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Ovarian cysts and tumours in children and adolescents

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Introduction

Ovarian masses are an uncommon finding in children and adolescents with an incidence of around 2.6/100000 per year excluding functional ovarian lesions of which the true incidence is unknown.[1,2] While ovarian tumours account for less than 1% of all cancers in children, the likelihood of malignancy found in ovarian masses in children and adolescents ranges from 9% -11%.[1,3] The most common ovarian masses identified in this age range are listed in Table 1. Up to 64% are neoplastic of which the large majority are germ cell tumours (GCT) (60-80%). Sex cord stromal cell tumours and surface epithelial tumours account for 5% and <20% respectively unlike in adult ovarian tumours where surface epithelial tumours predominate.[1,4,5]

Over treatment with oophorectomy of non-neoplastic and benign neoplastic lesions in this population can result in a significantly increased risk of early menopause and premature ovarian failure and its sequelae.[6] Not only are patients who have had a unilateral salpingo-oophorectomy more likely to be referred to infertility clinics, they have a shortened reproductive lifespan and decreased response to human menopausal gonadotrophins when compared to women with both ovaries.[7,8] To further compound the issue 10%-23% of patients with benign ovarian neoplasms have a lifetime risk of pathology in the contralateral ovary which could ultimately result in premature castration.[3,6]

As the majority of ovarian masses in this group are benign, contemporary approaches advocate for ovarian preservation by expectant management of asymptomatic ovarian cysts, detorsion of a torted ovary and cystectomy for benign neoplastic lesions. One should not neglect the important principle of always attempting to differentiate a malignant from a benign mass preoperatively as the management thereof differs significantly.[4,9] Failure to correctly identify malignant tumours could result in spillage at cystectomy and upstaging of disease as well as incomplete staging requiring second surgery and increased risk of relapse.[3,10]

Clinical presentation and diagnosis

History and Examination

Symptoms and signs are varied and non-specific in this heterogeneous group of tumours. In a study by Kirkhan et al 8.8% of the 114 patients who presented with adnexal masses were in fact asymptomatic and had a coincidental finding at the time of imaging for other disease.[9] Abdominal pain is the most common symptom, acute sharp pain associated with vomiting may be indicative of torsion or intermittent sharp pain demonstrating twisting and untwisting of the adnexa and cyclical pain in the menstruating patient may be as a result of endometriosis and associated endometriomas.[3,11] Severe pain with an acute abdomen could be as the result of cyst or tumour rupture. Malignant tumours are more likely to be larger in size and could present with abdominal swelling or a palpable mass with associated ascites and even hydrothorax.[1] In the rare instance of an estradiol-secreting granulosa cell tumour the prepubertal patient may present with precocious puberty namely onset of menstruation and signs of breast development, and the postmenarchal patient may present with menstrual irregularities.[10,12,13] Virilisation caused by testosterone secreting Sertoli-Leydig tumours may result in hirsutism, acne, deepening of the voice and clitoromegaly.[10] It is always important to enquire about sexual history and contraceptive use in the adolescent as tubo-ovarian abscess and pregnancy associated cysts are always possibilities.[3]

Table 1: Common benign and malignant ovarian masses in children and adolescents

Non-neoplastic benign
- Simple of follicular cysts
- Corpus luteal cyst
- Haemorrhagic cyst
- Endometrioma
- Ovarian torsion without associated tumour
- Ovarian abscess

Neoplastic benign
- Mature teratoma
- Epithelial tumour: serous or mucinous cystadenoma
- Thecoma
- Fibroma
- Borderline cystadenoma (low malignant potential)
- Gonadoblastoma (potential for malignant transformation)

Neoplastic malignant
- Immature teratoma
- Dysgerminoma
- Mixed germ cell tumour
- Yolk sac tumour
- Granulosa cell (juvenile) tumour
- Sertoli-Leydig cell tumour
- Choriocarcinoma (nongestational)
- Embryonal carcinoma
- Invasive epithelial carcinoma
- Metastatic

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Investigations
Tumour markers are not used routinely but play an important role in assisting in diagnosis in the setting of the complex suspicious ovarian mass, to facilitate preoperative planning and for follow up and monitoring of treatment response in the cancer setting. The British Society for Paediatric and Adolescent Gynaecology in their 2017 guideline recommend doing lactate dehydrogenase(LDH), alpha fetoprotein (AFP) and beta-human chorionic gonadotrophin (BHCG) testing for all complex ovarian masses that present in children and adolescents.[14] Tumour markers are non-specific, they may be elevated in 20% of benign tumours or other pathology and absence of a positive tumour marker does not rule out malignancy.[2,15] Table 2 show the relationship of the recommended tumour markers and germ cell tumours of the ovary.[3] Cancer antigen 125 (CA125) is less valuable in this population as it is elevated in epithelial ovarian carcinomas which are very rare, this tumour marker is also nonspecific and is often elevated in benign conditions such as normal menses, endometriosis and torsion.[10,11] Granulosa cell tumours are associated with increased oestradiol and inhibin while Sertoli-Leydig tumours will be associated with increased testosterone levels and inhibin. These tumour markers are not performed routinely.[11]

Table 2: Tumour markers and germ cell tumour of ovary[3]

	AFP	BHGG	LDH	Cal9-9
Immature teratoma	-	-	-	+
Dysgerminoma	-	-	+	-
Yolk sac tumour	+	-	-	-
Choriocarcinoma	-	+	-	-
Embryonal carcinoma	+	+	-	-

Imaging studies
Transabdominal or transvaginal ultrasonography (US) is the imaging modality of choice in assessing ovarian masses.[10] Transabdominal US alone can be used in young girls who are *virgo intacta*.[16] Features identified on ultrasound that are concerning for malignancy include large mass >8cm, solid components >2cm, papillary projections, ill defined borders, thick septations, associated pelvic or paraaortic lymphadenopathy as well as evidence of metastatic disease and ascites. Conversely obviously simple cystic structures are deemed benign and are considered for more conservative management.[6,17] Computed tomography (CT scan) and magnetic resonance imaging (MRI) are seldom used due to increased expense unless the US diagnosis is unclear or the extent of disease is unclear.[10]

Malignancy risk assessment
Many ultrasound based malignancy risk assessment algorithms have been validated for ovarian masses in premenopausal women. Some of these models have a sensitivity and specificity as high as 93% and 83% respectively, these however have not been validated in this population.[17] The algorithms may use age, CA125 and US features of the mass, however in this population most of the tumours are of germ cell origin and not epithelial and CA125 is not applicable. In 3 large studies analysing ovarian masses in children and adolescents there was no significant difference in age between those with malignant and benign tumours, however increased size and solid components on US were more commonly associated with malignancy.[1,2,4] Papic et al designed a model that combined 3 predictors in this population to determine if a mass is malignant or not, namely size ≥10cm, the presence of solid components on US and positive tumour markers (AFP, BHCG, and/or LDH). During validation negative scores on all the criteria had a 100% benign rate and a post-test probability rate for malignancy of 0.25%, but the sensitivity of the model in predicting malignant tumours was only 41% (CI 29-54%).[2,4,6]

Management
Expectant
Expectant management is appropriate in the setting where imaging is suggestive of a physiologic ovarian cyst which is< 8cm in the postpubertal patients and <5cm in the prepubertal patients.[10,14] These cysts may be simple thin walled follicular cysts or they may display a fine internal lace like echogenicity indicative of internal haemorrhage as can be seen in haemorrhagic corpus luteal cysts. The British Society for Paediatric and Adolescent Gynaecology states that simple cysts <5cm do not need any follow up unless the patient is prepubertal, and those at <7cm can be reassured and followed up with annual US.[14,18] Studies have shown that most functional cysts under 10cm are likely to resolve spontaneously within 6 weeks to 3 months.[19,20] Oral contraceptives have not been shown to accelerate the resolution of functional ovarian cysts and should not be used unless indicated for other reasons.[21] Surgery may be indicated for functional cysts if they are >8cm as they are less likely to resolve spontaneously and more likely to undergo torsion or rupture. However, simple functional cysts as large as 20cm have been shown to resolve spontaneously, so cysts slightly larger than 8cm can be managed conservatively at the clinicians discretion provided patients are well counselled on cyst accidents and are likely to follow up.[6,9] Note that increased size can also be associated with malignancy.[2]

Surgery
Ovary-sparing surgery (OSS) involves the preservation of normal ovarian tissue where possible provided there is no suspicion of malignancy. It is well documented that oophorectomy in this population group is associated with reduced ovarian reserve and may result in early menopause.[6] OSS techniques include ovarian cystectomy, minimally invasive cyst drainage techniques, cyst marsupialization, and detorsion of torted ovary. Table 3 describes the indications for surgery in children and adolescents with an ovarian mass adapted from the review by Amies Oelschlager et al.[10]

Table 3: Indications for surgery in children and adolescents with an ovarian mass

- Persistent symptoms in a functional cyst
- Clinical suspicion of torsion or acute abdomen
- Features suggestive of neoplasm (complex/solid, positive tumour markers, ascites)
- Failure of cyst resolution or cysts growth on serial imaging
- Large mass or complex mass or both
- Rapid virilisation or estrogenisation
- Malignancy - full staging surgery
- Mass complications - hydronephrosis

OSS techniques must be used for all ovarian cysts and masses that are most likely benign. Majority of neoplastic lesions are also benign and thus cystectomy should be the initial surgical goal unless there is a high suspicion of malignancy. For simple or follicular cysts that require surgery cyst drainage or cystectomy can be performed. Cyst drainage alone, however, is associated with recurrence. For more complex masses like endometriomas and mature teratomas cystectomies are advocated.[6] Very large ovarian cysts present as a challenge to the surgeon as it often appears that the cysts have replaced the ovary leaving nothing to preserve thereby resulting in oophorectomy. Histological review of ovarian cortices of ovaries maximally stretched by tumour have however been shown to demonstrate normal functional ovarian tissue.[6,22] Furthermore post operative studies comparing ovarian volume and antral follicles after resection of large tumours with little residual ovarian tissue revealed no significant difference when compared to the contralateral normal ovary after 3 menstrual cycles. In this scenario it is recommended that a superficial circumferential incision of the capsule is performed followed by mass excision while preserving capsular and hilar tissues.[2] This residual grossly normal tissue on the base of the mass often contains ovarian parenchyma. In the setting of benign neoplasias like mature teratomas the goal of surgery is to remove all the neoplastic tissue to avoid recurrence and preserve as much normal tissue as possible. This is done with meticulous dissection around the tumour.

Detorsion and cystectomy without complete oophorectomy of even an apparently necrotic looking torted ovary is currently recommended unless underlying malignancy is suspected.[9,10] The rate of malignancy in these specimens is documented to be as low as 0.4% to 3.5%.[3,6,23] There is an increasing body of evidence suggesting that there is full return to normal ovarian function in about 93% of patients.[2,23,24] Further motive to support conservative management is that there is a 3 -15% risk of developing a torsion or neoplasm of the contralateral ovary.[3] It was previously postulated that patients were at risk of pulmonary embolism following detorsion of an ovary due to stasis and thrombus formation in the ovarian veins.[3,11] However there have been no reported cases of thromboembolism following detorsion. Post operative surveillance is indicated to assess the ovary once the oedema has resolved to exclude any underlying masses. The role of oophoropexy remains unclear.[25]

The probability of OSS in this population has been show to increase if a gynaecologist is involved. This is most likely due to training and experience, gynaecologists are more familiar with conservative operations on the ovary and more comfortable to rule out the likelihood of malignancy preoperatively.[2,9] There is still much room for improvement as rates of OSS vary significantly, in a review of a large national database rates varied from 21.7% to 76.6% for benign ovarian neoplasms.[2,4]

For benign lesions a laparoscopic approach is indicated, it is well known to be associated with shorter hospital stay, decreased pain, better wound cosmesis and is more cost effective.[26] New modified cyst aspiration techniques allow for laparoscopic management of cysts larger than 25cm.[2,3] These include techniques such as extracorporal cystectomy following cyst drainage. There have been concerns about increased risk of spillage of cyst contents at laparoscopy and increased recurrence risk. In the study by Papic et al there was no difference in spillage rates between open and laparoscopic cystectomy.[2] It would also be important to mention that spillage from a mature teratoma only has a risk of chemical peritonitis in 0.2% of patients, provided the abdomen is thoroughly irrigated and suctioned.[27] Spillage is not associated with recurrence in mature teratomas.[6,13,14] A Cochrane review did not demonstrate increased recurrence rates between cystectomies done laparoscopically or open for benign disease.

While OSS is the ideal management approach for benign ovarian lesions, there may be some potential pitfalls if cystectomy has been performed on a misdiagnosed malignant tumour with possible intraoperative tumour rupture resulting in upstaging of the disease and the need for adjuvant chemotherapy. It is not known if intraoperative tumour rupture in this age group affects morbidity and mortality.[6,10]

Malignancy

If malignancy is suspected the goal of surgery is appropriate staging and removal of disease but with the aim of fertility preservation where possible. Laparotomy is recommended to facilitate complete staging.[3] Majority of the malignant tumours in this age group are of germ cell origin which not only tend to present at an earlier stage but are potentially curable with the advent of modern day chemotherapy.[28] The Children's Oncology Group recommended staging surgery for germ cell and sex cord stromal tumours includes collecting cytology on entry, inspection of peritoneum for implants and biopsy or excision where necessary, followed by palpation of lymph nodes with sampling of enlarged or firm nodes, inspection of omentum with biopsy of abnormal areas, inspection of opposite ovary with biopsy of abnormal areas and finally complete resection of involved ovary and fallopian tube if involved.[13] For epithelial cancers, cytoreductive surgery and lymphadenectomy is advocated to improve survival and response to chemotherapy. Studies have shown that the risk of incomplete surgical staging and it sequelae are significantly reduced if a gynaecologic oncologist is consulted.[29]

Frozen section to help establish the pathological cause intraoperatively and guide the extent of surgery required is not reliable in this setting. Sensitivity of frozen section declines significantly with the increasing size of tumours and it was found in a study by Eltabbakh et al that 23% of tumours that were declared borderline were in fact malignant on final histology.[10,30]

Special considerations

Mature teratoma

These are the most common benign ovarian neoplasms in this age group. On US they have a classic appearance, namely fat fluid levels, ''white ball'' appearance within the lesion indicative of a dermoid plug, a dermoid mesh representing long echogenic lines of hair floating in the cysts and ''tip of the iceberg'' appearance representing a partly echogenic mass. (3) These tumours do not resolve spontaneously, 14% develop a teratoma in the contralateral ovary within 3 years. Therefor OSS is preferable.(10,27)

Cystadenoma

Benign mucinous or serous cystadenomas are uncommon in children and adolescents. These tumours tend to be large and may present with pressure symptoms.[3] Cystectomy is the treatment of choice but recurrence have been described in a series of patients who have cyst rupture during surgery. Follow up of these patient is mandatory for this reason.[22]

Borderline tumours

Borderline epithelial ovarian tumours are known to recur in 11-36% of patients undergoing cystectomy but they have also been seen to recur in 15% of patients who underwent oophorectomy and 5.7% of patients having had a bilateral adnexectomy.[31] OSS with cystectomy alone can be considered in patients who desire fertility and in particular patients with

bilateral disease but close postoperative surveillance is necessary. Full staging is advocated even in those undergoing cystectomy as 20% have noninvasive and invasive metastatic implants.[32]

Malignant germ cell tumours
Dysgerminoma is the most common malignant GCT followed by immature teratomas, yolk sac tumours, embryonal carcinoma and choriocarcinoma. Fertility preservation is the surgical standard of care for these tumours namely oophorectomy followed by full staging surgery. Modern day chemotherapy postoperatively has seen an improvement in 5 year survival rates of up to 90 -95%.[3,27]

Sex cord and stromal tumours
This group of tumours includes granulosa cell tumours, thecomas, fibromas, Sertoli-Leydig tumours and combinations of the above. These only account for 5-8% of ovarian malignancies. The majority tend to present as a low-grade disease that usually follows a nonaggressive clinical course in younger patients. Surgery is based on fertility sparing principles as with GCTs. The need for chemotherapy is dependent on grade and stage of disease.[3]

Conclusion

Ovarian cysts and masses in children and adolescents comprise of a large heterogenous group of pathologies. Majority of the causes are benign and thus ovarian preservation should be prioritized to optimise future fertility and longevity. In an attempt to strive to improve our management of benign lesions by aiming to reduce unnecessary oophorectomy rates we must not forget the importance of appropriate preoperative malignancy risk assessment. Complete tumour excision and appropriate staging is crucial in the outcomes ofpatients with malignancy and is important in guiding the need for adjuvant therapy. Special considerations must be made to tumours that are benign and those with low malignant potential that present with the possibility of recurring.

References

1. *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;27(3):e73-e77.*
2. *Papic JC, Finnell SM, Slaven JE, Billmire DF, Rescorla FJ, Leys CM.Predictors of ovarian malignancy in children: overcoming clinical barriers of ovarian preservation. J Pediatr Surg. 2014;49(1):144-148.*
3. *Eskander RN, Bristow RE. Adnexal Masses in pediatric and Adolescent Females: A Review of the Literature. Curr Obstet Gynecol Rep. 2012;1(1):25-32.*
4. *Hermans AJ, Kluivers KB, Wijnen MH, et al .Diagnosis and treatment of adnexal masses in children and adolescents. Obstet Gynecol.2015;125(3):611-615.*
5. *Péroux E, Franchi-Abella S, Sainte-Croix D, et al. Ovarian tumors in children and adolescents: A series of 41 cases. Diagn Interv Imaging.2015;96(3):273-282.*
6. *Gonzalez DO, Minneci PC, Deans KJ. Management of benign ovarian lesions in girls: a trend toward fewer oophorectomies. Curr Opin Obstet Gynecol.2017;29(5):289-294.*
7. *Bristow RE, Nugent AC, Zahurak ML, et al. Impact of surgeon specialty on ovarian-conserving surgery in young females with an adnexal mass. J Adolesc Health. 2006;39(3):411-416.*
8. *A, Lass. The fertility potential of a women with a single ovary. Hum Repro Update. 1999;5:546-550.*
9. *Kirkham YA, Lacy JA, Kives S, Allen L. Characteristics and management of adnexal masses in a canadian pediatric and adolescent population. J Obstet Gynaecol Can.2011;33(9):935-943.*
10. *Amies Oelschlager AM, Gow KW, Morse CB, Lara-Torre E. Management of Large Ovarian Neoplasms in Pediatric and Adolescent Females.J Pediatr Adolesc Gynecol. 2016;29(2):88-94.*
11. *E, Lara-Torre.Ovarian neoplasias in Children. J Pediatr Gynecol. 2002;15(1):47-52.*
12. *Major T, Borsos A, Lampé L, Juhász B. Ovarian malignancies in childhood and adolescence. Eur J Obstet Gynecol Reprod Biol. 1995;63(1):65-68.*
13. *Amies Oelschlager AE, Sarwin R. Teratomas and Ovarian Lesions in Children. Surg Clin N Am. 2012;92(3):599-613.*
14. *Ritchie J, O'Mahony F,Garden A. Guideline for the management of ovarian cysts and children in adolescents. The British Society for Paediatric and Adolescent Gynaecology [Internet]. June2017.http://www.britspag.org [Accessed on 10 June 2018.]*
15. *Spinelli C, Pucci V, Buti I, et al. The role of tumour markers in the surgical approach of ocarian masses in pediatric age group: a 10-year study and literature review. Ann Surg Oncol.2012;19: 1766-1773.*
16. *Zolton JR, Maseelall PB. Evaluation of ovarian cysts in adolescents. Open J Obstet Gynecol. 2013;(3):12-16.*
17. *Kaijser J, Van Hoorde K, Van Calster B, et al. Diagnosing adnexal tumours before surgery: a criticalappraisal of recent evidence. The Obstetrician & Gynaecologist. 2015;17(3):163-171.*
18. *Domingos E, Johns J, Ross J.An update on the diagnosis and management of ovarian torsion. The Obstetrician & Gynaecologist.2012;14:229-236.*
19. *Spanos WJ. Preoperative hormonal therapy of cystic adnexal masses. Am J Obstet Gynecol.1973; 54(5):775-777.*
20. *Brandt ML, Helmrath MA. Ovarian cysts in infants and children. Semin Pediatr Surg.2005;14: 130-134.*
21. *Grimes DA, Jones LB, Lopez LM, Schulz KF. Oral contraceptives for functional ovarian cysts. 2014, Cochrane Database of Syst Rev [Internet]. 2014 [cited 2014 April 29]. Available from: http://www.cochrane.org/CD006134/FERTILREG_oral-contraceptives-to-treat-cysts-of-the-ovary*
22. *Chabaud-Williamson M, Netchine I, Fasola S, et al. Ovarian-sparing surgery for ovarian teratoma in children. Pediatr Blood Cancer.2011;57:429-434.*
23. *Oltman SC, Fischer A, Barber R, et al. Pediatric ovarian malignancy presenting as torsion: incidence and relevence. J Pediatr Surg.2010;45:135-139.*
24. *Templeman C, Hertweck SP, Fallat ME. The clinical coarse of unresected ovarian torsion. J Pediatr Surg.2000;35:1385-1387.*
25. *Broach AN, Mansuria SM, Sanfilippo JS. Pediatric and adolescent gynecologic laparoscopy. Clin Obstet Gynecol.2009;52:380-389.*
26. *Yuen PM, Yu KM, Yip SK, et al. A randomized prospective study of laparoscopy and laparotomy in the management of benign ovarian masses. Am J Obstet gynecol. 1997;177(1):109-114.*
27. *Vaysse C, Delsol M, Carfagna L, et al. Ovarian germ cell tumours in children. Management,survival and ovarian prognosis. A report of 75 cases. J Pediatr Surg.2010;45:1484-1490.*
28. *Dimopoulos MA, Papadimitriou C, Hamilos G, et al.Treatemnt of ovarian germ cell tumours with a 3-day bloemysin, etoposide and cisplatin regimen: a prospective mulitcenter study.Gynecol Oncol.2004;95(3):695-700.*
29. *Eskander RN, Bristow RE, Saenz NC, Saenz CC. A retrospective review of the effect of surgeon speciality on the management of 190 benign and malignant pediatric and adolescent adenxal masses. J Pediatr Adolesc Gynecol. 2011;24(5):282-285.*
30. *Eltabbakh GH, Charboneau AM, Eltabbakh NG. Laparoscopic surgery for large benign ovarian cysts. Gynecol Oncol. 2008;108(1):72-76.*
31. *Morice p, Camatte S, Hassan J, et al. Clinical outcomes and fertility after conservative treatement of borderline ovarian tumours. Fertil Steril. 2001;75(1):92-96.*
32. *Cadron I, Leunen K, Van Gorp T,et al. Managment of borderline ovarian neoplasms. J Clin Oncol. 2007;25(20):2928-2937.*