Thrombocytosis and CA125 as Predictor of Malignancy in Gynaecological Pelvic Mass

Najmah M. Miran * **FICOG, CABGO, DOG**

Abstract:

Background: Pelvic masses are common in women & can present at any age of woman life, it could be benign or malignant mass and may originate from gynecological organs like cervix, uterus, uterine adnexia, or from other pelvic organs like intestine, bladder, ureters, skeletal muscle, and bone.

Objective: We attempted to determine the increasing of platelet counts(> 450.000 /micro liter) and CA125serum level (> 35 U/mL) as useful tools for predicting and confirming malignancy in gynecological pelvic mass.

Patients and methods: A prospective unmatched hospital based case-control study carried out at Baghdad Teaching Hospital, about 126 women were enrolled in our study, divided into two groups 60 women were control group (free of gynecological pelvic mass). The other group includes 66 women above 15 years old with gynecological pelvic mass were all candidate for laparotomy.

Results: Serum CA125 and blood platelets count were tested for validity when used as a test to predict a diagnosis of malignancy in gynecological pelvic mass differentiating it from benign gynecological pelvic mass. Both tests showed a very high validity in diagnosis, with serum CA125 showing a marginally higher validity.

All studied subjects with a blood platelets count ≥ 385.000 and CA 125≥ 41.7were malignant, while everybody below this cut-off value was benign or healthy.

Conclusion: Both blood platelet count (≥385 X 10^3microlitter) &serum level of CA125 (≥41.7 U/mL) are useful predictor tools to confirm malignancy in gynecological pelvic mass.

Keywords: - thrombocytosis, Ca 125, malignancy, pelvic mass.

Fac Med Baghdad 2017; Vol.59, No.3
Received: June 2017
Accepted: Aug .2017

Introduction:

Pelvic masses are common in women & can present at any age of woman life. They may originate from gynecological organs like cervix, uterus, uterine adnexia, or from other pelvic organs like intestine, bladder, ureters, skeletal muscle, and bone. (1). Pelvic masses may be detected during a routine gynecological examination, found upon examination of a specific complaint, or found incidentally during radiological evaluation of the pelvis. It is considered that serum CA125 are helpful in the diagnostic evaluation of pelvic masses. An increase (ranging from 80 to 90%) of CA125 serum levels are associated with malignant non-mucinous epithelial ovarian tumors. CA125 represents the gold standard tumor marker for ovarian cancer in the diagnosis and follow up of treated patients (2,3). CA125 serum levels equal or below (35 U/ml) are normal. CA125 serum levels greater than (50-65 U/ml) (in the 80-90% of postmenopausal patients) is associated with a malignancy. Best sensitivity and specificity results have been reached by integrating different diagnostic techniques like clinical history, tumor markers and ultrasonography to create risk index (4). Thrombocytosis is the increase in platelet counts in the blood, and can be either primary or secondary. Although often symptomless (especially in secondary type), but it can predispose to thrombosis in some patients (5). In a healthy individual, a normal level of platelet ranges from (150–450 x 109/L). Tumor cells interact with all major components of the haemostatic system, including platelets. Platelets and platelet activation have been linked to key steps in cancer progression. The contribution of platelets to malignancy progression has been suggested to be organized process that underlies the pathobiology of cancer growth, propagation, maintenance & identify potential targets & directions for platelet-directed anticancer therapy in the future. Patients with reactive thrombocytosis and with solid tumors had higher levels of thrombopoietin than patients with nonneoplastic conditions associated with reactive thrombocytosis or essential thrombocytosis (6). Tumor related humeral factors with thrombopoietin-like activity (7) and overcompensated megakaryocytopoiesis due to tumor-induced disseminated intravascular coagulopathy(8) have been anticipated in the etiology of reactive thrombocytosis in patients with malignant disease. There is evidence suggesting that platelets play a role in the development of tumor metastasis. Tumor cell-platelet interactions may affect the process of metastasis at different levels (9).

**Dept. of obstetrics and gynecology, college of medicine/University of Baghdad.*
Email:knmzaf74@gmail.com

Patients &Methods:

This is a prospective unmatched hospital based case-control study conducted at Obstetrics & Gynecology Department at Baghdad Teaching Hospital over a period of one year from June 2015 to June 2016. One hundred & twenty six women were enrolled in our study, divided into two group 60 women were considered as control group (free of pelvic mass) which were considered as "voluntary entrants" into the study. The other group includes 66 women above 15 years old with gynecological pelvic mass diagnosed by clinical & imaging techniques (U/S, CT scan & MRI) those 66 patients were all candidate for laparotomy. A full history was taken from each woman including age, parity, marital status, obstetrical & gynecological history with detailed menstrual history (age of menarche, regularity, age of menopause and any abnormal vaginal bleeding), medical history, surgical history , family history of malignancy (breast , colon & ovary) , any previous personal history of ovarian cyst or malignancy , smoking & drug history (hormonal therapy , combined oral contraceptive pills ,chemotherapy & radiotherapy). A clinical examination was done including: General examination for any sign suggestive of malignancy (cachexia, anaemia, lymphoadenopathy … etc.) Thorough systemic examination of the chest & abdomen for any palpable organomegaly, other palpable masses & ascites. Full gynaecological examination was done to assess the mass size, consistency, tenderness, mobility, nature of the mass, relation to the uterus with the assessment of uterus & adnexia. Then, review of the ultrasonic reports (trans-abdominal or trans-vaginal) & other imaging techniques, was done to exclude non-gynecological causes of the mass & help reaching diagnosis. The exclusion criteria for those women were: Any patient with myeloproliferative disease. Any patient had recent or chronic infection. Any patient with autoimmune disease or SLE Any patient had medications, chemotherapy or radiotherapy which can affect platelets count. Postpartum or postoperative patients. Those who had recent trauma. Patient who had splenectomy. Those sixty six women were all candidates for laparotomy. After admission to the ward, routine preoperative investigations were done to all of those patients preparing them for laparotomy, which include chest X-ray, ECG, Blood tests: 10ml of venous blood was aspirated, 5ml of it was put in non EDTA tube & other 5ml was put in EDTA tube & shake gently to prevent clotting of sample. The first tube was sent for routine blood tests which include (blood group, Rh, blood sugar, blood urea, serum creatinine) and second tube for CA 125. The EDTA tube blood sample of each patient was sent to the laboratory to study the complete blood picture (& from this the HB & platelets count) by an automated method, which is done by using Beckman Coulter machine.The platelets count > $450x10^9$ /L was considered as thrombocytosis. Laparotomy was done then for each those sixty six patients by a senior gynecologist & diagnosis of the site & origin of the mass was conducted. Surgical staging of those with high suspicion of malignant ovarian tumor had been done at the time of laparotomy. All the specimens were send for histopathological exam. Those data of histopathology, platelets count, CA125 & Hb were subjected to statistical analysis (sensitivity, specificity, accuracy, NPV & PPV) which calculated to considered if it is statistically significant or not.

Results:

We have studied one hundred &twenty six women, 66 women were candidates for laparotomy. Pre-operative data were collected to be analyzed as follows: Forty one women of them (62.1%) had benign pathology and twenty five of them (37.9%) with malignant pathology. Their ages were ranged from (20-76) years , with the mean age for benign group was about (42.61 ± 12.51) years and (44.81 ± 12.1) years for the malignant groups while age range of healthy controls group was (17-52) years ,with mean age was about (29.5±8.5) years as show in table (1). The mean of parity was (4±2.6), (5±1.5) and (3±1.6) for benign, malignant and healthy control group respectively as shown in table (1) The mean of hemoglobin concentration in 3 groups were (10.7±1.5) , (10.9±2.6) and (11.6±1.1) for benign, malignant and healthy controls group respectively as shown in table (1). Both the benign & healthy control group show platelets count range were between (132-560) and (108-366) with mean (325.4± 116.3) & (232.9±70) respectively while malignant group the platelets range between (405-762) and the mean of it was (549.6±105.7). Table (1) also shows very obvious variation in range & the mean value of serum CA125 between 3 groups. The range of healthy control group was (8.3-38.3) and the mean was (17.8±11.3) while range of benign group was (12-65) and the mean was (30.8±11.1) , in contrast the malignant group rang was (34-185) & mean was (87.5±49.2).

Table (1): The difference in mean of selected parameters between the 3 study groups

Study groups	N	Age (years)	Parity	Blood Hb (gm/dl)	Blood platelets count	Serum Ca125
Healthy controls	60	Range (17 to 52) Mean 29.5 SD 8.5 SE 1.1	Range (0 to 7) Mean 3 SD 1.6 SE 0.21	Range (9.1 to 14) Mean 11.6 SD 1.1 SE 0.14	Range (108 to 366) Mean 232.9 SD 70 SE 9.04	Range (8.3 to 38.3) Mean 17.8 SD 11.3 SE 3.58
Benign pelvic mass	41	Range (20 to 76) Mean 42.61 SD 12.51 SE 2.26	Range (0 to 9) Mean 4 SD 2.6 SE 0.47	Range (7 to 13.6) Mean 10.7 SD 1.5 SE 0.27	Range (132 to 560) Mean 325.4 SD 116.3 SE 19.17	Range (12 to 65) Mean 30.8 SD 11.1 SE 2.0
Malignant pelvic mass	25	Range (24 to 65) Mean 44.81 SD 12.1 SE 2.71	Range (2 to 7) Mean 5 SD 1.5 SE 0.32	Range (7 to 15.6) Mean 10.9 SD 2.6 SE 0.51	Range (405 to 762) Mean 549.6 SD 105.7 SE 24.12	Range (34 to 185) Mean 87.5 SD 49.2 SE 11.91
(NOVA)		<0.001	<0.05	<0.01	<0.001	<0.001

Table 2: The malignant – benign group difference in site of pelvic mass.

	Study group			
	Benign pelvic mass		Malignant pelvic mass	
	N	%	N	%
Site of pelvic mass				
Uterus	23	56.1	8	32.0
Ovary	18	43.9	14	56.0
Cervix	0	0.0	3	12.0
Total	41	100.0	25	100.0

Table 3: Frequency distribution of cases with benign pelvic mass by histopathology.

Pathologic type of pelvic mass	N	%
Corpus leutium cyst	4	9.8
Mucinous cyst adenoma	1	2.4
Dermoid cyst	6	14.6
Endomterioma	4	9.8
Fibroid	22	53.7
hemorrhagic cyst	1	2.4
invasive mole	1	2.4
serous cyst adenoma	2	4.9
Total	41	100.0

Table (4): Frequency distribution of cases with malignant pelvic mass by histopathology.

Pathologic type of pelvic mass	N	%
mucinous adenocarcinoma	6	24.0
endometrial adenocacinoma	4	16.0
serous adenocarcinoma	6	24.0
leiomyosarcoma	4	16.0
sequemous cell carcinoma of cervix	3	12.0
granulosa cell tumour	1	4.0
immature teratoma	1	4.0
Total	25	100.0

Discussion:

New studies have addressed the prognostic impact and prevalence of thrombocytosis in different gynecological and non-gynecological malignancies (10, 11). CA125 has also been tested for the ability to differentiate benign from malignant pelvic masses. The ability to predict whether a tumor is benign or malignant before surgery is important (12). The most prevalent type of pelvic tumors (benign or malignant) in this study was the ovarian tumor (benign 43.9%, malignant 56%). In Iraq, cancer of the ovary is relatively a common form of malignancy representing (3.2%) of all female cancer and second to the cervical carcinoma in the female genital tract (13,14,15).Majmudar T, et al in UK (2008) (16) concluded in their study that benign ovarian tumors are the main presentation of pelvic tumors. In developing countries, The incidence of cancer is increasing (17, 18). The predominant pathological type of pelvic benign tumor in this study was fibroid (53.7%). This finding is consistent with Sschwärzler P, et al study in UK (1998) (19). Ashraf A, et al in Pakistan (2012) (20) and Makwana H, et al in India (2013)(21). The predominant pathological type of pelvic malignant tumor in this study was mucinous and serous cyst adenocarcinoma. This finding is inconsistent with Ashraf A, et al study in Pakistan (2012) (20) and Makwana H, et al study in India (2013) (21) in which the serous cyst adenocarcinoma was the prevalent pathological type. In the present study ANOVA analysis revealed mean age of the studied patients was significantly higher among patients with malignant pelvic mass ($p<0.001$). This

result is consistent with finding of Kline RC, et al study in USA (2010) (22) and Berker B, et al study in UK (2010) (23). The incidence of ovarian cancer is low in young women and epithelial ovarian cancers are not known to occur before menarche, and most of them (though rare) are germ cell tumor, serous borderline tumors and juvenile granulosa cell tumor. Age specific incidence is 40/100,000 by the age of 50 and rises to 50 per 100,000 women by the age of 65 years (24). ANOVA analysis of this study revealed a significant lower hemoglobin level among patients with malignant pelvic type as compared to healthy women ($P<0.01$). This finding is similar to results of Gücer F, et al study in Turkey (2004)(25) and Rani AK, et al study in India (2012) (26). The present study revealed by ANOVA analysis a significant increase in platelets count among patients with malignant pelvic tumor ($p<0.001$). This finding is consistent with results of previous Iraqi literature by Al-Nakaash N, et al study (2008) (27)which reported that high preoperative platelet count in women presenting with pelvic mass may predict a final diagnosis of cancer . ANOVA analysis in the present study revealed significant increase in serum CA125 among patients with pelvic malignant tumor ($p<0.001$). This finding is similar to results of Asher V, et al study in UK (2010) (28), Kulkarni M, et al study in USA (2013) (29) and Rani AK, et al study in India (2012) (26).CA125 is a high molecular weight glycoprotein and is the most useful tumor marker for epithelial ovarian carcinoma (30). The study of parity history of participated women by ANOVA analysis revealed significant increase of parity number among patients with malignant pelvic tumor ($p<0.05$). This finding is consistent with results of Valentine L, et al study in Sweden (2006) (31). Many literatures have found that a higher number of ovulatory cycles are associated with an increasing risk for ovarian cancer (32). ROC curve analysis in the present study revealed that serum CA125 and thrombocytosis were significant predictors of malignant pelvic tumors among patients with pelvic mass ($p<0.001$). This finding is consistent with results of Moore RG, et al study in USA (2007) (33). ROC curve analysis in the present study revealed that serum CA125 and thrombocytosis were significant predictors of pelvic tumors (malignant and benign) among healthy women ($p<0.001$). This finding is consistent with results of Yavuzkan A, et al study in Turkey (2013) (34). In the same direction, this study revealed that the sensitivity of using both serum CA125 and platelets count as predictor of pelvic tumors was 100% among healthy females with appropriate predictive value. In the past 20 years, different investigators have proposed risk of malignancy indexes (RMIs) to successfully discriminate malignant from benign masses on an objective basis (35). Four different indexes utilizing CA125 levels, findings of malignancy on performed USG and menopausal status as the basic variables have yielded a sensitivity ranging from 71-86.8%, and a specificity ranging from 91-96% (35). Any studies evaluating RMI scales in Asian and Pacific countries have reported different cut-off values compared to those originally reported by the investigators who proposed these indexes at the first place (36). On the other hand, according to the report by van denAkker et al. (37)from Holland, a cut-off value of 200 for RMI-3 and 450 for RMI-4 showed the best performance and yielded success rates similar to that reported by the original investigators (37).

Conclusions:

Both CA125 and thrombocytosis are important predictors of pelvic tumors in women. Combined CA125 and thrombocytosis assessment reflect the possibility of malignancy Increased serum CA125 (≥41.7U/ml), high platelets count (≥385 x 109 / micro liter), lower hemoglobin levels, older age and high parity were more prevalent among women with malignant pelvic tumor.

References:

1. Jean Noel Buy , Michel Ghossain "GynecologicalImaging A Reference Guide to Diagnosis" Springer-Verlag Berlin Heidelberg (2013) ; 2 : 17-46

2. Bast RC, Badgwell D, Lu Z, Marquez R, Rosen D, Liu J, Baggerly KA, Atkinson EN,Skates S, Zhang Z, Lokshin A, Menon U, Jacobs I, Lu K. New tumor markers: Ca125 and beyond. Int J Gynecol Cancer (2005);15(suppl.3):274-281.

3. Duffy MJ. Tumor Markers in Clinical Practice: A Review Focusing on Common Solid Cancers. Med PrincPract. (2012) May 15.

4. Jacobs I, Stabile I, Bridges J, Kemsley P, Reynolds C, Grudzinskas J, Oram D. Multimodal approach to screening for ovarian cancer. Lancet (1988);1(8580):268-71.

5. Eustace D, Han X, Gooding R, Rowbottom A, Riches P and Heyderman E: Interleukin-6 (IL-6) functions as an autocrine growth factor in cervical carcinomas in vitro. GynaecolOncol 50:15-9, (1993)

6. Espanol I, Hernandez A, Cortes M, Mateo J and Pujol-Moix N:Patients with thrombocytosis have normal or slightly elevated thrombopoietin levels. Haematologica, (1999);84: 312-316.

7. Von Knorring J, Selroos O and Scheinin TM: Haematologic findings in patients with renal carcinoma. Scand J UrolNephrol, (1981);15: 279-83,

8. Edwards RL, Rickles FR, Moritz TE, Henderson WG, Zacharski LR, Forman WB, Cornell CJ, Forcier RJ, O'Donnel JF and Headley E: Abnormalities of blood coagulation tests in patients with cervical cancer. Am J ClinPathol, (1988);88: 596-602.

9. Honn KV, Tang DG and Crissman JD: Platelets and cancer metastasis: A causal relationship. Cancer Metastasis Rev, (1992); 11: 325-41.

10. Gadducci A, Cosio S, Zola P, et al: Surveillance procedures for patients treated for epithelial ovarian

cancer: A review of the literature. Int J Gynaecol Cancer,(2007) ; 17:21-31.

11. Sugiyama T, Nishida T, Komai K, et al: Comparison of CA 125 assays with abdominopelvic computed tomography and transvaginal ultrasound in monitoring of ovarian cancer. Int J GynaecolObstet, (1996) ; 54:251-256.

12. Skates SJ, Menon U, MacDonald N, et al: Calculation of the risk of ovarian cancer from serial CA-125 values for preclinical detection in postmenopausal women. J ClinOncol,(2003) ; 21:206-210.

13. Jean RA, Rene G, Jonathan SB., Novak's Gynaeology, 13thedition, Lippineott Williams &Ikins, (2002) ;5,32:1245-1302.

14. Al-Saadi ZA, Al-Saleem T. and Alash N. Ovarian tumors in the medical city hospital - A clinicopathologic study J. Fac. Mod. Baghdad, (1988); 30 (4):421426.

15. Ibraheem KS., and Majeed, A.M. cancer in the north part of Iraq. (Nenavah province) Iraqi M. J., (1987); 35 (2): 33-36.

16. Majmudar T, Abdel-Rahman H. Pelvic mass – diagnosis and management. Obstetrics, Gynaecology and Reproductive Medicine Volume,(2008); 18, (7): 193–198.

17. Parkin DM, Muir CS, Whelan SL et al. eds. Cancerincidence in five countries. Lyon: IARC, (1997); 8:1028-9.

18. Pisani P. Burden of cancer in developing countries.IARC Scientific Pub,(1994); 129: 31-9.

19. Schwärzler P, Concin C, Bösch H, Berlinger A, Wohlgenannt K, Bourne TH. An evaluation of sonohysterography and diagnostic hysteroscopy for the assessment of intrauterine pathology. Ultrasound ObstetGynaecol,(1998); 11:337–342.

20. Ashraf A, Shaikh S, Ishf K, Akram A, Kamal F, Ahmad N. The relative frequency and histopathological pattern of ovarian masses. Biomedica,(2012); 28: 98-102.

21. Makwana H, Maru A, Lakum N, Agnihotri A, Trivedi N, Joshi J. The relative frequency and histopathological pattern of ovarian masses-11 years study at tertiary care center. International Journal of Medical Science and Public Health,(2014); 3 (1): 81-84.

22. Kline RC, Bazzett-Matabele LB. Adnexal Masses and Malignancies of Importance to the Colorectal Surgeon. Clin Colon Rectal Surg,(2010); 23:63–71.

23. Berker B, Pabuccu EG. Laparoscopic Management of Suspicious Adnexal Masses. Available on: http://laparoscopy.blogs.com/prevention_management_3/2010/07/lapa

24. Westhoff C: Ovarian cancer. Annu Rev Public Health,(1996); 17:85-96.

25. Gücer F, Tamussino K, Keil F, Balkanli-Kaplan P, Yüce MA. Thrombocytosis in Gynecologic Malignancies. Anticancer Research, (2004) ; 24: 2053-2060.

26. Rani AK, Kapoor D. Ruptured ovarian endometrioma with an extreme rise in serum CA 125 level — a case report ovarian endometrioma with very high CA-125 level. Gynecologic Oncology Reports,(2012); 2: 100-101.

27. Al-Nakaash N, Abd Al-Hasan M, Ghazi W. Thrombocytosis as a Predictor of Malignancy in Patients with a Pelvic Mass. Iraqi J. Comm. Med., Apr. (2008); 21(2): 115-119.

28. Asher V, Hammond R, Duncan TJ. Pelvic mass associated with raised CA 125 for benign condition: a case report. World Journal of Surgical Oncology ,(2010); 8:28.

29. Kulkarni M, Bhandiwad A, Sunila R. CA-125 as a surrogate marker in a clinical and pathological study of pelvic mass at a tertiary care hospital. Journal of Evolution of Sciences,(2013); 2 (26): 4778-4782.

30. Shiau CS, Chang MY, Chiang CH, Hsieh CC, Hsieh TT. Ovarian endometrioma associated with very high serum CA-125 levels. Chang Gung Med J,(2003) ; 26: 695–699.

31. Valentin L, Ameye L, Jurkovic D, Metzger U, Lecuru F, Van. "Which extrauterine pelvic masses are difficult to correctly classify as benign or malignant on the basis of ultrasound findings and is there a way of making a correct diagnosis?" Obstetrics and Gynecology, (2006) ; 27 (4): 438-44. Available on: http://dx.doi.org/10.1002/uog.2707

32. Terry KL, Titus-Ernstoff L, McKolanis JR, Welch WR, Finn OJ, Cramer DW. Incessant ovulation, mucin 1 immunity, and risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev, (2007) ; 16: 30–35.

33. Moore RG, BastRCJr. How Do You Distinguish a Malignant Pelvic Mass From a Benign Pelvic Mass? Imaging, Biomarkers, or None of the Above? Journal of Clinical Oncology, (2007) ; 25 (27): 4159-4161.

34. Yavuzcan A, Caglar M, Ozgu E, Ustun Y, Dilbaz S, Ozdemir I, et al. Should Cut-Off Values of the Risk of Malignancy Index be Changed for Evaluation of Adnexal Masses in Asian and Pacific Populations? Asian Pac J Cancer Prev, (2013) ; 14 (9), 5455-5459.

35. Yamamoto Y, Yamada R, Oguri H, Maeda N, Fukaya T. Comparison of four malignancy risk indices in the preoperative evaluation of patients with pelvic masses. Eur J ObstetGynecolReprodBiol, (2009) ; 144: 163-7.

36. Bouzari Z, Yazdani S, Ahmadi MH, et al. Comparison of three malignancy risk indices and CA-125 in the preoperative evaluation of patients with pelvic masses. BMC Res Notes, (2011) ; 4: 206.

37. Van den Akker PA, Zusterzeel PL, Aalders AL, et al. External validation of the adapted risk of malignancy index incorporating tumor size in the preoperative evaluation of adnexal masses. Eur J ObstetGynecolReprodBiol,(2011);159:422-5.