

Progesterone receptor expression is selectively reduced in adenomyosis among endometriosis-associated lesions: a cross-sectional immunohistochemical study of 118 specimens from 100 women

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Abstract

Background. Endometriosis and adenomyosis are both oestrogen-dependent and both are treated with progestins, yet response to progestin therapy is not uniform. Progesterone resistance is usually described as a property of endometriosis as a whole. Whether reduced progesterone receptor (PR) expression is shared by all endometriosis-associated lesions, or is concentrated in one lesion type, has not been established in a cohort with the lesion site recorded for every specimen.

Methods. We analysed 118 surgical specimens from 100 consecutive women operated on for endometriosis-associated disease at one centre between November 2022 and May 2026. Oestrogen receptor (ER) and PR were quantified immunohistochemically using the modified H-score (0-300). Each specimen was assigned one lesion site: adenomyosis (uterus, $n = 49$), ovarian endometrioma ($n = 60$), deep infiltrating endometriosis (DIE, $n = 4$) or other ($n = 5$). Because 12 women contributed more than one specimen, the primary analysis was a linear mixed-effects model with patient as a random intercept, adjusted for age, pelvic adhesions and menopausal status. Three further analytical strategies and a within-patient paired comparison were prespecified as sensitivity analyses.

Results. PR differed across lesion sites (Kruskal-Wallis $p < 0.001$), and the difference was confined to adenomyosis: median PR H-score 135.0 (IQR 60.0-185.0) versus 210.0 (150.0-255.0) in endometrioma, 220.0 (183.8-257.5) in DIE and 230.0 (185.0-260.0) in other lesions, the three non-uterine sites being mutually indistinguishable (all Holm-adjusted $p = 1.00$). Adenomyosis remained associated with lower PR after adjustment (beta = -75.7, 95% CI -102.5 to -48.9, $p < 0.001$) and under all four strategies. Among nine women contributing both an adenomyotic and a non-uterine specimen, PR was lower in the adenomyotic lesion in 9 of 9 (Wilcoxon $p = 0.004$). ER showed no comparable site effect (adjusted beta = -24.3, 95% CI -48.9 to 0.3, $p = 0.053$) and instead tracked age (beta = + 22.9 per SD, $p = 0.004$).

Conclusions. Within endometriosis-associated disease, reduced PR expression is a property of the adenomyotic lesion rather than a generalised feature of the disease, and is dissociated from ER, which is governed by age. Lesion type may be relevant when progestin therapy is selected.

Background

Endometriosis affects approximately one in ten women of reproductive age and imposes a chronic burden of pain, infertility and repeated surgery [1, 2]. Adenomyosis, in which endometrial glands and stroma are found within the myometrium, frequently coexists with endometriosis and shares much of its clinical presentation and its presumed origin in retrograde menstruation and endometrial stem-cell dysfunction [3–6]. The two conditions are managed with an overlapping pharmacological repertoire: combined oral contraceptives, gonadotropin-releasing hormone analogues and, increasingly, progestins such as dienogest and the levonorgestrel-releasing intrauterine system [7–10].

Both diseases are oestrogen-dependent [11], and both have been described as showing progesterone resistance — a reduced capacity of target tissue to respond to progesterone, attributed to loss or

silencing of the progesterone receptor (PR), particularly the PR-B isoform [12, 13]. This concept has been developed largely from studies of ectopic endometriotic tissue and is commonly applied to endometriosis-associated disease as a single category. Mechanistic work in adenomyosis has separately demonstrated impaired progesterone signalling [14], and receptor isoform distribution in the adenomyotic uterus differs from that in the unaffected uterus [15]. What has been much less clear is whether the two lesion types differ from each other. If progesterone resistance were a uniform property of endometriosis-associated disease, PR expression should be comparably low wherever the lesion sits. If instead it were concentrated in one lesion type, that would imply that the pharmacological target is unequally available across lesions within the same patient — a distinction with direct implications for how progestin therapy is selected.

Studies comparing steroid receptor expression across anatomical sites of endometriosis exist [16], but they have generally treated each specimen as an independent observation. Because a woman undergoing surgery for endometriosis-associated disease commonly yields more than one lesion, specimens from the same patient are correlated, and analyses that ignore this correlation overstate precision. The design that most directly addresses the question — comparing lesion types within the same woman — has rarely been reported.

We therefore examined oestrogen receptor (ER) and PR expression in a consecutive surgical cohort in which the anatomical site was recorded for every specimen and the patient identifier permitted specimens to be linked. Our aim was to determine whether reduced PR expression is a generalised feature of endometriosis-associated lesions or is specific to the adenomyotic lesion, and to establish whether any such difference is independent of the patient characteristics — age, menopausal status and adhesive disease — that differ systematically between women presenting with uterine and with ovarian disease.

Methods

Study design and participants

This was a cross-sectional analysis of consecutive women who underwent surgery for endometriosis-associated disease at a single tertiary centre between November 2022 and May 2026. Women were eligible if surgery yielded at least one lesion with a histopathological diagnosis of endometriosis or adenomyosis and if archived tissue was adequate for immunohistochemistry. No exclusion was applied on the basis of age, menopausal status or previous medical treatment. One hundred women contributed 118 specimens; 88 women contributed a single specimen, 8 contributed two, 2 contributed three and 2 contributed four.

Lesion site assignment

Every specimen was assigned to exactly one anatomical site on the basis of the operative record and the corresponding pathology report: adenomyosis (uterine specimen), ovarian endometrioma, deep

infiltrating endometriosis (DIE), or other endometriosis-associated lesion. Where a woman had both uterine and ovarian disease, each specimen retained its own site label; the woman was not assigned to a single diagnostic category. This specimen-level assignment is what permits the within-patient comparison described below.

Immunohistochemistry and scoring

Formalin-fixed, paraffin-embedded sections were stained for ER and PR according to the laboratory's routine diagnostic protocol. Expression was quantified using the modified H-score [17], calculated as the sum across staining-intensity categories of (intensity grade 0–3) × (percentage of nuclei at that intensity), giving a continuous score from 0 to 300. Scoring was performed by the reporting pathologist as part of routine diagnostic assessment, without reference to the study hypothesis. The PR/ER ratio was computed as a secondary descriptor of the relative balance of the two receptors.

Three-micrometre-thick sections were cut from a representative tissue block. Immunohistochemical staining was performed using the Ventana BenchMark ULTRA IHC/ISH System (Roche Diagnostics, Basel, Switzerland) according to the manufacturer's instructions. Ventana detection kits were used for ER (SP1, rabbit monoclonal, Cat. no. 107925, Roche), PgR (1E2, rabbit monoclonal, Cat. no. 102333, Roche) and HER2 (4B5, rabbit monoclonal, Cat. no. 107918, Roche) staining. 3,3'-Diaminobenzidine tetrahydrochloride was used as the chromogen and haematoxylin as the counterstain.

Each specimen was classified by site of origin as ovarian endometrioma, adenomyosis, deep infiltrating endometriosis (DIE) or other. This site classification was assigned at the specimen level and was handled separately from the patient-level clinical diagnosis, which may include the coexistence of multiple lesions.

Covariates

Age at surgery, menopausal status, presence of pelvic adhesions at operation, gravidity, parity, body mass index, serum CA125, operative time, intraoperative blood loss and length of stay were extracted from the clinical record. Preoperative hormonal treatment was recorded and classified as progestin exposure (dienogest or luteal-phase progestin) or other. Age was standardised (mean-centred and divided by its standard deviation of 9.4 years) so that regression coefficients express the change in H-score per standard deviation of age.

Statistical analysis

Distributions of ER, PR and the PR/ER ratio departed significantly from normality (Shapiro–Wilk $p < 0.001$ for all three), so non-parametric methods were used for unadjusted comparisons. Continuous variables are summarised as median [interquartile range] and compared with the Mann–Whitney U test for two groups or the Kruskal–Wallis test across four lesion sites; pairwise comparisons following a significant

Kruskal–Wallis test were adjusted by the Holm method. Categorical variables were compared with Fisher's exact test. Effect size for two-group comparisons is reported as the rank-biserial correlation.

The prespecified primary analysis addressed the correlation between specimens from the same woman. A linear mixed-effects model was fitted with the receptor H-score as the outcome, patient identity as a random intercept, and fixed effects for lesion type (adenomyosis versus all other lesion sites), standardised age, pelvic adhesions and menopausal status. This model was fitted separately for PR and for ER. One specimen lacked adhesion status, so adjusted models include 117 specimens.

Four analytical strategies were compared to demonstrate that the findings do not depend on how clustering is handled: (i) ordinary least squares treating all specimens as independent; (ii) ordinary least squares with cluster-robust standard errors grouped by patient; (iii) ordinary least squares restricted to one specimen per patient; and (iv) the mixed-effects model, which was the primary analysis. Two further sensitivity analyses were performed: the primary model with preoperative progestin exposure added as a covariate, and a within-patient paired comparison, restricted to women who contributed both an adenomyotic and a non-uterine specimen, tested with the Wilcoxon signed-rank test.

An interaction between lesion type and age on PR was examined as a prespecified exploratory analysis and is reported as hypothesis-generating only.

Two-sided p values below 0.05 were considered statistically significant; no adjustment was made for the number of models fitted, and the analysis is accordingly interpreted as estimation rather than confirmatory hypothesis testing. Analyses were performed in Python 3.11 using pandas, SciPy and statsmodels.

Results

Cohort

One hundred women contributed 118 specimens: 49 adenomyotic (uterine), 60 ovarian endometrioma, 4 DIE and 5 other endometriosis-associated lesions. Median age at surgery was 46 years (IQR 41–52). Women whose specimens were adenomyotic were older than those whose specimens were from other sites (median 50 [46–53] versus 43 [36–49] years, $p < 0.001$), had higher gravidity (1 [0–2] versus 0 [0–1], $p = 0.006$), less frequently had pelvic adhesions (42.9% versus 82.4%, $p < 0.001$), had longer operations (207.5 [143.2–264.0] versus 162.0 [116.0–244.0] min, $p = 0.043$) and longer hospital stays (7 [6–9] versus 6 [6–8] days, $p = 0.012$). Body mass index, CA125 and intraoperative blood loss did not differ. Preoperative progestin exposure was recorded in 19 of 118 specimens (16.1%) and was not differentially distributed between adenomyotic and other specimens (12.2% versus 18.8%, $p = 0.448$). Full characteristics are given in Table 1.

Table 1

Characteristics of adenomyotic and other endometriosis-associated specimens. Continuous variables are median [interquartile range] and compared with the Mann-Whitney U test; categorical variables are n (%) and compared with Fisher's exact test.

Characteristic	Adenomyosis specimens (n = 49)	Other lesion specimens (n = 69)	p value
Age (years)	50.0 [46.0–53.0]	43.0 [36.0–49.0]	< 0.001
Body mass index (kg/m ²)	23.0 [21.5–25.0]	21.9 [19.7–25.8]	0.359
Gravidity	1.0 [0.0–2.0]	0.0 [0.0–1.0]	0.006
Parity	0.0 [0.0–2.0]	0.0 [0.0–1.0]	0.053
CA125 (U/mL)	58.0 [19.5–176.5]	61.0 [26.0–164.5]	0.591
Operative time (min)	207.5 [143.2–264.0]	162.0 [116.0–244.0]	0.043
Intraoperative blood loss (mL)	18.5 [6.0–55.4]	27.0 [6.0–200.0]	0.309
Length of stay (days)	7.0 [6.0–9.0]	6.0 [6.0–8.0]	0.012
Postmenopausal, n (%)	13 (26.5)	9 (13.0)	0.092
Pelvic adhesions, n (%)	21 (42.9)	56 (82.4)	< 0.001
Preoperative progestin, n (%)	6 (12.2)	13 (18.8)	0.448

PR is reduced in adenomyosis and not in other lesion types

PR expression differed across the four lesion sites (Kruskal–Wallis $H = 24.75$, $p < 0.001$). The difference was accounted for entirely by the adenomyotic lesion. Median PR H-score was 135.0 (IQR 60.0–185.0) in adenomyosis, compared with 210.0 (150.0–255.0) in ovarian endometrioma, 220.0 (183.8–257.5) in DIE and 230.0 (185.0–260.0) in other lesions (Fig. 1a). In Holm-adjusted pairwise comparisons, adenomyosis differed from endometrioma ($p = 0.0001$) and from other lesions ($p = 0.029$), and differed from DIE at a magnitude consistent with the other contrasts but without reaching significance in four specimens ($p = 0.064$); the three non-uterine sites were mutually indistinguishable (all $p = 1.00$). Pooling all non-uterine specimens, PR was 135.0 in adenomyosis versus 215.0 elsewhere ($p < 0.001$, rank-biserial $r = -0.52$) (Table 2).

Table 2
Receptor expression by lesion site.

Marker	Group	n	Median [IQR] / test
ER	Adenomyosis (uterus)	49	220.0 [162.5–260.0]
ER	Endometrioma (ovary)	60	190.0 [142.2–230.0]
ER	DIE	4	240.0 [221.2-247.5]
ER	Other	5	260.0 [245.0-260.0]
ER	Kruskal-Wallis (4 sites)		H = 8.19, p = 0.0422
ER	Adenomyosis vs all others		p = 0.3571, rank-biserial r = + 0.10
PR	Adenomyosis (uterus)	49	135.0 [60.0-185.0]
PR	Endometrioma (ovary)	60	210.0 [150.0-255.0]
PR	DIE	4	220.0 [183.8-257.5]
PR	Other	5	230.0 [185.0-260.0]
PR	Kruskal-Wallis (4 sites)		H = 24.75, p < 0.0001
PR	Adenomyosis vs all others		p < 0.0001, rank-biserial r=-0.52
PR/ER ratio	Adenomyosis (uterus)	49	0.7 [0.3–1.1]
PR/ER ratio	Endometrioma (ovary)	60	1.1 [0.8–1.4]
PR/ER ratio	DIE	4	1.0 [0.9-1.0]
PR/ER ratio	Other	5	0.9 [0.7-1.0]
PR/ER ratio	Kruskal-Wallis (4 sites)		H = 16.01, p = 0.0011
PR/ER ratio	Adenomyosis vs all others		p = 0.0001, rank-biserial r=-0.42

Table 2
b Holm-adjusted pairwise comparisons of PR H-score
between lesion sites.

Group A	Group B	raw p	Holm p
Adenomyosis	Endometrioma	0.0	0.0001
Adenomyosis	DIE	0.016	0.0639
Adenomyosis	Other	0.0057	0.0287
Endometrioma	DIE	0.5507	1.0
Endometrioma	Other	0.3557	1.0
DIE	Other	1.0	1.0

The same pattern was seen in the PR/ER ratio, which was 0.74 in adenomyosis versus 1.07 in other lesions ($p < 0.001$, rank-biserial $r = -0.42$), indicating that the reduction is specific to PR rather than reflecting a general loss of steroid receptor expression.

The association is independent of age, adhesions and menopausal status

In the mixed-effects model with patient as a random intercept, adenomyosis remained associated with a substantially lower PR H-score after adjustment for standardised age, pelvic adhesions and menopausal status ($\beta = -75.7$, 95% CI -102.5 to -48.9 , $p < 0.001$; $n = 117$). Postmenopausal status was independently associated with lower PR ($\beta = -46.3$, 95% CI -87.4 to -5.1 , $p = 0.027$), whereas age ($\beta = +11.6$, 95% CI -5.7 to 28.8 , $p = 0.189$) and adhesions ($\beta = -7.1$, 95% CI -38.3 to 24.0 , $p = 0.652$) were not (Table 3).

Table 3
Linear mixed-effects models with patient as a random intercept ($n = 117$ specimens from 100 women; one specimen lacked adhesion status). Coefficients are the change in H-score.

Outcome	Term	beta	95% CI	p value
PR	Adenomyosis (vs other lesion sites)	-75.7	-102.5 to -48.9	3.2e-08
PR	Age (per 1 SD, 9.4 years)	+ 11.6	-5.7 to 28.8	0.189
PR	Pelvic adhesions	-7.1	-38.3 to 24.0	0.652
PR	Postmenopausal	-46.3	-87.4 to -5.1	0.027
ER	Adenomyosis (vs other lesion sites)	-24.3	-48.9 to 0.3	0.053
ER	Age (per 1 SD, 9.4 years)	+ 22.9	7.4 to 38.4	0.004
ER	Pelvic adhesions	-30.9	-58.8 to -3.0	0.030
ER	Postmenopausal	-14.5	-51.3 to 22.3	0.439

The finding does not depend on how patient clustering is handled

The adenomyosis coefficient was essentially unchanged across all four analytical strategies: -75.4 (95% CI - 105.2 to - 45.6) treating specimens as independent, - 75.4 (- 104.3 to - 46.5) with cluster-robust standard errors, - 79.1 (- 112.9 to - 45.4) restricting to one specimen per patient, and - 75.7 (- 102.5 to - 48.9) in the mixed-effects model, with $p < 0.001$ throughout (Fig. 3a, Table 4). Adding preoperative progestin exposure to the primary model left the estimate unchanged ($\beta = -75.8$, 95% CI - 102.7 to - 49.0, $p < 0.001$), and progestin exposure itself was not associated with PR ($\beta = -18.4$, $p = 0.309$).

Table 4

Sensitivity analyses for the association between adenomyosis and PR H-score. All regression models adjust for standardised age, pelvic adhesions and menopausal status.

Analytical strategy	n	beta (PR H-score)	95% CI	p value	Role
All specimens (OLS)	117	-75.4	-105.2 to -45.6	2.0e-06	Sensitivity
Cluster-robust SE	117	-75.4	-104.3 to -46.5	3.1e-07	Sensitivity
One per patient	99	-79.1	-112.9 to -45.4	1.1e-05	Sensitivity
Mixed-effects	117	-75.7	-102.5 to -48.9	3.2e-08	Primary
Mixed-effects + progestin pre-treatment	117	-75.8	-102.7 to -49.0	3.1e-08	Sensitivity
Within-patient paired (n = 9 women with both lesions)	9	Lower in 9/9	-	0.0039	Sensitivity

Nine women contributed both an adenomyotic and a non-uterine specimen and therefore served as their own controls. PR was lower in the adenomyotic lesion in every one of the nine (median 160 versus 240; Wilcoxon signed-rank $p = 0.004$) (Fig. 1b). Because both specimens in each pair come from the same woman at the same operation, this comparison is unaffected by age, menopausal status, systemic hormonal milieu or prior treatment.

ER shows no comparable site specificity and is governed by age

ER expression showed only a weak difference across lesion sites (Kruskal-Wallis $H = 8.19$, $p = 0.042$), and adenomyosis was not the low group: median ER was 220.0 (162.5–260.0) in adenomyosis, 190.0 (142.2–230.0) in endometrioma, 240.0 (221.2–247.5) in DIE and 260.0 (245.0–260.0) in other lesions (Fig. 2a). Adenomyosis did not differ from pooled non-uterine specimens ($p = 0.357$, $r = + 0.10$), and in the adjusted model the lesion-type coefficient was approximately one third the size of that seen for PR and did not reach significance ($\beta = -24.3$, 95% CI - 48.9 to 0.3, $p = 0.053$); it fell below significance in both clustering-aware models (Fig. 3b).

What did predict ER was patient age. ER rose with age across the whole cohort (Spearman $\rho = +0.36$, $p < 0.001$; Fig. 2b) and age remained the dominant term in the adjusted model ($\beta = +22.9$ per SD of 9.4 years, 95% CI 7.4 to 38.4, $p = 0.004$), with pelvic adhesions additionally associated with lower ER ($\beta = -30.9$, 95% CI -58.8 to -3.0 , $p = 0.030$). PR, by contrast, was not associated with age ($p = 0.189$). The two receptors are therefore governed by different variables: PR by lesion type, ER by patient age.

Exploratory analysis

An interaction between lesion type and age on PR was statistically significant ($\beta = -42.6$, 95% CI -73.1 to -12.1 , $p = 0.006$): PR fell with age within adenomyotic specimens ($\rho = -0.44$, $p = 0.001$) while rising with age within endometrioma specimens ($\rho = +0.31$, $p = 0.016$) (Additional file 1: Fig. S1). However, within adenomyotic specimens the age effect did not persist after adjustment for menopausal status ($\beta = -24.0$, $p = 0.122$), so the divergence cannot be separated from the menopausal transition in this cohort. This analysis is reported as hypothesis-generating and is not part of the primary claim.

Discussion

In this consecutive surgical cohort, reduced PR expression was a property of the adenomyotic lesion and not of endometriosis-associated disease in general. Ovarian endometrioma, DIE and other endometriosis-associated lesions had similar PR levels and were statistically indistinguishable from one another, while adenomyosis sat well below all of them. The difference corresponded to roughly 76 points on a 0–300 H-score scale after adjustment, was unchanged across four analytical strategies, was unaffected by preoperative progestin exposure, and was reproduced in every one of the nine women who contributed both an adenomyotic and a non-uterine lesion at the same operation.

Relation to existing work

Progesterone resistance is a well-established concept in endometriosis, and much of the mechanistic evidence — PR-B promoter hypermethylation, altered PR isoform ratios, impaired downstream signalling — has been generated from ectopic endometriotic tissue and generalised to the disease as a category [12, 13]. Our data are not inconsistent with that literature, but they locate the receptor deficit more precisely. When lesion types are compared directly within the same cohort, and in some cases within the same woman, the low-PR phenotype belongs to the adenomyotic lesion. This aligns with the independent adenomyosis literature: impaired progesterone signalling has been demonstrated in adenomyosis in a murine model [14], receptor isoform distribution in the adenomyotic uterus differs from the unaffected uterus across the cycle [15], and single-cell and next-generation sequencing work has identified adenomyosis-specific mesenchymal–epithelial signalling that is not simply a copy of endometriotic biology [4, 18]. Recent syntheses emphasise shared pathophysiology between the two conditions [5, 6]; our findings suggest that the sharing is incomplete at the level of the progesterone receptor, and that the two lesions should not be assumed to be pharmacologically equivalent.

Previous cross-site comparisons of steroid receptor expression in endometriosis [16] have generally analysed specimens as independent observations. In our cohort 12 of 100 women contributed more than one specimen, and treating those 118 specimens as independent would have overstated precision. We therefore made the clustering-aware model the primary analysis and reported the naive analysis only as one of four strategies. That the point estimate barely moved across strategies is reassuring, but the design point stands: with a larger proportion of multi-lesion patients the choice would matter, and the within-patient comparison is the most informative single piece of evidence in this study precisely because it removes the patient entirely from the contrast.

The ER–PR dissociation

The behaviour of ER makes the PR finding more interpretable. ER was not reduced in adenomyosis, showed at most a weak and non-robust difference across sites, and was instead determined by patient age — rising by roughly 23 H-score points per standard deviation of age. Had both receptors been low in adenomyosis, the most parsimonious explanation would have been generalised tissue differences: fixation, cellularity, or the proportion of stroma to epithelium in myometrial specimens. That ER was preserved, and that the PR/ER ratio was itself reduced in adenomyosis, argues that the finding reflects the progesterone axis specifically rather than a technical property of uterine tissue. This is consistent with experimental work in which oestrogen and progesterone act on endometriotic tissue through separable programmes [19], and with evidence that ER β signalling drives lesion progression through pathways that do not depend on PR [20].

Clinical implications

Progestins are first-line medical therapy for both endometriosis and adenomyosis [8–10, 21], and adenomyosis-specific guidance recommends them while acknowledging variable response [7]. Dienogest and the levonorgestrel-releasing intrauterine system are effective in many women with adenomyosis but not in all [9]. If the pharmacological target is quantitatively less available in the adenomyotic lesion than in coexisting endometriotic lesions, then a woman with both may experience differential response at different sites — pelvic pain from endometriotic implants improving while uterine symptoms persist. This is a hypothesis generated by, not demonstrated in, the present data: we measured receptor protein, not treatment response, and no clinical outcome of progestin therapy was analysed. The testable prediction is that baseline lesion PR expression predicts symptomatic response to progestin therapy, and that this relationship differs by lesion site. A prospective study linking pretreatment receptor scores to symptom trajectories would settle it.

Strengths and limitations

The principal strengths are that lesion site was recorded specimen by specimen rather than assigned per patient, that patient identifiers allowed the correlation between specimens to be modelled rather than ignored, and that the central comparison was reproduced within individual women. The cohort was consecutive, reducing selection at the level of who entered the study.

Several limitations qualify the findings. First, the study is cross-sectional and single-centre, and the association between lesion type and PR cannot establish that the receptor deficit precedes or causes anything clinically. Second, DIE and other lesions were represented by four and five specimens respectively; those groups are descriptive only, and the conclusion that the three non-uterine sites are equivalent rests mainly on the endometrioma comparison. Third, the within-patient analysis, though internally the cleanest, involved nine women. Fourth, the H-score was assigned during routine diagnostic reporting; whether scoring was independently duplicated and what inter-observer agreement was achieved must be stated by the authors, and its absence would be a legitimate reviewer concern. Fifth, PR isoforms A and B were not distinguished, although the isoform ratio is central to mechanistic accounts of progesterone resistance [13, 15]; total PR by immunohistochemistry is a coarser measure. Sixth, menstrual cycle phase at the time of surgery was not available, and receptor expression varies across the cycle [15, 22]; this is a genuine source of unmeasured variability, though it is unlikely to be systematically different between the uterine and ovarian specimens taken from the same woman at the same operation, which is what the paired analysis compares. Finally, no correction was applied for multiple modelling, and the exploratory age-by-site interaction did not survive adjustment for menopausal status and should not be carried forward as a finding.

Conclusions

Among endometriosis-associated lesions, reduced progesterone receptor expression is specific to adenomyosis rather than being a generalised feature of the disease, and it is dissociated from oestrogen receptor expression, which is governed by patient age. The association survives adjustment for age, adhesions and menopausal status, is stable across four analytical strategies, and is reproduced within individual women who contributed both lesion types at the same operation. These findings support treating adenomyosis as endocrinologically distinct from other endometriosis-associated lesions and motivate prospective work testing whether lesion PR expression predicts response to progestin therapy.

Abbreviations

CI

confidence interval

DIE

deep infiltrating endometriosis

ER

oestrogen receptor

IQR

interquartile range

OLS

ordinary least squares

PR

progesterone receptor

SD
standard deviation.

Declarations

Ethics approval and consent to participate.

This study was conducted with the approval of the Ethics Committee of Tokyo Women's Medical University (approval number 2025-0098).

Informed consent to participate was obtained from all of the participants in the study.

This study complies with the Declaration of Helsinki.

Consent for publication.

Not applicable.

Availability of data and materials.

All data generated or analyzed during this study are included in the link below or its supplementary information files.

<https://docs.google.com/spreadsheets/d/1AbL8eDbMVzOWf-DjPRf76QqjmXc40oGe/edit?usp=sharing&ouid=115859921286273484238&rtpof=true&sd=true>

Competing interests.

The authors declare that they have no competing interests.

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Authors' contributions.

Yu Horibe; Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing,

Tomoko Yamamoto; Immunostaining, Resources

Kei Koshimizu; Data Curation, Investigation

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Figures

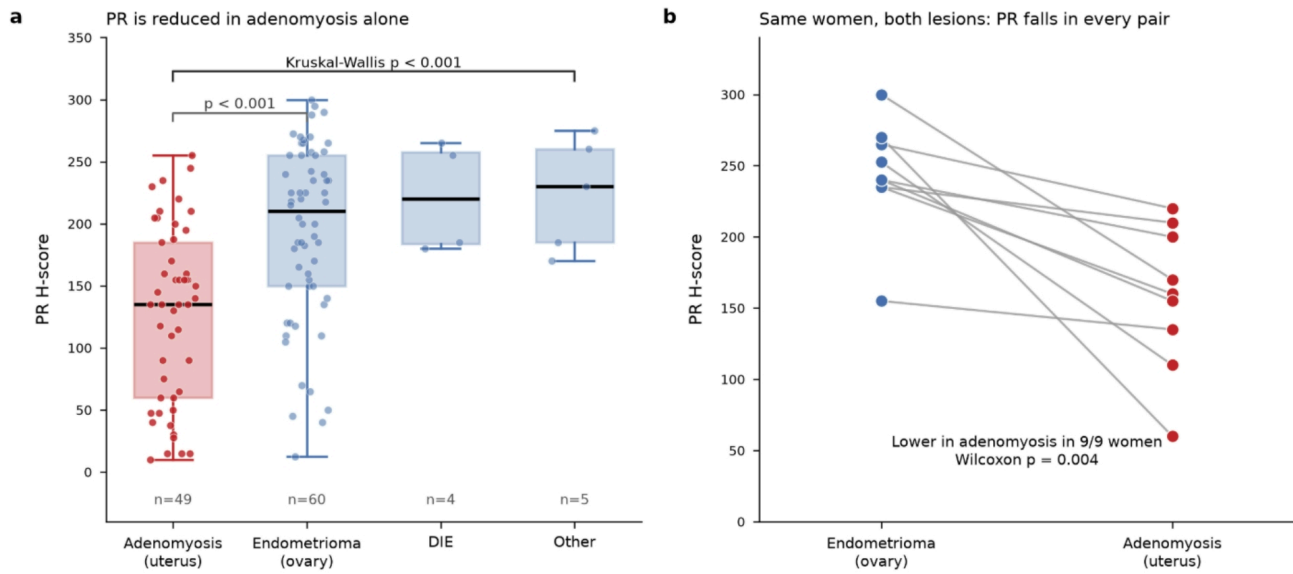


Figure 1

Progesterone receptor expression is reduced in adenomyosis alone. **a** PR H-score by lesion site; boxes show median and interquartile range with individual specimens overlaid, n per group indicated below each box. Brackets show the overall Kruskal-Wallis test and the Holm-adjusted adenomyosis-versus-endometrioma contrast. **b** Within-patient comparison restricted to the nine women who contributed both an ovarian endometrioma and an adenomyotic specimen at the same operation; each line joins one woman's two specimens.

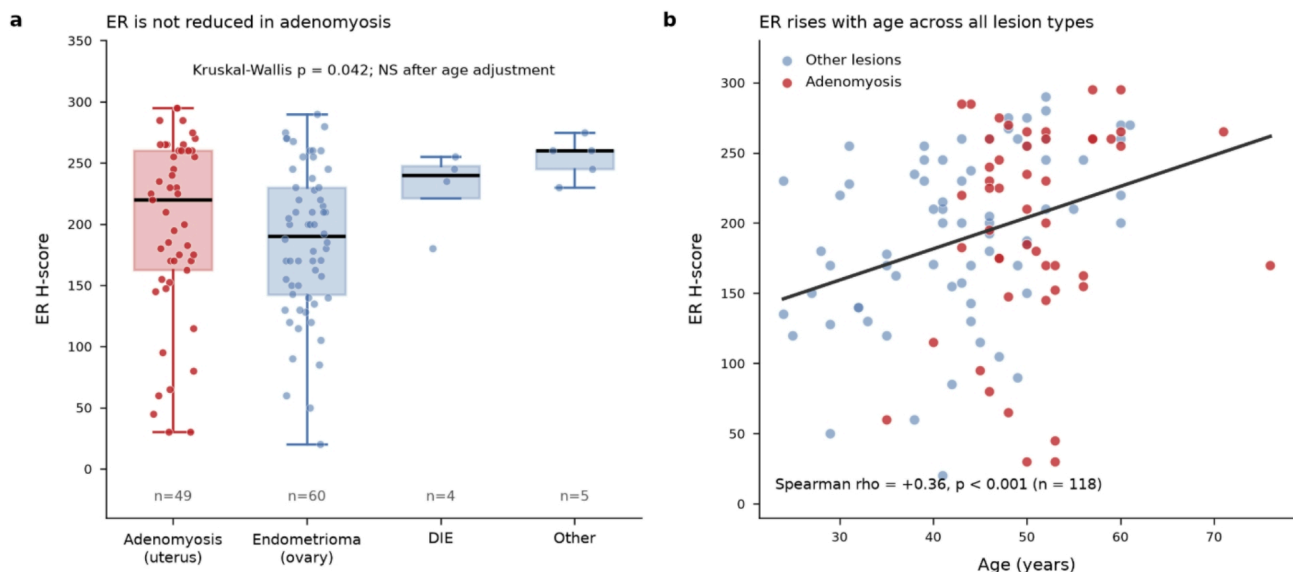


Figure 2

Oestrogen receptor shows no comparable site specificity. a ER H-score by lesion site; the difference across sites is weak and adenomyosis is not the low group, and the site effect does not persist after adjustment for age. b ER plotted against age at surgery for all 118 specimens, with adenomyotic specimens highlighted; the fitted line is the ordinary least-squares fit across the whole cohort.

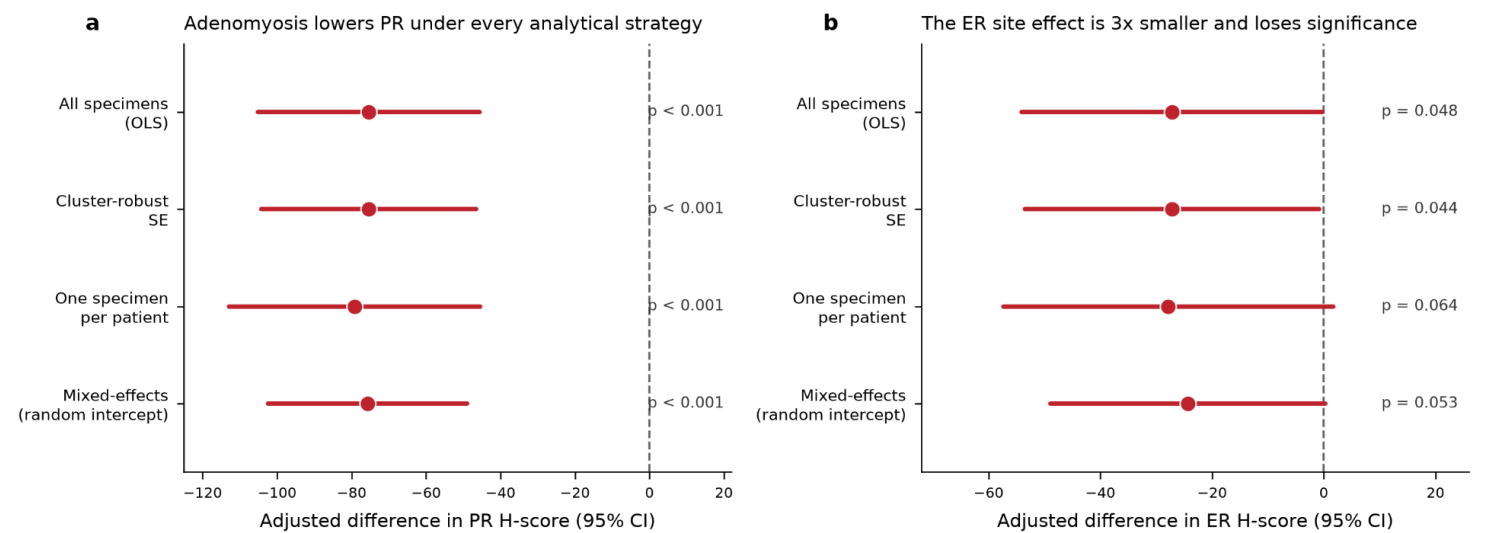


Figure 3

The adenomyosis-PR association is stable across analytical strategies. Adjusted difference in receptor H-score for adenomyosis versus all other lesion sites, estimated under four strategies for handling repeated specimens from the same woman. Points are point estimates, horizontal bars 95 % confidence intervals, dashed line the null. a PR. b ER. All models adjust for standardised age, pelvic adhesions and menopausal status.

Supplementary Files

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