ORIGINAL ARTICLE

Adnexal Masses in Perimenopausal Women: How Effective is Color Flow Mapping and Pulse Doppler Waveform Studies in detecting Malignancy Preoperatively?

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ABSTRACT

Objective: This prospective study was undertaken to assess the sensitivity and specificity of color flow mapping and pulse Doppler waveform in identifying malignancy preoperatively in adnexal masses in perimenopausal women.

Materials and methods: A total of 100 cases with adnexal masses in perimenopausal women were scanned, underwent color flow mapping and pulsed Doppler waveform studies. These cysts were divided into three groups according to their ultrasound appearance – cystic, mixed cystic and solid. All the adnexal mases were removed surgically and sent for histopathological study.

Results: The sensitivity and specificity of color flow mapping in identifying malignant ovarian tumors was 63.6 and 87.0% respectively. In the case of solid cysts, color flow mapping identified all malignant tumors. But, color flow mapping missed malignancies in cystic and mixed cystic masses. To improve detection rates, we used Doppler waveform studies and used resistance index less than 0.4 as the indicator of malignancy and found overall sensitivity and specificity of 90.9 and 92.3%, which was higher than that of color flow mapping.

Conclusion: To conclude ultrasonic color flow mapping and pulse Doppler waveform studies used preoperatively on adnexal masses in perimenopausal women are widely available, performed rapidly and relatively easily, cost-effective and a reliable noninvasive method to predict malignancy preoperatively.

Keywords: Adnexal masses, Color flow mapping, Neovascularization, Pulsed, Doppler waveform, Resistivity index.

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INTRODUCTION

Adnexal masses in perimenopausal women present a special diagnostic challenge, in part because benign adnexal masses greatly outnumber malignant ones. Determination of a degree of suspicion for malignancy is critical and is of particular importance in gynecological practice, first to discriminate benign and malignant masses and second for the choice of appropriate surgical treatment; as in many centers the type of surgery performed (laproscopy *vs* laprotomy) depends on the probability of malignancy. Majority of adnexal masses in the perimenopausal women are non-neoplastic cysts but 25% of these are malignant.[1]

Endovaginal ultrasonography is the most practical modality for assessment of ovarian tumors because it is readily available and has a high negative predictive value.[2-4]

The optimal ultrasound technique and diagnostic criteria to use, when characterizing a suspected ovarian neoplasm are still controversial. Papillary formations on the inside of cyst wall and hyperechoic solid component are the most statistically significant predictors of a malignant ovarian mass.[5,6] Ultrasound and morphologic parameters have a sensitivity of 80% and specificity of 93% that make this examination a standard for ovarian mass diagnosis.[7]

Doppler flow measurement and assessment of tumor vascularity by Doppler energy increased the confidence with which a correct diagnosis can be made. Color and pulsed Doppler sonography depicts the vascularity of the pelvic organs and can be used for assessment of angiogenesis in tumor masses producing insights in tumor histology.[8,9]

Benign lesions tend to initiate new tumor blood vessel formation peripherally from pre-existing host vessels, whereas malignant tumors tend to initiate new tumor blood vessel formation centrally.[10-12] Waveform analysis is based on the fact that malignant tumor vessels are morphologically abnormal. They lack smooth muscle in their walls, demonstrate an irregular course and arteriovenous shunt formation.[13-16] In addition, malignant tumor vessels generally have low impedance, which causes high diastolic flow and low systolic-diastolic variation. Some differentiation between benign and malignant masses is achieved by quantifying these differences.

Two indexes have been used in analyzing Doppler waveforms: The pulsatility index and the resistance index. Both increase with increasing distal vascular resistance and the two indexes have a high correlation. A comparison of different studies have shown that resistance index less than 0.4 and pulsatility index less than 1.0 are generally considered to be suspicious for malignancy.[17-23]

So a prospective study was embarked to assess the usefulness of ultrasound color flow mapping and pulsed

Doppler waveform in differentiating between benign and malignant adnexal masses in perimenopausal women preoperatively.

MATERIALS AND METHODS

Among 100 perimenopausal women (between July 2008 and July 2011) with the mean age of 42.7 years (range 38-52 years) with clinically detected adnexal masses attending the Outdoor Department of Malhotra Nursing Home and Test Tube Baby Center and referrals from radiologists underwent ultrasound scanning, color flow mapping and pulsed Doppler waveform analysis.

For adnexal masses less than 10 cm, transvaginal scanning was performed and for those larger than 10 cm both transabdominal and transvaginal scanning was done. The size and structural features of the adnexal masses were noted by the basic scan and accordingly they were classified into three categories–cystic, mixed cystic and solid. After the basic scan, the machine settings were adjusted for maximum color sensitivity at flow velocities of 3 cm/sec. Intensities for color and pulse Doppler modes were kept below 92 mW cm^2 spatial peak temporal average.

To avoid luteal flow, the premenopausal women were preferably examined in the early follicular phase of the menstrual cycle (day 1-10). Impedence to flow was measured and the resistivity index was calculated for the new vessels formed at the periphery and center of the mass. The cutoff value of resistance index (RI) < 0.4 was taken as the significant value for the study.

Subsequently, all the 100 women underwent laparotomy and a thorough histopathological examination of the adnexal masses was done.

OBSERVATIONS

Among 100 perimenopausal women with clinically diagnosed adnexal masses were assessed for the study.

The mean age of these women was 42.7 years (ranging between 38-52 years), mean parity of 2.6 (ranging from nullipara to 5 para), with a mean BMI of 25 kg/m^2 belonging mainly to the lower socioeconomic group (68%) (Table 1).

Eleven women gave history of infertility and treatment taken for the same but none of their adnexal masses were found to be malignant.[4] Women gave a significant history of tobacco use and one of them had a cystadenoma of borderline malignancy.[13] Women gave a significant history of oral contraceptive use for more than 2 years and one of the two women who gave family history of ovarian cancer had an adnexal mass which on histopathology revealed a poorly differentiated adenocarcinoma.

Table 1: Patients characteristics of perimenopausal women taken in the study with adnexal masses

Sl. no.	*Patient characteristics*	*Value*
1	Mean age	42.7 years (38-52 years)
2	Mean parity	2.6 (Nullipara – 5 para)
3	Mean BMI	25 kg/m²
4	Socioeconomic status	
	• Upper	11%
	• Middle	21%
	• Lower	68%
5	Relevant history	
	• Infertility	11%
	• Smoking/tobacco use	4%
	• OCP use	13%
	• Family history of ovarian/ breast/colon cancer	2%
6	Asymptomatic	26%
7	Symptomatic	74%
	• Abdominal/pelvic pain	42.7%
	• Bloatedness	32.4%
	• Abnormal vaginal bleeding	18.8%
	• Others	6.1%

BMI: Body mass index; OCP: Oral contraceptive pills

It was surprising that, 26% of the women were asymptomatic and adnexal masses were incidental findings on transabdominal scanning done as a routine or referred to us from other fraternities. Seventy-four percent of the women were symptomatic with abdominal or pelvic pain being complained by the maximum majority (42.7%).Other complaints being bloatedness, abnormal vaginal bleeding, nausea, generalized weakness, weight loss and body pains (Table 1).

The size and structural features of the adnexal masses were noted by the basic scan and accordingly they were classified into three categories—cystic, mixed cystic and solid (Table 2). These cases were further subjected to color flow mapping and pulsed Doppler waveform studies. Twenty-two malignances and 78 benign masses were identified on histopathological examination of the adnexal masses removed after laparotomy (Table 3).

Table 2: Ultrasonographic categorization of adnexal masses

S. no.	*Ultrasound appearance*	*Number of cases*
1	Cystic	32
2	Mixed cystic	62
3	Solid	06
Total		100

Table 3: Correlation of histopathology results with color flow mapping in detecting malignancy in adnexal masses

Color flow mapping	*Number of cases*	*Histopathology*	
		Malignant	*Benign*
Neovascularization present	24	14	10
Neovascularization absent	76	8	68
Total	100	22	78

The malignant masses were granulosa cell carcinoma (1), cystadenocarcinoma of borderline malignancy (3), cysadenocarcinoma (3), papillary serous cystadenocarcinoma (2) and adenocarcinoma (13). The benign lesions were endometrioma (15), mesothelial cyst (12), serous cystadenoma (18), mucinous cystadenoma (15), cystic teratoma (6), hemorrhagic corpus luteum cyst (5), cystadenofibroma (2), sclerosing stromal cell tumor (3) and paratubal cyst (3).

Twenty-four of the masses showed neovascularization (positive color flow mapping), whereas 76 had negative color flows (Table 3). The overall sensitivity and specificity of color flow mapping in identifying malignant ovarian tumors was 63.6 and 87% respectively (Table 5).

In 26 cases the pulsed Doppler RI was found to be less than 0.4 (positive RI), whereas 74 cases had higher values (negative RI) (Table 4). The overall sensitivity and specificity of pulsed Doppler waveform studies with an RI < 0.4 in identifying malignant ovarian tumors was 90.9 and 92.3% respectively (Tables 8 and 9).

Sixteen of the ovarian tumors were simple cysts and all were found to be negative for color flow mapping (Table 4), but later two malignancies (Table 5) were detected giving a false-negative rate of 12.5% and sensitivity of 0% (Table 6). When pulse Doppler studies were done in these cases, three cases were found to be positive and 13 negative (RI > 0.4). Out of the three positive cases, two were malignant and one benign, whereas all the 13 negative cases were benign. This method gave the false-negative rate of 0% and sensitivity of 100% (Tables 7 and 8).

Table 4: Correlation of histopathology results with pulsed Dopper waveform (RI < 0.4) in detecting malignancy in adnexal masses

Pulsed Doppler waveform resistivity index)	*Number of cases*	*Histopathology*	
		Malignant	*Benign*
Resistivity index < 0.4	26	20	6
Resistivity index > 0.4	74	2	72
Total	100	22	78

Table 6: Details of type of malignancy seen on histopathological examination in different categories of adnexal masses

S. no.	*Type of adnexal mass*	*Number of malignant cysts*	*Histpathological details*
1	Cytic	4	• Granulosa cell carcinoma (1) • Cystadenoma of borderline malignancy (3)
2	Mixed cytic	12	• Cystadeno-carcinoma (3) • Papillary serous adeno carcinoma (2) • Adenocarcinoma (7)
3	Solid	6	• All adenocarcinoma

Sixty-two mixed cystic adnexal masses were identified in which 18 masses were positive for color flow mapping and 44 were negative. Out of the 18 positive masses, eight were found to be malignant and another four mixed cystic masses reported negative on color flow mapping were found to be malignant on histopathology (Table 5).

This gave a sensitivity and specificity of 66.6 and 80% respectively. Fourteen cases in this group showed an RI < 0.4 (Positive) out of which 10 were found to be malignant, whereas 46 out of 48 masses with negative RI indices were found to be benign giving a sensitivity and specificity rates of 63.3 and 81.2% respectively (Tables 8 and 9).

Six women presented with solid masses and were all found to have positive color flow mapping and RI values <0.4. All these masses were later confirmed malignant on histology, giving a sensitivity rate of 100% for both the methods (Tables 5, 8 and 9).

DISCUSSION

Ultrasound remains the study of choice in the initial evaluation of suspect adnexal masses, because it is relatively inexpensive, noninvasive and widely available. Transabdominal ultrasound, endovaginal ultrasound or both should be performed for the evaluation of adnexal masses.[4,6,8,24] Preliminary studies[5,6,8] that were performed in an attempt to screen for or identify early-stage ovarian carcinoma, especially in postmenopausal women, used transabdominal ultrasound and were unable to help to identify morphologic characteristics that would allow

Table 5: Details of correlation of color flow mapping and histopathological examination in different categories of adnexal masses

S. no.	*Type of adnexal mass*	*Number of cases*	*Color flow mapping*	*Histopathology*	
				Malignant	*Benign*
1	Cystic	32	All negative	4	28
2	Mixed cystic	62	18 positive *44 negative	84	10
3	Solid	6	6 positive	6	40

*Positive implies presence of neovascularization on color flow mapping

Table 7: Diagnostic indices of color flow mapping alone in identification of malignancy in adnexal masses

Type of adnexal mass	*Sensitivity (%)*	*Specificity (%)*	*False positive (%)*	*False negative (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*
Cystic	0	100	NV* absent in all	12.5	NV absent in all	87.5
Mixed cystic	66.6	80.0	20	33.3	44.4	90.0
Solid	100	NV* present in all	0	NV present in all	100	NV present in all
Overall	63.6	87	41.6	10.5	58.3	89.4

*NV: Neovascularization

Table 8: Details of correlation of Doppler waveform (RI < 0.4) and histopathological examination in different categories of adnexal masses

Type of adnexal mass	*No. of cases*	*RI*	*Histopathology*	
			Malignant	*Benign*
Cystic	32	6 Positive*	4	2
		26 Negative	—	26
Mixed cystic	62	14 Positive	10	4
		48 Negative	2	46
Solid	6	6 Positive	6	—

*Positive means RI < 0.4

Table 9: Diagnostic indices of pulsed Doppler waveform (RI < 0.4) in detection of malignancy in adnexal masses

Type of adnexal mass	*Sensitivity (%)*	*Specificity (%)*	*False positive (%)*	*False negative (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*
Cystic	100	92.8	33.3	0	66.6	100
Mixed cystic	83.3	81.2	8	16.6	71.4	95.8
Solid	100	—	—	0	100	—
Overall	90.9	92.3	27.2	2	76.9	97.2

Table 10: Comparison of the present study with other studies showing the diagnostic indices of color flow mapping in detecting malignancy in adnexal masses

Study (Name of worker with years)	*No. of cases with adnexal masses*	*Color flow mapping*	*Histopathology*		*Sensitivity (%)*	*Specificity (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*
			Malignant	*Benign*				
Hata et al (1989)[39]	16	12 Positive	8	4	100	50	66.6	100
		4 Negative	—	4				
Weiner et al (1992)[40]	53	16 Positive	16	—	94.1	100	100	94.1
		17 Negative	1	16				
Kawai et al (1992)[41]	24	11 Positive	8	3	88.8	80	72.7	92.3
		13 Negative	1	12				
Kurjak et al (1992)[42]	147	25 Positive	23	2	100	50	66.6	100
		122 Negative	—	122				
Zanetta et al (1994)[43]	80		33	47	85	91	—	89
Stein et al (1995)[44]	161		46	123	77	69	49	89
Sawicki et al (2001)[45]	280		71	209	—	93.6	66.8	79.8
Present study	50	24 Positive	14	10	63.6	87	58.3	89.4
		76 Negative	8	68				

differentiation of benign from malignant masses. The advent of high-frequency endovaginal probes allowed high-resolution imaging of the pelvic organs in general and of the ovaries in particular. Endovaginal ultrasound has allowed markedly improved resolution for uterine and adnexal imaging and is essential for imaging adnexal masses whose nature is not apparent at transabdominal ultrasound.[4,24,25]

Ultrasound, whether transabdominal or endovaginal, relies on morphologic assessment of the tumor to distinguish

between benign and malignant disease. Morphologic features including thick, irregular walls and septa, papillary projections, solid and moderately echogenic loculi have been described as suggestive of malignant tumor.[13,24-26] Many morphologic scoring systems have been proposed and are based on the wall thickness, inner wall structure, septal characteristics and echogenicity of the lesion. The sensitivity of morphologic analysis with US in predicting malignancy in ovarian tumors has been shown to be 85 to 97%, whereas its specificity ranges from 56 to 95%.[4,13,26-29]

Color Doppler US of ovarian masses helps identify vascularized tissue and can assist in differentiating solid tumor tissue from nonvascularized structures. It is also used in conjunction with pulsed Doppler US to identify vessels for waveform analysis.[28-31]

Tumor angiogenesis factors are important in rapid formation of new capillaries (neovascularization) in malignant tumors. Color flow mapping and pulsed Doppler ultrasound detects blood flow changes in these low-resistance vessels. These appear as continuously fluctuating color rather than the pulsatile color seen with normal arteries.

Color blood flow imaging and Doppler waveform analysis have been used as diagnostic tools to differentiate between benign and malignant adnexal masses by many workers as shown in Table 10.

In the present study, the use of color flow mapping in preoperative identification of malignancy in adnexal masses had an overall sensitivity and specificity of 63.6 and 87% respectively with a negative predictive value of 89.4% and positive predictive value of 58.3%.

Out of the 32 cystic masses color flow mapping had a false-negative rate of 12.5% and four malignances were missed. Since, malignancy is less suspected in simple cysts color flow mapping alone appears unreliable in this situation where it is probably needed the most.

When color flow mapping was performed on 42 mixed cystic masses, four out of the 12 malignancies (66.6%) were missed by color flow mapping.

Similarly, all the six solid adnexal masses showed positive color flow mapping and were found to be malignant on histopathological examination.

Therefore, color flow mapping alone may not be very reliable in differentiating between benign and malignant ovarian masses especially in simple and mixed cystic adnexal masses.

To improve the detection rates of color flow mapping, we used pulse Doppler waveform studies to measure the impedance to blood flow to differentiate between benign and malignant ovarian masses. For our study, the parameter we used was the RI which has been found to be the most sensitive and reliable indicator of malignancy in adnexal masses especially taking the cutoff as RI < 0.4. Taking this parameter and cutoff value; the overall sensitivity, specificity and positive predictive value in detecting malignancy was 90.9, 92.3 and 76.9% respectively which were much higher than those of color flow mapping (Table 9).

Kurjak et al[30] conducted a study on 14,000 patients with adnexal masses and found 56 malignancies. All but two showed abnormal color flow patterns with RI < 0.4. The reported sensitivity, specificity and positive predictive value in their study was 96.4, 99.8 and 98.2% respectively.

Doppler ultrasound has yielded variable results in distinguishing benign from malignant masses, with a sensitivity of 50 to 100% and a specificity of 46 to 100%.[13,27-34] Differing results are partly due to varying threshold values and corresponding trade-offs between sensitivity and specificity.

Problems[35] associated with Doppler ultrasound include operator dependence and lack of standard criteria in distinguishing benign from malignant waveforms. Moreover, in cases in which septations, papillae and solid areas of tumor are absent, it is difficult to detect signal for waveform analysis. In addition, certain Doppler indexes can be misleading in premenopausal women and usually have a lower specificity because physiologic alterations in the ovary due to the menstrual cycle cause lowered blood vessel resistance, thereby mimicking malignancy. Finally, acute inflammatory adnexal disease and endometriosis are common conditions associated with an increased number of capillaries and dilatation of blood vessels, which causes a low pulsatility index.

In a study by Reles et al[13] the sensitivity of color Doppler US was 80% and the specificity only 67% in premenopausal patients, whereas in postmenopausal patients, the sensitivity and specificity were 93 and 83% respectively.

Recently, three dimensional (3D) power Doppler qualitative analysis[36-38] of tumor angiogenesis has shown promising results in accurate detection of ovarian malignancy preoperatively in a number of studies and these may be able to overcome the problems with color Doppler studies. At present, higher equipment costs and more sophisticated operator skills make 3D ultrasound technology limited to only few centers, routine two-dimensional ultrasonography with color Doppler studies are still valuable screening modalities.

Workers are also exploring the use of microbubbles as an US contrast agent to improve color flow mapping.

Sonicated albumin microbubbles used in the field of cardiology have shown to improve pulsed Doppler signals and color flow imaging.

CONCLUSION

US till date remains the study of choice in the initial evaluation of suspect adnexal masses because it is relatively inexpensive, noninvasive and widely available.[39]

Accurate preoperative assessment of adnexal masses is important as it affects the counseling, preoperative preparation and intraoperative and postoperative management of the cases. It would also avoid inappropriate laparoscopic excision of malignant ovarian tumors and avoid unnecessary laparotomies done on the perimenopausal women with benign adnexal masses.

In our study, color flow mapping alone had a high sensitivity of 100% in identifying malignancy in solid adnexal masses. But it failed to identify 66.6 and 100% of malignances in mixed cystic and cystic adnexal masses respectively.

The study further showed that the addition of pulse Doppler waveform studies using RI < 0.4 as cutoff increased the sensitivity, specificity and positive predictive value in detecting malignancies in all types of adnexal masses and specially in simple cysts and mixed cystic adnexal masses where color flow mapping alone showed poor results.

To conclude, ultrasonic color flow mapping and pulse Doppler waveform studies used preoperatively on adnexal masses in perimenopausal women are widely available, performed rapidly and relatively easily, cost-effective and a reliable noninvasive method to predict malignancy preoperatively.

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