

Ovarian cysts

Distinguishing the physiological from the concerning

NICHOLAS B. COMNINOS MB BS, MPH(Extn), FRACGP, FACHSHM

SHANNON F. ZAWADA BSc(Hons), MB BS, MMed, FRANZCOG

PHILLIPA RAMSAY MB BS, FRANZCOG, DDU, COGU

DEBORAH J. BATESON MB BS, MA(Oxon), MSc(LSHTM)

KIRSTEN I. BLACK MB BS, MMed, FRANZCOG, DDU, MFSRH, PhD

Ovarian cysts occur frequently in women of all ages and can be physiological, benign or malignant. As cysts often first present in primary care, it is important that GPs assess the cyst and determine appropriate follow up. Patient history, age, menopausal status and physical examination will help determine the risk of a concerning cyst and whether referral to a specialist is warranted. First-line investigations include transvaginal ultrasound and, in some cases, testing for cancer antigen 125 levels.

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Dr Comninus is a General Practitioner; and Advanced Trainee in Sexual Health Medicine, Sydney Sexual Health Centre, South Eastern Sydney Local Health District, Sydney. Dr Zawada is a Visiting Medical Officer Obstetrician and Gynaecologist at Canterbury Hospital, Sydney Local Health District, Sydney; and a Lecturer in Perinatal and Women's Health, Central Clinical School, The University of Sydney, Sydney. Dr Ramsay is a Visiting Medical Officer Obstetrician and Gynaecologist at Royal Prince Alfred Hospital, Sydney; and Associate Lecturer in Discipline of Obstetrics, Gynaecology and Neonatology, Faculty of Medicine and Health, The University of Sydney, Sydney. Clinical Associate Professor Bateson is the Medical Director of Family Planning New South Wales, Sydney; and a Clinical Associate Professor, Discipline of Obstetrics, Gynaecology and Neonatology, The University of Sydney, Sydney. Professor Black is the Joint Head of Discipline of Obstetrics, Gynaecology and Neonatology, The University of Sydney, Sydney, NSW.



Ovarian cysts can be physiological, benign or malignant. Although most ovarian cysts encountered in general practice are of no clinical concern, certain scenarios warrant further investigation, follow up and/or specialist referral. We present a structured approach to assessment based on common clinical scenarios (Flowchart), allowing GPs to distinguish physiological from more concerning ovarian cysts.

Ovarian cyst prevalence and classification

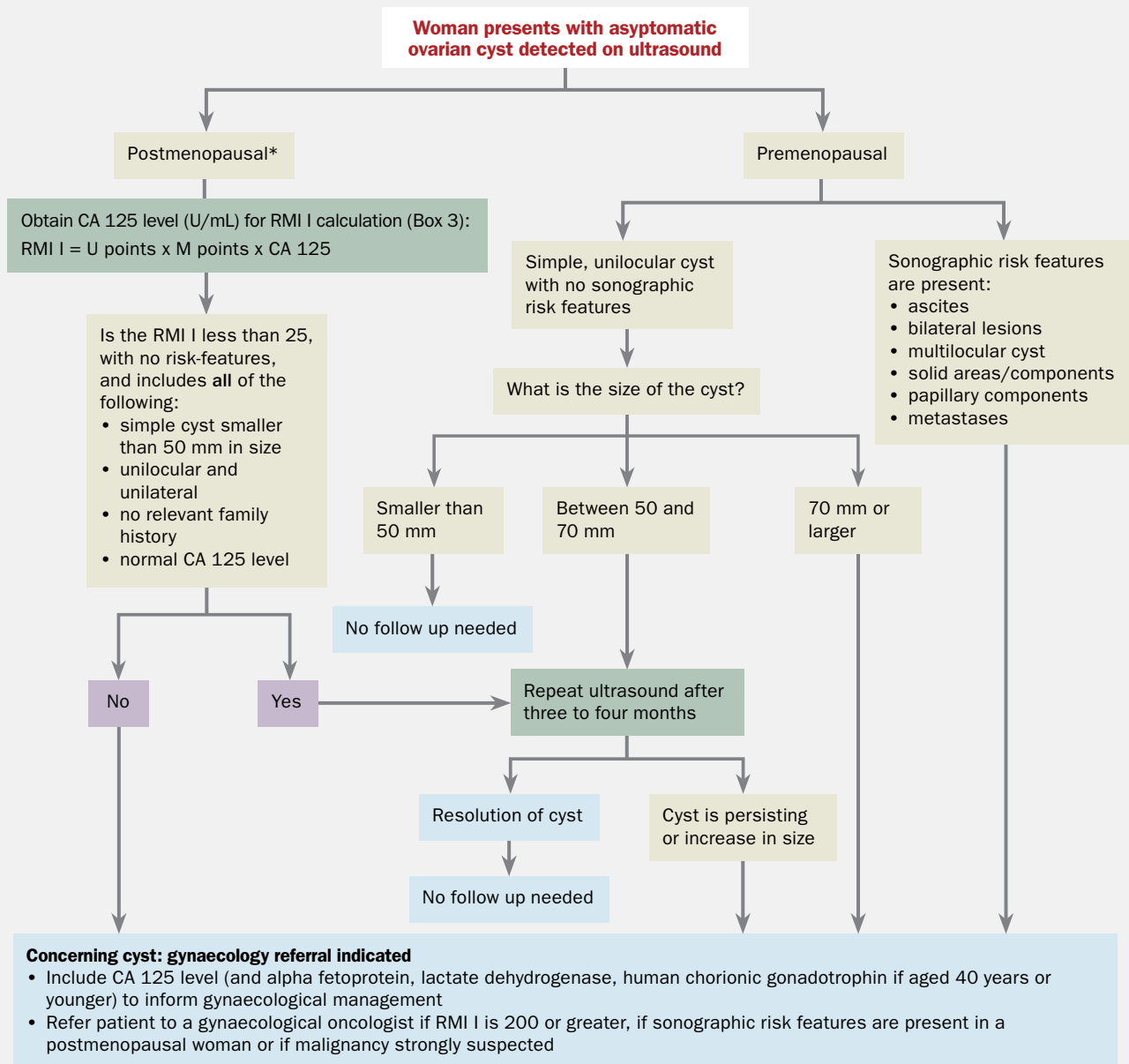
Ovarian cysts occur frequently in women of all ages. Their prevalence has been reported at 6.6% in asymptomatic premenopausal women and 14% among postmenopausal women.^{1,2} Common types of ovarian cysts include physiological or functional cysts (often ovulation related), haemorrhagic cysts, dermoid cysts, endometriomata, cystadenomas and malignant cysts (Box 1).^{3,4} Although most cysts are benign, ovarian carcinoma has an overall incidence of 9.8/100,000 in Australia, with a peak age at diagnosis of between 65 and 69 years.⁵ Late cancer diagnosis correlates with poor outcomes, underscoring the need for early diagnosis in the general practice setting.

Many women with cysts will present to GPs after incidental discovery on imaging/radiology. Key challenges include distinguishing physiological from concerning cysts, determining follow-up requirements and knowing when to refer to a specialist. The key clinical features, investigations and management points for GPs to consider are discussed in this article.

History and examination

Key clinical features guiding the management of ovarian cysts are outlined in Box 2.^{3,6-8} A patient history should assess risk factors for ovarian malignancy, including older age, postmenopausal status, nulliparity, *BRCA* mutations, Lynch syndrome and a family history of ovarian or breast cancer. According to recent international guidelines, age and menopausal status are particularly crucial in assessing ovarian cysts as ovarian cancer is much more common with advancing age^{3,4,6,7} and cysts after the menopause are unlikely to be oestrogen-related. GPs should ask about contraception, as physiological cysts may be more unexpected among women using contraceptive methods that suppress ovulation.

AN APPROACH TO MANAGING WOMEN WITH ASYMPTOMATIC OVARIAN CYSTS DETECTED ON ULTRASOUND



Abbreviations: CA 125 = serum cancer antigen 125; M = menopausal status; RMI = risk of malignancy index; U = ultrasound.

* Cystic lesions smaller than 1 cm in postmenopausal patients (no menstrual period for 12 months or aged over 50 years if patient has had hysterectomy) are usually deemed clinically inconsequential.⁴

GPs should also enquire about bloating or increased abdominal girth, early satiety, or the new onset of unexplained urinary symptoms.⁷ Although such symptoms are nonspecific, their persistent or frequent presence without clinical explanation should prompt investigation.⁷ Other

symptoms that warrant investigation include unexplained weight loss, fatigue or bowel habit changes, particularly in those aged 50 years and over.⁷

Physical examination includes recording body mass index, performing an abdominal examination for ascites and

masses, and a pelvic bimanual examination to assess the mass and its tenderness, nodularity and mobility.³ Where a combination of these symptoms are present in an older patient, or ascites or a pelvic mass is noted, immediate specialist referral is appropriate.

1. CAUSES AND CLASSIFICATION OF OVARIAN AND RELATED CYSTS³

Benign ovarian

- functional cysts
- endometriomas
- serous cystadenomas
- mucinous cystadenomas
- mature teratomas (dermoid cysts)

Benign nonovarian

- paratubal cysts
- hydrosalpinges
- abscesses (tubo-ovarian, appendiceal, diverticular)
- peritoneal pseudocysts
- pelvic kidneys

Primary malignant ovarian

- epithelial carcinoma-ovary, fallopian tube, peritoneum
- germ cell tumours
- sex-cord stromal tumours

Secondary malignant ovarian

- metastases

2. KEY CLINICAL FEATURES: ASSESSING OVARIAN CYSTS^{3,6-8}

History

- Persistent or frequent symptoms warranting evaluation for malignancy (especially if aged 50 years or over) such as:
 - abdominal/pelvic pain
 - urinary frequency or urgency
 - early satiety, bloating
- Ovarian malignancy can also present with nonspecific symptoms such as:
 - unexplained fatigue
 - weight loss
 - bowel habit change
- Acute ovarian event (e.g. torsion):
 - acute, intermittent lower abdominal pain (often but not always unilateral)
 - nausea and vomiting
 - fever and collapse
- Often asymptomatic

Examination

- General:
 - body mass index
 - vital signs
 - temperature
- Abdomen:
 - tenderness
 - mass
 - ascites
 - peritonism
- Bimanual pelvic examination:
 - mass presence
 - size, tenderness
 - nodularity
 - mobility

First-line investigations

Transvaginal ultrasound

Transvaginal ultrasound is recommended to assess ovarian cyst size and classification.

Benign cysts

In premenopausal patients, simple cysts of less than 50mm in size (Figure 1) without ultrasound risk features do not require follow up (Flowchart).³ These ‘functional’ physiological cysts usually resolve after several menstrual cycles. Referral to a

provider who specialises in gynaecological ultrasound is recommended. If there are sonographic features of a dermoid cyst (Figure 2) or an endometrioma and the sonologist is clear that this is the diagnosis, no further investigation of the cyst is needed.

Cysts warranting further surveillance and/or specialist referral

Cysts that are 50 to 70 mm in size should be monitored with repeat transvaginal ultrasound after three to four months (Flowchart). Cysts persisting or increasing in size are less likely to be functional, and warrant specialist referral.³ Because larger

cysts (more than 70 mm in size) are often more difficult to assess sonographically, specialist referral is recommended to determine the appropriate next steps.^{3,9-11} Any cysts with sonographic risk features such as bilateral lesions, multilocular, solid or papillary components, or evidence of ascites or metastases (Flowchart) require immediate specialist referral. Although ultrasound can predict risk of malignancy with an overall sensitivity of 86 to 91% and specificity of 68 to 83%,¹⁰ no single ultrasound feature alone can definitively establish malignancy without a histological diagnosis arranged by the specialist.³ Additionally, although Doppler flow assessment at ultrasound may be informative for cyst characterisation, it cannot be used in isolation to determine malignancy risk.^{12,13}

Cancer antigen 125 blood test

The cancer antigen (CA) 125 blood test is the most useful adjunctive investigation for large or enlarging cysts, symptoms (above), cysts with sonographic risk features and any cyst in a postmenopausal patient. CA 125 measurement is used for the risk of malignancy index (RMI) calculation and to guide specialist investigation and



Figure 1. A simple cyst on ultrasound imaging, delineated by red markings.



Figure 2. A dermoid cyst on ultrasound imaging, delineated by red markings.

3. RISK OF MALIGNANCY INDEX (RMI) I³

RMI I = Ultrasound findings (U points) x Menopausal status (M points) x CA 125 level (U/mL)

Ultrasound findings (U points):

- 0 points: no features (unilocular)
- 1 point: one feature
- 3 points: two to five features
- Ultrasound findings: multilocular cyst, solid area, bilateral lesions, ascites, metastases

Menopausal status (M points):

- 1 point: premenopausal
- 3 points: postmenopausal (no menstrual period for 1 year or over 50 years of age if hysterectomy)

CA 125 level (U/mL):

- Actual level

Example: A multiloculated cyst (1 point) in a postmenopausal patient (3 points) with a CA 125 level of 40 U/mL. RMI I = 1 x 3 x 40 = 120.

management. The RMI has evolved through four iterations – RMI I to IV – with RMI I the most widely used and validated.⁴ Therefore, RMI I will be used throughout this article. The RMI I incorporates menopausal status, cyst features on transvaginal ultrasound and CA 125 level (Box 3), and is the most effective model for predicting suspected malignancy.^{3,9} However, GPs need to be aware that a normal CA 125 level (below 35 IU/mL) can be falsely reassuring in early malignancy and does not definitively exclude ovarian cancer. CA 125 may also be less sensitive in borderline ovarian tumours.^{3,14}

CA 125 in premenopausal patients

For asymptomatic ovarian cysts occurring before menopause, GPs should not routinely use the CA 125 level to determine the need for specialist referral. Rather, they should only measure CA 125 when the decision for specialist referral has already been made (based on factors discussed above), as levels may inform specialist management.³ Premenopause, CA 125 elevations can occur due to a variety of

conditions (Box 4)¹⁵ and levels cannot reliably differentiate benign from malignant lesions.³ When referring patients aged 40 years and younger to the specialist, GPs should also perform blood tests including alpha fetoprotein, human chorionic gonadotrophin and lactate dehydrogenase levels because germ cell tumours are more common in this group.³

CA 125 in postmenopausal patients

GPs should measure CA 125 levels in postmenopausal patients with ovarian cysts to allow RMI I calculation and subsequently decide on the need for specialist referral (Flowchart). CA 125 is a better indicator of the malignancy risk of ovarian cysts in postmenopausal patients than in premenopausal patients.⁴ A meta-analysis has shown that a CA 125 level of 35 IU/mL or higher in postmenopausal patients has a sensitivity of 69 to 87% and specificity of 81 to 91% for the detection of ovarian cancer.¹⁰

Other blood tests

Other serum biomarkers are generally not recommended when investigating ovarian cysts in primary care settings. CA 19-9 is a biomarker used in the investigation of gastrointestinal and pancreatic cancers. Recent studies have found no clear diagnostic benefits associated with CA 19-9 measurement for ovarian cysts, and its use is not recommended.¹⁶ Human epididymis protein 4 (HE4) has been used alongside CA 125 (without ultrasound features) to calculate the predictive 'risk of malignancy algorithm' (ROMA).^{8,17} Conversely, the International Ovarian Tumour Analysis (IOTA) Group has produced a risk classification system based on sonographic features alone, without serum markers.¹⁸ In practice, however, the RMI I (combining ultrasound features with CA 125 level) remains the most widely used and endorsed model for predicting suspected malignancy.

Management of ovarian cysts

GP management

For simple cysts smaller than 50 mm in asymptomatic patients or when a confident

4. CAUSES OF CA 125 ELEVATION¹⁵

Gynaecological

- functional ovarian cysts
- pregnancy
- endometriosis
- adenomyosis
- fibroids
- malignancy (e.g. epithelial ovarian, fallopian tube)

Nongynaecological

- cirrhosis
- acute and chronic kidney injury
- systemic infections
- autoimmune and connective tissue diseases
- malignancy (e.g. breast, colorectal, haematological)

sonographic diagnosis of a benign cyst has been made by an experienced radiologist, reassurance is appropriate. Larger simple cysts (50 to 70 mm in size) in premenopausal patients should be followed up with repeat imaging after three to four months to assess for resolution or persistence (Flowchart). Given the potential increased risk of torsion, GPs should advise patients with ovarian cysts to seek urgent medical attention in the unlikely event of acute lower abdominal pain.^{19,20}

Specialist referral

Specialist referral is indicated for ovarian cysts with one or more ultrasound risk features, larger cysts (more than 70 mm in size), cysts of size 50 to 70 mm that persist on repeat imaging or cysts in postmenopausal patients in the context of a non-reassuring RMI I (Flowchart and Box 3).

Clinicians should have a very low threshold for specialist referral for ovarian cysts among patients with known genetic risk factors for ovarian cancer (such as *BRCA* mutations). Although referral will usually be to a gynaecologist, direct referral to a gynaecological oncologist is recommended in certain circumstances, such as a high RMI I in a postmenopausal patient or the presence of ultrasound risk

features.^{4,7} Specialist management can include further imaging and monitoring of serum markers, diagnostic laparoscopy, cystectomy for tissue diagnosis or, for those with a higher malignancy risk, a full staging laparotomy and frozen section with or without tissue debulking under gynaecological oncology.

Cyst aspiration is generally not recommended because if the cyst is malignant, this can result in a higher risk of recurrence.^{3,8} For asymptomatic simple ovarian cysts in women of reproductive age, no specific medical therapy has been shown to hasten cyst resolution, with a Cochrane review demonstrating no benefit to the use of hormonal contraceptives.³

If the specialist opts for observation, patients may be discharged back to their GP for a period of ongoing surveillance. Many patients can cease surveillance where there has been resolution of the cyst or no significant change for 12 months, but specific management recommendations will depend on the clinical scenario.⁴

Other considerations for GPs

Other specific cyst-related diagnoses may be suggested depending on the clinical context and can include:

- acute adnexal torsion, requiring urgent emergency care^{19,20}
- endometriomas, indicating significant endometriosis, even in the absence of symptoms
- cysts in pregnancy, which can pose a higher risk of adnexal torsion^{19,20}
- theca lutein cysts in the context of assisted reproductive technology or, rarely, due to gestational trophoblastic disease.

A detailed discussion of the work-up and management of these conditions is beyond the scope of this article.

Finally, ovarian cysts can be associated with significant anxiety and it is important to sensitively reassure patients when appropriate. Avoiding unnecessary surveillance, investigations and referral for those at very low risk is another important consideration.

Conclusion

GPs commonly encounter ovarian cysts and although many cysts will be functional and benign, the opportunity for follow up or referral in concerning scenarios should not be missed. In distinguishing physiological from concerning cysts, relevant clinical information, risk factors for malignancy and ultrasound risk features are key considerations. Transvaginal ultrasound is the initial investigation of choice but other testing, including measurement of CA 125 levels in some circumstances, can stratify risk. GPs have a crucial role in providing reassurance where appropriate and in deciding which cases to follow up and/or refer. **MT**

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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KIRSTEN I. BLACK MB BS, MMed, FRANZCOG, DDU, MFSRH, PhD

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