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# Response to progestin-based therapy in endometrial intraepithelial neoplasia: An exploratory biomarker study

Kieran Seay [a,b], Maia Hare [a,b], Jin Cao [a,c], Arielle Katcher [a,b], Meredith Akerman [d], Semir Beyaz [e], Gary L. Goldberg [a,b,e,f], Marina Frimer [a,b,f,*]

[a] Northwell Health, New Hyde Park, NY, USA
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Northwell Health, Zucker School of Medicine at Hofstra/Northwell, Long Island, NY, USA
[c] Department of Pathology, Northwell Health, Zucker School of Medicine at Hofstra/Northwell, Long Island, NY, USA
[d] Biostatistics Unit, Office of Academic Affairs, Northwell Health, Long Island, NY, USA
[e] Cold Spring Harbor Laboratory, Long Island, NY, USA
[f] Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, USA

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ABSTRACT

*Objective:* With the incidence of endometrial intraepithelial neoplasia (EIN) rising among premenopausal women, fertility-sparing management with progestin-based therapy is increasingly utilized, yet a substantial proportion of patients fail to respond. This study explored associations between baseline tissue biomarker expression and response to progestin-based therapy in premenopausal women with EIN.

*Methods:* This was a single-institution retrospective cohort study of premenopausal women with EIN undergoing conservative management between March 2015 and December 2023. Immunohistochemical expression of progesterone receptor A (PR-A), progesterone receptor B (PR-B), and glucagon-like peptide-1 receptor (GLP-1R) was evaluated in pre-treatment and post-treatment endometrial biopsy specimens. Treatment response was dichotomized as complete response (CR) or progesterone resistance (PGR), defined as failure to achieve CR within 12 months of initiating progestin-based therapy. Associations between biomarker expression and treatment response were explored using descriptive and regression analyses.

*Results:* Endometrial biopsies were analyzed from 28 premenopausal patients prior to the initiation of progestin-based therapy. Baseline PR-A expression was significantly lower among non-responders in both glandular and stromal compartments. A pre-treatment PR-A:PR-B ratio $\leq 1$ was associated with progesterone resistance in glandular tissue, whereas pre-treatment GLP-1R expression was not significantly associated with treatment response. Post-treatment glandular GLP-1R expression differed between groups, with a higher proportion of high expression observed among non-responders (54.6% vs. 6.7%, $p = 0.021$).

*Conclusion:* In this exploratory cohort, baseline progesterone receptor expression patterns were associated with response to progestin-based therapy. These findings warrant validation in larger, prospective studies.

## 1. Introduction

The incidence of endometrial intraepithelial neoplasia (EIN) and well-differentiated endometrial cancer is rising rapidly among premenopausal women, driven largely by the increasing prevalence of obesity and metabolic syndrome. For young patients desiring fertility preservation or those who are medically unfit for surgery, conservative management with progestin-based therapy has become a standard approach. However, a significant proportion of patients exhibit progesterone resistance, with failure to achieve complete response occurring in up to 30–40% of cases. Identifying objective biomarkers that can predict treatment response at the time of diagnosis remains a critical unmet need in optimizing care for these patients. (Bassette and Ducie, 2024; Nees et al., 2022; Knez et al., 2021).

Progesterone mediates its effects through two main nuclear receptor isoforms: progesterone receptor A (PR-A) and progesterone receptor B (PR-B). Preclinical and clinical studies have suggested that an imbalance in these isoforms—specifically a low PR-A:PR-B $\leq 1$ ratio—may be implicated in the development of progesterone resistance. However, literature regarding the baseline predictive value of assessing both

* Corresponding author at: 270-05 76th Avenue New Hyde Park, NY 11040, USA.
*E-mail address:* mfrimer@northwell.edu (M. Frimer).

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isoforms prior to conservative management of EIN remains limited (Sletten et al., 2017; Sletten et al., 2019).

Beyond classical hormonal signaling, metabolic pathways have emerged as promising avenues for therapeutic intervention. Glucagon-like peptide-1 receptor (GLP-1R) agonists, initially developed for type 2 diabetes (T2DM) and weight management, have demonstrated anti-proliferative effects in various malignancies. Recent large-scale clinical data suggest that the combination of GLP-1R agonists and progestin therapy is associated with a significantly lower risk of progressing to endometrial cancer in patients with benign uterine disease or hyperplasia. While these clinical associations suggest that GLP-1R signaling may enhance progestin sensitivity, the direct baseline expression of GLP-1R in human EIN tissue and its correlation with subsequent response to progestin-based therapy have not been thoroughly characterized (Onstad et al., 2016; Bhaskaran et al., 2014; Violette et al., 2023; Yen et al., 2026).

To address these knowledge gaps, this study was designed with a twofold objective. First, we sought to explore whether baseline immunohistochemical expression of PR-A and PR-B, as well as the calculated PR-A:PR-B $\leq 1$ ratio, are associated with treatment response in a cohort of premenopausal women with EIN undergoing progestin therapy. Second, we aimed to characterize baseline and post-treatment tissue expression of GLP-1R in this same cohort to investigate its potential relationship with therapeutic outcomes.

## 2. Methods

### 2.1. Study protocols

This was a retrospective cohort study conducted at a single academic medical center. Institutional Review Board (IRB) approval was obtained for this study (Northwell Health; IRB 23–0903). Because of the retrospective nature of the investigation, a waiver of informed consent was granted. We identified a cohort of premenopausal women diagnosed with EIN between March 2015 and December 2023 who elected conservative management with progestin-based therapy. To be eligible for inclusion, patients were required to have an adequate pre-treatment baseline endometrial biopsy and at least one follow-up biopsy available for review.

Patients were treated predominantly with a 52 mg levonorgestrel-releasing intrauterine system (LNG-IUS). Alternative regimens included daily oral megestrol acetate, daily oral medroxyprogesterone acetate (MPA), or a combination of the LNG-IUS and oral MPA. Therapeutic surveillance consisted of serial endometrial biopsies obtained approximately every three months. Pre-treatment and follow-up endometrial tissue samples were obtained via Pipelle aspiration or hysteroscopy-guided curettage at the discretion of the treating physician. All biopsy specimens were independently assessed by two trained gynecologic pathologists blinded to the clinical outcomes and each other's diagnoses. There were no discrepancies between reviewers.

Response biopsies were classified as complete response (CR) or progesterone resistance (PGR). CR was defined as the presence of ordinary proliferative endometrium or endometrium showing progesterone effect, while PGR was defined as failure to achieve CR within 12 months of initiating progestin-based therapy (Gallos et al., 2013).

### 2.2. Immunohistochemistry

Tissue specimens were formalin fixed, embedded in paraffin wax, and cut into 4-5 μm. Antigens were retrieved by boiling in 10 mM citrate buffer (pH 6.0) and endogenous peroxidase was quenched in methanol containing 3% hydrogen peroxide. GLP-1R(1:100; bs-1559R Bioss Antibiodies) primary antibody was incubated for 60 min at room temperature. PR-A(1:150; Clone 16 Novocastra) and PR-B(1,100; Clone hPRa 2 Thermo Fisher) primary antibodies were incubated for 60 min at 37 °C. All reagents were obtained from the ImmPRESS Excel Staining Kit (Vector Laboratories) and slides were processed according to manufacture's instructions.

Expression of PR-A and PR-B was evaluated separately in the endometrial glands and the stroma using a semiquantitative histological score (H-score) according to the formula: H-score $= \Sigma(P_i \text{ x } i) / 100$), where $P_i$ denotes the intensity of staining ranging from 1 to 3. This calculation yielded a mean H-score for each patient ranging from 0 to 3 (Sletten et al., 2019). PR-A:PR-B ratios were calculated by dividing the PR-A H-score by the PR-B H-score separately for glandular and stromal compartments. GLP-1R expression was quantified using the Allred scoring system, which sums a proportion score and an intensity score to yield a final score ranging from 0 to 8. The proportion score ranged from 0 to 5 based on the estimated percentage of stained cells, while the intensity score ranged from 0 to 3 (0 for none, 1 for weak, 2 for intermediate, and 3 for strong). For the purposes of binary classification in this study, an Allred score $< 3$ was considered low, while higher scores were considered high expression (Kanda et al., 2018).

### 2.3. Statistical analysis

Descriptive statistics were generated for CR and PGR groups. Group comparisons were performed using appropriate parametric or non-parametric tests. Logistic regression models were used to explore associations between biomarker expression and treatment response, with adjustment for polycystic ovary syndrome in exploratory multivariable analyses. Model discrimination was assessed using the area under the receiver operating characteristic curve. All analyses were performed using SAS version 9.4, R version 4.2.1, and RStudio.

## 3. Results

### 3.1. Study population

Twenty-eight premenopausal women diagnosed with EIN who elected fertility-sparing management with progestin-based therapy were included in this cohort. Following initiated treatment, 15 patients (53.6%) achieved a complete response (CR). The remaining 13 patients (46.4%) were classified as having progesterone resistance, failing to achieve a complete response within 12 months of initiating progestin-based therapy. Baseline demographic and clinical characteristics are summarized in Table 1. A history of polycystic ovary syndrome (PCOS) was more common among patients with PGR compared with those achieving CR (53.8% vs. 13.3%, $p = 0.042$). Baseline endometrial biopsy specimens from all 28 patients were adequate and included for immunohistochemical analysis.

### 3.2. Baseline receptor expression and treatment response

Mean H-score expression levels for PR-A and PR-B in the pre-treatment endometrial glands and stroma are summarized in Table 2. Patients who exhibited PGR demonstrated significantly lower baseline PR-A expression in both the stroma ($p = 0.003$) and the glands ($p = 0.007$) compared with complete responders. Baseline PR-B expression did not differ significantly between the groups in either the stroma or the glands.

Baseline GLP-1R expression in the glands and stroma is also summarized in Table 2. While not statistically significant ($p = 0.229$), 53.3% of women who achieved a complete response had high GLP-1R expression in the stroma compared to 30.8% in the PGR group. This trend was not seen in the high GLP-1R expression in the glandular tissue.

### 3.3. Post-treatment expression changes

Post-treatment biopsy specimens were available for 26 patients as two patients were insufficient for additional IHC staining and analysis. Overall, in the endometrial glands, there was a statistically significant

**Table 1**
Characteristics of the study population related to progesterone response and resistance. Descriptive statistics (mean ± standard deviation for continuous variables; frequency and percent for categorical variables) were calculated for each group. Asterix *$P < 0.01$. All participants had opted to undergo conservative therapy with either levonorgestrel-releasing intrauterine system 52 mg (LNG-IUS 52), oral medroxyprogesterone acetate (MPA) daily, megestrol acetate daily, or a combination of LNG-IUS 52 and oral MPA.

| Characteristic | Best Response | | *p*-value |
|---|---|---|---|
| | Complete Response (CR) $N = 15$ | Progesterone Resistance (PGR) $N = 13$ | |
| Race/Ethnicity | | | 0.908 |
| Non-Hispanic White | 3 (20.00%) | 4 (30.77%) | |
| Non-Hispanic Black | 5 (33.33%) | 2 (15.38%) | |
| Hispanic | 4 (26.67%) | 3 (23.08%) | |
| Asian | 2 (13.33%) | 3 (23.08%) | |
| Multiracial | 1 (6.67%) | 1 (7.69%) | |
| Age at Diagnosis | | | 0.964 |
| Mean ± SD | 37.84 ± 8.75 | 36.77 ± 4.38 | |
| Body Mass Index | | | 0.406 |
| Mean ± SD | 44.13 ± 15.05 | 37.92 ± 11.41 | |
| Medical History | | | |
| PCOS | 2 (13.33%) | 7 (53.85%) | **0.042*** |
| Diabetes | 4 (26.67%) | 2 (15.38%) | 0.655 |
| Hypertension | 2 (13.33%) | 1 (7.69%) | 1.000 |
| Treatment | | | |
| LNG-IUD | 13 (86.67%) | 10 (76.92%) | 0.639 |
| Megace | 0 (0.00%) | 1 (7.69%) | 0.464 |
| Provera | 0 (0.00%) | 1 (7.69%) | 0.464 |
| LNG-IUD+ Oral | 2 (13.33%) | 1 (7.69%) | 1.000 |
| Duration of Treatment | | | 0.112 |
| Mean ± SD | 225.93 ± 117.83 | 151.31 ± 52.25 | |

decrease in the expression of both PR-A and PR-B when comparing the initial expression to the response expression level ($p < 0.001$ and $p = 0.003$, respectively) (Table 2).

A significant interaction was observed between the response groups and time. Patients exhibiting progesterone resistance showed a more pronounced decrease in glandular PR-A expression after the initiation of progesterone therapy compared to those individuals who achieved a complete response ($p = 0.030$). In addition to a downregulation of PR-A and PR-B after the initiation of progestin-based therapy, the overall proportion of patients with high GLP-1R expression in the glands also decreased from baseline ($p = 0.015$). However, this change in GLP-1R expression was not observed in the stromal tissue. There was no significant interaction between the response groups and time when evaluating GLP-1R expression.

### 3.4. Predictive utility of PR-A:PR-B ratios

The association between PR-A:PR-B ratios and progesterone resistance was explored in glands, stroma, and combined tissue compartments (Supplementary Table 1). Patients with a baseline PR-A:PR-B ratio $\leq 1$ in endometrial glands were more likely to demonstrate progesterone resistance compared with those with ratios >1 (OR 7.58, 95% CI 1.2–48.0, $p = 0.0314$). Similar findings were observed in stromal tissue (OR 16.33, 95% CI 1.6–163.4, $p = 0.0176$). Multivariable models adjusting for PCOS were performed for exploratory purposes only. After adjustment, PR-A:PR-B ratios ≤1 in glands and stroma remained associated with progesterone resistance, though estimates were imprecise with wide confidence intervals (Supplementary Table 1). Receiver operating characteristic analyses suggested moderate diagnostic accuracy (AUC range 0.70–0.82) for ratios in stroma, glands, and combined tissue compartments.

**Table 2**
Expression of PR-A, PRA—B, and GLP-1R in endometrial glands and stroma in initial biopsies and response biopsies related to progestin-based therapy resistance and response. Asterix *P < 0.01.

| | Best Response | | p-value* |
|---|---|---|---|
| | Complete Response (CR) | Progesterone Resistance (PGR) | |
| **Initial PR-A Expression (Mean ± SD)** | | | |
| Stroma | 1.73 ± 0.75 | 0.72 ± 0.72 | **0.003*** |
| Glands | 1.97 ± 0.65 | 0.97 ± 0.88 | **0.007*** |
| **Initial PR-B Expression (Mean ± SD)** | | | |
| Stroma | 0.55 ± 0.37 | 0.46 ± 0.43 | 0.440 |
| Glands | 1.07 ± 0.85 | 0.72 ± 0.78 | 0.296 |
| **Initial GLP-1R Expression Stroma (%)** | | | 0.229 |
| Low | 7 (46.67%) | 9 (69.23%) | |
| High | 8 (53.33%) | 4 (30.77%) | |
| **Initial GLP-1R Expression Glands (N,%)** | | | 1.000 |
| Low | 5 (33.33%) | 5 (38.46%) | |
| High | 10 (66.67%) | 8 (61.54%) | |
| **Response PR-A Expression (Mean ± SD)** | | | |
| Stroma | 1.00 ± 0.70 | 0.70 ± 0.63 | 0.221 |
| Glands | 0.67 ± 0.74 | 0.59 ± 0.69 | 0.583 |
| **Response PR-B Expression Stroma (Mean ± SD)** | | | |
| Stroma | 0.40 ± 0.29 | 0.40 ± 0.33 | 0.921 |
| Glands | 0.27 ± 0.18 | 0.42 ± 0.47 | 1.000 |
| **Response GLP-1R Expression Stroma (N, %)** | | | 0.620 |
| Low | 13 (86.67%) | 8 (72.73%) | |
| High | 2 (13.33%) | 3 (27.27%) | |
| **Response GLP-1R Expression Glands (N, %)** | | | **0.021*** |
| Low | 14 (93.33%) | 5 (45.45%) | |
| High | 1 (6.67%) | 6 (54.55%) | |

## 4. Discussion

In this retrospective exploratory analysis, baseline tissue biomarker expression was associated with response to progestin-based therapy in premenopausal women with EIN. Patients with progesterone resistance demonstrated lower baseline PR-A expression and lower PR-A:PR-B ratios compared with complete responders. In contrast, baseline GLP-1R expression was not associated with treatment response, although post-treatment glandular GLP-1R expression differed between response groups.

These findings expand upon prior work demonstrating the prognostic and relapse-associated significance of progesterone receptor isoforms in EIN and early endometrial cancer. Previous studies have primarily focused on relapse after an initial successful response. For instance, Sletten et al. demonstrated that a baseline PR-A:PR-B $\leq 1$ predicted disease relapse after progestin therapy withdrawal in women with EIN. Our data build upon this by suggesting that PR-A expression and PR-A:PR-B ratios may also be highly relevant in predicting the failure to achieve an initial treatment response, supporting their potential role as candidate predictive markers at the time of diagnosis (Sletten et al., 2017; Sletten et al., 2019; Jongen et al., 2009). In addition, our data demonstrated that the observed differences in PRA:PRB ratio are likely driven primarily by PR-A expression, as PR-B did not differ between groups. Thus, PR-A expression may be the more clinically relevant predictive marker.

Interestingly, glandular PR-A and PR-B expression decreased significantly post-treatment from pre-treatment levels, suggesting that exogenous progestin downregulates expression of its own receptor. This decrease was found to be significantly more pronounced in the

expression of glandular PR-A in patients with progesterone resistance, indicating that sustained expression of PR-A is likely important in a successful response to progestin-based therapy. These findings may offer a potential biological explanation for the high recurrence rate of EIN following medical management noted in the literature, as a sharp downregulation of the protective PR-A isoform could confer secondary progesterone resistance and relapse (Gallos et al., 2012).

Our cohort was restricted to premenopausal women and therefore relatively young. The relationship between age and progestin response in EIN is unclear, with conflicting data on whether younger age predicts outcomes (Kailasam et al., 2026). In our cohort, younger age was closely linked to chronic anovulation, which was more common among non-responders (53.8% vs. 13.3%, $p = 0.042$) and may attenuate progestin efficacy through sustained unopposed estrogen exposure. Notably, non-responders had lower baseline PR-A expression and were more likely to have a PR-A:PR-B ratio $\leq 1$, suggesting that the metabolic and molecular milieu associated with this young population—rather than age itself—may be the more relevant determinant of response.

Obesity and T2DM are known risk factors for EIN due to the hormonal effects of increased estrogen and insulin levels. Consequently, GLP-1 receptor agonists have garnered substantial attention for their potential role in the fertility-sparing treatment of endometrial malignancies. Recent large-scale clinical data has established that the addition of GLP-1R agonists to progestin therapy is associated with a significantly reduced risk of progression to endometrial cancer in patients with hyperplasia (Yen et al., 2026). While our study did not find that pre-treatment GLP-1R expression directly predicted response, the observation that post-treatment glandular GLP-1R expression differed between response groups suggests that GLP-1R expression may reflect evolving disease biology or treatment-related changes in the tissue. Our findings do not establish a causal role for GLP-1R signaling in progesterone resistance, but given the emerging clinical data supporting its therapeutic benefit, further translational and mechanistic studies are highly warranted.

Novel features of this research include restricting the analysis strictly to premenopausal women who are more likely to choose medical management, and the inclusion of both pre- and post-treatment progesterone receptor expression profiles. However, several limitations must be noted, including the retrospective design, small sample size, single-institution cohort, and wide confidence intervals resulting in imprecise estimates. These factors limit generalizability and preclude making definitive clinical conclusions.

Fertility-sparing management of EIN requires careful patient selection given the risk of non-response and progression. While hysterectomy remains definitive therapy, progestin-based treatment is frequently pursued in young patients desiring future fertility. Our findings suggest that progesterone receptor isoform profiling, particularly baseline PR-A expression and PR-A:PR-B ratios, may aid in future risk stratification at the time of diagnosis. However, these markers must be considered purely investigational pending validation in larger, prospective cohorts.

## Author contribution

All authors have contributed equally to this research and manuscript preparation. All authors contributed together to the conception and design of the project, the acquisition, interpretation and analysis of data. All authors contributed to the drafting of this article and to the final approval of the version to be published.

## CRediT authorship contribution statement

**Kieran Seay:** Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Maia Hare:** Writing – original draft, Investigation, Data curation. **Jin Cao:** Methodology, Formal analysis, Data curation. **Arielle Katcher:** Writing – review & editing, Investigation, Data curation. **Meredith Akerman:** Writing – review & editing, Formal analysis. **Semir Bayez:** Resources, Investigation. **Gary L. Goldberg:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Investigation, Conceptualization. **Marina Frimer:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2026.102134.

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