Original Research Article

Benign versus malignant adnexal masses: Does addition of Color and Spectral Doppler over and above the Gray Scale Ultrasound improves diagnostic efficacy

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Abstract: The present prospective study aimed at evaluating the relative value of Gray scale Ultrasound (US) alone and in combination with Color and Spectral Doppler in differentiating benign and malignant adnexal masses. Out of 122 adnexal masses in 106 patients (16 patients had bilateral adnexal masses), at histopathology 83 (68%) were benign and 39 (32%) were malignant. Gray scale US correctly diagnosed 74 adnexal masses (89.16%) as benign and 34 (87.18%) as malignant while Gray scale US combined with Color and Spectral Doppler correctly identified 79 adnexal masses (95.18%) as benign and 37 masses (94.88%) as malignant. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in differentiating benign and malignant adnexal masses with Gray scale ultrasound alone was 89%, 87%, 94% and 79% respectively whereas when Gray scale ultrasound was combined with color and spectral doppler both sensitivity and specificity increased to 95%, PPV increased to 98% and NPV increased to 90%. Thus, Gray scale US combined with Color and Spectral Doppler is superior to Gray scale US alone in differentiating benign and malignant adnexal masses. So, we propose addition of Color and Spectral Doppler to Gray scale US in preoperative characterization of all adnexal masses in terms of benign and malignant, so as to establish more accurate and early definitive diagnosis, thereby guiding most appropriate intervention.

Keywords: Adnexal masses, Malignant, Color Doppler, Spectral Doppler, Gray Scale Ultrasound, Histopathology

INTRODUCTION

The finding of an adnexal mass in a women usually raises anxiety because of the possibility of malignancy. Surgery is often required solely to exclude the possibility of malignancy and about 1/3rd of tumors operated upon for suspected ovarian cancer turn out to be benign [1]. Strangely the ovarian tumors, which appear most frequently, are usually physiological in origin, produce acute symptoms and receive the most radical of all treatment. In contrast, malignant tumors of ovary are the most lethal of all gynecological tumors and usually remain silent until treatable [2]**.** Thus, adequate characterization of an adnexal mass is important both to determine which patient need surgery and to help define the type of surgery and whether a surgical subspecialist is needed [3].

Out of all the imaging modalities available today, Ultrasonography (USG) is the primary imaging modality used to identify and characterize adnexal masses, as it is readily available, non invasive and has a high negative predictive value [1,3]. Previous studies had shown that it is possible to estimate the risk of malignancy on the basis of ultrasound morphology and to discriminate between benign and malignant adnexal tumors [3-6]. The addition of Color Doppler further allows assessment of tumor vascularity and flow pattern [7]. A recent meta analysis has demonstrated the increase in diagnostic accuracy in pre-operative differentiation of benign and malignant adnexal masses when using the B-Mode USG in combination with Color and Spectral Doppler as compared to the B-Mode USG alone[2]. The present study tests the ability of Color and Spectral Doppler in differentiating benign from the malignant adnexal masses by identifying tumor vascularity.

MATERIAL AND METHODS

This prospective and diagnostic study was carried out in the Department of Radio-diagnosis, M.G.I.M.S., Sewagram from 2009 to 2012 in female patients of all age groups presenting with adnexal masses. Premenopausal women with simple cyst of less than 3 cm in diameter and women with ectopic

pregnancy were excluded from this study. Thus, total 106 patients with 122 adnexal masses were included in the study (16 patients had bilateral adnexal masses). The USG findings were correlated with histopathological diagnosis which was considered as gold standard.

The study was approved by the Ethical and Research Committee of the Institute. All patients of adnexal masses were evaluated after written informed consent. Patients were examined using LOGIQ 500 MD MR3 WIPRO GE sonography machine. The endovaginal probe of frequency 5.5-7 MHz and curvilinear probe of frequency 2-5 MHz were used.

Study Technique

To avoid luteal flow, premenopausal women were examined from day 1 to 12 of menstrual cycle [8]. Transabdominal USG was done in all cases, followed by transvaginal sonography (TVS) wherever necessary. TVS was not performed in patients who were not willing to undergo TVS and virgin patients with adnexal mass. All adnexal masses were first evaluated with Gray Scale sonography and subsequently Color and Spectral Doppler examination was done.

The internal architectural details of each adnexal mass were imaged by scanning in various planes and following morphological features were recorded on Gray Scale: Site; laterality (unilateral/bilateral); size; consistency [cystic, mixed predominantly (more than two-thirds) cystic, mixed predominantly (more than two-thirds) solid and solid]; echogenicity (anechoic, low echogenicity, low echogenicity with echogenic core, mixed echogenicity, high echogenicity of internal contents); ancillary findings (fluid in cul-de-sac and ascitis) [9,10].

In cystic or mixed predominantly cystic adnexal masses, the following internal morphologic characteristics were evaluated systematically: Wall thickness (thin ≤ 3 mm and thick > 3mm) ; Inner wall border (smooth or irregular) ; Locularity (unilocular or multilocular); Internal echoes; septations (thin ≤ 3 mm or thick >3 mm, regular or irregular); Papillary projections (defined as any solid projection into the cyst cavity from the cyst wall with a height ≥ 3 mm; solid area or nodule (defined as an echogenic structure not protruding in a cystic portion or protruding in a cystic portion but usually of a larger size with a more or less round shape, homogeneous, or with degenerative changes (particularly necrosis)[10,11,12].

In solid or mixed predominantly solid adnexal masses, external contour (regular or irregular), areas of necrosis and areas of calcifications were evaluated.

Based on the morphologic characteristics on Gray scale US, the masses were classified as benign or malignant. A malignant tumor was diagnosed on Gray scale in the presence of any of the following morphologic features [8] :

- Thick irregular wall
- Thick irregular septations
- Presence of papillary projections
- Presence of irregular solid areas or nodules

A benign mass was diagnosed when the mass did not present any of the findings of malignant tumors or when it had typical pattern of a benign ovarian mass [10, 8] which are depicted in Figures 7 to 17.

After complete morphological assessment of the masses on Gray scale, Color Doppler examination was done. The presence or absence of color flow in the different portions of the masses was analyzed as follows:

- In cystic or mixed predominantly cystic adnexal masses, the presence or absence of color flow in the wall (mural), septa, papillary projection, solid area or nodule was assessed [8]. The masses in which both mural and septal flow was seen, the flow was recorded as septal [13].
- In solid or mixed predominantly solid adnexal masses, the color flow was recorded as central or peripheral depending upon the localization of blood vessel whether it was closer to the center or the edge of solid lesion respectively [14]. The masses where the color flow was seen in both central and peripheral locations, flow was recorded as central [13].
- The presence of color flow in thick irregular wall or septa, papillary projections, irregular solid areas or nodules, characterized as malignant at Gray scale sonography indicated the hypervascularised nature of this portion and hence the mass was diagnosed as Malignant [8].
- If a mass was characterized as malignant on Gray scale and later on Color Doppler sonography there was absence of color flow in the lesion or in above mentioned portions, it indicated the hypovascularised nature. So, the mass was diagnosed as Benign on basis of Color Doppler USG [8].
- After Color Doppler examination, the masses were evaluated on Spectral Doppler. A range gate was placed across an appropriate vessel and the flow velocity waveform was displayed. In the absence of arterial flow, the mass was considered as benign while in the presence of arterial flow, the mass was considered malignant for a RI ≤ 0.4, PI ≤ 1.0 or PSV ≥ 15 cm/sec [8].

Statistical analysis

The findings were tabulated and Statistical analysis was done using EPI info software (version 3.4.3). Chi square test was applied wherever applicable and p value was calculated. The p value < 0.05 was considered as statistically significant. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for Gray scale sonography alone and in combination with Color and Spectral Doppler by 2x2 contingency table.

Fig-1: Serous cystadenocarcinoma of ovary: Cystic mass with papillary projections showing vascularity and low resistance arterial flow

Fig-2: Serous cystadenocarcinoma of ovary: Mixed predominantly solid mass with areas of necrosis showing vascularity and low impedance high velocity flow on Doppler
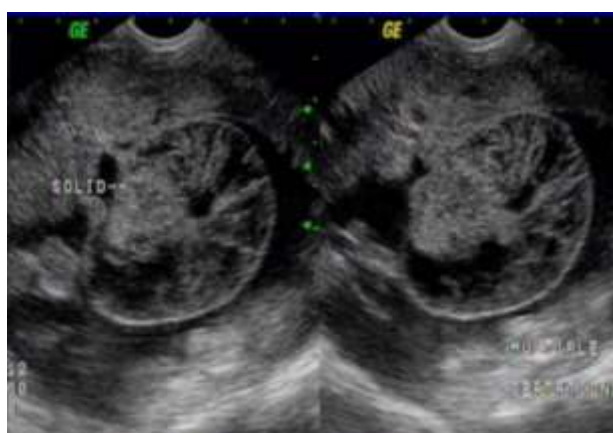

Fig-3: Mucinous cystadenocarcinoma of ovary: Mixed predominantly cystic mass showing thick irregular septations and irregular echogenic solid area with ascites

Fig-4: Mucinous cystadenocarcinoma of ovary: Mixed predominantly solid mass with irregular external contour showing central vascularity and low RI ,PI and high PSV

Fig-5: Dysgerminoma: Irregular solid mass with predominant central vascularity on Color Doppler

Fig-6: Endometroid carcinoma: Cystic mass with irregular solid nodule showing vascularity on Color Doppler
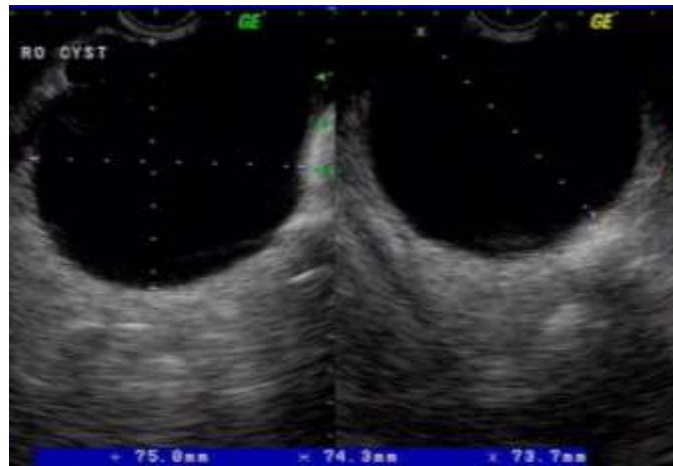
Fig-7: Simple ovarian (serous) cyst: Unilocular anechoic cystic mass with thin smooth wall

Fig- 8: Mucinous cyst: Unilocular cystic mass showing diffuse low level internal echoes

Fig-9: Mucinous cyst adenoma of ovary: Multiloculated cystic mass with thin regular septations and dense internal echoes (simulating solid areas) with no significant flow on Color Doppler

Fig-10: Mucinous cyst adenoma of ovary: Multiloculated cystic mass with smooth inner wall and thin regular septations containing low level internal echoes

Fig-11: Hemorrhagic cyst: Cystic mass with retracted clot giving a reticular appearance of internal echoes and interdigitating septations with no vascularity on Color Doppler
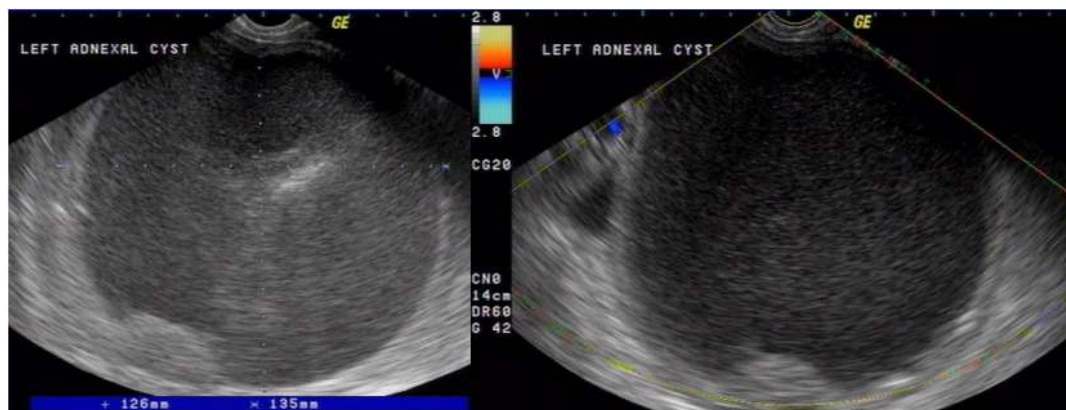

Fig-12: Endometrioma: Unilocular cystic with homogenous low level internal echoes and an echogenic solid area showing no vascularity on Color Doppler
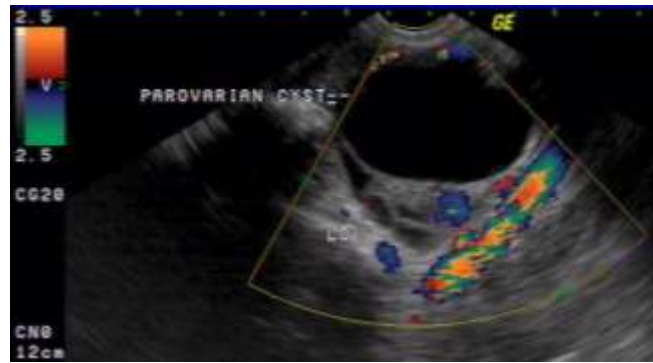
Fig-13: Par ovarian cyst: Cystic mass in left adnexa close to but separate from left ovary

Fig-14: Dermoid cyst of ovary: Cystic mass with echogenic area (Fat) and multiple linear floating hyperechogenic interfaces (Dermoid mesh) with absent vascularity on Color Doppler

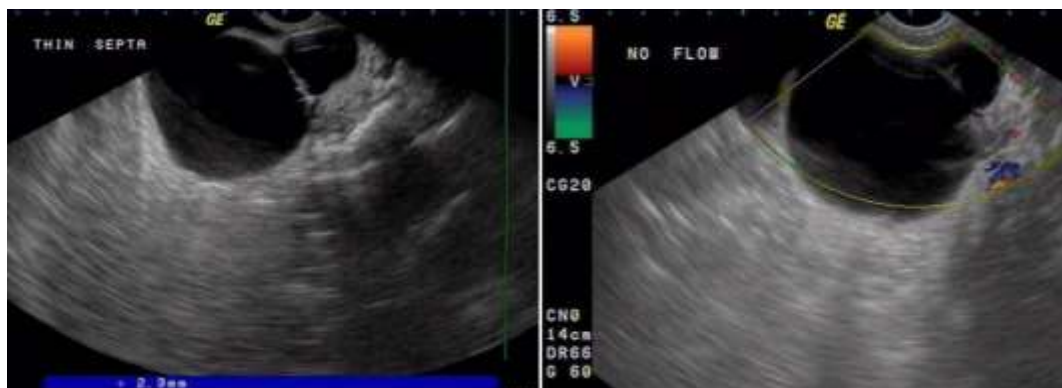**Fig-15: Dermoid cyst of ovary: Highly echogenic right ovarian mass showing no vascularity on Color Doppler**

Fig-16: Serous cyst adenoma of ovary: Anechoic cystic mass with smooth inner wall and thin regular septa showing no vascularity on Color Doppler
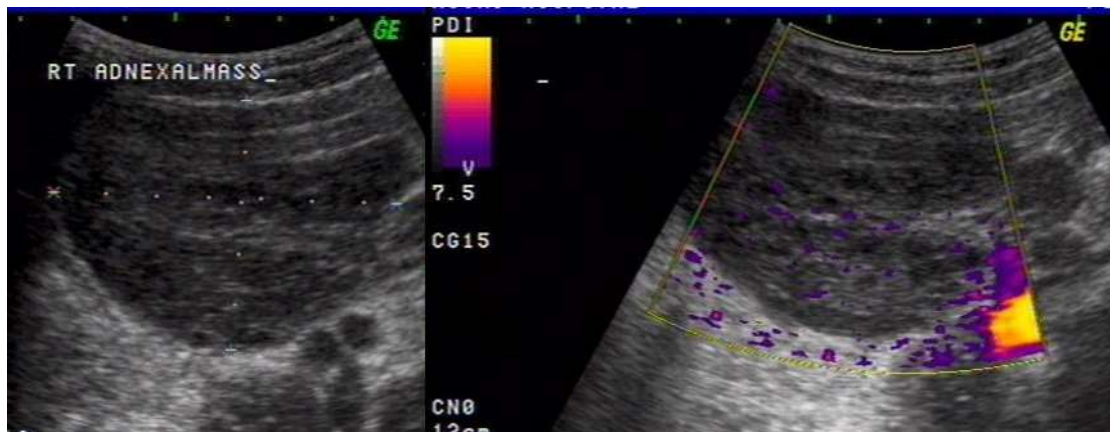
Fig-17: Ovarian thecoma: Low echogenicity solid mass with absent flow on Power Doppler

RESULTS

Total 106 patients were included in the study, out of these 16 had bilateral adnexal masses, so a total of 122 adnexal masses were evaluated and analyzed in the study. On histopathology out of 122 adnexal masses, 83 (68%) were found to be benign and 39 (32%) were found to be malignant. The distribution of Benign and Malignant adnexal Masses according to their various morphologic characteristics on Gray scale and Color and spectral Doppler US are depicted in Table 1 and 2 respectively. Correct Prediction of the Nature of Adnexal Mass in terms of Benign and Malignant on Gray scale US alone and Gray scale US combined with Color and Spectral Doppler (Correlated with Histopathology) is shown in Table 3 and 4 respectively. Efficacy of Gray Scale Ultrasound alone and in Combination with Color and Spectral Doppler in differentiating Benign and Malignant adnexal Masses is depicted in Figure 18.

Table 1: Morphological features assessed in differentiation of Benign and Malignant Adnexal masses (histopathologically proven) on Gray scale US

Features	Benign (%)	Malignant (%)	p value (if applicable)
Age > 50 years	12.04	43.59	< 0.01
Postmenopausal status	22.90	53.85	< 0.01
Size > 10 cm	39.75	46.15	0.59
Bilaterality	12.05	56.41	<0.001
Solid consistency	14.46	33.33	<0.001
Anechoic lesion	24.10	2.56	<0.001
Thick wall	17.39	50	-
Irregular inner wall	8.70	80	<0.001
Multilocularity	47.83	85	< 0.01
Thick irregular Septations	2.90	45	<0.001
Presence of Papillary projections	4.35	75	<0.001
Presence of irregular solid areas or nodules	10.14	65	<0.001
Irregular external contour	0	89.47	-
Ascites	7.22	66.67	<0.001

Table 2: Color and Spectral doppler features assessed in differentiation of Benign and Malignant Adnexal masses (histopathologically proven)

Features	Benign (%)	Malignant (%)	p value (if applicable)
Presence of vascularity in mass	40.96	100	-
Septal vascularity	9.62	20.50	0.80
Central vascularity	4.82	46.14	< 0.01
Papillary projections with vascularity	0	35	-
Solid area or nodules with vascularity	4.35	85	-
RI ≤ 0.4	12.04	94.87	<0.001
PI ≤ 1.0	16.86	92.30	<0.001
PSV ≥ 15 cm/s	19.28	87.18	<0.001

Table 3: Correct Prediction of the Nature of Adnexal Mass in terms of Benign and Malignant on Gray scale Ultrasound alone (Correlated with Histopathology)

Diagnosis on Gray scale USG alone	Histopathological Diagnosis				Total
	Benign		Malignant		
	No. of masses	Percentage	No. of masses	Percentage	
Benign	74	89.16%	05	12.82%	**79**
Malignant	09	10.84%	34	87.18%	**43**
Total	**83**	**100%**	**39**	**100%**	**122**

Table 4: Correct Prediction of the Nature of Adnexal Mass in terms of Benign and Malignant on Gray scale Ultrasound Combined with Color and Spectral Doppler (Correlated with Histopathology)

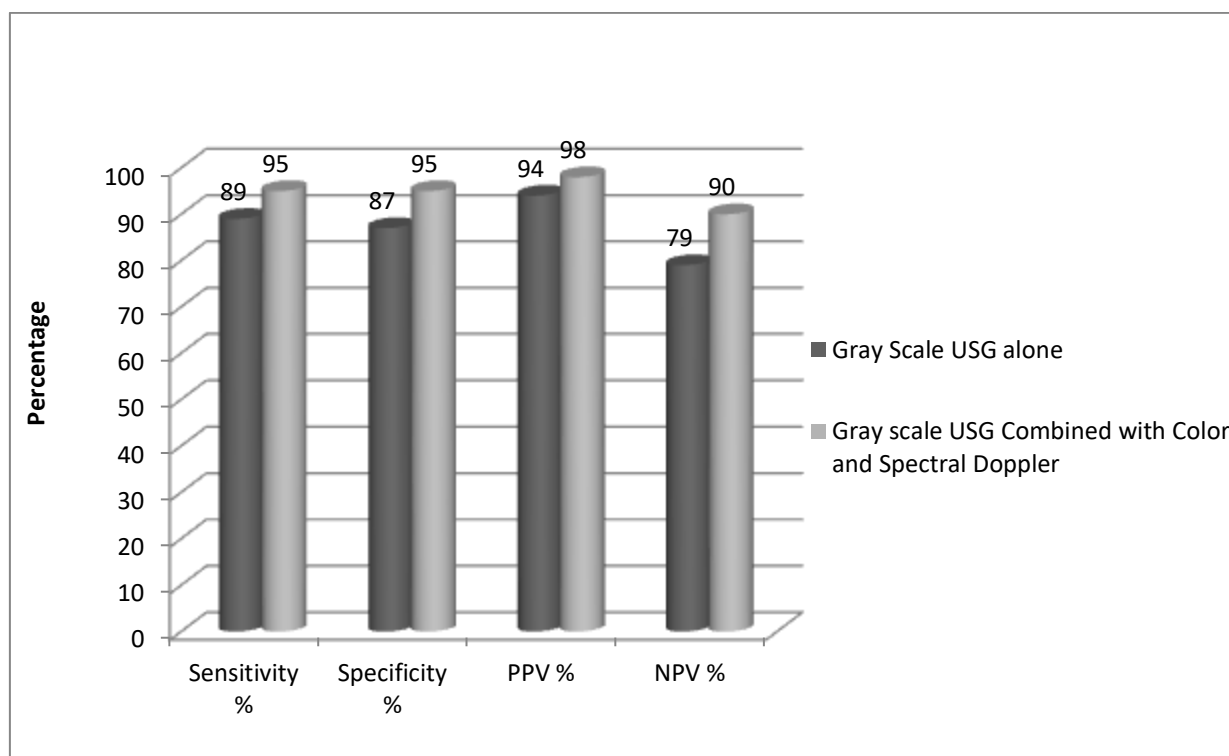| Diagnosis on Gray scale USG Combined with Color and Spectral Doppler	Histopathological Diagnosis				Total
	Benign		Malignant		
	No. of cases	Percentage	No. of cases	Percentage	
Benign	79	95.18 %	02	5.12%	**81**
Malignant	04	4.82%	37	94.88%	**41**
Total	**83**	**100%**	**39**	**100%**	**122**

Fig-18: Efficacy of Gray Scale Ultrasound alone and in Combination with Color and Spectral Doppler in differentiating Benign and Malignant Adnexal Masses

DISCUSSION

The preoperative assessment of adnexal tumors remains a major challenge for the clinicians. Advances in surgery have provided more treatment options, but their potential usefulness depends on the prior assessment of the mass using noninvasive procedures [4]. USG has become the first-step imaging technique for characterizing adnexal masses and is shown to be useful for selecting the best surgical approach [15].

The introduction of Color Doppler scanning allowed the assessment of tumor vascularity [7]. However, the usefulness of Color Doppler ultrasound in the diagnosis of adnexal malignancy has been a subject of enormous debate with varying opinions on the efficacy of Color and Spectral Doppler [2]. The major reason for controversy being, the large overlap of normal and abnormal blood flow measures between benign and malignant adnexal tumors studied with Color Doppler ultrasound [16].

With this background, in the present study 106 patients with 122 adnexal masses were evaluated prospectively on Gray scale, Color Doppler and Spectral Doppler and the diagnostic accuracy of Gray scale ultrasound alone and in combination with Color and Spectral Doppler in differentiation of benign and malignant adnexal masses was compared. The final histopathological diagnosis was considered Gold standard for comparison of results.

Out of total 122 masses included in study, on histopathology 83 (68%) were found to be benign and 39 (32 %) were found to be malignant. Except the size and wall thickness, all other Gray scale features assessed in the study were significantly helpful in discriminating benign from malignant adnexal masses. In our study, maximum cases of benign adnexal masses were found in 5-10 cm size group (53.02%) while maximum (46.15%) malignant adnexal masses occurred in >10 cm size group. However, the difference in size between benign and malignant group was not statistically significant (p=0.59, not significant).Sassone AM *et al.*[9] , Brown DL *et al*[13] and Yoruk P *et al.* [17] also reported no significant association of size of mass with malignancy in their respective studies.

Although majority (82.61%) of the cystic and mixed predominantly cystic adnexal masses in benign group had thin wall, in malignant group half of the adnexal masses had thin wall and half had thick wall. Thus, wall thickness could not be related with malignancy. These findings are consistent with the study of Singh U et al who also reported no significant relationship between wall thickness and malignancy in adnexal masses [1].

The detection of malignancy in adnexal mass by means of Color Doppler evaluation of velocity and vessel compliance was based on the theory of Folkman *et al.;* [18]. According to which metabolically active, dividing cancer cells produce an angiogenesis factor that stimulates new blood vessel formation. These new tumor vessels are morphologically abnormal because they lack intimal smooth muscles, which are necessary for increasing peripheral vascular resistance[18].

Color flow Doppler imaging allows the detection of small, newly formed tumor blood vessels. Benign lesions tend to initiate this tumor blood vessel formation peripherally from the existing host vessels whereas malignant tumors tend to initiate new tumor blood vessel growth centrally. Malignant tumor vessels are morphologically abnormal in that they lack intimal smooth muscles in their walls, show an irregular course and have increased arteriovenous shunting.

On color Doppler, flow was demonstrated more commonly in malignant adnexal masses while majority of benign adnexal masses had absent flow. The distribution of the mural and septal vascularity in benign and malignant cystic and mixed predominantly cystic masses was not found to be statistically significant (p=0.80, not significant). Taori K *et al.;* [2] in their study encountered almost equal distribution of tumor vascularity in cystic ovarian neoplasms in wall and septae. In solid and mixed predominantly solid adnexal masses, 46.14% of adnexal masses in malignant group had central flow versus only 4.82% in benign group. Thus central vascularity in a solid adnexal mass was found to be significantly associated with malignancy (p<0.01, significant). Similar findings are reported in previous studies [1, 2,7,13, 19].

None of the papillary projections in the benign cystic and mixed predominantly cystic adnexal masses had vascularity whereas 35% of papillary projections in the malignant category showed vascularity. Hassen K *et al.;* [11] also reported absent color flow in all papillary projections in benign ovarian masses while all papillary projections in the malignant ovarian masses demonstrated flow. All solid areas or nodules in the malignant cystic and mixed predominantly cystic adnexal masses had positive color flow in contrast to only 4.35% of solid areas or nodules in benign adnexal masses with positive vascularity. Stein SM *et al.;* [20] in their series found internal flow in 77% of solid components in malignant adnexal masses compared to 31% in benign adnexal masses. Buy JN *et al.;* [8] also reported vascularity in all solid portions in the malignant adnexal masses in their study.

In our study the malignant adnexal masses more commonly revealed RI $\leq$ 0.4 (94.87%), PI $\leq$ 1.0 (92.30%) and PSV $\geq$ 15 cm/sec (87.18%) when compared with benign adnexal masses (12.04%, 16.86%, and 19.28% respectively). With some minor variation in cut off values chosen, the most of previous studies also encountered significantly lower RI, lower PI and higher PSV values in the malignant adnexal masses in comparison to benign adnexal masses [1, 2, 13, 18, 19, 21, 22, 23, 24, 25, 26, 27].

On Gray scale US alone, 74 (89.16%) out of 83 histopathologically confirmed benign adnexal masses were correctly diagnosed. 9 benign adnexal masses were wrongly labeled as malignant by Gray scale US. One serous cyst adenoma was wrongly diagnosed as malignant as it showed papillary projections. One serous cystadeno fibroma was wrongly labeled as malignant because of presence of irregular echogenic solid nodule. Out of 2 cases of mucinous cyst adenoma misdiagnosed as malignant, 1 had dense internal echoes which resembled irregular solid area while other 1 had thick irregular septations and papillary projections. One mucinous cyst adenoma with Brenner's tumor had papillary projections with irregular solid nodule and 2 Brenner's tumors had irregular solid

nodule so they were considered as malignant on Gray scale US. One twisted hemorrhagic ovarian cyst and one endometrioma had complex appearance with dense internal echoes and irregular echogenic solid area (representing blood clot) which favored malignancy and were mislabeled as malignant masses. Buy JN et al [8], Alcazar JL *et al.;* [7], Jain KA [10] also misdiagnosed similar lesions in their series as malignant on Gray Scale US.

On addition of the Color and Spectral Doppler US out of total 83 histopathologically confirmed benign adnexal masses, 79 (95.18%) were correctly diagnosed. Color and Spectral Doppler correctly diagnosed all benign adnexal masses which were diagnosed on Gray scale Ultrasound. In addition it also correctly diagnosed 5 benign adnexal masses which were misdiagnosed as malignant on Gray scale ultrasound. On Color Doppler, 1 serous cyst adenoma had no flow in papillary projections and 1 serous cystadeno fibroma had no flow in echogenic nodule so they were correctly diagnosed as benign. No vascularity was seen on Color Doppler in 1 case of mucinous cyst adenoma thereby suggesting the presence of mucinous component. One case of twisted hemorrhagic ovarian cyst and one case of endometrioma revealed no vascularity and were therefore correctly identified as benign. Buy JN *et al.;* [8], Kinkel K *et al.;* [28] in their series were also able to correctly diagnose similar lesions as benign only after the addition of Color Doppler.

However, on Color and Spectral Doppler, 1 case of mucinous cyst adenoma revealed low resistance high velocity flow (RI-0.3,PI-1.0,PSV-18 cm/s) in thick irregular septations, one case of mucinous cyst adenoma with Brenner's tumor had low impedance high velocity (RI-0.4,PI-1.0,PSV-16cm/s) flow in irregular solid component and both cases of Brenner's tumor also showed low resistance high velocity flow (RI-0.3,PI-0.9,PSV-20 cm/s and RI-0.4,PI-1.0,PSV-18cm/s) in irregular solid nodules. Thus, they were misdiagnosed as malignant even on addition of Doppler over the Gray scale findings. . Madan R et al[19] in their study also encountered difficulty in differentiating benign from malignant mucinous tumors of ovary because of considerable overlap of Doppler indices.

Thus while Gray scale US correctly diagnosed 74 (89.16%) out of total 83 benign adnexal masses, the addition of Color and Spectral Doppler increased the number of correct diagnosis to 79 (95.18%).

When Gray scale Ultrasound alone was used out of 39 malignant adnexal masses confirmed on histopathology, 34 (87.18%) were correctly diagnosed while 5 malignant adnexal masses were wrongly labeled as benign.

Out of these 5 malignant adnexal masses, 2 were serous cystadenocarcinoma which were purely cystic and one was mucinous cystadenocarcinoma which was cystic mass without any papillary projections or solid areas and hence considered benign. . Luxman D *et al.;* [29] in their series also reported 1 serous and 1 mucinous cystadenocarcinoma which were completely cystic. One dysgerminoma appeared as well defined solid mass with regular borders so was misdiagnosed as benign. One squamous cell carcinoma arising in dermoid appeared as cystic mass with regular solid mural nodule and was wrongly labeled as benign.

On addition of Color and Spectral Doppler, 37 (94.88%) out of total 39 histopathologically confirmed malignant adnexal masses were correctly diagnosed as malignant.

Except 2 cases of serous cystadenocarcinoma with high resistance low velocity mural flow (RI-0.6,PI-1.4,PSV-12cm/s and RI-0.5,PI-1.2,PSV-10cm/s), which were still misdiagnosed as benign, all other 3 malignant adnexal masses which were wrongly labeled as benign on Gray scale were correctly diagnosed by the addition Color and Spectral doppler. On doppler, mucinous cystadenocarcinoma revealed high velocity low resistance flow (RI-0.4,PI-0.7,PSV-15cm/s) in wall and squamous cell carcinoma arising in dermoid cyst showed low resistance high velocity flow (RI-0.4,PI-0.6,PSV-16cm/s) in regular solid mural nodule. All these features favored malignancy and thereby allowed correct diagnosis of malignancy in these masses.

One false negative case of dysgerminoma on Gray scale, revealed central vascularity with low impedance high velocity flow (RI-0.4, PI-0.9, PSV-20cm/s) on addition of Doppler and was thus correctly identified as malignant. Buy JN *et al.;* [8] in their series were able to correctly diagnose malignancy in 3 solid tumors only because of presence of numerous blood vessels in echogenic portion.

Thus, 34 (87.18%) out of total 39 malignant adnexal masses were correctly diagnosed by Gray scale ultrasound whereas addition of Color and Spectral Doppler increased the number to 37 (94.88%).

The sensitivity (95%), specificity (95%), PPV (98%) and NPV (90%) values were higher when Gray scale US combined with Color and Spectral Doppler was used for differentiating benign and malignant adnexal masses as compared to Gray scale ultrasound alone (89%,87%,94%,79% respectively). These results are comparable to previous standard studies [1, 2, 8, 21, 23, 25, 30, 31, 32].

CONCLUSIONS

The present study demonstrates increase in sensitivity, specificity, PPV and NPV in pre-operative characterization of adnexal masses in terms of benign and malignant when using Gray scale USG in combination with Color and Spectral Doppler as compared to Gray Scale USG alone. Except the size, wall thickness and site of vascularity in cystic adnexal masses, all other Gray scale and Doppler features assessed in the study are significantly helpful in differentiating benign from malignant adnexal masses. Thus, we strongly recommend that Gray scale ultrasound should be combined with Color and Spectral Doppler in a diagnostic system to achieve better characterization and differentiation of benign and malignant adnexal masses.

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