Accuracy of preoperative prediction of malignancy in ovarian mass by ultrasound examination and CA 125 serum level

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Abstract:
Background: Ovarian cancer is the second most common malignancy of the female reproductive system and one of the leading lethal gynecologic malignancies. Screening of ovarian cancer in certain high risk groups is very important due to unspecificity and late appearance of symptoms. Its risk factors include positive family history, older age of menopause and low parity as pregnancy protects against ovarian cancer. **Objectives:** to compare the accuracy of preoperative prediction of malignancy in ovarian mass by morphological ultrasound (US) examination, Doppler indices and CA 125 serum level with the result of histopathological examination mass after laparotomy. **Methods:** One hundred and four cases of ovarian masses predicted to be malignant by US examination and CA 125 serum level were subjected to laparotomy and histopathological examination. The main outcome measures in the ovarian masses were: a- the US signs of malignancy [such as solid mass, multiple septation in cystic mass, mixed solid and cystic components, thick cyst wall (> 3 mm), nodule in a cyst wall] , b- Doppler indices(resistance index and pulsatility index) , c- CA125 serum level, and d- histopathological examination findings after laparotomy. **Results:** The histopathology identified 20 benign (**B**) and 84 malignant (**M**) ovarian masses. The benign tumors were 9(45%) endometroitic cyst, 6(30%) pseudomucinous cyst adenoma and 5(25%) serous cyst adenoma. The malignant ones included 43(51.2%) papillary serous cyst adenocarcinoma 18(21.4%) endometrioid adenocarcinoma , 10(11.9%) pseudomucinous cyst adenocarcinoma, 5(5.9%) clear cell adenocarcinoma, 2(2.4%) papillary serous borderline cyst adenocarcinoma, 2(2.4%) borderline serous adenocarcinoma, 1(1.2%) serous adenocarcinoma, 1(1.2%) borderline endometroid adenocarcinoma, 1(1.2%) dysgerminoma and 1(1.2%) Pseudomucinous borderline cyst adenocarcinoma]. The US showed no morphological signs of malignancy in 10 [9.6% (9 **M** vs. 1 **B**)] masses, thick cyst wall and mixed solid & cystic components 1(1%) **M**; thick cyst wall1 and nodule in the cyst wall 1(1%) **M**, mixed solid and cystic components 15[14.4% (14 **M vs.** 1 **B**)], solid components 17(16.3%) **M**, thick cyst wall (> 3 mm) 27[26% (10 **M vs.** 17 **B**)] and nodules in the cyst wall in 33[31.7% (32 **M** vs. 1 **B**)] masses. Doppler studies of ovarian mass vasculature showed that < 0.4 resistance index and < 1 pulsatility index prevailed significantly in 83 and 82 malignant masses respectively (P< 0.001) while CA125 serum cutoff level 30 IU/ ml alone failed to differentiate between the benign and malignant masses **Conclusion:** using CA125 serum cutoff level 30 IU/ ml combined with US grey scale or color Doppler examination can discriminate between benign and malignant adnexal masses especially in positive Doppler indices.

INTRODUCTION

Ovarian cancer (OC) is the second most common malignancy of the female reproductive system and one of the leading causes of death among gynaecologic malignancies.[1] The disease is more common in industrialized nations, with the exception of Japan. In the United States, females have 1 % to 2.5% (1 out of 40-60 women) lifetime

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chance of developing OC. Older women are at highest risk. More than half of the deaths from OC occur in women between 55 and 74 years of age and approximately one quarter of OC deaths occur in women between 35 and 54 years of age.[2] There are no statistics that describe disease incidence in Egypt. Signs and symptoms of OC are frequently absent early and when they exist they may be subtle. In most cases, the symptoms persist for several months before being recognized and diagnosed.[3] The five-year survival rate for all stages of OC is 47%.[4] For cases where a diagnosis is made early in the disease, when the cancer is still confined to the primary site, the five-year survival rate is 92.7 %.[5]

So prognosis is good for women diagnosed at an early stage, whereas the majority, diagnosed at later stages, is likely to survive less than 5 years.[6]

Symptoms as bloating, fullness, and pressure in the abdomen are the most prominent symptoms. Pain and fatigue are also important, followed by problems in urination and constipation.[7] Ovarian cancer is neither an asymptomatic disease nor a so-called 'silent killer'. Recent studies have demonstrated that patients at all stages of the disease have symptoms.[8,18,19] Examination can reveal abdominal or pelvi-abdominal mass only in the late stages and bimanual pelvic examination can reveal adenexal mass or fullness.[9,20]

Studies exploring the value of screening those women for OC are lacking and urgently required. Even though population-based screening for OC is not recommended, and although there is no level of evidence that this group of women should undergo screening, it seems prudent that, until evidence is available, measurement of CA 125 levels and transvaginal ultrasound should be undertaken at least on yearly basis.[21]

CA125 is still the most extensively studied biomarker for possible use in the early detection of OC, and has proved valuable in both detection and disease monitoring.[23,24] CA125 is elevated in the serum of most

women with OC, but pre-operative serum levels of CA125 are below the conventional cutoff level of 35 U/ml in roughly 50% of clinically detected stage I cases [25] and in the majority of women with occult cancers identified at prophylactic surgery.[26]

Using vaginal ultrasound examination can add to the predictive value of CA125. US morphological signs of malignancy include large ovarian volume more than 18 ml before menopause and 8 ml after, thick cyst wall, solid component in ovarian mass, mixed solid and cystic component, nodule in the cyst wall and abnormal vascular pattern proved by Doppler study [27,28,29].

Objectives:

To evaluate the accuracy of preoperative prediction of malignancy in ovarian mass by the morphological ultrasound examination, Doppler indices and CA 125 serum level.

Methods:

Following approval by Alexandria Faculty of Medicine Institutional Ethics Committee, 104 patients with ovarian masses that fulfilled the inclusion criteria attending the outpatient clinic of Oncology Department of El-Shatby University Hospital were included in the study after taking their consents. The study was the "One-shot prospective case study" without control group. The main inclusion criteria were ovarian mass with one or more of the followings a- Ultrasonographic (US) signs of malignancy [such as solid component, mixed solid and cystic component, nodule in the cyst wall, thick cyst wall (more than 3mm)], b- Doppler studies of ovarian mass vessels (including resistance index (RI) and pulsatilty index (PI) with a cut level values of less than 0.4 for RI and less than 1 for PI.[31,32] For enrolment in the study there should be: 1- at least one positive US sign whether morphological appearance or Doppler indices. 2- This positive US sign must be combined with CA 125 serum level more than 30 u/ml.[30] Patients with these criteria were admitted and subjected to laparotomy and histopathological examination of the ovarian masses. The women were

examined with both real-time 3.5-5 MHz transabdominal transducer and 5.5-7 MHZ vaginal transducer.

Laparatomy was done to all cases at El-Shatby University Hospital and histopathological examination was done to all ovarian masses at the Clinical Pathology Department of the Main University Hospital.

Table (1) Sample size of one group according to disease prevalence

Formula	$$n = \frac{t^2 \times p(1-pr)}{m^2}$$
Description:	**n** = required sample size **t** = confidence level at 95% (standard value of 1.96) **p** = estimated prevalence of ovarian carcinoma (estimated as 1 %) **pr** = probability(0.4) **m** = margin of error at 5% (standard value of 0.5)
Calculation of sample size (N):	
n=	$\frac{1.96^2 \times 10.0(1-.4)}{.5^2}$
n =	$\frac{3.8416 \times 6}{.25}$
n =	$\frac{23.0496}{.25}$
n =	92.1 ≈ 92

This table showed that the sample size should be more than 92 cases.

RESULTS

Histopathology reports of the ovarian masses showed that 43 masses were papillary serous cystadenocarcinoma, 2 papillary serous borderlines cystadenocarcinoma, 1 serous adenocarcinoma, 2 borderlines serous adenocarcinoma, 18 endometrioid adenocarcinoma, 1 borderline endometroid adenocarcinoma, 10 pseudomucinous cyst adenocarcinoma, 1 pseudomucinous borderline cyst adenocarcinoma, 1 dysgerminoma, 5 clear cell adenocarcinoma, 5 serous, 6 pseudomucinous cyst adenoma, and 9 endometriotic cysts. Malignant masses were 84 and benign ones were 20.

Regarding the ultrasonographic signs, 10 cases showed any morphological sign of malignancy, 17 showed solid components, 15

mixed solid and cystic components, 33 nodule in the cyst wall, 27 thick cyst wall (> 3 mm), 1 thick cyst wall and mixed solid and cystic component and 1 showed thick cyst wall and nodule in the cyst wall. Doppler studies of tumor vasculature showed that the resistance index was less than 0.4 in 83 cases and the pulsatility index was less than 1 in 82 cases.

Table (2): Distribution of the studied ovarian masses according to the histopathological diagnosis.

Diagnosis		Ovarian mass		Total
		Malignant	Benign	
Borderline endometroid adenocarcinoma	no.	1	0	1
	%	1.2%	.0%	1.0%
Clear cell adenocarcinoma	no.	5	0	5
	%	5.9%	.0%	4.8%
Dysgerminoma	no.	1	0	1
	%	1.2%	.0%	1.0%
Endometriod adenocarcinoma	no.	18	0	18
	%	21.4%	.0%	17.3%
Endometroitic cyst	no.	0	9	9
	%	.0%	45%	8.7%
Pseudomucinous border line cyst adenocarcinoma	no.	1	0	1
	%	1.2%	.0%	1.0%
Pseudomucinous cyst adenocarcinoma	no.	10	0	10
	%	11.9%	.0%	9.6%
Papillary serous border line cyst adenocarcinoma	no.	2	0	2
	%	2.4%	.0%	2.0%
Papillary serous cyst adenocarcinoma	no.	43	0	43
	%	51.2%	.0%	41.3%
Pseudomucinous cyst adenoma	no.	0	6	6
	%	.0%	30%	5.7%
Serous cyst adenocarcinoma	no.	1	0	1
	%	1.2%	.0%	1.0%
Serous cyst adenocarcinoma border line	no.	2	0	2
	%	2.4%	.0%	1.9%
Serous cyst adenoma	no.	0	5	5
	%	.0%	25.0%	4.8%
Total	no.	84	20	104
	%	100.0%	100.0%	100.0%
X^2		84.0		
P		0.0001*		

Table (2) described the histopathological diagnosis of the studied patients. Malignant cases were 84 and benign cases were only 20. (p=0.0001). Using CA125 serum level and ulrasonographic examination of ovarian masses, there was a significant difference between the benign and malignant cases.

Table (3) Distribution of the studied ovarian masses according to the ultrasonographic morphological signs.

	Malignant		Benign	
	no.	**%**	**no.**	**%**
Positive finding	**75**	**89.3**	**19**	**95.0**
No finding	**9**	**10.7**	**1**	**5.0**
Total	**84**		**20**	
X^2		**0.29**		
P		**0.58**		

Table (3) showed that by using ultrasound alone, the ultrasonographic morphological signs of malignancies were respectively seen in 75 (89.3%) and 19 (95%) malignant and benign masses with no significant difference in-between (p=0.58)

Table (4): Comparison between the mean age, resistance index, pulsatility index and CA 125 of the benign and malignant cases

		no	**Mean**	**S.D.**	**t-test**	**P**
Age	Malignant	84	51.13	5.566	39.970	0.0032*
	Benign	20	42.45	5.306		
Resistance index	Malignant	83	.323	.0979	103.046	.0001*
	Benign	20	.575	.1070		
Pulsatility index	Malignant	82	.72	.150	102.356	.0001*
	Benign	20	1.11	.176		
CA 125	Malignant	84	79.98	25.328	1.957	.165
	Benign	20	70.45	34.916		

Table (4) showed that there was no significant difference between benign and malignant cases regarding CA125 level, but there were significant differences

between them with respect to age, pulsatility index and resistance index. Eighty three malignant ovarian masses showed resistance index Less than 0.4 and 82 malignant cases showed pulsatility index less than 1 as malignancy induces new blood vessels formation that lack muscle wall which decreases resistance to blood flow and increases diastolic blood flow and this is shown by Doppler indices of the study.

Table (5) Comparison between benign and malignant cases regarding the ultrasonographic malignant signs.

Ultrasonographic signs		Group		
		Malignant	**Benign**	**Total**
Mixed solid and cystic components	no.	14	1	15
	%	16.7	5.0	14.4
No suspicious sign of malignancy	no.	9	1	10
	%	10.7	5.0	9.6
Nodule in the cyst wall	no.	32	1	33
	%	38.1	5.0	31.7
Solid component	no.	17	0	17
	%	20.2	0.0	16.3
Thick cyst wall (more than 3mm)	no.	10	17	27
	%	11.9	85.0	26.0
Thick cyst wall, nodule in wall	no.	1	0	1
	%	1.2	0.0	1.0
Thick cyst wall, Mixed solid and cystic components	no.	1	0	1
	%	1.2	0.0	1.0
Total	no.	84	20	104
	%	100.0	100.0	

Table (5) showed that the frequency of the US morphological signs of malignancy among cass of the study. The solid component ultrasonographic malignant sign was present in 17 malignant cases while it was not present in any benign case.

Receiver operating characteristics (ROC) Curve

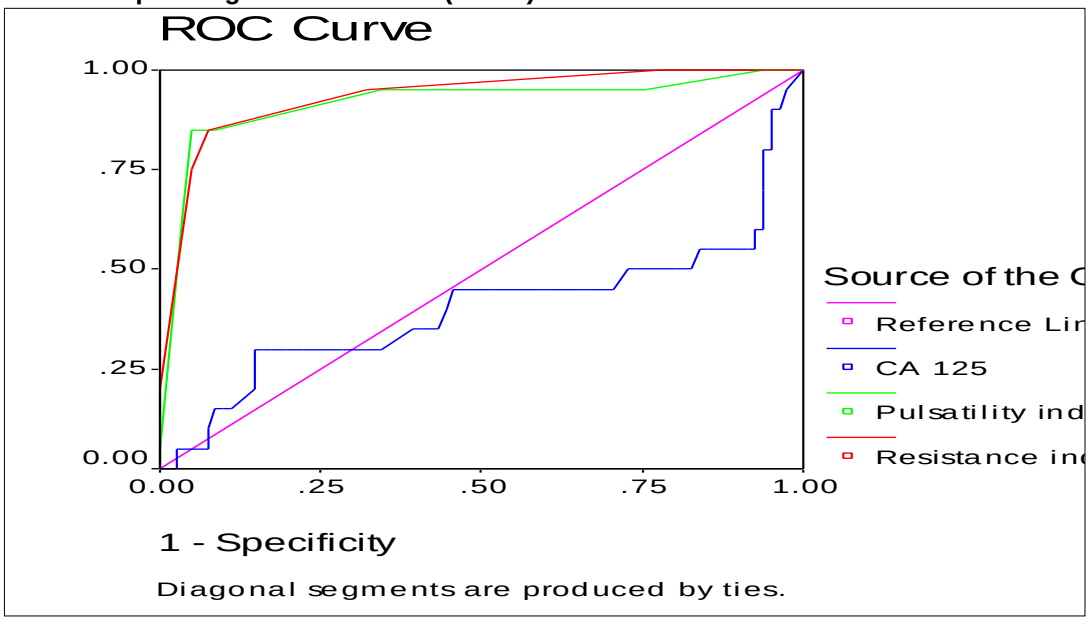

Table (6) Area under the ROC Curve

Test Result Variable(s)	Area	Std. Error(a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Resistance index	.933	.032	.000	.870	.996
Pulsatility index	.916	.044	.000	.830	1.003
CA 125	.402	.086	.178	.233	.572

The test result variable(s): resistance index, pulsatility index, CA 125 had at least one tie between the positive actual state (malignant) group and the negative actual state (benign) group. Statistics may be biased. a Under the nonparametric assumption b Null hypothesis: true area = 0.5.

Table (7) Coordinates of the ROC curve

Test Result Variable(s)	Positive if Greater Than or Equal To(a)	Sensitivity	Specificity
Resistance index	.450	.850	.074
Pulsatility index	.65	.950	.753
CA 125	36.00	.800	.951

ROC curve showed that CA125 was neither sensitive nor specific to differentiate between benign and malignant ovarian cases while both pulsatility index and resistance index were specific and sensitive to differentiate between them

DISCUSSION

Differentiation between benign and malignant adnexal masses is very important before management. If the mass shows high malignancy index, the management includes vertical midline incision, aspiration cytology, complete abdominal inspection and palpation, total abdominal hysterectomy with bilateral salpingoopherectomy, omentectomy, random peritoneal biopsy as well as pelvic and paraaortic lymph node sampling.[33]

Differentiating benign from malignant tumors might be achieved by several methods such as clinical signs and symptoms, serum CA 125 and ultrasound.[34]

Nonetheless, using one item alone to differentiate between benign and malignant cases shows low positive predictive value. For example, in predicting malignancy in ovarian tumors, abdominal ultrasonography had a positive predictive value of 39% and a negative predictive value of 94%. If a negative sonogram had been relied upon, 6% of malignant ovarian tumors in postmenopausal women might have been missed.[35]

Also, serum levels of CA125 have been used widely for distinguishing benign from malignant pelvic masses. However, CA125 is elevated in only about half of stage I/II ovarian cancer patients. Lowering the cutoff of CA125 less than 30 IU/ML would increase its sensitivity in detecting

cancer but result in many false positives in patients with benign conditions.[36]

In the study of van Nagell et al, the transvaginal grey scale US had a sensitivity of 85.0%, specificity 98.7%, a positive predictive value of 14.01%, and a negative predictive value of 99.9%.[37] Tailor et al using CA125 serum level and morphological vaginal ultrasonographic examination showed that sensitivity of ultrasound screening was 92% and the specificity was 97.8%.[38] Varras concluded that the combination of physical examination with serum CA-125 levels and pelvic ultrasound scan seemed to improve the sensitivity and specificity of predicting the adnexal malignancies in postmenopausal women. In contrast, in premenopausal women, the consideration of CA-125 levels with Doppler ultrasonographic findings might confuse the differential diagnosis of ovarian masses.[39]

In the current study, we attempted to use the combination of the ultrasonographic morphological appearance, Doppler indices and CA125 serum level to differentiate between benign and malignant ovarian masses .Our results revealed that using the ultrasound grey scale examination together with Doppler indices of mass vascularity (at least one of them is positive) combined with CA125 serum cutoff level more than 30 IU/ML succeeded significantly to differentiate between the benign (n=20) and malignant(n=84) ovarian masses (p=0.0001). Using the ultrasound morphological picture alone failed to differentiate between benign and malignant ovarian masses (p=0.58). The malignant morphological ultrasound signs have been seen in 75 out of 84 malignant patients and all benign (20) cases except for one. Solid component ultrasonographic sign was the most accurate sign in the differentiation between benign and malignant ovarian masses as it was present in 17 malignant cases while it was seen in either benign case.

As regards the Doppler indices, both

pulsatility index and resistance index were sensitive and specific in the differentiation between both benign and malignant groups In the same context, CA125 serum cutoff level more than 30 IU / ml level was not significantly either sensitive or specific enough to discriminate between the two groups.

CONCLUSION

From the current study, it is concluded that using CA125 with serum cutoff level > 30 IU/ml combined with ultrasonographic grey scale or color Doppler examination can effectively discriminate between benign and malignant adnexal masses especially with positive Doppler indices.

REFERENCES

1. Malik A. Maternal Deaths in a tertiary health care centre of Odisha. *Obstet Gynaecol Today.* 1997; 11: 17.
2. Stöppler C, Shiel J, William C. Ovarian cancer symptoms, early warning signs, and risk factors. Medicine Net. 2011; 88:400-2
3. Piek JM, Van Diest PJ, Verheijen RH. Ovarian carcinogenesis: an alternative hypothesis. Adv. Exp. Med. Biol.2008; 622: 79–87.
4. Johannes, Laura. Test to Help Determine if ovarian masses are cancer. Wall Street J. 2010; 3:1-22.
5. Edwards BK, Howe HL, Ries LAG l. Annual report to the nation on the status of cancer. Cancer .2002; 94:2766-72.
6. Ries LAG, Kosary CL, Hankey BF, Miller BA, Harras A, Edwards BK. SEER cancer statistics review, National Cancer Institute.1997; 97:2789.
7. Goff BA, Mandel LS, Muntz HG, Melancon CH. Ovarian cancer diagnosis: Results of a national ovarian cancer survey. Cancer. 2000; 89:2068–75.
8. Luesley D. The clinical presentation of ovarian carcinoma. In: Blackledge GRP, Jordon JA, Shingleton HM, eds. Textbook of gynecological cancers. London: WB Saunders, 1991:152–3.
9. Riman T, Persson I, Nilsson S. Hormonal aspects of epithelial ovarian cancer: review of epidemiological evidence. Clin Endocrinol (Oxf). 1998; 49:695–707.
10. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. Br J Cancer. 1989; 60:592–8.
11. Tsilidis KK, Allen NE, Key TJ, Dossus L, Lukanova A, Bakken K, et al. Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition. Br J Cancer. 2011; 105(9):1436-42.
12. Gayther SA, Pharoah PD. The inherited genetics of ovarian and endometrial cancer. Curr Opin Genet Dev. 2010; 20(3):231-8.
13. Salehi F, Dunfield L, Phillips KP, Krewski D, Vanderhyden BC Risk factors for ovarian cancer: an overview with emphasis on hormonal factors. Toxicol Environ Health B Crit Rev. 2008;11(3-4):301-21.
14. Sueblinvong T, Carney ME. Current understanding of risk factors for ovarian cancer. Curr Treat Options Oncol. 2009; 10(1-2):67-81.

15. Huncharek M, Geschwind J, Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. Anticancer Research. 2003; 23(2C):1955-60
16. Schouten LJ, Rivera C, Hunter DJ, Spiegelman D, Adami HO, Arslan A, et al. Height, body mass index, and ovarian cancer: a pooled analysis of 12 cohort studies. Cancer Epidemiol Biomarkers Prev. 2008; 17(4):902-12.
17. Borgfeldt C, Andolf E. Cancer risk after hospital discharge diagnosis of benign ovarian cysts and endometriosis. Acta Obstet Gynecol Scand. 2004; 83(4):395-400.
18. Hamilton W, Peters TJ, Bankhead C, Sharp D. Risk of ovarian cancer in women with symptoms in primary care: population based case-control study. BMJ. 2009;339:b2998-
19. Rossing MA, Wicklund KG, Cushing-Haugen KL, Weiss NS. Predictive Value of symptoms for early detection of ovarian cancer. JNCI J Natl Cancer Inst. 2010; 102(20): 1599.
20. National Collaborating Centre for Cancer. Ovarian cancer. The recognition and initial management of ovarian cancer. London (UK): National Institute for Health and Clinical Excellence (NICE). 2011;122:28-9.
21. Denny L, Hacker NF, Gori J, Jones III HW, Ngan HYS, Pecorelli S. Staging classification and clinical practice. Guidelines for Gynecologic Cancers. 2000;70:207-312.
22. Menon U, Jacobs IJ. Ovarian cancer screening in the general population: current status. Int J Gynecol Cancer. 2001; 11: 3-6
23. Kenemans P, Yedema CA, Bon GG, Von Mensdorff-Pouilly S. CA 125 in gynecological pathology. Eur J Obstet Gynecol Reprod Biol. 1993; 1, 2:115-24.
24. Jacobs IJ, Menon U. Progress and challenges in screening for early detection of ovarian cancer. Mol Cell Proteomics. 2004;4:355-66.
25. Nathalie Scholler, Nicole CA-125 as tumor markers for epithelial ovarian carcinoma. Urban Cancer. 2001; 92(11):2837-44.
26. Olivier RI, Lubsen-Brandsma MA, Verhoef S, Van Beurden M. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. Gynecol Oncol. 2006; 100(1):20-6.
27. Sassone AM, Timor-Tritsch IE, Artner A, Westhoff C, Warren W. Transvaginal sonographic characterization of ovarian disease. Obstet Gynecol.1991; 78:70–76.
28. De Priest PD, Shenson D, Fried A. morphology index based on sonographic findings in ovarian cancer. Gynecol Oncol. 1993; 51:7–11.
29. Kurjak A, Zalud I, Alfirevic Z. Evaluation of adnexal masses with transvaginal color ultrasound. J Ultrasound Med 1991; 10: 295–299.
30. Sobiczewski P, Dańska-Bidzińska A, Rzepka J, Kupryjańczyk J, Gujski M, et al. Evaluation of selected ultrasonographic parameters and marker levels in the preoperative differentiation of borderline ovarian tumors and ovarian cancers. Gynecol Obstet. 2012; 286(6): 1513–19.
31. Bourne T, Campbell S, Steer C, Whitehead M, Collins WP. Transvaginal color flow imaging: a possible new screening for ovarian cancer. Br Med J. 1989; 299:1367–70.
32. Kurjak A, Zanid I, Alfirevic Z. Evaluation of adnexal masses with transvaginal color ultrasound. J Ultrasound Med. 1991; 10:296–7.
33. Gershenson DM. Management of early ovarian cancer: germ cell and sex cord-stromal tumors. Gynecol Oncol 1994; 55: 62.
34. Mousavi AS, Sassone, Timmerman D;

Erdogan N. Development Panel on Ovarian Cancer, Asian Pacific J Cancer Prev.2009; 10: 139-42.
35. Hill T. Power Doppler of abnormal vessels within an ovarian carcinoma. Family practice journal. 2003; 15: 9.
36. Jacobs I, Bast RC, Jr. The CA 125 tumour-associated antigen: a review of the literature. Hum Reprod. 2000; 4: 1-12.
37. Van Nagell JR Jr, DePriest PD, Ueland FR, DeSimone CP, Cooper AL, McDonald JM, Pavlik EJ, Kryscio RJ. Ovarian cancer screening with annual transvaginal sonography, Cancer. 2007; 109(9):1887-96.
38. Tailor A, Bourne TH, Campbell S, Okokon E, Dew T, Collins WP. Results from an ultrasound-based familial ovarian cancer screening clinic: a 10-year observational study, Ultrasound Obstet Gynecol. 2003; 21(4):378-85.
39. Varras M. Benefits and limitations of ultrasonographic evaluation of uterine adnexal lesions in early detection of ovarian cancer. Clin Exp Obstet Gynecol. 2004; 31(2):85-98.