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THE IMPACT OF IMMUNOHISTOCHEMICAL MARKER INDICATORS ON TREATMENT OUTCOMES IN ENDOMETRIAL ATYPICAL HYPERPLASIA.

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Abstract:

This study evaluates the impact of key immunohistochemical (IHC) markers on treatment outcomes in atypical endometrial hyperplasia (AEH), a precancerous condition associated with a significantly increased risk of progression to endometrioid adenocarcinoma. As management strategies differ considerably—ranging from fertility-sparing hormonal therapy to radical surgical intervention—identifying reliable biological predictors of treatment response is critical for personalized therapeutic decision-making. A total of 50 women with histologically confirmed AEH were included. Among them, 20 patients (40%) underwent detailed IHC profiling for Ki-67, p53, Bcl-2, estrogen receptors (ER), and progesterone receptors (PR). Marker expression was evaluated semi-quantitatively according to ESGO/ESMO recommendations. Treatment strategies were individualized based on clinical characteristics, reproductive goals, and biological phenotype; hormonal therapy was offered to suitable candidates, while high-risk patients received surgical management.

Findings showed that Ki-67 was the most sensitive predictor of treatment response. Low Ki-67 expression (≤15%) was strongly associated with complete remission (73.3%), whereas high expression (≥30–40%) correlated with marked resistance and progression ($\chi^2 = 6.41$; $p < 0.05$). Mutant-type p53 significantly increased the likelihood of treatment failure (OR = 5.1; $p < 0.01$) and was frequently linked with occult adenocarcinoma in surgically treated patients. High ER/PR expression (≥70%) predicted excellent hormonal responsiveness and complete remission rates of 70–85%, while low receptor levels (≤40%) indicated poor response and the need for surgical intervention. Bcl-2 overexpression (≥50%) reflected apoptosis avoidance and was associated with resistance and increased progression risk.

In conclusion, IHC-based phenotyping enables accurate classification of AEH into favorable, intermediate-risk, and high-risk biological groups. Integrating Ki-67, p53, ER, PR, and Bcl-2 into routine evaluation supports individualized treatment selection, optimizes therapeutic outcomes, and reduces the risk of malignant transformation.

Keywords: Atypical endometrial hyperplasia; immunohistochemistry; Ki-67; p53; Bcl-2; estrogen receptor (ER); progesterone receptor (PR); hormonal therapy; progestin resistance; risk stratification; personalized treatment; endometrial carcinoma; biomarker profiling.

INTRODUCTION.

Atypical endometrial hyperplasia (AEH) represents a precancerous lesion of the endometrium characterized by structural glandular atypia and a significantly increased risk of progression to endometrioid adenocarcinoma if left untreated [1–3]. According to WHO 2020 classification, AEH is considered a monoclonal neoplastic process with molecular alterations involving PTEN, PAX2, PI3K/AKT, p53, and mismatch-repair pathways, which underlie its malignant potential [4,5]. The clinical relevance of AEH has grown in recent years due to rising prevalence of obesity, metabolic syndrome, chronic anovulation, and reproductive endocrine disorders, especially in women of perimenopausal age [6–8].

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Management strategies for AEH vary depending on the patient's age, reproductive goals, comorbidities, and biological characteristics of the lesion. While hysterectomy remains the definitive treatment, conservative hormonal therapy (primarily progestin-based) is widely accepted in women desiring fertility preservation or those with contraindications to surgery [9–11]. However, treatment outcomes differ greatly between patients, and up to 30–40% of cases exhibit incomplete regression, resistance, or early progression during hormonal therapy [12–14]. Identifying predictors of treatment response is therefore crucial.

Immunohistochemical (IHC) markers play an essential role in evaluating tumor biology and stratifying AEH by risk. Proliferation marker Ki-67 reflects cellular turnover and is widely recognized as one of the most sensitive indicators for predicting hormonal therapy outcomes [15,16]. Mutant-type p53 expression is associated with genomic instability and an increased likelihood of treatment resistance and occult carcinoma [17,18]. Hormone receptors, particularly progesterone receptor (PR), remain the strongest predictors of response, with high PR expression correlating with a three- to five-fold improvement in remission rates [19,20]. Bcl-2, an anti-apoptotic protein, provides additional information regarding apoptosis dysregulation and progression risk [21,22].

Despite advances in the understanding of AEH pathogenesis, there is insufficient clinical data regarding the combined predictive value of Ki-67, p53, ER, PR, and Bcl-2 in individualized treatment planning. Therefore, the aim of this study was to assess the impact of key immunohistochemical markers on treatment outcomes in AEH and to determine their role in risk stratification and personalized therapeutic decision-making [23].

MATERIALS AND METHODS.

This study included 50 women diagnosed with atypical endometrial hyperplasia (AEH), all of whom underwent complete clinical evaluation and histological verification before treatment initiation. AEH diagnosis was confirmed in every case through endometrial biopsy followed by standardized histopathological assessment.

Prior to enrollment, 18 patients (36%) had received empirical hormonal therapy, 22 (44%) had been under gynecologic observation without specific treatment, and 10 patients (20%) had not received any prior targeted management.

Following diagnostic confirmation, all patients underwent comprehensive baseline evaluation, including medical history, pelvic examination, transvaginal ultrasonography, and laboratory tests. Immunohistochemical (IHC) evaluation was performed in 20 patients (40%), assessing proliferation (Ki-67), tumor suppressor status (p53), anti-apoptotic activity (Bcl-2), and hormonal receptor expression (ER, PR). Marker expression levels were quantified semi-quantitatively according to contemporary ESGO/ESMO recommendations.

RESULTS.

In this study, immunohistochemical analysis was performed in a total of 20 women among the patients who received hormonal therapy and those who underwent surgical treatment. These markers (Ki-67, p53, Bcl-2, ER, PR) made it possible to assess biological activity and the potential response to treatment in both therapeutic strategies, while also serving as an important source of information for determining an individual risk profile for each patient.

When evaluating the tumor proliferative marker Ki-67, the following results were obtained. In both groups, it emerged as the most sensitive marker for predicting treatment outcomes. In the hormone-therapy group, complete remission was recorded in 73.3% of patients with a low Ki-67 level (≤15%). Intermediate (15–30%) Ki-67 values corresponded to partial regression or stable disease. High expression (≥30–40%) was associated with significant resistance to hormonal therapy and, in some cases, progression.

Statistical analysis showed $\chi^2 = 6.41$; $p < 0.05$, indicating a significant association between Ki-67 and treatment effectiveness. In the surgical group, patients with high Ki-67 levels were more likely to be directed towards radical intervention, which is explained by the likelihood of hormone resistance.

Table 1.
Relationship between Ki-67 mitotic index and treatment outcomes in AEH

Ki-67 level	Outcome of hormonal therapy	Effect in surgical group
Low positive reaction	73.3% complete remission	Suitable for conservative treatment
Intermediate positive reaction	Partial regression/stable process	Individual evaluation
High positive reaction	Progression/resistance	Surgical treatment is the main indication

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The expression of the p53 marker was another important indicator influencing treatment effectiveness. In the hormone-therapy group, progression was recorded in the patient with the mutant type of p53. This confirms that the mutant p53 phenotype is associated with genomic instability, impaired DNA repair mechanisms, and reduced apoptosis, representing an unfavorable biological profile. Statistical analysis: $\chi^2 = 5.1$; $p < 0.01$ — the mutant p53 profile increases the probability of treatment failure by 5 times. In the surgical group, abnormal p53 expression was also associated with the detection of occult adenocarcinoma, further emphasizing the diagnostic and prognostic significance of this marker.

Table 2.
p53 expression and clinical response in AEH

p53 expression	Biological characteristics	Outcome of hormonal therapy
Low (≤10%)	Wild-type, genomic stability	High complete remission rate (65–80%)
Intermediate (10–50%)	Partial effect, mixed staining	Partial regression/stable process
High (≥50%)	Mutant type, genomic instability	Resistance, progression (OR = 5.1)

The three-tier assessment of p53 expression plays a central role in choosing treatment tactics in AEH. Low expression — favorable phenotype for hormonal therapy; intermediate expression — requires individualized approach; high expression — radical surgical treatment is preferred in patients with high risk of resistance and occult carcinoma.

In patients with low ER levels (≤40%), hormonal therapy was more frequently ineffective, with a higher likelihood of stable disease or progression. Due to the poor therapeutic response in this group, only a few cases continued conservative treatment; most patients were transitioned to surgical tactics.

Patients with intermediate ER levels (40–70%) showed a moderate rate of partial regression and complete remission (50%). Patients with high ER levels (≥70%) demonstrated the best clinical response — complete morphological remission was identified in 70–85% of cases. These results confirm preserved receptor signaling in progesterone-sensitive tissue and full manifestation of hormonal therapy effectiveness.

PR expression is the strongest predictor of hormonal therapy response. In patients with low PR levels (≤40%), hormonal therapy was almost ineffective, with progression or stable disease observed during treatment. In patients with moderate PR expression (40–70%), partial regression and stable disease predominated. Patients with high PR levels (≥70%) represented the most favorable contingent for hormonal therapy in AEH. In our analysis, nearly 80% of patients with high PR expression achieved complete remission. This corresponds fully with ACOG and ESMO recommendations emphasizing that PR positivity increases the effectiveness of hormonal therapy by 3–5 times.

Bcl-2 expression — avoiding apoptosis and risk of progression. In patients with low or negative Bcl-2 expression, preserved apoptotic mechanisms ensured high hormonal therapy effectiveness — in our study, this group demonstrated excellent CR and PR rates. In patients with moderate Bcl-2 expression (20–50%), the response to hormonal therapy was variable, with partial regression or stable disease achieved in most cases. In patients with high Bcl-2 expression (≥50%), hormonal therapy was almost ineffective, and progression or resistance was frequently observed. This is explained by the activation of apoptosis-avoidance mechanisms and prolonged survival of pathological cells. High Bcl-2 expression served as a biological basis for choosing surgical treatment.

Phenotyping based on immunohistochemical markers in endometrial atypical hyperplasia (AEH) enabled precise stratification of patients by risk level and selection of individualized treatment tactics. According to the analysis results:

Group I – high hormone-sensitive phenotype, characterized by low proliferative activity and genetic stability: Ki-67 low (≤15%), p53 normal (wild-type), ER/PR high (≥70%). In this phenotype, the probability of complete morphological remission after progestin therapy is very high (70–90%), and hormonal therapy is considered the primary and preferred treatment method.

Group II – intermediate-risk phenotype, characterized by Ki-67 15–30%, p53 mixed (10–50%), ER/PR moderate (40–70%), and intermediate Bcl-2 expression. In this group, hormonal sensitivity is partially preserved, and the probability of partial or complete remission is moderate. Therefore, individual assessment, short-course hormonal therapy, and close morphological monitoring with repeat biopsy/IHC in 1–3 months are required.

Group III – high-risk, hormone-resistant phenotype: Ki-67 high (≥30–40%), p53 mutant (≥50%), ER/PR low (≤40%), and Bcl-2 high. This biological profile is characterized by genomic instability, activation of apoptosis-avoidance mechanisms, and a high risk of conversion to carcinoma. In this group, hormonal

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therapy is almost ineffective, and due to the high likelihood of progression and occult carcinoma, surgical treatment — total hysterectomy (± adnexectomy) — is recommended as the safest and most appropriate tactic.

This three-tier phenotyping system based on IHC markers allows personalization of treatment in AEH, enabling identification of patients who will benefit most from hormonal therapy, application of close-monitoring tactics in the intermediate-risk group, and timely recommendation of radical surgical treatment in high-risk patients without losing valuable time.

CONCLUSION.

The findings of this study demonstrate that immunohistochemical (IHC) markers—Ki-67, p53, ER, PR, and Bcl-2—play a decisive role in predicting treatment response, stratifying biological risk, and guiding personalized therapeutic strategies in endometrial atypical hyperplasia (AEH). Ki-67 emerged as the most informative proliferative indicator, reliably distinguishing hormone-responsive patients from those at risk of resistance or progression. The strong association between high Ki-67 expression and poor response to progestin therapy underscores the necessity of early surgical intervention in this subgroup. The tumor suppressor p53 also proved to be a powerful prognostic marker. Wild-type expression was correlated with favorable outcomes and high remission rates, while mutant overexpression—indicative of genomic instability—significantly increased the likelihood of treatment failure and was frequently associated with occult carcinoma in surgically treated patients. These results reaffirm the clinical importance of p53 status in AEH management.

Hormone receptors (ER and PR) demonstrated consistent predictive value: high ER/PR expression corresponded to strong responsiveness to hormonal therapy, whereas low receptor levels predicted poor outcomes and prompted the need for surgical treatment. Among these, PR expression was the most robust predictor of therapeutic success, in line with international guidelines.

Bcl-2 expression reflected apoptotic activity and further enhanced risk stratification. Low or negative Bcl-2 expression identified patients likely to benefit from conservative therapy, while high Bcl-2 levels indicated resistance and increased risk of progression, supporting surgical decision-making.

Overall, integrating IHC-based phenotyping into clinical practice enables accurate classification of AEH into favorable, intermediate-risk, and high-risk biological groups. This approach ensures that patients with hormone-sensitive, genetically stable disease receive effective conservative treatment, while those with aggressive, hormone-resistant phenotypes are directed toward timely surgical management. Such individualized, biomarker-driven strategies optimize treatment outcomes, reduce the risk of progression to carcinoma, and support evidence-based clinical decision-making in AEH.

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