



Histopathological Profile of Uterine Adnexal Masses and Correlation with Serum CA 125 of Benign & Malignant Adnexal Masses

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Abstract

The detection of uterine adnexal mass with associated raised serum CA 125 level is highly suspicious for ovarian cancer, but there are various other benign and malignant adnexal pathologies that mimic the above findings, especially in premenopausal women in our country as seen in our case study. The aims and objectives of this study were to study the histopathological spectrum of uterine adnexal mass and correlation of serum CA125 with benign & malignant masses, determine the incidence rate, age distribution and histopathological pattern of adnexal mass in operated specimens, to study the frequency of benign and malignant neoplasms of ovary in this region and also to study the cut off values of Serum CA-125 in Benign and Malignant ovarian lesions. The present study had revealed various facets of epithelial ovarian tumours keeping comparable results with different studies. Among all cases 64.71% of the cases were benign, 5.88% borderline and 29.41% malignant. Benign tumours clustered a decade earlier than malignant tumours. The epithelial tumours are the most common tumours. Unless better methods of prevention, early diagnosis and/or curative treatment are introduced, a gradual rise in the mortality rate from uterine adnexal cancer, especially ovarian cancer is expected in this country.

Introduction

Uterine adnexa refers to adjoining anatomical parts of the uterus. It includes the fallopian tubes and ovaries and associated vessels, ligaments and connective tissues.¹

Mass usually originates from ovary or fallopian tube. However, it may arise from various other mentioned structures. Any lump or mass found within adnexa of uterus is abnormal and needs to be evaluated.² They may be benign or malignant.³

Adnexal masses present a diagnostic dilemma; the differential diagnosis is extensive, and most masses are benign^{1,2,3}. However, without

histopathological diagnosis, a definitive diagnosis is generally precluded.

Uterine adnexal mass, especially ovarian cancer popularly known as 'the silent killer', is a dreaded disease because of its vague, non-specific symptoms and late presentation. Worldwide, it is the 7th most common cause of cancer and 8th most common cause of cancer related death among women¹.

Incidence of uterine adnexal cancer in India is lower than that of Western countries. The present study was undertaken to assess the situation of adnexal tumours, not only cancers but

also benign as well as borderline tumours, among patients admitted in this hospital and correlation serum CA 125 was analysed for early detection of cancer.

In the past, physicians relied on the findings of a pelvic examination to diagnose an adnexal mass. With the introduction of imaging modalities including transabdominal and vaginal ultrasonography⁴, Doppler colour scans, and MRI, more characterization of the internal structure of the mass (i.e wall complexity, mass contents) is possible.^{5, 6, 7, 8}

In girls younger than 9 years, 80% of ovarian masses are malignant and are generally germ cell tumours^{9, 10}.

During adolescence, 50% of adnexal neoplasms are mature cystic teratomas or dermoid cysts.

In sexually active adolescents, one must always consider a tubo-ovarian abscess as the cause of an adnexal mass.^{11, 12}

In women of reproductive age who have had adnexal masses removed surgically, most are benign cysts or masses, 10% of masses are malignant.¹³

Serum CA 125 is an antigenic determinant on a high-molecular-weight glycoprotein recognized by a monoclonal antibody (OC 125). The full-length CA 125 glycoprotein contains more than 11,000 amino acids in its proteinaceous core and has been termed Muc16 to reflect the mucin like nature of the antigen and is now identified as a new member of the protein family of mucins.²¹

CA 125 is expressed by more than 80% of non-mucinous epithelial ovarian carcinomas and is found in most carcinomas of Müllerian origin, including fallopian tube and primary serous peritoneal carcinoma.²²

In addition, it can be expressed by several benign and physiologic conditions also. Serum CA 125 is the only tumour marker recommended for clinical use in the diagnosis and management of ovarian cancer mainly. CA 125 is the only tumour marker recommended for clinical use in the diagnosis and management of cancer. Declining CA 125 levels have been shown to correlate with treatment

response, even when disease is not detectable with physical examination or imaging. In this setting, serial CA 125 testing has more clinical utility than a single determination.

Material and Methods

The case series include those cases (234 cases) that presented between April 2016-March 2017 at our institution as resected specimen of uterine adnexal mass and correlated with elevated serum level of CA125, however on complete workup by radiological investigations (USG/CT scan/MRI Scan), diagnostic laparoscopy/ therapeutic laparotomy with histopathology examination of operative specimen or biopsy material. The Serum CA 125 level more than 35 units/ml was considered as elevated.

Statistical Analysis

We found total 234 cases of uterine adnexal masses, including benign, borderline and malignant types. The detailed results were as follow

Parameters

Regarding age, 72.06% of all cases were from 30 – 59 years. Maximum number of cases were in 4th decade (25%), followed by equal number of cases in 5th and 6th decade (23.53%). The youngest and oldest members of the study population were 14 years and 80 years old respectively. Mean age of presentation was 36 years, median 46 years, standard deviation 18.05.

Table 1: Distribution of Adnexal Mass in Total Population According To Age (N=234)

Age (Years)	Patients	
	Number	Percentage (%)
0 – 9	0	0.00
10 – 19	4	1.70
20 – 29	45	19.23
30 – 39	60	25.64
40 – 49	55	23.50
50 – 59	55	23.50
60 – 69	17	7.26
Total	234	100.00

Table 2: Distribution of the Benign Lesions According To Age (n=154)

Age (yrs)	Serous	Mucinous	Brenner	Endometr ioma	Germ cell tumour	SCF	Total
0-9	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0 (0%)
10-19	0 (0%)	3 (8.58%)	0 (0%)	0 (0%)	9 (50%)	0	13 (8.9%)
20-29	12 (16.2%)	7 (20%)	2 (40%)	4 (28.5%)	4 (40%)	1 (50%)	38 (24.6%)
30-39	42 (41.46%)	9 (28.65%)	0 (0%)	6 (57.1%)	1 (10%)	1 (50%)	52 (33.7%)
40-49	18 (21.23%)	4 (14.76%)	0 (0%)	2 (14%)	0 (0%)	0 (0%)	23 (14.9%)
50-59	14 (16.23%)	7 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19 (12.3%)
60-69	3 (4.85%)	2 (8.88%)	1 (60%)	0 (0%)	0 (0%)	0 (0%)	9 (5.8%)
Total	91 (100%)	32 (100%)	3 (100%)	14 (100%)	14 (100%)	2 (100%)	154 (100%)

Table 3: Distribution of Malignant Tumours According to Age (n=66)

Age (yrs)	SCA	MCA	Endo metriod CA	Clear cell CA	Germ cell CA	Sex cord CA	Metastatic CA	Number %
0-9	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
10-19	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
20-29	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (33%)	0 (0%)	0 (0%)	1 (1.5%)
30-39	7 (14.2%)	3 (25%)	0 (0%)	2 (66%)	2 (33%)	1 (50%)	0 (0%)	15 (22.7%)
40-49	19 (42.8%)	5 (50%)	2 (0%)	1 (33%)	0 (0%)	1 (50%)	0 (0%)	28 (42.3%)
50-59	14 (35.7%)	1 (25%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)	19 (28.7%)
60-69	3 (7.14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (4.5%)
Total	44 (100%)	9 (100%)	1 (100%)	3 (100%)	3	2 (100%)	2 (100%)	66 (100%)

Table 4: Age malignancy cross tabulation

AGE * MALIGNANCY Crosstabulation

AGE		MALIGNANCY		
		NO	YES	Total
BELOW 40	Count	103	20	123
	Expected Count	80.9	42.1	123.0
40 AND ABOVE	Count	51	60	111
	Expected Count	73.1	37.9	111.0
Total	Count	154	80	234
	Expected Count	154.0	80.0	234.0

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	37.040 ^a	1	.000		
Continuity Correction ^b	35.380	1	.000		
Likelihood Ratio	38.223	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	36.882	1	.000		
N of Valid Cases	234				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 37.95.

b. Computed only for a 2x2 table

Data analysis shows that P value is < .05, so it is a significant study.

Investigation Findings

We studied the cases according to serum CA125 level. Among the benign tumours, there were 32 cases of benign tumours (19.09%) including 21 serous and 8 mucinous cystadenoma, which had high CA125 level. Among 3 cases of Brenner tumour, 1 had CA125 level of 79.83 U/ml. Rest 6 cases had CA125 level slightly raised than normal range of <35 U/ml. The highest level of CA125

noted, among the benign tumours in the study population, was 702.9 U/ml, found in a case of serous cystadenofibroma. We found that in all cases of malignant tumours CA125 levels were raised. Lowest level noted among carcinomas was 44.3 U/ml, detected in a mucinous carcinoma. Mucinous carcinomas though had raised CA125 levels, but these were lesser than that of serous carcinomas. The highest level was 4500 U/ml, found in a serous carcinoma. Among the fourteen borderline tumours, 3 had CA125 level <35 U/ml and one had 44.8 U/ml.

Table 5: Distribution of Patients with Benign Tumour According to Serum CA125 Level (n=154)

CA125 U/ml	Number of patients (%)						Total (%)
	SC	MC	Brenner	MCT	Endo	SCF	
<15	38(42.30%)	11(34.71%)	0 (0%)	10(71.4%)	6(50%)	1(50%)	66(43%)
15-30	28(30.77%)	10(31.65%)	2(75%)	0(0%)	5(41.6%)	0(0%)	45 (28%)
30-45	4(4.85%)	3(9.38%)	0 (0%)	2(14.2%)	3(25%)	1(50%)	13(8.5%)
45-60	7 (7.69%)	4 (12.58%)	0 (0%)	2(14.2%)	0(0%)	0(0%)	13(8.5%)
60-75	3 (3.85%)	0 (0%)	0 (0%)	0(0%)	0(0%)	0(0%)	3 (1.9%)
75-90	0 (0%)	0 (0%)	1(25%)	0(0%)	0(0%)	0(0%)	1(0.6%)
>90	11(12.5%)	4 (12.58%)	0 (0%)	0(0%)	0(0%)	0(0%)	15(9.7%)
Total	91 (100%)	32 (100%)	3 (100%)	14 (100%)	12 (100%)	2 (100%)	154 (100%)

Table 6: Distribution of Patients with Borderline and Malignant Tumours According To Serum CA125 Level (n=80)

CA125 level(U/ml)	Malignant		Number of patients						Number (%)
	Borderline	Malignant	Malignant						
			SCA	MCA	Endometrial	Ovarian CA	Germ cell CA	Str. cell CA	
<60	2 14.3%	4 33%	1 33.3%	1 25%	2 75%	2 75%	1 50%	16 (20%)	
60-120	3 21.4%	2 22%	1 33.3%	2 75%	1 25%	1 25%	1 50%	13 (16.27%)	
120-180	4 28.6%	5 11.4%	0 0%	0 0%	0 0%	0 0%	0 0%	10 (12.2%)	
180-240	2 14.3%	1 2.2%	0 0%	0 0%	0 0%	0 0%	0 0%	3 (3.75%)	
240-300	1 7.10%	2 4.5%	0 0%	0 0%	0 0%	0 0%	0 0%	3 (3.75%)	
300-360	2 14.2%	12 27.1%	0 0%	0 0%	0 0%	0 0%	0 0%	14 (17.5%)	
>360	0 0%	17 38.7%	2 22%	1 33.3%	0 0%	0 0%	0 0%	20 (25%)	
Total	14 100%	44 100%	9 100%	3 100%	3 100%	3 100%	2 100%	80 (100%)	

Table 7: malignancy and serum marker cross tabulation

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
MALIGNANCY * MARKER	234	100.0%	0	.0%	234	100.0%

MALIGNANCY * MARKER Crosstabulation

			MARKER		Total
			LESS THAN 35	35 AND ABOVE	
MALIGNANCY	POSITIVE	Count	14	47	61
		Expected Count	40.1	20.9	61.0
	NEGATIVE	Count	140	33	173
		Expected Count	113.9	59.1	173.0
Total		Count	154	80	234
		Expected Count	154.0	80.0	234.0

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	67.367 ^a	1	.000		
Continuity Correction ^b	64.815	1	.000		
Likelihood Ratio	66.256	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	67.079	1	.000		
N of Valid Cases	234				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 20.85.

b. Computed only for a 2x2 table

Histopathological Findings

We found that majority of the tumours were benign in nature (64.71%). Malignant tumours constituted 28.41% of total population. 5.88% of the cases were of borderline type. Among benign tumours, 59.09% were serous tumours and 20.12% were benign mucinous tumours. Only three cases of Brenner tumour were noted in the study population. Among the benign serous tumours, most common tumour type was serous cystadenoma, constituting 59.09% among the benign serous group, followed by serous cystadenofibroma belonging to 1.4% . .

The most common type of malignant tumour was serous cystadenocarcinoma, constituting 66.7% of all carcinomas, followed by mucinous cystadenocarcinoma (13.7%). Three cases (4.5%)

each of endometrioid carcinoma and of clear cell carcinoma were detected among the malignant tumours.

Overall, serous tumour was most prevalent, constituting 58.82% of the total population studied. Among the serous tumours, 65% were benign and 35% were malignant. Next most common type was mucinous tumour, constituting 36.76% of total population. It had 68% of benign, 16% each of borderline and malignant tumour types. Endometrioid carcinoma was detected in three case (1.47% of the total population). Three cases were of transitional type (1.94%), germ cell tumour /mal (4.5%) and two cases of sex-cord stromal tumour /mal (3.15%) of the total population.

Table 8: Distribution of Patients According to Nature of Tumours (N=234)

Nature of tumours	Patients	
	Number	Percentage (%)
Benign	154	64.71 (%)
Borderline	14	5.88 (%)
Malignant	66	29.41 (%)
Total	234	100 (%)

Table 9: Distribution of Benign Tumours According To Types (n=154)

Types of benign tumours	Patients	
	Number	Percentage (%)
Serous	91	59.09 (%)
Mucinous	32	20.12 (%)
Brenner	3	1.9 (%)
Mature cystic teratoma	14	9.7%
Endometrioma (Chocolate cyst)	12	7.7%
Cystadenofibroma	2	1.4%
Total	154	100 (%)

Table 10: Distribution of Malignant Tumours According to Tumours Types (n=66)

Types	Patients	
	Number	Percentage (%)
Serous cystadenocarcinoma	44	66.7 (%)
Mucinous cystadenocarcinoma	9	13.7 (%)
Endometrioid adenocarcinoma	3	4.5 (%)
Clear cell carcinoma	3	4.5 (%)
Germ cell tumour (Mal)	2	3.15(%)
Seroli-Leidig cell tumour	2	3.15(%)
Dysgerminoma	1	1.15(%)
Undifferentiated/Krukenburg tumour	2	3.15(%)
Total	66	100 (%)

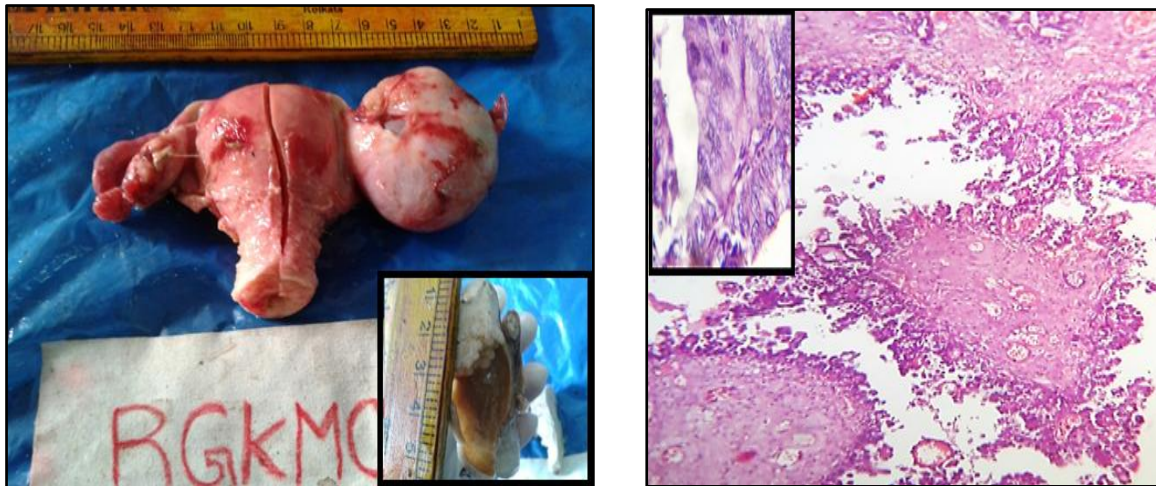


Fig 1: Gross and microscopic appearance of serous cystadenocarcinoma ovary

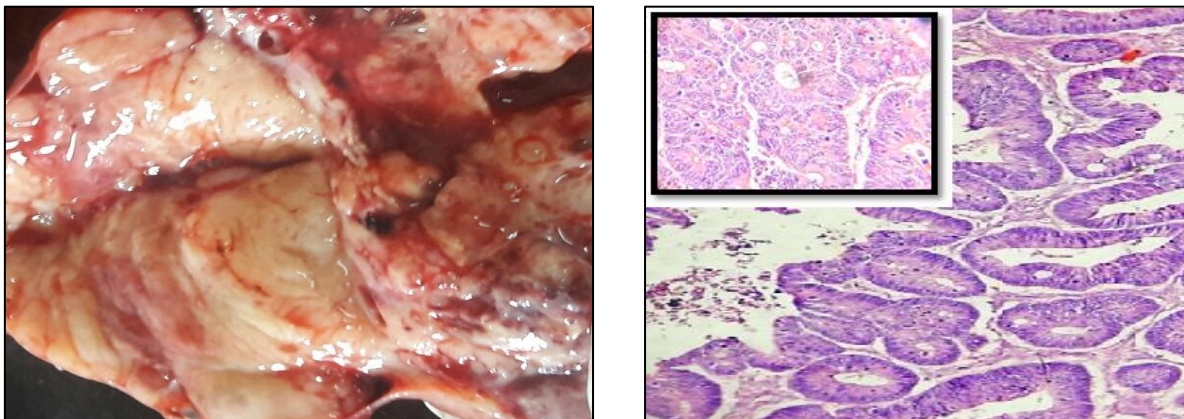


Fig 2: Endometrioid adenocarcinoma ovary gross & microscopic appearance

Result

In short, the present study had revealed various facets of epithelial ovarian tumours keeping comparable results with different studies. These findings need to be confirmed by a larger prospective cohort.

1. Benign tumours clustered a decade earlier than malignant tumours. Main bulk of malignant tumours (80%) was in 5th & 6th decade, in contrast to benign tumours where main bulk (56.82%) was in 3rd & 4th decade.

2. 64.71% of the cases were benign, 5.88% borderline and 29.41% malignant. Overall, serous tumours were the most prevalent one, constituting 58.82% of the total population studied, of which 65% were benign and 35% were malignant.

3. Among the malignant tumours 60% presented in advanced stage (III & IV), of which 95% were serous carcinomas.

4.92.86% of the serous carcinomas were of high grade, of which 71.43% were of advanced stage (III & IV).

5. Unilateral ovarian tumours were more common, constituting 82.35% of total population than bilateral tumours for benign, borderline as well as malignant tumours.

6. Among the tumours 25% were partly solid partly cystic, of which 76.47% cases were malignant. The tumours that were completely solid (7.35%), all were malignant.

7. We studied the cases according to serum CA125 level. Among the benign tumours, 71% of the cases had CA125 level <30 U/ml. However, there were 32 cases of benign tumours (19.09%) including 21 serous and 8 mucinous cystadenoma which had high CA125 level.

8. When we analysed the malignant tumours, we found that in all cases of malignant tumours CA125 levels were raised. Lowest level among

carcinomas was 44.3 U/ml, detected in a mucinous carcinoma. Mucinous carcinomas though had raised CA125 levels, but these were lesser than that of serous carcinomas. The highest level was 9900 U/ml, found in a serious carcinoma. Among the fourteen borderline tumours, 3 had CA125 level <35 U/ml and one had 44.8 U/ml.

CA 125 is the only marker recommended for clinical use in the diagnosis and management of ovarian cancer mainly. There are many indications in which the determination of CA 125 levels is recommended.

Discussion

The spectrum of uterine adnexal masses is very wide. In the present study total 234 patients admitted in the Department of G&O, R G Kar Medical College & Hospital, Kolkata, selected by the predetermined sampling technique were incorporated. This observational, descriptive, cross-sectional study has pointed out certain important characteristics of uterine adnexal masses. Present study results have been compared to different published studies over different parameters.

Our study results matched with the studies done by Lataifeh et al (2005)²⁴, Goff et al (2000)²⁵. All of them described pain abdomen as the most common presenting complaint. They described 12.3% of the cases presented with abnormal bleeding PV which was very close to our results.

Our study results corroborated with Mondal et al (2011)²⁵, where they described mean age 47 years for benign tumours and 55.4 years for malignant tumours and Rubin et al (1994)²⁶ where the mean age of the patients with early epithelial ovarian cancers (stage I and II) was 53 years. Small sample size, limited study duration might be the reason behind this disparity.

Our study results corroborated with Risch et al (1996)¹⁸ where they revealed that increase in parity was associated with significant protective trends in risk. It is well accepted fact that incidence of ovarian tumour increases with decrease in parity, that is explained by incessant

ovulation theory. Our study results had not differed from it showing more cases in lower parity and lesser number of cases in higher parity. Our study results corroborated with Morrow et al²⁶ where they described that among the benign serous tumours 20% were bilateral and among the malignant serous tumours 50% were bilateral.

The results corroborated with Kawamoto et al²⁹ where they described 60% of the epithelial ovarian tumours were benign, 35% malignant, 5% of low-malignant-potential (borderline) type. The present study echoed with McCluggage (2011)³⁰ where 68-71% of ovarian carcinomas were of serous type.

Our study corroborated with Phukan et al (2013)³¹ where about 59.1% cases were at advanced stage (III & IV).

Our study corroborated with study of WHO³² classification of tumours of female reproductive organs, where leiomyoma is the most common solid tumour of broad ligament and most common cystic tumour is serous cystadenoma.

Conclusion

With our currently expanding elderly population, diseases that become progressively more frequent with aging are expected to expand in number in near future. Unless better methods of prevention, early diagnosis &/or curative treatment are introduced, a gradual rise in the mortality rate from uterine adnexal cancer, especially ovarian cancer is expected in this country. The challenge for the next decade would be to use rational combinations offering maximal clinical benefit at minimal cost. The challenge is obvious, as early diagnosis of ovarian carcinoma is a tough job, due to non-specific symptoms.

Over the past several years, significant progress has been made in the treatment. Conventional modality of treatment is cytoreductive surgery, followed by carboplatin and paclitaxel. Neoadjuvant chemotherapy, followed by interval debulking and post-surgery chemotherapy, is preferred for advanced stage carcinomas. However, development of novel therapeutic

approaches is the need of the hour, as we have to minimise chemotoxicity. With increasing knowledge of serum marker study, immunology, and targeted therapy, we are able to see some light at the end of the tunnel. The present study has laid, to some extent, the groundwork necessary to begin such newer approaches against ovarian carcinomas.

We were severely constrained by limited study duration, small sample size, which we need to overcome, to obtain the exact impression among general population at large.

We can conclude from our discussion that ultrasonography is definitely an important non-invasive investigation and is helpful in diagnosing most cases of functional ovarian cysts, benign ovarian neoplasm and ovarian malignancy; but the histopathological examination of specimen obtained from laparotomy/laparoscopy of adnexal mass is the gold standard for confirming the diagnosis. Although bimanual palpation of the adnexal masses may not allow a very specific diagnosis, clinically useful information can usually be obtained and hence it is particularly useful as a first step in assessment of adnexal masses and as an adjunct to morphological assessment of ovarian lesions. However no single diagnostic aid can be used to determine the pathological adnexal masses. Hence a multifaceted diagnostic approach should be used for a definite diagnosis and management of uterine adnexal mass.

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