**CA-125 for Diagnosis and Follow up of Pelvic Endometriosis**

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**Abstract: Background:** The development of a non-invasive and accurate diagnostic biomarker for endometriosis is urgently needed. **Objective:** Evaluate the accuracy of serum cancer antigen 125 (CA 125) in diagnosis and follow up of pelvic endometriosis. **Materials and Methods**:In our prospective clinical study, 136 patients had collected from the outpatient clinic of the department of obstetrics and gynecology of Sohag teaching hospital. Their ages ranged from 18 to 45 years with mean ages were 28 and 29 years for study and control cases respectively. All patient had a high probability of endometriosis by clinical examinations, all these patients underwent for full history taking, abdominal and vginal examinations, abdominal and vaginal ultrasound and then laparoscopy. After laparoscopy patients was divided into two groups; *Group A (case study group):* consists of 71 patients with sure diagnosis of endometriosis. *Group B (control group):* consists of 65 patients with no endometriosis.Before laparoscopy and After eight hours fasting, all patients will have a venipuncture to col­lect 5 mL of blood sample for measurement of serum level of CA-125 by ELISA:- The first sampling would collect at the 3rd day of the menstrual cycle before any intervention either medical or surgical. The second sampling would collect after 3 months of hormonal treatment or after surgical removal of endometriotic lesion by laparoscopy. **Results:** Sensitivity and specificity values for CA-125 U/ML were calculated Assuming that the endoscopy is the gold standard test, and the mathematic mean of the values of CA-125 of the Group B (control cases) (which =13.67 IU/ml) was used in our study as a cutoff point for diagnosis of endometriosis. The mean values of CA-125 in study group were 30.7 IU/ml and 13.7 IU/ml before and after 3 months of treatment respectively. The sensitivity and specificity of CA-125 in diagnosis of pelvic endometriosis were 47.88% and 61.53% respectively. The sensitivity for minimal to mild cases was 2.70% while the sensitivity for moderate to severe case was 92.85%. **Conclusion:** Cancer antigen CA -125 is poor screening test for endometriosis; it is a poor diagnostic test for minimal to mild cases while it is a good diagnostic test for moderate to severe cases. Elevation that occurs in the CA-125 value after sometimes of management is a good sign of recurrence or reactivation of the disease. So, we can use CA-125 test for follow up patients after management of endometriosis.

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**Keywords:** Diagnosis of endometriosis, CA-125, pelvic endometriosis.

**1. Introduction**

Endometriosis is defined as the presence of endometrial-like tissue outside the uterine cavity and associated with a constellation of symptoms, including chronic pelvic pain, dysmenorrhoea, dyspareunia, dyschezia and subfertility ***(Falcone, Lebovic; 2011) (Sinaii et al; 2008) (1) (2).***

Endometriosis affects 6–10% of women of reproductive age in the general population; however, its prevalence is 35–50% in women with pain, infertility or both ***(Giudice and Kao; 2004) (3).*** As endometriosis can be progressive in up to 50% of women, early non-invasive diagnosis has the potential to offer early treatment and prevent progression. Ideally, decreased levels of such a test during/after treatment would also correlate with decreased pelvic pain and increased fertility. Such a test would be useful to women especially with endometriosis which is not diagnosed by transvaginal ultrasound (TVU) ***(Kennedy et al; 2005) (4).***

CA-125 is the cell surface antigen expressed by derivatives of coelomic and müllerian epithelia, including endocervix, endometrium, fallopian tube, peritoneum, pleura, and pericardium. CA-125 has found application as a [tumor marker](https://en.wikipedia.org/wiki/Tumor_marker) or [biomarker](https://en.wikipedia.org/wiki/Biomarker) that may be elevated in the blood of some patients with specific types of [cancers](https://en.wikipedia.org/wiki/Cancer), or other conditions that are benign ***(Duraisamy, et al; 2006) (yin, et al; 2002) (5) (6).***

**Patient and methods**

Our study is a case-control study, a total of 136 patients underwent to full medical history to investigate the presence of six symptoms most commonly associated with endo­metriosis, Pel­vic examination was the next step, searching for retro-uterine nodules, thickening of the uterosacral ligament or pelvic masses. Pelvic and transvaginal ultra­sound and laparoscopy. After laparoscopy, patients would be divided into two groups:

1. The first group A (case study group) consisted of 71 patients with a diagnosis of endometriosis confirmed by pathological examination if indicated. This group subdivided according to age into two groups;.

* Group 1: Age ≤ 30 years old.
* Group 2: Age > 30 years old.

2- The second group B (control group) consisted of 65 patients without endometriosis.

This study had conducted at department of Obstetrics and Gynecology of Sohag teaching hospital. Patients collected from the outpatient clinics through the period from March 2014 to December 2016.

**Sampling**

Before laparoscopy and after eight hours fasting, all patients would have a venipuncture to col­lect 5 mL of blood sample for measurement of serum level of CA-125 by ELISA. The first sampling would collect at the 3rd day of the menstrual cycle before any intervention either medical or surgical. The second sampling would collect after 3 months of hormonal treatment or after surgical removal of endometriotic lesion by laparoscopy. Blood samples were collected in sterile tubes, immediately transported to the laboratory and Serum level of CA-125 were measured by ELISA

**Inclusion criteria**

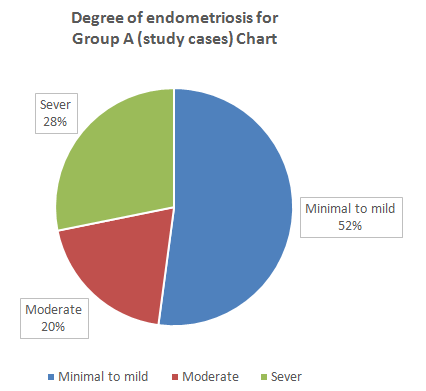
1. age between 18 and 45 years,
2. Patients with endometriosis clinical suspicion, fertile or subfertile.
3. absence of hormone therapy within three months prior to consultation,
4. Absence of au­toimmune diseases confirmed by history and laboratory tests, when necessary.

**Exclusion criteria**

This study will exclude:

1. Age < 18 years and >45 years.
2. Patients unfit for laparoscopy or hormonal treatment.
3. Patients with autoimmune diseases confirmed by history and/or laboratory tests.
4. Hormonal therapy or surgical intervention before blood sampling.

**3. Results**



**Chart 1: Degree of endometriosis for Group A (study cases)**

**Table 1: Group A (study cases) descriptive analysis**

|  |  |  |  |
| --- | --- | --- | --- |
|  | age | CA-125 U/ML at 3rd of menstruation | CA-125 U/ML after 3 months of treatment |
| Mean | 28.11268 | 30.70704225 | 13.70873239 |
| Standard Deviation | 4.967176 | 34.52303713 | 11.38152073 |
| Range | 20 | 144.5 | 49 |
| Minimum | 20 | 1.5 | 3 |
| Maximum | 40 | 146 | 52 |
| Count | 71 | 71 | 71 |

**Table 2: Group B (control cases) descriptive analysis**

|  |  |  |
| --- | --- | --- |
|  | age | CA-125 U/ML |
| Mean | 29.38462 | 13.67385 |
| Standard Deviation | 5.578117 | 6.534985 |
| Range | 21 | 27.7 |
| Minimum | 19 | 1.3 |
| Maximum | 40 | 29 |
| Count | 65 | 65 |

**Table 3: differences between Group A (study cases), and Group B (control cases)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Comparative parameters | | Group A (study cases) | Group B (control cases) | | result | |
| P value | significance |
| Age: | Mean | 28.11268 | 29.38462 | | 0.16 | insignificant |
| Standard Deviation | 4.967176 | 5.578117 | |
| Range | 20 | 21 | |
|  | | | at 3rd of menstruation | after 3 months of treatment | at 3rd of menstruation = 0.001 | significant |
| CA-125 U/ML: | Mean | 13.67385 | 30.70704225 | 13.70873239 |
| Standard Deviation | 6.534985 | 34.52303713 | 11.38152073 | after 3 months of treatment = 0.98 | insignificant |
| Range | 27.7 | 144.5 | 49 |

**Table 4: Sensitivity and specificity of CA-125 in diagnosis of endometriosis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Endoscopic diagnosis** | | | | |
| **Serum CA-125** |  | **Diseased** | **Free** | **total** |
| **+ ve** | **34** | **25** | **59** |
| **- ve** | **37** | **40** | **77** |
| **Total** | **71** | **65** | **136** |

Sensitivity of Serum CA-125= 34 ÷ 71 = 0.4788 = 47.88%.

Specificity of Serum CA-125= 40 ÷ 65 = 0.6153 = 61.53%.

**Table 5: Sensitivity of CA-125 for minimal to mild endometriosis:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Endoscopic diagnosis | | | | |
| Serum CA-125 |  | Diseased | Free | Total |
| + ve | 1 | 0 | 1 |
| - ve | 36 | 0 | 36 |
| Total | 37 | 0 | 37 |

* Sensitivity of Serum CA-125 for minimal to mild disease= 1 ÷ 37 = 0.0270 = 2.70%

**Table 6. Sensitivity of CA-125 for moderate endometriosis:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Endoscopic diagnosis | | | | |
| Serum CA-125 |  | Diseased | Free | total |
| + ve | 13 | 0 | 13 |
| - ve | 1 | 0 | 1 |
| Total | 14 | 0 | 14 |

* Sensitivityof Serum CA-125 for moderate disease = 13 ÷ 14 = 0.9285 = 92.85%

**Table 7: Sensitivity of CA-125 for severe endometriosis:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Endoscopic diagnosis | | | | |
| Serum CA-125 |  | Diseased | Free | total |
| + ve | 20 | 0 | 20 |
| - ve | 0 | 0 | 0 |
| Total | 20 | 0 | 20 |

* Sensitivity of Serum CA-125 for severe disease = 20 ÷ 20 = 1 = 100%.

**Table 8: Sensitivity of CA-125 for moderate to severe endometriosis:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Endoscopic diagnosis | | | | |
| Serum CA-125 |  | Diseased | Free | total |
| + ve | 33 | 0 | 33 |
| - ve | 1 | 0 | 1 |
| Total | 34 | 0 | 34 |

* Sensitivityof Serum CA-125 for moderate to severe disease = 33 ÷ 34 = 0.9705 = 97.05%.

In our study the mean age of case study group A and control group B were 28.11 and 29.38 years respectively, the standard deviation of both groups A and B were 4.967 and 5.578 respectively. There were insignificant difference between the two age groups with P=0.14. In all study cases, there were a positive correlation between age and degrees of endometriosis with correlation coefficient (r) = 0.14194, while there were a negative correlation between age and CA-125 values with correlation coefficient (r) = -0.03643. Also correlation between age and CA-125 values in control group revealed a negative correlation with Correlation coefficient (r) = -0.00542.

**4. Discussion**

Establishing a correct diagnosis of endometriosis is often problematic, because the presenting symptoms can be non-specific and associated with a number of different conditions ***(Giudice and Kao, 2004) (7)***. Imaging methods such as transvaginal ultrasound and magnetic resonance imaging may help to identify ovarian endometriomas or a rectovaginal endometriotic nodule, but they have no value in diagnosing peritoneal endometriosis. Consequently, it is recommended that pelvic endometriosis should be diagnosed surgically ***(Kennedy et al., 2005) (8).***

The sensitivity and specificity of CA-125 test in diagnosis of endometriosis were 47.88% and 61.53% respectively, The test has a poor diagnostic value for minimal to mild cases with sensitivity was 2.70% only while it has a good diagnostic value for moderate to severe cases with sensitivity 97.05%. Our results are in concordance with the study done by [**Abrão**](https://www.ncbi.nlm.nih.gov/pubmed/?term=Abr%C3%A3o%20MS%5BAuthor%5D&cauthor=true&cauthor_uid=10458545) **et al. in (1999)** (tumor markers in endometriosis), which concluded that CA-125 is the only important marker in the diagnosis of stages III/IV of endometriosis, especially when blood samples for its determination are obtained during the first 3 days of the menstrual cycle **(9)**.

Our results are in concordance with the review by ***Maiorana et al. in (2007)*** which indicated that CA-125 may be more accurate at diagnosing women with later stages of disease **(10)**, also [***Bedaiwy***](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bedaiwy%20MA%5BAuthor%5D&cauthor=true&cauthor_uid=14734195) ***And*** [***Falcone***](https://www.ncbi.nlm.nih.gov/pubmed/?term=Falcone%20T%5BAuthor%5D&cauthor=true&cauthor_uid=14734195) ***in (2004)*** in their review (laboratory testing for endometriosis) concluded that CA-125 has limited diagnostic accuracy in the identification of early stage endometriosis **(11).** ***Bianchi et al in (2003)*** in his review; (Correlation between CA-125 marker with the presence and severity of pelvic endometriosis) concluded that Patients with severe endometriosis, or grade IV, showed statistically significant higher levels of CA-125 compared to women without endometriosis or with grades I, II or III of the disease **(12).**

Also our results of cutoff point, sensitivity and specificity were in concordance with the study by ***Maria Szuber et al. in (2012)*** whose researched on serum and peritoneal fluid concentration of CA-125 and found that Cancer antigen 125 is a well-known biomarker for endometriosis and helpful in daily clinical practice when endometriosis is suspected. The cutoff value in serum suggesting endometriosis with 68% sensitivity is 11 IU/ml **(13).**

[**Hirsch**](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hirsch%20M%5BAuthor%5D&cauthor=true&cauthor_uid=27173590)  **et al.** **in (2016)** searched in their study to evaluate the diagnostic accuracy of serum cancer antigen 125 (CA-125) for endometriosis. They concluded that Pooled specificity was 93% (95% CI 89-95%) and sensitivity 52% (95% CI 38-66%). CA-125 was significantly more sensitive for the diagnosis of moderate or severe endometriosis compared with minimal disease (63%, 95% CI 47-77% versus 24%, 95% CI 19-32%, P-value = 0.001). The study also concluded that CA 125 performs well as a rule-in test facilitating expedited diagnosis and ensuring investigation and treatment can be confidently tailored for the management of endometriosis. Unfortunately, a negative test, CA 125 < 30 units/ml, is unable to rule out endometriosis **(14).**

In our study three patients represented with recurrent endometriomas and associated with increased CA-125 but to a lesser extent than the previous values. In spite of this we found that the disease was more extensive than in the first laparoscopies so the value of cancer antigen CA-125 has no clear relation to the extent of endometriosis. So follow up of the diseased cases after management by measurement of CA-125 will not give the complete picture about the extent of the disease, but it may gives a hint that the disease is still active or present especially in sever and moderate cases. Our results are in concordance with the review of Chen et al. in (1998) which concluded that CA-125 is a valuable adjuvant in the follow-up of recurrence in patients with advanced endometriosis and initially elevated CA-125 levels. It is not an effective screening tool for patients with dysmenorrhea, or for monitoring therapy.

The value of CA-125 may be shooting as we met with one case during this study; this case was excluded from the study as she was 16 years old which was less than the lower limit of age in our study. This case was complaining of chronic pelvic pains and dysmenorrhea. Ultrasound and MRI revealed right adnexal cystic mass related to the right ovary, CA-125 was more than 1200 IU/ML in two different laboratories, so the patient was referred to an oncologist and after surgical exploration; massive adhesion was found so right oopherectomy, appendectomy with omenal biopsy was performed for fear of malignancy. Histopathological examinations of the tissues revealed sever endometriosis with right ovarian endometrioma.

**5. Conclusion**

ONE of the major challenges facing gynecologists is the inability to diagnose endometriosis without the need for laparoscopy or laparotomy. Also, there is an important question; what we mean by the cure of endometriosis? Is it the complete surgical removal of the lesions without residuals? Or is it the relive of pain after treatment? Is it the increase in pregnancy rate in cases of infertility? At present, there are no reliable markers of this disease.

In conclusion, cancer antigen CA-125 is poor screening test for endometriosis; it is a poor diagnostic test for minimal to mild cases while it is a good diagnostic test for moderate to severe cases. The sensitivity and specificity of CA-125 test in diagnosis of endometriosis were 47.88% and 61.53% respectively at a cutoff point 13.67 IU/ml.

The significant decrease in CA-125 values after management of endometriosis; is it a sure sign of curability? This is vague as secondary look laparoscopy hadn't performed. But elevation that occurs in the CA-125 value after sometimes of management is a good sign of recurrence or reactivation of the disease. So, we can use CA-125 test for follow up patients after management of endometriosis.

It I important to refer that CA-125 value itself has no direct relation to the extent of endometriosis.

**Recommendations**

* Endometriosis resembles cancer in some degree as growth, distributions, recurrence and spread (local, lymphatic and iatrogenic). So we have to look at endometriosis as a series disease affecting the quality of life of many women. Also we must searching about one treatment for one disease regardless of women complaining from infertility, chronic pelvic pain, dysparunia or else.
* The use of CA-125 as a diagnostic test at a cutoff point 13.67 IU/ML with the presence of at least two of the six cardinal symptoms of pelvic endometriosis with other findings during examination, this will be a good diagnostic test for moderate to severe cases with sensitivity as high as 97.05%.
* The use of the glycoprotein CA-125 for screening of endometriosis is unreliable due to poor sensitivity for minimal and mild cases.

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