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A clinicopathological study of ovarian masses and their tumour markers in adolescents

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Abstract
There are several numbers of benign and malignant lesions occurring within the ovaries and Benign ovarian cysts being the most common among adolescents and child bearing age and constitute about 90% of ovarian tumours.
Aim & Objectives: A Prospective observational study, to assess the clinical manifestations along with its tumor markers and histopathological pattern of ovarian masses in adolescents in Sri Ramachandra Institute of higher education and Research between September 2016 and September 2018.
Methods: The study included adolescent age group between 11-19 years.Patients were explained about the study in detail following which detailed clinical history and physical examination were recorded. Routine laboratory parameters along with tumour markers were sent and postoperatively the excised specimen was sent for histopathology. Then the results were analysed.
Results: Among 101 patients, the common age of presentation in our study was among 17 to 19 years (54.4%) and common presenting complain was pain abdomen (70.2%). In our study, Benign ovarian masses were more common in adolescent age group. Simple serous cyst (34.7%) was the most common pathology among the benign ovarian masses. CA 125 was observed to be elevated in benign ovarian tumors -simple serous cyst (19.8%) and serous (5%) and mucinous cystdenoma (2%). AFP, LDH, and β-hCG were found to have high positive rate for germ cell tumors. CA 19-9 was observed to be elevated in dermoid cyst (5%) and Mucinous Cystadenoma (2%), and CEA was found to be elevated in Dermoid cyst (2%).
Conclusion: One should aim for an accurate diagnosis and timely intervention. While surgical intervention should target to preserve fertility, adhesion prevention measures should be employed in benign ovarian masses. Tumor markers are helpful tool for diagnosis but not reliable when used in isolation and has a limited value in differentiating benign from malignant pelvic masses.

Keywords: fertility, adolescents, tumor markers, histopathology

Introduction
A female's risk at birth of having ovarian tumor sometime in her life is 6.0-7.0%, of having ovarian cancer is almost 1.5% and dying from ovarian cancer is 1.0%[1]. Benign serous tumors can occur at any age but are more common in reproductive age group. Serous carcinomas are extremely rare in first two decades of life. In patients under age of 21, approximately 60.0% ovarian tumors are germ cell tumors, accounting for two third of ovarian cancers in 1st two decades of life [1]. Majority of the ovarian masses in adolescent are functional in nature and remains asymptomatic or resolve with minimal treatment. However, ovarian cysts can herald an underlying malignant process. They commonly present with abdominal pain, a lump or menstrual irregularities [2]. Ovarian carcinoma is the 5th most common cause of cancer related deaths in Western world and leading cause of death from gynaecologic malignancy [3, 4, 5]. There is no reliable mean for early detection except for genetic screening in high risk individuals[5].In order to overcome the difficulties in diagnosing the variants of malignant ovarian tumors, tumors markers plays a vital role. No "universal" tumor marker that can detect any type of cancer has been found. Another important characteristic of tumor markers is that, noncancerous conditions can cause the levels of certain tumor markers to increase. Moreover, tumor markers have not been identified for every type of cancer. Hence this study was conducted to assess the clinical manifestations along with its tumor markers and histopathological pattern of ovarian masses in adolescents.

Materials and Methods
Study design: This study was conducted as a Prospective observational study in the

Department of Obstetrics and Gynecology in Sri Ramachandra Medical College and Research Institute, Sri Ramachandra University, a tertiary care teaching hospital located in Chennai during the period of September 2016 to September 2018.

Inclusion criteria: Adolescent girls between 11-19 years of age.

Sample size: A total of 101 patients, who got admitted in department of obstetrics and gynecology, during the study period were included in this study.

Data collection: The individual participant was explained about the study and they were also assured that, their identity would be kept strictly confidential and they have the option to refuse participation in the study. After taking the Patient's and parents written informed consent, detailed clinical history including history of pain abdomen, history of menstrual disturbances, history of abdominal distension and other complaints was collected using a proforma. Either the excised specimen or biopsy specimen of the patients was sent for histopathology. Also blood samples were collected for assessing the presence of tumor markers like CA 125, CA 19-9, beta HCG, CEA, LDH and AFP. Reference ranges for CA 125 (<35 U/L) [6]CA 19-9 (<37 kU/L) [7], beta HCG (<5 U/L) [8], CEA (<3 mcg/L) [9] LDH (<220 U/L) [10] and AFP (<20 IU/ml) [11]. The histopathological findings and titers of the tumor markers were documented in the same proforma.

Results

In this present study among 101 patients there were 55 (54.4%) patients in the age group of 17-19 years. In the age group of 14-16 years there were 36 (35.6%) participants and 10 (9.9%) participants in the age group of 11-13 years.

Table 1: Age distribution of the participants

Age group	Frequency (percentage)
11-13 years	10 (9.9)
14-16 years	36 (35.6)
17-19 years	55 (54.4)

Among all the patients the most common clinical presentation was pain abdomen 71 (70.2%) patients, mass with pain abdomen was found in 11 (10.8%) of the participants, 2 (1.98%) participants were found having mass with abdominal distension. 17 (16.8%) patients presented with some other complaints other than pain and mass abdomen.

Table 2: Proportion of participants with clinical presentation

Clinical presentation	Frequency (percentage)
Pain abdomen	71 (70.2)
Mass with abdominal distension	2 (1.98)
Mass with pain abdomen	11 (10.8)
Other complaints	17 (16.8)

In this current study among 101 patients, histopathology showed simple Serous Ovarian Cyst for 35 (34.7) patients and Hemorrhagic cyst for 16(15.8) patients. Serous cystic adenoma was found in histopathology in 16 (15.8%) patients. 18 (17.8%) participants presented with dermoid cyst in the pathological finding, Histopathological report was found to be mucinous cystic adenoma, endometriotic cyst, germ cell tumor, malignant serous papillary carcinoma and dysgerminoma in 4,4,1,1,1 patients respectively.

Table 3: Proportion of Histopathological findings

Histopathological findings	Frequency (percentage)
Simple Serous Ovarian Cyst	35 (34.7)
Hemorrhagic cyst	16(15.8%)
Serous cystic adenoma	16 (15.8)
Mucinous Cystic adenoma	4(4)
Endometriotic Cyst	4(4)
Dermoid Cyst	18(17.8)
Germ Cell Tumors	7(6.9)
Malignant Serous Papillary Carcinoma	1(1)

Among the study participants, Ca 125 marker was positive in 40(39.6%) of all the patients, Ca 19-9 was positive in 8 (7.9%) and remaining 93 (92.1%) of the study participants were negative for Ca 19-9 marker. 4 patients were positive for AFP among 101 participants. CEA marker was positive for 2 (2%) patients and B-HCG was positive in 1 (1%) patient among all 101 study participants.

Table 4: Proportion of participants with positive tumor markers

Tumor markers	Tumor markers positive Frequency (percentage)	Tumor markers negative Frequency (percentage)
Ca 125	40(39.6)	61(60.3)
Ca 19-9	7(6.9)	94 (93)
AFP	4(4)	97 (96)
CEA	2 (2)	99 (98)
B-HCG	1 (1)	100 (99)
LDH	10 (9.9)	91(90.1)

In this study with histopathological findings, among 35 cases of simple serous ovarian cyst for 20 (19.8%) of them had elevated Ca-125 marker. Out of 16 (15.8%) cases with hemorrhagic cyst 5 patients had elevated Ca-125 marker. Out of 16 (15.8%) cases with serous cystadenoma 5 patients had elevated Ca-125 marker. Mucinous cystadenoma was seen in 4 patients of them 2 had raised Ca-125 marker and dermoid cyst and malignant serous papillary carcinoma cases, Ca-125 was elevated in 7 (6.9%) and 1(1%) patient respectively.

Ca 19-9 was found to be normal in all patients who showed simple serous ovarian cyst in their histopathology report. Among 4 patients with mucinous cystadenoma 2 (2%) patients had elevated Ca19-9 markers. Among histopathological finding with dermoid cyst positive for 18 (17.8%) patients, Ca19-9 marker was raised for 5 patients. Among the patients who had Hemorrhagic cyst, serous cystadenoma, endometriotic cyst, germ cell tumors Ca19-9 was found to be normal.

AFP marker was found to be normal in all patients with simple serous ovarian cyst, Hemorrhagic cyst, serous cystadenoma, mucinous cystadenoma, Endometriotic Cyst, Dermoid Cyst, Malignant Serous Papillary Carcinoma and dysgerminoma in their histopathology report. AFP was specific for germ cell tumor and it was found to be elevated in patient having germ cell tumor changes in the histopathology report.

B-HCG marker was found to be normal in all patients with simple serous ovarian cyst, Hemorrhagic cyst, serous cystadenoma, mucinous cystic adenoma, Endometriotic Cyst, Dermoid Cyst, Malignant Serous Papillary Carcinoma and dysgerminoma in their histopathology report. B-HCG was found to be positive in case of germ cell tumor and it was elevated in patient having germ cell tumor changes in the histopathology report.

In this present study, LDH tumor marker was found to be elevated in patients having serous cystadenoma and mucinous

cystic adenoma and dysgerminoma. Among 16 (15.8%) patients of serous cystadenoma 7 (6.9%) patients had raised LDH values and among 4 patients of Mucinous Cystadenoma 2 (2%) had raised LDH value and 1 case of dysgerminoma where LDH was elevated.

CEA tumor marker was found to be elevated in dermoid cyst cases, among 18 (17.8%) patients, 2 (2%) were having raised CEA values. For patients with other histopathological findings CEA was found to be normal.

Discussion

Ovarian tumours are reported to be 2% of all the cases among children and adolescents [12].

In this study, the most common age of presentation was 17-19 years. Five patients with malignant ovarian tumor were under 17-19 years of age and two patients with histopathology of mixed germ cell tumor, embryonaltumor were under 14-16years and one Patient with histopathology of immature germ cell tumor was under 11-13 years. Benign ovarian masses peak between 17-19 years. The incidence of malignant tumours is higher than in adult Germ cell tumours andmake up to half to one third of ovarian neoplasm in girlsup to 19 years of age in the study by Shultz K *et al*, [13].

In the present study pain abdomen was the most common presenting complaint followed by other complaints such as menstrual irregularities being the next common presenting complaint. Pain was the main presenting complaint followed by abdominal distension and torsion in Lind forte series [14].

According to data from western countries 75-80% ovarian tumors were benign [15]. Huffman [16] reported that 30% of 999 tumours and Breenand Maxson 27% of 1309 tumours in children and adolescents were malignant [12, 17]. In another study 92.8% lesions were benign and 6.2% were malignant [18]. In our study, 92% ovarian masses were benign and 7.9% were malignant. Hassan *et al*. [19] reported germ cell tumors comprised 49.1% of all malignant ovarian tumors in girls through age 19.In this study, under 19 years of age, among 8 patients with malignant ovarian tumors, 7 patients had Germ cell tumors and one patient had malignant serous papillary carcinoma, thus showing preponderance of Germ cell tumors among adolescents. Among 93 patients with benign ovarian masses, 35(34.7%) had simple serous ovarian cyst, thus showing functional cyst being more common among adolescents. In this study, 16 (15.8%) patients had histopathology of serous cystic adenoma and 18 (17.8%) patients had histopathological report of dermoid cyst, thus showing Dermoid cyst being most common histopathological finding among benign germ cell tumors and Serous cystic adenoma being most common histopathology among being ovarian epithelial tumor adolescents.

Ultrasound was the basic, non-invasive imaging modality for patients presenting with ovarian masses having sensitivity of 89% and specificity of 73%.[20]CT Scan and MRI scan was done in solid ovarian tumors preoperatively to assess the stage of the tumour. Patients with histopathology of dermoid cyst showed sonographic features of cystic lesion with echogenic mass with multiple calcification components and no internal vascularity. For most of the benign ovarian masses, sonographic features revealed cystic lesion with solid component less than 5 mm and no internal vascularity. Malignant germ cell tumors revealed sonographic features of both solid and cystic components. One Patient who had Malignant serous papillary carcinoma had a MRI finding of cystic lesion with junctional nodule and intramural nodule.

Laparoscopic approach is adopted whenever possible in view of fertility preservation. Pansky M *et al* demonstrated in a study where premenarchal girls were managed by laparoscopic ovarian cystectomy [21, 22]. Cystectomy procedure done for benign ovarian cysts allows preservation of ovarian cortex. There is risk of intraoperative spillage of cyst contents during manipulation with cystectomy, and this is problematic if the cyst exhibits borderline or frank malignancy, or if a dermoid spills with its risk of peritonitis and subsequent adhesion formation. In our study, 83 patients underwent laparoscopic approach and 18 patients underwent laparotomy approach. Surgical intervention is directed towards preservation of reproductive function unless malignancy is diagnosed definitely at the time of surgery on frozen section conservative surgery should be undertaken. It is preferable to subject the patient to second procedure after the final pathological specimens are reviewed [23] Among 101 patients, 8 had malignant ovarian tumour.

One patient underwent staging laparotomy with bilateral DJ stenting with biopsy and diagnosed to have embryonal carcinoma following which the patient was managed with chemotherapy.

One patient who had dysgerminoma underwent laparotomy with left ovariectomy and salpingectomy and omental biopsy followed by a second procedure one month later which is laparoscopic pelvic lymph node dissection and in fracolicomentectomy and currently has underwent fourth cycle chemotherapy. T hree patients with immature ovarian teratoma had underwent laparotomy with unilateral oopherectomy and partial salpingectomy and currently undergoing chemotherapy. One Patient with Yolk sac tumor had underwent laparotomy with left salpingoopherectomy and was further managed with chemotherapy. The chemotherapeutic agents for management were Bleomycin, Etoposide and Cisplatin there have been no long termreports of congenital abnormalities in children born tomothers who received this chemotherapy [24].

Assessment for early detection of ovarian cancer can be achieved with tumor markers such as CEA, Ca 19-9, and Ca 15-3 combined with Ca 125 levels [25, 26]. In our study, elevation of tumour markers for various histopathology of ovarian masses were observed. The tumour markers studied were CA 125, Ca 19-9, CEA, AFP, LDH and beta HCG.

Screening with a Ca-125 measurement and trans-vaginal ultrasonography every 6 months has been recommended for high-risk women[27,28]In our study CA 125 was positive for 40(39.6%) out of which 19.8% was simple serous cyst. Ca125 was elevated more than 45U/L for malignant serous papillary carcinoma, thereby showing significant higher levels in malignant tumor. In our study Ca125 levels were predominantly elevated for ovarian tumors with epithelial origin. The diagnostic efficiency of Ca 125 in the literature usually ranges between 70 and 90% [29, 30]. But elevated Ca125 can also be detected in non malignant gynaecological conditions. Malkasion [31] studied 59 patients with histologically proven benign ovarian cysts. Out of these patients 17 had elevated concentrations of CA 125 (12 > 35 units/ml, 4 > 65 units/ml and 1 > 2000 units/ml).In another study by Dixia [32] using 153 patients with benign pelvic masses, 10 patients had CA 125 concentrations >188 units/ml and one patient had a value of more that 400 units/ml. In our study benign ovarian masses had CA 125 levels of 35-45 U/L and malignant tumour has levels of more than 45 U/L. Studies have demonstrated that isolated elevation of CA 125 is of limited value and hence radiological evaluation is also necessary for accurate diagnosis.

In this study, CA 19-9 was elevated (>35kU/L) for 7(6.9%) patients of which 5 patients had dermoid cyst and 2 patients had

mucinous cystic adenoma. Studies have shown that elevation of CA-19-9 was also observed in some cases of mature cystic teratoma [33, 34, 35]. Steinberg found that markedly high levels of CA-19-9 antigen (Greater than 1,000 U/mL) are almost relevant to malignant tumors [36] Also, Cho and Kyung [37] concluded that CA-19-9 was much more elevated in mucinous borderline and malignant tumors than in benign tumors. In contrast, our study shows elevation of CA 19-9 more common in benign ovarian tumours than malignant.

Ito *et al*. demonstrated the presence of CA19-9 in the bronchial mucosa and glands of ovarian mature cystic teratoma by immune his to chemical staining [38].

Studies have shown that Elevated levels of β-hCG can be seen in some patients with pure dysgerminoma, mixed germ cell tumor, embryonal carcinoma, and ovarian choriocarcinoma [39]. In our study both alpha fetoprotein and Beta Hcg were elevated in Germ cell tumors. Beta Hcg was elevated (>5u/L) in mixed germ cell tumor and AFP was elevated (>20IU/L) in four patients [40], patients with immature teratoma, one patient with mixed germ cell tumor and one patient with embryonal carcinoma).

In our study LDH was elevated in 10 patients. Significant elevation (>320 U/L) was observed in dysgerminoma and elevation between 220-320U/L was observed in 7 patients with serous cystic adenoma and 2 patients with mucinous cystic adenoma. In another study [41] LDH was elevated in 16/39 (41%) cases of epithelial carcinoma, but was not specific for histological types. In contrast, all 8 cases of dysgerminoma, 1 of immature teratoma and 2 of endodermal sinus tumor showed extremely elevated LDH levels. Also a study has shown the positive rate of LDH for malignant germ cell tumors of the ovary was 94.5% [42].

In this study CEA was elevated (>3mcg/L) for two patients with dermoid cyst.

However, single detection serum CA125, CA199 and CEA had little value for epithelial ovarian cancer detection with low sensitivity or specificity. Several published studies has demonstrated that combination detection serum CA125, CA199 and CEA can provide satisfactory diagnostic value for epithelial ovarian cancer [43, 44].

Conclusion

Early and correct diagnosis should be aimed. Any solid component in the ovarian masses should raise the suspicion of malignancy and detailed evaluation is necessitated. Surgical management should aim for preservation of fertility and for benign ovarian masses adhesion prevention strategies should be adopted. Tumor markers are helpful tool for diagnosis but not reliable when used in isolation and has a limited value in differentiating benign from malignant pelvic masses. The patient characteristics and radiological information provides crucial additional information on which to base a diagnosis. Published literatures are few on this subject and there is a need for study with larger sample size

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