RESEARCH COMMUNICATION

E-flow Doppler Indices for Prediction of Benign and Malignant Ovarian Tumors

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Abstract

Objective: To determine the validity of pulsatility and resistance index of transabdominal Doppler ultrasound (e-flow) in distinguishing between benign and malignant adnexal masses. Methods: A cross-sectional descriptive study was conducted on patients scheduled for elective surgery due to adnexal masses at Maharaj Nakorn Chiang Mai Hospital, Thailand, between April 2006 and March 2008. All patients were sonographically evaluated for pulsatility and resistance indices aided with color e-flow within 24 hours of surgery. The examinations were performed by the same experienced sonographer, who had no information on the patients, to differentiate between benign and malignant adnexal masses based on Doppler indices. The final diagnoses were based on either pathological or operative findings, used as gold standards. Results: Three hundred and twenty-nine patients were recruited and 23 were excluded, since the masses were finally not proven to be adnexal, for example with intrauterine myomas. Of the remaining 306 cases available for analysis, 191 were benign and 115 were malignant. The sensitivity and specificity of the pulsatility index for distinction were 93.0% and 92.7%, respectively and the values for the resistance index were 94.8 % and 93.2%. Conclusions: Pulsatility and resistance indices with transabdominal Doppler ultrasound (e-flow) have high accuracy for differentiating between benign and malignant adnexal masses.

Key Words: Adnexal mass - pulsatility index - resistance index - Doppler ultrasound - ovarian tumor diagnosis

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Introduction

The differentiation of benign from malignant adnexal masses is of great value, because therapeutic approach is markedly different between the two entities. Benign ovarian masses, functional changes or neoplasms, need more conservative approach, either close observation or laparoscopic surgery, whereas malignant tumors require urgent laparotomy in most cases with planned systematic consultation of available oncologists. Several attempts have been made to distinguish between the conditions, especially using pelvic ultrasound based on either morphological appearance (Sassone et al., 1991; Lerner et al., 1994; Valentin, 1999a; 1999b; Ferrazzi et al, 2005) or Doppler waveforms (Bourne et al., 1989; Hata et al., 1989; Kurjak et al., 1991; Kurjak et al.,1993). With high-resolution ultrasound machines, color Doppler ultrasound has been proposed as a possible technique for differentiation of benign from malignant adnexal masses as well as for early diagnosis of ovarian carcinoma for several years (Hata et al., 1989; Kurjak et al., 1993). Some reports showed the superiority of this technique in screening ovarian cancer (Bourne et al., 1989; Kurjak et al., 1991), other reported the ability in differentiating benign from malignant tumors preoperatively (Kawai et al., 1992; Weiner et al., 1992; Fleischer & Andreotti, 2005). However, color Doppler application in such previous reports was often needed transvaginal ultrasound approach and this might be inconvenient to some patients. Currently, high-resolution color Doppler with extended flow (e-flow) has been developed, resulting in higher sensitivity in detection of blood flow in minute vessels even during transabdominal examination. Therefore, the purpose of the present study was to determine the sensitivity and specificity of pulsatility index (PI) and resistance index (RI), derived from transabdominal color Doppler e-flow, in differentiating benign from malignant ovarian tumor.

Materials and Methods

Between April 2006 and March 2008, 329 patients were admitted to Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University for elective surgery because of detection of an adnexal mass either by pelvic examination or ultrasonography elsewhere or both. Exclusion criteria consisted of known diagnoses of ovarian malignancy which was scheduled for second look operation, and

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patients undergoing operation beyond 24 hours after ultrasound examination. All of these women were counseled and invited to join the study with written informed consent.

All subjects underwent ultrasound examination within 24 hour of surgery by the same experienced examiner who had no any clinical information of the patients. The women were examined with real-time 3.5-5 MHz transabdominal curvilinear transducer connected to and Aloka model SSD alpha-10 (Tokyo, Japan). After thorough conventional examination, transabdominal color Doppler blood together with extended-flow (e-flow) examination was performed. On the color Doppler ultrasound examination, the sampling point on the line of the pulsed Doppler beam was positioned where the colored dots within the tumor revealed the presence of vessels and these positions were followed those proposed by Kurjak et al(Kurjak et al, 1993c). When no blood flow was detectable within the tumor, a signal was recorded by peripheral areas or the adnexal branch of the ovarian artery or uterine artery.

Both pulsatility index (PI) and resistance index (RI) were calculated. The value of each artery was calculated from a curve fitted to the average waveform over three cardiac cycles.

The formulas used for PI and RI were PI = (S-D)/ mean and RI = (S-D)/S respectively, when S is the peak Doppler frequency shift and D is the minimum. Signals from various areas within the tumor were determined but the lowest PI and RI were considered for data analysis. Furthermore, the area distribution of visualized vessels in the adnexal masses was also categorized and recorded as center of the mass, in the septum, in the papillae, at tumor wall or peri-tumor areas.

The final diagnosis as gold standard was based on either pathological findings or intraoperative findings in case of no pathological specimen. The pathological diagnosis of borderline tumor was classified as malignancy. Therefore all of adnexal masses were divided into 2 groups as benign and malignant adnexal masses.

The sensitivity and specificity of various cut-off levels of PI and RI were calculated and the proper PI and RI for differentiating the tumors were determined by receiver operator characteristic curve (ROC curve). All data were analyzed using SPSS software version 15.0 (Chicago, USA).

Results

Between April 2006 and March 2008, 329 patients initially diagnosed as ovarian tumors were recruited to undergo e-flow color Doppler ultrasound examinations. Twenty-three patients were excluded because of pathological diagnoses of non-ovarian tumor including subserous myoma, hydrosalpinx, etc. The remaining 306 were analyzed. All were successfully performed via transabdominal ultrasound. The mean (+ SD) age of the patients was 43.4+14.0 years (range 13-79 years). One hundred and thirteen (36.9%) were nulliparous. Most patients (205 women, 67.0%) were in reproductive age, 96 (31.4%) were menopausal and 5 of them were in pre-menarche period.

Table 1. Distribution of the Final Pathological Diagnoses of the Adnexal Masses

Benign tumors		
Mucinous cystadenoma	21	6.9
Serous cystadenoma	17	5.6
Endometriotic cyst	56	18.3
Mature teratoma (Dermoid cyst)	36	11.8
Follicular cyst, Simple cyst	13	4.2
Hemorrhagic cyst	4	1.3
Subserous myoma	4	2.4
Hydrosalpinx, TOA	5	1.6
Thecoma, fibroma	6	2.0
Other Benign tumors	20	6.6
Low malignant potential tumor		
LMP mucinous cystadenoma	12	3.9
Cancer		
Serous cystadenocarcinoma	31	10.1
Mucinous cystadenocarcinoma	10	3.3
Endometrioid carcinoma	18	5.9
Clear cell carcinoma	6	2.0
Endodermal sinus tumor	4	1.3
Immature teratoma	2	0.7
Dermoid squamous cell carcinoma	2	0.7
Dysgerminoma	3	1.0
Metastatic adenocarcinoma	13	4.2
Sex cord stromal tumor	6	2.0
Other malignant tumors	8	2.6
Total	306	100.0

Histopathological examinations revealed 191 (62.4%) benign tumors, 12 (3.9%) low malignant potential tumors and 103 (33.7) malignant tumors. Table 1 summarizes the type of ovarian tumors in this study.

Of 306 cases, the mean PI values of tumor arteries were 1.73 (+0.33), 0.97 (+0.26) and 0.88 (+0.2.9) for benign tumor, low malignant potential tumor and cancer, respectively. When cancer and low malignant potential tumors were considered together, their mean PI was 0.89 (+0.29). The mean PI in the benign and malignant group was significantly different (Student's T test, $p<0.001$). Based on receiver-operating characteristics (ROC) curve (Figure 1a) with area under curve of 0.960 (95% Confidence interval; 0.936; 0.984), the best cut-off PI was 1.20, which gave sensitivity and specificity of 93.0% and 92.7%, respectively (Table 2).

The mean RI values were 0.81 (+0.16), 0.50 (+0.12) and 0.44 (+0.11) for benign tumor, low malignant potential tumor and cancer, respectively. The mean RI was 0.45 (+0.12) if malignant and borderline tumors were considered together. The mean RI in the benign and malignant group was significantly different (Student's T test, $p<0.001$). Based on receiver-operating characteristics (ROC) curve (Figure 1b) with area under curve of 0.955 (95% Confidence interval; 0.927; 0.982), the best cut-off RI was 0.62, which gave sensitivity and specificity of 94.8% and 93.2%, respectively (Table 3).

Blood flow velocity waveforms within the tumors were detected in all cases of the malignant group and in 104 of 191 cases of the benign one. In the remaining 87 patients, blood flow was detected only in either the ovarian artery or adnexal branch of the uterine artery. The sites of detected vessels are summarized in Table 4.

Table 2. Diagnostic Indices of the Pulsatility Index. Color e-flow Dopper for differentiating benign from malignant adnexal masses, using a cut-off value of 1.20

Pulsatility Index	Benign	Malignant	Total
PI < 1.20	107	14	121
PI > 1.20	8	177	185
Total	115	191	306

Table 3. Diagnostic Indices of the Resistance Index. Color e-flow Dopper fo differentiating benign from malignant adnexal masses, using a cut-off value of 0.62

Resistance Index	Benign	Malignant	Total
RI < 0.62	109	13	122
RI > 0.62	6	178	184
Total	115	191	306

Table 4. Vessel Distribution in Adnexal Masses

Location	Total	Benign	Malignant	
			Low	High
Central areas	54	19 (35.2)	4 (7.4)	31 (57.4)
Peripheral areas	27	16 (59.3)	3 (11.1)	8 (29.6)
In the septae	56	28 (50.0)	3 (5.4)	25 (44.6)
In the papillae	68	36 (52.9)	1 (1.5)	31 (45.6)
At the tumor wall	18	9 (50.0)	1 (5.6)	8 (44.4)
Peri-tumor*	83	83 (100)	-	-
Total	306	191 (62.4)	12 (3.9)	103 (33.7)

*No vessels in tumor

Discussion

Differentiation of benign from malignant tumors might be achieved by several methods such as clinical signs and symptoms, serum CA 125(NIH Consensus Development Panel on Ovarian Cancer, 1995; Erdogan et al., 2005; Mousavi et al., 2006), and ultrasound (Sassone et al, 1991a;Timmerman et al, 1999). Conventional ultrasound parameters for the differentiation of malignant from benign tumors are based merely on morphological features. The introduction of color Doppler ultrasound, especially high-resolution color e-flow Doppler with higher sensitivity in detection of blood flow in minute vessels, might allow a step forward from morphological to functional evaluation of the masses. The theoretical background comes from the observation that the new tumor vessels that grew as a result of angiogenesis differ from the normal vessels with respect to cellular composition, basement membrane structure and permeability. As a result, the hemodynamics of these vessels are changed (Kurjak et al., 1993b).

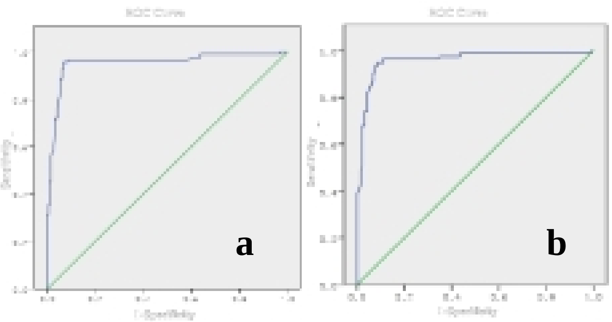

Figure 1. Receiver Operating Characteristic (ROC) Curve of a) PI and b) RI in Differentiating Benign from Malignant Adnexal Masses

Considering angiogenesis as a neoplastic marker for malignancy, color Doppler ultrasound allowing a better insight in the biological behavior of the tumor, the early diagnosis of cancer could become possible by detecting neovasculairazation in the tumor (Bourne et al., 1989; Kurjak et al., 1993; Rieck et al., 2006; Fleischer & Andreotti, 2005).

In previous studies, some authors suggested the existence of clear cut-off points of PI and RI of benign and malignant tumors; Kurjak et al (1991) reported only one false positive and two false negative results in a screening program involving 624 benign ovarian tumors and 56 malignant tumors by using a cut-off value of RI 0.4. Sengoku et al (1994) reported sensitivity and specificity of 81.3% and 91.7% respectively when the cut-off value of PI 1.5 were used. Timor-Tritsch et al (1993) reported the RI value of 0.4 had sensitivity 93.8% and specificity of 98.7% which was different from the study of Zanetta et al (RI 0.56)(1994).

In the present study 54% of benign and 100% of malignant including borderline tumors had detectable arterial blood flow in the tumors using a color Doppler unit. This information may enable us to conclude that tumor without detectable blood flow is very unlikely to be malignant. Our cut-off PI value of 1.24, giving the sensitivity and specificity of 95.1% and 88.3%, respectively, was different from the study of Sengoku et al (1994) but was consistsent with the data reported by Weiner et al (1992). Considering RI value of 0.64 as the cut-off point, the sensitivity and specificity were 95.1% and 90.3% respectively, slightly different from the studies of Timor-Tritsch et al (1993) and Zanetta et al (1994) in which RI values were 0.4 and 0.56 respectively.

The scanning approach (transvaginal or transabdominal) and frequency of the probes might partially explain inconsistent results reported previously by different authors (Zanetta et al., 1994a). Unlike previous reports in which they firstly used transabdominal probe and then transvaginal probe is performed if transabdominal examination was unable to visualize, our study with e-flow color Doppler we could identify the tumor in all cases. This may be the advantage of new high-resolution ultrasound technology permitting us avoiding the inconvenience of transvaginal approach.

Although there are different opinions about cut-off values, all authors agree that recognition of angiogenesis as a reference point for malignant changes within the ovary has proved to be a highly sensitive parameter. Given that neovascularizartion is an obligate event in malignant change, this recognition may enable us to observe the earliest stages in ovarian oncongenesis.

The bias in this study might have existed. This was due to the fact that Doppler evaluation of the tumor was not a blind method as the examiner had known the morphology of the tumor from conventional sonographic images. Therefore, the nature of the mass could have been anticipated. Consequently, the signs of neovascularization in tumors considered benign by conventional ultrasound might be missed by insufficient evaluation of the vascularitiy, whereas the tumors with suspicion of malignancy would be examined more thoroughly until the expected lowest PI and RI were found. However, we tried to examine all arterial signals to find out the lowest ones in each case to reduce the bias described.

In the future, research should be directed to compare the new color e-flow Doppler ultrasound with other modalities other than conventional ultrasound, especially three-dimensional color Doppler for detecting ovarian malignancy. Because of low incidence of ovarian cancer, one can initiate this ovarian malignancy screening program in high-risk population so that the efficacy of this method can be evaluated.

In conclusion, pulsatility and resistance index of transabdominal Doppler ultrasound (e-flow) has high accuracy in differentiating between benign and malignant adnexal masses.

References

NIH Consensus Development Panel on Ovarian Cancer (1995) Ovarian cancer. Screening, treatment, and follow-up. JAMA, **273**, 491-7.

Bourne T, Campbell S, Steer C, Whitehead MI, CollinsWP (1989). Transvaginal colour flow imaging: a possible new screening technique for ovarian cancer. *BMJ*, **299**, 1367-70.

Erdogan N, Ozcelik B, Serin IS, Akgun M, Ozturk F (2005) Doppler ultrasound assessment and serum cancer antigen 125 in the diagnosis of ovarian tumors. *Int J Gynaecol Obstet*, **91**, 146-50.

Ferrazzi E, Lissoni AA, Dordoni D, et al (2005). Differentiation of small adnexal masses based on morphologic characteristics of transvaginal sonographic imaging: a multicenter study. *J Ultrasound Med*, **24**, 1467-73.

Fleischer AC, Andreotti RF (2005). Color Doppler sonography in obstetrics and gynecology. *Expert Rev Med Devices*, **2**, 605-11.

Hata T, Hata K, Senoh D, et al (1989). Doppler ultrasound assessment of tumor vascularity in gynecologic disorders. *J Ultrasound Med*, **8**, 309-314.

Kawai M, Kano T, Kikkawa F, et al (1992). Transvaginal Doppler ultrasound with color flow imaging in the diagnosis of ovarian cancer. *Obstet Gynecol*, **79**, 163-7.

Kurjak A , Predanic M , Kupesic-Urek S, Jukic S (1993). Transvaginal color and pulsed Doppler assessment of adnexal tumor vascularity. *Gynecol Oncol*, **50**, 3-9.

Kurjak A, Zalud I, Alfirevic Z (1991). Evaluation of adnexal masses with transvaginal color ultrasound. *J Ultrasound Med*, **10**, 295-7.

Lerner,J.P., Timor-Tritsch,I.E., Federman,A., & Abramovich,G. (1994) Transvaginal ultrasonographic characterization of ovarian masses with an improved, weighted scoring system. Am.J.Obstet.Gynecol., 170, 81-85.

Mousavi,A.S., Borna,S., & Moeinoddini,S. (2006) Estimation of probability of malignancy using a logistic model combining color Doppler ultrasonography, serum CA125 level in women with a pelvic mass. Int.J Gynecol Cancer, 16 Suppl 1, 92-98.

Rieck GC, Pugh ND, Fiander AN (2006). Power Doppler in the assessment of pelvic masses in a low risk group. *J Obstet Gynaecol*, **26**, 222-4.

Sassone AM, Timor-Tritsch IE, Artner A, Westhoff C, Warren WB (1991). Transvaginal sonographic characterization of ovarian disease: evaluation of a new scoring system to predict ovarian malignancy. *Obstet Gynecol*, **78**, 70-6.

Sengoku K, Satoh T, Saitoh S, Abe M, Ishikawa M (1994). Evaluation of transvaginal color Doppler sonography, transvaginal sonography and CA 125 for prediction of ovarian malignancy. *Int J Gynaecol Obstet*, **46**, 39-43.

Timmerman D, Schwarzler P, Collins WP, et al (1999). Subjective assessment of adnexal masses with the use of ultrasonography: an analysis of interobserver variability and experience. *Ultrasound Obstet Gynecol*, **13**, 11-6.

Timor-Tritsch LE, Lerner JP, Monteagudo A, Santos R (1993). Transvaginal ultrasonographic characterization of ovarian masses by means of color flow-directed Doppler measurements and a morphologic scoring system. *Am J Obstet Gynecol*, **168**, 909-13.

Valentin L (1999a) Prospective cross-validation of Doppler ultrasound examination and gray-scale ultrasound imaging for discrimination of benign and malignant pelvic masses. *Ultrasound Obstet Gynecol*, **14**, 273-83.

Valentin L (1999b). Pattern recognition of pelvic masses by gray-scale ultrasound imaging: the contribution of Doppler ultrasound. *Ultrasound Obstet Gynecol*, **14**, 338-47.

Weiner Z, Thaler I, Beck D, et al (1992). Differentiating malignant from benign ovarian tumors with transvaginal color flow imaging. *Obstet Gynecol*, **79**, 159-62.

Zanetta G, Vergani P, Lissoni A (1994) Color Doppler ultrasound in the preoperative assessment of adnexal masses. *Acta Obstet Gynecol Scand*, **73**, 637-41.