Color Doppler Ultrasonography for Prediction of Malignant Ovarian Tumors

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Abstract

The purpose of this cross-sectional study was to evaluate whether the pulsatility index determined by the color Doppler sonography could be used to distinguish between benign and malignant ovarian tumors. A total of 120 patients who had their ovarian tumors removed surgically at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University were included in the study. Each patient had color Doppler sonography performed prior to laparotomy. The Doppler results were compared to the histological diagnosis of the ovarian tumors. Of the 113 patients whose intratumoral blood flow could be evaluated, the pulsatility index was significantly lower in malignant lesions than in benign lesions (0.85 ± 0.46 *vs* 1.63 ± 0.64, $p<0.001$). The sensitivity, specificity, and accuracy of the pre-operative pulsatility index (≤ 1.0) in detecting malignant ovarian tumors were 82.9 per cent, 80.8 per cent, and 81.4 per cent, respectively; with 65.9 per cent positive predictive value, 91.3 per cent negative predictive value, 19.2 per cent false positive rate, and 17.1 per cent false negative rate. The present results suggest that color Doppler sonography may be a useful clinical tool in the pre-operative evaluation of ovarian masses. However, the pulsatility indexes showed considerable overlap between benign and malignant lesions, indicating that color Doppler sonography has limitations in the differentiation of benign from malignant ovarian masses. The cost of the equipment and experience requirement also limits its use in general gynecologic practice.

Key word : Color Doppler Ultrasonography, Pulsatility Index, Ovarian Tumor

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Ovarian tumors are common diagnostic and management problems for physicians. Differentiation of benign from malignant adnexal masses represents one of the most challenging problems in gynecologic practice. To determine whether an ovarian tumor is malignant, various diagnostic procedures have been used including physical examination, gray-scale ultrasound[1] and tumor markers such as CA-125[2,3]. Conventional sonography is extensively used in the diagnosis of adnexal masses but lacks specificity in distinguishing benign from malignant lesions[4-8]. CA-125 is used as a marker for non-mucinous ovarian adenocarcinoma[9]. The positive and negative predictive values of this marker for ovarian malignancy are generally low[4,5,10,11], so it is mainly used in the post-operative follow-up of patients undergoing chemotherapy. A new and better technique for accurate differentiation of benign and malignant disease would reduce unnecessary anxiety and improve triage of appropriate ovarian tumors to a gynecologic oncologist.

The theoretical background for the introduction of color Doppler sonography (CDS) comes from the observation that angiogenesis and neovascularization in malignant tumors results in a high number of additional, atypical tumor vessels[12,13], which cause a decreased blood flow resistance. However, the usefulness of CDS is now controversial due to the overlap in the values obtained from benign and malignant lesions[14-16] and their relatively poor correlation[6,17-19]. The purpose of this study was to determine the accuracy of CDS in the detection of ovarian cancer on the basis of the pulsatility index (PI).

MATERIAL AND METHOD

Between June 2000 and September 2001, the authors studied all patients with suspected ovarian tumors who were admitted for elective surgery at the Division of Gynecology, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University. All color Doppler examinations were performed and evaluated by the same physician (P.S). Sonography was done on an Toshiba (Eccocee) SSA-340A unit. Most patients were scanned transabdominally with a PVF-375 MT, 3.75-MHz transducer. In some patients whose tumors could not be evaluated clearly, transvaginal ultrasound was done with the PVF-621 VT, 5-MHz transducer. A minimum of three waveforms were obtained from any areas of flow within or around the ovary. The PI (systolic peak - diastolic peak/mean) was calculated electronically, with the lowest value taken as representative of the most suspicious pathologic characteristic. PI greater than 1.0 was considered representative of high-impedance flow (Fig. 1), and values

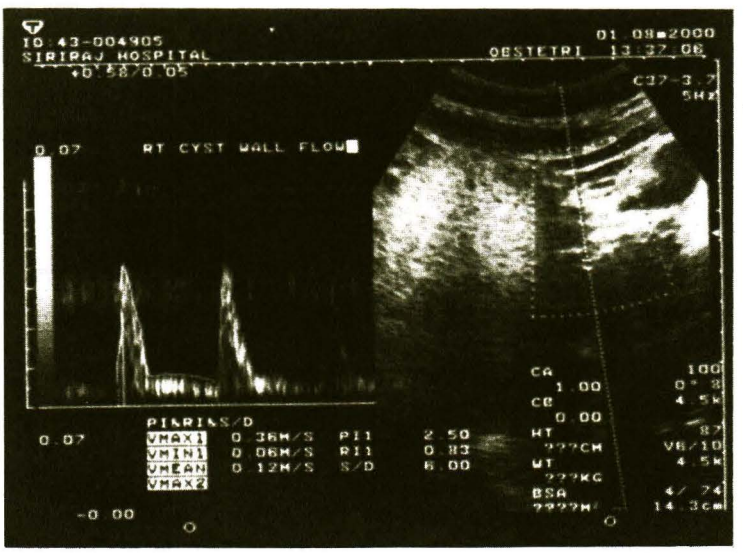

Fig. 1. Doppler waveform of the lesion demonstrates high-impedance flow (PI = 2.5). Final diagnosis: benign cystic teratoma.

of less than or equal 1.0 were considered to indicate low-impedance flow (Fig. 2). Tumors were categorized as either benign or suspicious of being malignant by Doppler sonography before surgery. All tumors were examined histologically according to the World Health Organization Classification[20]. Patients with previous surgery for ovarian cancer, metastatic tumor to the ovary, and tumors of non-ovarian origin were excluded.

Statistical significance between benign and malignant groups was assessed with Student *t*-test. The PI was related to the benign or malignant nature of the ovarian tumor by contingency table methods and evaluated for significance by Chi-square analysis.

RESULTS

A total of 120 patients with primary ovarian tumor had CDS performed and underwent laparotomy. The patients' age ranged from 12-81 years with a mean age of 41 ± 14 years. Half of the patients (50.8%) were nulliparous and one-fourth were in the post-menopausal period. The most common presenting symptoms were abdominal pain (30.8%) and palpable mass (30%). Common epithelium was the most common histological type, comprising 65.8 per cent and germ cell was the second most common tumor, comprising 19.2 per cent. One-third of the tumors (29.2%) were malignant, and nearly half of the patients (45.7%) had advanced stage of disease (Table 1).

In seven of 120 patients, no flow could be detected within the mass or immediately adjacent to it, and these cases were excluded from the analysis. Of the remaining 113 patients, PI was significantly lower in malignant lesions than in benign lesions (0.85 ± 0.46 *vs* 1.63 ± 0.64, p<0.001). The PI of advanced ovarian cancer tended to be lower than that of early disease. However, it was not statistically significant (p=0.226).

Comparison of PI and histopathologic diagnosis of ovarian tumor is shown in Table 2. The sensitivity and specificity were 82.9 per cent (95% CI, 67.3-91.9) and 80.8 per cent (95% CI, 70.7-88.0), respectively. The positive predictive value was 65.9 per cent (95% CI, 51.1-78.1) and the negative predictive value was 91.3 per cent (95% CI, 82.3-96.0) with a false positive and negative rate of 19.2 per cent and 17.1 per cent, respectively. The accuracy rate of PI was 81.4 per cent (95% CI, 72.8-87.9).

DISCUSSION

Ovarian cancer is the leading cause of death among gynecologic malignancies in the United States[21,22]. In Thailand, it comprises about 16 per cent of all gynecologic cancers and is the second

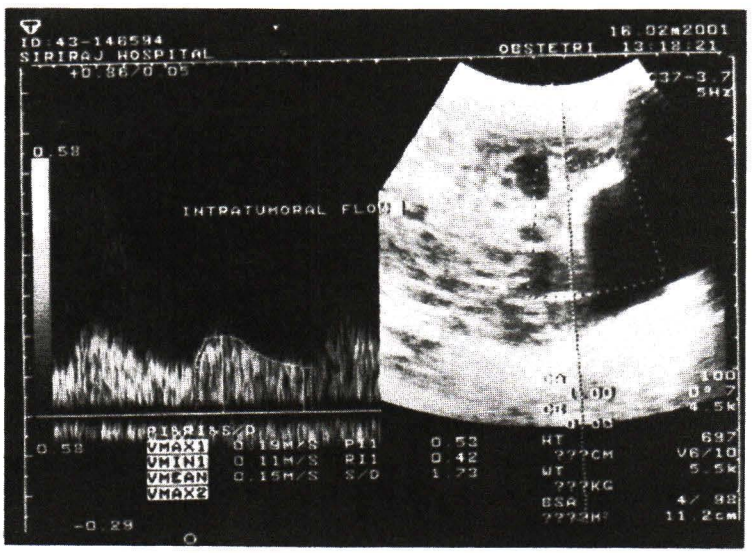

Fig. 2. Doppler waveform of the lesion demonstrates low-impedance flow (PI = 0.53). Final diagnosis: granulosa cell tumor.

Table 1. Distribution of ovarian tumors according to tumor type, tumor potential and staging (malignant tumor).

	Number	Per cent
Tumor type	120	100
Common epithelium	79	65.8
Germ cell	23	19.2
Stromal cell	4	3.3
Others (including tumor-like conditions)	14	11.7
Tumor potential	120	100
Benign	85	70.8
Malignant	35	29.2
Staging (malignant tumor)	35	100
Early stage (1 or 2)	18	51.4
Advanced stage (3 or 4)	16	45.7
Undetermined	1	2.9

Table 2. Contingency table arranged to show the prediction of malignant ovarian tumor by pulsatility index.*

Color Doppler ultrasound	Histopathology		Total
	Malignant	Benign	
PI ≤ 1.0 (positive)	29	15	44
PI > 1.0 (negative)	6	63	69
Total	35	78	113

* sensitivity, 82.9 per cent (29/35); specificity, 80.8 per cent (63/78); positive predictive value, 65.9 per cent (29/44); negative predictive value, 91.3 per cent (63/69).

most common cancer of the female genital tract after cervical cancer[23]. Ovarian cancer is very insidious and silent in terms of signs and symptoms. It is one of the most challenging problems in gynecology, since it is often detected in more advanced stages, resulting in a high fatality rate[24]. Current methods to differentiate benign from malignant ovarian tumors (eg, physical examination, chemical markers such as CA-125, and gray-scale ultrasound) have fallen short of expectation. CDS has been proposed as an additional method for distinguishing benign from malignant ovarian masses. This idea is based on the premise that malignant masses will have low-impedance flow due to internal neovacularization [14,25-27]. The authors used the PI in the analysis because it is a more accurate measurement of ovarian blood flow. The PI is less susceptible to random error than the resistance index because it measures the mean of many points in the waveform and is claimed to be more sensitive to subtle vascular change[28,29]. PI of less than 1.0 was used to indicate malignant tumor, as initially proposed by Bourne et al[25]. Although lesions with no flow have been considered benign, some authors have shown absence of flow in malignant lesions as well[4,10,15,26,30]. So, the authors excluded seven patients whose intratumoral blood flow could not be detected from the analysis.

The present results show that malignant lesions tend to have a low-impedance flow and benign lesions have a high-impedance flow. However, a significant overlap in individual values of PI for benign and malignant lesions was found, with 19.2 per cent of benign lesions in the present study showing low-impedance flow and 17.1 per cent of malignant lesions showing high-impedance flow. These findings are similar to those in recent published reports that also showed a considerable overlap in impedance between benign and malignant adnexal masses[15,30,31]. Sensitivity, specificity and

accuracy of CDS in the present study are somewhat lower than those previously reported[4,5,10,14,25,27]. This may be attributed to the fact that most of the patients in this study had CDS done transabdominally. Timor-Tritsch et al[32] demonstrated that the vaginal approach produces a greater image resolution than the abdominal, thus allowing detailed assessment of ovarian masses. Secondly, three-fourths of the patients were in pre-menopausal status. CDS can be misleading in pre-menopausal women and usually shows lower specificity[33] because physiologic alterations in the ovary, due to the menstrual cycle, can cause lowered blood vessel resistance[34,35]. Serial Doppler measurements would be desirable in pre-menopausal patients but could not be performed in this study because the patients underwent surgery on the day following admission to the hospital. The observation that PI of advanced ovarian cancer tends to be lower than that of early disease in the present study, is similar to that reported by Weiner et al[10]. However, the difference is not statistically significant. This may be attributed to the small number of malignant lesions in the present study.

In conclusion, although CDS shows promise as a noninvasive tool for differentiating adnexal mass, a significant number of benign lesions with PI of less than or equal to 1.0 was found, indicating a considerable overlap of benign and malignant lesions showing low-impedance flow. Moreover, the cost of the equipment and the experience required for this technique limits its universal application in gynecologic practice.

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REFERENCES

1. Campbell S, Bhan V, Royston P, Whitehead MI, Collins WP. Transabdominal ultrasound screening for early ovarian cancer. BMJ 1989; 299: 1363-7.
2. Bast RC Jr, Klug TL, St.John E, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Eng J Med 1983; 309: 883-7.
3. Kuzuya K, Nozaki M, Chihara T. Evaluation of CA-125 as a circulating tumor marker for ovarian cancer. Acta Obstet Gynaecol Jpn 1986; 38: 949-57.
4. Kawai M, Kano T, Kikkawa F, Maeda O, Oguchi H, Tomoda Y. Transvaginal Doppler ultrasound with color flow imaging in the diagnosis of ovarian cancer. Obstet Gynecol 1992; 79: 163-7.
5. Zanetta G, Vergani P, Lissoni A. Color Doppler ultrasound in the pre-operative assessment of adnexal mass. Acta Obstet Gynecol Scand 1994; 73: 637-41.
6. Bromley B, Goodman H, Benacerraf BR. Comparison between sonographic morphology and Doppler waveform for the diagnosis of ovarian malignancy. Obstet Gynecol 1994; 83: 434-7.
7. Lerner JP, Timor-Tritsch IE, Federman A, Federman A, Abramovich G. Transvaginal ultrasonographic characterization of ovarian masses with an improved, weighted scoring system. Am J Obstet Gynecol 1994; 170: 81-5.
8. Reles A, Wein U, Lichtenegger W. Transvaginal color Doppler sonography and conventional sonography in the pre-operative assessment of adnexal mass. J Clin Ultrasound 1997; 25: 217-25.
9. Klug TL, Bast RC Jr, Niloff JM, Knapp RC, Zurawski VR. Monoclonal antibody immunoradiometric assay for antigenic determinant (CA 125) associated with human epithelial ovarian carcinoma. Cancer Res 1984; 44: 1048-53.
10. Weiner Z, Thaler I, Beck D, Rottem S, Deutsch M, Brandes JM. Differentiating malignant form benign ovarian tumors with transvaginal color flow imaging. Obstet Gynecol 1992; 79: 159-62.
11. Di-Xia C, Schwartz PE, Xinguo L, Zhan Y. Evaluation of CA 125 levels in differentiating malignant from benign tumors in patients with pelvic masses. Obstet Gynecol 1988; 72: 23-7.
12. Jain RK. Determinants of tumor blood flow: A review. Cancer Res 1988; 48: 2641-58.
13. Blood C, Zetter B. Tumor interactions with the vasculature: Angiogenesis and tumor metastasis. Biochem Biophy Acta 1990; 1032: 89-118.
14. Fleischer AC, Rodgers WH, Rao BK, et al. Assessment of ovarian tumor vascularity with transvaginal color Doppler sonography. J Ultrasound Med 1991; 10: 563-8.
15. Tekay A, Jouppila P. Validity of pulsatility and resistance indices in classification of adnexal

tumors with transvaginal color Doppler ultrasound. Ultrasound Obstet Gynecol 1992; 2; 338-44.
16. Tekay A, Jouppila P. Controversies in assessment of ovarian tumors with transvaginal color Doppler ultrasound. Acta Obstet Gynecol Scand 1996; 75: 316-29.
17. Levine D, Feldstein VA, Babcook CJ, Filly RA. Sonography of ovarian masses: poor sensitivity of resistance index for identifying malignant lesions. AJR Am J Roentgenol 1994; 162: 1355-9.
18. Valentin L, Sladkevicius P, Marsal K. Limited contribution of Doppler velocimetry to the differential diagnosis of extrauterine pelvic tumors. Obstet Gynecol 1994; 83: 425-33.
19. Schneider VL, Schneider A, Reed K, Hatch KD. Comparison of Doppler with two-dimensional sonography and CA 125 for prediction of malignancy of pelvic masses. Obstet Gynecol 1993; 81: 983-8.
20. Seroy SF, Scully RE, Sobin IH. Histological typing of ovarian tumors: International histological classification of tumours, No.9. Geneva: World Health Organization, 1973.
21. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1997. CA Cancer J Clin 1997; 47: 5-27.
22. Piver MS, Baker TR, Piedmonte M, Sandecki AM. Epidemiology and etiology of ovarian cancer. Semin Oncol 1991; 18: 177-85.
23. Deerasamee S, Martin N, Sontipong S, et al, eds. Cancer in Thailand, Vol. 2, 1992-1994. Lyon: International Agency for Research on Cancer, 1999: 62-4.
24. Tortolero-Luna G, Mitchell MF, Rhodes-Morris HE. Epidemiology and screening of ovarian cancer. Obstet Gynecol Clin North Am 1994; 21: 1-23.
25. Bourne T, Campbell S, Steer C, Whitehead MI, Collins WP. Transvaginal color flow imaging: A possible new screening technique for ovarian cancer. BMJ 1989; 299: 1367-70.
26. Kurjak A, Zalud I, Alfirevic Z. Evaluation of adnexal masses with transvaginal color ultrasound. J Ultrasound Med 1991; 10: 295-7.
27. Fleischer AC, Rodgers WH, Rao BK, Kepple DM, Jones HW. Transvaginal color Doppler sonography of ovarian masses with pathologic correlation. Ultrasound Obstet Gynecol 1991; 1: 275-8.
28. Salem S, White LM, Lai J. Doppler sonography of adnexal masses: The predictive value of the pulsatility index in benign and malignant disease. AJR 1994; 163: 1147-50.
29. Loquet P, Pipkin FB, Symonds EM, Rubin PC. Influence of raising maternal blood pressure with angiotensin II on utero-placental and feto-plecental blood velocity indices in the human. Clin Sci 1990; 78: 95-100.
30. Brown DL, Frates MC, Laing FC, DiSalvo DN, Doubilet PM, Benson CB. Ovarian masses: Can benign and malignant lesions be differentiated with color and pulsed Doppler US ? Radiology 1994; 190: 333-6.
31. Hamper UM, Sheth S, Abbas FM, Rosenshein NB, Aronson D, Kurman RJ. Transvaginal color Doppler sonography of adnexal masses: Differences in blood flow impedance in benign and malignant lesions. AJR 1993; 160: 1225-8.
32. Timor-Tritsch IE, Bar-Yam Y, Elgal S, Rottem S. The technique of transvaginal sonography with the use of a 6.5 MHz probe. Am J Obstet Gynecol 1988; 158: 1019-24.
33. Fleischer AC, Cullinan JA, Kepple DM, Williams LL. Conventional and color Doppler transvaginal sonography of pelvic masses: A comparison of relative histologic specificities. J Ultrasound Med 1993; 12: 705-12.
34. Wu CC, Lee CN, Chen TM, Shyu MK, Hsieh CY, Chen HY. Incremental angiogenesis assessed by color Doppler ultrasound in the tumorigenesis of ovarian neoplasms. Cancer 1994; 73: 1251-6.
35. Thaler I, Manor D, Rottem S, Timor-Tritsch IE, Brandes JM, Itskowitz J. Hemodynamic evaluation of the female pelvic vessels using a high-frequency transvaginal image-directed Doppler system. J Clin Ultrasound 1990; 18: 364-9.

การใช้คลื่นเสียงคัลเลอร์ด็อพเลอร์ในการทำนายเนื้องอกรังไข่ชนิดร้าย

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ทำการวิจัยแบบตัดขวางเพื่อประเมินความถูกต้องของการใช้คลื่นเสียงคัลเลอร์ด็อพเลอร์ในการทำนายเนื้องอกรังไข่ โดยใช้ค่า pulsatility index ที่น้อยกว่าหรือเท่ากับ 1.0 ผู้ป่วยนรีเวชที่ได้รับการผ่าตัดเนื้องอกรังไข่จำนวน 120 คน จะได้รับการตรวจคลื่นเสียงคัลเลอร์ด็อพเลอร์ดูการไหลเวียนของเลือดในเนื้องอกรังไข่ทางหน้าท้องหรือทางช่องคลอด ที่ภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล โรงพยาบาลศิริราช มหาวิทยาลัยมหิดล หลังจากนั้นทำการเปรียบเทียบค่า pulsatility index กับผลการตรวจเนื้องอกรังไข่ทางพยาธิวิทยา ผู้ป่วยจำนวน 113 คนที่สามารถวัดการไหลเวียนของเลือดในเนื้องอกรังไข่ได้ พบว่าค่าเฉลี่ยของ pulsatility index ในเนื้องอกรังไข่ชนิดร้ายต่ำกว่าเนื้องอกรังไข่ธรรมดาอย่างมีนัยสำคัญทางสถิติ (0.85 $\pm$ 0.46 *vs* 1.63 $\pm$ 0.64, p<0.001) ค่า pulsatility index ที่น้อยกว่าหรือเท่ากับ 1.0 ในการทำนายเนื้องอกรังไข่ชนิดร้าย พบว่ามีความไวร้อยละ 82.9, ความจำเพาะร้อยละ 80.8, ค่าทำนายผลบวกร้อยละ 65.9, ค่าทำนายผลลบร้อยละ 91.3, ผลบวกลวงร้อยละ 19.2, ผลลบลวงร้อยละ 17.1, และความถูกต้องร้อยละ 81.4 สรุปว่าคลื่นเสียงคัลเลอร์ด็อพเลอร์มีประโยชน์ในการทำนายเนื้องอกรังไข่ก่อนการผ่าตัด อย่างไรก็ตาม สิ่งที่เป็นข้อจำกัดของการใช้วิธีนี้ คือ ความคาบเกี่ยวของค่า pulsatility index ที่พบทั้งในเนื้องอกรังไข่ธรรมดาและชนิดร้าย นอกจากนี้ เครื่องมือยังมีราคาแพง และต้องการผู้มีประสบการณ์ในการตรวจและการแปลผล ทำให้ไม่เป็นที่แพร่หลายในการตรวจทางนรีเวชทั่วไป

คำสำคัญ : คลื่นเสียงคัลเลอร์ด็อพเลอร์, เนื้องอกรังไข่

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