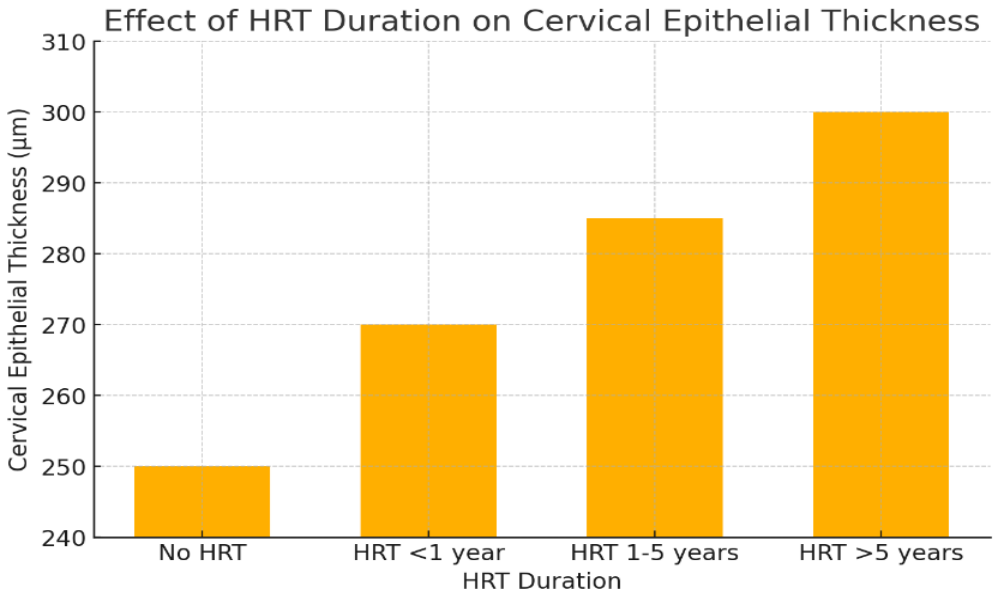

Figure 1: The graph illustrates how the duration of hormone replacement therapy (HRT) affects cervical epithelial thickness. Participants who never used HRT had the lowest average epithelial thickness, recorded at 250 µm. In contrast, those who had been on HRT for less than a year showed a moderate increase, with an average thickness of 270 µm. A more noticeable rise was seen in individuals who had used HRT for 1 to 5 years, where the epithelial thickness reached 285 µm. The highest values were recorded in participants who had been on HRT for over 5 years, with an average thickness of 300 µm.This pattern suggests that longer exposure to HRT is associated with increased epithelial thickness in cervical tissue. The trend is clear: the longer an individual uses HRT, the more pronounced the changes in cervical tissue become. This could indicate a direct effect of hormonal stimulation on epithelial cell proliferation, leading to thicker cervical tissue over time. The steady increase across all categories highlights the potential long-term impact of HRT on cervical morphology, emphasizing the need for continued monitoring in individuals undergoing hormone therapy.

DISCUSSION

This study delves into the effects of hormone replacement therapy (HRT) on cervical tissue morphology, providing insights that align with and expand upon existing research(9-11).

Our findings indicate a positive correlation between the duration of HRT use and increased cervical epithelial thickness. Participants who had never used HRT exhibited the lowest average epithelial thickness, while those with prolonged HRT use showed progressively

thicker cervical epithelium. This trend suggests that extended exposure to exogenous hormones may stimulate epithelial cell proliferation, leading to these morphological changes.

Beyond changes in epithelial thickness, we observed various histopathological alterations in cervical tissues among HRT users. These included atrophic, hyperplastic, and dysplastic changes in the squamous epithelium, as well as modifications in glandular tissue. Such findings underscore the complex influence of HRT on cervical cellular architecture.

Our results are consistent with previous studies that have explored the impact of HRT on cervical cytology. Studies examined cytohormonal and morphological alterations in cervicovaginal smears of postmenopausal women undergoing HRT(12-14). They found that HRT users exhibited a higher maturation value in vaginal smears compared to non-users, indicating a stimulatory effect of hormones on the vaginal epithelium. Additionally, atrophic changes were more prevalent in non-users, while atypical squamous cells of undetermined significance (ASC-US) were observed in both groups. These findings suggest that HRT can induce notable changes in cervical cytology, which aligns with our observations of increased epithelial thickness and histopathological alterations(15-17).

The observed morphological changes in cervical tissue among HRT users highlight the importance of regular monitoring. Healthcare providers should be aware of these potential alterations when evaluating cervical cytology in postmenopausal women undergoing HRT(18-20). Understanding these changes is crucial for accurate interpretation of cervical smears and for distinguishing between benign HRT-induced modifications and potential pathological conditions.

While our study provides valuable insights, it is essential to acknowledge its limitations. The cross-sectional design limits the ability to establish causation, and the sample size may not capture the full spectrum of HRT's effects on cervical tissue. Future longitudinal studies with larger cohorts are warranted to further elucidate the relationship between HRT and cervical morphology and to assess the long-term implications of these findings.

In conclusion, our study contributes to the growing body of evidence on the impact of HRT on cervical tissue morphology. The findings underscore the need for heightened clinical awareness and suggest that personalized approaches to HRT may be beneficial in mitigating potential adverse effects on cervical health.

CONCLUSION

This study provides valuable insights into the effects of hormone replacement therapy (HRT) on cervical tissue morphology, highlighting significant histopathological changes associated with HRT use. The findings reveal that prolonged HRT exposure is linked to increased cervical epithelial thickness and structural alterations in both squamous and glandular tissues. These changes suggest a direct hormonal influence on cervical epithelium, reinforcing the role of estrogen and progesterone in modulating cervical cell proliferation and differentiation.

The results align with previous studies that have demonstrated hormonal stimulation of epithelial tissues in postmenopausal women. However, the presence of histopathological variations, including atrophic and hyperplastic changes, emphasizes the complexity of HRT’s effects on cervical morphology. While most alterations appear benign, regular cervical screening remains crucial to distinguish between physiological changes induced by HRT and potential pathological conditions.

Given these findings, healthcare providers should consider individualized HRT regimens, balancing benefits with potential risks. Monitoring cervical tissue response in long-term HRT

users can aid in optimizing treatment strategies while minimizing unintended effects. Further longitudinal research with larger sample sizes is needed to deepen our understanding of how different HRT formulations, dosages, and durations influence cervical health.

In conclusion, this study underscores the importance of careful HRT management and routine gynecological assessments in postmenopausal women. A personalized approach to hormone therapy, combined with continued cervical screening, can help ensure optimal reproductive health outcomes in women undergoing HRT.

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