Serum carcinogenic antigen (CA)-125 and CA 19-9 combining pain score in the diagnosis of pelvic endometriosis in infertile women

H. Zhu, H. Lei, Q. Wang, J. Fu, Y. Song, L. Shen, W. Huang

Department of Gynecology and Obstetrics, West China Second University Hospital, Sichuan University, Chengdu (China)

Summary

Objective: To define the utility of serum carcinogenic antigen (CA)-125 and CA 19-9 combining pain score in the prediction of pelvic endometriosis in infertile women. *Materials and Methods:* Serum CA-125 and CA 19-9 were measured using immunoradiologic methods during the follicular phase preceding laparoscopy for infertility. Values obtained were correlated with the occurrence and severity of endometriosis. Receiver operating characteristic (ROC) curve was applied to assess the utility of serum CA-125, CA 19-9, and pain score in preoperative preparation. Cut-off value of CA-125 and CA 19-9 was defined. *Results:* The study enrolled 294 infertile women receiving laparoscopy between July 2010 and September 2011. Ninety-four patients were diagnosed with endometriosis and 200 patients without. Preoperative serum CA-125 and CA 19-9 levels were significantly different between the two groups. ROC curve analyses of serum CA-125 and CA 19-9 set a cut-off value of 18.25 IU/ml and 13.15 IU/ml, producing a sensitivity of 64.8% and 84.8%, a specificity of 81.9% and 51.6%, a positive predictive value (PPV) of 63.6% and 46.1%, and a negative predictive value (NPV) of 81.0% and 87.4%, respectively. Combined-analyses of CA-125 and CA 19-9 produced a sensitivity of 72.4%, a specificity of 81.9%, a PPV of 62.3%, and a NPV of 81.8%. Combined-analyses of serum CA-125, CA 19-9 and pain score produced a sensitivity of 71.0% and a specificity of 74.0%. *Conclusions:* Preoperative CA-125 and CA 19-9 levels combining pain score can be useful for the prediction of pelvic endometriosis and may be included in the evaluation of unexplained infertile women.

Key words: Carcinogenic antigen 125; Carcinogenic antigen 19-9; Endometriosis; Infertility; Pain score.

Introduction

Endometriosis is one of the most important and distressing gynecological disorders affecting the female fertility potential. It was estimated that the evidence of endometriosis is present in 25-50% of infertile women, while 30-50% of women with endometriosis are infertile [1, 2]. Recent studies showed that infertile women with minor endometriosis have a reduced chance of natural conception compared to those with otherwise unexplained infertility [3-6]. In addition, a randomized controlled trial [7] demonstrated improved natural conception rate following surgical treatment of visible endometriotic lesions. The findings indicate that the presence of visible minor lesions alone may have an adverse effect on natural conception, and the availability of laparoscopic surgery as an effective treatment of minimal and mild endometriosis renders early detection of the cause of subfertility possible.

At present, there is no reliable method to detect pelvic endometriosis except for direct visualization of lesions at laparoscopy. The latter is, however, invasive, costly, and may result in potential complications. Although the diagnosis is based on clinical manifestations, the clinical symptoms are often misleading. Since Barbieri *et al.* [8] first demonstrated the association between elevated serum carcinogenic antigen (CA)-125 level and the presence of moderate and severe endometriosis, early identification of patients at increased risk is assisted by serum CA-125 assay in the subfertility work-up. In contrast to laparoscopy, serum CA-125 measurement is inexpensive, and able to identify a subgroup of patients who are more likely to benefit from early laparoscopy. The diagnostic performance of serum CA-125 assay has been assessed by several studies, with varied cut-off values proposed. However, no consensus has been reached so far, and the clinical application of this biomarker is thus limited, especially in infertile women.

In order to achieve a better performance, attempts have been made to combine serological test of CA 125 with CA 19-9, which was suggested positively correlated with the severity of endometriosis [9]. However further investigations revealed inconsistent results, and the diagnostic value of the combined biomarkers is questioned [10, 11].

The present authors conducted a prospective study to evaluate the correlations between the above two biomarkers and pelvic endometriosis among infertile women. The study also explored the diagnostic value of combined serum CA-125

Table 1. — *Age, pain scores, duration of infertility, and serum CA-125 and CA 19-9 levels between patients with pelvic endometriosis and controls.*

	Age	Duration of infertility	Pain scores	CA-125	CA 19-9
Pelvic endometriosis	28.81± 3.75	3.90± 2.56	4.00± 2.65	30.74± 45.11	31.13± 27.88
Controls	28.95± 4.33	4.67± 3.11	1.82± 2.21	15.02± 12.37	17.63± 15.58
p	0.778	0.060	0	0.001	0

and CA 19-9 assays, along with the clinical pain scores in the aforementioned clinical scenario.

Materials and Methods

Subjects

Patients who underwent laparoscopy for infertility at the West China Second University Hospital Sichuan University from July 2010 to September 2011 were included. Infertility was defined as failure to achieve pregnancy after unprotected intercourse for one year and above. All patients were advised to avoid exogenous hormones for at least three months before laparoscopy. To avoid any adverse influence of anatomical factors, patients with cysts detected by preoperative ultrasonography were excluded. The study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of Sichuan University. Written informed consent was obtained from all participants.

Systematic laparoscopic evaluation of all pelvic peritoneal surfaces and structures was performed on all patients. Pelvic endometriosis was quantified by the revised American Fertility Society (AFS, 1985) score. Perioperative complications were recorded.

Preoperative serological tests of serum CA-125 and CA 19-9 were performed, and the concentrations were measured with chemiluminescence immunoassay (CLIA).

A multivariate stepwise logistic regression analysis was performed to establish a predictive model, which was transformed into a scoring system. Receiver operating characteristic (ROC) curves were constructed to assess the discriminative power of each biomarker, by measuring the area under the ROC curve (AUC). An operating point was selected on the ROC curve corresponding to a specificity of 70% or higher, and sensitivity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were evaluated. All test results with a *p*-value below 0.05 were reported as significant.

Results

Patients

A total number of 294 patients with the preoperative diagnosis of infertility were recruited prospectively in the study. The age of patients ranged from 20 to 42 years, with a mean age of 33.7±7.0 years. The age, pain scores, duration of infertility, and serum CA-125 and CA 19-9 levels between patients with pelvic endometriosis and control group are listed in Table 1. There was no significant difference in the mean age and the duration of infertility between
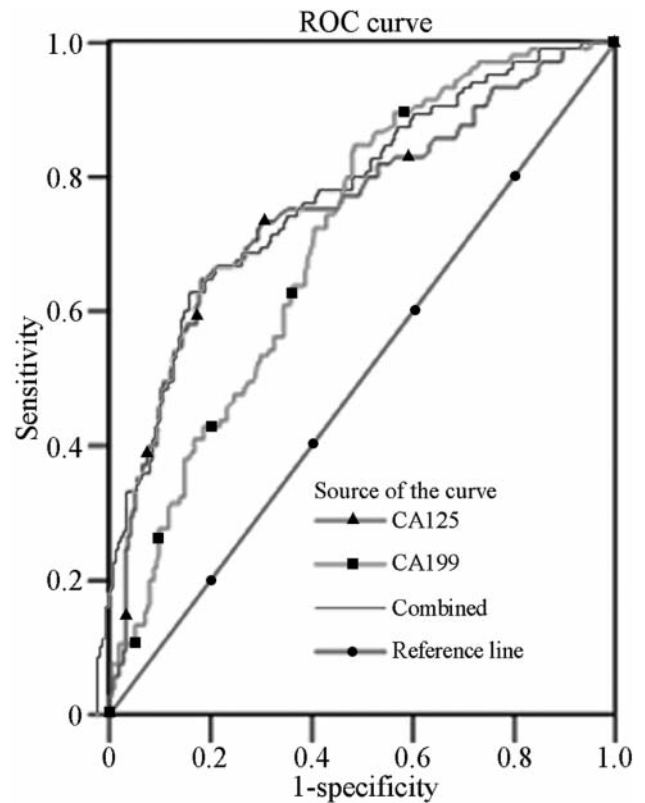

Figure 1. — Receiver operative characteristic curve of serum CA-125, CA 19-9, and combined values for the differentiation of pelvic endometriosis.

the pelvic endometriosis and control group. Most of the patients with endometriosis are stage I and II (75.4%).

Biomarkers

The levels of CA-125 and CA 19-9 in patients with pelvic endometriosis were significantly higher as compared to patients without endometriosis ($p < 0.05$). The pain scores of patients with pelvic endometriosis were higher than those without endometriosis ($p = 0$). The mean serum CA-125 and CA 19-9 concentrations (IU/ml) in patients with AFS-r stage I, II, III, and IV endometriosis were 17.1 ± 8.3 / 17.9 ± 9.8, 28.1 ±2 0.4 / 22.7 ± 18.1, 47.1 ± 77.0 / 50.5 ± 35.1, and 55.2 ± 29.2 / 53.9 ± 34.7, respectively. ROC curve analyses of serum CA-125 and CA 19-9 levels set a cut-off value of 18.25 IU/ml and 13.15 IU/ml (AUC 0.755 and 0.707, respectively; 95% confidence interval, 0.690-0.813) (Figure 1) and this gave a sensitivity of 64.8%/84.8%, a specificity of 81.9%/51.6%, a PPV of 63.6%/46.10%, and a NPV of 81.0%/87.4%, respectively. Combined-analyses gave a sensitivity of 72.4%, a specificity of 81.9%, a PPV of 62.3%, and a NPV of 81.8% (AUC 0.798, 95% confidence interval) (Table 2).

Table 2. — *Sensitivity, specificity, Youden's index and cut-off value of serum CA-125, CA 19-9, and combined concentration in the diagnosis of pelvic endometriosis.*

	Sensitivity	Specificity	Youden's index	Cut-off value
CA125	0.648	0.819	0.467	18.25
CA19-9	0.848	0.516	0.364	13.15
Combined CA125 and CA19-9	0.724	0.819	0.448	31.42

Discussion

The diagnosis of endometriosis is difficult and delayed because of the non-specific symptoms and may result in social and work-related problems for the patient [12]. Two-thirds of women undergoing laparoscopy for pelvic pain or infertility are subjected to potential risks, as well as the cost associated with this procedure without actually having endometriosis [13]. The development of a simple blood test as a marker for screening of endometriosis would reduce the number of unnecessary interventions and would therefore be very useful [14]. The quest to develop a diagnostic test of endometriosis has mostly concentrated on the levels of CA125 and other cytokines [15].

Many studies have shown the usefulness of serum CA-125 assay in the detection of endometriosis. Xavier *et al.* [11] reported a specificity greater than 90% for a cut-off value of 22.6 IU/ml, and Kitawaki *et al.* [16] found that the highest accuracy (78.8%) and the maximum diagnostic value (61.2%) were achieved when 20 IU/ml was used as the cut-off value. A meta-analysis [17] evaluated the value of serum CA-125 assay in the detection of endometriosis, and the results showed a specificity of 85% and sensitivity between 20% and 50%. Mihalyi *et al.* [18] found that moderate–severe endometriosis was diagnosed with a sensitivity of 100% (specificity 84%) and minimal–mild endometriosis was detected with a sensitivity of 87% (specificity 71%) during the secretory phase. Meanwhile, minimal-mild endometriosis was diagnosed with a sensitivity of 94% (specificity 61%) during the secretory phase and with a sensitivity of 92% (specificity 63%) during the menstrual phase. Recently, Mohamed *et al.* showed that there was a statistically significant difference in serum CA-125 level in the patients with endometriosis and those without endometriosis [19]. However, detailed dissection on the study of pelvic endometriosis in infertile women is still needed. The present study showed a significant difference of the levels of serum CA-125 between the patients with endometriosis and the controls ($p < 0.01$). The authors also found the levels of CA-125 increased progressively with the stages of AFS-r in endometriosis and the cut-off value was 18.25 IU/ml, which gave a sensitivity of 64.8% and a specificity of 81.9%, respectively. The results were consistent with other studies, which showed that CA-125 might be considered as a reliable method to detect pelvic endometriosis in infertile women.

In former studies, the results of serum level of CA 19-9 in patients for detecting endometriosis were contradictory [9-11]. The latest study [20] reported that the mean levels of CA 19-9 were significantly elevated at all stages of endometriosis and indicted that endometriosis might be the source of high CA 19-9 levels. The present study showed the similar result, and gave a cut-off value of 13.15 IU/ml, with a sensitivity of 84.8% and a specificity of 51.6%. This indicated that serum CA 19-9 might predict the patients with endometriosis. The discrepancy in the earlier studies might be due to the differences in study designs or patients selection bias. The AUC of the combination marker is 0.798, with a sensitivity of 72.4%, and specificity of 81.9%, which means that the combination biomarker demonstrates a higher clinical utility in diagnosis of pelvic endometriosis.

In the present study, there was a statistical difference in the pain scores between patients with pelvic endometriosis and control group. This demonstrated that pain scores can be used as a valuable marker in the diagnosis of pelvic endometriosis when used in combination with CA-125 and CA 19-9.

Considering the cost-effectiveness and simplicity of the test, the present authors believe that CA-125 and CA 19-9 together with pain scores should be included in the evaluation of unexplained infertility in women. Meanwhile, considering the relatively low sensitivity of these markers, further prospective studies or multi-center studies involving larger number of patients suitable for proper comparisons are needed to explore the value of these markers in detecting pelvic endometriosis.

References

[1] Mahmood T.A., Templeton A.: "Pathophysiology of mild endometriosis: review of literature". *Hum. Reprod.,* 1990, *5*, 765.
[2] Christman G.M., Halme J.K.: "Pathophysiology of endometriosis-endometriosis". *Hum. Reprod. Update.,* 1992, *2*, 371.
[3] Collins J.A., Wrixon W., Janes L.B., Wilson E.H.: "Treatment-independent pregnancy among infertile couples". *N. Engl. J. Med.*, 1983, *309*, 1201.
[4] Collins J.A., So Y., Wilson E.H., Wrixon W., Casper R.F.: "Clinical factors affecting pregnancy rates among infertile couples". *Can. Med. Assoc. J.*, 1984, *130*, 269.
[5] Collins J.A., Rowe T.C.: "Age of the female partner is a prognostic factor in prolonged unexplained infertility: a multicenter study". *Fertil. Steril.*, 1989, *52*, 15.
[6] Snick H.K., Snick T.S., Evers J.L., Collins J.A.: "The spontaneous pregnancy prognosis in untreated subfertile couples: the Walcheren

primary care study". *Hum. Reprod.*, 1997, *12*, 1582.

[7] Marcoux S., Maheux R., Berube S., Bérubé S.: "Laparoscopic surgery in infertile women with minimal or mild endometriosis". *N. Engl. J. Med.* 1997, *337*, 217.

[8] Barbieri R.L., Niloff J.M., Bast R.C. Jr, Scaetzl E., Kistner R.W., Knapp R.C.: "Elevated serum concentrations of CA-125 in patients with advanced endometriosis". *Fertil. Steril.*, 1986, *45*, 630.

[9] Harada T., Kubota T., Aso T.: "Usefulness of CA19-9 versus CA125 for the diagnosis of endometriosis". *Fertil. Steril.*, 2002, *78*, 733.

[10] Somigliana E., Vigano P., Tirelli A.S., Felicetta I., Torresani E., Vignali M., Di Blasio A.M.: "Use of the concomitant serum dosage of CA 125, CA 19-9 and interleukin-6 to detect the presence of endometriosis. Results from a series of reproductive age women undergoing laparoscopic surgery for benign gynaecological conditions". *Hum. Reprod.,* 2004, *19*, 1871.

[11] Xavier P., Beires J., Belo L., Rebelo I., Martinez-de-Oliveira J., Lunet N., Barros H.: "Are we employing the most effective CA-125 and CA 19-9 cut-off values to detect endometriosis"? *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2005, *123,* 254.

[12] Donnez J., Squifflet J., Casanas-Roux F., Pirard C., Jadoul P., Van Langendonckt A.: "Typical and subtle atypical presentations of endometriosis". *Obstet. Gynecol. Clin. North. Am.*, 2003, *30*, 83.

[13] Socolov R., Butureanu S., Angioni S., Sindilar A., Boiculese L., Cozma L., Socolov D.: "The value of serological markers in the diagnosis and prognosis of endometriosis: a prospective case-control study". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2011, *154*, 215.

[14] Garry R.: "Diagnosis of endometriosis and pelvic pain". *Fertil. Steril.*, 2006, *86*, 1307.

[15] Bedaiwy M.A., Falcone T., Sharma R.K., Goldberg J.M., Attaran M., Nelson D.R., Agarwal A.: "Prediction of endometriosis with serum and peritoneal fluid markers: a prospective controlled trial". *Hum. Reprod.*, 2002, *17*, 426.

[16] Kitawaki J., Ishihara H., Koshiba H., Kiyomizu M., Teramoto M., Kitaoka Y., Honjo H.: "Usefulness and limits of CA-125 in diagnosis of endometriosis without associated ovarian endometriomas". *Hum. Reprod.*, 2005, *20*, 1999.

[17] Mol B.W., Bayram N., Lijmer J.G., Wiegerinck M.A., Bongers M.Y., van der Veen F., Bossuyt P.M.: "The performance of CA-125 measurement in the detection of endometriosis: a metaanalysis". *Fertil. Steril.* 1998, *70*, 1101.

[18] Mihalyi A., Gevaert O., Kyama C.M., Simsa P., Pochet N., De Smet F., *et al*.: "Non-invasive diagnosis of endometriosis based on a combined analysis of six plasma biomarkers". *Hum. Reprod.*, 2010, *25*, 654.

[19] Mohamed M.L., El Behery M.M., Mansour S.A.: "Comparative study between VEGF-A and CA-125 in diagnosis and follow-up of advanced endometriosis after conservative laparoscopic surgery". *Arch. Gynecol. Obstet.* 2013, *287*, 77.

[20] Kurdoglu Z., Gursoy R., Kurdoglu M., Erdem M., Erdem O., Erdem A.: "Comparison of the clinical value of CA 199 versus CA 125 for the diagnosis of endometriosis". *Fertil. Steril.*, 2009, *92*, 1761.

Address reprint requests to:
W. HUANG, M.D.
Department of Gynecology and Obstetrics
West China Second University Hospital
Sichuan University
No. 20, Section 3, South Renmin Road
Chengdu 610041 (China)
e-mail: weihuangcn@126.com