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Correlation Between microRNA-let-7a and microRNA-10b Expression and KRAS and E-Cadherin Gene Expression in the Endometrium of Patients with Adenomyosis

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ABSTRACT: Adenomyosis is a common benign gynecological disorder associated with chronic pelvic pain and infertility, for which current treatments are limited to symptom relief and are often unsuitable for women seeking pregnancy. Altered E-cadherin expression and dysregulation of microRNAs, including let-7a and miR-10b, have been implicated in adenomyosis pathogenesis, but their relationship with the proposed target genes KRAS and E-cadherin has not been well characterized in this condition. This cross-sectional study compared the relative expression of miRNA-let-7a, miR-10b, KRAS, and E-cadherin in endometrial tissue from women with adenomyosis (n=17) and without adenomyosis (n=15) recruited at Dr. Cipto Mangunkusumo Hospital, Jakarta [AUTHOR VERIFICATION REQUIRED: total analytical sample], and examined the associations between miRNA-let-7a and KRAS, and between miR-10b and E-cadherin, using quantitative PCR and Pearson correlation. E-cadherin expression was significantly lower in the adenomyosis group than in the non-adenomyosis group (0.39 vs 1.36; $p=0.001$). No significant between-group differences were found for miRNA-let-7a ($p=0.288$), miR-10b ($p=0.320$), or KRAS ($p=0.509$). miRNA-let-7a showed a weak negative correlation with KRAS in the non-adenomyosis group ($r=-0.287$, $p=0.300$) but not in the adenomyosis group ($r=0.024$, $p=0.926$). miR-10b showed weak-to-moderate negative correlations with E-cadherin in both groups, neither statistically significant (adenomyosis: $r=-0.147$, $p=0.572$; non-adenomyosis: $r=-0.350$, $p=0.201$). These findings support an association between reduced E-cadherin expression and adenomyosis but do not establish a direct regulatory relationship between the investigated microRNAs and their proposed target genes. Larger, molecularly stratified studies with functional validation are warranted.

1. INTRODUCTION

Adenomyosis is a benign but clinically burdensome gynecological disorder, with an estimated incidence of up to 20% among women of reproductive age (Upson and Missmer, 2021; Chapron et al., 2020). It is strongly associated with chronic pelvic pain, abnormal uterine bleeding, and infertility, and its diagnosis remains challenging because clinical presentation overlaps substantially with other benign gynecological conditions (Struble et al., 2016; Chapron et al., 2020). Current treatment options are largely limited to symptomatic relief with analgesics, hormonal manipulation, or surgery; these approaches carry significant side effects and are frequently contraindicated in women who wish to conceive (Taran et al., 2013).

At the molecular level, adenomyosis is characterized by abnormal endometrial cell proliferation and impaired apoptosis, aberrant invasion of endometrial tissue into the myometrium, and features consistent with epithelial-to-mesenchymal transition (EMT), including altered cell-adhesion protein expression (Vannuccini et al., 2017; Polyak and Weinberg, 2009). These processes share molecular features with malignant transformation, including dysregulated RAS/MAPK signaling and altered expression of cell-adhesion molecules such as E-cadherin (Khan et al., 2022).

MicroRNAs (miRNAs) are short non-coding RNAs that post-transcriptionally regulate gene expression and are increasingly recognized as contributors to the molecular pathogenesis of adenomyosis and endometriosis (Rohloff et al., 2018; Christopher et al., 2016). Because a single miRNA can regulate multiple targets and a single target can be regulated by several miRNAs, characterizing miRNA-target relationships in specific disease contexts is an important step toward understanding their biological relevance and, eventually, their therapeutic potential.

MicroRNA let-7a is a well-characterized tumor-suppressor miRNA that regulates members of the RAS oncogene family, including KRAS, by binding to the 3'-untranslated region of its target transcript (Johnson et al., 2005; Kumar et al., 2008). Dysregulation of let-7a has been described in various conditions involving abnormal cell proliferation, including malignancy (Gilles and Slack, 2018), and reduced let-7a expression has previously been reported in uterine junctional-zone smooth muscle in adenomyosis (Huang et al., 2021). KRAS itself has been found to harbor somatic mutations in a substantial proportion of adenomyosis lesions, supporting its relevance to disease biology (Inoue et al., 2019; Chao et al., 2023).

MicroRNA-10b has been shown to directly target ZEB1 and PIK3CA, with downregulation of ZEB1 associated with increased E-cadherin expression and reduced Akt phosphorylation, and its dysregulation has been linked to increased invasiveness of adenomyotic epithelial cells (Guo et al., 2015). E-cadherin, a transmembrane glycoprotein central to epithelial cell-cell adhesion, has previously been reported to be reduced in adenomyosis and endometriosis, consistent with a more invasive epithelial phenotype (Halbleib and Nelson, 2006; Kaszak et al., 2020).

Although the individual relationships between let-7a and KRAS, and between miR-10b and E-cadherin, have been described in other tissue contexts, the extent to which these associations hold in human adenomyosis endometrial tissue particularly in the Indonesian population has not been adequately characterized.

This study aimed to compare the expression of miRNA-let-7a, miR-10b, KRAS, and E-cadherin in endometrial tissue from women with and without adenomyosis, and to evaluate the associations between miRNA-let-7a and KRAS, and between miR-10b and E-cadherin, in each group.

2. MATERIALS AND METHODS

2.1 Study design and setting

This was a cross-sectional study with comparative and correlation analyses. Tissue sampling was conducted at Dr. Cipto Mangunkusumo Hospital (RSCM), Jakarta, and molecular analyses (RNA isolation, reverse transcription, and quantitative PCR) were performed at the Human Reproduction, Infertility and Family Planning Cluster, Indonesian Medical Education and Research Institute (IMERI), Faculty of Medicine Universitas Indonesia, Salemba. The study was conducted from January to March 2023.

2.2 Study population and participants

The target population comprised women with adenomyosis in Indonesia; the accessible population comprised women undergoing hysteroscopy, laparoscopy, or operative laparotomy at RSCM who met the eligibility criteria below. Participants were enrolled by consecutive sampling from the gynecology and fertility outpatient clinics. Tissue samples were obtained during clinically indicated procedures; procedures were not performed solely for research purposes. All participants underwent transvaginal ultrasonography for assessment of adenomyosis, together with clinical history and physical examination.

2.3 Eligibility criteria

Adenomyosis group: women of reproductive age with a diagnosis of adenomyosis, not pregnant, not receiving hormonal therapy, who provided written informed consent.

Non-adenomyosis group: women of reproductive age without a diagnosis of adenomyosis or endometriosis, with infertility and an indication for hysteroscopy, not pregnant, not receiving hormonal therapy, who provided written informed consent.

Exclusion criteria (both groups): uterine myoma, malignancy, or pelvic infection/pelvic inflammatory disease.

2.4 Sample size and sampling

The minimum sample size was calculated using the formula for a correlation-based analytic study, with a two-sided type I error of 5% ($Z\alpha=1.96$), type II error of 20% ($Z\beta=0.84$), and a minimum correlation coefficient considered meaningful of $r=0.6$, yielding a minimum requirement of 19 participants. The final analytical sample comprised 17 participants in the adenomyosis group and 15 in the non-adenomyosis group. The source thesis Results section reports a total of 32 participants (17+15), while the thesis abstract reports a total of 31; this discrepancy should be reconciled against the original recruitment and laboratory datasets before submission.

2.5 Clinical assessment and tissue collection

Endometrial tissue was obtained via hysteroscopy, laparoscopy, or operative laparotomy, depending on the clinical indication for each participant. Diagnosis of adenomyosis was based on clinical history, physical examination, transvaginal ultrasonography, and, where available, histopathological assessment.

2.6 RNA extraction

Total RNA, including miRNA, was extracted from endometrial tissue biopsies using the miRNeasy Mini Kit (Qiagen). Briefly, tissue samples (20–30 mg) were disrupted and homogenized in RLT lysis buffer (600 μ L) using an ultrasonic disruptor for 20–40 seconds. Lysates were centrifuged at $17,000 \times g$ for 3 minutes, and the supernatant was processed with one volume of 70% ethanol before sequential loading onto QIAamp spin columns with RW1 and RPE wash steps, following the manufacturer's protocol. RNA was eluted in 30–50 μ L RNase-free water and stored at -80°C .

2.7 miRNA cDNA synthesis and qPCR

Complementary DNA was synthesized from isolated RNA using the TaqMan MicroRNA Reverse Transcription Kit (catalogue no. 4366596; Thermo Fisher Scientific, USA), with thermal cycling at 16°C for 30 minutes, 42°C for 30 minutes, and 85°C for 5 minutes, followed by a 4°C hold. Quantitative real-time PCR for miRNA-let-7a and miR-10b was performed using TaqMan Fast Advanced Master Mix (5 μ L), nuclease-free water (2 μ L), TaqMan Advanced miRNA Assay (0.50 μ L), and cDNA (2.50 μ L) in a 10 μ L reaction, with cycling conditions of 95°C for 20 seconds (polymerase activation) followed by 40 cycles of 95°C for 3 seconds and 60°C for 30 seconds. U6 small nuclear RNA was used as the endogenous reference for miRNA quantification. [AUTHOR VERIFICATION REQUIRED: TaqMan assay catalogue/ID numbers for miRNA-let-7a and miR-10b were not identified in the available source material and should be confirmed.]

2.8 KRAS and E-cadherin expression analysis

RNA purity and concentration were assessed using a NanoPhotometer P Class Submicroliter Cell spectrophotometer. Complementary DNA for KRAS and E-cadherin was synthesized using the Toyobo ReverTra Ace qPCR RT Master Mix with gDNA Remover, using a standardized RNA template concentration of 25 ng/ μ L in a final volume of 6 μ L, with genomic DNA removal at 37°C for 5 minutes and reverse transcription at 37°C for 15 minutes, 50°C for 5 minutes, and 98°C for 5 minutes. [AUTHOR VERIFICATION REQUIRED: KRAS and E-cadherin primer sequences, assay chemistry, reaction composition, and real-time PCR cycling conditions could not be confirmed from the available source material, which contains a primer and

cycling-condition table for an unrelated gene (FTO) at this point in the protocol. It is not clear whether this reflects a template/copy-paste error in the source document or an additional, unreported assay; this must be clarified and the correct KRAS and E-cadherin assay details obtained from the original laboratory records before submission.

2.9 Relative expression calculation

Relative expression of miRNA-let-7a, miR-10b, KRAS, and E-cadherin was calculated using the comparative threshold cycle ($2^{-\Delta\Delta Ct}$) method (Livak method). For each target, ΔCt was calculated as the difference between the target Ct and the Ct of the endogenous reference; $\Delta\Delta Ct$ was calculated relative to a designated calibrator sample; and relative expression was expressed as $2^{-\Delta\Delta Ct}$. [AUTHOR VERIFICATION REQUIRED: the reference gene used for normalization of KRAS and E-cadherin expression should be explicitly confirmed from the laboratory record.

2.10 Statistical analysis

Descriptive statistics were used to summarize participant characteristics. Between-group comparisons of relative expression for miRNA-let-7a, miR-10b, KRAS, and E-cadherin were performed using one-way analysis of variance (ANOVA); because only two groups were compared, this is statistically equivalent to an independent-samples comparison under the same distributional assumptions. Associations between miRNA-let-7a and KRAS, and between miR-10b and E-cadherin, were assessed using Pearson's correlation coefficient (r) within each group. Correlation strength was interpreted as follows: $|r| < 0.1$, no correlation; 0.1–0.3, weak correlation; 0.3–0.5, moderate correlation; and 0.5–1.0, strong correlation, regardless of statistical significance. A p -value < 0.05 was considered statistically significant. Analyses were performed using SPSS/AMOS or Stata version 14. Normality and homoscedasticity of the underlying data were not explicitly documented in the source analysis and are therefore not asserted here.

2.11 Ethical considerations

The study was submitted to and approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia.

3. RESULTS AND DISCUSSION

3.1 Participant characteristics

A total of 32 tissue samples were analyzed (17 from the adenomyosis group and 15 from the non-adenomyosis group). Mean age was higher in the adenomyosis group (35.83 ± 5.4 years) than in the non-adenomyosis group (29.43 ± 5.7 years), consistent with the recognized association of adenomyosis with older reproductive age (Brosens et al., 2014). Participant characteristics and relative expression of the four study variables are summarized in Table 1.

3.2 Differential expression of miRNA-let-7a, miR-10b, KRAS, and E-cadherin

Comparative analysis showed a statistically significant difference in E-cadherin expression between the adenomyosis and non-adenomyosis groups (0.39 ± 0.41 vs 1.36 ± 0.95 ; $p=0.001$), with lower E-cadherin expression in adenomyosis tissue. No statistically significant between-group differences were found for miRNA-let-7a ($p=0.288$), miR-10b ($p=0.320$), or KRAS ($p=0.509$), although mean expression of miRNA-let-7a and miR-10b was numerically lower in the adenomyosis group than in the non-adenomyosis group (Table 1; Figure 2). E-cadherin was therefore the only marker with a statistically significant between-group difference in this study.

3.3 Association between miRNA-let-7a and KRAS

In the non-adenomyosis group, a weak negative correlation was found between miRNA-let-7a and KRAS expression ($r=-0.287$, $p=0.300$); in the adenomyosis group, no correlation was observed ($r=0.024$, $p=0.926$) (Table 2; Figure 3). Neither correlation reached statistical significance.

Let-7a is known to regulate RAS-family transcripts, including KRAS, through direct binding to the 3'-untranslated region of the target mRNA (Johnson et al., 2005), and this let-7a/KRAS relationship has previously been described in non-small-cell lung tumors (Kumar et al., 2008). To our knowledge, this is the first study to examine this specific association in adenomyosis. Somatic KRAS mutations have been reported in a substantial proportion of adenomyosis lesions 37.1% in one series (Inoue et al., 2019) and 24% in another, using next-generation sequencing (Chao et al., 2023) and it is plausible that the absence of a demonstrable let-7a/KRAS correlation in the adenomyosis group reflects molecular heterogeneity, since not all adenomyosis

lesions carry KRAS mutations. Because this study measured KRAS expression rather than KRAS mutation status, it cannot determine whether mutational status modifies the let-7a/KRAS relationship; this remains an important question for future work. The absence of a significant correlation in this study should not be interpreted as evidence against let-7a-mediated regulation of KRAS in adenomyosis; it may instead reflect limited statistical power given the sample size.

3.4 Association between miR-10b and E-cadherin

Weak-to-moderate negative correlations were found between miR-10b and E-cadherin expression in both groups, neither reaching statistical significance (adenomyosis: $r=-0.147$, $p=0.572$; non-adenomyosis: $r=-0.350$, $p=0.201$) (Table 3; Figure 4).

MiR-10b has been shown to directly target ZEB1 and PIK3CA, with overexpression of miR-10b downregulating ZEB1 and thereby increasing E-cadherin expression in adenomyotic epithelial cells (Guo et al., 2015). In the present study, E-cadherin expression was significantly lower in adenomyosis, but the correlation between miR-10b and E-cadherin was negative rather than positive in both groups, and not statistically significant. This pattern suggests that reduced E-cadherin expression in adenomyosis in this cohort was not accompanied by a corresponding reduction in miR-10b expression, and indicates that E-cadherin regulation in adenomyosis is likely influenced by multiple mechanisms beyond miR-10b alone — for example, transcriptional repressors such as ZEB2, SNAIL1, SNAIL2, and TWIST1/2, and other signaling pathways implicated in epithelial-to-mesenchymal transition (Kaszak et al., 2020; Polyak and Weinberg, 2009). MiR-10b has also been reported to modulate endometriotic cell invasiveness through binding to syndecan-1 rather than through E-cadherin alone (Schneider et al., 2013), consistent with the interpretation that miR-10b's biological effects in endometrial pathology are not limited to a single target transcript.

3.5 Biological interpretation

Taken together, these findings are consistent with a conceptual model in which miRNA dysregulation contributes to altered molecular signaling, which in turn influences epithelial cell adhesion, proliferation, and migration, ultimately shaping adenomyotic lesion biology. This is offered as a plausible mechanistic interpretation rather than a causal pathway directly demonstrated by this cross-sectional study; association does not establish causation, and the correlations observed here were, with one exception, not statistically significant.

3.6 Comparison with previous evidence

The significantly lower E-cadherin expression observed in adenomyosis tissue in this study is consistent with previous reports of reduced E-cadherin in adenomyosis and endometriosis and supports a role for impaired epithelial adhesion and EMT-related processes in disease pathogenesis (Halbleib and Nelson, 2006; Kaszak et al., 2020). The absence of significant between-group differences for miRNA-let-7a, miR-10b, and KRAS contrasts with some prior reports of reduced let-7 family and miR-10b expression in adenomyosis (Huang et al., 2021), and may reflect differences in sample size, population, tissue source, or assay methodology between studies.

3.7 Clinical and translational implications

MicroRNAs have been proposed as potential biomarkers and therapeutic targets in gynecological disease (Rohloff et al., 2018; Christopher et al., 2016). The findings of this study do not establish miRNA-let-7a or miR-10b as validated biomarkers or therapeutic targets in adenomyosis; rather, they highlight E-cadherin as a molecule of interest warranting further investigation, and underscore that the proposed miRNA-target relationships require validation in larger, adequately powered cohorts before any clinical application can be considered.

3.8 Study limitations

- [1] The cross-sectional design precludes causal inference between miRNA expression and target gene expression.
- [2] The sample size was relatively small, limiting statistical power, particularly for the correlation analyses.
- [3] Participants were recruited from a single center, which may limit generalizability.
- [4] Adenomyosis is likely a molecularly heterogeneous condition, and this study could not stratify participants by molecular subtype.
- [5] No longitudinal follow-up was performed.
- [6] No independent validation cohort was available.

- [7] No functional experimental validation (for example, miRNA overexpression or knockdown assays) was performed.
- [8] KRAS mutation status was not assessed; only KRAS expression was measured.
- [9] Correlation between miRNA and target-gene expression cannot, by itself, establish direct molecular targeting.
- [10] Several methodological details from the source thesis required author verification prior to submission (see accompanying Author Verification Checklist), including the final analytical sample size, eligibility of one non-adenomyosis participant, the exact ethics approval number, and the assay details for KRAS and E-cadherin quantification.

4. CONCLUSION

In this cross-sectional study of endometrial tissue from women with and without adenomyosis, E-cadherin expression was significantly lower in the adenomyosis group. No statistically significant differences were found in miRNA-let-7a, miR-10b, or KRAS expression between groups. The correlations between miRNA-let-7a and KRAS, and between miR-10b and E-cadherin, were not statistically significant in either group. These findings support an association between altered E-cadherin expression and adenomyosis but do not establish a direct regulatory relationship between the investigated microRNAs and their proposed molecular targets. Larger studies with molecular stratification, KRAS mutation analysis, and functional validation are warranted before miRNA-let-7a or miR-10b can be considered as biomarkers or therapeutic targets in adenomyosis.

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AUTHOR CONTRIBUTIONS

Wahyuni Saddang: Investigation, Data Curation, Formal Analysis, Writing Original Draft; R. Muharam: Conceptualization, Supervision, Writing Review & Editing; Mila Maidarti: Conceptualization, Supervision, Writing Review & Editing; Kanadi Sumapraja: Supervision, Writing Review & Editing; Gita Pratama: Writing Review & Editing; Rizka Yurianda: Writing Review & Editing.

FUNDING

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

This study involving human participants was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia. All participants provided written informed consent before study procedures. The study was conducted in accordance with applicable ethical principles for research involving human participants.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to applicable ethical and institutional restrictions.

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FIGURE LEGENDS

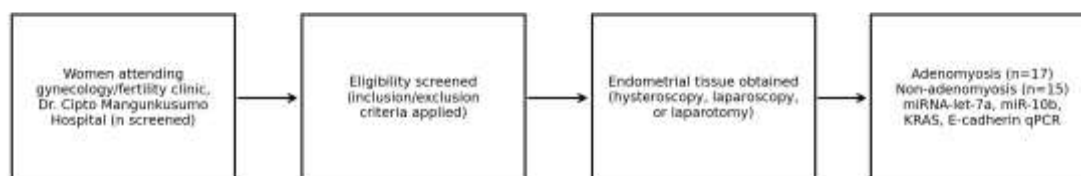


Figure 1. Study workflow. Women attending the gynecology/fertility clinic at Dr. Cipto Mangunkusumo Hospital were screened against the inclusion and exclusion criteria; endometrial tissue was obtained during clinically indicated hysteroscopy, laparoscopy, or laparotomy and assigned to the adenomyosis (n=17) or non-adenomyosis (n=15) group for quantification of miRNA-let-7a, miR-10b, KRAS, and E-cadherin expression.

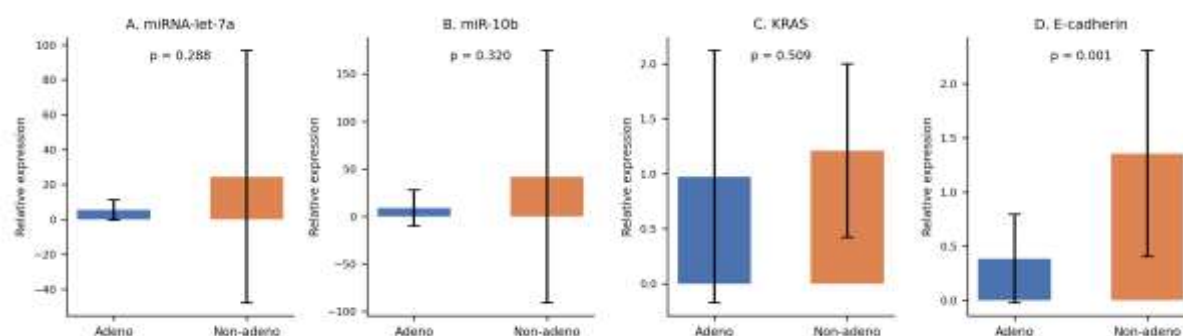


Figure 2. Comparison of relative expression of (A) miRNA-let-7a, (B) miR-10b, (C) KRAS, and (D) E-cadherin between the adenomyosis and non-adenomyosis groups. Bars represent group mean relative expression $\pm$ SD; p-values are from one-way ANOVA. Only the E-cadherin comparison (D) reached statistical significance (p=0.001).

TABLES

Table 1. Clinical characteristics and relative expression of miRNA-let-7a, miR-10b, KRAS, and E-cadherin in adenomyosis and non-adenomyosis groups.

Variable	Adenomyosis (n=17)	Non-adenomyosis (n=15)	p-value
Age (years), mean $\pm$ SD	35.83 $\pm$ 5.4	29.43 $\pm$ 5.7	—
miRNA-let-7a, mean $\pm$ SD (range)	5.44 $\pm$ 5.77 (0.09–19.96)	24.46 $\pm$ 72.42 (0.00–279.25)	0.288
miR-10b, mean $\pm$ SD (range)	8.93 $\pm$ 18.93 (0.04–79.65)	41.81 $\pm$ 132.91 (0.00–520.05)	0.320
KRAS, mean $\pm$ SD (range)	0.97 $\pm$ 1.15 (0.02–3.34)	1.21 $\pm$ 0.79 (0.42–2.83)	0.509
E-cadherin, mean $\pm$ SD (range)	0.39 $\pm$ 0.41 (0.02–1.28)	1.36 $\pm$ 0.95 (0.17–3.24)	0.001

Values are relative expression (arbitrary units, $2^{-\Delta\Delta Ct}$ method) unless otherwise noted. P-values from one-way ANOVA. Total analytical sample reported as n=32 (17+15) in the source Results and n=31 in the source Abstract

Table 2. Correlation between miRNA-let-7a and KRAS relative expression.

Group	n	r (p-value)	Interpretation
Adenomyosis	17	0.024 (p=0.926)	No correlation, not significant
Non-adenomyosis	15	-0.287 (p=0.300)	Weak negative correlation, not significant

Table 3. Correlation between miR-10b and E-cadherin relative expression.

Group	n	r (p-value)	Interpretation
Adenomyosis	17	-0.147 (p=0.572)	Weak negative correlation, not significant
Non-adenomyosis	15	-0.350 (p=0.201)	Moderate negative correlation (by magnitude), not significant