Original Article

A study of biomarkers CA-125 CA 19-9 and CA 15-3 in endometriosis

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Abstract

Introduction: Endometriosis is a common, benign, gynaecological disorder characterised by the presence of functional endometrial glands and stroma in sites other than the uterine mucosa. Considerable efforts are currently being devoted to the identification of possible biomarkers of the disease to make its diagnosis less invasive and more accessible. The first and most frequently used marker is CA-125, and it has been extensively studied, however other markers that had been tested are CA 19-9, CA 15-3. The objective of the present study is to evaluate the efficacy of these biochemical markers for the diagnosis of endometriosis. **Methods:** This study was carried out over a period of one year (Oct 2014 to Sept 2015). 100 cases were enrolled in the study and were divided in two groups. Study group (Group A) included 50 patients with pelvic endometriosis diagnosed by ultrasonography and confirmed by surgical procedure (laparoscopy and or laparotomy). Control group (Group B) included 50 patients without endometriosis confirmed by laparoscopy done for bilateral tubal ligation. The severity of endometriosis was staged according to revised American Society for Reproductive Medicine (rASRM) classification. Peripheral blood sample (5ml) was collected by venipuncture. Blood was centrifuged @ 1200 rev/ min for 4 min and the supernatant was stored at less than 20 degree Celsius until blood examination. Concentration of CA 125, CA 19-9 and CA 15-3 was determined by chemiluminescence using automated analyser. **Results and Conclusion:** In our study, CA125 came out to be the biomarker with maximum sensitivity (93.62%) and specificity (88.68%) followed by CA19-9 with sensitivity and specificity of 89.58% and 86.54% respectively, followed by CA15-3 with sensitivity and specificity of 85.37% and 74.58% respectively for the diagnosis of endometriosis.
Keywords: Endometriosis biomarkers, CA 125, CA 19-9, CA 15-3.

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Received Date: 14/02/2016 Revised Date: 20/03/2016 Accepted Date: 02/04/2016

Access this article online	
Quick Response Code:	Website: www.statperson.com
	DOI: 10 April 2016

INTRODUCTION

Endometriosis is a common, benign, gynaecological disorder characterised by the presence of functional endometrial glands and stroma in sites other than the uterine mucosa. It is known to cause dysmenorrhoea (70%), chronic pelvic pain (40%), subfertility (35%), dyspareunia (33%) and menstrual irregularities (16%); which leads to increased burden in terms of healthcare costs and quality of life[1,2]. A recent survey done in 7025 women with endometriosis (European Endometriosis Alliance., 2006)[3] demonstrated that 65% of the women were first misdiagnosed with another condition and 46% had to see five doctors or more before they were correctly diagnosed. There was an average delay of 8 years between the onset of symptoms and the diagnosis of endometriosis[4,5]. Therefore, the need to develop biomarkers for detection and early diagnosis of minimal-mild endometriosis has become the priority in endometriosis research[6]. Considerable efforts are currently being devoted to the identification of possible biomarkers of the disease to make its diagnosis less invasive and more accessible. The first and most frequently used marker is CA-125, and Bast *et al.*[7] first reported its application. CA -125 has been extensively studied, however other markers that had been tested are CA 19-9, CA 15-3. The objective of the present study is to evaluate the efficacy of these biochemical markers for the diagnosis of endometriosis.

MATERIAL AND METHODS

The study was conducted in Department of Gynaecology and Obstetrics, SMGS Hospital and Department of

How to site this article: Preeti Sharma, Shashi Gupta, Nivedita Prashar, B R Bhagat, Gopal Sharma. A study of biomarkers CA-125 CA 19-9 and CA 15-3 in endometriosis. *International Journal of Recent Trends in Science and Technology*. April 2016; 18(3): 469-472. http://www.statperson.com (accessed 12 April 2016).

Biochemistry, Government Medical College and Hospital Jammu, over a period of one year extending from Oct 2014 to Sept 2015. 100 cases were enrolled in the study and were divided in two groups. Study group (Group A) included 50 patients with pelvic endometriosis diagnosed by ultrasonography and confirmed by surgical procedure (laparoscopy and or laparotomy). Control group (Group B) included 50 patients without endometriosis confirmed by laparoscopy done for bilateral tubal ligation. Inclusion criteria for Group A was absence of previous medical or surgical treatment for endometriosis, absence of other diseases of uterus, fallopian tubes, ovaries and confirmed diagnosis of endometriosis by laparotomy or laparoscopy. Inclusion criteria for Group B were age 20-40 years and absence of endometriosis confirmed by laparoscopy done for bilateral tubal ligation. The severity of endometriosis was staged according to revised American Society for Reproductive Medicine (rASRM) classification. Based on this scale, moderate to severe endometriosis was observed in 26 women and 24 women were diagnosed with minimal and mild disease. The ethical committee approved the study protocol and written informed consent was taken from each woman before sample collection. Laboratory Tests: Peripheral blood sample (5ml) was collected by venipuncture. Blood was centrifuged @ 1200 rev/ min for 4 min and the supernatant was stored at less than 20 degree Celsius until blood examination. Concentration of CA 125, CA 19-9 and CA 15-3 then determined by chemiluminescence using automated analyser in the Department of Biochemistry, Super specialty Hospital, Government Medical College Jammu. Reference value of biomarkers (Hui D *et al*., 2011) [8]: CA-125 < 35 kU/l, CA 19-9< 37 kU/l and CA 15-3 < 28 kU/l. Statistical analysis of all the data collected was done using Statistical Package of Social Science, SPSS version 16.0 of windows. Comparison between two groups was done using t-test. Chi square test was used to check association. p value less than 0.05 was taken as significant.

RESULTS

Table 1: Marker comparison in both groups

Markers	Mean ± SD		p-value
	Group A (n=50)	Group B (n=50)	
CA 125	68.12±37.68	18.66±8.24	<0.0001
CA 19-9	55.86±19.71	14.96±5.52	<0.0001
CA 15-3	33.86±11.68	16.82±7.23	<0.0001

Table 2: Grade of endometriosis and CA 125, CA19-9 and CA15-3

Grade	Mean ± SD		
	CA 125(U/ml)	CA 19-9(U/ml)	CA 15-3(U/ml)
Minimal	47.25 ± 21.64	46.25 ± 25.20	24.25 ± 7.27
Mild	51.55 ± 19.85	48.80 ± 19.44	31.65 ± 10.57
Moderate	79.67 ± 46.18	61.52 ± 12.64	35.57 ± 9.62
Severe	102.60 ± 21.77	69.80 ± 20.22	43.20 ± 19.92

From this table we analyse that serum levels of all the three biomarkers were raised in patients with endometriosis, and as the severity of the disease is increased, their levels shows ascending trend.

Table 3: Sensitivity, specificity, PPV, NPV of CA 125 (Group A)

Variables	Per cent	95% CI
AUC	0.810	0.689-0.931
Sensitivity	93.62	82.46 – 98.66
Specificity	88.68	76.97 – 95.73
Positive predictive value	88.00	75.69 – 95.47
Negative predictive value	94.00	83.45 – 98.75
p-value	<0.0001	

Table 4: Sensitivity, specificity, PPV, NPV of CA 19-9 (Group A)

Variables	Per cent	95% CI
AUC	0.732	0.588-0.877
Sensitivity	89.58	77.34 – 96.53
Specificity	86.54	74.21 – 94.41
Positive predictive value	86.00	73.26 – 94.18
Negative predictive value	90.00	78.19 – 96.67
p-value	<0.0001	

Table 5: Sensitivity, specificity, PPV, NPV of CA 15-3 (Group A)

Variables	Per cent	95% CI
AUC	0.663	0.510-0.817
Sensitivity	85.37	70.83 – 94.47
Specificity	74.58	61.58 – 85.02
Positive predictive value	70.00	55.39 – 82.14
Negative predictive value	88.00	75.69 – 95.47
p-value	**<0.0001**	

Table 6: Sensitivity, specificity, PPV, NPV of CA 125 in different grades of endometriosis

Variables	Minimal and Mild		Moderate and Severe	
	Per cent	95% CI	Per cent	95% CI
Sensitivity	86.36	65.09 – 97.09	89.29	71.77 – 97.73
Specificity	90.38	78.97 – 96.80	97.92	88.93 – 99.95
Positive predictive value	94.00	83.45 – 98.75	96.15	80.36 – 99.90
Negative predictive value	45.83	22.55 – 67.18	94.00	83.45 – 98.75
p-value	0.0001			0.0001

Table 7: Sensitivity, specificity, PPV, NPV of CA 19-9 in different grades of endometriosis

Variables	Minimal and Mild		Moderate and Severe	
	Per cent	95% CI	Per cent	95% CI
Sensitivity	68.42	43.45 – 87.42	77.78	54.74 – 91.38
Specificity	80.00	67.03 – 89.57	89.80	77.77 – 96.60
Positive predictive value	54.17	32.82 – 74.45	80.77	60.65 – 93.45
Negative predictive value	88.0	75.69 – 95.47	88.00	75.69 – 95.47
p-value	0.0003			0.0001

Table 8: Sensitivity, specificity, PPV, NPV of CA 15-3 in different grades of endometriosis

Variables	Minimal and Mild		Moderate and Severe	
	Per cent	95% CI	Per cent	95% CI
Sensitivity	77.27	54.63 – 92.18	83.33	65.28 – 94.36
Specificity	86.54	74.21 – 94.41	97.83	88.47 – 99.94
Positive predictive value	70.83	48.91 – 87.38	96.15	80.36 – 99.90
Negative predictive value	90.00	78.19 – 96.67	90.00	78.19 – 96.67
p-value	0.0001			0.0001

Table 9: Comparison of sensitivity, specificity, PPV and NPV in different biomarkers

Variables	CA125 (%)	CA19-9 (%)	CA15-3 (%)
Sensitivity	93.62	89.58	85.37
Specificity	88.68	86.54	74.58
PPV	88.00	86.00	70.00
NPV	94.00	90.00	88.00
p-value	<0.0001	<0.0001	<0.0001

Table 10: Sensitivity, specificity, PPV, NPV of combined biomarkers

Variables	Percent (%)	95% CI
Sensitivity	64.86	47.46-79.79
Specificity	76.92	46.19-94.96
PPV	88.89	70.84-97.65
NPV	43.48	23.19-65.51
Positive likelihood ratio	2.81	1.01-7.80
Negative likelihood ratio	0.46	0.27-0.78

DISCUSSION

Present study revealed that the mean levels of CA125 were 68.12U/ml in patients with endometriosis whereas it was 18.66 U/ml in patients without endometriosis, which was statistically significant. Study by Mihalyi A *et al.* [9] reported that the mean values of CA125 were 22U/ml in patients with endometriosis and 13.0U/ml in controls. In our study serum CA125 shows the sensitivity of 93.62% and specificity of 88.68% in diagnosis of the disease when 35U/ml is used as a cut-off value, which is comparable with the study by Agic A *et al* [10] and Mihalyi A *et al* [9]. In our study sensitivity and specificity of serum CA19-9 is 89.58% and 86.54% in diagnosis of endometriosis using serum level of 37U/ml as cut-off. Harada *et al.* [11] found that the serum CA19-9 levels in patients at any age of endometriosis were significantly higher than in patients without endometriosis. But Mol BW *et al* [12] found less association between elevated CA19-9 levels and endometriosis. Abrao MS *et al.* [13] studied the concentrations of CA125, CA19-9, CA15-3, carcinoembryonic antigin (CEA), alpha-fetoprotein (AFP) and beta-2 microglobulin (B2 MG) in 35 patients with endometriosis and 15 patients without endometriosis. In their study, they found that mean CA125 concentrations were altered in patients with endometriosis, but all patients studied presented with normal CEA, AFP and B2MG concentrations. Small variations detected in CA19-9 and CA15-3 had no statistical significance. They conclude that CA125 is the only important marker in the diagnosis of stage 3-4 of endometriosis. Use of serum biomarkers seem to be promising as a non-invasive method for diagnosis of endometriosis, but further research is necessary before any of the above biomarker is recommended in routine clinical care as our study sample is small. For use of these biomarkers as a routine diagnostic measure, we need to study their behaviour at a larger scale. Limitation of the present study is that stress directly before the surgery might affect the levels of serum biomarkers.

CONCLUSIONS

Thus, from our study and related literature, serum CA125 seems to be most useful biomarker for early diagnosis of the disease as well as in patients with moderate to severe disease. Also the use of combination of biomarkers CA125, CA19-9 and CA15-3 may not help much in the diagnosis of the disease as compared to when individual marker is used.

REFERENCES

1. Fourquet J, Gao X, Zavala D et al. Patients report on how endometriosis affect health, work and daily life. Fertil Steril 2010; 93:2424-28
2. Mcleod BS, Retzloff MG. Epidemiology of endometriosis: an assessment of risk factor. Clin Obstet Gynaecol 2010; 53:389-96
3. European Endometriosis Alliance. Endometriosis, 2006. www.endometriosis.org
4. Ballard KD, Lowton K, Wright JT. What's the delay? A qualitative study of women's experience of reaching a diagnosis of endometriosis. Fertil Steril 2006; 85:1296-301
5. Zondervan KJ, Yudkin PL, Vessey MP, Dawes MG, Barlow DH, Kennedy ST. Prevalence and incidence of chronic pelvic pain in primary care: evidence from a national general practice database. Br J Obstet Gynaecol 1999; 106: 1149-55
6. Rogers PA, D' Hooghe TM, Fazleabas A et al. Priorities for endometriosis research: recommendations from an international consensus workshop. Reprod Sci 2009; 16:335-46
7. Bast RC Jr, Klug TL, St John E, Jenison E, Niloff JM, Lazarus H, Berkowitz RS, Leavitt T, Griffiths CT, Parker L, Zurawski VR Jr, Knapp RC. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med. 1983; 309:883–887.
8. Hui D, Leung A, Padwal R. Approach to Internal Medicine: A Resource Book for Clinical Practice 3rd Ed. Springer New York Dordrecht Heidelberg London 2011; 7:221.
9. Mihalyi, A., O. Gevaert, C.M. Kyama, P. Simsa, Nathalie Pochet, F De Smet, B De Moor, et al. 2010. "Non-invasive Diagnosis of Endometriosis Based on a Combined Analysis of Six Plasma Biomarkers." Human Reproduction 25 (3): 654–664.
10. Agic A, Djalali S, Wolfler MM, Halis G, Diedrich K, Hornung D. Combination of CCR1 mRNA, MCP1, and CA125 measurements in peripheral blood as a diagnostic test for endometriosis. Reprod Sci. 2008 Nov; 15(9):906-11. doi: 10.1177/1933719108318598.
11. Harada T, Kaponis A, Iwabe T, Taniguchi F, Makrydimas G, Sofikitis N, Paschopoulos M, Paraskevaidis E, Terakawa N. Apoptosis in human endometrium and endometriosis. Hum Reprod Update 2004;10(1): 29-38
12. Mol BW, Bayram N, Lijmer JG, Wiegerinck MA, Bongers MY, van der Veen F, Bossuyt PM. The performance of CA-125 measurement in the detection of endometriosis: a meta-analysis. Fertil Steril. 1998 Dec; 70(6):1101-8.
13. Abrão MS1, Podgaec S, Pinotti JA, de Oliveira RM. Tumor markers in endometriosis. Int J Gynaecol Obstet. 1999 Jul; 66(1):19-22.

Source of Support: None Declared
Conflict of Interest: None Declared