**Original Research Article**

# How successful is color flow mapping and pulsed Doppler studies in predicting histologically confirmed benign and malignant adnexal masses in perimenopausal women

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## ABSTRACT

**Background:** Adnexal masses in perimenopausal women presents a specific diagnostic challenge because benign masses outnumbers malignant masses. Majority of adnexal masses are benign but 25% are malignant. The objective of this study was to see the effectiveness of transvaginal colour Doppler in predicting malignancy in adnexal masses in perimenopausal women.
**Methods:** Clinically detected adnexal masses were subjected to transabdominal ultrasound scan (for basic characterization of mass into solid, cystic, mixed) then transvaginal scan and neovascularization, resistivity index (RI) was measured. Subsequently all patients underwent laparotomy. Histopathological reports obtained, and correlation done between USG and histopathology.
**Results:** Among cystic masses neovascularization was present in 4 cases, among them benign and malignant masses were equal in number. Among mixed masses neovascularization was present in 17 cases 9 were malignant 8 benign, among solid masses all cases where neovascularization was detected were malignant. Neovascularization was absent in 12 cystic masses and 11 mixed masses, and all were benign. Kappa value calculated for tumour status and neovascularization is 0.610 which is substantially agreement with neovascularization as predictor of malignancy. Sensitivity, specificity, positive predictive value and negative predictive value of neovascularization for cystic masses are 100, 85, 50, 100(%) respectively. Sensitivity, specificity, positive predictive value and negative predictive value of neovascularization for mixed masses are 100, 57.89, 52.94, 100(%) respectively. Sensitivity and positive predictive value of neovascularization for solid masses is 100(%). Sensitivity specificity positive predictive value and negative predictive value of RI for cystic masses: 100, 92.8, 66.6, 100 (%) respectively. Sensitivity specificity positive predictive value and negative predictive value of RI for mixed masses: 77.7, 89.4, 77.7, 89.4(%). Sensitivity positive predictive value of RI for solid masses 100%.ROC curve analysis shows cut off value for differentiating between benign and malignant masses is 0.4. Less than 0.4 has more chance of malignancy.
**Conclusions:** Transvaginal Doppler ultrasound must be done preoperatively for adnexal mass characterization.

**Keywords:** Adnexal mass, Neovascularization, Pulsitility index, Resistivity index

## INTRODUCTION

Adnexal masses in perimenopausal women presents a specific diagnostic challenge because benign masses outnumber malignant masses. Majority of adnexal masses are benign but 25% are malignant. Determination of suspicion of malignancy is important in gynaecological practice to discriminate between benign and malignant tumours.[1] Lack of reliable diagnostic tests is a major obstacle for better treatment of ovarian tumours, an

accurate preoperative diagnosis provides better preoperative and intraoperative management and decreases morbidity and mortality of the patients.

Transvaginal sonography is widely used for the diagnosis as it is readily available and increased negative predictive value.[2-4] Optimal ultrasound technique and diagnostic criteria of malignant ovarian neoplasm for suspected ovarian malignancy are still controversial. Papillary formation on inner cyst wall and hyperechoic solid component are most satisfactory predictors.[5,6] Ultrasound and morphologic parameters have a sensitivity and specificity of 80% and 93% that make this a standard for ovarian tumour diagnosis.[7]

Folkmans theory of neovascularization in which tumour cells elaborate tumour angiogenesis factor causing mitosis of endothelial cells and neocapillaries.

Benign tumours form blood vessels peripherally from host blood vessels. Malignant tumours form blood vessels centrally.[8-10] Waveform analysis is based on the fact that malignant tumours are morphologically abnormal because they lack smooth muscles in their walls and demonstrate irregular course and arteriovenous shunt formation. Malignant tumours have low impedance which causes increased diastolic flow and systolic and diastolic variation. Such differentiation between benign and malignant tumours is achieved by quantifying these differences.[11-14]

Doppler flow measurement and assessment of tumour vascularity by Doppler increases the confidence with which correct diagnosis can be made.[15-16] A comparison of various studies has shown that that RI 0.4 and PI <1 is highly suggestive of malignancy.[17-23] Conventional USG lacks specificity to differentiate between benign and malignant masses. So, this study is conducted to see the effectiveness of colour flow mapping and pulsed Doppler studies in determining the nature of tumour.

## METHODS

50 perimenopausal women attending OPD, Gynecology SSKM hospital with clinically and radiologically detected adnexal mass were included in the study after taking into consideration the inclusion and exclusion criteria.

### Inclusion criteria

- Women between 38 and 55 years with clinically and sonographically detected adnexal masses
- Informed volunteers giving written consent
- Patients who are willing for regular follow-up.

### Exclusion criteria

- Women with adnexal masses with hemodynamic instability
- Women with adnexal masses with chronic kidney and thyroid abnormalities denying surgery
- Women with poor general condition not fit for surgery
- Those with ectopic pregnancy and subserous fibroids confirmed as adnexal mass on sonography.

The present study was an observational study.

After detailed history and clinical examination, patients with suggestive history and clinically detected adnexal mass are informed about the study and consent taken. Then after proper counselling conventional USG done to detect and confirm adnexal mass.

Size of adnexal masses is detected by basic scan. For adnexal masses less than 10 cm TVS performed and those greater than 10 cm both TAS and TVS performed. Basic scan is used to differentiate the masses into solid, cystic and mixed.

To avoid luteal flow premenopausal women are examined in early follicular phase of menstrual cycle (D1-D10). Then RI and PI were calculated in centre and periphery of the mass for any vessel or in any place if mass is persistent for several months. The lowest RI PI values were used for analysis, that is vessel with lowest impedance.

Machine settings were adjusted to optimal Doppler parameters. Subsequently all women underwent laparotomy and histopathological examination of adnexal masses. Machine used was Philips HD 7 ultrasound machine.

Data would be summarized by routine descriptive statistics namely mean, standard deviation for numerical variables and categorical and other variables. Histopathological diagnosis would be considered as gold standard.

Ability of stated radiological investigations to predict malignancy would be quantified through calculation of sensitivity, specificity, and positive and negative predictive value. Attempt would also be made to calculate kappa coefficient.

Software used was MedCalc version 11.6 [Mariakerke, Belgium: MedCalc Software 2011.

## RESULTS

50 perimenopausal women attending OPD, Gynecology SSKM hospital with clinically and radiologically detected adnexal mass were analysed in the study.

Mean age of the study group is 48.48 years. Mean parity and BMI are 2.32 and 26.2 kg/m² respectively. Family history and tobacco and OCP use present in 8%, 12%, 18% of cases respectively (Table 1).

### Table 1: Patient's characteristics.

| Characteristics | |
|---|---|
| Mean age | 48.48 years |
| Mean parity | 2.32 |
| Mean BMI | 26.2 |
| **Relevant history** | |
| Family history | 8% |
| Tobacco  use | 12% |
| OCP use | 18% |

Table 2 shows that main symptom of the patients was abdominal pain and distension, next to it is abnormal bleeding and others (jaundice, respiratory distress in advanced cases) in 26 % of cases.

### Table 2: Patients symptoms.

| Abdominal pain and distension | 98% | 49* |
|---|---|---|
| Abnormal bleeding | 36% | 18* |
| Dyspepsia | 32% | 16* |
| Others (diarrhoea jaundice vomiting dyspnoea) | 26% | 13* |

*Number of patients

Basic characterization of masses was done into solid cystic and mixed.

Majority of cystic masses were benign, and all solid masses were malignant, and out of 28 mixed masses 9 were malignant and rest benign (Table 3).

### Table 3: Comparison of distribution of USG type between benign and malignant growths.

| Codes X | USG type | | | |
|---|---|---|---|---|
| **Codes Y** | Tumour status | | | |
| | Codes X | | | |
| **Codes Y** | **Cystic** | **Mixed** | **Solid** | |
| Benign | 14 | 19 | 0 | 33 (66.0%) |
| Malignant | 2 | 9 | 6 | 17 (34.0%) |
| | 16 (32.0%) | 28 (56.0%) | 6 (12.0%) | 50 |
| Chi-square | 14.986 | | | |
| DF | 2 | | | |
| Significance level | P <0.001 | | | |
| Contingency coefficient | 0.480 | | | |
| How much likely lesion to be malignant if it is solid compared to non-solid? | | | | |
| | **Solid** | **Non-solid** | | |
| Malignant | 6 | 11 | | |
| Benign | 0 | 33 | | |

So more the lesion has solid component more likely the lesion is malignant.

Table 4 shows that 4 cystic masses showed neovascularization on USG and of them 2 were malignant. 17 mixed masses show edneovascularization, of them 9 were malignant. All solid masses were malignant and showed neovascularization.

### Table 4: Details of correlation of neovascularization with histopathology in different categories of adnexal masses.

| Type of mass | Number of cases | Neovascularization positive | HPE: histopathology | |
|---|---|---|---|---|
| | | | **Benign** | **Malignant** |
| Cystic | 16 | 4 | 2 | 2 |
| Mixed | 28 | 17 | 8 | 9 |
| Solid | 6 | 6 | 0 | 6 |

### Table 5: Details of correlation of neovasculatization with histopathology in different categories of adnexal masses.

| Type of mass | Number of cases | Neovascularization absent | HPE: Histopathology | |
|---|---|---|---|---|
| | | | **Benign** | **Malignant** |
| Cystic | 16 | 12 | 12 | 0 |
| Mixed | 28 | 11 | 11 | 0 |
| Solid | 6 | 0 | 0 | 0 |

Table 5 shows that 12 cystic masses showed absent neovascularization on USG and of them 12 were benign. 11 mixed masses showed absent neovascularization of them 11 were benign.

Correlation of tumour status and neovascularization Kappa value for presence of neovascularization during USG with malignant nature of the adnexal mass is .610 which means there is substantial agreement between neovascularization and malignant adnexal mass which is shown in Table 6.

Sensitivity, specificity, PPV, NPV of colour flow mapping (neovascularization) are 100, 85.7, 50, 100 (%) respectively for cystic masses. For mixed masses sensitivity, specificity, PPV, NPV are 100, 57.8, 52.94, 100 (%) respectively. And for solid masses sensitivity and PPV are 100% each depicted in Table 7.

**Table 6: Correlation with neovascularization with tumour status.**

| Observer A | Tumour status | | |
|---|---|---|---|
| Observer B | Neovascularization | | |
| | **Observer A** | | |
| **Observer B** | 0 | 1 | |
| 0 | 23 | 0 | 23 (46.0%) |
| 1 | 10 | 17 | 27 (54.0%) |
| | 33 (66.0%) | 17 (34.0%) | 50 |
| Kappa | 0.610 | | |
| Standard error | 0.102 | | |
| 95% CI | 0.411 to 0.809 | | |

**Table 7: Diagnostic indices of neovascularization in detecting malignancy in adnexal masses.**

| Type of mass | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| Cystic | 100 | 85.7 | 50 | 100 |
| Mixed | 100 | 57.89 | 52.94 | 100 |
| Solid | 100 | nil | 100 | nil |

Analysis of RI (Doppler waveforms) shows that RI cut off value of 0.4 has a sensitivity 88.24%, specificity 90.91%, positive likelihood ratio of 9.71, negative likelihood ratio of 0.13 as shown in ROC curve.
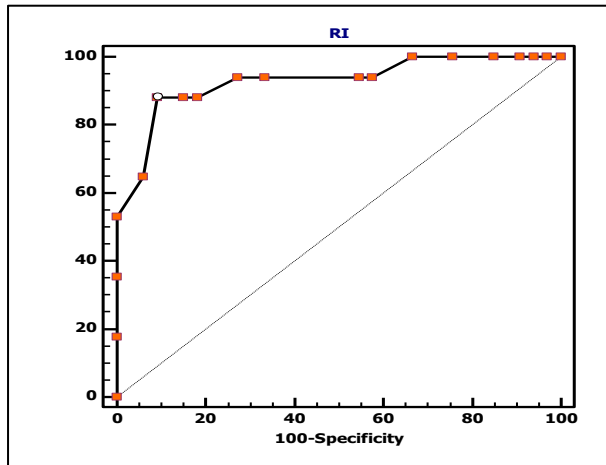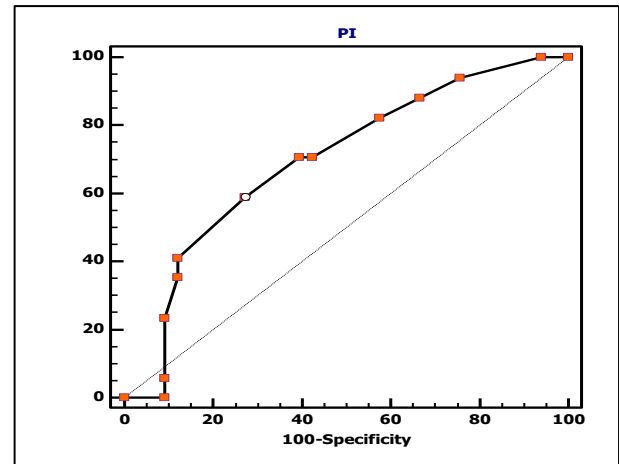


Area under the ROC curve (AUC): 0.929; Standard Error a: 0.0412; 95% Confidence Interval b: 0.819 to 0.982; z statistic: 10.418; Significance level P (Area=0.5): <0.0001

**Figure 1: ROC curve analysis for malignancy prediction for RI.**

Analysis of PI (Doppler waveforms) shows that PI cut off value of 0.8 has a sensitivity 58.82%, specificity 72.73 %, positive likelihood ratio of 2.16, negative likelihood ratio of 0.5 as shown in ROC curve. So, RI (Doppler waveforms) is further considered for differentiating between benign and malignant masses. RI positive in 3 cystic masses, of them 2 were malignant. RI positive in 9

mixed masses of them 7 were malignant. All solid masses were RI positive and malignant shown in Table 8.



Area under the ROC curve (AUC): 0.698; Standard Error a: 0.0782; 95% Confidence Interval b: 0.552 to 0.820; z statistic: 2.530; Significance level P (Area=0.5): 0.0114

**Figure 2: ROC curve analysis for malignancy prediction for PI.**

**Table 8: Details of correlation of Doppler waveforms (RI) with histopathology in different categories of adnexal masses.**

| Type of mass | Number | RI positive | HPE | |
|---|---|---|---|---|
| | | | Benign | Malignant |
| cystic | 16 | 3 | 1 | 2 |
| mixed | 28 | 9 | 2 | 7 |
| solid | 6 | 6 | 0 | 6 |

All RI negative masses were benign except mixed character masses in which 2 were malignant out of 17 RI negative masses shown in Table 9.

**Table 9: Details of correlation of Doppler waveforms(RI) with histopathology in different categories of adnexal masses.**

| Type of mass | Number | RI negative | HPE | |
|---|---|---|---|---|
| | | | Benign | Malignant |
| cystic | 16 | 13 | 13 | o |
| mixed | 28 | 19 | 17 | 2 |
| solid | 6 | 0 | 0 | 0 |

**Table 10: Diagnostic indices of doppler waveforms in detecting malignancy in adnexal masses.**

| Type of mass | sensitivity | specificity | PPV | NPV |
|---|---|---|---|---|
| Cystic | 100 | 92.8 | 66.6 | 100 |
| Mixed | 77.7 | 89.4 | 77.7 | 89.4 |
| Solid | 100 | NIL | 100 | NIL |

So, for cystic masses sensitivity, specificity, PPV, NPV of RI in detecting malignancy 100, 92.8, 66.6, 100(%)

respectively. For mixed character masses sensitivity, specificity, PPV, NPV of RI in detecting malignancy 77.7, 89.4, 77.7, 89.4 (%) respectively. Sensitivity and PPV of RI in detecting malignancy for solid masses 100% each.

## DISCUSSION

50 perimenopausal women with adnexal masses were assessed for the study. Mean age of patients was 48.84 years. Mean parity was 2.32. Mean BMI was 26.2kg/m² as shown in Table 1.

Family history of ovarian cancer was present in 8% of patients. Most common cancer detected in this group was serous and borderline cystadenocarcinoma. Tobacco use was present in 12% of patients and OCP use in 18% of patients. As per Table 2, abdominal pain with distension was most common symptom present in 98% of cases. Abnormal bleeding in 32% of cases. Among other symptoms jaundice, vomiting, diarrhoea, dyspnoea was present in 26% of cases.

Ultrasound whether transabdominal or transvaginal relies on morphological features for characterization of the type of mass. Morphology means wall thickness, loculi, septa, septal thickness.[13,24,31] Many scoring systems have been proposed overall sensitivity ranges from 85 to 97% and specificity from 56 to 95%. Various studies on morphology done by Ferazzi E, Kujrak A, Lerner JP, Tritsch T.[25-31]

Scoring system described by Sassone et al, is as follows:[24]

- Inner wall structure: smooth, irregular (<3mm), papillarities, lesion mostly solid
- Wall thickness in mm: <3mm, >3mm, and mostly solid lesions
- Septa: no septa, <3mm thickness, more than 3mm thickness
- Echogenicity: low, mixed, high echogenicity, low echogenic with echogenic core.

Each is assigned a point and score >9 is high risk for malignancy.

In the present study masses are characterized into cystic, mixed and solid. As shown in Table 3, among 16 cystic masses 14 are benign, among 19 mixed masses 9 malignant and rest benign. All 6 solid masses were malignant. Chi-square test shows value 14.98, contingency coefficient is 0.48, and p value is <0.001 which is highly significant. Also, that among malignant masses 6 were solid and 11 were non-solid. Neither of benign masses were solid. So as solidity of mass increases chances of malignancy increases. Odds ratio calculated is 37.87. So, type of the mass is also important for determining whether it is benign and malignant. In

order to improve sensitivity and specificity color flow mapping neovascularization was introduced.[26,27,32]

Neovascularization identifies these low resistance vessels in malignant tumors. There are continuous fluctuations in blood flow rather than pulsatile flow of blood in normal vessels. Various workers did study in this matter: Hata et al, Weiner et al, Kawai et al, and Zanetta et al etc.[26,33,34]

Hata et al conducted study with 16 number of adnexal masses. Of them 12 were neovascularization positive and 4 negative. Histopathology among positive masses 8 were malignant, 4 benign. All negative cases were benign. sensitivity, specificity, PPV, NPV 100, 50, 66.6, 100 (%) respectively.[26]

Another study conducted by Zanetta et al, results were sensitivity, specificity, NPV 85, 91, 89 (%) respectively.[35] Another study, by Sawicki et al specificity, PPV, NPV were 93.6, 66.8, 79.8. (%).[36]

In the present study following facts about neovascularization:

Neovascularization is an important parameter in diagnosing the character of adnexal masses. Among cystic masses neovascularization was present in 4 cases, among them benign and malignant masses were equal in number. Among mixed masses neovascularization was present in 17 cases 9 were malignant 8 benign, among solid masses all cases where neovascularization was detected were malignant. Neovascularization was absent in 12 cystic masses and 11 mixed masses, and all were benign as shown in Table 4 and 5.

Kappa value calculated for tumour status and neovascularization is 0.610 which is substantially agreement with neovascularization as predictor of malignancy as shown in Table 6.

Sensitivity, specificity, positive predictive value and negative predictive value of neovascularization for cystic masses are 100, 85, 50, 100 (%) respectively. Sensitivity, specificity, positive predictive value and negative predictive value of neovascularization for mixed masses are 100, 57.89, 52.94, 100 (%) respectively. Sensitivity positive predictive value of neovascularization for solid masses 100 (%) each as shown in Table 7.

To improve the detection rate Doppler waveforms with resistivity index pulsatility index was introduced for further characterization of masses. In the present study among cystic masses RI was positive in 3 cases of them 2 were malignant. Among mixed masses RI was positive in 9 masses of them 7 were malignant. All solid masses where RI were positive were malignant. Sensitivity specificity positive predictive value and negative predictive value of RI for cystic masses 100, 92.8, 66.6, 100 (%) respectively. Sensitivity specificity positive predictive value and negative predictive value of RI for

mixed masses 77.7, 89.4, 77.7, 89.4 (%). Sensitivity positive predictive value of RI for solid masses 100% each as shown in Table 8, 9 and 10.

Kujrak et al conducted a study in 14000 patients where 56 was found to be malignant. All but two showed abnormal Doppler, RI less than .4 with a Sensitivity specificity positive predictive value of 96.4, 99.8, 98.2 (%) respectively.[37]

In various studies sensitivity specificity varied from 50-100% and 46-100% respectively due to variation in thresholds in various studies. RI patterns in the present study shows that lowest value is .2 and highest value is 1.5. Arithmetic mean is 64.95% confidence interval for mean is 0.54-0.73. Median 0.62, standard deviation is 0.3249, standard error 0.04595.

ROC curve shows that if RI .4 is taken as the demarcating line between benign and malignant adnexal masses then sensitivity is 88%, specificity is 90% and positive likelihood ratio is 9.71. As the demarcating value increases sensitivity increases but specificity and positive likelihood ratio decreases drastically as shown in curve.

PI patterns in the present study shows that lowest value is 0.5 and highest value is 1.4. Arithmetic mean is .97-95% confidence interval for mean is 0.90-1.04, median 1, standard deviation is 0.2365, Standard error 0.0345. ROC curve shows that if PI 0.8 is taken as the demarcating line between benign and malignant adnexal masses then sensitivity is 58%, specificity is 72% and positive likelihood ratio is 2.16. As the demarcating value increases sensitivity increases but specificity and positive likelihood ratio decreases drastically as shown in curve.

Pulsatility index was not very much predictive of malignancy in the present study. p value is 0.0114. Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio are 58.82, 72.73, 2.16, and 0.57 respectively. In contrast RI has p value of <0.0001. Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio are 88.24, 90.91, 9.71, and 0.13 respectively which is much better when compared to PI. Studies by Salem S, also shows the limitations of PI.

However, the pulsatility indexes showed considerable overlap between benign and malignant lesions, indicating that Doppler sonography has severe limitations in the differentiation of benign from malignant adnexal disease on the basis of low-impedance flow (pulsatility index <1.0).

### Problems associated with Doppler analysis:[38]

- Lack of standardizes criteria for differentiation benign and malignant waveforms
- In premenopausal women there is change in character of blood vessels in ovary, they become low resistance vessels, so they can appear malignant

- In absence of septa, solid areas it is difficult to detect RI, PI values
- In extreme inflammation like pelvic inflammatory disease and endometriosis there is abundance of low resistance vessels

Recently power Doppler has been introduced for better characterization of mass but due to more cost and requirement of skill it is limited to few centers. Now sonicated albumin microbubbles are introduced for better Doppler signals.[39]

## CONCLUSION

Ultrasound remained the investigation of choice in preoperative assessment of the type of adnexal mass because it is widely available, non-invasive, and low cost.

Accurate preoperative diagnosis allows accurate operative planning and postoperative management, it prevents laparoscopic excision of masses in malignant tumours and inappropriate laparotomy done on benign masses in menopausal age group.

In the present study sensitivity for detecting malignancy was 100% for solid masses but for other type of masses prediction improved with application of Doppler parameters. So, USG must be used preoperatively for prediction of malignancy in adnexal masses in perimenopausal women.

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