

This item is the archived peer-reviewed author-version of:

The multidisciplinary approach to ovarian tumours in children and adolescents

Reference:

Van Heerden Jaques, Tjalma Wiebren.- The multidisciplinary approach to ovarian tumours in children and adolescents
European journal of obstetrics and gynecology and reproductive biology - ISSN 0301-2115 - Amsterdam, Elsevier, 243(2019), p. 103-110
Full text (Publisher's DOI): <https://doi.org/10.1016/J.EJOGRB.2019.10.032>
To cite this reference: <https://hdl.handle.net/10067/1650940151162165141>

Journal Pre-proof

The multidisciplinary approach to ovarian tumours in children and adolescents

J. van Heerden, W.A. Tjalma



PII: S0301-2115(19)30488-9
DOI: <https://doi.org/10.1016/j.ejogrb.2019.10.032>
Reference: EURO 11035

To appear in: *European Journal of Obstetrics & Gynecology and Reproductive Biology*

Received Date: 17 June 2019
Revised Date: 2 October 2019
Accepted Date: 17 October 2019

Please cite this article as: van Heerden J, Tjalma WA, The multidisciplinary approach to ovarian tumours in children and adolescents, *European Journal of Obstetrics and Gynecology and Reproductive Biology* (2019), doi: <https://doi.org/10.1016/j.ejogrb.2019.10.032>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier.

The multidisciplinary approach to ovarian tumours in children and adolescents

J. van Heerden^{1*} jaques.vanheerden@uza.be, W. A. Tjalma^{2,3}

¹ Paediatric Haematology and Oncology, Antwerp University Hospital, University of Antwerp, Belgium

² Multidisciplinary Breast Clinic, Unit of Gynaecological Oncology, Antwerp University Hospital, University of Antwerp, Belgium

³ Department of Obstetrics and Gynaecology, Antwerp University Hospital, University of Antwerp, Belgium

Correspondence:

Dr Jaques van Heerden, Department of Paediatrics, Antwerp University Hospital, Wilrijkstraat 10, Edegem, 2650, Belgium.

ABSTRACT

Ovarian tumours in children and adolescents are rare diseases. Although the majority of tumours are benign, the diagnosis and management present various challenges that require a wide range of expertise. The multidisciplinary team ensures not only accurate diagnosis and correct and minimally invasive management, but also minimal psychological impact and the preservation of fertility. This article outlines the multidisciplinary team approach to ovarian masses in children and adolescents. The team includes paediatric oncologists, gynaecological surgeons, pathologists, radiologists, fertility experts, geneticists and psycho-social services.

Keywords: ovary; mass; children; adolescents; multidisciplinary treatment

ARTICLE

Introduction

Paediatric ovarian tumours are rare disorders with a crude incidence rate of 2.6–3/100 000 girls per year [1]. The clinical presentation varies according to age groups and differs from adults. In children most tumours are benign with approximately 30% of tumours being malignant [2]. Ovarian malignancies constitute less than 3% of all childhood malignancies [1]. In both children and adolescents anatomical and physiological processes can be dysregulated in the presence of ovarian tumours [3]. The heterogeneous presentation and variable aetiologies necessitate a coordinated multidisciplinary team approach. Management should be curative, function sparing, minimally invasive and sensitive to the psycho-emotional impact on this vulnerable population. The aim of this article was to evaluate the most important considerations in a child with an ovarian tumour.

Methodology

A comprehensive literature review of publications on Pubmed, Medline, Global Health, Embase, ScieLo and Google Scholar with medical subject headings in keeping with pelvic tumours in children and adolescents were done. Articles were limited to English language articles or conference abstracts after 1995. Articles or studies with more than 5 patients were included. The aim was to evaluate the multidisciplinary team in the management of pelvic tumours in children. Limited articles described the management beyond the biological aspects. Supplemental references were sought to support or elaborate on article findings. Therefore, the important themes are discussed as a descriptive article. The flow diagrams and tables were constructed for descriptive purposes.

History

The patient history guides the initial differential diagnosis and investigational strategy [3]. At first contact the management trajectory of a patient by the multidisciplinary team is established and complements the diagnostic and management process.

Adolescent health

During the primary interview with adolescents, basic age-related information is important and includes the history regarding menstrual habits related to menarche, volumes and dysmenorrhea. The interview must be conducted in a secure environment in a non-threatening and non-judgemental way [4]. Only selected persons should be present, importantly those relating to the support of the child and medical personnel vital to obtaining consent and in the management of the tumour [5].

Establishing the sexual history indicates if trans-vaginal examinations are possible and pregnancy tests should be performed before any interventions or treatment is done. It is advisable to include a pregnancy test for documentation purposes, regardless of the history. The increased risk for sexually transmitted diseases associated with sexual contact should be determined [3].

Inheritance patterns

Most ovarian tumours are due to somatic mutations caused by factors acquired during a patient's lifetime. Inherited predispositions or germline mutations follow an autosomal dominant pattern and stem from both the maternal and paternal lineages [6].

Family and genetic history (see Table 1)

Screening for ovarian tumours in asymptomatic children and adolescents is not advised. A lower threshold for screening patients may be dictated by family and genetic information suggestive of a predisposition to ovarian tumours. The history of first-order relatives remains the most important predictor for ovarian malignancies. This is true especially if the history is from the paternal lineage [6]. Although a bi-directional relationship exists between ovarian tumours in adolescence and childhood and cancer predisposition syndromes, they are very rare. Mucinous epithelial malignancies and, to a larger degree, non-epithelial malignancies form the majority of this group. Dicer-1 syndrome, rhabdoid predisposition syndrome type 2 and Peutz-Jeghers syndrome have the highest association with ovarian pathology [7], whereas juvenile granulosa cell tumours are specifically associated with Ollier and Marfucci syndromes [8]. Table 1 illustrates cancer predisposition and ovarian tumour associated syndromes with their distinguishing clinical features. Meigs' syndrome is defined as the presence of ascites and/or hydrothorax in association with a benign ovarian tumour. In this syndrome the tumours are commonly leiomyomas and fibromas [9, 10].#

Table 1: Predisposition syndromes		
Prevalence	1/3	2/3
Grade	Low grade/borderline	High grade
Mutations	MMR SMARCA4 PTEN, KRAS, BRAF, PIK3CA, ERBB2, CTNNB1, ARID1A PPP2R1A,	BRCA1/BRCA2 TP53 DICER1
Types of mutation	Somatic	Germline Somatic
Syndromes	Lynch syndrome Gorlin syndrome	Li-Fraumeni syndrome Ollier syndrome Marfucci syndrome
Clinical	Cystic or confined to ovary	Aggressive or metastatic disease
Origin		Fallopian tube histology related ovarian pathology associated with TP53 [11]

Clinical pathology

Pathological processes can occur along embryonal remnants, ectopic tissue and the ovaries [12]. The three main cell types of ovaries are responsible for diverse pathology. The coelomic epithelium gives rise to epithelial malignancies, whereas the stromal layer is responsible for gonadal stromal tumours [12]. Germ cell tumours originate within the primordial germ cells that migrate from yolk sac to gonads early in the development [1; 13]. Various other pathologies are related to aetiology rather

than histology [14]. Diagram 1 illustrates a clinical approach to the differential diagnoses with regard to anatomy and pathology.

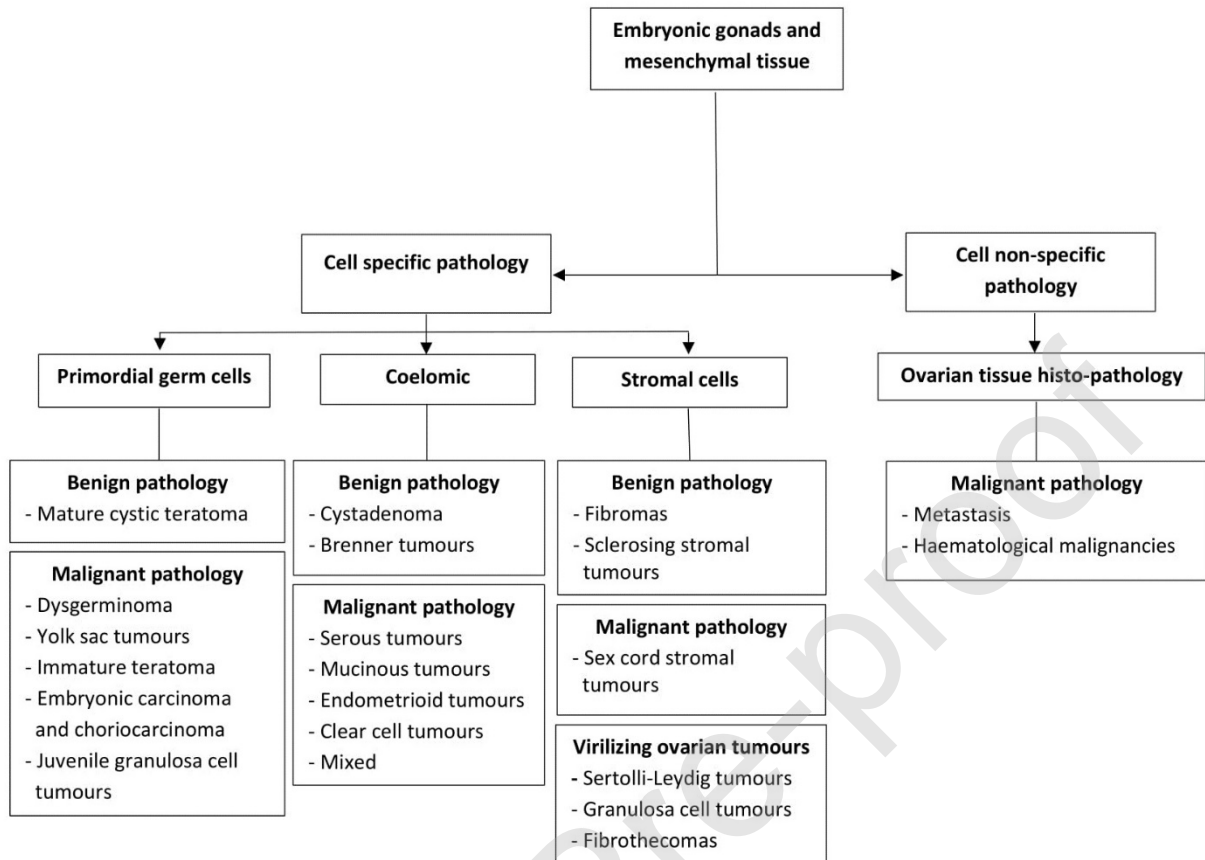


Diagram 1: A clinical approach to the histo-pathology of ovarian tumours

Age

During the prepubertal age, tumours are mainly of germ cell origin, including teratomas and dysgerminomas. Over 60% of tumours occurring in post pubertal ages are mainly epithelial neoplasms, with the most aggressive forms prevalent with increasing age into adulthood [15]. Although not limited to these values, the incidence of tumours increases from the age of 8–9 years with a peak at 18 years of age [15]. Germ cell tumours characteristically present at the ages of 2–5 years of age [16] (see Table 2).

Table 2: Age-related pathology	
Germ cell tumours	
Mature cystic teratoma	6–20yrs
Immature teratoma	6–20yrs
Embryonal carcinoma	10–20yrs
Yolk sac tumour	10–30yrs
Dysgerminoma	15–19yrs
Sex cord stromal tumours	
Juvenile granulosa cell tumours	<30yrs
Sclerosing stromal tumour	<30yrs
Sertoli-Leydig cell tumour	<30yrs
Thecoma-fibroma	>30yrs
Epithelial tumours	<20yrs
Gonadoblastoma	10–30yrs
Lymphoma or leukaemia	Any age
Benign pathology	
Meigs' syndrome	From prepuberty

Symptomatology

Symptoms correlate to the initial size and pathology, but not with the malignant potential of the tumour [17]. A patient could be asymptomatic or present with general non-specific general symptoms such as fatigue, fever and loss of weight. A high index of suspicion for malignant disease and progressive disease is prudent, especially with increasing symptoms and treatment-refractory clinical presentations [17]. In children the primary features are due to hormonal dysregulation, most often precocious puberty. Virilization, precocious puberty and hirsutism are present with hormone secreting masses such as Leydig cell tumours producing male sex hormones. Up to 30% of ovarian masses can present with signs of precocious puberty [2]. Sex cord stromal tumours can produce excess oestrogen resulting in precocious puberty, menstrual abnormalities, endometrial pathology or fibrocystic breast disease [18, 19].

Secondary symptoms due to obstruction such as analgesia resistant pain, urinary urgency, frequency and incontinence may develop in relation to the mass effect on the urinary tract system [17]. Bloating, constipation, nausea and vomiting is associated in adolescents and adults as well as dyspareunia in sexually active individuals [17]. Symptoms of paraneoplastic syndromes can be present before the primary ovarian symptomatology. These systemic effects are associated with the tumour and not due a direct effect of local tumours or metastases, but an auto-immune, hormonal or endocrine nature [20]. In children these syndromes mainly include nervous system disorders, connective tissue disorders and hematologic disorders, but can also include cutaneous disorders and nephrotic syndrome [20]. Neurologic presentations are frequently described in relation to ovarian disease and range from general non-specific symptoms to focal signs and behavioural changes. In the presence of unexplained symptomatology, further diagnostics should be done to identify local disease [21].

Radiology

The clinical presentation, tumour markers and radiological imaging contribute the most valuable differential information for diagnosis and subsequent treatment [1]. As the pathology in the paediatric and adolescent populations are notably distinct from that of adult populations, the interpretation of imaging by radiologists plays a vital role in setting up the differential diagnoses [1]. During the diagnostic evaluation the essential information for management comprises the anatomical location, the consistency, the possible pathological nature and the proximity to vital structures [1, 22]. Abdominal ultrasonography is the primary choice of imaging for screening, but CT-scan or MRI is important for peri-surgical planning.

The importance of imaging is to distinguish between potential benign or malignant tumours (see Table 3) [23, 24].

Radiological information	Benign	Malignant
Size	<10cm	>10cm
Locality	Single lesion	Multiple lesions
	Unilateral	Bilateral
Consistency	Cystic	Solid
	Homogenous	Heterogeneous
Shape	Well circumscribed	Invasive or metastatic
Calcifications	Not present	Present
Ascites	Generally, not present	Generally present

In general, most virilizing tumours are solid, well circumscribed, and without metastasis, ascites and calcifications. Cystic variance is associated with granulosa cell tumours. Macroscopic morphological identification might prove difficult as some tumours present as small masses [18]. The Simple IOTA ultrasound rules include increased blood flow compared to minimal or no blood flow in the mass as a malignant feature [25].

Ascitic fluid

Ascites, either as an exudate or as a transudate, can be a presenting sign of ovarian pathology and is present in approximately a third of patients [2, 26]. Ascites is not limited to malignant tumours but can be associated with benign tumours such as fibromas [10, 27]. Many speculative theories exist regarding the production of ascites in the presence of ovarian tumours. These include peritoneal irritability by the primary or metastatic tumours, obstructed lymphatic flow and absorption patterns, increased tumour ascites production and inflammatory cytokine stimulation often seen in the presence of tumours [28].

A combination of tumour markers and cytology on ascetic fluid can be diagnostic for ovarian tumours with a sensitivity of up to 90%, specificity of up to 96.5%, positive predictive values of 85.7%, and a negative predictive value of 97.6% [26,29]. The diagnostic significance of ascitic fluid is supported by the accurate correlation between tumour markers in the blood and ascetic fluid [30]. Post therapy determination of tumour markers in ascetic fluid has been described, but is limited by the absence of ascetic fluid due to treatment. Applying the triad model of diagnostics in malignancies, the presence of ascites and increased tumour markers in the presence of a mass has a

high sensitivity for malignant potential, yet definitive pathology to confirm the diagnosis is still important [30].

Direct visualization of pathogenic cells in ascetic fluid may serve as primary diagnostic medium where a biopsy is not be feasible. Increased leucocytes and proteins are associated with the presence of a malignancy [30,31]. In high malignant potential tumours, and to a lesser degree in low malignant potential tumours, positive cytological findings in ascetic fluid are related to pathology, stage and prognosis [26]. Non-ovarian malignancies, such as gastro-intestinal tumours or Krukenberg tumours, with distinguishing signet-ring cells, can also be distinguished through direct visualization and staining techniques. Genetic mutations and deletions, such as loss of heterozygosity and p53 mutations, can also be determined with the help of ascetic fluid [31].

In the rare cases where a haematological malignancy is suspected, flowcytometry plays a major role in the determination of the diagnosis. Ovaries contain B- and T-cell lymphocytic lineages within cortical granulomas, and rare lymphocytes are present in the ovarian stroma, follicles and corpora lutea [32,33]. Therefore, ovaries are potential organs for primary haematological malignancies. Although it has been reported that up to 1.5–2% of adult ovarian malignancies are of primary haematological origin, the incidence in children and adolescents is low [32,33]. The most common lymphomas of the ovaries in children are Burkitt's lymphoma or Burkitt-like lymphoma [32,33].

For both haematological and non-haematological malignancies, determining the presence of malignant cells in the ascetic fluid has implications for staging, and thus for treatment. In the absence of overt ascites pre-operatively, an intra-operative peritoneal fluid sample with malignant cells upstages patients to IC and IIC classification according to the FIGO staging. This has significant risk classification and treatment implications. The principle of upstaging and increased treatment intensity applies to haematological tumours, such as Burkitt's lymphoma, in the presence of malignant ascites [32,33].

Tumour markers

Role of tumour markers

Tumour markers, especially in blood and ascites, are essential pre-operative diagnostics of ovarian tumours to delineate between benign and malignant lesions (see Table 4) [1]. These biomedical markers are products of tumours or responses by the host. They serve as confirmation of the presence, pathological nature or malignant potential of the tumour. The level can contribute to identifying the secretory quality of a tumour, prognostication in the case of malignant germ cell tumours, and the long-term screening for relapse potential [34].

Although certain non-specific markers indicate the possibility of a malignancy, they have limited diagnostic specificity, whilst some specific markers should be evaluated against age-related values. These limitations do not disqualify the essential contribution of these markers with regard to clinical symptoms and imaging in management [34,35].

Ovarian associated tumour markers:

Tumour marker	Malignant diagnosis	Non-ovarian malignancy	Non-malignant variability
Alpha fetoprotein (AFP)	Yolk sac tumour Immature teratoma Embryonal carcinoma Sertoli-Leydig cell tumour (rare)#	Hepatoblastoma Hepatocellular carcinoma	Physiological variability Liver disease
Beta-human chorionic gonadotropin (β-hCG)	Choriocarcinoma Embryonal carcinoma Dysgerminoma (rare)#	Down syndrome	Physiological variability
Lactate dehydrogenase (LDH)	#Dysgerminoma	Haematological malignancies Abdominal malignancies Bone tumours	Haemolysis Various tissue pathologies and necrosis
CA-125	#Epithelial tumours	Breast cancer Endometrial malignancy	Benign breast disease Endometriosis Liver disease
Inhibin A	#Granulosa cell tumour		
Calcium (Ca⁺⁺)	Sex cord stromal tumours	Bone tumours Rhabdoid tumours	Parathyroid disease
Human epididymis protein 4 (HE4)	Malignant and borderline epithelial ovarian tumours	Non-small and small cell lung cancer	Cystic fibrosis

Interpretation of tumour markers

Various factors influence the evaluation of results, including age, anatomical site, histology and clinical stage of tumours. Yet tumour markers are validated, non-invasive tests with significant sensitivities and specificities that aid the diagnosis, prognostication and therapeutic monitoring of childhood malignancies [36]. LDH, AFP and β -hCG have been established as the most reliable markers in the classification of germ cell tumours in low, intermediate and high-risk groups. LDH has proven invaluable in the diagnosis of both nodal and extra-nodal haematological malignancy and as a measure of the degree of haemolysis of tumour bulk [35].

The absence of tumour markers do not exclude malignancies, as only about 50% malignant tumours present with raised values. Both the histological differences in different age groups and the genetic profile of tumours contribute to the complexity of interpreting results [37]. Hormone profiles change during normal development from a neonate to puberty and physiological values as well as the relevant isoforms of hormones varies.

Karyotyping

Chromosomal rearrangements aid in the determination of pathology subtypes, the identification in the activation of oncogenes, predisposition in developing of drug resistance and loss of tumour suppressor gene function [38].

Planning of management

The preservation of fertility and reproductive potential is paramount whilst applying the standard of care with the least morbidity [39,40]. All patients with a risk to reproductive potential during surgical interventions and administration of chemotherapy and radiotherapy should be counselled by a fertility specialist to discuss preservation options. Fertility can be preserved by various techniques, which should be discussed with the patient and caretakers prior to interventions that may be harmful to fertility [39, 40]. The two main procedures for preservation are: oocyte cryopreservation and ovarian tissue cryopreservation with pregnancy rates varying between 4–60%. Ovarian tissue cryopreservation is the only viable option for prepubertal patients, whilst oocyte cryopreservation should only be offered in patients where treatment delays are possible as it requires ovarian stimulation before oocyte harvesting [39, 40].

Role of pathologist and haematologist

Various body fluids, such as effusions or ascites, that are obtainable from less invasive techniques, such as punctures, should be aspirated for cytological evaluations or flow cytometry. A definitive diagnosis may prevent further invasive sampling. This may impose limitations on further biological testing.

Obtaining a frozen section during operative procedures may assist in navigating the extent of operative procedures by distinguishing between benign and malignant lesions [41, 42].

A pre-operative discussion with both the pathologist and haematologist may assist in determining the amount of sampling needed for accurate diagnosis and the request of further biological tests to aid diagnosis.

Surgical interventions

The final step after a careful multidisciplinary preparation for an ovarian tumour is surgery with a frozen section to aid in diagnostics. The aim is to decide on a surgical approach that is congruent with the expected pathology. A mass should be excised intact to avoid the spilling of potential malignancy cells. The approach is not only taken for therapeutic reasons but also to enable further diagnostics related to staging and direct visualization of abdominal structures (see Diagram 2) [43]. The main considerations remain the potential diagnosis that indicated the procedure, objectives during the intervention, preventing co-morbidities, preserving fertility and, but not primarily, the aesthetics of the incision, especially in adolescent females [43].

The size of the incision must validate the technical aspects of the surgery related to the tumour size, further exploration of organs and lymph nodes as well as sampling. To avoid the spilling of tumours, especially in larger masses, a laparotomy should be done in addition to a laparoscopy. Alternatively, it is possible to excise the mass and puncture it in a laparoscopic bag. This achieves a reduction the tumour size without spilling, but allows a removal by port site [44].

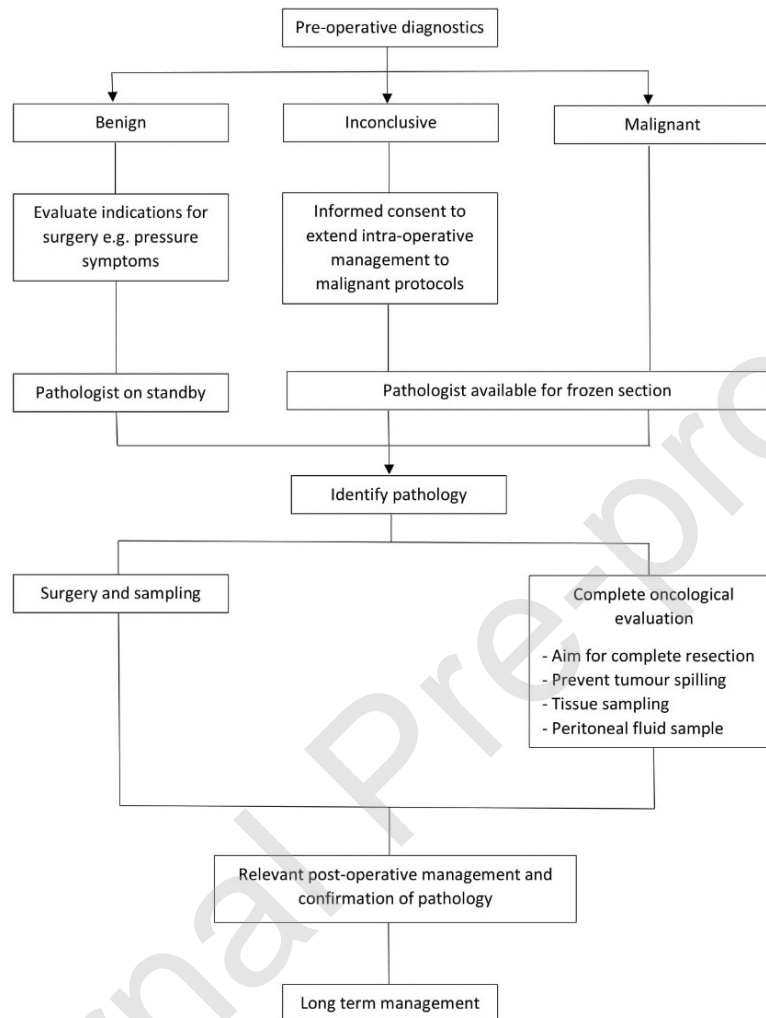


Diagram 2: Surgical approach to ovarian tumours

Medical interventions

Medical treatment is dictated by the final diagnosis. With an oncological diagnoses, a paediatric oncologist must be consulted, and speciality related physicians for benign diagnoses. Further supportive care, such as oestrogen replacement therapy in a case of bilateral ovariectomy, must be initiated.

Atypical clinical presentations

In cases where clinical and diagnostic testing do not correlate or define a conclusive diagnosis, pathologies normally reserved for adults should be considered. For these purposes tumour markers,

such as carcinoembryonic antigen (CEA), and diagnoses more prevalent in older ages, such as carcinomas and myomas, can be investigated [34]. Malignant and borderline epithelial ovarian tumours in the paediatric and adolescent population are extremely rare but can be diagnosed by an elevated human epididymis protein 4 tumour marker [45,46].

Auxiliary services

Since patients in paediatrics, reproductive health and oncology are in vulnerable situations, psychosocial support through social services, psychologists, cultural and religious liaisons must always be offered.

Ethics

When managing ovarian disease, several ethical factors are intrinsic to patient care and influence medical, emotional and psychological health originating from identity, fertility and planning for the future in terms of family planning and sexual health [47]. Informed consent forms part of both medical and surgical management to ensure that no harm or minimal negative short- or long-term irreversible effects with consideration of the risk-to-benefit ratio, are discussed [48]. Weighing psycho-emotional aspects such as aesthetics during large incisions for oncological management, in the presence of potential life-threatening diagnosis, are a priority [48]. This is especially true where loss of fertility or permanent internal and external scarification may occur. There are several considerations when a conclusive diagnosis will only be made during abdomino-pelvic surgery, which ranges from a basic diagnostic biopsy, removal of tissue and lifesaving interventions. Counselling should be provided in the presence of caretakers and psychologists as part of the multi-disciplinary team [48]. For these purposes team discussions may include religious representatives, adolescent health specialists, social services and even ethics committee representatives [49].

Genetic counselling

Genetic counselling is important for three main reasons: Firstly, when a genetically linked disease is diagnosed that forms part of a syndrome with future sequelae, extensive counselling must be done and a long-term management plan for the screening, possible prevention and interventions for symptoms should be planned [50-52]. Secondly, where inherited diseases are diagnosed the risks of carrying them over to future children must be discussed [50-52]. Thirdly, in inherited diseases the risk of the development of the disease in other family members must be assessed and the family counselled, especially in autosomal dominant diseases [50-52].

Multidisciplinary team approaches

Collaborative management partners share the responsibility to assess the scope of the health problem, planning the management and supporting the patient and family through the various hospital systems. This must be done in consideration not only of the culture, traditions and social importance of the patients, but also of various team members with their respective expertise, to enable the full decision-making capacity of all stakeholders involved. Everybody should benefit from the information and skills of the team to ensure the most beneficial and comprehensive medical care. This may include research opportunities that could benefit others beyond the treatment team.

Conclusion

Ovarian tumours in children and adolescents are rare and predominantly benign, yet can present with local pressure symptoms or systemic symptoms of virilization. A high index of suspicion for malignant pathology, constituting a third of ovarian tumours, is important. During management a multidisciplinary team is essential for the physical and psycho-emotional wellbeing of this vulnerable population of patients.

Declaration of interests

None

References

1. Heo SH, Kim JW, Shin SS, Jeong SI, Lim HS, Choi YD, et al. Review of ovarian tumors in children and adolescents: Radiologic-pathologic correlation. *Radiographics* 2014 Nov–Dec; 34(7): 2039–55. doi: 10.1148/rg.347130144.
2. Biggs W, Marks S. Diagnosis and management of adnexal masses. *Am Fam Physician* 2016; 93(8): 676–81.
3. Omar HA, et al, eds. Pediatric and adolescent sexuality and gynaecology. Principles for the primary care clinician. Nova Science Publishers, Inc, New York, 2010. Chapter 11: Ovarian tumours in children and adolescents, p597–627.
4. Sacks D, Westwood M. An approach to interviewing adolescents. *J. Paediatr Child Health* 2003; 8(9): 554–56.
5. Ehrman WG, Matson SC. Approach to assessing adolescents on serious or sensitive issues. *Pediatr Clin North Am* 1998; 45(1): 189–204.
6. Eng KH, Szender JB, Etter JL, Kaur J, Poblete S, Huang RY; et al. Paternal lineage early onset hereditary ovarian cancers: A familial ovarian cancer registry study. *PLoS Genet* 2018; 14(2): e1007194.
7. Foulkes W, Kamihara J, Evans D, Diller L. Cancer surveillance in gorlin syndrome and rhabdoid tumor predisposition syndrome. *Clin Cancer Res* 2017; 23(12): e62–67.
8. Goudie C, Witkowski L, Vairy S, McCluggage WG, et al. Paediatric ovarian tumours and their associated cancer susceptibility syndromes. *J Med Genet* 2018; 55: 1–10.
9. Santangelo M, Battaglia M, Vescio G, Sammarco G, Gallelli G, Vetere A, et al. Meigs' syndrome: Its clinical picture and treatment. *Ann Ital Chir* 2000; 71(1): 115–19.
10. Tarnowski B, Krolewski P. True and pseudo-Meigs syndrome. *Ginekol Pol* 1998; 69(11): 813–16.
11. Erickson BK, Conner MG, Landen CN Jr. The role of the fallopian tube in the origin of ovarian cancer. *Am J Obstet Gynecol.* 2013; 209(5): 409–14.
12. Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology, 7th ed. Philadelphia: Lippincott-Williams and Wilkens, 2015. Chapter 35: Germ cell tumors, p899–918.
13. Zhang M, Jiang W, Li G, Xu C. Ovarian masses in children and adolescents: An analysis of 521 clinical cases. *J Pediatr Adolesc Gynecol* 2014 Jun; 27(3): e73–77.

14. Oltmann SC, Fischer A, Barber R, Huang R. Pediatric ovarian malignancy presenting as ovarian torsion: Incidence and relevance. *J Pediatr Surg* 2010; 45(1): 135–39.
15. Toss A, Tomasello C, Razzaboni E, Contu G, Grandi G, Cagnacci A, et al. Hereditary ovarian cancer: Not only *BRCA* 1 and 2 genes. *BioMed Res Int* 2015; Article ID 341723, <http://dx.doi.org/10.1155/2015/341723>.
16. Shanbhogue, A, Shanbhogue, K, Prashad, S, et al. Clinical syndromes associated with ovarian neoplasms: A comprehensive review. *Radiographics* 2010; 30: 903–19.
17. Givens V, Mitchell G, Harraway-Smith C, Reddy A, Maness DL. Diagnosis and management of adnexal masses. *Am Fam Physician* 2009; 80(8): 817.
18. Outwater EK, Marchetto B, Wagner BJ. Virilizing tumors of the ovary: Imaging features. *Ultrasound Obstet Gynecol* 2000; 15: 365–71.
19. Wang PH, Chao HT, Liu RS, Cho YH, Ng HT, Yuan CC. Diagnosis and localization of testosterone-producing ovarian tumors: Imaging or biochemical evaluation. *Gynecol Oncol* 2001; 83, 596–98.
20. Shanbhogue, A, Shanbhogue, K, Prashad, S, et al. Clinical syndromes associated with ovarian neoplasms: A comprehensive review. *Radiographics* 2010; 30: 903–19.
21. Kayser M, Kohler C, Dalmau J. Psychiatric manifestations of paraneoplastic disorders. *Am J Psychiatry* 2010; 167: 1039–50.
22. Lazar E, Stolar C. Evaluation and management of pediatric solid ovarian tumours. *Semin Pediatr Surg*; 1998, 7(1): 29–34.
23. Papic JC, Finell SE, Slaven JE, Billmire D, Rescorla FJ, Leys CM, et al. Predictors of ovarian malignancy in children: Overcoming clinical barriers of ovarian preservation. *J Pediatr Surg* 2014; 49(1): 144–48.
24. Madenci A, Levine B, Laufer M, Boyd TK, Voss SD, Zurakowski D, et al. Preoperative risk stratification of children with ovarian tumours. *J Pediatr Surg* 2016; 51 1507–12.
25. Garg S, Kaur A, Mohi JK, Sibia PK, Kaur N. Evaluation of IOTA Simple Ultrasound Rules to Distinguish Benign and Malignant Ovarian Tumours. *J Clin Diagn Res*. 2017;11(8):TC06–TC09.
26. Janagam C, Atla B. Study of ascitic fluid cytology in ovarian tumors. *Int J Res Med Sci*. 2017 Dec; 5(12): 5227–31.
27. Tjalma WAA. Ascites, pleural effusion, and CA 125 elevation in an SLE patient, either a Tjalma syndrome or, due to the migrated Filshie clips, a pseudo-Meigs syndrome. *Gynecol Oncol* 2005; 97: 288–91.
28. Yamanishi Y, Koshiyama M, Ohnaka M, et al. Pathways of metastases from primary organs to the ovaries. *Obstet Gynecol Int* 2011; Article ID 612817, 6 pages, <https://doi.org/10.1155/2011/612817>.
29. Karoo R, Lloyd T, Garcea G, Redway H, Robertson G. How valuable is ascitic cytology in the detection and management of malignancy? *Postgrad Med J* 2003; 79: 292–94.
30. Tuzun Y, Celik Y, Bayan K, Yilmaz S, Dursun M, Canoruc F. Correlation of tumour markers in ascitic fluid and serum: Are measurements of ascitic tumour markers a futile attempt? *J Int Med Res* 2009; 37(1): 79–86.
31. Parrella P, Zangen R, Sidransky D, Nicol T. Molecular analysis of peritoneal fluid in ovarian cancer patients. *Mod Pathol* 2003; 16(7): 636–40.
32. Norris HJ, Jensen RD. Relative frequency of ovarian neoplasms in children and adolescents. *Cancer* 1972; 30(3): 713–19.
33. Schultz KA, Sencer SF, Messinger Y, Neglia JP, Steiner ME. Pediatric ovarian tumors: A review of 67 cases. *Pediatr Blood Cancer* 2005; 44(2): 167–73.

34. Sandoval JA, Malkas LH, Hickey RJ. Clinical significance of serum biomarkers in pediatric solid mediastinal and abdominal tumors. *Int J Mol Sci* 2012; 13: 1126–53.
35. Oltmann SC, Garcia N, Barber R, Huang R, Hicks B, Fischer A. Can we preoperatively risk stratify ovarian masses for malignancy? *J Pediatr Surg* 2010; 45(1): 130–34.
36. Jobling T, Mamers P, Healy DL, MacLachlan V, Burger HG, Quinn M, et al. A prospective study of inhibin in granulosa cell tumors of the ovary. *Gynecol Oncol* 1994; 55(2): 285–89.
37. Masque-Soler N, Szczepanowski M, Leuschner I, Vokuhl C, Haag J, Calaminus G, et al. Absence of BRAF mutation in pediatric and adolescent germ cell tumors indicate biological differences to adult tumors. *Pediatr Blood Cancer* 2011; doi: 10.1002/pbc.24005.
38. Bernardini M, Weberpals J, Squire JA. The use of cytogenetics in understanding ovarian cancer. *Biomed Pharmacother* 2004; 58(1): 17–23.
39. Burns K, Hoefgen H, Strine A, Dasgupta R. Fertility preservation options in pediatric and adolescent patients with cancer. *Cancer* 2018 May 1; 124(9): 1867–76.
40. Resetkova N, Hayashi M, Kolp LA, Christianson MS. Fertility preservation for prepubertal girls: Update and current challenges. *Curr Obstet Gynecol Rep* 2013; 2(4): 218–25.
41. Abudukadeer A, Azam S, Zunong B, Mutailipu AZ, Huijun B, Qun L. Accuracy of intraoperative frozen section and its role in the diagnostic evaluation of ovarian tumors. *Eur J Gynaecol Oncol* 2016; 37(2): 216–20.
42. Hashmi AA, Naz S, Edhi MM, Faridi N, Hussain SD, Mumtaz S, et. al. Accuracy of intraoperative frozen section for the evaluation of ovarian neoplasms: An institutional experience. *World J Surg Oncol* 2016; 14: 91.
43. Raghaven R, Arya P, China S. Abdominal incisions and sutures in obstetrics and gynaecology. *Obstet Gynaecol* 2014; 16: 13–18.
44. Amer N, Amer M, Mishra R. Different techniques of tissue retrieval from abdominal cavity during minimal access surgery. *World J Laparosc Surg* 2013; 6(2): 63–68.
45. Nasioudis D, Alevizakos M, Holcomb K, Witkin S. Malignant and borderline epithelial ovarian tumors in the pediatric and adolescent population. *Maturitas*. 2017; 96: 45–50.
46. Gucer F, Kiran G, Canaz E, Kilinc M, et al. Serum human epididymis protein 4 can be a useful tumor marker in the differential diagnosis of adnexal masses during pregnancy: a pilot study. *Eur J Gynaecol Oncol*. 2015;36(4):406-9.
47. Crawshaw M. Psychosocial oncofertility issues faced by adolescents and young adults over their lifetime: A review of the research. *Hum Fertil (Camb)* 2013; 16(1): 59–63.
48. Beauchamp TL, Childress JF. Principles of biomedical ethics. 6th ed. New York, NY: Oxford University Press, 2008.
49. Barbour RS, Porter MA, Peddie VL, Bhattacharya S. Counselling in the context of fertility and cancer: Some sociological insights. *Hum Fertil (Camb)* 2013; 16(1): 54–58.
50. American Society of Clinical Oncology. American Society of Clinical Oncology policy statement update: Genetic testing for cancer susceptibility. *J Clin Oncol* 2003; 21(12): 2397–406.
51. Godard B, Hurlimann T, Letendre M, Egalite N; INHERIT BRCA. Guidelines for disclosing genetic information to family members: From development to use. *Fam Cancer* 2006; 5(1): 103–16.
52. Laberge A. Duty to warn at-risk family members of genetic disease. *Virtual Mentor* 2009; 11(9): 656–60.