Global Journal of Medicine & Public Health

The Insight to the Fertility of the Patients Presenting with Malignant Ovarian Germ Cell Neoplasias with Respect to Its Diagnosis & Management - A Study Conducted in a Tertiary Care Hospital

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ABSTRACT

Background

The ovarian germ cell tumours account for 2.6% of all ovarian malignancies and usually occur in the first two decades of life. Arising from epithelium, the stroma & the follicular component of the ovary, they are gonadoblastoma, mature teratoma, dysgerminoma, yolk sac tumour, embryonal carcinoma, immature teratoma & chorio-carcinoma.

Method

A retrospective observational study was conducted in IPGMER & SSKM Hospital over a period of three years (2020-2023) at the Gynaecology & Obstetrics department along with the radiology & pathology department. The study aimed to elucidate the fertility stature of the patients who presented with these tumours & were subjected to the treatment involving cross- sectional imaging combined with the histopathological diagnosis & the surgeries performed thereafter.

Result

In our study, apart from the regular MOGCT (malignant ovarian germ cell tumours), NET (neuroectodermal tumors) was found in nearly 25% of the study population, along with dysgerminoma (27.5%), immature teratomas (27.5%), dermoid (15 %) & yolk - sac tumours (5 %) as the rest. Viable pregnancies in these patients were achieved in due course, thereby proving the fact that proper diagnosis & the subsequent treatment of these entities will yield the desirable outcome with respect to achieving pregnancy.

Conclusion

Literature substantiates that 18.8- 55.7% of such patients may achieve favorable pregnancies with a combination of a near accurate diagnosis, staging & surgeries, which are the cornerstone of the treatment. Nevertheless, surgery should be tailored according to age, interest in preserving fertility, and the stage of the disease.

GJMEDPH 2024; Vol. 13, issue 4 | OPEN ACCESS

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Conflict of Interest—none | Funding—none

INTRODUCTION

Ovarian malignant germ cell tumours, as per the recorded literature & statistics, are usually found to occur in the first two decades of life, with a percentage of 2.6 % of all documented ovarian neoplasia[1]. Generally, ovarian neoplasms, arise from the different elements of the ovarian tissue namely the epithelia, stroma & the follicular elements namely gonadoblastoma, mature teratoma, dysgerminoma, yolk sac tumour, embryonal carcinoma, immature teratoma & chorio-carcinoma (scripted irrespective of the benign & malignant potential). They evolve generally due to a spectrum of factors which are but not limited to, aneuploidies, problem with the DNA methylation, haywire increments in the copies, aberrant/ arrested migration of the primordial germ cells (PGC) during embryogenesis & certain mutations. These unique cohorts of neoplasias are generally observed in the midline or the near midline sites of the body. Treatment of such a disease is generally attributable to a large number of factors, but all would lead to a fertility sparing scheme, whether conservative or surgical. Most of the patients with such a disease usually presents with frank amenorrhea, nonspecific abdominal pain along with constitutional symptoms & therefore, a proper evaluation, diagnosis & treatment as specified are thoroughly warranted.

Methodology

The study as described is an observational retrospective study and was conducted at IPGMER & SSKM Hospital, in the Gynaecology & Obstetrics department, maintaining a coherence/ liaison with the department of pathology in the aforesaid institute. 40 patients over a time span of 3 years (2020 - 2023) with the lesion of interest as the main inclusion criteria was extensively studied from the available records. Hemodynamically unstable patients who reported in the emergency department and those who were categorized as high-risk patients were excluded from the study. There were infrequent consultations with the radiotherapy department & patients requiring Oncotherapeutics who were referred were also excluded from the study. clinical examinations, MRI/CT cross sections, along with PET-CT for the study en- bloc, guided biopsies & staining without IHC or FISH, sometimes laparotomies with omental dissections & rarely Trans- vaginal sonogram was deployed. Post the Diagnosis, surgeries pertaining to a unilateral salpingo-oophorectomy, sometimes accompanied by contralateral cystectomy, to spare the fertility of the patient was performed with no recordable re- exploration & such patients who wished pregnancy were thereafter monitored every quarterly till desirable outcomes or anything of relevance was achieved. Patients who deferred a pregnancy were also excluded from the study.

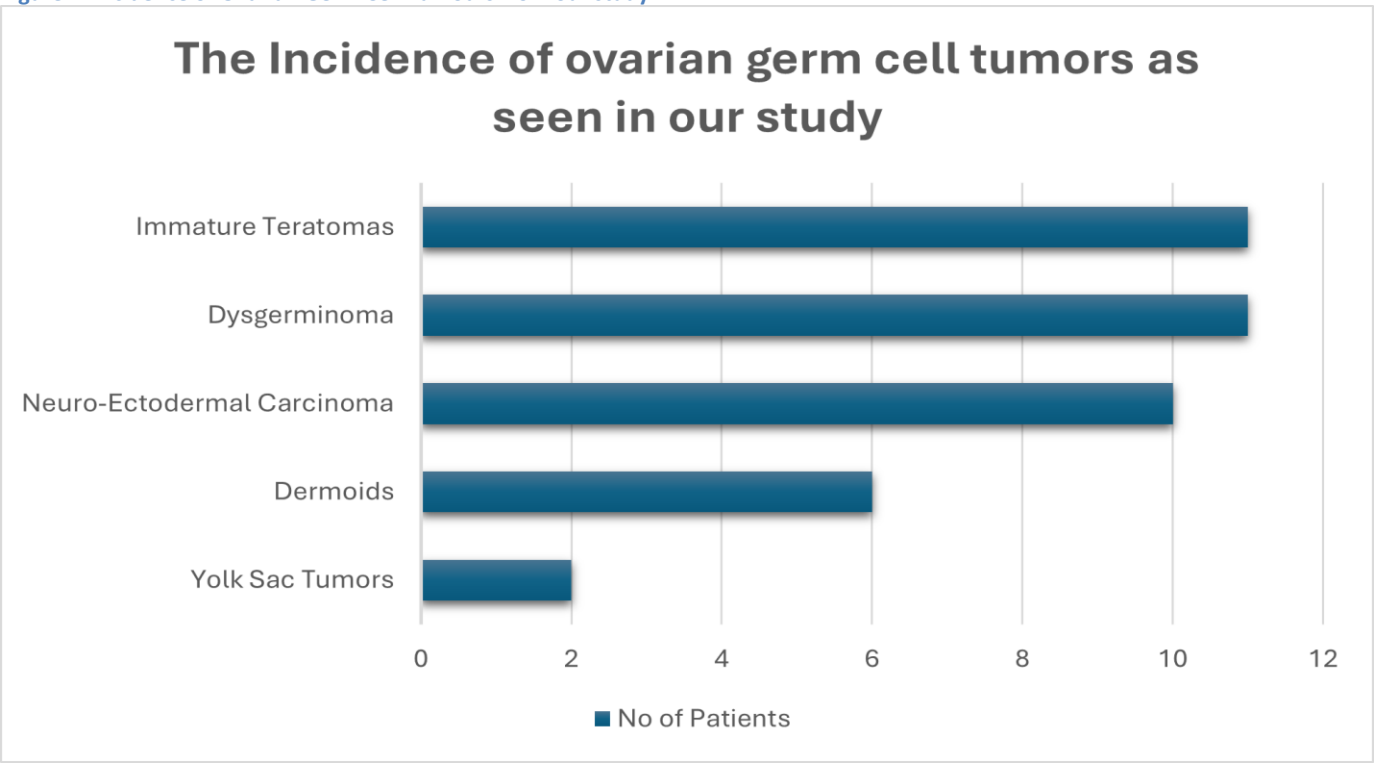
RESULTS

In our study, out of 50 odd patients, 7 of them reported with uncanny vitals due to torsion & 3 of them due to acute abdomen later stamped as cases of frank peritonitis after cross - section imaging & laboratory results were excluded. The 40 patients that were left were included in our study. They had incidences of unilateral dysgerminoma (11 patients, 27.5 %), immature teratomas (11 patients, 27.5 %), neuro-ectodermal carcinoma (10 patients, 25%), Dermoid (6 patients, 15%), yolk sac tumours (2 patients, 5 %) being the rest **(Figure 1).** Thirty-five patients in the study were staged T1bNoMo, three patients of immature teratomas pertaining to stages T1C1NoMo & two patients with yolk sac tumours with T2N1Mo .out of the forty patients who were thoroughly observed, twenty patients opted out for a pregnancy which were largely attributable to the social stigmata. Now, out of the rest 20 patients, yolk sac tumours (T2) who were subjected to follow ups after bilateral adnexal manipulation were deferred from pregnancy, & the rest of the eighteen patients treated with "fertility sparing surgeries' were allowed pregnancies. The latter was not subjected to any hormonal supplementation apart from the regular anti- natal advice along with checkups for the disease & finally had successful pregnancies except one of a dysgerminoma who had suffered a miscarriage.

A surprising entity that was translated against the literature was the finding of a large section of neuroectodermal carcinomas where the ovary is not a major site of such a neoplasia to develop. Nevertheless, dysgerminomas & immature teratomas were abundant & those patients that were subjected to surgeries to preserve fertility did yield favourable outcomes.

ISSN# 2277-9604

Figure 1: Incidence of Ovarian Germ Cell Tumours from our study



DISCUSSION

Ovarian Germ cell tumours (OGCT) are thought to be rare entities, which occur in young females & do constitute a 2-3% of all the ovarian malignancies. Studies reveal that it has an increasing incidence in the black population as compared to the Surveillance, Epidemiology, and End Results (SEER) database[2]. It has been observed that outcomes regarding the clinical stature have been improving for such a neoplasia owing to their resemblance to the testicular cancers due to overlaps in the treatment due to effective surgical staining aided by advanced radiology & precise pathology modalities combined with cost effective chemotherapeutic regimens & fertility preserving surgeries. These neoplasms are classified as primitive germ cell tumours, bi- or triphasic tumours, monodermal & somatic type tumours. They are further subclassified as dysgerminoma, endodermal sinus tumours (yolk sac tumour), embryonal tumours, embryoma, non-gestational choriocarcinoma, mixed germ cell tumours in the cohort of the primitive germ cell tumours, immature teratoma, mature teratoma, solid, cystic (dermoid), fetiform teratoma in bi / tri-phasic tumours, thyroid lesions (struma ovarii), carcinoid, neuroectodermal, carcinoma, melanocytic, sarcoma, sebaceous, pituitary type under the monodermal & somatic type tumours. This classification has been engineered by W.H.O. Pinto et al[3] states that dysgerminoma & immature teratomas are the most common variant of OGCTs, accounting for 65- 75 %, followed by Yolk Sac tumours (14. 5 %) & mixed GCTs (5.3%). OGCTs are usually unilateral; however, 10–15% of dysgerminoma and 5– 10% of the mixed OGCT subtype are found to be bilateral. The clinical features of such neoplasias often are attributable to abdominal enlargement with diffuse abdominal pain, sometimes intractable/ nonspecific & may result in an acute abdomen with or without haemodynamic instability due to rupture of the tumour (TLS), haemorrhage or a frank torsion, due to which special emphasis with respect to the diagnosis is made. Physical examination, pelvic examination with a colposcopy aided PAP test, cross sectional imaging, guided biopsies, some tumour markers, PET scans, sometimes a trans -vaginal sonogram & finally laparotomies would facilitate the diagnosis & staging of the lesion **(Figure 2, Figure 3)**

ISSN# 2277-9604

Figure 2: Ovarian Cancer Stages (Image source- https://weillcornell.org/services/obstetrics-and-gynecology/gynecologic-oncology/conditions-we-treat/ovarian-cancer)

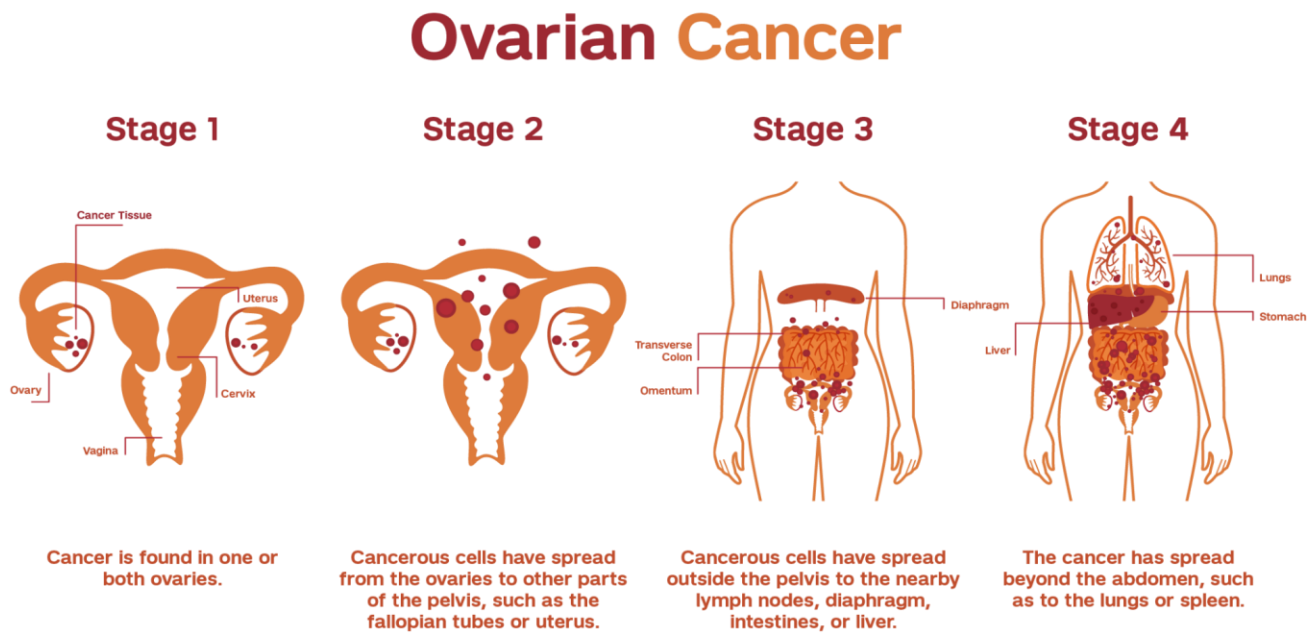


Figure 3: FIGO and TNM staging system for ovarian cancer (2014) (Image Source: https://doi.org/10.3802/jgo.2018.29.e56)

FIGO	TNM	Surgical-pathologic findings
I	T1	Tumor confined to ovaries
IA	T1a	Tumor limited to 1 ovary (capsule intact); no tumor on ovarian surface; no malignant cells in the ascites or peritoneal washings
IB	T1b	Tumor limited to both ovaries (capsules intact); no tumor on ovarian surface; no malignant cells in the ascites or peritoneal washings
IC		Tumor limited to 1 or both ovaries, with any of the following
IC1	T1c1	Surgical spill
IC2	T1c2	Capsule ruptured before surgery or tumor on ovarian surface
IC3	T1c3	Malignant cells in the ascites or peritoneal washings
II	T2	Tumor involves 1 or both ovaries with pelvic extension (below pelvic brim) or primary peritoneal cancer
IIA	T2a	Extension and/or implants on uterus and/or fallopian tubes
IIB	T2b	Extension to other pelvic intraperitoneal tissues
III		Tumor involves 1 or both ovaries, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA1	T1/T2-N1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven)
IIIA1(i)		Metastasis up to 10 mm in greatest dimension
IIIA1(ii)		Metastasis more than 10 mm in greatest dimension
IIIA2	T3a2-N0/N1	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IIIB	T3b-N0/N1	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
IIIC	T3c-N0/N1	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)
IV	Any T, any N, M1	Distant metastasis excluding peritoneal metastases
IVA	Any T, any N, M1a	Pleural effusion with positive cytology
IVB	Any T, any N, M1b	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Now, immunohistochemistry of such lesions such as SALL4 and placental alkaline phosphatase for germ cell differentiation, (OCT4, CD117, and D2-40) for dysgerminoma, (α-fetoprotein and glypican-3) for yolk sac tumour, (OCT4, CD30, and SOX2) for embryonal neoplasia, (calretinin, inhibin, SF-1, FOXL2) for sex cord-stromal differentiation, and (melan-A) for steroid cell tumours will focus on the accuracy of the diagnosis. Saani et al[4] proposes Bleomycin, etoposide, and cisplatin (BEP) therapy to be the gold standard of chemotherapy in the patient though the issue of OncoTherapeutics have not been elucidated in this citation. It has been observed that, most patients (> 60 %) have been diagnosed at an early stage, which if operated with an aim to preserve fertility & to prevent mortality, has been found to reach as high as 90%. Such records are scripted here since maximally, all the patients have been treated on a surgical approach with a few moving on to the neo-adjuvant or adjuvant onco-therapeutic regimen. Whereas such a proposition on fertility rates, which happens to be our major concern, looks doubtful with dubious results[5] with a reported pregnancy ranging from 18.8- 55.7%. Here we had offered the standard surgical care of salpingo-oophorectomy with optimal debulking, peritoneal washings & omental biopsy for a majority of the patients as the lesions described were unilateral, but in certain cases where the disease was found to be aggressive in nature owing to the differentiation, contralateral cystectomy was also considered, which is the standard guideline in treating lesions of such nature. Some studies suggest re-exploration of the abdomen in cases of immature teratomas, but such facts have not been dissected well in our study. Refractory diseases, though minimal, will be sent for further evaluation subjectable to advanced chemotherapy.

CONCLUSION

Ovarian germ cell tumors are rare, but unlike epithelial ovarian cancers they could be early detected and diagnosed. Clinical signs and symptoms are abdominal distension or acute abdomen. Cross-sectional imaging starting with an USG & to proceed with higher tools of radiology young females may raise the suspicion of an OMGCT. Pathology is a cornerstone in the diagnosis of these classes of neoplasia. Due to the rarity of this pathology, IHC must be implemented.

Surgery should be tailored according to age, interest in preserving fertility, and the stage of the disease. Non-aggressive surgeries in contrast to those deployed in epithelial lesions such as unilateral salpingo-oophorectomy is considered the actual standard of surgical treatment for young patients in an early stage of the disease, sparing the contralateral ovary for surgical manipulation. Advanced stages of such may require PET scans with adjuvant chemotherapy with platinum- based combinations. It must be noted that irradiation with isotopes holds no significance in the treatment of such lesions. Sequential follow ups with imaging, tumor markers such as AFP, β-hCG, and LDH (though non- specific) is indicated & is deemed unique for the patient.

ISSN# 2277-9604

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