

Evaluation the Progesterone and Estrogen Receptor (PR & ESR) Level and Their Role in Medical Treatment of Patients with Endometriosis

Tahereh Poordast

Shiraz University of Medical Sciences

Saeed Alborzi

Shiraz University of Medical Sciences

Ziba Kiani

Shiraz University of Medical Sciences

Elham Askary

Shiraz University of Medical Sciences

Kefayat Chamanara

Shiraz University of Medical Sciences

Navid Omidfar (✉ omidfar@gmail.com)

Shiraz University of Medical Sciences

Mansoureh Shokripour

Shiraz University of Medical Sciences

Alimohammad Keshavarz Hesam Abadi

Shiraz University of Medical Sciences

Research

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Abstract

Background

As the endometriosis is a hormone dependent disease, this study designed to determine a cut-off point for selecting the appropriate treatment based on the hormone receptors of endometriosis lesions.

Methods

In this retrospective cohort study, all symptomatic endometriotic patients, between March 2017 to March 2019, was divided into two groups: responding and non-responding to hormone therapy following endometriosis surgery. Pathological slides of 72 patients were immunohistologically evaluated for progesterone (PR) and estrogen receptor (ESR) levels.

Results

Based on the rock curve, the presence of 70% of estrogen (P value: 0.001) and 80% of progesterone receptors (P value = 0.005), as well as 60% estrogen (P value: 0.1065) and 40% of progesterone receptors (P value: 0.1699) in the pathology sample based on H score can predict the appropriate response to hormonal treatment of dyspareunia and dysmenorrhea respectively. Dysmenorrhea in the presence of endometrioma showed the best response to OCP compared to the progesterone treatment (69.4% versus 27.8%), while the response of dyspareunia in the presence of the DIE lesions showed the best response to progesterone treatment (75% versus 27.8%).

Conclusion

Response to treatment of dysmenorrhea and dyspareunia is directly related to the increase of H score. Gynecologist can make the right hormonal treatment based on the specific pattern of IHC staining obtained from patients 'surgical specimens, which leads to improved quality of life and also effective pain reduction after operation as well as recurrent rate.

Background

Endometriosis is a complex disease that is commonly seen in women of reproductive age and is defined as the presence of endometrial glands and stroma outside the uterine cavity [1]. It is characterized by the presence of dyspareunia, dysmenorrhea and infertility in about 10% of women of reproductive age [2].

The goal of treatment for this disease is to reduce inflammation and disease activity and thus reducing the pain. For this purpose, several treatments have been suggested, including hormonal and non-hormonal therapies (GnRH, OCP, Progestin, NSAIDs, and etc.) [3].

The pathophysiology of endometriosis is not fully understood, but estrogen dependence and progesterone resistance have been shown to cause and maintain the endometriotic lesions [4]. In the endometrial implants, estradiol typically stimulates cell proliferation and progesterone stimulates cell differentiation. The function of ovarian hormones is mediated by estrogen (α and β) or (1 and 2) and progesterone receptors (A and B). Previous studies have shown that in endometriosis lesions, overexpression of hormone receptors including high ER2 / ER1 ratio and, also decreased PR expression plays a role. This receptor-mediated signal disorder affects cellular behavior and causes different responses to hormonal therapies [5].

One of the most common hormonal treatments for endometriosis is the use of progesterone or compounds containing it. Progesterone (preg-4-ene-3, 20-dione) is a natural cholesterol catabolite of cyclopentanephthofentanthrene (cyclopentanoperhydrophenanthrene) that is naturally produced in the corpus luteum [6]. Progesterone works by regulating endometrial decidualization and inhibiting estrogen derived endometrial proliferation [6, 7]. However, in some patients it has been observed that despite the similarity of serum progesterone levels in healthy and endometriotic women, endometriosis lesions do not respond adequately to the progesterone [8]. It seems Progesterone receptor (PR) expression changes in endometriosis lesions [9–11].

Although available sources strongly support the benefits of long-term use of hormone therapy after surgery to prevent recurrence and disease-related symptoms, especially dysmenorrhea, lack of improvement in some patients may suggest an inappropriate response to the routine hormonal therapies in these cases. This is especially true for those who relapse despite receiving the hormone therapy after surgery [6, 10, 12, 13].

In addition, the production of estradiol (intracrine and paracrine) in endometriotic lesions increases the concentration of steroid hormones and enhances the estrogenic effect. Endometriotic lesions exert a lower level of estradiol inactivation compared to eutopic endometrium, which may further enhance local effect. Few studies have investigated the role of progesterone receptor in patients with endometriosis and its effect on treatment failure and recurrence of disease in some of these patients [6, 13–15], however they focused on dysmenorrhea and endometrioma recurrence rather than dyspareunia and DIE lesions [15].

Therefore, the aim of this study was to measure the levels of progesterone (PR) and estrogen receptors (ESR) in endometriosis lesions and determine a cut-off for selecting the appropriate treatment based on the hormone receptors of these lesions to help improve the quality of life of patients with endometriosis better than before.

Methods

This study was designed as a retrospective cohort study. We enrolled all symptomatic patients aged 20 to 45 years in whom endometriosis was confirmed by physical examination, history taking, and imaging techniques who were referred to two referral governmental hospitals between March 2017 to March 2019.

The approval of the local ethics committee was obtained (Code: IR.SUMS.REC.1398.1395), and all the patients gave informed consent to the protocol.

The inclusion criteria were as follows: women with a definitive diagnosis of endometriosis based on pathology report, complete demographic and follow-up information even with a phone call, those whose VAS score in any of pain symptoms of endometriosis (dysmenorrhea or dyspareunia) was moderate to severe before surgery [16], with data about pain response to progesterone-based therapies after surgical treatment, unwillingness to conceive until at least two years after surgery, tendency to continue treatment, even though they knew they would not have a routine and monthly menstruation period and those who have had regular follow-ups after surgery.

Exclusion criteria were as follows: incomplete demographic and follow-up information, those with diseases such as GI or urinary tract diseases, as well as those with PID disease, taking hormonal or infertility drugs up to six months before surgery and having previous endometriosis surgery, FSH>10 before operation, or age >45 at the time of operation, those who stopped taking the drug after the operation for any reason or used it irregularly and existence of concomitant malignancy and unavailability of pathology slides.

Patients' records were used to collect data. Demographic information including patients' age, BMI, pain symptoms, the stage of endometriosis disease according to ASRM (American society for reproductive medicine) classification, affected area, type of hormone therapy, duration of treatment and response to treatment were recorded in a checklist.

During operation after all adhesions were lysed and excised by sharp dissection to fully mobilize the ovaries and ovarian cystectomy, all areas of superficial active endometriosis involving the other ovary or the pelvic peritoneum were fulgurated. Deep infiltrative endometriosis lesions located in the utero-sacral, retrocervical, rectovaginal area, Douglas pouch, rectum and bladder were separated and resected from the surrounding normal tissue with preserving important structures such as ureter, uterine vessels and pelvic nerves.

Patients were aware of the two methods of treatments before their operation, and they had been informed that none has been proven to be superior yet. All of them were on stage three or four of diseases according to the ASRM classification.

Medical treatment was started on the day of discharge for patients based on the patient's preference, which included 30 mg daily medroxyprogesterone or contraceptive pills with 0.03 mg ethinyl estradiol and 15 ug desogestrel. All patients were followed for at least 12 months after surgery (8 to 25 months).

The sample size was determined by NCSS software, 80% power and the first type error of 5% and using similar articles (sensitivity = 93%).

After patients selection based on inclusion and exclusion criteria and extracting the required data from patients' records, Pathological slides were examined and stained immunohistochemically for PR and

ESR.

First, the samples in paraffin was cut to a size of 5 micrometers and placed on a slide [17, 18]. The slides are deparaffined and hydrated by a series of washes with xylene and ethanol. After rinsing in distilled water for 5 minutes, the slides are immersed in 0.01M sodium citrate buffer for 15 minutes and then cooled for 45 minutes.

Then the slides are rinsed in PBS 1% (Tween 20) PBST for 5 minutes and cut with a hydrophobic pen. Endogenous peroxidase is quenched for 5 minutes with 3% hydrogen peroxide and then rinsed with PBST for 5 minutes. Non-specific binding with 5% natural goat serum in PBST is blocked for 1 hour at room temperature.

The primary used antibodies (PR H-190) (sc _7208; 1: 800) were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). The slides were incubated with the initial antibody at 4 ° C overnight. Normal goat IgG (Biotechnology Santa Cruz) was used as a negative control.

Natural endometrium on day 14 was also considered as a positive control. Goat antirabbit biotinylated secondary antibody was used for PR (Vector Laboratories, Burlingame, CA) and for 1 hour at room temperature.

Slides were washed in 1% PBS and incubated at ABC Elite (Vector Laboratories) for 30 minutes at room temperature and then washed again in 1% PBS and incubated with diaminobenzidine (Vector Laboratories) for 41 seconds.

Then exposed to hematoxylin as a counterstain for 30 seconds. Finally, the slides were rinsed with ethanol and xylene for 5 minutes and washed and mounted by Permount (Thermo Fisher Scientific, Waltham, MA) [6, 19, 20].

H score for immunohistochemical staining was determined based on the percentage of receptor staining for each slide. Each slide was scored separately by two pathologists unaware of the subject, and H scores were averaged. The H score was calculated using the modified H score, which is expressed as: negative (score 0), weak positive (score 1), positive (score 2) and strongly positive (score 3) [7, 19].

Finally, the collected data were entered in SPSS software version 20. For the final analysis, patients were divided into two groups based on response to treatment and the data of the two groups were compared. Qualitative data were compared between the two groups using chi-square test and if necessary with Fisher's exact test, and quantitative data were compared using t-test. Kramer-Phi and Spearman tests were used to examine the correlation. P value less than 0.05 was considered statistically significant.

Results

96 patients who met the inclusion criteria were included in this study and the medical records of these patients were analyzed to evaluate their response to medical treatment. But in only 72 patients, tissue

samples were sufficient for pathological examination

Demographic characteristics based on the improvement of dysmenorrhea or dyspareunia were the same for the respondent and non-respondent groups and were not statistically significant (Table 1). Mean age of patients was 34.71 ± 6.01 and the mean BMI was 24.04 ± 4.16 .

Table 1
Demographic characteristics and clinical data of patients with endometriosis

Variable		Recovery based on dysmenorrhea(N)		P value	Recovery based on dyspareunia(N)		P value
		Yes	No		Yes	No	
Economic situation	Poor	32	8	0.472	30	5	0.694
	Normal	27	7		24	3	
	Rich	6	0		4	0	
Infertility	Yes	8	2	1.000	7	2	0.607
	No	62	14		53	8	
Menstrual cycle	Regular	58	11	1.000	49	5	0.131
	Irregular	19	4		16	5	
Type of treatment	GNRH-a	1	0	0.895	1	0	0.588
	OCP	41	8		29	6	
	Progesterone	38	8		37	4	

N: number of patients. GNRH-a: gonadotropine releasing hormone agonist

Based on ROC chart analysis with two threshold strategy, all patients were classified into 3 groups based on estrogen and progesterone receptor density: High (H-score ≥ 80), medium (H-score 6 to 80) and low (H-score ≤ 5) and also for the estrogen receptor density: High (H-score ≥ 70), medium (H-score 6 to 70) and low (H-score ≤ 5) (Tables 2).

H-score ≤ 5 was selected due to high sensitivity (100%) and H-score ≥ 80 for the PR and ≥ 70 for the ERS were selected due to high specificity (100%).

Response to treatment of dysmenorrhea and dyspareunia was directly related to the increase of H score, which is shown in Table 2. Due to the very small sample size in the group with a low H score, we cannot trust the results obtained in this group.

Table 2
Prediction of Response based on dysmenorrhea and dyspareunia using PR and ESR Status

		Recovery based on dysmenorrhea (N)			Recovery based on dyspareunia (N)		
		Yes	No	Response rate%	Yes	No	Response rate%
PR	High	36	8	81.8	29	2	93.5
H-SCORE	Medium	33	5	86.8	28	5	84.8
	Low	3	0		3	0	
ER	High	40	8	83.3	36	2	94.7
H-SCORE	Medium	32	5	86.5	24	5	82.8
	Low	1	0		1	0	

The ROC curve (Figure 1) for predicting the dysmenorrhea response is based on the H score, which shows the area below the curve 0.677 for ESR (95% CI: 0.559 to 0.780). This predicts the good response of dysmenorrhea to treatment with a sensitivity of 77.27 and a specificity of 55.56 in the presence of 60% estrogen receptor in the tissue sample (P value: 0.1065).

And for PR, the area below the curve shows 0.642 (95% CI: 0.523 to 0.750). This predicts the response to treatment of dysmenorrhea with a sensitivity of 95.45 and a specificity of 33.33 in the presence of 40% of progesterone receptors in the tissue sample (P value: 0.1699).

The ROC curve for predicting the dyspareunia response is based on the H score for the ESR, which shows the area below the curve 0.743 (95% CI: 0.620 to 0.842).

This predicts the response of dyspareunia to treatment with a sensitivity of 60.66 and a specificity of 100 in the presence of 70% estrogen receptor in the tissue sample (P value: 0.001).

And for PR shows the area under curve 0.742 (95% CI: 0.619 to 0.842).

This predicts the response of dyspareunia to treatment with a sensitivity of 41.67 and a specificity of 100 in the presence of 80% of progesterone receptors in the tissue sample (P value = 0.005).

According to Table 3, the improvement of dysmenorrhea and dyspareunia in tubular lesions did not depend on the type of treatment, and all tubular lesions responded to OCP and progesterone similarly.

Table 3
Endometriosis pain relief based on the location and type of treatment

		OCP	Progesterone
Recovery of dysmenorrhea	OMA	69.4%	27.8%
	DIE	28.6%	71.4%
	Tube	50%	50%
Recovery of dyspareunia	OMA	55.4%	41.2%
	DIE	25%	75%
	Tube	50%	50%

In the case of endometrioma, dysmenorrhea respond better to the OCP, but about dyspareunia significant difference between OCP and progesterone in relieving pain does not exist.

In the case of DIE lesions, the response of dysmenorrhea and dyspareunia to progesterone treatment was, obviously better than OCP.

According to Table 4, In the case of OMA, DIE and tubal lesions dysmenorrhea will respond better to treatment if estrogen and progesterone receptor levels are higher than cutoff point.

The percentage of patient with estrogen receptor over than cut off point in OMA and Tubal lesion is higher than DIE lesions, and the percentage of patient with progesterone receptor over than cut off point in DIE is higher than OMA and Tubal lesions, although this difference is not statistically significant.

Table 4
Percentage of patients recovering from pain based on lesion location and hormone receptor

Receptor	Improvement of dysmenorrhea				Improvement of dyspareunia			
	ESR		PR		ESR		PR	
Receptor cut of	>60	<60	>40	<40	>70	<70	>80	<80
Percentage of patients in each group								
OMA	75.6	24.4	90.2	9.8	70.7	29.3	43.9	56.1
DIE	67.7	32.3	86.7	13.3	61.3	38.7	60	40
Tube	78.6	21.4	78.6	21.4	78.6	21.4	57.1	42.9

Discussion

In this study, we showed that the levels of progesterone and estrogen receptors in endometriosis lesions could strongly predict the response of these patients to drug therapy (including OCP and progesterone). Our results showed that the response to treatment of dysmenorrhea and dyspareunia is directly related to the increase of H score, which is shown in Table 2.

Based on previous studies in this field as well as studies on breast lesions, we decided to perform an innovation and set a threshold for the amount of estrogen and progesterone receptors in endometriosis lesions. Therefore, we set a cut-off point to predict the response to treatment of these lesions with the following goals: to improve the quality of life in these patients and define the reduction of the financial burden of this disease on society due to the long-term need for treatment and follow-up in these patients. So for predicting the appropriate response of dyspareunia to treatment based on the Roc curve (P value <0.05) we set a 70% threshold for tissue estrogen and a 80% for progesterone receptors and 60% threshold for tissue estrogen and a 40% for progesterone receptors (P value>0.05) to predict the appropriate response of dysmenorrhea to treatment .

Few studies have examined the status of PR and ESR and its role in predicting response to treatment in patients with endometriosis [12, 21, 22]. Similar to us, in a study conducted by Flores et al in 2018, they examined the status of the progesterone receptor and its role in predicting the response of endometriosis lesions to progesterone treatment. Histopathologic (H) score was used to determine the qualitative status of PR. H score was higher in respondents than non-respondents patients. Treatment response status was strongly associated with progesterone receptor status. They concluded depending on the number of receptors in endometriosis, different hormone-based therapies can be used after surgery. So determining the amount of progesterone receptor may be very helpful in determining a new goal-based approach to the treatment of endometriosis lesions [12].

In 2017, Hou et al. examined the role of predictive biomarkers in the accurate treatment of endometriosis. They investigated the effect of bazedoxifene (BZA) and medroxy progesterone acetate (MPA) on the expression of progesterone receptor (PR), estrogen receptor (ER) and aromatase enzyme (CYP19A1) genes in cell culture media obtained from patient biopsy with endometriosis. They concluded that the degree of PR expression may predict progesterone resistance as well as response to treatment of endometriosis lesions [23].

It remains to be seen whether the heterogeneity observed in the expression of hormone receptors in different types of tissues can explain the difference in patients' response to hormone therapy?

In our study, in the case of OMA, DIE and tubal lesions dysmenorrhea and specially dyspareunia will respond better to treatment if estrogen and progesterone receptor levels are higher than cutoff point. As we showed in Table 4 the percentage of patient with estrogen receptor over than cut off point in OMA and Tubal lesions is higher than DIE, and the percentage of patient with progesterone receptor over than cut off point in DIE is higher than OMA and Tubal lesions, although this difference is not statistically significant. Due to the higher number of progesterone receptors in the tubal and DIE lesions compared to OMA, the better response of dyspareunia in these lesions to progesterone treatment can be justified. Our

data also confirm previous findings that showed variable levels of progesterone receptors in various endometriosis lesions, so it is best to treat all endometriosis lesions based on the expression of their hormone receptors [24].

Similar to us Colón-Caraballo et al in 2018 conducted a study aimed at expressing the concentrations of the steroid receptor hormones in different types of endometriotic lesions and also eutopic endometrium. This comparison was performed between endometriosis and normal women (control group) using tissue microarray method (TMA). They showed that ovarian lesions showed the lowest expression of ESR1 (alpha estrogen) and PGR (progesterone) and the highest expression of ESR2 (beta estrogen), while the fallopian tube lesions had the highest expression of all 3 receptors. The highest ESR2: ESR1 ratio was observed in ovarian and endometrial secretory lesions [25]. Other studies in this area also show overexpression of ESR2 / ESR1 in endometriosis tissues, which lead to increase proliferation in lesions and also induced progesterone resistance [13, 26, 27]. There is a clear association between ESR, and PR expression and its secretion cycle with the development and progression of endometriosis. Increased expression of B estrogen receptor leads to more local production of estrogen as well as suppression of progesterone receptors in endometriosis tissue. In addition, there is a lack of progesterone receptors in these tissues, which leads to progesterone resistance, which is commonly reported as estrogen-dependent and progesterone-resistant in the endometriosis tissue [28]. Thus, the IHC expression characteristics of nuclear isoforms of ESR and PR in target tissue sampled during surgery can predict the response to commonly prescribed drugs.

Given that the overexpression of ESR2 / ESR1 in hormone-dependent malignancies such as breast and prostate cancer, and also endometrial cancers, is associated with the high grade tumoral process and predicts clinical outcome including overall survival rate of patients, we can use the results of this study for the same purposes in patients with endometriosis [19, 29].

According to Table 3, the improvement of dysmenorrhea and dyspareunia in tubular lesions did not depend on the type of treatment, and all tubular lesions responded to OCP and progesterone similarly. Here Sampson's hypothesis is strengthened that removing the tubes and clearing the pelvis of endometriosis lesions eliminates the pathophysiology of the disease [2]. But in the case of endometrioma, dysmenorrhea may respond better to treatment with the OCP, however in dyspareunia doesn't exist significant difference between OCP and progesterone in relieving pain .In the case of DIE lesions, the response of dysmenorrhea and dyspareunia to progesterone treatment was better than OCP.

So, we found that there was a difference in progesterone receptor levels between patients and even in an individual, based on the type of endometriotic lesions. This issue can predict the response of treatment in endometriotic patients and help to choose a better treatment for each patient and may prevent recurrence of the disease after surgery.

Significant improvement of dyspareunia compared to dysmenorrhea in our study supports the results that extra pelvic endometriosis lesions have higher levels of PR than ovarian endometrioma lesions [30].

The results show that a gynecologist can make the right hormonal treatment (such as OCP and Progesterone) based on the specific pattern of IHC staining obtained from patients' surgical specimens, which leads to improved quality of life and also effective pain reduction after operation in these patients. Thus, recurrence of the disease in the reproductive ages can be prevented by prescribing appropriate treatment.

The limitation of our study is the lack of estrogen subtype determination, because by comparing the difference in ESR2 / 1 ratio in endometrioma and other DIEs lesions.

Abbreviations

PR

Progesterone

ESR

Estrogen receptors

ASRM

American society for reproductive medicine

GNRH-a

Gonadotropine releasing hormone agonist

BZA

Bazedoxifene

MPA

Medroxy progesterone acetate

TMA

Tissue microarray method

Declarations

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Authors' contributions

TP: Conception, design of study and data revising; SA: design of study & final approach; ZK: Patient recruitment & data collection; EA: Data interpretation & manuscript preparation; KC: Patient recruitment, drafting & design; NO: Conception, design of study and data revising; MS: Patient recruitment, drafting & design; AKHA: Data analysis and interpretation; All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate: The approval of the local ethics committee was obtained (Code: IR.SUMS.REC.1398.1395), and all the patients gave informed consent to the protocol. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments.

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

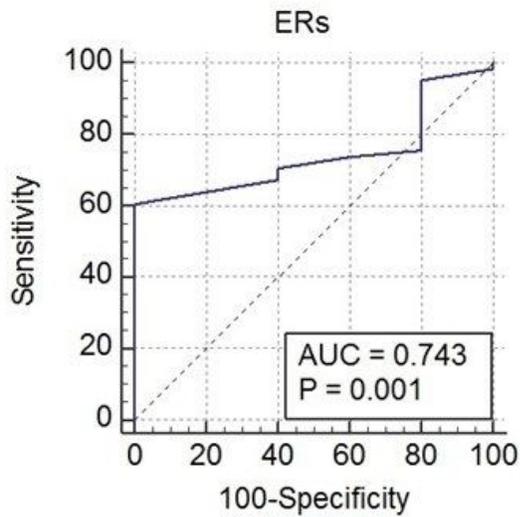
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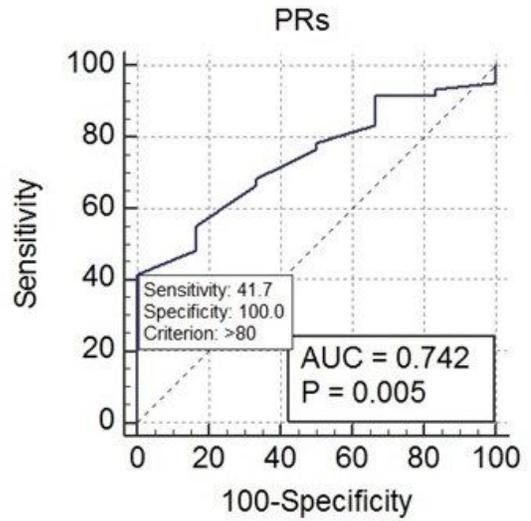
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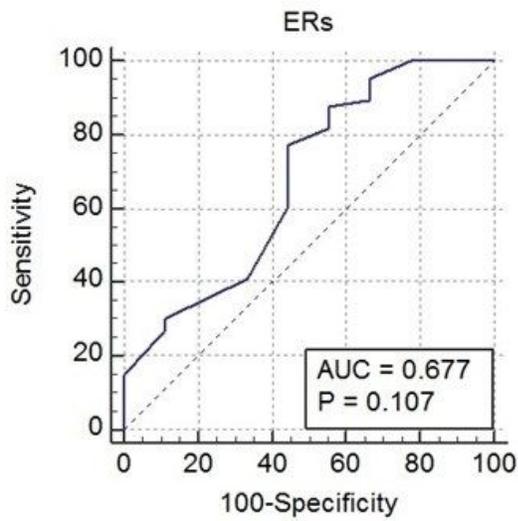
Figures



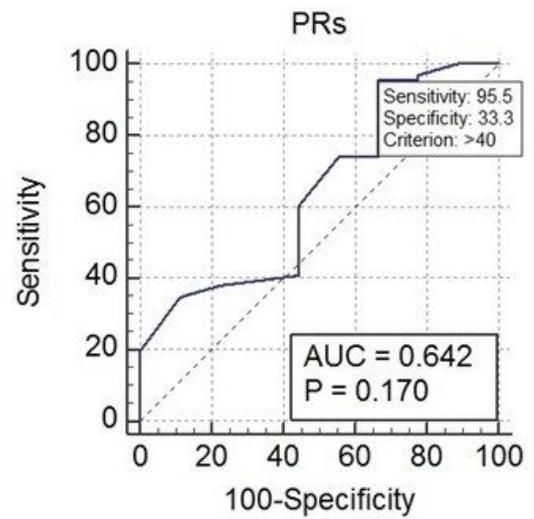
A



B



C



D

Figure 1

ROC curve for predicting the dysmenorrhea (A, B) and dyspareunia (C, D) response to treatment based on H score of PR and ESR.