Fertility-Sparing Surgery for a Prepubertal Female with Malignant Ovarian Germ Cell Tumor

Sharon L. Peñarubia MD, Stella Marie L. Jose MD, FPOGS, FPIDSOG and Ina S. Irabon, MD, FPOGS, FPSRM, FPSGE
Department of Obstetrics and Gynecology, University of Perpetual Help Dalta Medical Center, Las Pinas City

Malignant ovarian germ cell tumors are rare ovarian malignancies accounting for 3 to 5% of all ovarian malignancies. They are mostly seen in adolescents and young women and are usually unilateral making fertility preservation imperative. Raised alpha-feto protein level is the hallmark of this tumor. Presented is a case of a premenarcheal 13 year old female diagnosed with yolk sac tumor and who underwent fertility-sparing surgery and adjuvant platinum-based chemotherapy post-operatively, with good outcome. In young patients, conservative surgery with adjuvant chemotherapy has made the preservation of fertility possible, even in patients with advanced disease. The increase in cure rates has shifted the focus of recent studies to the long term menstrual, reproductive, and gynecologic outcomes in these patients.

Keywords: malignant ovarian germ cell tumor, prepubertal female

Introduction

Yolk sac tumor (YST) of the ovary, also known as endodermal sinus tumor, is a rare malignant ovarian germ cell tumor (MOGCT). It accounts for 1% of all ovarian malignancies. It is frequently seen among adolescents and young women, which makes it imperative to preserve fertility during management. Adjuvant chemotherapy consisting of Bleomycin-Etoposide-Cisplatin (BEP) regimen has greatly improved the outcomes of these tumors. Before the advent of combination chemotherapy, YST was almost always universally fatal. The introduction of chemotherapeutic regimens greatly improved outcome, especially following the addition of cisplatin. Survival rates reached excellent values, even for patients with advanced stage tumors.[1,2]

This paper aims to present a case of an adolescent who was diagnosed with YST, the clinical signs and symptoms she presented with, and how she was managed conservatively and monitored post-operatively. The authors also present related literature on the prognosis and long term outcomes, which include favorable reproductive outcomes and long term survival rates for young patients who underwent conservative surgery and adjuvant chemotherapy.

The Case

This is a case of a 13-year old premenarcheal female who was admitted due to severe abdominal pain. One week prior to admission, the patient had high fever (Tmax 39ºC), temporarily relieved by intake of Paracetamol 500mg tablet. Five days prior to admission, with recurrence of high fever, she consulted her pediatrician who initially assessed her to have dengue fever. Complete blood count, urinalysis, and dengue NS1 antigen showed normal results. She was sent home with unrecalled medications.

One day prior to admission, the patient had severe hypogastric pain which prompted consultation at the emergency room. On physical examination, breasts and pubic hair

were noted to be Tanner Stage 2. There was decreased breath sounds on the base of both lung fields, abdomen was noted to be slightly distended, with normoactive bowel sounds, guarding, no tenderness on deep palpation nor fluid wave. Whole abdominal ultrasound was requested, which showed a complex pelvoabdominal mass probably ovarian in origin measuring 18.0cm x 13.7cm x 7.5cm, predominantly solid (70%), with septations and minimal intralesional vascularity. The patient was advised admission and was subsequently referred to the OB-GYN service for evaluation and co-management.

On physical examination by the gynecologist, there was board-like rigidity of the abdomen with guarding, generalized tenderness, and a slightly movable, solid pelvoabdominal mass enlarged to approximately 20cm x 15cm, located at the midline. The primary working impression was Ovarian New Growth, right, probably malignant, in complication. The initial plan was to do stat exploratory laparotomy, but there was no parental consent given. Patient was closely monitored in the wards. Vital signs were stable while at the wards. Transrectal ultrasound showed a cystic right ovarian mass, measuring 21.12cm x 23.1cm x 9.72cm, thick-walled (1.12 cm) with multiple septations, and a solid component measuring 8.22cm x 11.4cm x 8.53cm. There was fluid in the culdesac. Color-flow imaging was suggestive of a malignant ovarian new growth (SASSONE=12, malignant features by IOTA). Tumor markers requested revealed elevated results for CA 125 (373.99 U/ml), alphafetoprotein (>8,000 IU/ml) and LDH (423 U/L); beta Hcg (< 2.00 mIU/ml) levels were within normal.

On the 2nd hospital day, after comprehensive discussion with the patient's parents, consent for exploratory laparotomy was finally given. Preoperative internal exam done under anesthesia revealed a small cervix and uterus. On rectovaginal exam, there was good sphincteric tone, smooth and pliable parametria, with no extra or intraluminal masses nor nodulations noted. A gynecologic oncologist was on stand-by for possible complete surgical staging, and referral to surgery was also done for possible adhesiolysis.

Upon exploration, there was note of a moderate amount (~200 cc) of straw-colored ascitic fluid. Palpation of the liver, subdiaphragmatic area, intestines, peritoneum revealed absence of nodularities or implants. A sample of peritoneal fluid was aspirated for cell cytology. The right ovary was converted to approximately 18cm x 12cm x 8cm mass with smooth capsule with thinned-out posterior wall. It had a 3cm point of rupture at the posterior area exuding straw-colored

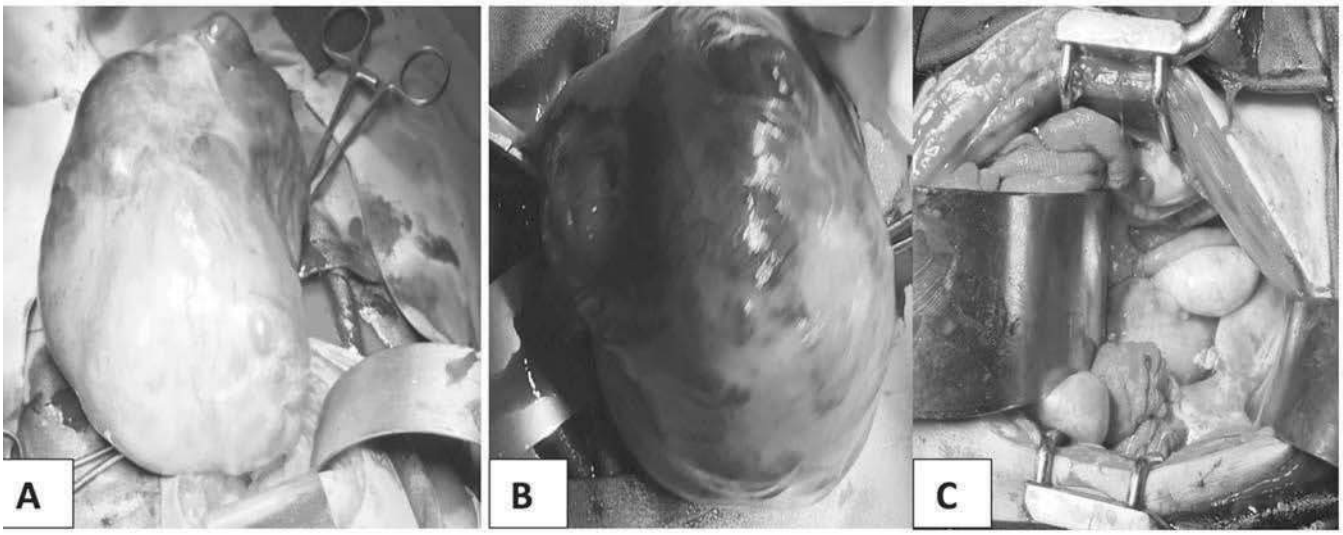

Figure 1. (A) The right ovary was converted to approximately 18cm x 12cm x 8cm mass with smooth capsule with thinned-out posterior wall. (B) It had a 3cm point of rupture at the posterior area exuding straw-colored fluid. (C) The right fallopian tube, left fallopian tube, and left ovary were grossly normal.

fluid. There were no adhesions between the right ovary and the peritoneum and the other pelvic structures. The right fallopian tube, left fallopian tube, and left ovary were grossly normal (Figures 1 A-C). On cut section, the right ovary showed hemorrhagic and brain-like necrotic tissues (Figure 2). A right salpingooophorectomy, infracolic omentectomy, pelvic lymph node dissection was done, and intraoperative staging was Stage I-C. The specimens were sent for histopathology. The estimated blood loss was 200 cc. She recovered uneventfully and was discharged on the 3rd day post-op, improved and stable.

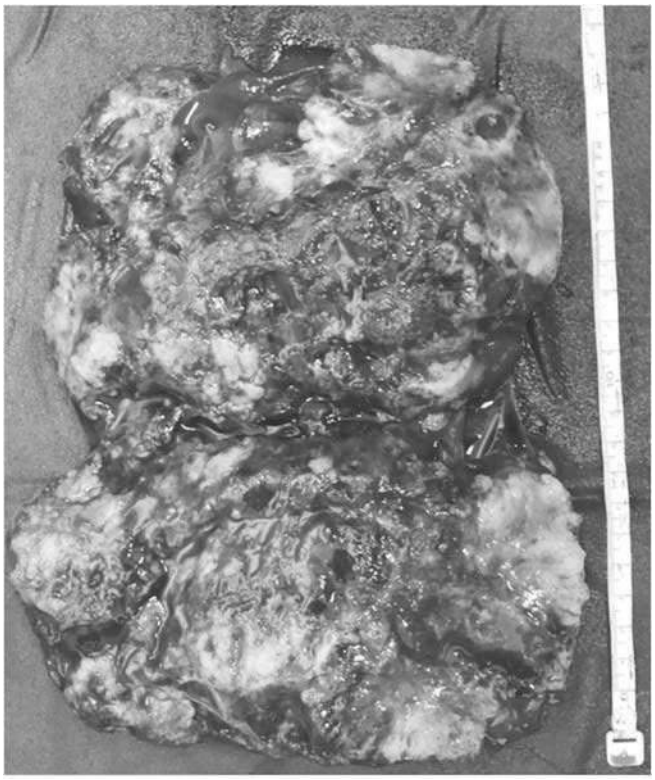

Figure 2. On cut section, the right ovary showed hemorrhagic and brain-like necrotic tissues.

Histopathologic diagnosis revealed a germ cell tumor: yolk sac tumor of the right ovary (Figure 3) with tumor metastasis in 1 out of 2 left pelvic lymph nodes; negative for tumor all 4 right pelvic lymph nodes (Figure 4), omentum; congestion, omentum (Figure 5); positive for atypical cells, peritoneal fluid (Figure 6); no diagnostic abnormality, right fallopian tube (Figure 3).

Final diagnosis was Germ cell tumor, yolk sac tumor, Stage III-C, right ovary. The patient is now on BEP (Bleomycin, Etoposide, and Cisplatin) chemotherapy.

Discussion

Etiology and Clinical Presentation

Ovarian germ cell tumors (OGCT) constitute 15 to 20% of all the ovarian tumors.

They originate from the primitive germ cell and gradually differentiate to mimic tissues of either the embryonic origin like ectoderm, endoderm and mesoderm or of the extraembryonic tissues like the yolk sac and trophoblast. The

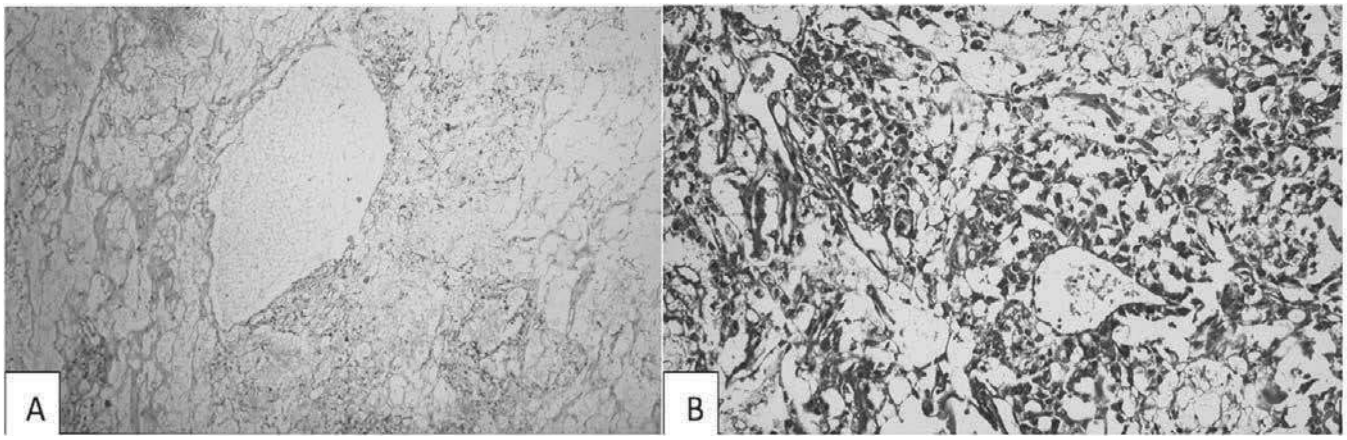

Figure 3. Histopathologic images showing a microcystic pattern of the tumor, composed of a loose network of small cystic spaces forming a honeycomb pattern. The microcysts are lined by flat cells with pleomorphic hyperchromatic nuclei. (A) Scanning view (B) HPO

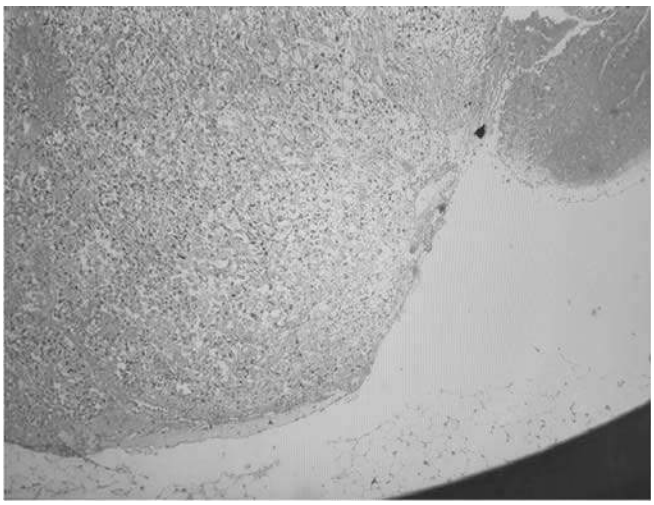

Figure 4. Microscopic image of lymph node negative for tumor

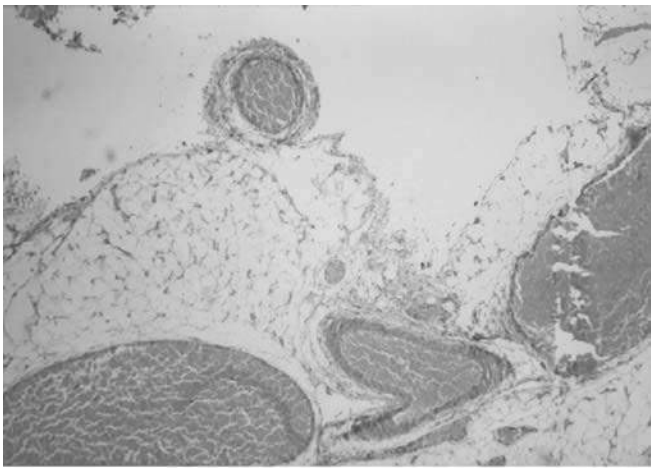

Figure 5. Microscopic image of omentum showing congestion

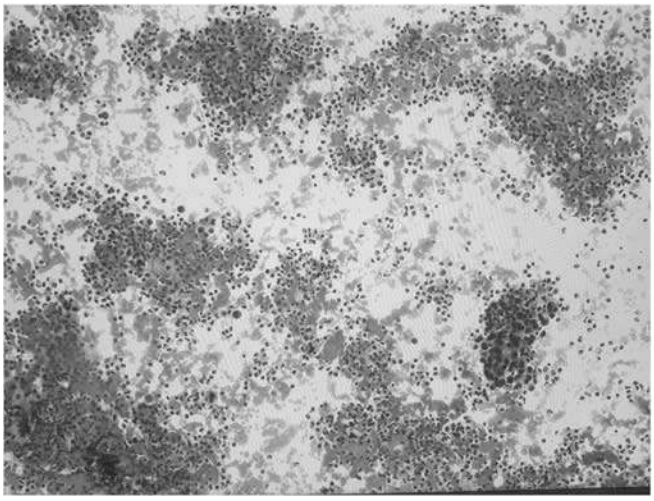

Figure 6. Microscopic image of peritoneal fluid smear showing atypical cells

specific type of tumor depends on the degree of differentiation. a germinoma would develop if there is no differentiation; with differentiation, embryonal carcinoma would develop and with extraembryonic differentiation, a yolk sac tumor or a choriocarcinoma.[2]

Malignant OGCTs account for 3 to 5% of all the ovarian malignancies. In females younger than 20, they represent approximately 60% of malignant ovarian tumors. The age of the patients ranges from 6 to 69 years with a median of 16-20 years.[3] This study's index patient is 13 years old.

Yolk sac tumor (also called endodermal sinus tumor), though rare (incidence of 1%), is the second most common histopathological subtype of MOGCT after dysgerminoma.[2]

The clinical symptoms of yolk sac tumor include a rapidly enlarging pelvic mass which extends to the abdomen and is associated with pain and abdominal distention. Other symptoms are vaginal bleeding, fever, ascites or peritonitis secondary to torsion, infection or tumor rupture. Ascites may lead to diffuse abdominal tenderness, decreased bowel sounds and decreased breath sounds at lung bases. It is almost always unilateral and the size of the tumor vaies from 7cm to 40 cm. Index patient here presented with abdominal pain, abdominal enlargement, fever and decreased breath sounds. Intraoperatively, there was moderate ascites and a huge unilateral mass (18 cm) with point of rupture.[3]

Diagnosis

Pre-operative diagnosis is difficult, as yolk sac tumors do not have a specific radiological image. It can appear cystic with signs of hypervascularization and areas of hemorrhage. Diagnosis is histopathological. Histologically, the malignant tissue resembles the structure found in early embryonic development - the Schiller Duval bodies. Although it is diagnostic of yolk sac tumors, absence does not exclude diagnosis.[2]

Management

Complete surgical excision of the tumor is the first step of management followed by adjuvant

therapy.[3] Considering the chemotherapy-sensitive nature of these tumors, fertility-sparing cytoreductive surgery (FSCS) seems a reasonable approach in initial treatment even for patients with advanced stage.[7] Advanced disease is not usually accompanied by contralateral ovarian disease and should not necessarily contraindicate conservative surgery. Fertility-sparing or conservative surgery and a combination chemotherapy are appropriate for young patients who desire to retain their fertility, especially since these tumors are almost always unilateral.[3] A retrospective study that reviewed the outcomes of the treatment in patients with malignant ovarian germ cell tumors concluded that for advanced diseases, conservative surgery is indeed advisable in patients with yolk sac tumors.[4]

Appropriate surgical treatment for patients where fertility needs to be preserved consists of laparotomy with unilateral salpingooophorectomy, peritoneal cytologic studies, omentectomy, multiple peritoneal and abdominal biopsies and resection of all visible disease.[5] However, it is recommended that patients with bulky disease in the abdomen, pelvis and retroperitoneum should be surgically cytoreduced to optimal residual disease if possible. Second-look laparotomy is still controversial. But as long as AFP can be used to monitor the disease, then second-look laparotomy may not be needed.[3] The index patient here underwent right salpingooophorectomy, infracolic omentectomy, pelvic lymph node dissection (intraoperative Stage I-C). The contralateral ovary and fallopian tubes were grossly normal and no residual tumors were left behind. Her AFP levels are being monitored regularly, and are noted to have declined to within normal limits. She is likewise advised to undergo ultrasound to monitor possible recurrence of the tumor on the contralateral ovary.

In the past, outcome was very poor and the disease was almost always fatal. But with the refinement of chemotherapeutic regimens in the last several decades, survival rates have improved dramatically and fertility-preserving surgery has become possible. Three courses of BEP (bleomycin, etoposide, cisplatin) is the current standard therapy and four courses are recommended in case of bulky residual disease after surgery.[5] Elevated alpha-feto protein (AFP) is the hallmark of yolk sac tumors and a rapid decline post-operatively (or during chemotherapy) indicates absence of residual tumor after surgery and a good overall survival rate. The efficiency of chemotherapy is related to the normalization of the AFP levels.[6] The index patient here is undergoing multi-agent chemotherapy (BEP regimen).

Neoadjuvant chemotherapy followed by interval fertility-sparing conservative surgery may be a reasonable option in patients with extensive disease, when initial debulking is not an option or where poor general condition or clinical findings suggest an increased risk of surgical morbidity or preclude fertility-sparing surgery. This is currently not the standard of care but deserves future study. In some rare situations, when any remaining ovarian tissue means high risk, BSO may be performed with the uterus preserved for possible assisted reproduction with donor egg.[7]

Follow-up of these patients includes monitoring of AFP levels post-op or during chemotherapy, soon after the end of the treatment and during the 2 years after the end of chemotherapy. An annual pelvic ultrasound is recommended in cases of conservative surgery in order to screen for a contralateral recurrence.[9,8]

Prognosis and Reproduction After Surgery and Chemotherapy

Factors related to good prognosis are no ascites at presentation, stage I disease, less than 42 days to AFP normalization, fertility-sparing surgery and a serum AFP half-life less of 10 days. The index patient definitely has a very good prognosis especially in terms of long-term overall survival rate. Progressive or recurrent ovarian tumor after treatment with BEP chemotherapy has been reported to be associated with a poor prognosis.[9]

Two retrospective studies of patients with ovarian yolk sac tumor concluded that postsurgery satisfactory AFP decline (defined as normalization of AFP after the first or second cycles of postsurgery chemotherapy, $P = 0.006$) was an

independent significant prognostic factor for patient survival.[10,11] Another retrospective study showed that presence of residual tumor is a significant prognostic factor for primary treatment failure.[12] For the index patient, levels of post-operative tumor markers have normalized, including AFP and Ca125. No residual tumors were left intraoperatively.

A retrospective review[13] of 74 patients with MOGCT treated by conservative surgery (retaining the uterus and contralateral ovary to preserve ovarian function) with or without chemotherapy showed that survival for patients with Stage I disease was 98.2% and 94.4% for patients with advanced disease stages. During chemotherapy 61.7% of patients developed amenorrhea but 91.5% of the women resumed normal menstrual function upon completion of chemotherapy. Fourteen healthy live births were recorded in the chemotherapy group and there were no documented birth defects. There was 1 case of infertility (1.4%). This study proves that majority of patients with MOGCT who have received combination chemotherapy resume normal ovarian function and can expect a normal fertility rate and healthy offsprings.

A multicenter retrospective investigation evaluated the reproductive safety of BEP regimen for patients with yolk sac tumor who underwent conservative surgery. The study concluded that BEP regimen is a relatively safe chemotherapeutic treatment in terms of preserving the female reproductive function, as majority (70%) of the patients who received BEP recovered their menstrual cycles and eventually conceived and gave birth to healthy offsprings.[14]

A retrospective study by Kang, et al.[15] which included females as young as 6 years old who were given high dose BEP regimen for yolk sac tumors, concluded that BEP regimen did not seem to impair ovarian function.

A case report by Tesic, et al.[16] presented a patient who had yolk sac tumor and received a combined treatment of conservative surgery and adjuvant chemotherapy. A few years later, the patient gave birth to a baby girl with pes varus.

Counseling

Very young patients diagnosed with a malignancy, especially those who undergo surgery and several sessions of chemotherapy need to be referred for psychosocial counseling and debriefing to help address any stress-induced psychological distress, or possibly a post-traumatic stress disorder. Psychosocial distress is almost always associated with depression and anxiety.

This subgroup of patients and their parents should also be referred to a reproductive endocrinologist for counseling regarding future reproductive plans, and the possible occurrence of premature ovarian failure or decreased ovarian reserve secondary to chemotherapy, leading to early menopause or infertility. Although many retrospective studies have shown the safety profile of BEP on reproductive function, post-therapy recovery of gonadal function remains unpredictable. Therefore, it is important to inform patients of this possible side effect of their treatment and all the options available to prevent premature ovarian failure or decreased ovarian reserve. As survival worries may deviate from important life dreams, it is advisable to anticipate and facilitate the long-term perspectives that may not be readily apparent to young patients, and even their parents, in this sensitive situation.[17]

They may be offered ovarian cryopreservation prior to chemotherapy and transplant the ovarian tissue once the patient is declared in remission. Fertility preservation is becoming an emerging field of reproductive medicine allowing these patients to have their own biological children, in the unfortunate event that a premature ovarian failure ensues after chemotherapy.

Conclusion and Recommendations

Although yolk sac tumors are potentially fatal, its chemosensitive nature and the advent of new generation chemotherapeutic drug regimens have allowed fertility-sparing conservative surgery and combination chemotherapy as primary treatment for young patients who desire to retain their fertility, and so attempts to conserve reproductive function should always be considered. A multidisciplinary

approach, involving the gynecologist, pediatrician, oncologist, reproductive endocrinologist and psychologist should be offered to all young patients with a diagnosis of MOGCT.

References

1. Umezu T, et al. Long-term outcome and prognostic factors for yolk sac tumor of the ovary. Nagoya J Med Sci 2008; 29-34.
2. Sharma C, Shah H, Shenoy NS. Ovarian yolk sac tumor in a girl - A case report. Developmental Period Medicine 2017; 101-3.
3. Aziz MF. Current management of malignant germ cell tumor of the ovary. Gan To Kagaku Ryoho 1995; 22 Suppl 3: 262-76. Review.
4. Linasmita V, Srisupundit S, Wilailak S, Tangtrakul S, Israngura N, Bullangpoti S. Recent management of malignant ovarian germ cell tumors: a study of 34 cases. J Obstet Gynaecol Res 1999; 25(5): 315-20.
5. Dällenbach P, Bonnefoi H, Pelte MF, Vlastos G. Yolk sac tumours of the ovary: an update. Eur J Surg Oncol 2006; 32(10): 1063-75. Epub 2006 Sep 22.
6. Royal College of Obstetrics and Gynecology. Management of Female Malignant Ovarian Germ Cell Tumors. 2016.
7. Li J, Wu X. Current strategy for the treatment of ovarian germ cell tumors: Role of extensive surgery. Curr Treat Options Oncol 2016; 17(8): 44. doi: 10.1007/s11864-016-0416-2.
8. Garcia V, Toral JA, Siasu, ML. Malignant ovarian germ cell tumors: Clinical characteristics, treatment and outcomes: The experience in a tertiary government institution. Phil J Oncol 9: 35-44.
9. Umezu T, et al. Long-term outcome and prognostic factors for yolk sac tumor of the ovary. Nagoya J Med Sci 2008; 29-34.
10. Wang X, Ma Z, Li Y. Ovarian yolk sac tumor: The experience of a regional cancer center. Int J Gynecol Cancer 2016; 26(5):884-91. doi:10.1097/IGC.0000000000000704.
11. de la Motte Rouge T, Pautier P, Genestie C, Rey A, Gouy S, Leary A, Haie-Meder C, Kerbrat P, Culine S, Fizazi K, Lhommé C. Prognostic significance of an early decline in serum alpha-fetoprotein during chemotherapy for ovarian yolk sac tumors. Gynecol Oncol 2016; 142(3): 452-7. doi: 10.1016/j.ygyno.2016.07.005. Epub 2016 Jul 8.
12. Lee CW, Song MJ, Park ST, Ki EY, Lee SJ, Lee KH, Ryu KS, Park JS, Hur SY. Residual tumor after the salvage surgery is the major risk factors for primary treatment failure in malignant ovarian germ cell tumors: a retrospective study of single institution. World J Surg Oncol 2011; 9: 123. doi: 10.1186/1477-7819-9-123.
13. Low JJ, Perrin LC, Crandon AJ, Hacker NF. Conservative surgery to preserve ovarian function in patients with malignant ovarian germ celltumors. A review of 74 cases. Cancer 2000; 89(2): 391-8.
14. Satoh T, Aoki Y, Kasamatsu T, Ochiai K, Takano M, Watanabe Y, Kikkawa F, Takeshima N, Hatae M, Yokota H, Saito T, Yaegashi N, Kobayashi H, Baba T, Kodama S, Saito T, Sakuragi N, Sumi T, Kamura T, Yoshikawa H. Administration of standard-dose BEP regimen (bleomycin+etoposide+cisplatin) is essential for treatment of ovarian yolk sac tumour. Eur J Cancer 2015; 51(3): 340-51. doi: 10.1016/j.ejca.2014.12.004. Epub 2015 Jan 2.
15. Kang H, Kim TJ, Kim WY, Choi CH, Lee JW, Kim BG, Bae DS. Outcome and reproductive function after cumulative high-dose combination chemotherapy with bleomycin, etoposide and cisplatin (BEP) for patients with ovarian endodermal sinus tumor. Gynecol Oncol 2008; 111(1): 106-10. doi: 10.1016/j.ygyno.2008.05.033. Epub 2008 Jul 25.
16. Tesic M, Novakovic P, Sloboda L, Horvat E. Pregnancy following treatment of an adolescent with yolk sac tumour. Eur J Gynaecol Oncol 1996; 17(1): 55-8.
17. Zavras N, Siristatidis C, Siatelis A, Koumarianou A. Fertility risk asssessment and preservation in male and female prepubertal and adolescent cancer patients. Clin Med Insights Oncol 2016; 10: 49-57. Published online 2016 Jun 28. doi: 10.4137/CMO.S32811.