CLINICAL PATHOLOGICAL STUDY OF OVARIAN TUMOURS IN ADOLESCENT AND YOUNG WOMEN- A PROSPECTIVE STUDY

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ABSTRACT

BACKGROUND

Ovarian cancer is the third commonest cancer in Indian women accounting for 5% of cancers. The age adjusted incidence rates vary from 2.2 to 8.3 in various registries across the country, highest being in Delhi at 8.3%. The cumulative rate (0-69 years) in India is 0.93%. Ovarian tumour in young age is quite rare and reported to be 2% of all the cases seen. Sometimes, ovarian tumours are diagnosed incidentally on ultrasound. Ovarian tumours that occur in young girls can be discovered due to symptoms on physical examination and through imaging studies.

The aim of the study is to study about ovarian tumours in adolescent and young women about the incidence, clinical presentation, types and treatment.

MATERIALS AND METHODS

It is a prospective and nonrandomised case study. The cases were studied for presenting symptoms and signs, ultrasound examination, surgical procedures performed, staging if tumour is malignant and sites of extraovarian involvement and histological findings has to be collected. Data was compiled and analysed. A prestructured proforma was used to collect the data.

RESULTS

Malignant tumours affected the age group 26-30 years most commonly as compared to the benign tumours group in whom 21-25 years was common. Malignant masses were more common in the nulliparous group and in the upper middle class and in the higher socioeconomic class and had a strong association with ovulation induction drugs and infertility.

CONCLUSION

In women less than 30 years, most masses, which present tend to be benign and that risk factors for malignancy are nulliparity, infertility, positive family history.

KEYWORDS

NA - Not Applicable, TAH + BSO + BPLND - Total Abdominal Hysterectomy + Bilateral Salpingo-Oophorectomy + Bilateral Pelvic Lymph Node Dissection, NC - Neoadjuvant Chemotherapy, USO - Unilateral Salpingo-Oophorectomy, BSO - Bilateral Salpingo-Oophorectomy.

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BACKGROUND

Ovarian cancer is the third commonest cancer in Indian women accounting for 5% of cancers. The age adjusted incidence rates vary from 2.2 to 8.3 in various registries across the country, highest being in Delhi at 8.3%. The cumulative rate (0-69 years) in India is 0.93%. Ovarian tumour in young age is quite rare and is reported to be seen in 2% of all the cases. Due to infrequent occurrence, most gynaecologists are not familiar with special problems inherent with these neoplasms. They range from benign cysts to highly aggressive malignant tumour. Ovarian masses are divided into nonneoplastic and neoplastic entities according to World Health Organization (WHO) criteria.

Ovarian masses pose diagnostic as well as therapeutic challenges because of their rarity and presentation. Patients with ovarian tumours may have a varied presentation ranging from asymptomatic cases detected incidentally to symptomatic patients with abdominal discomfort, acute abdominal pain or signs of peritonitis that can be difficult to differentiate from acute appendicitis.

Sometimes, ovarian tumours are diagnosed incidentally on ultrasound. Ovarian tumours that occur in young girls can be discovered due to symptoms, physical examination and through imaging studies. Most ovarian cysts in young girls are asymptomatic. Management of such cases should be done very carefully and should be managed conservatively. Counselling of the patient and relatives is very important. If surgery is indicated, then the aim should be towards preservation of functional ovarian tissue.

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Aims and Objectives of Study

1. Incidence of ovarian tumours in adolescent and young women (<30 years).
2. Various clinical presentations of ovarian tumours among the patients enrolled in the study.
3. Various clinical types of ovarian tumours in and their treatment aspects among the patients enrolled in the study.
4. To study the various histopathological patterns of ovarian tumours in adolescent and young women.

MATERIALS AND METHODS

The study was a prospective nonrandomised case study conducted on all patients attending Department of Gynaecology and met a predefined criteria at the A.J. Institute of Medical Sciences and Research Centre during the period from October 2014 to June 2016 on whoever diagnosed to have ovarian tumour and consented to take part in study. The study was initiated after obtaining ethical clearance from the institutions ethical clearance committee.

Inclusion Criteria

1. Age from menarche to 30 years.
2. All type of ovarian tumours of size more than 3 cms.

Exclusion Criteria

1. Patients before menarche and above 30 yrs.
2. All pregnant women.
3. Patients or patient party refusal.

Method of Collection of Data- Patients attending Department of Gynaecology and Oncology in age range from menarche to 30 years who were diagnosed with ovarian tumours and consented to take part in study during the study period were included.

These cases were studied for presenting signs and symptoms, ultrasound reports, surgical procedure performed, staging if tumour is malignant and sites of extraovarian involvement and histological findings has to be collected. Data was compiled and analysed.

A prestructured proforma was used to collect the data.

The following parameters were studied.

1. Age, occupation, education and socioeconomic status.
2. Marital status, parity index.
3. Clinical features like pain abdomen, mass per abdomen, etc.
4. Risk factors- Family history of cancer.
5. Elevated tumour markers.
6. USG or MRI findings.
7. Laparotomy/laparoscopy findings.
8. Surgical procedures.
9. Histopathological features.

RESULTS AND OBSERVATIONS

The study was a prospective nonrandomised case study conducted on patients diagnosed as having ovarian tumours attending Department of Gynaecology and met a predefined criteria at the A.J. Institute of Medical Sciences and Research Centre during the period from October 2014 to June 2016. In our study, we evaluated 150 cases of ovarian masses in which 11 were malignant and 139 benign. These were our observations.

Demographic Data

Benign	23.58
Malignant	25.91

Table 1. Age Distribution

The mean age of ovarian tumour in our study was 25.91 ± SD 4.6 years, mean age of benign ovarian tumour in our study was 23.58 years ± SD 3.8 years, and the mean age of malignant ovarian tumour in our study was 25.91 ± SD 5.7 years.

Benign	13.15 years ± SD 1.8 years
Malignant	11.36 years ± SD 1.7 years

Table 2. Age at Menarche

The age at menarche in benign ovarian tumour in our study was 13.15 years ± SD 1.8 years and the mean age at menarche in malignant ovarian tumour in our study was 11.36 ± SD 1.7 years.

Age in Years	Benign Frequency	% Benign	Malignant Frequency	% Malignant
Less than 15 years	4	3	1	9
16-20 years	21	15	2	18
21-25 years	64	46	2	18
26-30 years	50	36	6	55
Total	**139**	**100**	**11**	**100**

Table 3. Age of Presentation- Group Wise

The most common age of presentation of the benign group was 21-25 years and of the malignant group was 26-30 years.

Group		Frequency	Percent	Valid Percent	Cumulative Percent
Benign	Yes	113	81.3	81.3	81.3
	No	26	18.7	18.7	100
Total		**139**	**100**	**100**	
Malignant	Yes	9	81.8	81.8	81.8
	No	2	18.2	18.2	100
Total		**11**	**100**	**100**	

Table 4. Marital Status

81% of the cases in the study in each group were married.

Group		Frequency	Percent	Valid Percent	Cumulative Percent
Benign	Unmarried	26	19.4		
	0 (nulliparous)	4	2.2	21.6	21.6
	1	8	5.8	5.8	27.3
	2	89	64	64	91.4
	3	10	7.2	7.2	98.6
	4	2	1.4	1.4	100
Malignant	0	6	54.5	54.5	54.5
	1	3	27.3	27.3	81.8
	Unmarried	2	18.2	18.2	100
	Total	**11**	**100**	**100**	**P value <0.023**

Table 5. Parity

As per our study, malignant ovarian tumours were more common in the nulliparous as compared to the benign group 'p' value <0.023.

Group		Frequency	Percent	Valid Percent	Cumulative Percent
Benign	Low (SES 5)	8	5.8	5.8	5.8
	Middle (SES 2, 3, 4)	116	83.5	83.5	89.2
	High (SES 1)	15	10.8	10.8	100
	Total	**139**	**100**	**100**	
Malignant	Low (SES 5)	1	9.1	9.1	9.1
	Middle (SES 2, 3, 4)	5	45.5	45.5	54.5
	High (SES 1)	5	45.5	45.5	100
	Total	**11**	**100**	**100**	**P value <0.001**

Table 6. Socioeconomic Status

Malignant were more common in the upper middle class and in the higher socioeconomic class 'p' value <0.001 based on Kuppuswamy scale, Kuppuswamy 1 was taken as high SES, Kuppuswamy 2, 3, 4 as middle and Kuppuswamy 5 as low income group in our study.

RISK FACTORS

Group		Frequency	Percent	Valid Percent	Cumulative Percent
Benign	Yes	13	9.4	9.4	9.4
	No	100	71.9	71.9	81.3
	Unmarried (not applicable)	26	18.7	18.7	100
	Total	**139**	**100**	**100**	
Malignant	Yes	8	72.7	72.7	72.7
	No	1	9.1	9.1	81.8
	Unmarried (not applicable)	2	18.2	18.2	100
	Total	**11**	**100**	**100**	**P value <0.05**

Table 7. Infertility

The above table and graph shows the association of infertility as a risk factor in ovarian tumour. In our study, we found that ovarian malignancy has strong association with infertility 'p' value <0.05.

Group		Frequency	Percent	Valid Percent	Cumulative Percent
Benign	No	139	100	100	100
Malignant	Yes	4	36.4	36.4	36.4
	No	7	63.6	63.6	100
	Total	**11**	**100**	**100**	**P value <0.016**

Table 8. Family History of Cancer

The graph and table above show a positive association of ovarian cancer with family history of ovarian cancers. Those who had a family history of cancer had a higher incidence of ovarian cancers 'p' value <0.016.

Group		Frequency	Percent	Valid Percent	Cumulative Percent
Benign	Yes	13	9.4	9.4	9.4
	No	100	71.9	71.9	81.3
	Unmarried (not applicable)	26	18.7	18.7	100
	Total	**139**	**100**	**100**	**P <0.025**

Malignant	Yes	8	72.7	72.7	72.7
	No	1	9.1	9.1	81.8
	Unmarried (not applicable)	2	18.2	18.2	100
	Total	**11**	**100**	**100**	**P <0.025**

Table 9. Ovulation Induction Drugs

The above table and graph show a positive correlation of ovarian malignancy with drugs used to induce ovulation in infertility cases. The 'p' value was less than 0.025, which is statistically significant.

Clinical Features, Pain Abdomen

	Diagnosis	Pain Abdomen	Abdominal Distension	Dysmenorrhea	Mass Abdomen	Menstrual Irregularity
Benign	Endometrioma	69	0	92	0	23
	Dermoid cyst	5	0	0	0	1
	Mucinous cystadenoma	1	0	0	4	0
	Serous cystadenoma	3	1	0	0	0
Malignant	Granulosa cell tumour	1	1	0	2	0
	Immature teratoma	0	0	0	1	0
	Mucinous cystadenocarcinoma	1	1	0	1	0
	Serous cystadenocarcinoma	2	1	0	1	0

Table 10. Clinical Symptoms

In our study, on evaluation of the clinical features, abdominal pain was seen in 55% and 36% of cases of benign and malignant tumours, respectively. The next common symptom in the benign group was dysmenorrhea seen in 92 cases almost all of which were endometrioma, abdominal distension and mass abdomen were predominantly seen in the malignant group.

Group			Frequency	Percent	Valid Percent
Benign	Valid	U/L	122	87.7	87.7
		B/L	17	12.3	12.3
		Total	**139**	**100**	**100**
Malignant	Valid	U/L	6	54.5	54.5
		B/L	5	45.5	45.5
		Total	**11**	**100**	**100**

Table 11. Laterality

In our study, out the 17 cases in benign and 5 cases had bilateral ovarian tumours.

CA-125	Benign	Benign %	Malignant	Malignant %
<100	14	10	0	0
101-500	135	90	0	0
500-1000	0	0	7	63
>1000	0	0	4	36

Table 12. Tumour Markers

In all cases of benign ovarian masses, the level of CA125 was less than 500 and in the malignant cases the level was above 500. The mean CA125 in the benign and malignant group was 144 and 1444.75, respectively, and other markers like AFP in one case of immature teratoma and inhibin B in granulosa cell tumour were raised.

Group		Frequency	Percent	Valid Percent	Cumulative Percent
Benign	Endometrioma	109	78.4	78.4	78.4
	Dermoid cyst	10	7.2	7.2	85.6
	Mucinous cystadenoma	7	5	5	90.6
	Serous cystadenoma	13	9.4	9.4	100
	Total	**139**	**100**	**100**	
Malignant	Granulosa cell tumour	2	18.2	18.2	18.2
	Immature teratoma	1	9.1	9.1	27.3
	Mucinous cystadenocarcinoma	2	18.2	18.2	45.5
	Serous cystadenocarcinoma	6	54.6	54.6	100
	Total	**11**	**100**	**100**	

Table 13. HPE

As shown in the graph and table above on evaluation of histopathology, serous cystadenocarcinoma was the most common neoplasm in the malignant group and endometrioma was the common benign tumour in the benign group.

Group Treatment Given		Frequency	Percent
Benign	USO	13	9.4
	H + BSO	1	0.7
	ULO	17	12.2
	Cystectomy	108	77.7
	Total	**139**	**100**
Malignant	NC followed by TAH + BSO + BPLND	3	27.3
	TAH + BSO + BPLND	2	18.2
	ULO	4	36.4
	USO	1	9.1
	USO + omental biopsy + left ovarian biopsy	1	9.1
	Total	**11**	**100**

Table 14. Treatment

Year	Number of Malignant Cases	Benign	Total
2006	10	180	190
2007	10	206	216
2008	14	247	261
2009	18	268	286
2010	15	260	275
2011	16	268	284
2012	15	277	292
2013	18	272	290
2014	20	267	287
2015	22	280	302
2016	28	312	340

Table 15. Prevalence of Ovarian Tumours

DISCUSSION

The study was a prospective nonrandomised case study with 150 cases between October 2014 to June 2016 in Gynaecology Department of A.J. Institute of Medical Sciences and Research Centre who presented as ovarian tumour under the age group of 30. Of these cases, 11 (3%) were malignant and 139 (97%) benign.

Comparison of Cases Studied- In a study by Couto et al,[1] approximately 80% of all ovarian tumours were benign, 16% were malignant, the rest being borderline malignant, which is similar to our study. Similarly, Gangadhar Swamy et al[2] studied a total number of 120 cases, among them 86 were benign, 4 were borderline and 30 were malignant tumours.

The below table compares a few studies with our studies.

Study	Benign	Malignant	Borderline
Our	139 (97%)	11 (3%)	-
Couto F 1993[1]	80%	16%	4%
Gangadhar Swamy[2]	86 (71.6%)	30 (25.0)	4 (3.0)
Ahmed et al[3]	59.1	40.81	0.2
Pilli et al[4]	75.2	21.8	2.8
Gupta et al[5]	72.9	22.9	4.1

Table 16. Comparison of a Few Studies with our Study in Terms of Distribution of Cases

Laterality- 85% tumours were unilateral, which is similar to the study by Gangadhar Swamy[2] in whose study 80% of ovarian tumours were unilateral.

Study	U/L	B/L
Our	85.7%	14.7%
Gangadhar Swamy[2]	80%	20%

Table 17. Comparison of a Few Studies with Our Study in Terms of Laterality

Histopathological Patterns- Serous cystadenoma was the commonest pattern, which is similar to the other studies done on Indian population.

Study	Commonest Histopathology in Malignancy
Our	Serous cystadenocarcinoma
Thanikasalam[6]	Serous cystadenocarcinoma in Indian teratomas among the Malays, Chinese
Gangadhar Swamy[2]	Serous cystadenocarcinoma
Kanthikar[7]	Serous cystadenocarcinoma

Table 18. Comparison of a Few Studies with Our Study in Terms of Commonest Histopathology

Kanthikar in his study showed that based on histomorphological features, incidence of surface epithelial tumours were commonest (67.14%), followed by germ cell tumours (22.85%), sex cord (5.71%) and metastatic (4.28%).[7] Similar observations were seen in our study and in study by Couto F et al,[1] Pilli et al[4] and Gupta et al.[5]

Comparison of Parity with Diagnosis- There was statistically significant association of malignant tumours with parity ($p < 0.023$). Nulliparity having higher risk of malignancy and parous women having significantly lower risk. In study by Kanthikar,[7] incidence of nulliparity (20%) and malignancy was comparable to our study. Comparison of infertility and ovulation induction drugs with diagnosis showed among nulligravid women, attempts for more than 5 years to become pregnant compared with attempts for less than 1 year increased the risk of ovarian cancer 2.67-fold (95%, Confidence Interval (CI): 1.91, 3.74). Fertility drug use in nulligravid women was associated with borderline serous tumours (OR = 2.43, 95%, CI: 1.01, 5.88), but not with any invasive histologic subtypes. Endometriosis (OR = 1.73, 95%, CI: 1.10, 2.71) and unknown cause of infertility (OR = 1.19, 95%, CI: 1.00, 1.40) increased cancer risk.

According to the studies by Rossing et al,[8] Ron et al,[9] Whittemore. Fertility-related procedures and infertility were related to an increased risk of cancer.

Elaine Ron[9] did a study on cancer incidence in a cohort of infertile women and found that analysis by infertility diagnosis demonstrated no significant excess of total cancer incidence; the standardised incidence ratio was 1.3 (95%, CI = 0.8-1.8) for infertility due to hormonal deficiency, 0.7 (95%, CI = 0.3-1.4) for mechanical infertility, 1.6 (95%, CI = 0.6-3.6) for infertility of the male partner and 1.1 (95%, CI = 0.5-2.2) for unclassified diagnosis. Site-specific analyses revealed a significantly increased risk (8.0; 95%, CI = 2.5-19.3; four cases observed, 0.50 expected) of endometrial cancer for the hormonal group and a no significant excess of breast cancer and melanoma. A subsequent, larger and more rigorous study by Rodriguez[10] found that the use of clomiphene resulted in a 2.3 times increased risk for ovarian cancer in nulligravid women (95%, CI: 0.5-11.4).

Comparison of Family History with Diagnosis- Hereditary ovarian cancer is a well-established entity and epidemiologic studies have estimated that it accounts for approximately 5-10 percent of epithelial ovarian cancer.[10,11] There was statistically significant association of malignant masses with family history with a 'p' value <0.016. Malignant were more common in those with family history. In our study, 4 cases of positive family history showed bilateral tumours with significant tumour marker values. Of the 11 cases of malignancies, 3 were found to be advanced cases and received neoadjuvant chemo followed by surgery.

In a study done by Loman, Niklas et al[12] women who carry disease specific alleles for BRCA1 and BRCA2 are at significantly higher risk of epithelial ovarian cancer than women in the general population. A total of 97 case subjects had at least one first- or second-degree relative with breast or ovarian cancer; 34 (14%; 95% confidence interval (CI) = 9.6% to 18%) cases had at least two first- or second-degree relatives, 22 (8.8%; 95%, CI = 5.3% to 12%) had one first-degree relative and 41 (16%; 95%, CI = 12% to 21%) had one second-degree relative with either cancer. If two females affected with breast or ovarian cancer who were related through an unaffected male were also defined as first-degree relatives, than a higher number of case subjects, 120 (48%; 95%, CI = 42% to 54%) had at least one first-degree or second-degree relative with breast or ovarian cancer.

Sixteen (6.8%; 95%, CI = 4.0% to 11%) BRCA1 mutation carriers and five (2.1%; 95%, CI = 0.70% to 4.9%) BRCA2 mutation carriers were identified that in their study of eighteen cases (2%) and 24 controls (1%) reported a history of ovarian cancer in a first-degree relative. The corresponding multivariate adjusted Odds Ratio (OR) was 1.9 (95%, confidence interval (CI) 1.1-3.6).

The risk of ovarian cancer was elevated in women reporting a family history of breast cancer (OR = 1.6, 95%, CI 1.1-2.3), but no significant association emerged with a family history of endometrial cancer (OR = 1.3, 95%, CI 0.8-1.7).

A history of ovarian cancer in first-degree relatives doubles the risk of ovarian cancer and a history of breast and/or ovarian cancer in first-degree relatives increases ovarian cancer risk by 50% as shown by Sekine et al.[13]

Comparison of Final Diagnosis with Age- There was statistically significant association of benign and malignant tumours with age ($p=0.045$). It is a well-known fact that benign tumours are commoner in younger subjects as was shown in our study.

Comparison of Clinical Presentations- In our study, on analysis of clinical symptoms, abdominal pain was seen in 55% (benign cases) and 36% (malignant cases). The next common symptom in the benign group was dysmenorrhea seen in 92 cases, almost all of which were endometrioma. Abdominal distension and mass per abdomen were predominantly seen in the malignant group. Of the 150 cases, 5 were incidentally detected when sonography was done for other reasons. Malignant ovarian tumours are not associated with any specific symptoms. Abdominal pain is the most common presenting symptom of ovarian tumours (57%), followed by a palpable abdominal or pelvic mass (46%) as shown in a study by Strickland JL et al.[14] This is

similar to our study in which the most common presenting complaint was abdominal pain seen in 81 patients. Patients may also present with nausea, vomiting, poor appetite, weight loss, constipation and urinary frequency or they may be asymptomatic with the tumour being detected incidentally.

A Review of Ovarian Neoplasms in Adolescents- Fortunately, most ovarian tumours in adolescents are benign with only 6% to 10% of them being malignant. The incidence of ovarian neoplasms in paediatric age group is 2.6 per 1,00,000 girls.[15] Approximately, 2% of all ovarian cancers occur in females below 25 years.[15] The most common ovarian tumours in adolescence are germ cell tumours (55%).

In another study by Hatzipantelis and Dinas,[16] it was shown that sex cord-stromal tumours comprise 10% of paediatric ovarian tumours, majority of patients fell in the subgroup 14-16 years age. Majority harbouring ovarian malignancy belonged to subgroup 17-19 years. Clinical presentation in the majority was mass abdomen and abdominal distension. Histopathology was benign in 11 cases and malignant in 4. All 4 malignancies were found to be to nonepithelial on histopathology. This finding is similar to our study where we found 3 patients in the adolescent age group, which were all sex cord stromal tumours.

Ultrasound findings of multiloculations, papillary projections, increased vascularity and presence of solid foci goes more in favour of malignancy.[14] Although, sex cord-stromal tumours present in a broad age group, the majority tend to present as a low-grade disease that usually follows a nonaggressive clinical course in younger patients.[16]

Luteinised the coma associated with sclerosing peritonitis is usually a bilateral and hormonally inert tumour that occurs in younger age (avg. 28 years).[17]

Unlike fibroma, the coma and adult GCTs, sclerosing stromal tumour and Sertoli-Leydig cell tumour are more likely to occur in young women approximately 80% of reported cases are under 30 years of age.[18,19]

CONCLUSION

In our study, positive correlation found between malignancy and nulliparity, infertility and positive family history. The most common histopathological pattern among adolescent age group was sex cord-stromal cell tumour and epithelial ovarian malignancies were increasing with increase in age. Under the age group of 30, most of the tumours presented as benign and treated with conservative approach with intention to retain menstrual and reproductive function. In certain cases, unilateral oophorectomy was done for the patients' benefit.

Limitations- The study was conducted in a tertiary care reference hospital, may not reflect the problems of population at large. The study was also conducted in a limited duration and on an age group of less than 30, which may not reflect the higher incidence of malignancy in the perimenopausal and postmenopausal age group.

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