OVARIAN MALIGNANCIES IN CHILDREN:A FIVE YEAR REVIEW

DISSERTATION

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CERTIFICATE

Certified that this dissertation titled "**OVARIAN MALIGNANCIES IN CHILDREN:A FIVE YEAR REVIEW**",is the original work done by **Dr.K.SHUBHA**, under our guidance in the Department of Paediatric Surgery, Institute of Child Health and Hospital for Children, Madras Medical College, during the period of her post graduation in M.Ch. Paediatric Surgery from 2004 to 2007.

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TABLE OF CONTENTS

INTRODUCTION

Ovarian tumors are rare accounting for 1% of childhood malignancies. Unlike adult tumors, two thirds of the pediatric ovarian malignancies are of germ cell origin. Tumors of epithelial and stromal origin occur less frequently. As with testicular tumors, the incidence of germ cell ovarian tumors parallel gonadotrophin release implicating hormonal factors in the aetiology.

The prognosis and the treatment strategies for malignant pediatric tumors have also changed drastically over the last few years. The outlook was dismal in the pre-chemotherapy era. But with the advent of platinum based chemotherapy in the 1980s, the prognosis for these tumors has altered dramatically. It has also facilitated the re-definition of risk groups. Since then, chemotherapy regimes have been sequentially modified to reduce the toxicity while maintaining survival rates.

Surgical approach has also evolved to a more tailored approach.

As we move into the future, with higher success rates in the overall survival, the highlight is now on reducing the toxicity of the chemotherapy regimes. Ongoing studies are now evaluating conservative surgeries in the hope of reducing the overall morbidity. An attempt is being made to redefine surgical principles in the hope of improving the quality of life without compromising the overall survival.

With more survivors of childhood cancer, interest is now being focused on the delayed effects on treatment and its impact on potential fertility patterns. More stress

is now being laid on maintaining the reproductive abilities of these patients and a number of studies are ongoing in this direction.

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AIMS & OBJECTIVES

- To review the presentation, treatment and histology of ovarian tumors in children.
- To note the accuracy of diagnostic imaging and operative staging .
- To calculate the survival rates.
- To assess the effect of chemotherapy on the attainment of menarche in those surviving in the peripubertal age group.

REVIEW OF LITERATURE

Gynecological lesions account for 2% of childhood cancers[23]. Of these, 60% - 70% arise in the ovary. The concept that the incidence of malignancy was higher in the young has now been revisited. In a 43 year review, Gibbon et al[13] noted that malignant ovarian tumors were more frequent in the second decade.

The North American Cancer Registries report released in 1993 revealed that 1.2% of ovarian cancers occurred between birth and 9 years.[33]

Due to this rarity of ovarian tumors in children, earlier approaches to management were based on the guidelines from review of adult literature. But, with widening of our knowledge of cancer biology, realization has now dawned that children are not just 'miniature' adults. The juvenile forms of the disease represent distinct entities, which often present at a less advanced stage and have a more favorable natural history and response to therapy.

W.H.O. CLASSIFICATION OF OVARIAN TUMORS

1. **Surface epithelial stromal tumors**

   1.1. Serous tumors

   1.2. Mucinous tumors

   1.3. Endometroid tumors

   1.4. Clear cell tumors

   1.5. Transitional cell tumors

   1.6. Squamous cell tumors

   1.7. Mixed epithelial tumors

   1.8. Undifferentiated and unclassified tumors

2. Sex cord-stromal tumors

   2.1. Granulosa – stromal cell tumors

      2.1.1 Granulosa cell tumor group

         2.1.1.1. Adult

         2.1.1.2. Juvenile

      2.1.2. Tumors in the thecoma – fibroma group

   2.2. Sertoli-stromal cell tumors

2.3. Sex cord – stromal tumors (mixed or unclassified)

2.3.1. Sex cord tumors with annular tubules

2.3.2. Gynandroblastoma

2.4. Steroid cell tumors

3. Germ cell tumors

3.1. Primitive germ cell tumors

3.1.1. Dysgerminoma

3.1.2. Yolk sac (endodermal sinus) tumor

3.1.3. Embryonal carcinoma

3.1.4. Polyembryoma

3.1.5. Non gestational choriocarcinoma

3.1.6. Mixed germ cell tumors

3.2. Biphasic or triphasic teratomas

3.2.1. Immature

3.2.2. Mature

3.3 Monodermal teratomas

4. **Germ cell sex-cord-stromal tumors**

4.1. Gonadoblastoma

4.2. Mixed germ cell sex-cord stromal tumor (non gonadobastoma origin)

5**. Tumors of rete ovarii**

6**. Miscellaneous tumors**

6.1. Small cell carcinomas, hypercalcemic type

6.2. Gestational choriocarcinomas

6.3. Soft tissue tumors non specific to the ovary

7. **Tumor like conditions**

8. **Lymphoid and haemopoietic tumors**

9. **Secondary tumors**

GERM CELL TUMORS

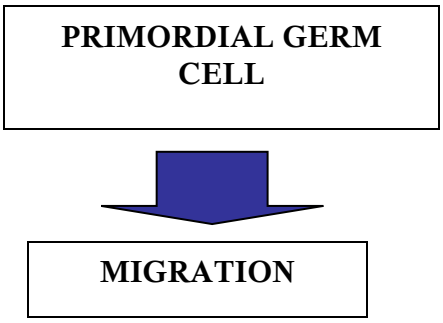
EMBRYOGENESIS & HISTOGENESIS

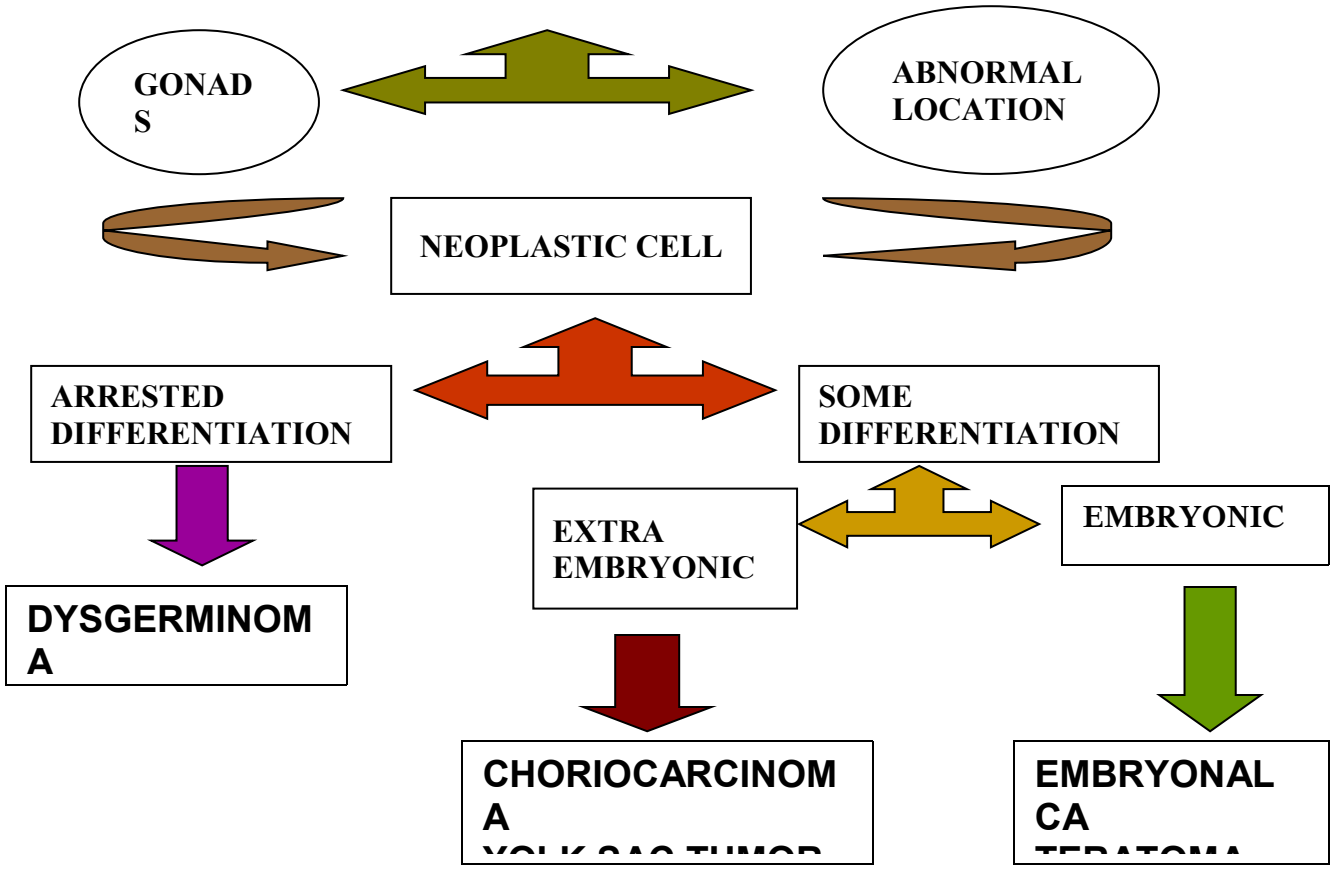
Germ cell tumors share a common cell of origin-the primordial germ cell, yet they remain a heterogeneous group with variations in age, site of presentation and histopathology. This stems from the differences in the stage of germ cell development at tumorigenesis.

Primordial germ cells are first evident in the extra-embryonic yolk sac by the IVth week of gestation. These migrate through the mesentry to the gonadal ridge, a process that is mediated by the c-kit receptor and its ligand, the stem cell factor.

The current model for germ cell development resulted from the work of Dixon and Moore (1952), Teilum(1976)and Mostofi (1973).These totipotent germ cells can travel down normal differentiation pathways and become oocytes. However, if these germ cells travel down abnormal pathways, dysgerminomas or embryonal carcinomas (totipotent tumor cells) can occur. If the embryonal cells undergo further differentiation

along intraembryonic pathways, teratomas result. Extraembryonic differentiation results in a yolk sac tumor or a choriocarcinoma. This model explains the tumor markers produced by certain tumor types. Endodermal sinus tumors produce alpha fetoprotein just like the fetal yolk sac. Likewise, choriocarcinoma produces human chorionic gonadotrophin just like the normal placenta.





TUMORIGENIC MODEL FOR GERM CELL TUMORS

GERM CELL TUMORS

Germ cell tumors are probably the most varied of all pediatric malignancies. They account for 3% of childhood cancers[12].They show a bimodal distribution in infancy and during adolescence. As they arise from a common totipotent

progenitor, it is possible to have a wide variety of histologies co-existing within the same tumor.25% have multiple histologic components[12].Co-existing elements of benign teratoma are particularly common in the mediastinal and ovarian locations[4].

The classification of immature teratomas as benign or malignant still remains a matter of debate. These tumors are graded by the neuroepithelial elements that they contain. There is always the remote possibility of missing malignant elements in large tumors. A review of the pathology of immature teratomas between 1990 to 1995 by the Pediatric Oncology Group and the Children's Cancer Study Group documented increased risk of high grade immaturity with the presence of microscopic foci of endodermal sinus tumor. This was noted in as many as 83% of the specimens and was the only important risk factor for recurrence in immature teratomas at all sites and ages[15].Thus, high grade immature teratomas are often included in the malignant germ cell category and treated with chemotherapy[2].

CLINICAL FEATURES:

Clinical presentations do not differentiate between benign and malignant tumors. Abdominal pain is the most frequent symptom[7]. It may be acute with a crescendo pattern as in torsion. Such situations commonly lead to the mistaken pre-operative diagnosis of appendicitis in a right sided lesion. Some have a more insidious onset of pain with distension developing over time. Other symptoms include nonspecific

anorexia, nausea, vomiting or urinary frequency and urgency if compression of the pelvic organs occur.

Endocrine activity is seen in 10% of cases[17] and may cause precocious puberty. This is due to the production of HCG, most commonly associated in patients with dysgerminomas, endodermal sinus tumors and choriocarcinomas, though more frequently in sex cord tumors.

Virilisation due to androgen excess occurs in endodermal sinus tumors, Sertoli-Leydig cell tumors and dysgerminomas in older children .

CLINICAL FEATURES OF PAEDIATRIC OVARIAN TUMORS

TUMOR TYPE	MEDIAN AGE	RELATIVE FREQUENCY	FEATURES
Dysgerminoma	16yrs.	24%	Rapidly developing, 14-25% with other germ cell elements. Extremely radiosensitive.
Teratoma	11-14 yrs.	10-30%	Grading system based on amountof neuroepithelial elements,prognosis

			varies inversely with stage and grade, 30% have raised AFP
Mixed malignant germ cell tumors	16 yrs	11%	40% premenarchal, 30% sexually precocious,AFP and HCG may be raised.
Gonadoblastoma	8-10 yrs	1%	Associated with dysgenetic gonads and gonadal maldevelopment. Removal of both gonads is treatment of choice.
Others: choriocarcinoma, polyembryoma	NA	<1%	Rare in children

BILATERAL TUMORS:

Bilateral tumors were seen in 8% of girls in the POG/CSG series[34].Most of them were benign teratomas. For girls with bilateral tumors, careful evaluation of both the ovaries should be done to identify the possibility of organ sparing surgery on the

lesser involved side. Benign teratomas mostly show a well demarcated plane of separation from the normal parenchyma of the ovary. This makes enucleation without violation of the tumor capsule possible in such situations.

TUMOR MARKERS:

Germ cell tumors are associated with various biological markers[24].They are useful in the identification and management of these tumors. Of these, αFP and βHCG are most readily measured.

αFP is an α1 globulin, which is the predominant serum binding protein in the fetus. It is produced by the fetal liver, gastrointestinal tract and yolk sac. Peak concentrations are demonstrated at 12-14 wks of gestation. The levels fall progressively after birth to plateau at the normal level of 10 ng/dl. at one year of age. The half life is 5-7 days. Raised levels are seen in endodermal sinus tumors or embryonal carcinomas. Following successful removal of the tumour, progressive fall in levels occur. But, abrupt escalation can occur in chemotherapy induced tumor lysis. Abnormal levels are also seen in pancreatic, lung, liver and gastrointestinal malignancies as also in benign conditions causing altered liver function like hepatitis or cholestasis secondary to exposure to general anaesthesia,phenytoin or methotrexate. In such situations, measurement of the ratio of concavalin αFP binding to the unbound fraction helps to detect if the source is from the tumor cells.

βHCG is a glycoprotein produced by the placental syncitiotrophoblasts. It

has a short half life of 20-30 hrs. So it disappears rapidly following disappearance of tumor. <5mIU/ml. can be detected in the serum of healthy individuals. Raised levels are noted in choriocarcinomas or clones of syncitial trophoblastic giant cells seen in germinomas and adult embryonal carcinomas. Post chemotherapy lysis, iatrogenic hypogonadism due to raised levels of leutinising hormone that causes cross-reactivity, multiple myeloma and cancers of the liver, breast, lung and bladder also cause rise in titres.

LDH is a glycolytic enzyme used in assay of germ cell tumors. It is, however, hampered by the lack of specificity for any histological subtype. Increased levels are noted in dysgerminomas.

CA125 related to the tissues of the coelomic epithelium and Mullerian ducts is of value in ovarian tumors of epithelial and stromal origin.[18]

Since germinomas and embryonal carcinomas have no reliable serum markers and 20% of ovarian masses are malignant, the current recommendation is to approach all ovarian neoplastic masses in girls as if it were malignant.

PATTERN OF TUMOR MARKERS IN OVARIAN MALIGNANCIES

HISTOLOGICAL SUBTYPE	CA125	AFP	β-HCG	LDH
EPITHELIAL				
Borderline	+			
Carcinoma	+			
GERM CELL				
Dysgerminoma			+	+
Yolk sac		+	+	
Immature teratoma				
Choriocarcinoma			+	
Embryonal		+	+	
Sertoli Leydig cell gp		+		

IMAGING:

USG is the initial modality of choice in the evaluation of potential ovarian pathology in all age groups. Though accuracy in differentiating between benign and malignant lesions has not yet been established, fairly reliable sonographic characteristics are present which point to a malignant process.

Highly echoic solid components without demonstrable or measurable inner wall[28] and the presence of papillae[3] are strongly suggestive of malignancy.

CT &MRI are useful when the origin of the pelvic mass cannot be assessed by ultrasound[18]. Focal solid components with occasional cystic areas and coarse

calcifications are markers for caution. Direct extension into other pelvic structures or distant sites like the liver or lung can also be assessed by CT. MRI is also well suited for pelvic lesions owing to its superior tissue contrast resolution.[14]

FIGO STAGING OF OVARIAN TUMORS:

STAGE	EXTENT OF DISEASE
0	No evidence of primary tumor
I **IA**	Tumor confined to ovaries Tumor limited to one ovary, capsule intact. No tumor on ovarian surface. No malignant cells in ascites or peritoneal washings.
IB	Tumor limited to both ovaries, capsule intact. No tumor on ovarian surface. No malignant cells in ascitic or peritoneal washings
IC	Tumor limited to one or both ovaries, with any of the following: Capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings.

II	Tumor involves one or both ovaries with pelvic extension
IIA	Extension to or implants on the uterus or tubes or both. No malignant cells in ascites or peritoneal washings.
IIB	Extension to other pelvic organs. No malignant cells on ascites or peritoneal washings
IIC	IIA or IIB with positive malignant cells in acsites or peritoneal washings.
III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis or regional lymph node metastasis.
IIIA	Microscopic peritoneal metastasis beyond the pelvis.
IIIB	Macroscopic peritoneal metastasis beyond the pelvis 2cm. or less in greatest dimension.
IIIC	Peritoneal metastasis beyond the pelvis more than 2cm. in greatest dimension or regional lymph node metastasis
IV	Distant metastasis beyond the peritoneal cavity.

CHILDREN'S ONCOLOGY GROUP STAGING OF

OVARIAN GERM CELL TUMORS

STAGE	EXTENT OF DISEASE
I	Limited to ovary or ovaries, peritoneal washings negative for malignant cells No clinical, radiologic or histologic evidence of disease beyond the ovaries Tumor markers normal after appropriate post surgical half life decline Presence of gliomatosis peritonei does not upstage the tumor
II	Microscopic residual or positive lymph nodes(<2cm as measured by the pathologist) Peritoneal washings negative Tumor markers positive or negative Gliomatosis peritonei upstages the tumor
III	Lymph node with malignant metastatic nodule(>2cm as measured by the pathologist) Gross residual or biopsy only Contiguousvisceral

	involvement(omentum,intestine,bladder) Peritoneal washings positive for malignant cells Tumor markers positive or negative
IV	Distant metastasis,including liver

TREATMENT:

SURGERY:

Surgery is the mainstay of successful treatment. It involves complete tumor removal with conservation of pelvic structures. Revised surgical procedural guidelines as published by the Intergroup Study in 2004[4] include:

- Collection of ascitic fluid or washings (in the absence of ascites) on entering the peritoneal cavity.
- Examination of the peritoneal surface with biopsy or excision of any nodules.
- Examination and palpation of lymph nodes in the retroperitoneum (iliac and aorto-caval) with sampling of any firm or enlarged nodes.
- Inspection and palpation of the omentum with removal, if any, of adherent or abnormal areas noted.
- Inspection and palpation of the contralateral ovary with biopsy of any suspicious areas.

- Complete removal of the tumor bearing ovary, without violation of the tumor capsule in situ.
- Sparing the Fallopian tube if it is not adherent.

For tumors that are apparently invading neighbouring structures, initial biopsy only is recommended. PEB chemotherapy is highly effective in that it allows for tumor shrinkage. This opens up the possibility of fertility sparing post chemotherapy resection.

LAPAROSCOPY IN TUMOR RESECTION:

A word of caution in the use of laparoscopy[4] in ovarian malignancies is prudent. Key components in staging like ascitic cytology, inspection of the pelvic peritoneum, diaphragmatic surfaces and omentum is possible. But palpation of retroperitoneal nodes and intact delivery of the specimen, which are equally critical, prove difficult.

CHEMOTHERAPY :

On the basis of testicular cancer experiences of Einhorn and Donahue, cisplatin, bleomycin and vinblastine were made available for germ cell tumors in 1980.Advantages appeared to be the increased efficacy of cisplatin. The regime also required a shorter course than the standard two year schedule of vincristine,

cyclophosphamide and actinomycin–D. However, increased myelosuppression and peripheral neuropathy occurred due to the combination of cisplatin and vinblastine. There was also a 2% risk of bleomycin induced pulmonary fibrosis.

During the same year that the report was published, etoposide was introduced. By eliminating vinblastine and decreasing the total cumulative dose of bleomycin, PEB regime thus had the advantage of improving survival with an overall reduction in toxicity.

An eight year study from the COG that closed in 1992 evaluated PEB[31]. 91 of 93 patients were free of disease after a mean follow up of 38.6 months. Moreover, the risk of chemotherapy induced complications is low vis a vis the efficacy of platinum based regimes[32].

Currently ongoing phase III COG trials[5] initiated in November 2003 classifies germ cell tumors into 3 risk groups based on the nature of the primary and the stage. Low risk stage I ovarian tumors appear to do well with complete resection alone. Intermediate risk groups included stage II and III, who showed a 90% 3 year survival, are now being treated with modified shortened PEB regimes of 3 cycles every 21 days. Therapy is discontinued upon complete pathologic response and normal tumor marker values. High risk and recurrent tumors are being bombarded with high dose chemotherapy with autologous stem cell transplantation.

UNCLASSIFIED MALIGNANCIES:

These are a heterogenous group[26] with uniformly poor survival. Though predominantly in older age groups, reports of rhabdomyosarcomas in children <20 years have been published. Outcome is poor owing to the advanced stage at diagnosis.

Stromal and low grade endometrial sarcomas of the ovary arising from foci of ovarian endometriosis, albeit rare, have been reported in the second decade. Treatment of these advanced locally infiltrating tumors is radical with total abdominal hysterectomy with bilateral salpingo-oophorectomy followed by chemotherapy and radiation.

METASTATIC TUMORS:

Though rare, ovaries may be the site of metastasis[26] either by haematogenous, lymphatic, transcoelomic or direct spread. Just like the testis, it may harbour leukaemic deposits. Others include primaries from the stomach, colorectum, breast and rarely Wilms' or deposits from neuroblastomas.

IMPACT OF TREATMENT ON OVARIAN FUNCTION:

Survival rates of prepubertal gynaecological cancers are constantly improving. The other side of the coin, nevertheless, is that these life saving treatment schedules may carry the risk of infertility. Though chemotherapy may cause oocyte and follicular loss[25] and induce premature ovarian failure, most studies have shown normal reproductive potential in the long run[16,35]. Reports between the two schools

are controversial. In a study of patients who underwent fertility preserving surgery, Holzer[16] et al. who followed these women over 20 years showed that 23 of the 26 patients never conceived; indicating that fertility was seriously affected. However, Zonagnola's [35]paper showed quite the opposite with females maintaining normal ovarian function and reproductive potential after chemotherapy.Animal models have shown that although there are decreased estrogen levels, reduced litter sizes and earlier menopause, there is adequate compensation by the contralateral ovary.Thus fertility rates appear to be the same as age matched controls.

FUTURE TRENDS:

Further definition of biologic features is required to help select those patients who may not respond to first line chemotherapeutic regimes. Differentiating characteristics of adult and pediatric tumors that predict response to standard therapy is also needed. This also involves further insights into the genetics of these tumors.

Although there may exist unknown repair mechanisms after anticancer treatment, biological ovarian age in cancer survivors appears 10 years ahead of chronological age[22]. Hence attempts at oocyte or embryo cryopreservation[16] or vitrification are under trial. This is particularly indicated in cancers where treatment cannot be delayed for ovarian stimulation or the tumors which are hormone sensitive. Until now, by these, only one human birth has been reported. More importantly, critical issues like graft survival or the potential risk of transmission of malignant cells have to be addressed.

MATERIALS AND METHODS

A retrospective review of all ovarian malignancies treated at the Institute of Child Health between January 2001 and January 2006 was done.

48 patients with ovarian malignancies were identified. Defective case records of 5 patients owing to lack of essential data were excluded from the study. A structured proforma was prepared(vide infra).

The age at presentation, symptoms and nature of presentation were noted. The efficacy of imaging in pointing at the malignant nature of the lesion was also assessed. The tumor marker elevations vis-à-vis the histopathology was correlated.

Intraoperative features of the tumor, capsular integrity and associated anomalies were recorded. Pathological reports on gross and microscopic features of the tumor were compared with the intraoperative findings.

All patients received chemotherapy with a platinum based regime.The schedule followed at our Institute was

Bleomycin 15 units /sq.m. weekly for 5 weeks

Etoposide 100 mg/sq.m./day X 3 days

Cisplatin 20 mg/sq.m./day X 3 days

The latter two being administered once in 21 days for 4 cycles.

Postoperatively and thereafter periodic tumor marker estimation with imaging was

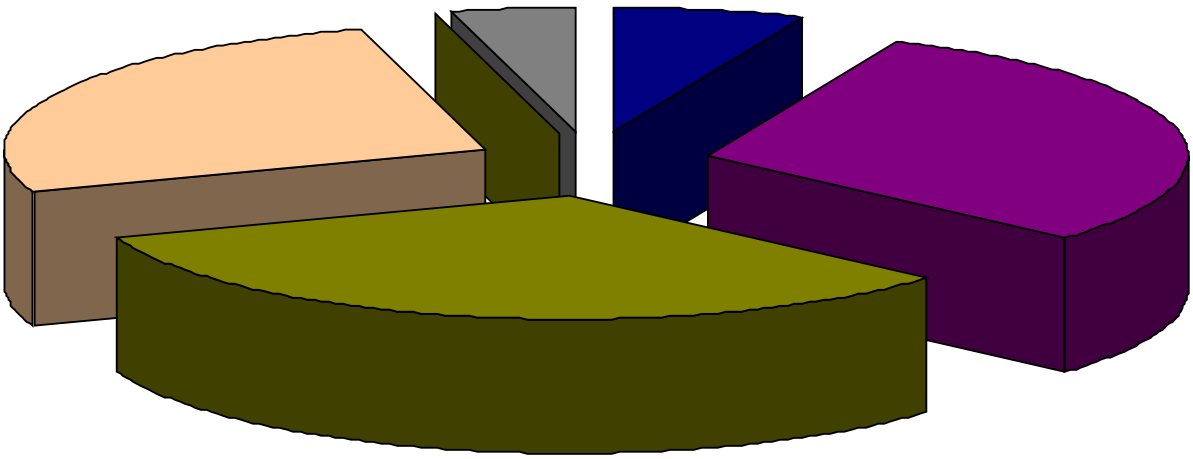
carried out.

Gonadal functions of these patients were evaluated during their visits to the tumor board review meets.At these visits,history and clinical examination regarding the age at menarche, adequacy of secondary sexual characters and nature of menstrual cycles were noted.Hormonal estimation,if indicated,was done.

Fertility could not be assessed as these children had not yet reached the age at which the full impact of the treatment could be checked.

Figure1: AGE DISTRIBUTION OF OVARIAN MALIGNANCIES

Figure 2: DISTRIBUTION OF SYMPTOMS



Acute abdomen
Pain abomen
Mass abdomen
Loss of weight/appetite
Precocious puberty

Figure 3: TUMOR HISTOLOGY

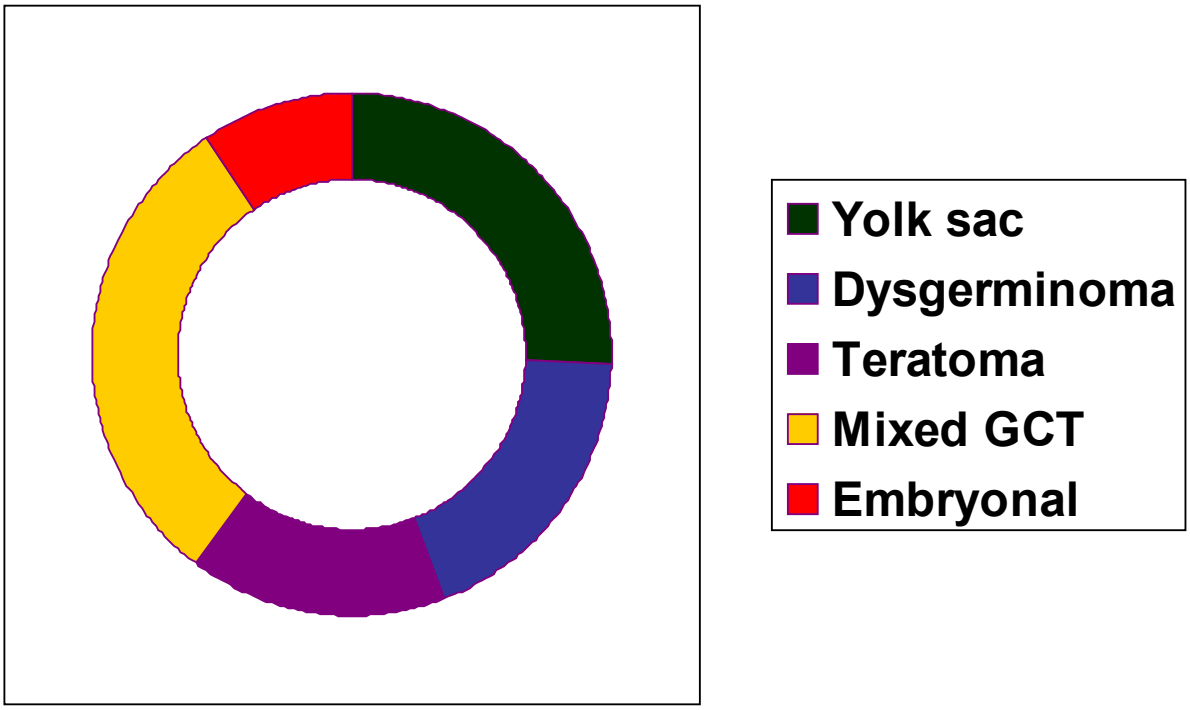
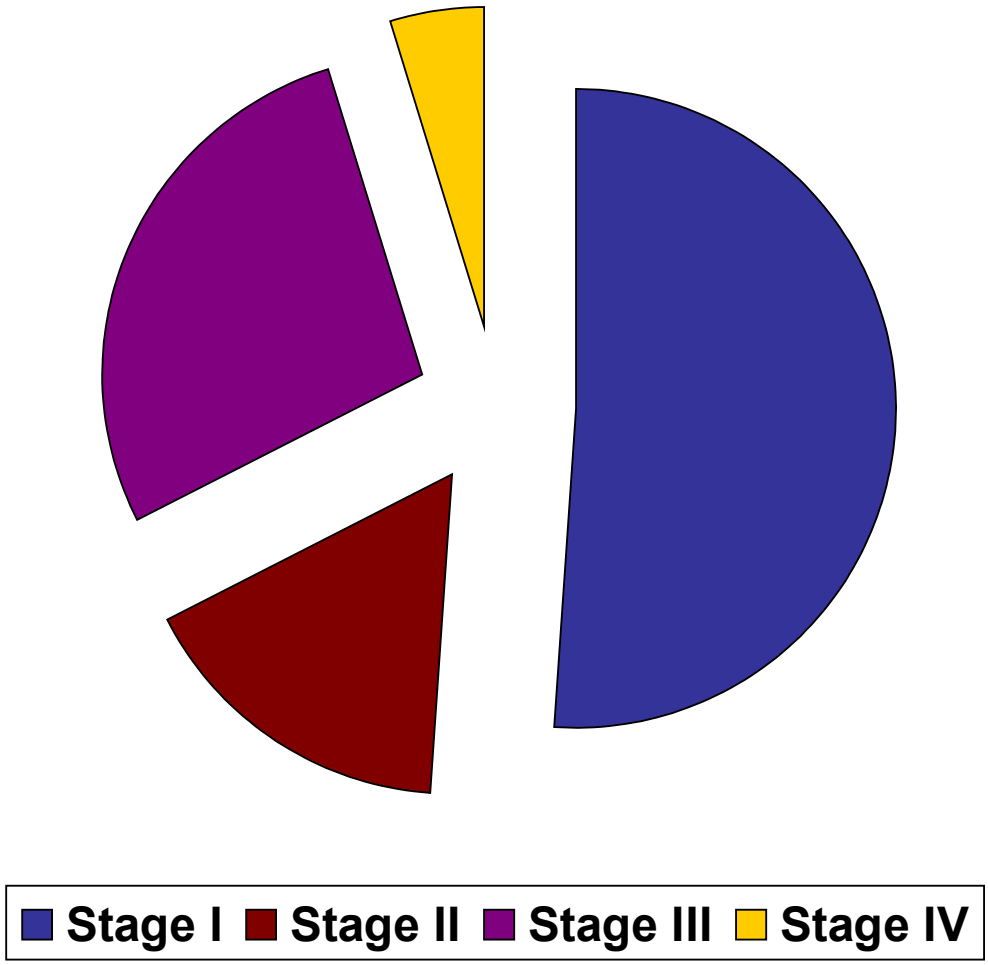


Figure 4:STAGE DISTRIBUTION



RESULTS

Of the total no. of ovarian tumors, 62.79% presented between 9 and 11 years confirming that these malignancies are more common in adolescent girls.

13.9% of the total presented with acute abdominal symptoms. In this setting, the pre operative diagnosis was often confused with peritonitis or appendicular pathology. Yet others had mass abdomen and insidious pain as the predominant complaints.This was similar to other reports in literature[7].All the 4 patients who presented with precocious puberty had embryonal carcinoma.

Ultrasonogram had a sensitivity of 83% and a specificity of 84% in pointing at a potential malignancy in our study.This corroborates with Tuladhar et al[28]. who reported a sensitivity of 85.7% and specificity of 83.8% of ultrasound as the initial imaging modality in ovarian malignancy.Of all the parameters, we found that the size of the lesion was an important parameter; the larger the dimension, the higher the possibility of malignancy. A similar finding was stated by Darrell et al[8]. that >10 cm. lesions were more likely to be malignant.

Pre-operative evaluation of the tumor markers were done for all cases in

the elective setting. The pattern of rise conformed to that found in literature.

Epithelial malignancies in reviews have accounted for < 15% of pediatric ovarian malignancies[8].Our series had none.

The most common histology was mixed tumors with teratoma elements in contrast to literature which states dysgerminoma to be the most frequent[20].

Bilateral tumors were seen in 8% of girls in the POG series[34].Our study had none.

The presentation of 13.9% in the acute setting (11% in the Intergroup Study)[4] produces the need for emergency operative intervention.This carries the problems of the lack of complete imaging information and the disadvantage of the unavailability of tumor markers. In such situations, as there are no clear cut gross characteristics to detect malignancy, ovarian lesions should be treated as potentially malignant, until proved otherwise[4].This avoids the loss of valuable information which affects staging and thereby, treatment if inadequate surgical staging measures are undertaken during exploration.

Tumor sizes ranged between 3 and 17 cms. The recommended surgical guidelines were not followed completely in all cases. The greatest deficit was the lack of appropriate lymph node sampling. Only 9% of them were sampled, all being negative for malignancy.

Preoperative rupture of the tumor capsule or accidental disruption during operative manipulation occurred in 3 patients. Surprisingly, this did not affect long term

survival.

Samples of ascitic fluid and peritoneal washings were obtained in 38 patients.Of these 31.5% were positive for malignancy.

Omentectomy was done in 36 patients. Histology perusal revealed that 30.25% showed malignant infiltration. The others were normal except one which showed an inflammatory pathology.

Though the contralateral ovary was examined in all cases, it was biopsied in only 2. Both were negative for malignant deposits. Some of the co-existent abnormalities noted were agenesis of the opposite ovary and a follicular cyst which regressed during the follow up period.

The surgeon's assessment of capsular integrity was not found to be reliable. This reaffirms Billimire et al[4] viewpoint that the pathologist has to examine the intact specimen to ensure that staging is not compromised.

2 large tumors which were adherent to the surrounding structures caused surgical difficulty. There was no evidence of local invasion to the neigbouring viscera. These tumors were resected primarily. There was greater blood loss and the duration of surgery was prolonged. However, they could be removed in toto without resecting any vital organ. 1 of these girls subsequently presented with adhesive bowel obstruction, necessitating resection anastomosis.

Stage grouping was done from the available information. The distribution of the various stages was as follows:

Stage I - 51.16%, Stage II – 16.27%, Stage III – 27.9%, Stage IV – 4.65%.

Based on the success of surgery alone in stage I testicular tumors in boys and the European experience with surgery only for stage I ovarian tumors, COG is presently evaluating the same. In our study, we administered chemotherapy for all stages. The schedule followed was the PEB regime. It resulted in a complication rate of 13.95% vis a vis that of 20%[10] in literature. The most recent intergroup trial for high risk malignant germ cell tumors in children from POG and CCG, 2% died of toxicity from therapy[6].Our series had none. However, morbidity in the form of liver cell and renal failure was noticed in our patients.

Of the 43 patients enrolled in our study, 4 have lost follow up. 2 have since succumbed to the disease. 9 girls have finished 5 years since the completion of treatment.The 5 year survival rate was 81.8% (all stages included).The maximum survivors were in stage I and stage II .Stage IV carried a dismal prognosis with no patient completing 5 year follow up. Reviews quote a 95% survival for stage I and 93.3% for stage IV.[4] Effective multiagent chemotherapy is probably the reason for these excellent survival rates.

Some studies however quote a lower survival of 54.8% for stage IV.[27] In our study, both the patients in stage IV presented with advanced disease with distant metastasis. Moreover,one patient was noncompliant with the chemotherapy schedule. Those with advanced disease and noncompliant with the treatment regime are at increased risk of treatment failure and death, thus stressing the need for patient

education.

Of those patients followed up after completion of treatment, 10 girls have since entered the peripubertal age.1 had a documented agenesis of the contralateral ovary at the time of surgery. All the others except one patient have attained menarche. This correlated with Noczynska's[21]etal observation. They stated that pubertal development and onset is normal despite unilateral ovariectomy. The mean age at menarche was 12.8 years. The menstrual cycles are regular and there has been an adequate development of secondary sexual characters. The lone patient who has not yet attained menarche underwent hormonal estimation which was normal. She is now undergoing gynecological evaluation for the same.

All these patients have not yet reached the age when impact on reproductive potential can be studied. Nevertheless, despite series quoting normal fertility patterns, we offer a guarded prognosis and a word of caution.

CONCLUSIONS

Review of ovarian tumors at our institute showed that germ cell tumors are highly treatable solid malignancies in the prepubertal age group.

- Most of these tumors present early making local control easy. This is further boosted by effective platinum based chemotherapy.
- As seen in our study,epithelial ovarian malignancies are rare in children.
- Ultrasonogram has a fairly good degree of reliability as an indicator of potentially malignant lesions. Nevertheless, it should be used only as an adjunct and not as the primary modality for diagnosis.
- In the acute setting, to prevent loss of significant information which might affect staging and treatment, it is better to treat all suspicious lesions as potentially malignant, until proved otherwise.
- The onset of puberty following chemotherapy is comparable with that of age matched controls.
- With the advent of newer agents and less toxic regimes, further trials are required to assess their impact on fertility. Their effects on the reproductive potential is a critical issue that needs to be addressed in the long run. Till such time that more

light is thrown on this ,caution has to be exercised.

- To quote Larsen et al[19].," though there may exist unknown repair mechanisms after anticancer treatment, the biological age of the ovaries is 10 years ahead of the chronological age." This important factor is to be stressed in the counseling of these patients.

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PROFORMA

NAME: **AGE:** **I.P.NO.**

Date of admission:

Date of surgery:

Date of discharge:

Informant: Reliability:

PRESENTING COMPLAINTS:

Presentation: Acute –

Chronic-

Symptoms & duration:

Pain abdomen

Abdominal distension

Mass abdomen

Loss of appetite

Loss of weight

Urinary symptoms:

S/O precocious puberty: bleeding per vaginum

breast development

Pubic/axillary hair growth

Other symptoms

FAMILY HISTORY: H/o malignancy

EXAMINATION:

Pallor

Adenopathy

Breast bud development

Axillary pubic hair distribution

P/A: Palpable mass (associated details)

Associated organomegaly

P/R:

INVESTIGATIONS:

Tumor markers: αFP

βHCG

USG abdomen: Size

Solid/cystic

Presence of papillae

Other features

CT scan:

CXR

OPERATIVE DETAILS:

Preoperative diagnosis:

Tumor characteristics: Torsion

Size

Capsular integrity

Intra operative spill

Fallopian tube involvement

Other features: Ascites/peritoneal washings

Omentectomy

Retroperitoneal lymph node sampling

Liver metastasis

Peritoneal and diaphragmatic surfaces

Contralateral ovary

Any other anomalies

PATHOLOGY:

Gross: Tumor size / weight

Histopathology: Tumor type/capsule integrity

Nodal status

Omental histology

Ascitic fluid cytology

POST OPERATIVE COMPLICATIONS:

Surgical:

Chemotherapy related:

STAGING :

FOLLOW UP:

Age at menarche

Nature of the menstrual cycles: Duration

Periodicity

Nature of flow

Breast development

Axillary & pubic hair development

Status of the contralateral ovary on imaging

Tumor markers(if elevated pre operatively)

Hormonal estimation (if done)

DURATION OF FOLLOW UP:

Table 1: Age distribution of ovarian malignancies

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AGE	NO.OF PATIENTS	PERCENTAGE
<5 YEARS	05	11.62
5-8 YEARS	07	16.27
9-11 YEARS	27	62.79
>12 YEARS	04	9.30

Table 2: Symptoms at presentation

SYMPTOM	NO.OF PATIENTS	PERCENTAGE
Acute abdomen	06	13.91
Mass abdomen	29	67.44
Pain abdomen	31	72.09
Loss of weight/appetite	25	58.13
Precocious puberty	04	9.30

Table 3: Tumor marker estimation

HISTOLOGY	αFP	βHCG
Dysgerminoma	_	_
Teratoma	+/-	_
Yolk sac tumor	+	_
Mixed germ cell	+/-	_
Embryonal	_	+

Table 4: Intra operative staging

PROCEDURE	NO.OF PATIENTS	PERCENTAGE
Retroperitoneal lymph node sampling	04	9.30
Biopsy of the opposite ovary	02	4.65
Ascitic/peritoneal washings	38	88.31
Omentectomy	36	83.7
Adhesions to surrounding structures	02	4.65

Table 5: Staging of ovarian tumors

STAGE	NO.OF PATIENTS	PERCENTAGE
I	22	51.16
II	07	16.27
III	12	27.9
IV	02	4.65

Table 6: Histology of ovarian tumors

HISTOLOGY	NO. OF PATIENTS	PERCENTAGE
Yolk sac tumor	11	25.58
Dysgerminoma	08	18.60
Teratoma	07	16.27
Mixed germ cell tumor	13	30.23
Embryonal	04	9.30

Table 7: Complications

COMPLICATION	NO. OF PATIENTS	PERCENTAGE
Febrile neutropenia	03	6.97
Jaundice	02	4.65
Renal failure	01	2.32
Adhesive obstruction	01	2.32

Table 8: Period of follow up and survival

STAGE I

NO.OF YEARS	NO.OF PATIENTS	PERCENTAGE
5 YEARS	04 (n=6)	66.66
4 YEARS	02 (n=2)	100
3 YEARS	02 (n=2)	100
2 YEARS	03 (n=3)	100
1 YEAR	02 (n=2)	100

STAGE II

NO.OF YEARS	NO.OF PATIENTS	PERCENTAGE
5 YEARS	05 (n=5)	100
4 YEARS	04 (n=6)	66.66
3 YEARS	04 (n=4)	100
2 YEARS	03 (n=3)	100
1 YEAR	01 (n=1)	100

STAGE III

NO.OF YEARS	NO.OF PATIENTS	PERCENTAGE
5 YEARS	NIL	NIL
4 YEARS	03 (n=4)	75
3 YEARS	01 (n=2)	50
2 YEARS	03 (n=3)	100
1 YEAR	02 (n=2)	100

NOTE: ***No survivors in stage IV.***

4 patients have lost follow up

2 have succumbed to the disease