

Combination of noninvasive methods in diagnosis of infertile women with minimal or mild endometriosis, a retrospective study in China

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Abstract

This study means to investigate a combination of noninvasive methods in diagnosis of minimal or mild endometriosis expecting to narrow down the range of laparoscopic exploration for female infertility.

It is a retrospective case control study of totally 447 patients suspected unexplained infertility before surgery were eligible from May 2012 to February 2017. Of these, 299 patients were laparoscopy-proved minimal or mild endometriosis group, the remaining 148 patients served as control group (normal pelvis). Preoperative age, duration of infertility, type of infertility, body mass index, baseline follicle-stimulating hormone, anti-Müllerian hormone, serum CA₁₂₅, clinical symptoms, findings on vagino-recto-abdominal examinations and pregnancy prognosis had been recorded. Every variable and their combinations were evaluated.

Any single factor had limited diagnostic value. The cut-off value for CA₁₂₅ was 19.25 IU/L. Parallel testing had a higher sensitivity at 81.3%. Serial tests of vagino-recto-abdominal examination combined with dysmenorrhea or positive CA₁₂₅ got reasonable sensitivity (51.4% and 49%), remarkable high specificities (95.7% and 100%) and Positive Predictive Value (96.4% and 100%). Multivariate logistic regression identified the following factors in decreasing order of importance: (1) vagino-recto-abdominal examinations, (2) CA₁₂₅, (3) dysmenorrhea, their ORs being 16.148, 3.796, and 2.809, respectively. The spontaneous pregnancy rate (50.8%) in minimal or mild endometriosis was higher than control (35.6%, $P = .043$).

A combination of noninvasive diagnostic methods had certain preoperative diagnostic value of minimal or mild endometriosis, which might benefit some patients from avoiding laparoscopic surgery.

Abbreviations: 95%CI = 95% confidence interval, AMH = anti-Müllerian hormone, ART = assisted reproductive technology, BMI = body mass index, CA₁₂₅ = carbohydrate antigen 125, FSH = follicle-stimulating hormone, NPV = negative predictive value, OR = odds ratio, PPV = positive predictive value, rAFS = the revised American Fertility Society.

Keywords: diagnosis, endometriosis, infertility, laparoscopy, noninvasive methods

1. Introduction

Endometriosis, a common gynecological disorder in which the endometrial-like glands and stroma grows outside the uterus,^[1]

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most commonly in the pelvis,^[2] is associated with pelvic pain, subfertility, dysmenorrhea and dyspareunia.^[3,4] It has been reported that the monthly fecundity rate is lower in women with minor endometriosis than in those with unexplained infertility.^[5] On other hand, the infertile women have been proved wide range (14–67%) of endometriosis by laparoscopy.^[6,7]

The optimal means of accurately diagnosing endometriosis in a timely manner is controversial. Diagnosis of endometriosis is usually delayed by an average of 8 to 11 years, which has significant consequences in terms of disease progression.^[8] Endometriosis can be classified into different phenotypes including ovarian endometriosis, peritoneal endometriosis, deep endometriosis and other types. It has been established that ultrasound and pelvic examination can quite accurately discriminate ovarian endometriosis from other ovarian cysts.^[9,10] They are also highly sensitive and specific for diagnosis of deep endometriosis.^[11] However, these noninvasive methods have limited capacity to diagnose superficial peritoneal disease and endometriosis-associated adhesions, mostly classified as minimal or mild endometriosis, namely the revised American Fertility Society (rAFS) classification system stages I and II; these patients are often classified as having unexplained infertility prior to surgery.

The current gold standard procedure for diagnosing endometriosis is laparoscopy.^[12,13] Laparoscopic surgery could give consideration to both diagnosis and treatment. The surgical destruction of minimal to mild endometriosis and associated adhesions was indeed demonstrated to enhance fecundity

comparing with diagnostic laparoscopy alone.^[14] It was reported that the fertility rate was significantly improved after the removal of minimal and mild endometriosis (4.7 per 100 person-months in the group with laparoscopic treatment group and 2.4 per 100 person-months in the diagnostic laparoscopy group).^[15] A study in 2014 concluded that women who had undergone complete removal of endometriotic lesions (n=399) subsequently had a higher implantation rate (30.9% versus 23.9%, $P=.02$), pregnancy rate (40.1% vs 29.4%, $P=.004$), and live-birth rate per ovum retrieval cycle (27.7% vs 20.6%, $P=.04$) than women who underwent diagnostic laparoscopy only (n=262).^[16] While, the disadvantages of IVF cannot be ignored, including the great expense (especially if more than one cycle is required), the inconvenience for frequent injections and monitoring for several weeks and the risks of multiple pregnancy and ovarian hyper-stimulating syndrome.^[17] But non-selective laparoscopy is also waste of medical resource as one-half to two-third of negative finding, let alone the complication of operation.^[18]

In the present study, we aimed to

- (1) evaluate the diagnostic value of a combination of noninvasive methods including evaluation of clinical symptoms, vagino-recto-abdominal examination and serum CA₁₂₅ (carbohydrate antigen 125) concentration for minimal and mild endometriosis so that can narrow down the population who need laparoscopic exploration and
- (2) verify the pregnancy prognosis after therapeutic laparoscopy.

2. Materials and methods

This is a retrospective case control study of patients who attended the Reproductive Center of the Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University between May 2012 and February 2017. This study was approved by the Reproductive Medical Ethics Committee of Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University, Hangzhou, China.

2.1. Patients

During the study period, 447 women were enrolled in this study. The flow chart was shown in Figure 1. They were selected from women who had undergone laparoscopy for evaluation of suspected unexplained infertility before surgery in our Laparoscopy Unit.

Women who had undergone laparoscopy for evaluation of infertility were divided into 2 groups according to their laparoscopic findings:

- (1) mild or minimal endometriosis group, endometriosis stage I or II according to the rAFS classification system;^[14] and
- (2) control group, normal pelvis. The revised inclusion and exclusion criteria are as follow:

Inclusion criteria were: suspected unexplained infertility prior to surgery, no pregnancy after more than 1 year without contraception, reproductive age between 20 and 40 years, regular menstrual cycles and partner with normal semen test.

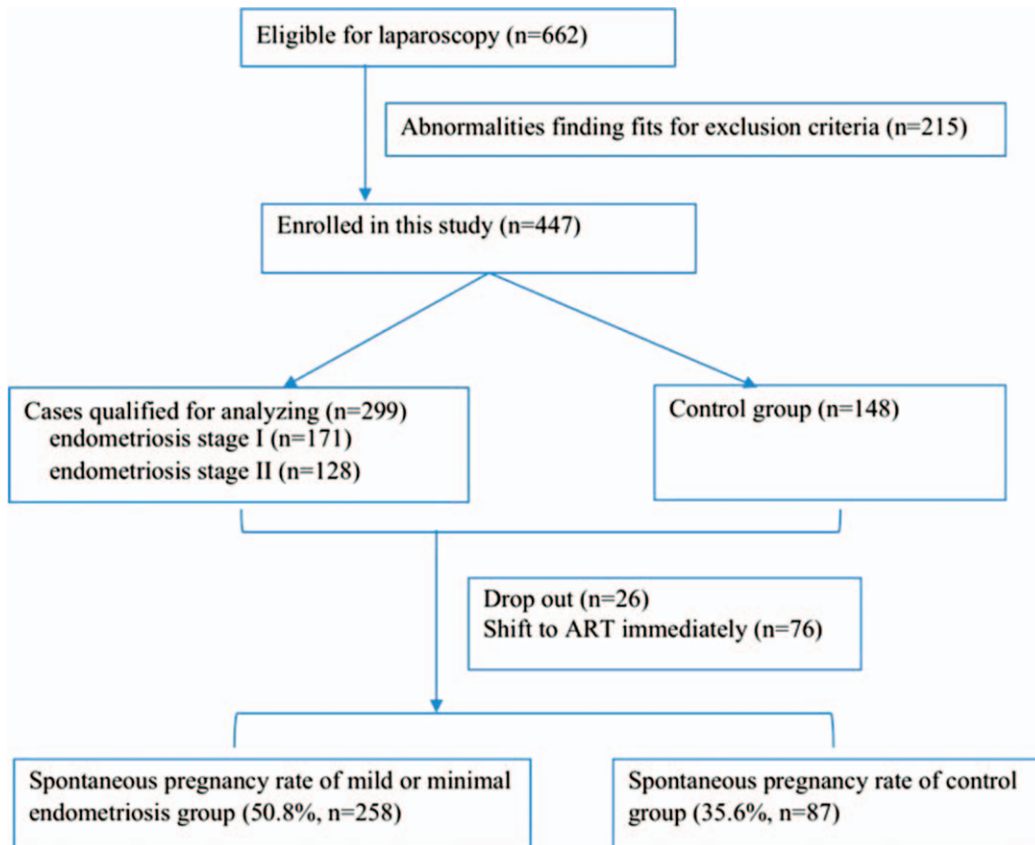


Figure 1. Flow chart.

Exclusion criteria were: finding tubal abnormality and inflammation related pelvic adhesion, acute abdomen, malignant tumor, uterine leiomyoma, adenomyosis, uterine malformation, rAFS endometriosis stage III or IV according to the America Fertility Society classification and other benign ovarian tumors during laparoscopy examination, and previous surgical treatment or medications for endometriosis.

2.2. Data collection and analysis

Data collected included age, duration of infertility, type of infertility, body mass index (BMI), baseline follicle-stimulating hormone (FSH) (day 3–5 of menstrual cycle), anti-Müllerian hormone (AMH), dysmenorrhea, other related symptoms (anal bulge and other intestinal symptoms, and/or dyspareunia, and/or chronic pelvic pain), positive signs on vagino-recto-abdominal examinations (tender posterior fornix nodules/pains, and/or tender uterosacral ligament nodules/pains) and pregnancy outcomes after surgery.

Vagino-recto-abdominal examinations were all performed by the same experienced chief Gynecologist within three days prior to surgery to ensure the examination was accurate. Serum CA₁₂₅ concentrations were measured during the mid-follicular phase within 30 days before surgery. FSH was measured within days 3 to 5 of the menstrual cycle before surgery.

2.3. Operative procedure

The whole abdomen was explored, including the pelvic peritoneum, reproductive organs, colonic space, sub septum, and hepatic and splenic surfaces. Minimal or mild endometriosis was diagnosed when typical red, blue, and/or brown endometriotic lesions were identified on the pelvic peritoneum and/or organ surfaces. Eradication by excision or ablation of all endometriotic lesions, relaxing of adhesions and restoration of normal anatomy were performed wherever possible, after which the laparoscopic diagnosis of endometriosis was confirmed by histopathological examination of the operative specimens. The pelvis was irrigated with 1000 mL normal saline before closure.

2.4. Pregnancy prognosis

Patients were followed up until March 2018. Only spontaneous pregnancies were analyzed. Cases were censored when the patient

failed to follow up or underwent any assisted reproductive technology (ART).

2.5. Statistical analysis

Data were analyzed using SPSS 21.0 software. ROC curves were used to calculate the cut-off point for serum CA₁₂₅ in diagnosis of infertile women with minimal or mild endometriosis. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each method was calculated. Variables were compared between groups by the χ^2 test. Logistic regression analysis was used to analyze combinations of various methods. The *P* value of <.05 was considered significant.

3. Results

Of the 447 women undergoing laparoscopy for investigation of suspected unexplained infertility, 299 patients had confirmed minimal or mild endometriosis finally, including endometriosis stage I (n=171) or II (n=128) according to the revised American Fertility Society classification system and the averages of the scoring were 2.62 ± 1.24 and 10.00 ± 3.13 , respectively. The other 148 was as control group (normal pelvis). No major complications of laparoscopy were recorded.

3.1. Preoperative patient characteristics

No differences were identified between the groups in mean age, duration of infertility, BMI, baseline FSH and AMH (all *P* > .05). Whereas, there showed significant differences in type of infertility, vagino-recto-abdominal examination, dysmenorrhea, other related symptoms and serum CA₁₂₅ concentration (all *P* < .05, in Table 1).

3.2. ROC curve for serum CA₁₂₅ and minimal or mild endometriosis

Table 1 showed that the average CA₁₂₅ of minimal or mild endometriosis group with infertility was 25.19 ± 14.94 IU/L, and the control group was 14.12 ± 7.93 IU/L, which were both lower than that of the traditional cut-off value of CA₁₂₅ (35 IU/L). Therefore, it could be better to find out a more appropriate cut-off value.

Table 1

Selected factors according to study group.

Characteristic	Endometriosis group (n=299)	Control group (n=148)	<i>P</i>
Age (yr)	30.84 ± 4.02	31.16 ± 4.11	.444
BMI (kg/m ²)	21.01 ± 2.52	21.21 ± 3.03	.739
Type of infertility (n)			.033
Primary	191	79	
Secondary	108	69	
Length of infertility (yr)	2.87 ± 2.06	2.80 ± 2.23	.746
Basic FSH (IU/L)	6.35 ± 2.12	6.84 ± 1.73	.271
AMH (ng/L)	3.39 ± 2.24	4.01 ± 2.08	.344
dysmenorrhea (n)	179	38	.000
Other related symptoms (n)	39	6	.002
vagino-recto-abdominal examination (n)	213	16	.000
CA ₁₂₅ (IU/L)	25.19 ± 14.94	14.12 ± 7.93	.000

AMH=anti-Müllerian hormone, BMI=body mass index, CA₁₂₅=carbohydrate antigen 125, FSH=follicle-stimulating hormone.

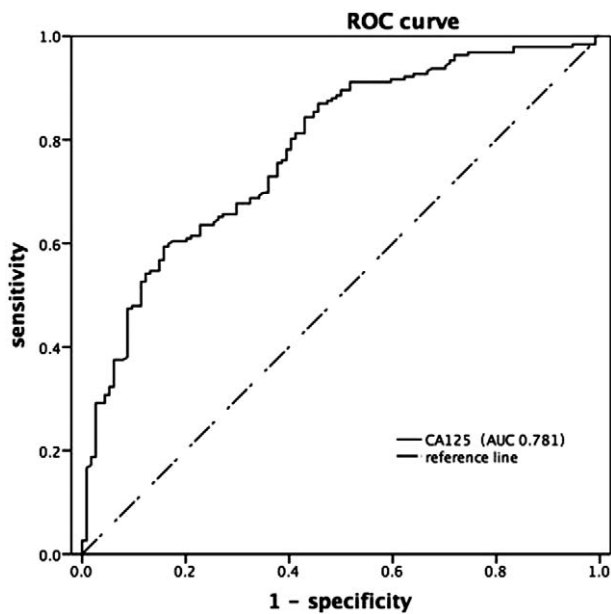


Figure 2. ROC curve of serum CA₁₂₅ in diagnosis of infertility with minimal or mild endometriosis.

The cut-off value for serum CA₁₂₅ determined by ROC curve for diagnosing infertility with minimal or mild endometriosis was 19.25 which were calculated according to the maximum Youden index, and the area under the curve was 0.781 (Fig. 2).

3.3. Diagnostic value of any single method

Any single method had limited diagnostic value, as summarized in Table 2. The sensitivities of dysmenorrhea, other related symptoms, vagino-recto-abdominal examination, and CA₁₂₅>

19.25IU/L for diagnosis of infertility with minimal or mild endometriosis were 59.9%, 13.0%, 71.2%, and 59.4%, respectively, all of which are insufficient, especially other related symptoms. However, their specificities were relatively better as follows: 74.3%, 95.9%, 89.2%, and 83.3%, respectively.

3.4. Diagnostic value of combinations of noninvasive methods

When parallel testing is used for diagnosis, it is positive if one of several indexes is diagnosed as positive. When serial testing is used for diagnosis, it is positive if all factors are positive. The sensitivity and specificity of combinations of diagnostic methods were assessed with the aim of identifying a combination that might be superior to any single variable.

- (1) Parallel testing had a high sensitivity of 81.3%, but an insufficient specificity of 58.8%.
- (2) Serial tests between two methods all presented high specificities (95.7–100%) and PPV (94.1–100%) values, but insufficient sensitivities of 9.7%-51%. The two combinations with a slightly higher sensitivity were vagino-recto-abdominal examination + dysmenorrhea and vagino-recto-abdominal examination + CA₁₂₅, as shown in Table 3.

3.5. Logistic regression analysis of various diagnostic methods

To further evaluate the ability of various methods to diagnose infertility with minimal or mild endometriosis, logistic regression analysis was carried out by using the groups as the dependent variable and the following factors, which were statistically significant according to univariate analysis, as independent variables: vagino-recto-abdominal examination, other related symptoms, type of infertility, dysmenorrhea, and serum CA₁₂₅

Table 2
Individual methods for diagnosing minimal or mild endometriosis before surgery.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P
Dysmenorrhea	59.9	74.3	82.5	47.8	.000
Other related symptoms*	13.0	95.9	86.7	35.3	.002
Vagino-recto-abdominal examination†	71.2	89.2	93.0	60.6	.000
CA ₁₂₅ >19.25‡	59.4	83.3	85.7	54.9	.000

NPV=negative predictive value, PPV=positive predictive value.
 *Symptoms, including anal bulge and other intestinal symptoms, and/or dyspareunia, and/or chronic pelvic pain.
 †Positive signs, including tender posterior fornix nodules/pains, and/or tender utero-sacral ligament nodules/pains.
 ‡CA₁₂₅ >19.25 indicates positive.

Table 3
Combined use of 2 methods for diagnosing minimal or mild endometriosis before surgery.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P
Vagino-recto-abdominal examination + Other related symptoms	10.6	98.9	95.7	33.3	.002
Vagino-recto-abdominal examination + dysmenorrhea	51.4	95.7	96.4	47.1	.000
Vagino-recto-abdominal examination + CA ₁₂₅ &	49.0	100	100	48.6	.000
Other related symptoms + dysmenorrhea	10.7	98.6	94.1	35.4	.000
Other related symptoms + CA ₁₂₅	9.9	99.1	95	39.5	.001
dysmenorrhea+CA ₁₂₅	37	97.4	95.9	47.8	.000

CA₁₂₅=carbohydrate antigen 125, NPV=negative predictive value, PPV=positive predictive value.
 &: CA₁₂₅ >19.25 indicates positive.

Table 4
Multivariate logistic regression analysis of methods used to diagnose infertility with minimal or mild endometriosis.

Factors	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
CA ₁₂₅ > 19.25	7.308 (4.13~12.929)	<.001	3.796 (1.633~8.826)	.002
Dysmenorrhea	4.318 (2.79~6.673)	<.001	2.809 (1.276~6.186)	.010
Pelvic examination	22.800 (11.0~47.015)	<.001	16.148 (1.547~39.833)	<.001
The related symptoms	3.550 (1.46~8.589)	.005	—	—
Type of infertility	0.647 (0.434~0.966)	.033	—	—

95%CI=95% confidence interval, OR=odds ratio.

concentration. Multivariate logistic regression identified the following variables in decreasing order of importance:

- (1) vagino-recto-abdominal examination,
- (2) CA₁₂₅,
- (3) dysmenorrhea, their ORs being 16.148, 3.796, and 2.809, respectively.

Other related symptoms and the type of infertility did not qualify for inclusion in the model. The result of logistic regression analysis is shown in Table 4.

3.6. Outcome of spontaneous pregnancies

Women unable to contact (n=26) or directly asked for ART postoperatively were excluded (n=76). Thus, 345 women were assessed for spontaneous pregnancy outcomes, including 258 in endometriosis group and 87 unexplained infertilities in control group.

The spontaneous pregnancy rate was 50.8% (131/258) in the endometriosis group, which appeared higher than in the unexplained infertility group (35.6%, 31/87) and the difference was statistically significant ($P=.043$).

4. Discussion

Most women with minimal or mild endometriosis have no specific symptoms, hence it is easy for it to escape diagnosis or be misdiagnosed.^[7] The current gold standard procedure for diagnosing endometriosis is laparoscopy,^[12,13] which also offers the option of simultaneous treatment of lesions and/or adhesions.^[19] The additional advantages of laparoscopic surgery by the public: treatment can be completed during the procedure, lower monetary and time cost, fewer adverse effects and complications, and mostly a single fetus.^[17] Unfortunately, being an invasive procedure, laparoscopy is associated with rare but significant potential risks.^[20] While it is not feasible for all infertile women to undergo laparoscopic diagnosis. A lack of proven noninvasive diagnostic methods has hindered the ability of clinicians to choose appropriate treatment, including surgery.

To the best of our knowledge, our study is the first to identify a combination of positive pelvic signs, serum biomarkers, and clinical symptoms for diagnosing minimal or mild endometriosis in infertile women. The most important goal of this study was to avoid missing the correct diagnosis in any infertile women with endometriosis or associated adhesions or other related pathology who might benefit from surgery.

4.1. Single noninvasive diagnostic methods

Few studies on diagnosis of minimal or mild endometriosis have been reported. In our series, any single noninvasive method had

limited sensitivity (13.0–71.2%) for such diagnoses, but good specificity (74.3–95.9%). Vagino-recto-abdominal examination was the most valuable of these methods, having 71.2% sensitivity and 89.2% specificity, reminding clinicians of the importance of careful pelvic examination, especially vagino-recto-abdominal examination, in assessment of a woman with suspected endometriosis. Vagino-recto-abdominal examination is low-risk and assists in locating disease, especially that in regions within easy reach of examining fingers such as the uterosacral ligaments and posterior compartment.^[21]

Serum biomarkers can be useful in women with a history of chronic pelvic pain and/or subfertility without evidence of endometriosis on ultrasound.^[8] CA₁₂₅ is the most widely-used serum-screening marker for endometriosis; however, its diagnostic value has always been controversial. One study has shown that using the usual cut-off for CA₁₂₅ (35 IU/L), the sensitivity for the diagnosis of endometriosis were poor (27%).^[22] Other study has shown that serum CA₁₂₅ concentration is a sensitive diagnostic indicator of stage III and IV endometriosis, but not of stage I or II or deep invasive endometriosis.^[23] Several studies have found high CA₁₂₅ concentrations during menstruation and the premenstrual late secretory phase,^[24] especially in women with endometriosis.^[16] However, fluctuations in CA₁₂₅ concentration during the menstrual cycle may affect the accuracy of this test. In our study, we measured CA₁₂₅ concentration during the mid-follicular phase to optimize the reliability of our assay and calculated a cut-off point for serum CA₁₂₅ of 19.25 for diagnosing minimal or mild endometriosis by constructing a ROC curve. Using this cut-off point, the specificity (83.3%) and PPV (85.7%) were good, whereas the sensitivity (59.4%) and NPV (54.9%) were poor. Other markers for diagnosing endometriosis comprise CA₇₂, CA₁₅₃, TAG₇₂, and CA₁₉₉, all of which reportedly have low sensitivity.^[25]

4.2. Combinations of diagnostic methods

As stated above, any single method has limited diagnostic accuracy. Several authors have investigated combinations of diagnostic methods. The combination of high serum CA₁₂₅ with detection of pelvic nodules reportedly has a sensitivity of 87% for diagnosing endometriosis, but does not assist its classification.^[26] Another study showed that noninvasive tools are useful in identifying women with ovarian, but not non-ovarian endometriosis.^[8] As to minimal or mild endometriosis, a few studies have reported diagnosis by noninvasive methods, mostly serum biomarkers. One study showed a combination of CA₁₂₅ (19.9 IU/L) and prolactin concentrations (14.8 ng/mL) allowed the diagnosis of minimal or mild endometriosis with sensitivity and specificity of 77% and 88%.^[22]

It would be fantastic to have a diagnostic method with high sensitivity and specificity; however, this is usually impossible. In

our study, parallel testing increased the diagnostic sensitivity to 81.3%, thus reducing the rate of misdiagnoses, whereas serial tests of two indicators significantly improved specificity (from 95.7% to 100%) and PPV (from 94.1% to 100%), thus greatly reducing the misdiagnosing rate, especially the vagino-recto-abdominal examination plus dysmenorrhea or CA₁₂₅. So we believe these 2 noninvasive serial tests will get a passable sensitivity and a wonderful low misdiagnosis rate for infertility with minimal or mild endometriosis besides laparoscopic exploration.

In our study, the ratio of primary infertility is higher in endometriosis group, which may due to the retrospective study with bias in sample selection. But, the infertility type was not an influential factor of diagnosis in the multivariate logistic regression analysis, which was carried out to quantify that vagino-recto-abdominal examination had the highest diagnostic value, followed by CA₁₂₅, clinical symptoms, which remind us to improve the gynecological examination skills, especially the vagino-recto-abdominal examination for the well-beings of patients.

Above all, we can say that a combination of noninvasive diagnostic methods had certain preoperative diagnostic value of minimal or mild endometriosis, which might benefit some patients from avoiding laparoscopic surgery.

4.3. Outcomes of spontaneous pregnancies

Our study verified a substantial spontaneous pregnancy rate (50.8%) in women with minimal or mild endometriosis, which was higher than control group (35.6%, $P = .043$). It might suggest that suspected minimal or mild endometriosis seem to be choosing laparoscopy firstly regarding of the good spontaneous pregnancy rate and the advantages of laparoscopy. While the unexplained infertile women with normal pelvis might search for a more effective method to get pregnancy, because of low spontaneous pregnancy rate.

4.4. Limitations of present study

There are some limitations in our paper regretfully. First, it is possible that recall bias existed as a retrospective study, so that the data relating to diagnosis of minimal or mild endometriosis and the spontaneous pregnancy rate should be considered preliminary, expecting to be confirmed by further prospective studies. Second, our result is based on a single center in a clear geographical area. It would be of interest to compare the data with other centers to determine if the same pattern could be observed elsewhere. Third, the accuracy of vagino-recto-abdominal examinations was depended on the Gynecologist's technical level, and there would be a learning curve to generalize this pre-surgical diagnosis method.

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Writing – original draft: Huaying Yu.

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