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ORIGINAL ARTICLE

Serum leucine-rich α2-glycoprotein as a possible marker for inflammatory status in endometriosis

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Abstract

Purpose: This study aimed to investigate whether serum leucine-rich α2-glycoprotein (LRG) is a useful diagnostic biomarker for endometriosis, including the evaluation of treatment efficacy and exploration of LRG production in endometriotic lesions.

Methods: Forty-three women with endometriomas were compared to 22 women with benign ovarian cysts and 30 women who underwent assisted reproduction as controls. Changes in serum LRG levels were assessed before and after surgery, and during dienogest treatment. LRG expression in endometriotic tissue samples was evaluated using immunoblotting.

Results: Serum LRG levels in the endometrioma group (80.0 ± 36.3 μg/mL) were significantly higher than those in the benign ovarian cyst (65.1 ± 27.0 μg/mL, $p = 0.0265$) and control (57.8 ± 22.3 μg/mL, $p = 0.0028$) groups. Serum LRG levels after endometrioma surgery were significantly lower than preoperative levels ($p = 0.0484$). Serum LRG levels consistently decreased during dienogest treatment. LRG expression levels were significantly higher in endometriotic tissues than in the normal endometrium.

Conclusion: Serum LRG, possibly derived from local and systemic origins, could be used as a potential biomarker for the diagnosis and treatment of endometriosis.

KEYWORDS
biomarker, dienogest, endometriosis, inflammation, LRG

1 | INTRODUCTION

Endometriosis is one of the most common diseases in women of reproductive age. The incidence is approximately 10% in women of reproductive age and may be as high as 20%–50%, especially in infertile women. Endometriosis is a chronic and progressive disease characterized by local inflammatory effects caused by endometrial-like tissues outside the uterus. Dysmenorrhea and chronic pelvic pain may reduce the quality of life in women with endometriosis.[1] The endometrium shed in retrograde menstrual blood is considered the primary source of endometriotic tissue.[2] Repetitive menstrual blood reflux allows a small initial endometrial lesion to grow larger; thus, endometriosis can be diagnosed by pelvic examination and/or ultrasound. Therefore, the delay between the first symptoms and the diagnosis of endometriosis may be between 8 and 10 years, as reported in various studies.[3,4]

Laparoscopy remains the gold standard for the diagnosis of hormone therapy-resistant endometriosis. Although transvaginal ultrasound and magnetic resonance imaging (MRI) have replaced direct observation by laparoscopy, laparoscopic diagnosis of endometriosis, which is otherwise undetectable, is decreasing because of its invasiveness, especially in younger women. Therefore, less invasive, and more feasible diagnostic markers have been investigated to reduce delayed diagnosis of endometriosis. These diagnostic markers are not only expected to help decrease the morbidity of untreated endometriosis, but also assess the effects of hormonal treatments. To date, the most studied serum marker of endometriosis is the cancer antigen 125 (CA125). However, despite its widespread use in clinical practice, the sensitivity and specificity of CA125 for the diagnosis of endometriosis are relatively low.[5]

Inflammatory cytokines are produced locally in inflammatory diseases, and proteins produced in the liver and other cells are elevated in response to inflammation; these may be useful markers for diagnosis and disease status. Leucine-rich α2-glycoprotein (LRG), whose serum concentration can be measured using enzyme-linked immunosorbent assay (ELISA)[6] is produced by various cells, such as macrophages and hepatocytes. Serum LRG levels have been reported to be useful markers for several inflammatory diseases, including ulcerative colitis and rheumatoid arthritis, where serum LRG levels are upregulated, reflecting inflammatory reactions.[7]

We investigated serum LRG levels in women with endometriosis to assess its usefulness as a diagnostic biomarker by comparing to women without endometriosis. We also evaluated the serum LRG decline after conservative surgery and hormonal treatment for endometriosis, and explored the local expression of LRG in endometriotic tissues.

2 | MATERIALS AND METHODS

2.1 | Patients and serum samples

Patients with endometrioma who visited the fertility clinic of Gunma University Hospital between January 2019 and January 2022 were enrolled in this study. All patients were diagnosed with endometrioma using MRI and/or transvaginal ultrasonography. We also recruited women without endometriosis, such as those with benign ovarian tumors, and infertile women without ovarian disease who underwent assisted reproduction as the control group. This study was approved by the ethics committee of Gunma University Graduate School of Medicine, and written informed consent was obtained from all participants. Serum samples were obtained from the women 1 month before and after surgery and stored at −80°C until assayed. Serum LRG concentrations were measured using an enzyme immunoassay kit (Human LRG Assay Kit; Immuno-Biological Laboratories Co., Ltd.), according to the manufacturer's instructions. During laparoscopic surgery, the cyst wall of an endometrioma is stripped from the surrounding normal ovarian tissues, or bipolar coagulation of the cystic wall is performed.

Serum samples from a previous report[8] were used to analyze changes in serum LRG levels during dienogest treatment (Dinagest 1 mg; Mochida Pharmaceutical) at 2 mg/day for 2 months, preoperatively, and 6 months, postoperatively. Ethics committee approval was obtained for secondary use of the samples.

2.2 | Tissue collection and immunoblotting

Tissue samples were obtained from surgically excised endometriomas and confirmed by pathological examination. Normal endometrial tissues were collected by curettage of the excised uteri from women with early cervical cancer. The menstrual cycle was determined by endometrial histology in the case of hysterectomy and by menstrual information and ultrasound findings in the case of cystectomy. Tissue samples were washed with phosphate-buffered saline and stored at −80°C. Proteins were extracted from frozen tissue samples and subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The proteins were then transferred onto polyvinylidene difluoride membranes and treated with a primary antibody against LRG (13224-1-AP; Proteintech Japan). The immunoreactive proteins were stained using an enhanced chemiluminescence (ImmunoSTAR; Fujifilm, WAKO). Relative band density normalized by β-actin was determined from light scans of resulting films using densitometric analysis software.

2.3 | Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows (version 22.0; International Business Machines Corporation). *p*-Values were calculated using a two-sided Student's *t*-test or Mann–Whitney *U* test for continuous variables, whereas categorical variables were compared using Fisher's exact test. The Wilcoxon signed-rank test and one-way repeated-measures analysis of variance were used for serial changes in measurements for the same participant. Statistical significance was set at $p < 0.05$. Receiver operating characteristic (ROC) curves were generated using JMP Pro 15 (JMP Statistical Discovery LLC).

3 | RESULTS

A total of 95 women were enrolled and the groups were comprised as follows: 30 in the control group, 43 in the endometrioma group, and 22 in the benign ovarian cyst group. Patient characteristics are shown in Table 1. Although there were significant differences in age between the three groups, serum LRG levels did not correlate with age (data not shown). Serum LRG levels are shown in Figure 1. The mean ± standard deviation/median of LRG concentrations were 57.8 ± 22.3/57.8, 65.1 ± 27.0/63.4, and 80.0 ± 36.3/74.4 μg/mL in the control, benign ovarian cyst and endometrioma groups, respectively. Serum LRG levels were significantly higher in the endometrioma

TABLE 1 Patient characteristics.

Variables	Endometrioma ($n=43$)	Benign ovarian cyst ($n=22$)	Control ($n=30$)	p[a]
Age (years, mean ± SD)	32.4 ± 5.0	28.7 ± 4.3	37.8 ± 4.5	<0.0001
Unilateral/bilateral (n [%])	29 (67)/14 (33)	16 (73)/6 (27)	N.A	0.7798
CA125 (U/mL, median [IQR])	49 (31.7, 92.5)	N.A	N.A	
Pathological type/ infertile factor (n)	N.A	MT, 12 SC, 4 MC, 5 Others, 1	Male, 5 Tubal, 1 Unexplained, 18 Others, 6	

Abbreviations: IQR, interquartile range; MC, mucinous cystadenoma; MT, mature teratoma; N.A, not applicable; SC, serous cystadenoma; SD, standard deviation.

[a]Student's t-test or Fisher exact test.

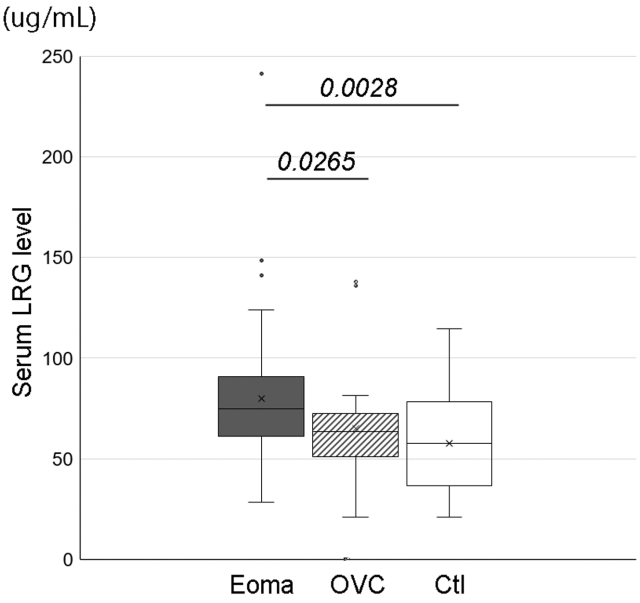

FIGURE 1 Comparison of serum levels of leucine-rich α2-glycoprotein (LRG). Serum LRG levels in endometrioma patients were significantly higher than those in patients with benign ovarian cysts and controls. The data are presented as box-and-whisker plots. The lines and crosses inside the boxes represent median and average values, respectively; the upper and lower limits of the boxes indicate interquartile ranges (IQR); the whiskers indicate total ranges or 1.5 times the IQR; and the small circles represent outliers. p values are represented in italicized numbers. Ctl, control; Eoma, endometrioma; OVC, benign ovarian cyst.

group than in the other groups ($p=0.0265$ vs. the benign ovarian cyst group; $p=0.0028$ vs. the control group). We evaluated ROC curves to validate the diagnostic accuracy of the LRG measurements (Figure 2). The cutoff value was 65.1 μg/mL for differentiating endometriosis from controls and benign ovarian cysts. The sensitivity, specificity, positive predictive value, and negative predictive value were 0.698, 0.673, 0.638, and 0.729, respectively. No significant correlation was found between the revised American Society for Reproductive Medicine (rASRM) scores and serum LRG levels (data not shown).

We subsequently compared the pre-and postoperative LRG levels in 26 women who underwent cystectomy and/or coagulation in the endometrioma group (Figure 3). The preoperative and one-month postoperative mean ± SD/median serum LRG levels were 77.8 ± 29.8/73.1 and 69.3 ± 20.1/71.9 μg/mL, respectively. Postoperative serum LRG levels were significantly lower than preoperative levels ($p=0.0484$). We evaluated the serial changes in serum LRG levels during dienogest treatment before and after cystectomy. We analyzed 10 women aged 23–42 years who underwent unilateral surgery (nine women) and bilateral surgery (one woman). Serum LRG levels showed a consistent downward trend during pre and postoperative dienogest treatments (Figure 4). Median (interquartile range) of serum LRG levels at the pretreatment, and 1, 3, and 6 months after dienogest intervention were 75.6 (68.9–81.2), 56.8 (54.9–72.5), 49.1 (45.9–60.5), and 39.2 (32.6–50.6) μg/mL, respectively.

To confirm the origin of LRG, which was elevated in the serum of patients with endometriosis, we compared LRG expression between endometriotic tissues and normal endometria. Western blotting showed a significant increase in LRG expression in endometriomas compared to that in a normal endometrium (3.70 ± 0.24 vs. 1 ± 0.02, $p=0.00019$, Figure 5).

4 | DISCUSSION

We found that the serum LRG levels in the endometrioma group were significantly higher than those in the control group without endometriosis and the group with other benign ovarian tumors. Furthermore, we demonstrated that serum LRG levels significantly reduced during dienogest treatment before and after surgery. Although the postoperative serum LRG levels were still measurable, the decrease in serum LRG was significant compared to the preoperative levels. Our results suggest that serum LRG can be a useful and noninvasive biomarker for detecting endometriosis and

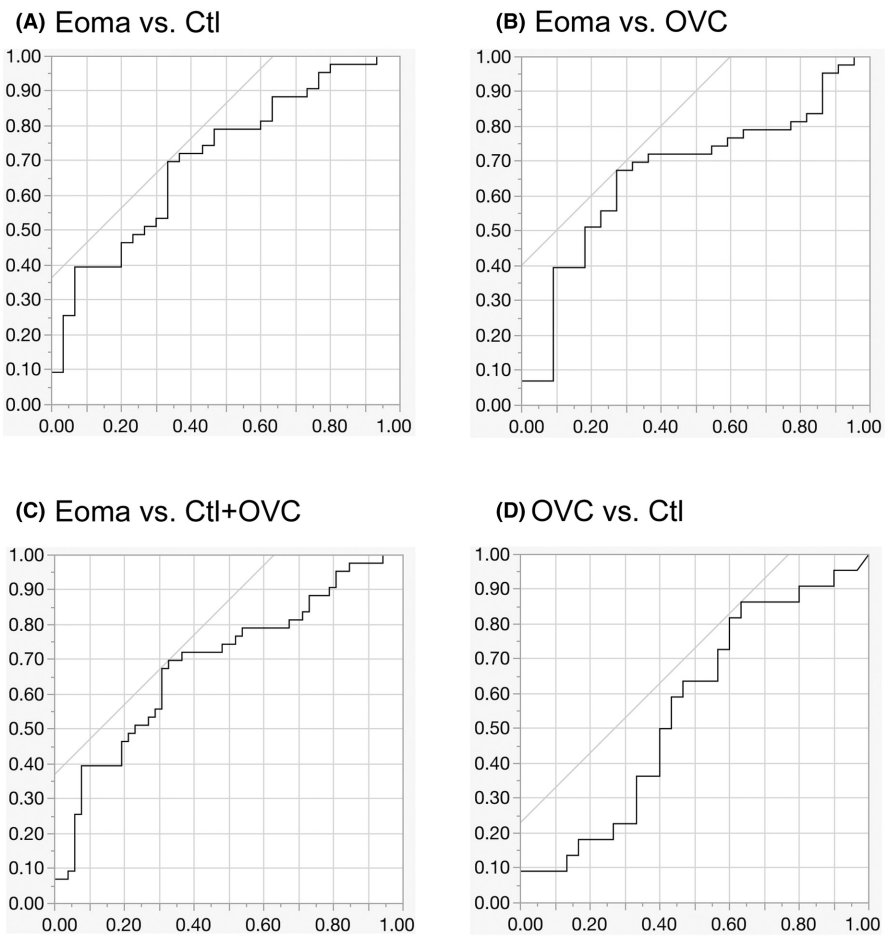

FIGURE 2 Receiver operating characteristic curves for differentiating endometriosis based on the serum levels of leucine-rich α2-glycoprotein (LRG). Ctl, control; Eoma, endometrioma; OVC, benign ovarian cyst. Area under the curves are (A) 0.707, (B) 0.691, (C) 0.670, and (D) 0.557.

assessing inflammatory conditions. Although serum LRG is also useful for ulcerative colitis and rheumatoid arthritis, it may still be helpful as an adjunctive diagnostic marker for endometriosis, because endometriosis is a much more common disease in reproductive-aged women. Furthermore, considering that LRG levels are decreased by progestins and surgery, this may be useful for the follow-up of disease status after the diagnosis of endometriosis.

Several biomarkers have been developed and assessed for less invasive detection of endometriosis. Among these, the tumor marker CA125 is one of the most widely investigated. CA125, a high molecular weight glycoprotein, has also been studied as a marker of ovarian malignancies.[9] Additionally, CA125 levels can be elevated during menstruation, even in healthy women.[10] The use of CA125 in the diagnosis of endometriosis is limited owing to its low specificity.[11]

Because endometriosis is an inflammatory disease, proinflammatory cytokines such as interleukins (ILs) and chemokines are locally upregulated.[12] Among these, IL-6 and IL-8 are produced by endometriotic cells, thereby influencing the pathophysiology of endometriosis.[13] Concentrations of IL-6 and IL-8 in the peritoneal fluid were higher in women with endometriosis than in those without endometriosis. IL-6 and IL-8 have been implicated in the pathophysiology of endometriosis via local inflammatory responses. However, it seems controversial whether IL-6 and IL-8 serum levels could be reliable diagnostic markers for endometriosis.[14] The application of serum levels of IL-6 and IL-8 as biomarkers of endometriosis is impractical.[15]

Based on the immunoblotting results, we found that LRG was produced in eutopic normal endometrial and endometriotic tissues. Using two-dimensional gel electrophoresis, uterine flushing has been shown to contain LRG isoforms.[16] Although the primary source of LRG in uterine flushing appears to be the endometrium, immunoblotting using tissue specimens revealed that the expression of LRG in endometriotic lesions was much stronger than that in the eutopic endometrium. Endometriosis is characterized by the extrauterine development of endometrium-like tissues. However, we did not explore the cells that produce LRG in endometrial and endometriotic tissues. Therefore, it is not clear how its expression is increased in endometriosis compared to that in the normal endometrium.

Our results indicate that endometriotic lesions produce LRG. However, it is unlikely that serum LRG proteins depend solely on locally produced LRG. Although more than half of the patients exhibited a decline in serum LRG levels after conservative surgery, the postsurgical decline did not reach an undetectable level. Additionally, hormonal treatment with dienogest significantly decreased the serum levels of LRG. These results suggested that LRG expression is regulated by inflammatory responses in the body. It has been reported that LRG, a positive acute-phase glycoprotein, mainly originates from the liver.[17] Serum LRG levels have been shown to increase in response to fetal infection, which is attributable to the fetal liver rather than the placenta.[18] Leucine-rich α2-glycoprotein is differently induced in the liver compared with C-reactive protein

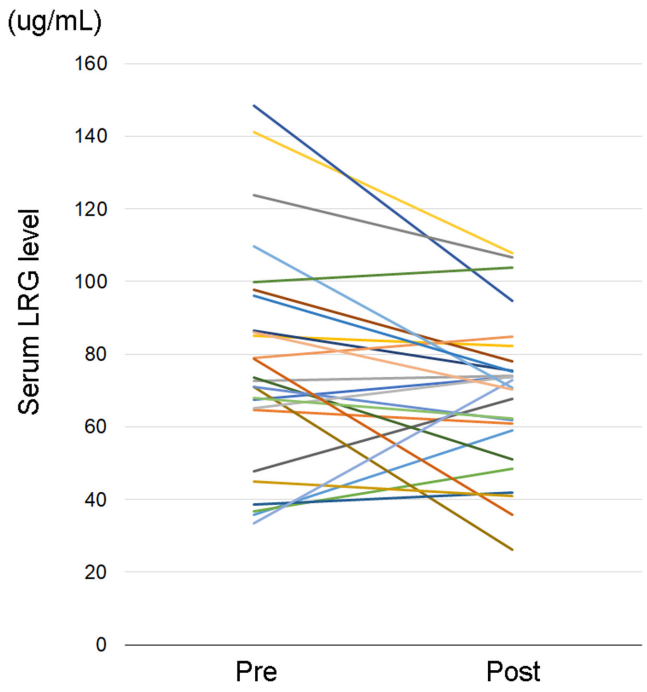

FIGURE 3 Preoperative and 1-month postoperative serum leucine-rich α2-glycoprotein (LRG) levels in the endometrioma group. The 1-month postoperative LRG levels were significantly lower than the preoperative levels ($p = 0.0484$).

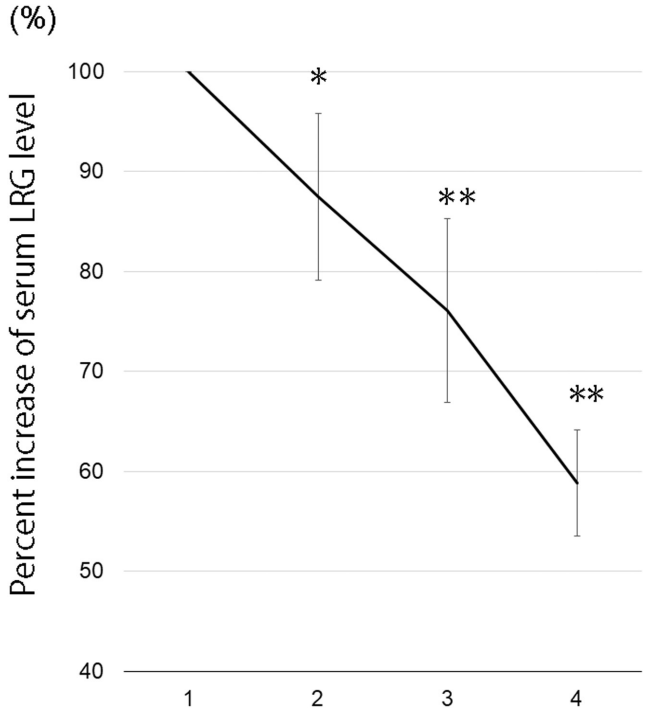

FIGURE 4 Serial change of percent increase in leucine-rich α2-glycoprotein (LRG) levels during continuous dienogest treatment before and after cystectomy. 1—pretreatment; 2—1 month after dienogest intervention; 3—3 months after dienogest intervention (1 month after cystectomy); and 4—8 months after dienogest intervention (6 months after cystectomy). Error bars indicate the standard error of the mean, $^{*}p < 0.05$, and $^{**}p < 0.01$, compared to the pretreatment level.

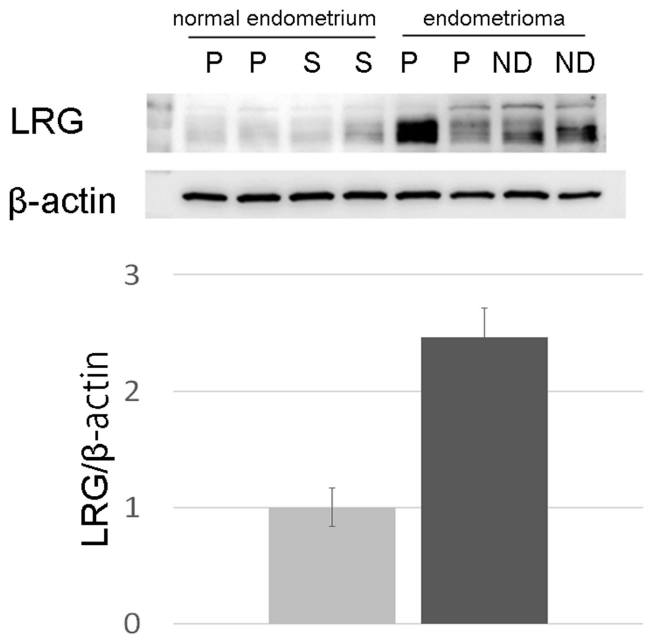

FIGURE 5 Western blot analysis of leucine-rich α2-glycoprotein (LRG) and β-actinin of normal human endometrium and endometrioma samples. Densitometric analysis results are shown in the lower panel. Protein contents in the four different sets of samples were quantified and normalized by β-actin signals. Normal endometrial LRG/β-actin was used as a control. Results are expressed as mean ± standard deviation. ND, not determined; P, proliferative phase; S, secretory phase.

(CRP). Although the induction of CRP mainly depends on IL-6 stimulation, LRG expression in liver cells is induced by not only IL-6 but also tumor necrosis factor α (TNF-α) and IL-22.[19] Altogether, the findings distinguish LRG as a possible unique, acute reactant from CRP. Therefore, the usefulness of LRG as an endometriosis biomarker should be highlighted.

The anti-inflammatory effects of progesterone in the uterus have long been reported. In vivo experiments using progesterone receptor-knockout mice have revealed that the progesterone receptor has strong anti-inflammatory effects in the uterus through the inhibition of macrophage and neutrophil recruitment by estrogen. Progestins such as dienogest downregulate IL-8 expression following diminished TNF levels in endometrial stromal cells.[20] Other alterations in the endometriosis-related immune system caused by dienogest include a decrease in the number of immune cells in the peritoneal fluid, decreased production of IL-1β by macrophages,[21] and the inhibition of IL-1β by endometriotic cells.[22] Dienogest, a progestin, downregulates local and systemic inflammatory responses by altering local immune cells in endometriotic lesions.

Evidence indicates that LRG is involved in modifying the transforming growth factor-β (TGF-β) pathway. LRG expression may increase the sensitivity of hepatoma cells.[23] Furthermore, LRG1 binds to endoglin, an accessory receptor of TGF-β, and leads to upregulation of Smad1/5/8 in the pro-angiogenic pathway of the endothelial cells.[24] Several studies have reported that TGF-β plays

significant roles in the development of endometriotic lesions. TGF-β is increased in the peritoneal fluid of women with endometriosis.[25] A mouse model established by allogeneic transplantation into Tgfb1-null mice demonstrated that the number and size of endometriotic lesions decreased compared to those in wild-type recipients.[26] A detailed review regarding TGF-β in the pathophysiology of endometriosis referred to decreased immune cells and increase cell growth and neoangiogenesis in endometriotic lesions.[25]

One of the limitations of our study was that we did not include women with minimal endometriosis without endometriomas. This means that the women recruited mostly corresponded to the moderate-to-severe stage of the rASRM scoring system. The variation in rASRM scores among these cases may be more dependent on the severity of adhesions than on the endometriotic lesions. This could explain why we did not find a significant correlation between the rASRM scores and serum LRG concentrations. Currently, guidelines for endometriosis recommend hormonal treatment for clinically diagnosed endometriosis, indicating that laparoscopic confirmation of endometriotic lesions is not required. Under these circumstances, biomarkers with higher sensitivity could help distinguish endometriosis from nonstructural causes of dysmenorrhea. Another limitation was that the clinical data could not specify the sources of serum LRG. However, LRG has also been reported to be a diagnostic and/or severity marker of other inflammatory diseases.[27,28]

In conclusion, elevated serum LRG levels can be used as a biomarker of endometriosis and its responsiveness to surgery and hormonal treatments. Further studies, including local and systemic functions of LRG in association with the pathophysiology of endometriosis, would help to understand the significance of LRG as a diagnostic marker and possible target molecule for endometriosis.

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CONFLICT OF INTEREST STATEMENT

Secondary samples from a researcher-initiated clinical trial were used in this study. S.O. and A.I. have no financial conflicts of interest. A.I. is an Editorial Board member of Reproductive Medicine and Biology and a coauthor of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.

ETHICS STATEMENT

This study was approved by the ethics committees of Gunma University and Nagoya University.

HUMAN RIGHTS STATEMENT AND INFORMED CONSENT

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), the Helsinki Declaration of 1964, and its later amendments. Informed consent was obtained from all patients for inclusion in the study.

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