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Original Article

Pathology Section

Clinicopathological Study of Ovarian Germ Cell Tumours in Tertiary Care Hospital, Tamil Nadu, India: A Cross-sectional Study

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ABSTRACT

Introduction: Ovarian germ cell tumours are a heterogeneous group of neoplasms derived from primitive germ cells of the embryonic gonad, either directly or indirectly. They can be classified as benign and malignant, with slow and rapid growth and spread, respectively. Benign ovarian germ cell tumours are common, while malignant tumours are rare and account for about 2.6% of all ovarian malignancies. They are more common in the second and third decades of life and typically present with abdominal mass, pain, and elevated serum tumour markers, which aid in primary diagnosis and follow-up.

Aim: To analyse the distribution of germ cell tumours in the ovary in relation to age, parity, mode of presentation, biochemical markers, histomorphological patterns, and immunohistochemical markers.

Materials and Methods: This cross-sectional study was conducted at Department of Pathology, Sree Balaji Medical College, Hospital and Research Institute, Chromepet, Chennai, Tamil Nadu, India. The study involved 86 ovarian specimens, of which 25 were germ cell tumours. Complete clinical history, radiological findings, and pre-operative laboratory test values were recorded. The ovarian specimens were carefully examined for gross appearances, fixed in 10% neutral buffered formalin for 24-48 hours, and subjected to histopathological processing, routine and special staining, and immunohistochemical study after observing the different morphological patterns of the ovarian specimens received.

Results: The age range of presentation was between 14 years and 58 years. Seventeen patients were parous (14 benign and 3 malignant), and eight (5 benign and 3 malignant) were nulliparous. Abdominal mass and abdominal pain were the most common modes of presentation. Out of 25 germ cell tumours, 19 were benign cystic mature teratomas, 2 were immature teratomas, 1 was a yolk sac tumour, 2 were dysgerminomas, and 1 was a carcinoid tumour, with 6 being malignant and 19 being benign tumours. Among the 6 malignant ovarian tumours, 5 cases had raised serum tumour markers {cancer antigen-125 (CA-125), Alpha-Fetoprotein (AFP)} pre-operatively, and the levels reduced and became normal after surgery. Among the 2 cases of immature teratoma, one was Grade-II and the other was Grade-III. For one case with mixed tumour components, CD-30 and α-fetoprotein immunohistochemical markers were performed, showing negative and positive results, respectively.

Conclusion: Among the histopathological subtypes, benign cystic teratomas were the most common ovarian germ cell tumours in this study. Both benign and malignant tumours presented with abdominal pain and abdominal mass. Most of the tumours were diagnosed between the ages of 21 and 40 years. In this study, α-fetoprotein immunohistochemical marker showed strong positivity, confirming a single tumour component.

Keywords: Alpha-fetoprotein, Dysgerminoma, Teratoma, Tumour marker, Yolk sac tumour

INTRODUCTION

Germ cell tumours are rare and complex groups of heterogeneous neoplasms, comprising both benign and malignant histologies. These tumours can occur at gonadal and extragonadal sites, most commonly in the gonads (ovaries and testes), and can face diagnostic challenges for reporting pathologists in advanced cases [1]. They arise from the totipotent primordial germ cells of the embryonic gonads [2] of their respective origins.

Ovarian germ cell tumours account for 20% of all ovarian neoplasms and are most commonly observed in children and young adults. They can present as monodermal tumours or as a combination of other elements, which is termed as mixed germ cell tumours. The most common malignant ovarian germ cell tumours include dysgerminoma, immature teratoma, yolk sac tumour, and mixed germ cell tumours. Less commonly, embryonal carcinomas, choriocarcinomas, and malignant struma ovarii can also occur. Malignant cases tend to behave aggressively, but the prognosis is good in younger women if fertility-preserving management is carried out [3].

Most of the tumours which are non-functional tend to present with relatively milder symptoms in the early stages, while hormonally active tumours may cause more evident clinical presentations. As the tumours grow larger, symptoms such as abdominal distension, pain, gastrointestinal and urinary tract symptoms, as well as symptoms related to tumour invasion, compression, or vaginal bleeding, may become apparent. Benign forms of the tumour are often asymptomatic and may be incidentally discovered [4].

Alpha-fetoprotein (AFP) has been consistently associated with all ovarian germ cell tumours containing yolk sac elements, while Human Chorionic Gonadotropin (HCG) serves as an indicator of trophoblastic differentiation [5]. The above mentioned tumour markers are diagnostic of ovarian malignant germ cell tumours and can be useful when measured in all young patients presenting with a pelvic mass. The clinical significance of these serum tumour markers is crucial for assessment, therapy, and follow-up.

Teratomas are believed to arise from a single germ cell after the first meiotic division, requiring cross-over and exchange of genetic material between homologous chromosomes. They develop from pluripotent descendants of activated germ cells, which can differentiate into either somatic or extraembryonic tissues [5]. In young patients, surgery should be conservative to preserve fertility. The prognosis is excellent as most cases are benign [6].

The present study aimed to determine various histomorphological findings, age group distribution, and clinical presentation, including

serum tumour markers. Immunohistochemical markers were also used in this study to rule out tumour coexistence.

MATERIALS AND METHODS

This cross-sectional study was conducted at Sree Balaji Medical College, Hospital, and Research Institute Chromepet, Chennai, Tamil Nadu, India, from April 2015 to September 2016 in the Department of Pathology, in concordance with the Department of Obstetrics and Gynaecology. Approval was obtained from the Institutional Ethical Committee (IEC number: 002/SBMC/IHEC/2015-93).

Inclusion criteria: All benign and malignant germ cell tumours of the ovary were included.

Exclusion criteria: All inflammatory, infective conditions, and other ovarian tumours were excluded.

Procedure

The study included complete clinical history, including presenting complaints, pre-operative serum tumour marker levels, and ultrasound findings. Out of all the ovarian specimens received during the study period, only 25 were classified as germ cell tumours. The specimens were fixed in 10% formalin for 24-48 hours, and then the grossing procedure was carried out, with photographs taken. External and cut surface gross features were described. Adequate tissue samples were taken from representative areas and subjected to tissue processing. Paraffin wax blocks were prepared for embedding the tissues. Three sections, 3-4 microns in thickness, were taken for staining with hematoxylin and eosin, and poly-L-lysine-coated slides were used for immunohistochemical markers such as AFP and CD30. Dako mouse monoclonal CD30 antibody (Ber-H2) and AFP IHC Antibody mouse monoclonal AP1 were used for immunohistochemical staining in one doubtful case. The collected data were compiled, including various parameters such as age, clinico-radiological findings, and detailed histopathological examination of the tissue sections for diagnosis.

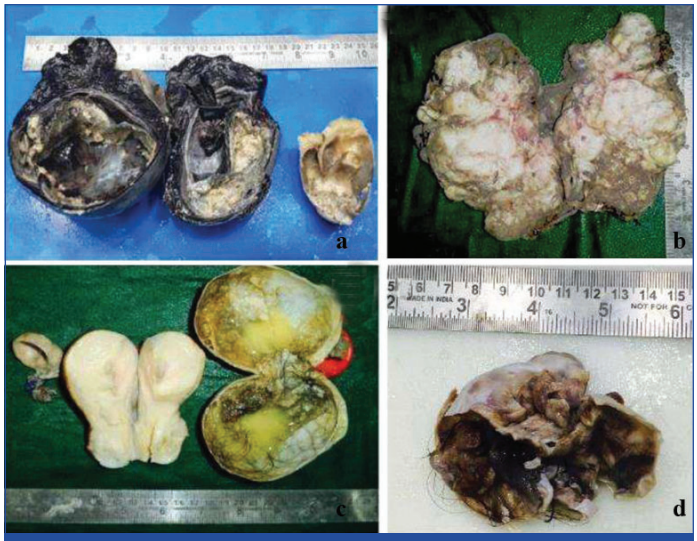
The pre-operative evaluation of serum tumour markers such as β-hCG, AFP, and CA-125 was performed with reference to their normal ranges [2] of 55-200 ng/mL, <20 ng/L, and <35 U/mL, respectively, in suspected ovarian malignancies. Biochemical values were evaluated in the laboratory using commercially available enzyme immune assay kits, and descriptive analysis was carried out.

STATISTICAL ANALYSIS

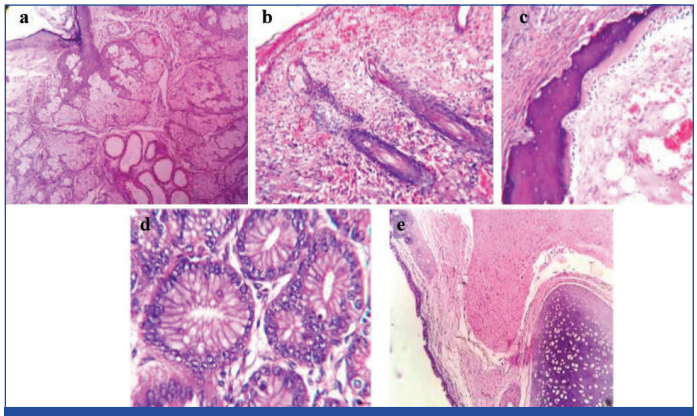
Descriptive statistics were used to analyse the cases.

RESULTS

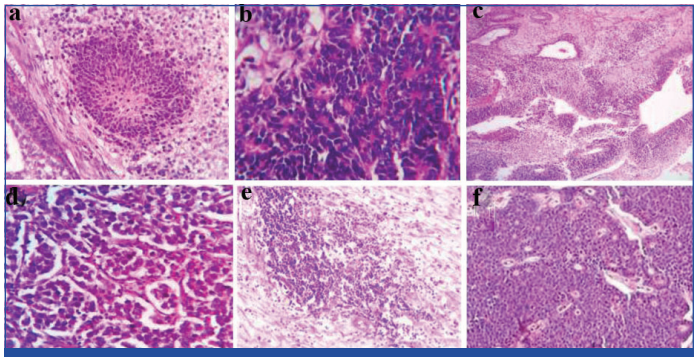
Out of the 19 cases of benign cystic teratoma [Table/Fig-1,2], three were found incidentally during appendicectomy, hysterectomy, and lower segment caesarean section. The distribution of malignant cases in this study is as follows: immature teratoma (2 cases) [Table/Fig-3], dysgerminoma (2 cases), yolk sac tumour (1 case), and carcinoid tumour (1 case). Associated conditions such as leiomyoma (3 cases), acute appendicitis (3 cases), pregnancy (1 case), hypertension (2 cases), prolapse (1 case), diabetes mellitus (2 cases), fever (1 case), and anaemia (1 case) were noted. One case was suspicious of both yolk sac elements and embryonal tumour components, for which two immunohistochemical markers (α-fetoprotein and CD30) were performed. The results showed positivity for α-fetoprotein and negative CD30 marker, confirming the absence of mixed components in that case [Table/Fig-4] (IHC). The histological distribution of ovarian germ cell tumours comprised 19 cases of mature teratoma (76%), two cases of immature teratoma (8%), dysgerminoma two cases (8%), yolk sac tumour one case (4%) and carcinoid one case (4%) [Table/Fig-5].



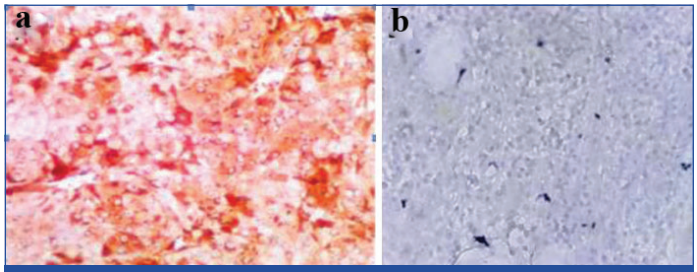
[Table/Fig-1]: Benign Cystic Teratoma (a) Gross: Right and left ovary: cyst with pultaceous material with hair follicle; (b) Gross picture of immature teratoma; E/s-breached capsule with solid and cystic areas (c&d) Gross picture of mature cystic teratoma showing yellow turbid fluid with hair follicles, tooth, pultaceous material and mixed with haemorrhagic areas.



[Table/Fig-2]: (H&E-Teratoma): (a&b) Picture showing skin with pilosebaceous and apocrine glands; (c) Bone tissue with adipose tissue and blood vessels; (d) Intestinal type of glands; (e) Respiratory epithelium, island of cartilage with glial tissue.



[Table/Fig-3]: HPF (400x): H&E: (a-c) (Immature Teratoma): Primitive neuro epithelium with hyperchromatic nuclei arranged in rosettes and Primitive neuroectodermal elements; (d) (Dysgerminoma) Large vesicular tumour cells with clear cytoplasm arranged in nests separated by fibrous stroma with lymphocytes; (e) (Yolk Sac Tumour) Tumour elements arranged in solid pattern merges with surrounding microcystic areas; (f) (Carcinoid Tumour): Nests of round to oval cells with clumped chromatin.



[Table/Fig-4]: (IHC): (a) Yolk sac elements showing strong cytoplasmic positivity to Alpha fetoprotein (AFP); (b) Tumour cells showing CD 30 Negative.

Tumour type	Number
Mature teratoma	19 (76%)
Immature teratoma	2 (8%)
Dysgerminoma	2 (8%)
Yolk sac tumour	1 (4%)
Carcinoid tumour	1 (4%)
Total	25 (100%)

[Table/Fig-5]: Distribution of germ cell tumours of ovary according to histological type.

The most common age group was between 21-30 years of age with 11 cases [Table/Fig-6]. Unilaterality was detected in 22 cases (88%), and bilateral involvement was observed in three cases (12%). The dimensions of the ovarian specimens with germ cell tumours in this study ranged from 2 to 14 cm [Table/Fig-7]. Out of the 25 ovarian tumours, 10 (36%) were cystic, 6 (24%) were solid, and mixed components were seen in nine cases (36%) [Table/Fig-8]. Among the 19 benign tumours, 14 were observed in parous women and five in nulliparous women [Table/Fig-9]. Among the six malignant cases, three were found in parous women and three in nulliparous women. The most common tumour was benign cystic teratoma, and the most common mode of presentation was abdominal mass with pain [Table/Fig-10]. Ultrasound findings of these tumours showed hyperechoic appearance in 15 cases (60%), hypoechoic appearance in four cases (16%), and mixed echoes in six cases (24%) [Table/Fig-11-13]. Serum tumour markers such as CA 125, AFP, and β-HCG were measured, and one or two markers were found to be elevated in malignant cases [Table/Fig-14].

Age group (years)	Number
0-10 years	0
11-20 years	4 (16%)
21-30 years	11 (44%)
31-40 years	5 (20%)
41-50 years	4 (16%)
51-60 years	1 (%)

[Table/Fig-6]: Distribution of ovarian germ cell tumours of ovary according to age.

Laterality	Number
Right	14 (56%)
Left	8 (32%)
Bilateral	3 (12%)
Size	**Number**
<5 cm	4 (16%)
5-10 cm	15 (60%)
>10 cm	6 (24%)

[Table/Fig-7]: Distribution of germ cell tumours of ovary according to laterality.

Gross findings	Number
Solid	6 (24%)
Cystic	10 (40%)
Mixed	9 (36%)
Total	25 (100%)

[Table/Fig-8]: Distribution of germ cell tumours of ovary according to gross morphology.

Type of tumour	Parous	Nulliparous
Benign (19)	14	5
Malignant (6)	3	3
Total	17	8
Percentage	68%	32%

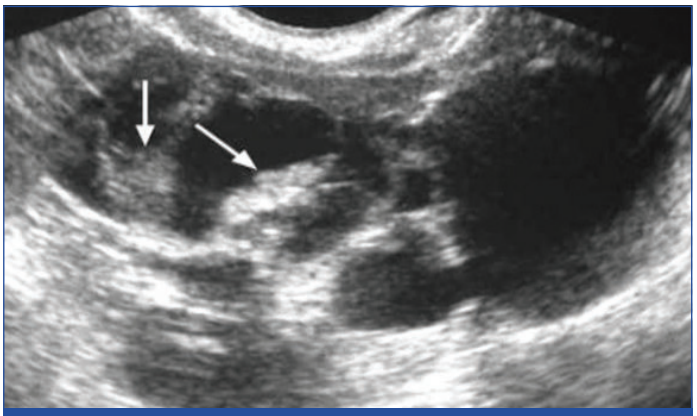
[Table/Fig-9]: Distribution of ovarian germ cell tumours with correlation of parity.

Clinical features	Number
Abdominal mass with pain	11 (44%)
Abdominal pain	5 (20%)
Abdominal distension	1 (4%)
Bleeding per vagina	3 (12%)
Right adnexal pain	2 (8%)
Menstrual disturbances	3 (12%)
Total	25 (100%)

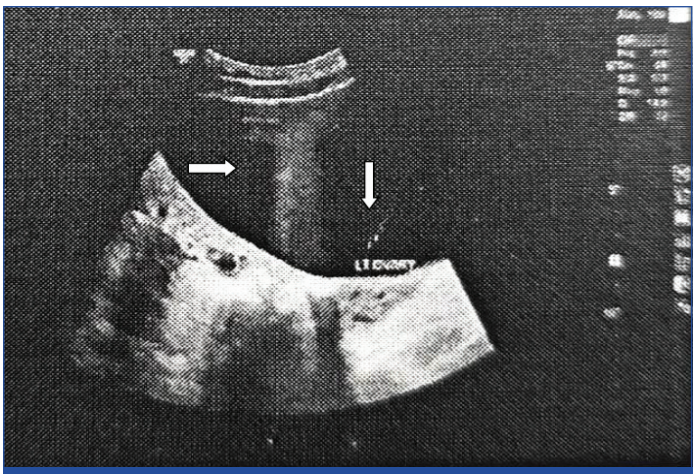
[Table/Fig-10]: Distribution of ovarian germ cell tumours according to the mode of presentation.

Findings	Number
Hyperechoic	15 (60%)
Hypoechoic	4 (16%)
Mixed echoes	6 (24%)
Total	25 (100%)

[Table/Fig-11]: Ultrasound findings of ovarian germ cell tumours.



[Table/Fig-12]: Hyperechoic and hypoechoic findings represent both solid and cystic components in right ovary.



[Table/Fig-13]: Left ovary showing a cystic lesion in case of benign cystic teratoma noted as hypoechoic findings.

Histopathological diagnosis	Age (years)	Tumour markers and its values		
		CA 125	β hCG	AFP
Immature teratoma-Grade-II	21 years	115 U/mL	Negative	Negative
Immature teratoma-Grade-III	18 years	Negative	Negative	6477 IU/mL
Yolk sac tumour IHC findings: α-fetoprotein positive CD 30 negative	21 years	Negative	Negative	1228 IU/mL
Dysgerminoma	58 years	63.5 U/mL	Negative	Negative
Dysgerminoma	28 years	58.9 U/mL	Negative	Negative

[Table/Fig-14]: Serum tumour marker with histopathological diagnosis.

The serum tumour markers were noted with many fold raise pre-operatively in malignant cases only.

DISCUSSION

The ovaries are intra-pelvic paired organs of female genital system which produces ova for fertilisation and also involved in developement of secondary sexual characters the ovaries are paired intra-pelvic organs of the female reproductive system that produces ova for fertilisation and contribute to the development of secondary sexual characteristics. Ovarian neoplasms originating from germ cells are the second largest group of tumours after surface epithelial tumours. They can be benign or malignant, with malignant cases being rare, accounting for about 2-5% of cases [7]. Present study included 25 ovarian germ cell tumours out of a total of 86 ovarian tumours observed, with 19 being benign cystic mature teratomas. These tumours are relatively common in younger women but can also occur in infants and older women. Pre-operative serum tumour markers were elevated in malignant cases.

Immunohistochemical staining was used in one case to confirm the presence of tumour tissue in the same gonad. The incidence of ovarian germ cell tumours in the present study (29.06%) was similar to previous studies by Sharma I and Chaliha T (30.39%) and Gupta SC et al., (31.08%) [5,8]. The incidence of benign cystic teratomas (18.6%) in this study was comparable to that reported by Rajan R (17.74%) [9]. Grossly, benign cystic teratomas appeared as cystic structures, while microscopic examination revealed elements from germ cell layers such as skin with pilosebaceous glands, bony and adipose tissue, intestinal glands, respiratory epithelium, and islands of cartilage with glial tissue [Table/Fig-2]. The age range in this study was 14 to 58 years, similar to the age distribution reported by Jadhav BJ and Shinde AM for all ovarian germ cell tumours and malignant ovarian GCTs. Most benign tumours occurred in the 3rd decade of life, while malignant cases were more common in the third and fourth decades. The mean age of patients in this study (29.8 years) was similar to that reported by Jadhav BJ and Shinde AM (29 years) [10].

Jadhav BJ and Shinde AM reported 11 ovarian germ cell tumours, with 8 patients (72.7%) being parous and three patients (27.3%) being nulliparous [10]. In this study, the majority of tumours occurred in parous women. The most common presenting symptom in this study was abdominal pain with a mass, followed by abdominal pain. Similarly, Jadhav BJ and Shinde AM also observed that pain associated with an abdominal mass (7/11-63.63%) was the most common symptom. Out of 25 ovarian germ cell tumours in this study, 17 women were parous and 8 were nulliparous. Among the parous women, 14 cases were benign and 3 cases were malignant. Among the nulliparous women, 5 cases were benign and 3 cases were malignant [10]. Lim FK et al., reported 13 malignant germ cell tumours of the ovary, with 9 patients being nulliparous and 4 being parous. They also observed that the mean tumour size was 15.69±10.51% [11]. In the present study, the majority (60%) of ovarian germ cell tumours presented on the left side. Two cases of benign mature cystic teratoma were found to be bilateral, and in another case, an immature teratoma was found on the right side while a benign cystic mature teratoma was on the left side. Similar findings were found in a study conducted by Mahalakshmi K (right 60%, left 36.7%, bilateral 3.3%) [12]. Caruso PA et al., reported that 10% of benign cystic teratomas are bilateral [13]. Srikanth S and Anandam G reported a bilateral dermoid cyst of the ovary in 2014, which is similar to the findings of this study [14]. Jha R and Jha S observed an equal number of cases on both the right and left sides, with none of the cases being bilateral [15]. The largest ovarian germ cell tumour encountered in this study was 14×11×5 cm, and the smallest was 2×1×0.5 cm, with tumour sizes ranging from 2 cm to 14 cm. Radiologically, out of 22/25 ovarian germ cell tumours, 14 cases showed cystic lesions, 2 cases showed solid lesions, and 6 cases showed mixed lesions. In this study, Smith HO et al., observed malignant degeneration in mature teratoma, constituting 2.9% [16]. Two cases of benign teratoma with malignant transformation (10%) were observed in the study conducted by Piura B et al., [17], Gupta N et al., did not find any malignant tumours of the ovary and only reported benign cystic teratomas [18].

Immature teratoma: These tumours constitute about 8% (2 cases) of all ovarian germ cell tumours in this study. They presented as Grade-II and Grade-III tumours with a significant increase in serum tumour markers. Grossly, these tumours were both solid and cystic and were also found with a breached capsule [Table/Fig-1b]. Microscopically, they showed primitive neuroepithelium with hyperchromatic nuclei arranged in the form of rosettes and primitive neuroectodermal elements [Table/Fig-3a-c]. Sharma I and Chaliha T reported an incidence of 0.98%, Sarkar R reported an incidence of 1.6%, De Backer A et al., reported six cases (13%), Zynger DL et al., reported four cases in the ovary, Chavan SS and Toppo SM reported four cases (4.34%), Sharma P et al., reported one case (0.77%), Deka M et al., reported one case, and Jha R and Karki S reported two cases among 26 ovarian tumours, which is comparable to the present study [5,19-25].

Dysgerminoma: Kurman RJ and Norris HJ stated that these tumours represent 13.5% of all ovarian germ cell tumours and most commonly occur in the 2nd and 3rd decades with unilateral presentation [26]. According to Freel JH et al., 80-85% of dysgerminomas occur before the age of 30 years, and 40-45% occur before the age of 20 years [27]. Mondal SK et al., reported that dysgerminoma is considered the most common tumour, constituting nearly 50% of all malignant ovarian germ cell tumours [28]. Garshenoson DM et al., observed that the right ovary is more commonly involved in these tumours [29]. Asadourian LA and Tayler HB stated that about 10% of these tumours are bilateral at operation, while Francisco C et al., stated that there is no bilateral involvement based on their 10 years of study involving 343 ovarian tumours [30,31]. Two cases of dysgerminoma were found in this study, representing 8% of all germ cell tumours. Sharma I and Chaliha T reported two cases (6.46%), Chavan SS and Toppo SM reported seven cases (7.6%), Gupta SC et al., reported an incidence of 3.53% [5,22,32]. Francisco C et al., (1993) reported an incidence of 2.9% [31], Sarkar R (1996) reported 5.3%, Deka M et al., reported 6 out of 12 cases, and Schultz KA et al., reported seven cases (7.4%) of dysgerminoma in their study [19,24,33]. Microscopically, these tumours showed large tumour cells with vesicular nuclei and clear cytoplasm arranged in nests separated by fibrous stroma with lymphocytes [Table/Fig-3d].

Yolk Sac tumour: Yolk sac tumour or endodermal sinus tumour is the 2nd most common highly malignant ovarian germ cell neoplasm [26]. It occurs more frequently in childhood and adolescence, with a mean age of 19 years, and is rare in women older than 40 years. Serum AFP levels are almost always elevated, and immunohistochemical markers such as AFP, Glypican-3, and cytokeratin show positivity [34]. One case of yolk sac tumour in this study showed positivity to AFP [Table/Fig-4]. Sharma I and Chaliha T reported an incidence of only 0.98%, Sarkar R reported an incidence of 2.1%, De Backer A et al., reported 3 out of 69 cases, Zynger DL et al., reported four cases, Chavan SS and Toppo SM reported two cases (2.17%), Deka M et al., reported two cases (1.81%), Jha R and Karki S reported 1 out of 26 cases (3.8%), Mondal SK et al., reported 12 out of 170 cases (1.25%), Francisco

C et al., (1993) reported an incidence of 0.29%, Schultz KA et al., reported two cases (3%), Ulbright TM reported an incidence of 1%, which is comparable to this study representing one case with an incidence of 4% [5,19-22,24,25,28,31,33,35]. Microscopically, the yolk sac elements were arranged in a solid pattern that merged with surrounding microcystic areas [Table/Fig-3e].

Embryonal carcinoma: Kurman RJ and Norris HJ in 1978 reported that embryonal carcinoma accounts for 5% of all malignant germ cell tumours of the ovary [26]. Ulbright TM and Benjapibal M et al., studies show an incidence of 0.2% and 2.8% of embryonal carcinoma, respectively [35,36].

Carcinoid tumour: Piura B et al., reported a 5% incidence of carcinoid tumours, which is similar to the current study. Microscopically, they show nests of round to oval tumour cells with clumped chromatin [Table/Fig-3f] [17].

Struma ovarii: Jadhav BJ and Shinde AM observed 1 out of 11 cases (9.09%), and Piura B et al., reported a 5% incidence of struma ovarii in their study [10,17].

Mixed germ cell tumours of ovary: In this study, no mixed germ cell tumours of the ovary were observed.

Limitation(s)

Firstly the smaller sample size, with only 25 cases were included in this study. Additionally, the study period was short, which may limit the generalizability of the findings to other populations. The conclusions drawn from the results can only be tentative and may only apply to the specific location where the study was conducted. Thirdly, all cases had pre-operative evaluation of all serum tumour markers, and only specific immunohistochemical markers were used. This may have limited the comprehensive assessment of tumour markers and potentially affected the accuracy of diagnosis. And lastly, this study lacks available data on post-treatment follow-up and information on the history of recurrences. This limits the understanding of long-term outcomes and the potential for assessing the effectiveness of treatment in these cases.

CONCLUSION(S)

This study carefully analysed ovarian germ cell tumours in terms of their incidence, parity, clinico-radiological presentation, association with elevated serum tumour markers, histopathological findings, and immunohistochemical staining. These tumours primarily affect the reproductive age group, posing a challenge in preserving fertility while ensuring patient cure. The study also identified various histomorphological findings from all three germ cell layers and their malignant counterparts. Histopathological examination and the use of immunohistochemical markers such as α-fetoprotein and CD30 played an essential role in confirming the diagnosis of these tumours.

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