Investigation and management of an ovarian mass

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Background

Ovarian masses are very common in pre- and postmenopausal women and are typically an incidental finding.

Objective

This article aims to provide a systematic approach to an ovarian mass for general practitioners including investigations, risk of ovarian cancer and referral considerations.

Discussion

Investigation for an ovarian mass includes both transvaginal and transabdominal ultrasound. Simple, anechoic cysts <5 cm in premenopausal women are likely to be benign and do not require further follow-up. The use of the cancer antigen 125 (Ca125) tumour marker can be unreliable in premenopausal women given the low sensitivity for ovarian cancer; however, it is useful in postmenopausal women. Ca125 is used in conjunction with ultrasound findings and is used to determine risk of ovarian cancer through the risk of malignancy index (RMI). Gynaecological oncology referral is reqired if RMI is >200. Complications of ovarian cysts include cyst rupture and torsion. Torsion is a gynaecological emergency and requires urgent review.

Keywords

ovarian neoplasms; ovarian diseases

Ovarian masses or cysts are very common and 10% of women have an operation during their life for investigation of an ovarian mass.[1] These masses are typically found in asymptomatic women who have imaging for another reason, or for investigation of non-specific abdominal or pelvic pain. In premenopausal women, these cysts are typically benign; however, it is important to determine if further investigation is required. The overall incidence of a symptomatic ovarian cyst in a premenopausal female being malignant is approximately 1 in 1000, increasing to 3 in 1000 at the age of 50 years.[1] The purpose of this article is to provide a systematic approach to an ovarian mass for general practitioners (GPs), outlining appropriate investigations and recommendations for specialist referral.

Initial assessment[2]

A thorough history should be taken, with specific attention to:
- Risk factors:
  - family history of breast, colon, uterine or ovarian cancer, hereditary ovarian cancer syndrome (BRCA gene mutation/Lynch syndrome)
- Protective factors
  - parity and breastfeeding (50% reduced risk)
  - combined oral contraceptive pill
- Menopause status
- Symptoms, including those of endometriosis or malignancy (persistent abdominal distension, change in appetite, pelvic pain, urinary urgency).

A careful examination, including an abdominal and vaginal examination, should be undertaken and the presence of lymphadenopathy assessed.

Investigations

Imaging

Ultrasonography

Transvaginal and transabdominal ultrasound views should be obtained.[1,3] This allows better differentiation and characterisation of the mass. The only definitive diagnosis of an ovarian mass is through histology; however, there are typical characteristics of certain structures seen on an

ultrasound. Although ultrasonography is the best mode of imaging we have for assessment of ovarian pathology, its sensitivity and specificity for the diagnosis of ovarian cancer is only 86–91% and 68–81% respectively.[3]

The International Ovarian Tumor Analysis (IOTA) Group has developed a list of characteristics for benign and malignant masses.[1,4,5] These rules are used in premenopausal women; however, similar characteristics are also used in the risk of malignancy index (RMI), which is discussed later. The IOTA Group rules are defined as benign or B-rules and malignant or M-rules (*Table 1*). Any patient with an M-rule should be referred to a gynaecologist.[4,5] The presence of ascites has

a positive predictive value of 95% for ovarian cancer.[6]

Computed tomography and magnetic resonance imaging

Ovarian masses may be seen on computed tomography (CT) and magnetic resonance imaging (MRI). These are typically incidental findings. Assessment with ultrasonography is required to further assess the character of the mass. The use of CT or MRI in the assessment of an ovarian mass does not improve the sensitivity or specificity obtained through ultrasonography in the detection of ovarian cancer. MRI may be useful in assessment of large cysts that are difficult to assess on an ultrasound.[1]

Tumour markers

Serum Ca125

Serum Ca125 is a glycoprotein antigen and is the most widely used tumour marker in the assessment of ovarian masses. In premenopausal women, Ca125 should be measured only if the ultrasound appearance of a mass raises suspicion of malignancy. It is unreliable in differentiating malignant from benign, as Ca125 >35 U/ml has a sensitivity and specificity for ovarian cancer of <80% (potentially as low as 50–60%).[3] It can also be raised in conditions such as endometriosis, fibroids, adenomyosis and pelvic infection. If Ca125 is elevated, consider repeating 4–6 weeks after the initial test.[7] Rapidly rising levels are more likely to be associated with malignancy rather than levels that do not change. Discussion with a gynaecological oncologist is recommended in patients with a Ca125 >250 U/ml.[1,3]

In postmenopausal women, Ca125 should be measured routinely. Ca125 of >35 U/ml has a sensitivity of 69–97% and specificity 81–93% for the diagnosis of ovarian cancer.[3] This result should then be used in conjunction with ultrasound findings and menopause status in RMI.

Human epididymis protein 4

Human epididymis protein 4 (HE4) is another tumour marker currently available for the assessment of ovarian cancer. It has a similar sensitivity as that of Ca125 in comparing ovarian cancer to healthy controls, but is not elevated in as many common benign gynaecological conditions. It is used in conjunction with Ca125 in the Risk of Malignancy Algorithm (ROMA).[8,9] HE4 can be falsely elevated in patients with impaired renal function, and can also be elevated in endometrial, primary liver and non-small cell lung cancer.[10] The American, UK and Australian guidelines do not address the usefulness of HE4 or ROMA in assessing risk for ovarian cancer. An HE4 level in isolation is difficult to interpret, and its usefulness in a clinical setting is being reviewed. HE4 is currently used in the USA for monitoring recurrence or progression of epithelial ovarian cancer.[3,8] HE4 is not currently

Table 1. IOTA Group ultrasound rules to classify masses as benign or malignant[1,4,5]	
Benign (B-rules)	**Malignant (M-rules)**
Unilocular cysts	Irregular solid tumour
Presence of solid components where the largest solid component <0.7 cm	Ascites
Presence of acoustic shadowing	At least four papillary structures
Smooth multilocular tumour with largest diameter <10 cm	Irregular multilocular solid tumour with largest diameter >10 cm
No blood flow	Very good blood flow

Table 2. Risk of malignancy index[1,6,15]	
Risk of malignancy index (RMI) = ultrasound findings x menopause status x Ca125 (U/ml)	
Findings	**Points**
Ultrasound findings include: • multilocular cyst • solid area • metastases • ascites • bilateral lesions	0 points: no features (unilocular) 1 point: 1 feature 3 points: 2–5 features
Menopausal status	1 point – premenopausal
	3 points – postmenopausal*
Ca125 (U/ml)	Actual level
Example For a postmenopausal* woman with a left multilocular cyst and Ca125 of 40 U/ml: RMI = 1 point for ultrasound x 3 points for postmenopausal x 40 U/ml RMI = 120, therefore, gynaecology referral would be recommended *Postmenopausal = no period for 1 year, or over 50 years in women who have had a hysterectomy	

covered by Medicare and costs approximately $45 for the patient.[11] It is not recommended as a screening test for ovarian cancer.

Other biochemical markers

Alpha-feta protein (AFP), human chorionic gonadotropin (hCG) and lactate dehydrogenase (LDH) are also recommended in women under 40 years who have a complex mass on ultrasound, as these can be elevated in germ cell tumours.[1,9]

Carcinoembryonic antigen (CEA) and cancer antigen 19.9 (Ca19.9) are two other tumour markers that are commonly ordered for the investigation of an ovarian mass; however, their application to clinical practice is unclear. The usefulness of these tests is not discussed in the UK and Australian guidelines. They are non-specific and can be elevated in benign and malignant non-gynaecological conditions. Ca19.9 may be useful in the assessment of mature

cystic teratomas; however, its usefulness in differentiating mature cystic teratomas from ovarian cancer is unclear.[12,13] CEA seems to be an independent prognostic factor for mucinous ovarian cancer.[14] Further investigation is required.

Risk of malignancy index

The risk of malignancy index (RMI) is the most widely used risk assessment for ovarian malignancy. Developed in 1990, it uses serum Ca125, menopausal status and findings on ultrasound (RMI = ultrasound findings x menopause status x Ca125 U/ml). It is particularly useful in the assessment of postmenopausal women. Moderate risk is a RMI value between 25–200, and RMI >200 is considered high risk. An RMI >200 has a sensitivity of 87% and specificity of 97% for ovarian cancer and therefore requires urgent assessment by a gynaecological oncologist (*Table 2*).[1,6,15]

Management

There are three main forms of management – conservative, surveillance and surgical management. Deciding which is the appropriate management is based on assessment of symptoms, ultrasound findings, menopausal status, RMI (if applicable) and risk factors. An approach to management is outlined in *Figure 1*.

Premenopausal women

Asymptomatic women with a simple ovarian cyst <5 cm on ultrasound do not require follow-up. These simple cysts will resolve within three menstrual cycles. For simple cysts of 5–7 cm, a repeat ultrasound should be obtained, and for cysts of >7 cm surgical intervention should be considered. If surgery is required, a laparoscopic cystectomy is the operation of choice, as aspiration can cause recurrence.[16,17]
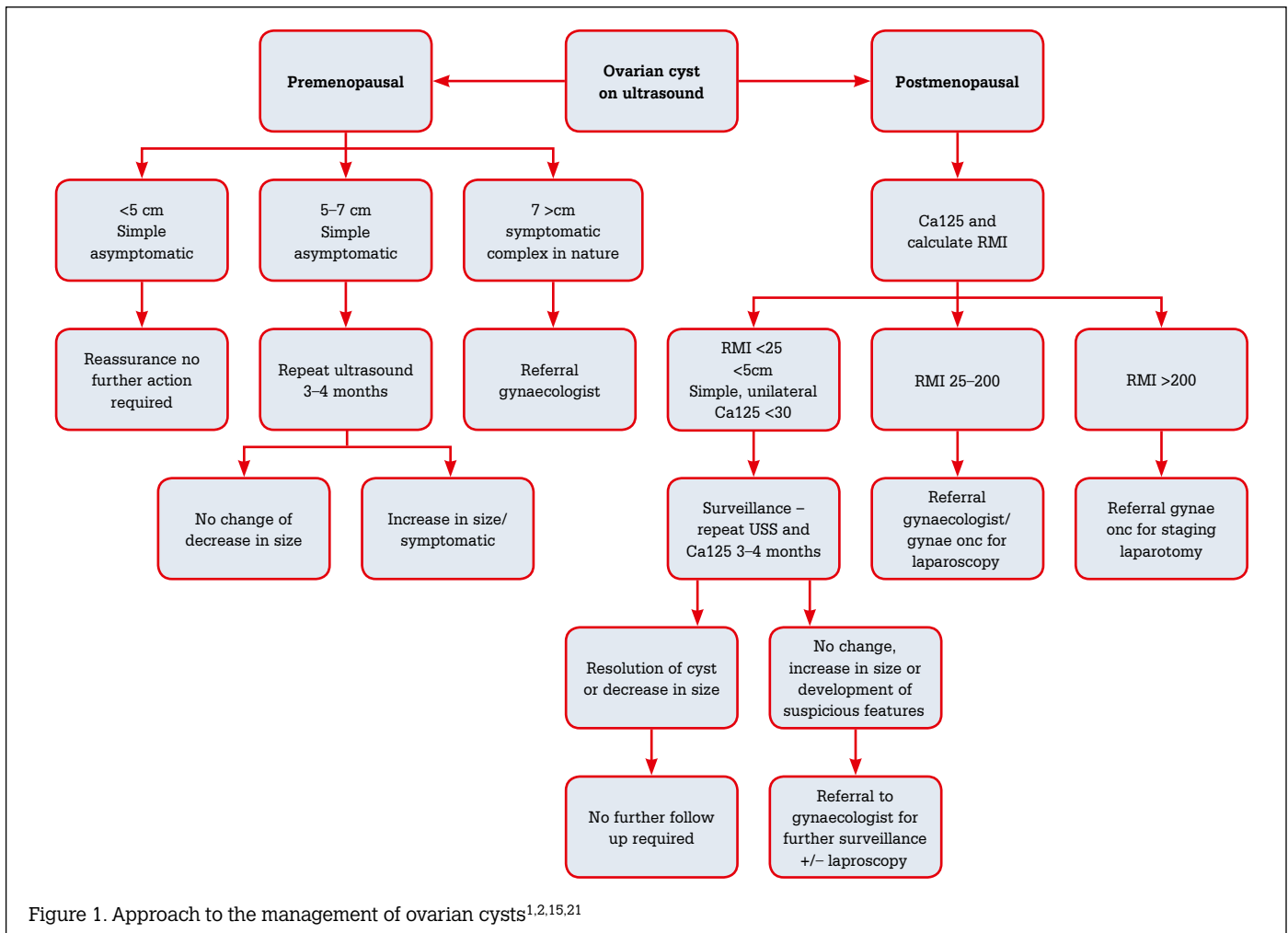

Figure 1. Approach to the management of ovarian cysts[1,2,15,21]

Postmenopausal women

Simple unilateral, unilocular ovarian cysts of <5 cm and low risk of malignancy (normal Ca125) can be managed conservatively as the RMI would be zero and 50% of these will resolve spontaneously in 3 months. Cysts of 2–5 cm should be rescanned in 3–4 months.[18–20] Women with a moderate-to-high risk RMI should be referred to a gynaecologist or gynaecological oncologist for consideration of surgical management. In addition, any woman who does not meet the criteria for conservative management should be offered surgical management. If malignancy is suspected, an oophorectomy is recommended rather than a cystectomy.[1,15,20] This allows removal of the cyst intact and prevention of spillage into the peritoneal cavity. A bilateral oophorectomy may be offered for postmenopausal women because the contralateral ovary may also be affected; however, there are no studies that have assessed malignancy after unilateral versus bilateral oophorectomy.[15,21]

Use of the combined oral contraceptive pill

Commencing the combined oral contraceptive (COC) pill does not hasten resolution of functional ovarian cysts, but can be used to prevent formation of cysts.[22,23]

Complications

Cyst rupture

Patients typically present with lower abdominal pain, and an ultrasound that shows free fluid in the abdomen with a collapsed cyst. An uncomplicated cyst rupture can be managed as an outpatient procedure with oral analgesia. Symptoms usually resolve within 24–72 hours. In women with a complicated cyst rupture and a large amount of free fluid/haemoperitoneum, management in a hospital setting with fluid resuscitation is recommended. Laparoscopy may be indicated if a patient becomes unstable or has ongoing pain.[23]

Ovarian torsion

Ovarian torsion involves a partial or complete rotation of the ovary onto its supporting ligaments, cutting off its blood supply. Presenting symptoms usually include sudden onset lower abdominal pain, nausea and vomiting with a palpable adnexal mass. The primary risk factor for ovarian torsion is an ovarian mass >5 cm.[24–26] Ovarian torsion is primarily a clinical diagnosis, but ultrasonography may be useful. One study showed a diagnostic accuracy of ultrasonography as 74.6%, with abnormal ovarian blood flow and presence of free fluid as the most diagnostic. Despite this, ultrasonography is not reliable in excluding an ovarian torsion.[26] Suspected ovarian torsion requires urgent gynaecological review. Surgery usually involves laparoscopy with de-torsion and ovarian conservation, but an oophorectomy may be performed if the ovary is not viable. Torsion is most commonly associated with benign conditions.[25,27]

Pregnant women with ovarian cysts

Ovarian masses are usually an incidental finding. The majority of these masses are benign and can be managed expectantly, as at least 50% resolve spontaneously during pregnancy.[28] The reported rate of complications with expectant management is <2%.[29] If a cyst is identified early on a dating ultrasound, a repeat ultrasound at 12–14 weeks should be performed to check if it has resolved.[29]

Operative intervention is indicated if malignancy is suspected, if there is an acute complication (eg torsion) or if the size is likely to cause obstetric or other problems. The ideal time of operation is after the first trimester, as this decreases the miscarriage rate and teratogenicity. The risk of ovarian cancer in pregnant women who are noted to have a cyst on ultrasound is <1%.[29,30]

Screening for ovarian cancer

For the general population, there are currently no national or international guidelines for screening for ovarian cancer. No investigation to date has been shown to have adequate sensitivity and specificity as a suitable screening test. A precursor lesion has yet to be identified. In particular, screening with transvaginal ultrasound has a high false-positive rate because of its inability to differentiate between malignant and benign masses. Serum Ca125 can be affected in a number of benign conditions and is elevated in

<50% of women with stage 1 ovarian cancer.[6]

Women with a very strong family history of breast and ovarian cancer should be referred for genetic counselling. Women who are carriers of the *BRCA1* mutation have a lifetime risk of ovarian cancer as high as 60%, and *BRCA2* as high as 40%.[6]

Key points

- Ultrasonography (transabdominal and transvaginal) is the main form of imaging in the assessment of ovarian masses.
- Ca125 can be unreliable in premenopausal women as it can be elevated in a number of benign conditions; however, it is useful in the assessment of postmenopausal women.
- RMI is used to assess risk of ovarian cancer and is based on menopause status, ultrasound findings and Ca125 levels.
- Unilateral, simple ovarian cysts that are <5 cm in premenopausal women are likely be functional cysts and no follow-up is required.
- Ovarian torsion is a clinical diagnosis and requires urgent gynaecological review.
- There is no routine screening for ovarian cancer for the general population.
- If concerned or unsure of management, seeking gynaecological advice is recommended.

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References

1. Royal College of Obstetricians and Gynaecologists. Management of suspected ovarian masses in pre-menopausal women. Green-Top Guideline. No 62. London: RCOG, 2011.
2. National Institute for Health and Clinical Excellence. Ovarian cancer: the recognition and initial management of ovarian cancer. NICE guidelines 122. London: NICE, 2011.
3. Myers ER, Bastian LA, Havrilesky LJ, et al. Management of adnexal mass. Evidence Rep Technol Assess 2006;130:1–145.
4. Timmerman D, Valentin L, Bourne TH, Collins WP, Verrelst H, Vergote I; International Ovarian Tumor Analysis (IOTA) Group. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. Ultrasound Obstet Gynecol 2000;16:500–05.

5   Timmerman D, Testa AC, Bourne T, et al. Logistic regression model to distinguish between the benign and malignant adnexal mass before surgery: a multicenter study by the International Ovarian Tumor Analysis Group. J Clin Oncol 2005;23:8794–801.

6   National Health and Medical Research Council. Clinical practice guidelines for the management of women with epithelial ovarian cancer. CP98. Camperdown: NHMRC, 2004.

7   Hensley ML, Robson ME, Kauff ND, et al. Pre- and postmenopausal high-risk women undergoing screening for ovarian cancer: anxiety, risk perceptions, and quality of life. Gynecol Oncol 2003;89:440–46.

8   Moore RG, McMeekin DS, Brown AK, et al. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecol Oncol 2009;112:40–46.

9   Shah CA, Lowe KA, Paley P, et al. Influence of ovarian cancer risk status on the diagnostic performance of the serum biomarkers mesothelin, HE4, and CA125. Cancer Epidemiol Biomarkers Prev 2009;18:1365.

10 Escudero JM, Auge JM, Filella X, et al. Comparison of serum human epididymis protein 4 with cancer antigen 125 as a tumor marker in patients with malignant and nonmalignant diseases. Clin Chem 2011;57:1534–44.

11 Price L. Tumour marker – HE4 and CA125 in ovarian cancer detection. Item 09148. Taringa (QLD): Sullivan Nicolaides Pathology, 2013.

12 Cho HY, Kim K, Jeon YT, Kim YB, No JH. CA19-9 elevation in ovarian mature cystic teratoma: discrimination from ovarian cancer – CA19-9 level in teratoma. Med Sci Monit 2013;19:230–35.

13 Ugur MG, Ozturk E, Balat O, Dikensoy E, Teke S, Aydin A. Do high levels of CA 19-9 in women with mature cystic teratomas of the ovary warrant further evaluation? Eur J Gynaecol Oncol 2012;33:207–10.

14 Høgdall EV, Christensen L, Kjaer SK, et al. Protein expression levels of carcinoembryonic antigen (CEA) in Danish ovarian cancer patients: from the Danish 'MALOVA' ovarian cancer study. Pathology 2008;40:487–92.

15 Royal College of Obstetrics and Gynaecologists. Ovarian Cysts in Postmenopausal Women. Green-Top Guideline. No 34. London: RCOG, 2010.

16 MacKenna A, Fabres C, Alam V, Morales V. Clinical management of functional ovarian cysts: a prospective and randomized study. Hum Reprod 2000;15:2567–9.

17 Levine D, Brown DL, Andreotti RF, et al. Management of asymptomatic ovarian and other adnexal cysts imaged at US: Society of Radiologists in Ultrasound Consensus Conference Statement. Radiology 2010;256:943–54.

18 Timmerman D, Testa AC, Bourne T, et al. Simple ultrasound-based rules for the diagnosis of ovarian cancer. Ultrasound Obstet Gynecol 2008;31:681–90.

19 Bailey CL, Ueland FR, Land GL, DePriest PD, Gallion HH, Kryscio RJ. The malignant potential of small cystic ovarian tumors in women over 50 years of age. Gynecol Oncol 1998;69:3–7.

20 Aubert JM, Rombaut C, Argacha P, Romero F, Leira J, Gomez-Bolea F. Simple adnexal cysts in postmenopausal women: conservative management. Maturitas 1998;30:51–54.

21 The American Congress of Obstetricians and Gynecologists. Management of adnexal masses. ACOG Practice Bulletin. July 2007; Vol 110; No 1.

22 Grimes DA, Jones LB, Lopez LM, Schulz KF. Oral contraceptives for functional ovarian cysts. Cochrane Database Syst Rev 2011;CD006134.

23 Bottomley C, Bourne T. Diagnosis and management of ovarian cyst accidents. Best Pract Res Clin Obstet Gynaecol 2009;23:711–24.

24 Houry D, Abbott JT. Ovarian Torsion: a fifteen-year review. Ann Emerg Med 2001;38:156.

25 White M, Stella J. Ovarian Torsion: 10-year perspective. Emerg Med Australas 2005;17:231–37.

26 Mashiach R, Melamed N, Gilad N, Ben-Shitrit G, Meizner I. Sonographic diagnosis of ovarian torsion: accuracy and predictive factors. J Ultrasound Med 2011;30:1205–10

27 Oltmann SC, Fischer A, Barber R, Huang R, Hicks B, Garcia N. Cannot exclude torsion – a 15-year review. J Pediatr Surg 2009;44:1212–16.

28 Whitecar MP, Turner S, Higby MK. Adnexal masses in pregnancy: a review of 130 cases undergoing surgical management. Am J Obstet Gynecol 1999;181:19.

29 Zanetta G, Mariani E, Lissoni A, et al. A prospective study of the role of ultrasound in the management of adnexal masses in pregnancy. BJOG 2003;110:578.

30 Leiserowitz GS, Xing G, Cress R, Brahmbhatt B, Dalrymple JL, Smith LH. Adnexal masses in pregnancy: how often are they malignant? Gynecol Oncol 2006;101:315.

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