Ibrahim Card Med J 2021; 11 (2): 33-39

Differentiation of Benign and Malignant Ovarian Tumour by USG and Serum CA-125

Sunandita Sarkar,[1] Shahela Jesmin,[2] Nahid Yusuf,[3] Anindita Sarkar,[4] Suravi Sarker[5]

ABSTRACT

Background & objective: Most ovarian tumors are diagnosed at advanced stage, when they have already been spread. There is no reliable diagnostic test or imaging technique available to distinguish benign from malignant cysts. The present study was undertaken to find the diagnostic accuracy of ultrasound and carcinogenic antigen-125 (CA-125) in the differentiation of benign from malignant ovarian tumors.

Methods: The study was carried out in the Department of Obstetrics & Gynecology, Rajshahi Medical College Hospital (RMCH), Rajshahi over a period of 2 years from July 2016 to June 2018. Patients attending at RMCH with clinical diagnosis of ovarian tumor (adnexal mass) and sonographically diagnosed as having ovarian mass of >8 cm were included in the study. A total of 75 such cases were consecutively included in the study. The sensitivity, specificity, positive and negative predictive values and overall diagnostic accuracy of ultrasound and CA-125 were judged against histopathological findings. Also, Kappa analysis was done to determine the strength of agreement between the two diagnostic modalities.

Result: Age distribution showed that about one-third (32%) of the patients was 50 or > 50 years old with median age of the patients being 40 years (range: 20 – 70 years). Nearly two-thirds (64%) of the patients were multipara and 41.3% were at menopausal stage. Over one-third (34.7%) of the masses were found to be malignant on ultrasonic examination. Over half (52%) of the patients had CA-125 level > 65 U/ml with median CA-125 being 80.7 U/ml. Histopathology reported that 44(58.7%) tumors were benign and the rest 31(41.3%) were malignant. The sensitivity of ultrasound in correctly detecting malignant ovarian tumors was 77.4%, while its specificity in correctly excluding malignancy was 95.4% with overall diagnostic accuracy of the test being 88%. The CA-125 at a cut-off value of 65 although demonstrated a higher sensitivity (83.9%) than USG, its specificity was lower (70.5%) than USG, with overall diagnostic accuracy being 76%. The consistency or strength of agreement between USG & CA-125 in differentiating malignant from benign ovarian tumors was evaluated using kappa-statistics which revealed a moderate agreement between the two diagnostic modalities.

Conclusion: The study concluded that ultrasound has optimum sensitivity and high specificity in differentiating malignant ovarian tumors from the benign ones. The CA-125, although exhibits a higher sensitivity than USG, its specificity is lower than USG. A moderate agreement between the two diagnostic modalities was observed. As USG has optimum sensitivity and high specificity with overall diagnostic accuracy being higher than CA-125, USG could be considered superior to CA-125 as a screening test for differentiation of malignant ovarian masses from the benign ones.

Key words: Benign, malignant, ovarian tumour, USG, serum CA-125 etc.

ORIGINAL ARTICLE

Author's information:

[1] ***Dr. Sunandita Sarkar****, MBBS, BCS, MS (Obstetrics and Gynecology), Registrar, Rajshahi Medical College, Rajshahi*

[2] ***Professor Dr. Shahela Jesmin,*** *Professor & Head, Department of Obstetrics and Gynecology, Rajshahi Medical College, Rajshahi*

[3] ***Dr. Nahid Yusuf,*** *Associate Professor, Department of Obstetrics and Gynecology, Rajshahi Medical College, Rajshahi*

[4] ***Dr. Anindita Sarkar,*** *MBBS, BCS, MD (Pathology), Assistant Professor, Rangpur Medical College.*

[5] ***Dr. Suravi Sarker,*** *MBBS, MS (Obstetrics and Gynecology), Department of Obstetrics and Gynecology, Rajshahi Medical College, Rajshahi.*

Correspondence: ***Dr. Sunandita Sarkar,*** *Mobile: 01721612555, E-mail: drsunanditamoon42@gmail.com*

INTRODUCTION:

Malignant ovarian tumor is responsible for the death of over 125,000 women worldwide each year and kills more women than all other gynaecologic cancers combined. It is the 2nd deadliest cancer for women and the 5th leading cause of cancer death in women worldwide.[1] Most ovarian tumors are diagnosed at an advanced stage, when they have already been spread. Early diagnosis of ovarian cancer when it is still confined to the ovaries has a much better outcome and can often be successfully treated. Unfortunately, the disease is often not recognized in its early stages for vague and nonspecific symptoms.[2] For these reasons when the ovarian cancer is diagnosed it is already spread outside the ovaries to the pelvis (stage II), the abdomen (stage III) or more distant sites (stage IV) and is far more difficult to treat successfully. This information suggests that an effective method of screening to detect early stage of ovarian cancer may save lives of many women.

In routine clinical practice, early detection of ovarian cancer can be achieved by ultrasound scanning and by tumor markers such as CA-125. Screening with CA-125 measurement and ultrasonography findings in every 6 months has been recommended for high-risk women. Preoperative disease classification for patients with ovarian masses, in particular discrimination between benign and malignant ovarian tumors, is important for optimal patient management. Currently, it is not clear whether subjective evaluation of an ultrasound image of an ovarian mass or determination of serum CA-125 levels is the best method to distinguish benign from malignant tumors. However, in a study it was seen that ultrasonographic findings can correctly classify 93% of the ovarian tumors as benign or malignant, while serum CA-125 can correctly classify at best 83% of the masses, when the results from both assays were compared with histological findings following surgery.[3]

The ovarian cancer mucin, CA-125, was first identified by the monoclonal antibody, OC 125 in 1981.[4] The CA-125 molecule is a glycoprotein and composed of a short cytoplasmic tail, a transmembrane domain, and an exceptionally large glycosylated extracellular domain. This large glycosylated mucin molecule is present within normal ovarian tissue. The CA-125 is the most widely used tumor marker for diagnosis of epithelial ovarian cancer. It is also used as a prognostic marker in patients with ovarian cancer to assess response to chemotherapy and to detect tumor recurrence. The level of CA-125 is found to be elevated in 50% of patients in the early stages of ovarian cancer, when treatment is most effective. CA-125 levels are elevated in 80% of women with advanced ovarian malignancy. A serial fall in CA-125 levels has been shown to be associated with response to treatment and a serial rise in CA-125 by 25% over three samples is almost 100% specific for disease progression.[5] On the other hand, ultrasonography examination of ovarian masses can also be used in some cases of benign and malignant tumors. The subjective evaluation of ultrasonography findings is highly accurate for an experienced examiner and is better than mathematical models at predicting whether ovarian tumors are malignant or benign. Ultrasound findings can also frequently identify the specific types of ovarian tumor.[3] The histology of surgically removed ovarian tissues is the final endpoint of the study. The histopathological analysis can establish the distinction of benign ovarian tumors from malignant ones. By far, there are no published reports comparing the diagnostic accuracy of CA-125 with that of ultrasound in the differentiation of malignant ovarian tumors from the benign ones. The present study was intended to find and compare the diagnostic accuracies of USG and CA-125 in differentiating malignant ovarian tumours from the benign ones.

METHODS:

This cross-sectional descriptive type study was conducted on Department of Obstetrics & Gynecology, Rajshahi Medical College, Rajshahi over a period of 2 years from July 2016 to June 2018. Patients presented with (clinically suspected of ovarian mass) attending in Department of Obstetrics & Gynecology Rajshahi Medical College Hospital, Rajshahi were the study population. All age group women having adnexal masses and patients present with sonographically diagnosed ovarian masses of

more than 8 cm were included in the study. A total 75 cases of ovarian mass were included. On obtaining ethical clearance from the Ethical Committee of Rajshahi Medical College, Rajshahi, and consent from patients the data collections commenced. Detailed history of the participating patients was noted before inclusion into the study to make clinical diagnosis of their diseases. Women with at least one persistent ovarian tumor underwent transabdominal ultrasonography, performed by an experienced sonologist. History also included age, parity, method of contraception used and family history of ovarian tumor and any history of pelvic surgery done earlier.

Examinations of the patients included general per abdominal, per vaginal and per rectal examinations. On examination, emphasis was given to the presence of ovarian tumor, its size, surface, mobility and consistency. Per rectal examination was also done to confirm the findings of per vaginal examination. Some relevant investigations for preparing the patient were also needed. Data were collected with the help of a structured questionnaire which contained all the variables of interest and were processed and analyzed using computer software SPSS (Statistical Package for Social Sciences). The test statistics used to analyze the data were descriptive statistics. The diagnostic accuracies (sensitivity, specificity) of the USG and CA-125 were evaluated by comparing the findings of the two diagnostic modalities with those of histopathology. The agreement between the two diagnostic modalities was tested using kappa statistics (k-statistics), whereby a kappa value of 0 – 0.2 was considered as poor agreement, 0.21-0.4 fair agreement, 0.41-0.6 moderate agreement, 0.61–0.8 good agreement and 0.91-1.0 as excellent agreement. The level of significance was set at 0.05 and $p < 0.05$ was considered significant.

RESULTS:

Age distribution shows that about one-third (32%) of the patients was 50 or > 50 years old, 20% 40-50 years, 17.3% 30-40 years, 18.7% 20-30 years and 12% were < 20 years old. The median age of the patients was 40 years and the youngest and the oldest patients were 20 and 70 years old respectively (Table I). Majority (88%) of the patients was married with median duration of marriage being 26 years (range: 15-55 years). Nearly two-thirds (64%) of the patients were multipara, 13% primipara and 23% grand multipara. Table III shows the menstrual profile of the study patients. Nearly half (47%) of the patients had regular menstruation, 12% irregular cycle and 41.3% had menopause. Over 70% reported average menstrual flow, 22.7% scanty flow and 6.8% had profuse bleeding. The median duration of period was 5 days and the median duration of menopause was 10 years. Approximately 63% of the masses were of 100 or < 100 sq. cm and the rest was over 100 sq. cm. The median size of the mass was 80.8 sq. cm. Over one-third (34.7%) of the masses were reported to be malignant on ultrasonic examination (Table II).

CA-125 Assay:

Over half (52%) of the patients had CA-125 level >65 and 34.7% had had < 35 U/ml with median CA-125 being 80.7 U/ml. The lowest and highest levels of CA-125 were 4.7 and 5800 U/ml respectively (Table III).

Histopathological findings:

Table IV shows the histopathological diagnoses of the ovarian tumours. Overall, 44(58.7%) tumours were benign and the rest 31(41.3%) were malignant in nature.

Accuracy of USG and CA-125 in differentiating malignant from benign ovarian tumours:

Table V shows the accuracies of the of two screening tests (USG and serum CA-125) in the differentiation of malignant ovarian tumours from the benign ones. The sensitivity of USG in correctly diagnosing malignant ovarian tumour was 77.4%, while the specificity of the test in correctly ruling out those who did not have malignancy was 95.4%. The positive and negative predictive values (PPVs) of the test were 92.3 and 85.7% respectively. The percentages of false positive and false negative yielded by the test were 7.7 and 14.3% respectively. The overall diagnostic accuracy of the test was 88.0%. The sensitivity of CA-125 at a cut-off value 65 was 83.9%, while the specificity of the test was

ORIGINAL ARTICLE

70.5%. The positive and negative predictive values (PPVs) of the test were 66.7 and 86.1% respectively. The percentage of false positive and false negative were 33.3 and 13.9% respectively. The overall diagnostic accuracy of the test was 76.0%. Table VI shows that the two diagnostic modalities had moderate agreement in the differentiation of malignant ovarian tumours from the benign ones (k-value = 0.552, p < 0.001). In 55.2% cases the two diagnostic modalities were in agreement.

Table I. Distribution of study subjects by demographic characteristics (n = 75)

Demographic Characteristics	Frequency	Percentage
Age (years)		
< 20	9	12.0
20-30	14	18.7
30-40	13	17.3
40-50	15	20.0
≥ 50	24	32.0
Marital status		
Married	66	88.0
Unmarried	9	12.0

* **Median age** = (40.0 ± 15.3) years; **range** = (15 – 70) years.

Table II. Distribution of patients by obstetric & reproductive profile (n = 75)

Obstetric & Reproductive Profile	Frequency	Percentage	Mean (range)
Parity			
Primi		13.0	---
Multi		64.0	---
Grand multi		23.0	---
Menstrual profile			
Menstrual cycle (n = 75)			
Regular	35	46.7	---
Irregular	9	12.0	---
Menopause	31	41.3	---
Menstrual flow (n = 44)			
Average	31	70.5	---
Scanty	10	22.7	---
Profuse	3	6.8	---
Median duration of period (days)	---	---	5.0(1.0-20.0)
Years of menopause (n = 31)	---	---	10.0(1.0-20.0)
USG profile of the ovarian mass			
Size of the mass (sq. cm)			
≤ 100	47	62.7	---
>100	28	37.3	---
Median (range)	---	---	80.8(14.7–399.0)
USG comment			
Benign	49	65.3	---
Malignant	26	34.7	---

Table III. Distribution of patients by serum CA-125 (n = 75)

CA-125 (U/ml)	Frequency	Percentage	Mean (range)
< 35	26	34.7	---
35 –65	10	13.3	---
>65	39	52.0	---
Median value (U/ml)	---	---	80.7(4.7 – 5800.0)

Table IV. Distribution of patients by histopathological findings of ovarian tumours

Findings	Frequency	Percentage
Variants of ovarian tumour		
Follicular cyst	2	2.7
Serous cyst adenoma	13	17.3
Serous cyst adenocarcinoma	5	6.7
Mucinous cyst	10	13.3
Mucinous cyst adenoicarcinoma	1	1.3
Germ cell tumour	12	16.0
Benign haemorrhagic cyst	12	16.0
Endometrioma	1	1.3
Papillary serous cyst adenoma	10	13.3
Undifferentiated carcinoima	3	4.0
Juvenile granulose cell tumour	1	1.3
Metatstatic squamous cell carcinoma	2	2.7
Adenocarcinoma (endometriod)	2	2.7
Metastatic adenocarcinoma	1	1.3
Histopathological comment		
Benign	44	58.7
Malignant	31	41.3

Table V. Diagnostic accuracies of USG and CA125 as screening test

Components of accuracy test	USG (%)	CA125 (%)
Sensitivity	77.4	83.9
Specificity	95.4	70.5
PPV	92.3	66.7
NPV	85.7	86.1
False +ve	7.7	33.3
False -ve	14.3	13.9
Diagnostic accuracy	88.0	76.0

Table VI. Test of agreement between abdominal USG and CA-125 by kappa statistics:

Characters studied or modalities of diagnosis	Measures of agreement	
	Kappa statistics	P-value
Abdominal USG CA-125 (U/ml)	0.552	< 0.001

DISCUSSION:

Ovarian tumors grow in combined cystic and solid formations. There is no reliable diagnostic test or imaging technique available to distinguish benign from malignant cysts The decision to operate is based on clinical findings, transvaginal sonography[6], computed tomography and/or magnetic resonance imaging, and CA-125 levels. Approximately 7 to 10 benign lesions are operated on for each case of ovarian cancer found.[7] Consequently, several patients undergo extensive surgical staging, including oophorectomy, without an assured diagnosis of a malignant tumor, resulting in increased morbidity. Thus, there would be both medical and socio-economic benefits if we could preoperatively identify patients with benign cysts and safely be able to recommend conservative laparoscopic staging operations.[8] However, most of the ovarian tumours are diagnosed at an advanced stage, when they have already been spread and when palliative treatment even cannot do much to enhance survival. So early diagnosis is of utmost significance to improve survival.

In the present study histopathological examination of the biopsy material taken from the tumor revealed that 58.7% of the tumors to be benign and the rest 41.3% malignant in nature. The sensitivity of ultrasound in correctly detecting malignant ovarian tumors was 77.4%, while its specificity in correctly excluding malignancy was 95.4% with overall diagnostic accuracy of the test being 88%. The CA-125 at a cut-off value of 65 although demonstrated a higher sensitivity (83.9%) than USG, its specificity was lower (70.5%) than USG, with overall diagnostic accuracy being 76%. As USG has optimum sensitivity and high specificity with overall diagnostic accuracy being 12% higher than that shown by CA-125, USG could be considered superior to CA-125 as a screening test for differentiation of malignant ovarian masses from the benign ones. Consistent with these findings, Calster et al[3] reported that USG was superior to serum CA-125 in discriminating between benign and malignant adnexal masses. They showed that USG correctly classified 93% of the tumors as benign or malignant, whereas serum CA-125 correctly classified at best 83% of the masses. Histologic diagnoses that were most often misclassified by CA-125 were fibroma, endometrioma and abscess and borderline tumors. USG correctly classified 86% of masses of these four histologic types as benign or malignant, whereas a serum CA-125 at a cutoff of value 30 U/ml correctly classified only 41% of them.

Guerriero and associates[9] reported that the serum CA-125 always had a lower sensitivity and specificity in comparison to USG in the diagnosis of endometrioma in terms of sensitivity and specificity. Alcázar and colleagues[10] reported that serum CA-125 compared to TVS had lower sensitivity (79.3 vs. 88.9%), specificity (84.6 vs. 91%) positive predictive values (79.3 vs. 84.2%) and negative predictive values (84.6 vs. 94.5%) respectively. Sharply contrasting to these findings, Finkler[11] demonstrated that the sensitivity and specificity for differentiating malignant ovarian masses from benign ones were highest for CA125 assays in postmenopausal patients, especially when these were used as the second diagnostic test.

Hartman and colleagues[12] in study in Brazil demonstrated that out of 110 ovarian tumors, 79(71.8%) were benign and 31(28.2%) were malignant on histopathology. Ultrasound criteria were applied in 91(82.7%) tumors which resulted in a sensitivity of 90% and a specificity of 87% in correctly classifying the tumours into benign and malignant, while CA125 at a cut-off value of 37.4 U/mL had a much lower sensitivity (69%) but a higher specificity (87.8%) than ultrasound. Transvaginal Ultrasonography (TVUS) combined with serum CA125 level measurements evaluated in the Sweden,[13] United Kingdom,[14,15] the United States,[16] and have shown further improvement in the differentiation of malignant from benign ovarian tumours with a sensitivity approaching 100%.[17,18] Because of the proximity of the ovaries to the transvaginal probe, detailed examination of the appearance and internal structure of the ovarian/adnexal mass can be performed. Screening decisions based on CA125 most commonly use a single-threshold screening rule that refers a woman to ultrasound if her CA125 concentration exceeds 30 U/mL when postmenopausal, or 25 U/ml when premenopausal.[19] CA125 is currently the established

tumour marker for the early detection of ovarian cancer recurrence, though a role for screening has not been demonstrated so far.[20] According to Berek and Bast, the serial measurement of CA125 has a high sensitivity, specificity and positive predictive value for the early detection of ovarian cancer.[21]

Recently, Skates et al. have shown that preclinical detection of ovarian cancer using serial CA125 levels interpreted according to the risk calculation significantly improves screening performance compared with a fixed cut off for CA125.[22] A majority of researchers use the widely accepted reference level of 35 U/mL.[20,23] However, It is important to be aware of the range of normal CA125 in each specific laboratory used, as many different assays are currently in use with different upper limit of the normal range. Using a CA125 cut-off value of 35 U/ml may not be appropriate for screening as women with naturally increased levels of CA125 experience many false – positives and probably do not reach 35 U/mL until at an advanced stage of their cancer.[18,24] Only 35% of the tumors confined to one ovary were associated with CA 125 levels >35 IU/mL, with a mean of 67 IU/mL, which is in contrast to 89% of tumors with extension outside the ovary (P = .012), with a mean of 259 IU/mL. As expected, there appeared to be a trend toward increased values with increased stage of disease.[25] A quantitative systematic review of 17 studies done by Medeiros et al[26] to estimate the accuracy of the cancer antigen (CA) 125 assay for the diagnosis of ovarian tumours. Diagnostic accuracy studies (n = 17) that evaluated CA-125 at a threshold of 65 U/ml for the diagnosis of ovarian tumours in women with clinically suspected adnexal masses treated surgically for ovarian tumours were included provisionally. Only three studies were considered to be of high methodological rigor as they fulfilled at least 55% of the quality criteria. The studies concluded that accuracy of CA-125 for the diagnosis of ovarian tumours was high. However, pooled results did not support the conclusion that the accuracy of CA-125 was high. The consistency or strength of agreement between USG & CA-125 in differentiating between malignant and benign ovarian tumors were also evaluated using kappa statistics which revealed a moderate agreement between the two diagnostic modalities. So, neither of the screening tests can be replaced by one another.

CONCLUSION:

The study concluded that ultrasound has optimum sensitivity and high specificity in differentiating malignant ovarian tumors from the benign ones with overall diagnostic accuracy being high. The CA-125 at a cut-off value of 65 although exhibits a higher sensitivity than USG, its specificity is lower than USG, with overall diagnostic accuracy being optimum. The consistency between USG & CA-125 in differentiating between malignant and benign ovarian tumors is moderate. So, neither of the screening tests can be replaced by one another for screening of ovarian masses. As USG has optimum sensitivity and high specificity, USG could be preferred as a routine screening procedure for preoperative diagnosis of ovarian masses, while CA-125, if available, can be used as an adjunct to USG screening procedure to improve screening performance.

REFERENCES:

1. Terzic J, Dotlic J. Serum Tumor Markers Evaluation in Patients with Adnexal Masses-Current Value in Everydays Clinical Practice. *Reprod Sys Sexual Disorders* 2012;1:1-2.
2. Chen L Berek JS. Patient information: Ovarian cancer diagnosis and staging (Beyond the Basics). *Ovarian cancer diagnosis and staging* 2014:1-6.
3. Calster BV, Timmerman D, Bourne T, Testa AC, Holsbeke CV. Discrimination between Benign and Malignant Adnexal Masses by Specialist Ultrasound Examination versus Serum CA-125. *J Natl Cancer Inst* 2007;99:1706-14.
4. Dijmarescu L, Gheta C, Tanase F, Comanescu A, Manolea M. Diagnosis Correlations in Ovarian Tumors. Printed edition ISSN: 2067-0656, Electronic edition ISSN: 2069-4032, 2014;40(2):1-5.
5. Guppy AE, Rustin GJS. CA 125 Response: Can it Replace the Traditional Response Criteria in Ovarian Cancer?. *The Oncologist October* 2002;7(5):437-43.
6. Granberg S, Wikland M, Jansson I. Macroscopic characterization of ovarian tumors and the relation to thehistological diagnosis: criteria to be used for ultrasound evaluation. *Gynecol Oncol* 1989;35:139–44.
7. Van Nagell JR, DePriest PD, Velond FR. Ovarian cancer screening with annual transvaginal sonography: findings of 25,000 women screened. *Cancer* 2007;109:1887-96.

8. Suh-Burgmann E. Long-term outcomes following conservative surgery for borderline tumor of the ovary: a large population-based study. *Gynecol Oncol* 2006;103: 841–47.

9. Guerriero S, Mais V, Ajossa S, Paoletti AM, Angiolucci M, Melis GB. Transvaginal ultrasonography combined with CA-125 plasma levels the diagnosis of endometrioma. *Fertility and Sterility* 1996;65(2):293-98.

10. Alcázar JL, Laparte C, Jurado M, Lopez-Garcia G. The role of transvaginal ultrasonography combined with color velocity imaging and pulsed Doppler in the diagnosis of endometrioma. *Fertility and Sterility* 1997;67(3):487–91.

11. Finkler NJ, Benacerraf B, Lavin PT, Wojciechowski C, Knapp RC. Comparison of serum CA 125, clinical impression, and ultrasound in the preoperative evaluation of ovarian masses. *Obstet Gynaecol* 1988;72(issue 4):659-64.

12. Hartman CA, Juliato CRT, Sarian LO, Toledo MC, Jales RM, Morais SS et al. Ultrasound criteria and CA125 as predictive variables of ovarian cancer in women with adnexal tumors. *Ultrasound Obstet Gynecol* 2012;40: 360–366. DOI:10.1002/uog.11201.

13. Einhorn N, Sjovall K, Knapp RC et al. Prospective evaluation of serum CA125 levels for early detection of ovarian cancer. *Obstet Gynaecol* 1992;80(1):14-18.

14. Jacobs I, Davies AP, Bridges J, Stabile I, Fay T, Lower A, Grudzinskas JG, Oram D. Prevalence screening for ovarian cancer in postmenopausal women by CA 125 measurement and ultrasonography. *BMJ* 1993;306(6884): 1030-4.

15. Menon U and Jacobs IJ. Ovarian cancer screening in the general population: current status. *Int J Gynecol Cancer* 2001;11(Suppl 1):3-6.

16. Gohagan JK, Prorok PC, Hayes RB and Kramer BS. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial of the National Cancer Institute: history, organization, and status. *Control Clin Trials* 2000;21(6): 51S-272S.

17. Karlan BY. The status of ultrasound and color Doppler imaging for the early detection of ovarian carcinoma. *Cancer Invest* 1997;15:265-9.

18. Urban N. Screening for ovarian cancer. We now need a definite randomised trial. *BMJ* 1999;319:1317-8.

19. Crump C, McIntosh MW, Urbal N, Anderson G and Karlan BY. Ovarian cancer tumor marker behavior in asymptomatic healthy women: implications for screening. *Cancer Epidem Biomark Prevent* 2000;9:1107-1111.

20. Alagoz T, Buller RE, Berman M, Anderson B, Manetta A and DiSaia P. What is normal CA125 level?. *Gynecol Oncol* 1994;53(1):93-7.

21. Berek JS and Bast RC Jr. Ovarian cancer screening. The use of serial complementary tumor markers to improve sensitivity and specificity for early detection. *Cancer* 1995;76(10):2092-6.

22. Skates SJ, Menon U, MacDonald N. Calculation of the risk of ovarian cancer from serial CA-125 values for preclinical detection in postmanpausal woman. *J Clin Oncol* 2003; 21:206s-210s.

23. Einhorn N, Syovall K, Krapp RC. Prospective evaluation of serum CA-125 levels for early detection of ovarian cancer. *Obstet Gynecol* 1992;80:14-18.

24. Urban N, Drescher C, Etzioni R and Colby U. Use of a stochastic simulation model to identify an efficient strategy for ovarian cancer screening. *Control Clin Trials* 1997;18:251-70.

25. Walter H. Gotlieb, David Soriano, Reuven Achiron, Yaron Zalel, Ben Davidson, Juri Kopolovic et al. CA 125 measurement and ultrasonography in borderline tumors of the ovary. *Am J Obstet Gynecol* 2000;183:541-6.

26. Medeiros LR, Rosa DD, da Rosa MI, and Bozzetti MC. Accuracy of CA 125 in the diagnosis of ovarian tumors: a quantitative systematic review. Review published: 2009.