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Review Article

Research progress of CA125 in endometriosis: Teaching an old dog new tricks

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ABSTRACT

After decades of research, we still face great challenges on endometriosis in terms of diagnosis and management. Serum CA125 has been used in the clinical practice in endometriosis, and many large-scale clinical trials have been conducted or are underway to determine potential use of serum CA125 levels in endometriosis. In this article, relevant articles that addressed endometriosis associated with CA125 were searched for and retrieved from the databases PubMed, Embase and the Cochrane Library. Here we provide an in-depth literature review to depict CA125 dynamic expression in female reproductive tract and to highlight the practical value of CA125 in diagnosing endometriosis, distinguishing the severity of the disease, monitoring the effect of treatment and reflecting malignant transformation. So far, the development of a risk stratification system based on biomarker CA125 for endometriosis may help clinicians in making novel and more efficient strategies for the detection and treatment of endometriosis. In order to improve CA125 specificity and sensitivity, further research is needed to determine its diagnostic cut-off value.

1. Background

Endometriosis is a benign and chronic gynecological disease affecting 5%–10% of women at reproductive age worldwide.[1] In spite of intensive studies and significant progress, the diagnosis of this disease remains a challenging issue for some cases, mostly due to lack of specific symptoms and/or laboratory test. It was reported that the diagnosis of endometriosis is often delayed, by an average of 8–11 years, which has significant consequences in terms of disease progression.[2] Detection with the use of noninvasive biomarkers can help the early diagnosis of endometriosis. CA125, also called mucin 16 (MUC16) which is encoded by the MUC16 mucin gene, is a glycoprotein expressed by epithelial ovarian tumors and various other pathological and normal tissues of Müllerian origin and detectable in the serum. Since its discovery in 1981, it has been widely used in the early detection, surveillance, and prognostic assessment of several human malignancies, including ovarian, pancreatic, breast, and lung.[3,4]

Although early studies mainly concentrated on the evaluation of diagnostic value of CA125 for malignancies, later research has expanded to its expression regulation, function, and therapeutic applications of benign diseases such as endometriosis. Serum CA125 represents a best-studied biomarker, and extensively used for the diagnosis and management of endometriosis. However, at present there is no uniform criteria for the use of CA125, its clinical application often relies on the personal or institutional judgment. Moreover, CA125 level is much affected by many physiological and benign conditions, which compromises its sensitivity and specificity. Although CA125 is far from an "ideal" biomarker in term of sensitivity and specificity, CA125 test is straightforward and well-accepted by patients, and multiple new applications have been developed. Objective review and evaluation of available data

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may help to clarify the confusions and provide guidance for better application of this important biomarker.

This review summarizes the current applications of CA125 for the diagnosis and management of endometriosis, analyze the factors affecting its sensitivity and specificity, and discuss potential applications for the detection of malignant transformation of endometriosis. In particular, we also focus on the limitation of this marker in clinical applications and prospective strategies targeting it (Fig. 1).

2. CA125 expression in female reproductive tract and its dynamic changes during the menstrual cycle

Multiple studies have been conducted to determine CA125 expression in female reproductive tract. Using avidin-biotin immunoperoxidase technique, Kabawat et al. demonstrated that CA125 protein was extensively expressed in fetal tissues including the amnion and derivatives of the coelomic epithelia such as the müllerian epithelium and the lining cells of the peritoneum, pleura, and pericardium. In adult tissues, CA125 protein was detected in the epithelium of fallopian tubes, endometrium and endocervix, and in the mesothelial cells of pleura, pericardium, and peritoneum, particularly in areas of inflammation and adhesion. However, the surface epithelium of normal fetal and adult ovaries which was thought to be derived from coelomic epithelium did not express CA125, except in inclusion cysts, areas of metaplasia, and papillary excrescences.[4] Further study showed that the cytosolic CA125 concentrations in the endometrium were 20-fold and two-fold higher than those measured in the ovary and the fallopian tube, respectively.[5] Another study by Mylonas et al. focused on CA125 expression in normal and hyperplastic endometrium with the use of immunohistochemical technique. The results confirmed CA125 expression in the glandular and luminal epithelial cells of the uterine endometrium as well as an increased expression in the late secretory (LS) over the early secretory (ES) phase during the menstrual cycle. Moreover, glandular and luminal cells of adenomatous hyperplasia (AH) III often expressed highest CA125 levels than their normal counterparts.[6]

Interestingly, experimental results by Kobayashi et al. indicated a hormonal regulation of CA125 biosynthesis in the eutopic endometrium. CA125 protein levels were significantly higher in eutopic endometrium obtained from early proliferative phase than those from the early secretory phase.[7] Abrão et al. found that CA125 presented the highest levels during the menstrual phase, between the first and third day of the cycle compared to the eighth and tenth day of the cycle(14.6 vs 9.69 IU/ml).[8] Bon et al. showed that serum CA125 values were highest during the menstrual phase and lowest during the follicular and peri-ovulatory phase in naturally cycling women.[9] McLemore et al. confirmed the results using two commercial assays for CA125 across the menstrual cycle in healthy women.[10] In addition, compared to CA125 content in the ovary and the fallopian tube, only endometrial CA125 content showed significant periodic changes, with the highest concentrations during the early proliferative and mid-secretory phase and the lowest concentrations during the early secretory phase.[5] Jäger et al. revealed that CA125 serum concentrations in normally menstruating women roughly parallel to the rise of the follicular diameter and E2 levels. After the luteinizing hormone (LH) surge and disappearance of the dominant follicle, the CA125 levels continued to increase or remained in the preovulatory range until progesterone levels had surpassed their peak concentrations, and tended to decline thereafter during the last days of luteal phase and throughout menstruation.[11]

Moreover, in the primary culture of endometrial cells, P4 did not affect, but medroxyprogesterone acetate (MPA) significantly inhibited, the in vitro production of CA125. Addition of estradiol (E2) to the culture medium blocked the MPA-mediated inhibition of CA125 expression.[7] These strongly support the estrogen and progesterone regulation of CA125 expression in the human endometrium.[11]

3. CA125 for diagnosis of endometriosis

3.1. Differences in CA125 expression between women with and without endometriosis

Nagamani et al. measured CA125 levels in 18 patients with laparoscopically diagnosed stage 2 to stage 4 endometriosis and in eight normally cycling control women during treatment and the 18-month follow-up period , the result showed that the mean CA125 level was significantly higher in women with endometriosis than in normal women (28.6 ± 5.1 (± SE) units/mL vs. 11.1 ± 1.1 units/mL).[12]

The association between an increased serum CA125 concentration and the presence of moderate and severe endometriosis has been observed since the mid-1980s. Barbieri et al. measured the preoperative serum CA125 levels of 147 patients undergoing diagnostic laparoscopy

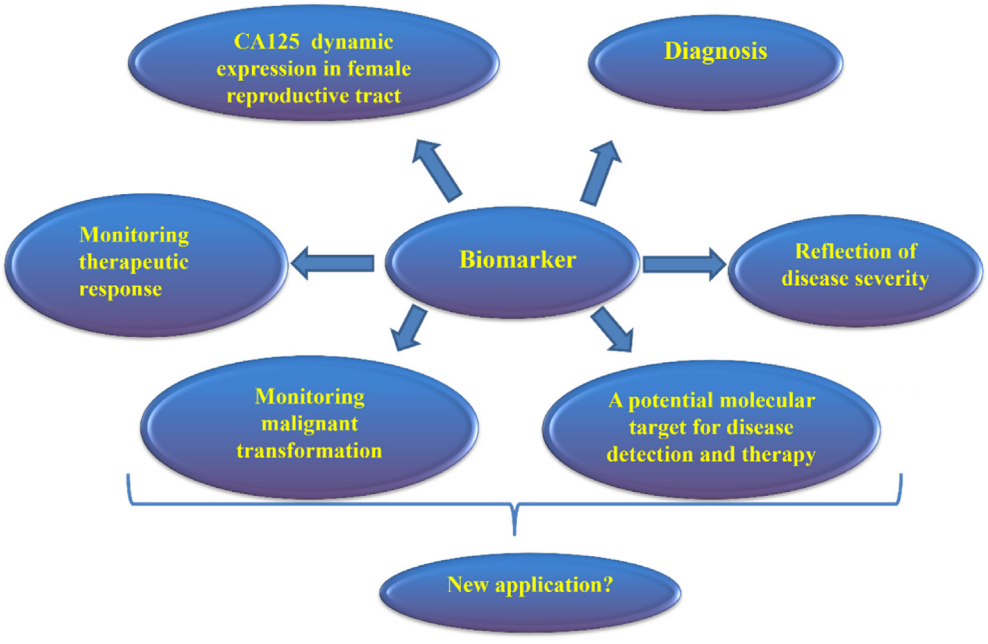

Fig. 1. The schematic diagram shows that as a biomarker, CA125 needs to be explained from the above aspects.

or laparotomy, and found that the serum CA125 concentrations were elevated in patients with stage III or IV endometriosis compared with controls with negative diagnostic laparoscopies (66.5 ± 14.5 vs 820 ± 0.59 U/ml, $p < 0.001$). Fifty-four percent of patients with stage III or IV endometriosis and 0% of the controls had CA125 levels > 35 U/ml. A lower percentage of patients with stage II endometriosis (13%) also had serum CA125 concentrations > 35U/ml. The authors further applied immunocytochemical techniques to demonstrate the presence of CA125 on the cell surface of endometriotic lesions.[13] These studies consistently showed that CA125 not only helped to diagnose endometriosis but also could differentiate stages.[12,14]

A meta-analysis by Shen et al. found that the serum CA125 concentration was associated with endometriosis in the overall population as well as the Caucasian subgroup, for both early and advanced diseases. This study reflects ethnic diversity of the clinical populations has no impact CA125 expression in endometriosis.[15]

3.2. CA125 cut-off values for diagnosis of endometriosis

Yu et al. measured CA125 concentration during the mid-follicular phase to optimize the reliability of their assay and calculated a cut-off point for serum CA125 of 19.25IU/l for diagnosing minimal or mild endometriosis by constructing a receiver operator characteristic (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.[16] Hirsch et al. conducted a prospective study to assess the diagnostic accuracy of CA125 serum test for diagnosing endometriosis in symptomatic women. At a cut-off level of 30 U/ml, a low sensitivity of 57% and high specificity of 96% were obtained. It was concluded that CA125 ≥ 30 U/ml is predictive of endometriosis in symptomatic women without evidence of any other concurrent gynecological disease.[17] Similarly, Hirsch et al. conducted a meta-analysis on twenty-two studies (16 cohort, six case-control) covering 3626 participants. The results showed that CA125 ≥ 30 u/ml is significantly more sensitive for the diagnosis of moderate or severe endometriosis compared with minimal disease, but CA125 < 30 u/ml is unable to rule out endometriosis.[18] In addition, Karimi-Zarchi et al. found that the best diagnostic cut-off level was 37 U/ml for premenopause women of endometriosis (57% sensitivity, 50% specificity), and 35 U/ml for postmenopause women (70% sensitivity, 59% specificity).[19]

3.3. Correlation between CA125 expression and menstrual cycle in endometriosis

The abovementioned reports showed that CA125 has been evaluated at different cut-offs, each generating a separate set of sensitivities and specificities for the diagnosis of endometriosis. The inconsistent results may be due to the fact that these studies were conducted in different menstrual cycle phase as the CA125 concentration is higher in the first cycle phase. CA125 levels tend to be higher during menstruation, possibly due to the increased inflammatory activity of the endometriotic cells.[20] Szubert et al. recruited patients in the early follicular phase to evaluate CA125 in serum and peritoneal fluid (PF) as an indicator of endometriosis. The study showed that the mean value of CA125 concentration in the endometriosis group was 33.98 U/ml vs. 9.3 U/ml in the control group and the mean value of CA125 in peritoneal fluid was 1241.88 U/ml in the non-endometriosis group versus 2640.23 U/ml in the study group; both results were statistically significant ($p < 0.05$).[21]

Kafali further assessed whether the differences between serum CA125 levels during menstruation and during the rest of the menstrual cycle can diagnose endometriosis clinically. Blood specimens were taken for CA125 determination during the menstrual period (days 2–4, from the start of menstruation) and on days of the menstrual cycle with no menstrual bleeding (days 10–15 from the start of menstruation). The mean concentrations of CA125 during menstruation and in the rest of the menstrual cycle in healthy women were 12.2 U/ml and 10 U/ml, respectively. In this group, the mean concentration of CA125 was on average of 22% higher during menstruation than during the rest of the menstrual cycle. The patients with endometriosis showed a similar pattern to that of normal women, but the difference in these patients was 198.3%. The mean concentrations of CA125 in these patients during menstruation and during the rest of the cycle were 35.8 U/ml and 12 U/ml, respectively. The mean concentration of CA125 during menstruation was significantly higher in patients with endometriosis than in normal women, but CA125 concentrations at other points in the menstrual cycle were similar in the two groups. ROC curve analyses set a cutoff value of 83% (the percentage increase in the CA125 level during menstruation compared with that on days without menstrual bleeding), which gives a sensitivity of 93% and specificity of 92%, with a corresponding likelihood ratio of 11.3. So they drew the conclusions that assessment of the differences in CA125 level during menstruation as against the remainder of the menstrual cycle may be used to diagnose endometriosis clinically.[20]

Another study by Akinwunmi et al. showed that the association between endometriosis and elevated CA125 was restricted to premenopausal women (14%), and there was no association between history of endometriosis and CA125 in postmenopausal women. This phenomenon may reflect the atrophy of the endometrium and endometriosis after menopause.[22]

In conclusion, there are no clear CA125 levels with sufficient efficacy can be stratified to diagnose endometriosis , but it is still a helpful parameter to diagnose endometriotic disease in patients in clinic.

4. The relationship between CA125 and clinical pathological characteristics of endometriosis

4.1. CA125 and endometriosis severity

Many reports showed that serum CA125 level could be used as an important predictor for severity of clinic pathological characteristic endometriosis.

Baek et al. measured serum CA125 levels in women with mild endometriosis (n = 9) and advanced endometriosis (n = 7), as well as healthy controls (n = 16). Results showed that CA125 varied with the severity of endometriosis. CA125 levels were 20.30 (13.97–27.10) IU/mL, 39.40 (23.50–161.00) IU/mL and 102.00 (41.90–182.45) IU/mL in healthy control group, mild endometriosis and advanced endometriosis group, respectively. CA125 levels were significantly different across the three groups with higher levels observed in both groups with endometriosis than that in healthy controls.[23] Karimi-Zarchi et al. found that the mean serum CA125 levels for American Society of Reproductive Medicine (ASRM) stages I, II, III, and IV endometriosis were 18.8 ± 0.9 IU/mL, 40.3 ± 2.8 IU/mL, 77.1 ± 3.5 IU/mL, and 182.4 ± 14.0 IU/mL, respectively. CA125 levels were significantly increased with advanced stages.[19] Chen et al. prospectively determined the serum CA125 in 157 women undergoing laparoscopy for dysmenorrhea. The sensitivity and specificity of serum CA125 for the diagnosis of endometriosis in these patients with dysmenorrhea were 61.1% and 87.5%, respectively. An increased CA125 (>35 U/ml) was found in 65/75 cases (86.70%) with advanced endometriosis, but in only 15/56 patients (26.8%) with minimal and mild endometriosis. The result indicated that CA125 could be an effective screening tool for patients with advanced endometriosis.[24]

These results are consistent with the hypotheses that superficial endometriosis is a physiological and intermittent condition in women during their reproductive years, whereas its progression, characterized as deep infiltrative endometriosis and/or endometrial ovarian cysts, is considered to be a true disease. Therefore, CA125 cannot distinguish mild (superficial) endometriosis from control group. It means that serum CA125 concentration may be a sensitive diagnostic indicator of severe endometriosis, but not of mild endometriosis, and the sensitivity of CA125 as an indicator increases associated with advancing stage of disease.

4.2. CA125 and pelvic organ adhesion

Karimi-Zarchi et al. measured serum CA125 levels in 87 women with endometriosis aged 21–54 years with pelvic pain, dysmenorrhea, or dyspareunia. The results showed that the mean serum CA125 was 49.93 ± 4.30 U/mL. The elevated preoperative serum CA125 level was significantly associated with clinico-pathological parameters including the stage of disease, adhesion score, and lesion size. On the other hand, there was no significant association found between the presurgical CA125 serum level and age, marital status, patient's complaints, or pelvic pain score.[19]Lee et al. undertook a study to evaluate the correlation of preoperative serum markers and intra-abdominal adhesions in endometriosis patients and to explore their clinical value for outcome prediction. The group with less than 28 points of adhesion scores was defined as a mild adhesion group, and a score of 28 or more as a severe adhesion group. CA125 concentration was significantly higher in severe adhesion group than in mild adhesion group. CA125 concentration, size of largest cyst and WBC are correlated with pelvic adhesions. The adhesion score was significantly higher in the CA125 $\geq$ 35 U/mL group than the CA125 $<$ 35 U/mL group. CA125 $\geq$ 35 U/mL showed 5.4 times higher probability of severe adhesions. Therefore, it can be concluded that patients with preoperative CA125 $\geq$ 35 U/mL are at high risk for pelvic adhesion.[25] In another study, authors attempted to investigate the factors that are associated with an elevated level of CA125 in endometriosis, and to study whether preoperative CA125 assay is useful to identify women who require preoperative bowel preparation. A total of 685 women undergoing surgery for endometriosis entered the study. Results showed that serum CA125 levels were significantly elevated in patients with more extensive adhesions to the peritoneum, omentum, ovary, fallopian tube, colon, and cul-de-sac, or with ruptured endometrioma. Then patients were classified with at least one of the three factors including dense omentum adhesion, ruptured endometrioma, and complete cul-de-sac obliteration as the high-risk group that required preoperative bowel preparation, and the others as the low-risk group. The results suggest that preoperative CA125 determination is helpful in deciding which women should receive preoperative bowel preparation, and that the endometriosis patients with preoperative CA125 levels higher than 65 IU/mL are at high risk for severe pelvic adhesions that require thorough preoperative bowel preparation.[26] However, Nagamani et al. found that CA125 level can predict active endometriosis lesions in patients with stage 3 and stage 4 endometriosis but is of no value for predicting adhesions.[12]

Adhesions cause major complications during surgery and may increase the risk of injury to the bladder, ureter, bowel and blood vessels. According to the above results, preoperative serum CA125 is considered as an important indicator for predicting patients with endometriosis and it should be considered when surgical management is suspected, especially if stage of disease, lesion size and adhesion score are undertaken.

4.3. CA125 and infertility

Besides adhesion, infertility is one of the major complications of endometriosis. The prevalence of endometriosis is as high as 40% in subfertile women. An estimated 25%–50% of women with infertility have endometriosis, and approximately 30%–50% of women with endometriosis have infertility.[27] Chen et al. showed that there was significant differences in CA125 among different endometriosis stages. However, mild patients (stage I/II) had more infertility, which might be due to the fact that infertile patients take the initiative to seek medical treatment earlier.[28]

Yu et al. conducted a study to evaluate the diagnostic value of a combination of noninvasive methods including evaluation of clinical symptoms, vagino-recto-abdominal examination and serum CA125 concentration for minimal and mild endometriosis so that it can narrow down the population who need laparoscopic exploration and verify the pregnancy prognosis after therapeutic laparoscopy. The results showed that the mean 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), and there was significant differences ($p < 0.05$).[16] Gica also found there was a statistically significant difference of the mean of CA125 values between fertile and infertile women with non-obstructive endometriois and the elevated serum CA125 levels was associated with an increased probability of being diagnosed with infertility.[29]

4.4. CA125 and deep invasive endometriosis

Deep invasive endometriosis (DIE) is a phenotype of endometriosis and represents a severe form of the disease and can affect many anatomical structures like the uterosacral ligaments, parametrium, bladder, and bowel. It's very difficult to perform a complete resection without organ injury or repair procedures, so an accurate preoperative diagnosis of DIE is of paramount importance. Topdagi Yilmaz et al. found that women with DIE had a statistically significant higher serum level of CRP and CA125 than women without DIE (CRP: 5.33 ± 4.40vs 4.657 ± 6.48, $p = 0.007$; CA125: 115.513 ± 160.94 vs 45.82 ± 31.22 IU/ml, $p < 0.001$). Moreover, higher levels of CRP and CA125 were also associated with severity of DIE (a bigger number of nodularity), but only serum CA125 was an independent predictor for women with ovarian endometrioma accompanied with DIE.[30]

Oliveira et al. further evaluated the performance of CA125 measurement in the menstrual and midcycle phases of the cycle, as well as the difference in CA125 levels between the two phases, for the early diagnosis of DIE. In both phases of the cycle, serum CA125 values were significantly higher in patients with DIE than those in controls. Median CA125 were 65.8 IU/ml (range 20.5–426.0 IU/ml) in DIE group and 16.6 IU/ml (range 8.0–35.9 IU/ml) in controls in the menstrual phase. In both groups, serum CA125 values were lower in midcycle than in menstrual phase. Median CA125 in the midcycle phase were 39.5 IU/ml (range 11.9–200.0 IU/ml) in DIE group and 16.4 IU/ml (range 5.4–30.8 IU/ml) in controls. The results indicated that CA125, especially its expression levels during menstruation and in midcycle, may be valuable for the diagnosis of deep endometriosis.[31] Barbosa et al. found a similar performance in patients with deep endometriosis. Serum CA125 levels were significantly higher in DIE group (55.2 ± 68.7 U/mL) compared to controls (22.5 ± 25.2 U/mL; $p < 0.001$). Some hypotheses tried to explain this increase: presence of blood and eutopic endometrial tissue into the peritoneal cavity due to retrograde menses, enlarged surface of endometrial tissue, and inflammatory reaction in the endometrial foci.[32] Bon et al. suggested that CA125 released from the endometrium can have access to the lymphatics and the circulation.[9]

4.5. Combination of biomarkers in endometriosis

The single test CA125 may lack specificity. Now more and more studies turn to CA125 in combination with other markers to establish a more efficient combined diagnostic model and a combination forecasting model to predict the severity of endometriosis.

Chen et al. showed that the AUCs of CA199, CA125, human epididymis protein 4 (HE4) and the combined diagnosis model as a novel approach for the early noninvasive diagnosis of endometriosis were 0.747, 0.867, 0.631 and 0.900 respectively ($p < 0.05$) while the AUC-value of the four markers in jointly diagnosis had a higher sensitivity (85.40%) than that of the individual index in endometriosis diagnosis. The results suggest that the combined diagnosis of four indices has significantly higher AUC than each index alone, which may provide a novel approach for the early noninvasive diagnosis of endometriosis.[28]

Dong et al. showed that serum anti-Müllerian hormone (AMH) level can predict the severity of endometriosis and low AMH level was an independent risk factor for postoperative infertility, while multivariate linear regression analysis revealed that serum CA125 level independently and negatively correlated with serum AMH level. Hence, they proposed

that preoperative serum AMH level combined with clinical parameters such as CA125 may help to predict the revised rASRM scores and severity of endometriosis.[33]

5. CA125 for monitoring endometriosis recurrence and therapeutic efficacy

5.1. CA125 and endometriosis recurrence surveillance

Recurrence is a common finding in patients with endometriosis who received surgical treatment. The mean postsurgical recurrence rate of endometriosis is estimated to be around 20% at 2 years follow-up and up to 50% (15.1%–56%) at 5 years follow-up.[34] Chen et al. assessed serum CA125 levels of 24 patients with advanced endometriosis were determined before surgery and one year after treatment. Fifteen patients with confirmed endometriosis recurrence by laparoscopy had elevated CA125 levels before (> 35 U/ml) and after therapy (> 60 U/ml). Nine patients with elevated CA125 levels before treatment and without recurrence had normal CA125 levels one year after therapy (< 35 U/ml).[24] Han et al. designed a study to investigate risk factors and biomarkers for the recurrent endometriomas. The results showed that serum CA125 level at recurrence was higher than the highest level of CA125 during follow-up in non-recurrence group (55.6 vs 21.3 U/mL, $p = 0.014$). This indicated that the last or highest level of serum CA125 during follow-up was a warning risk factor for postoperative recurrence.[35] Cho et al. measured preoperative and postoperative serum CA125 levels of 99 premenopausal women with stage III or IV who underwent laparoscopic surgery for endometrioma and received postoperative oral contraceptives (OC) or levonorgestrel-releasing intrauterine system (LNG-IUS) therapy. In this study, the multivariate regression analysis showed that only postoperative serum CA125 levels (LNG-IUS: Preoprerative vs Postoprerative: 117.0 ± 269.9 vs 30.9 ± 42.5 IU/ml; OC: Preoprerative vs Postoprerative: 124.1 ± 323.4 vs 27.3 ± 41.3 IU/ml) were significantly associated with endometrioma recurrence (hazard ratio 1.012, $p = 0.010$).[36]

Busacca et al. used elevated CA125, alone or in combination with pain recurrence, clinical diagnosis or relapse defined by ultrasound examination, as a criterion for recurrence. One of the criteria for recurrence is as follows: in women with elevated CA125 before the first operation and negative CA125 after operation, the CA125 value was twice as high as the normal value, with or without clinical signs or instrumental evidence. According to the criteria, the clinical data included 1037 women and the follow-up 4-year recurrence rates were 24.6%, 17.8%, 30.6% and 23.7%, respectively, for cases of ovarian, pelvic, deep, and ovarian and pelvic endometriosis ($p < 0.05$).[37] Küçükbaş et al. found that preoperative dysmenorrhoea, presence of non-cyclic pelvic pain (chronic pelvic pain), cyst size, preoperative CA125 levels and adhesion extension were associated with recurrent endometrioma after laparoscopic surgery. The cumulative recurrence incidence was 0.94 (1–0.036). Preoperative CA125 levels were 58.18 ± 63.12 IU/ml and 114.48 ± 74.13 IU/ml in non-recurrence group and recurrence group, respectively, and there was a statistically significantly difference.[38] Jiang et al. applied meta-analysis and found that endometrioma relapse was closely related to age at surgery, CA125 level, cyst size, dysmenorrhea, endometriosis-related surgery history, pre-operative medication, and rASRM score.[39]

It is important to recognize that the recurrence rates may be vary in women with ovarian, pelvic, or, in particular, deep endometriosis. In addition, a conservative surgery and/or an incomplete resection of the disease has been suggested to be linked to improved fertility and possibly increased recurrence rates. We must keep in mind that it is very important to closely monitor the CA125 levels of these patients after treatment.

5.2. CA125 and therapeutic efficacy

Many studies also suggested that serum CA125 level as the predisposing factor can predict the conservative treatment and surgical therapeutic response in patients with endometriosis.

Nagamani et al. measured serum CA125 levels of 18 patients with laparoscopically diagnosed stage 2 to stage 4 endometriosis and of eight normally cycling control women. All endometriosis patients were treated with either Danazol or Buserelin. Four of the patients who had recurrence of symptoms approximately 1 year after treatment had CA125 levels approaching pretreatment levels, and recurrence of endometriosis was confirmed by laparoscopy. This indicated that CA125 levels are helpful in monitoring therapy during treatment.[12] Han et al. applied catheter-directed sclerotherapy (CDS) with 95% ethanol for ovarian endometriosis. During a mean follow-up of 12.7 months, serum CA125 level decreased in all participants (Before CDS vs after CDS: 65.4 ± 49.49 vs 20.9 ± 13.1 U/mL, $p = 0.001$), with a decrease in pain score.[40] Koo et al. showed that both CDS and surgery for ovarian endometrioma have effective symptom relief for patients with symptomatic ovarian endometriomas, and meanwhile CA125 decreased in both CDS and surgery groups (CA125: Before CDS vs After CDS: 46.2 vs 21.5 U/mL, $p = 0.001$; Before surgery vs After surgery: 28.7 vs 8.8 U/mL, $p < 0.001$).[41]

Lee et al. performed a study to assess whether dienogest (DNG) is also effective in patients with recurrent endometriosis based on multicenter data of 121 women with clinically diagnosed recurrent endometriosis who were treated with DNG (2 mg daily) for more than 24 weeks. During the follow up, the mean CA125 level was 80.04 U/mL at baseline and decreased significantly to 33.11 U/mL after 24 weeks of DNG administration and lasted until 72 weeks.[42] Margatho et al. conducted a randomized trial to correlate endometriosis-associated pain with serum levels of etonogestrel (ENG), levonorgestrel (LNG), CA125 and soluble CD23 in users of the ENG implant or the 52-mg LNG-releasing intrauterine system for up to 2 years after device placement. Serum levels of CA125 decreased in the ENG implant (which blocks ovulation) users with significant reduction in endometriosis-related pain, dysmenorrhoea and chronic pelvic pain after 24 months' use of the device.[43]

In sum, following treatment of endometriosis, serum CA125 could be used as an argument for the therapeutic response.

6. CA125 and malignant transformation of endometriosis

Albeit at a low risk, the malignant transformation of endometriosis do exit, women with long-term endometriosis have a 4.2 times higher relative risk of ovarian cancer than the general population. Epithelial ovarian cancer (EOC) subtypes, specifically ovarian clear cell carcinoma (OCCC) and endometrioid ovarian carcinoma (EnOC) are directly related to endometriosis. This link between endometriosis and these EOC subtypes has been confirmed at the molecular pathology level through the presence of common mutations in cancer-associated genes.[44,45] CA125 and other serum biomarkers could be used to identify patients with high-risk of malignant transformation.

Kadan et al. observed that the serum CA125 levels tended to be higher in patients with malignant tumors, but the difference did not reach a statistical significance (204.9 vs. 66.9, $p = 0.1$). Logistic regression analysis showed that the odd ratios (OR) of serum CA125 to predict malignancy of endometriosis was 1.16. Relatively low sensitivity (61.3%) and specificity (58.05%) were obtained even with the best CA125 cutoff value (43 U/ml). Low-risk factors for malignant transformation included patient's age under 49 years, serum CA125 below 43 U/ml, cyst without solid components and size of less than 11 cm. Though serum CA125 level is not a significant predictor of malignant transformation, the authors recommended that surgical intervention should be strongly considered when serum CA125 increases in patients with asymptomatic ovarian mass-suspected endometrioma during follow up. Although based on retrospective data and a relatively small number of cases, the findings not only revealed a possibility of malignant transformation of endometriosis, but also indicated the potential value of CA125 for early detection of the malignancy.[46]

Check. reported a case of a 46-year-old women with a serum CA125 level that rose from 231 IU/mL to 1385 IU/mL within 5-month had a 23-mm ovarian cyst with classic pigmented benign lesions that looked like

endometriosis developed clear cell carcinoma five years later after ovarian biopsy. Therefore, the author suggested that a high level and/or rapid rise of serum CA125 levels should make it highly suspected that women with endometriosis eventually develop ovarian cancer until better markers are developed.[47] Dahiya et al. also found that higher levels of CA125 was a predictive factor of coexistent malignancy.[48] In addition, the combined use of HE4 and CA125 may much improve the screening efficiency of ovarian malignancy arising from endometriosis.[49]

7. CA125 as a molecular target for disease detection and therapy

Theranostic approaches that combine diagnostic imaging with treatment have been shown to improve the survival of patients in several advanced cancers that are difficult to treat. In this context, CA125 as theranostic agents, that combine diagnostic and therapeutic capabilities, are being explored to better detect, diagnose and treat ovarian cancer.[50] Sharma et al. reported that CA125 antibody conjugated to imaging contrast agents was a more sensitive detection tool in evaluation of ovarian cancer progression and recurrence. In their report, they synthesized a 89Zr-labeled variant of the B43.13 antibody-89Zr-DFO-mAb-B43.13 (DFO is desferrioxamine)-that targets CA125 with high affinity (KD = 1.2 nM) as a noninvasive visualization of CA125 expression by neoplastic cells to track lymph node metastases of high-grade serous ovarian cancer (HGSOC) via positron emission tomography (PET). Biodistribution studies revealed that 89Zr-DFO--mAb-B43.13 accumulated obviously in the OVCAR3 tumors, and reached 22.3 ± 6.3% injected dose per gram (%ID/g) at 72 h after injection. Meanwhile, activity concentrations greater than 50 %ID/g were observed in the ipsilateral lymph nodes of the xenograft-bearing mice which presented grossly metastasized ovarian cancer cells.[51]

Furthermore, CA125 and its ligands have been developed as potential immunotherapeutic agents for therapeutic intervention using monoclonal antibodies and immunotherapy. Oregovomab (MAb B43.13) is a high affinity murine monoclonal antibody, which can bind to CA125 both in the circulation and at the tumor site to induce therapeutic immunity directed against the tumor with a half-life of 44 h. Oregovomab combined with other chemotherapy drugs was simultaneously administered to show benefit in ovarian cancer patients. Brewer et al. showed the therapeutic effect of carboplatin-paclitaxel chemotherapy plus four immunizations with oregovomab (CPO) was unexpectedly greater than that of carboplatin-paclitaxel (CP) alone, with median progression free survival (PFS) of 41.8 months for CPO and 12.2 months (10.4–18.6 months) for CP. The oregovomab treatment did not lead to any change in toxicity profile from CP.[52]

The mechanism of chemoimmunotherapy with oregovomab may be as follows: the binding of oregovomab to CA125 causes antigen cross presentation, which leads autologous peripheral blood monoculear cell (PBMC)-derived dendritic cells to induce CD4 and CD8 T cellular immunity. While chemotherapeutic agents including carboplatin and paclitaxel can change the immunological micro-environment through inducing immunogenic tumor cell death and local release of related tumor antigen, alterations to T regulatory cells characteristics, and influence on the balance of cytokines in the tumor microenvironment. The activated anti-tumor immunity ultimately improves the outcomes achievable with standard cancer treatment with oregovomab.

Although oregovomab has not been applied for endometriosis, the promising results in ovarian cancer points to a new diagnosis and treatment strategy for better management of endometriosis.

8. Conclusion

As the most widely used serological marker in the study of endometriosis (as summarized in Fig. 2), CA125 has a certain practical value in the diagnosis of endometriosis, distinguishing the severity of the disease, monitoring the effect of treatment and reflecting malignant transformation. The development of a risk stratification system based on biomarker CA125 for endometriosis may help clinicians to decide which patients need medication or a gynecologic surgery. However, owing to

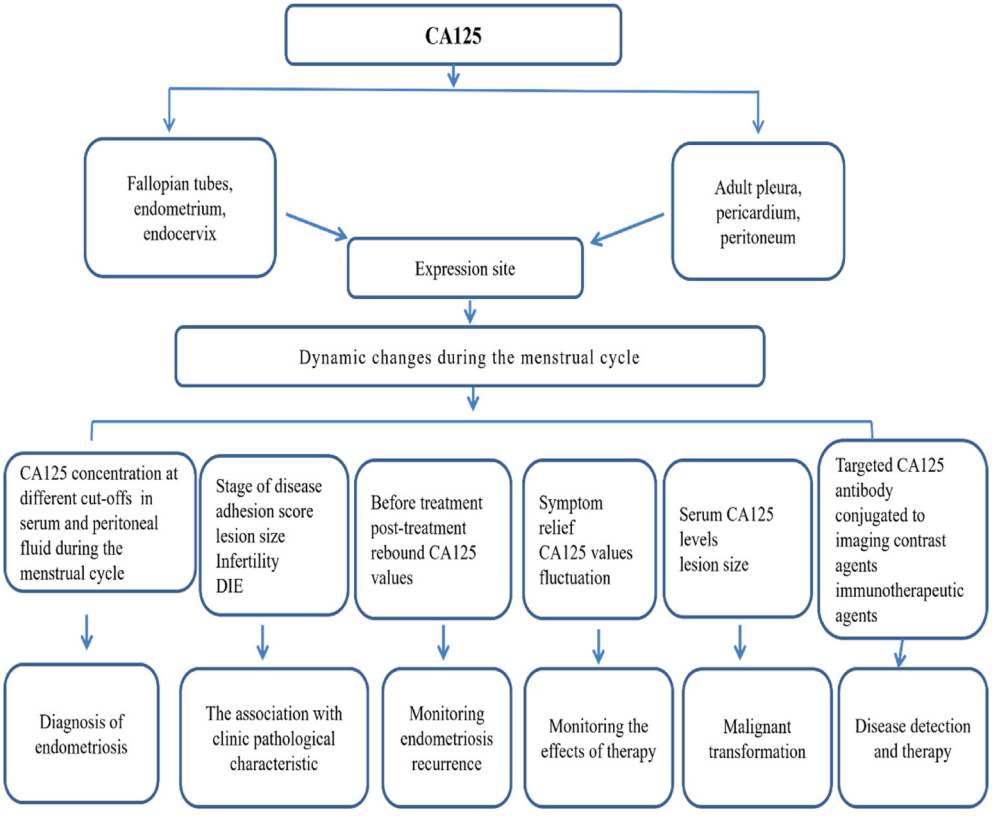

Fig. 2. CA125 expression site, regulating factors in physical condition and the application of CA125 for endometriosis management.

the serum CA125 level is affected by menstrual physiological changes and gynecological tumors, a level of 35U/ml should not be considered an absolute cut-off value to diagnose endometriosis. Although CA125 is not a reliable biomarker in diagnosis, there is a consensus that CA125 plays a critical role in assessing the severity of the disease. Several strategies for enhancing the reliability of CA125, including establishing a more efficient combined diagnostic model combination with other biomarkers such as HE4 have been proposed. Further research is needed to determine its diagnostic cut-off value to improve CA125 specificity and sensitivity. In addition, as a biomarker and predictor, CA125 has received much attention in the role of CA125-targeted noninvasive visualization and therapy. Therefore, continuous and systematic studies are still warranted to fully clarify the functional targets of CA125 involved in molecular network regulation to achieve benefits for patients with endometriosis. These studies will be the hotspot for further research.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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