Acta Obstet Gynecol Scand 2004: 83: 1012–1021
Printed in Denmark. All rights reserved

Acta Obstetricia et Gynecologica Scandinavica

REVIEW ARTICLE

Management of ovarian cysts

ULLA BRETH KNUDSEN[1], ANN TABOR[2], BERIT MOSGAARD[3], ERIK SOEGAARD ANDERSEN[4], JENS JOERGEN KJER[5], SUZANNE HAHN-PEDERSEN[6], KIM TOFTAGER-LARSEN[7] AND OLE MOGENSEN[1]

From the Department of Gynecology and Obstetrics, [1]Odense University Hospital, Odense, [2]Hvidovre Hospital, Hvidovre, [3]Herlev Hospital, Herlev, [4]Aalborg University Hospital, Aalborg, [5]Glostrup Hospital, Glostrup, [6]Private practitioner, Copenhagen and [7]Hilleroed Hospital, Hilleroed, Denmark

Acta Obstet Gynecol Scand 2004; 83: 1012–1021. © Acta Obstet Gynecol Scand 83 2004

Background. The treatment of an ovarian cyst relies on its nature, and accurate preoperative discrimination of benign and malignant cysts is therefore of crucial importance. This study was undertaken to review the literature concerning the preoperative diagnosis and treatment of ovarian cysts.
Methods. Articles concerning ovarian cysts from a MEDLINE literature search during the period 1985–2003 were included in addition to articles found as references in the initial publications.
Results. Different methods for discriminating between benign and malignant ovarian cysts are discussed. The diagnosis and the treatment are assessed in relation to age, menopausal status, pregnancy, and whether the cyst is presumed to be benign or malignant. In general, expectant management is the choice in premenopausal and pregnant women with non-suspicious cysts and normal levels of CA-125. In postmenopausal women, unilocular, anechoic cysts less than 5 cm in diameter together with a normal CA-125 may be followed up. Operation is recommended in women with cysts larger than 5 cm and/or elevated levels of CA-125. Women with symptoms should be operated regardless of age, menopausal status, or ultrasound findings.
Conclusions. The preoperative discrimination between benign and malignant ovarian cysts is a challenge. Multimodal methods improve the results of single modalities, but we still need improved preoperative diagnostic tools. Furthermore, these methods should be validated in consecutive patient populations large enough to give a reliable estimate of the method's sensitivity and specificity.

Key words: CA-125; ovarian cysts and pregnancy; ovarian cysts; ovarian masses; risk-of-malignancy index

Submitted 8 December, 2003
Accepted 11 April, 2004

The prevalence of ovarian cysts in the general population has not been described in detail. Screening studies have shown that around 7% of both premenopausal and postmenopausal women have ovarian cysts (1,2). The lifetime risk of ovarian cancer in women with no affected relatives is one in 60 (1.7%) (3). The relative risk to first-degree relatives is 3.1, and the relative risk increases to 7.18 in women, who have two or more first-degree relatives (4,5). The clinical problem in diagnosing an ovarian cyst is to exclude malignancy. Operation on benign lesions may be avoided, whereas a suspicion of malignancy should lead to an accelerated operative assessment by gynecologic oncologists.

The purpose of this review is to describe the present knowledge on how to diagnose and handle ovarian cysts in women without a familial predisposition to ovarian cancer.

Methods

This article is based on:

1) A review of the literature in MEDLINE on the mentioned key words from 1985 to 2003. (Key words: ovarian cysts, ovarian masses, ovarian cysts and pregnancy, risk-of-malignancy index, CA-125);
2) Additional articles found as references in the above-mentioned publications or papers recommended from specialists working in the field.

The literature consists predominantly of observational, uncontrolled studies, a few case–control studies, whereas only three studies are randomized controlled trials (RCTs) (35,55,57). Meta-analysis and reviews are included (27,54). The literature is included with the highest grade of evidence [Ia: meta-analysis, systematic reviews, and RCTs; IIa: controlled, not randomized studies, and cohort studies; III: case–control studies, etc. as classified internationally].

Diagnosis

The management of an ovarian cyst depends on a combination of several factors including age and menopausal status (A woman is considered to react physiologically as a premenopausal woman up to 1 year after termination of bleeding. Some articles have used the 50 years of age as the menopausal state has not been given. Malignant tumors: ovarian cancers and borderline tumors), symptoms, ultrasonographic features, unilateral/bilateral findings, size of the mass, and the level of serologic markers.

Age and menopausal status

Ovarian cysts in premenopausal women are common and usually benign including functional cysts or endometriomas. The risk of malignancy increases with age, and the majority of malignant tumors are diagnosed in postmenopausal women (6). The incidence of ovarian cancer increases from 15.7/100.000 at the age of 40 years to 54.0/100.000 at the age of 75 years (7); and in Denmark, only 17.9% of all ovarian cancers are found in women younger than 50 years of age (8).

Symptoms

Localized ovarian cancers generally have few or no symptoms, and this may cause delay in the use of appropriate diagnostic imaging techniques. Consequently, only 25% of women are diagnosed with disease limited to the ovaries (9).

In a prospective study of postmenopausal women, around 90% of women with ovarian cancer had symptoms in contrast to women with benign tumors who only had symptoms in 57% of the cases (10). Accordingly, Olson et al. (11) found that 93% of women with ovarian cancers had some kind of symptoms compared to only 42% of controls. Unusual bloating, fullness, pressure in the abdomen, unusual abdominal pain or lower back pain, and lack of energy were more common and persistent in ovarian cancer cases compared to controls (11). In the presence of symptoms, surgery may need to be expedited.

Ultrasonographic features

The result of an ultrasound scan depends on the skill and experience of the operator and even between experienced sonographers inter-observer variation is considerable (12). Ovarian cysts are mainly diagnosed by vaginal ultrasound, but once diagnosed, an abdominal scan may be complementary.

The diagnostic accuracy of an ultrasound scan can be more difficult in premenopausal women due to the cyclic changes caused by ovulation (13). Several features are to be taken into consideration in describing the sonographic features of adnexal tumors (14).

Most studies find that unilocular anechoic cysts less than 5 cm in diameter are seldom malignant even in postmenopausal women (1,15–19). The risk of malignancy is less than 1% in premenopausal and between 0.1 and 10% in postmenopausal women (15–20). Only 6% of cysts with a diameter of 3–5 cm were malignant in a cohort of postmenopausal women (16), whereas others found no malignancies in cysts with a diameter less than 5 cm (1,17).

Multilocular cysts are more often malignant than unilocular cysts (1,16,17,21). Granberg (21) found that 8% of multilocular cysts were malignant compared to only 0.3% of the unilocular cysts in a mixed population of pre- and postmenopausal women.

Solid parts, semisolid, mixed tumors are often related to malignancy (15,16,21–23). In premenopausal women, cysts with solid parts and semisolid and mixed tumors are found to be malignant in around 2–17% of cases (15,17). However, in postmenopausal women, these appearances are highly related to malignancy as 66.2% of cysts with cystic solid parts and 74% of solid tumors were malignant (16).

Papillary formations are correlated to malignancy and the risk of malignancy increased from 1.6 to 10% if a unilocular cyst contained solid parts or papillary formations (17). However, the presence of papillary formations on its own cannot be used to differentiate between benign or malignant cases (17).

The echogenicity of the cyst content cannot discriminate between benign or malignant cysts (16), neither can the thickness of the cyst wall or the presence of septae (21).

The diameter of the cyst is positively correlated to the risk of malignancy (6,16,21,22). No borderline or malignant diagnoses were made in unilocular cysts measuring <75 mm, whereas cysts with a complex ultrasound structure were malignant in 7.2% of the cases if the diameter was >79 mm (17).

Bilateral abnormal adnexal masses on an ultrasound scan increase the risk of malignancy 2.8-fold in a mixed population of pre- and postmenopausal women (22).

Ascites

Free fluid in the pouch of Douglas was found in 40% of malignant cases and in 5% of benign cases in postmenopausal women (16). In premenopausal women, the figures were 48% compared to around 12% (15). The presence of ascites may thus increase the likelihood of malignancy fourfold in premenopausal women and eightfold in postmenopausal women (15,16). This is an indication for operation, though increased fluid in the pouch of Douglas can be seen in association with benign cysts (15,16).

Morphologic scoring systems

The presence of papillary proliferations, septae, and solid areas within the cyst alone cannot be used to distinguish between benign and malignant tumors. In combination, however, various scoring systems based on ovarian volume and morphology have been introduced (23–25). These scoring systems have a sensitivity of 82–100% and a false-positive rate of 8–20%. The most important predictive factors are the presence of papillary proliferations from the cyst wall (24) and solid parts in the cyst (23). The features that shall be noted in ultrasound scanning are summarized in Table I, while use of these structures to discriminate between non-suspicious and suspicious ovarian cysts is summarized in Table II.

Doppler flow

Color doppler flow imaging shows vascular changes within the ovary. The results of this technique have, however, been disappointing, as it does not seem to improve the diagnostic accuracy between benign and malignant tumors from the morphologic appearance detected using gray-scale ultrasound (23). A recent multicenter study suggested, however, that in complex pelvic masses color Doppler imaging could be of some benefit in the differential diagnosis between benign and malignant masses (26). In a meta-analysis of the effectiveness of different ultrasonographic techniques to characterize ovarian masses, Kinkel et al. (27) found in 46 of the included studies (5159 subjects) that there were significantly better results from combining techniques than for morphologic information, Doppler ultrasonographic indexes or color Doppler flow imaging alone.

Table I. Features of an ovarian cyst

Numbers of locules
Presence of solid parts (septum and solid papillary proliferations)
The diameter of the cyst/tumor
Presence of cysts/tumors in the contralateral ovary
Fluid in the pouch of Douglas

Magnetic resonance imaging and computed tomography scans

Computed tomography (CT) has been compared in a prospective study to ultrasound in the diagnosis of persistent (3 months) ovarian cysts in premenopausal women (28). Ultrasound scan had a better accuracy (the overall agreement between a test result and the actual outcome was evaluated by a calculated Kappa index) in the diagnosis of almost all lesions except cystic teratomas. Most studies using magnetic resonance imaging (MRI) and CT as diagnostic tools are on small samples, and only few have evaluated the techniques in relation to differentiating between benign and malignant masses (29–31). MRI does not seem to add further information to the nature of an adnexal mass than ultrasound, even though MRI was superior to Doppler ultrasound and CT in the diagnosis of malignancy in women suspected of having ovarian cancer (32).

Cytology

The sensitivity of cytological analysis of fluid from ovarian cysts is unreliable (25–80%), and puncture of cysts cannot be used for diagnostic purposes (33–36). Furthermore, the spillage of malignant cells during puncture may increase the stage of an ovarian cancer (37), and for these reasons, puncture of an ovarian cyst should be avoided.

CA-125

Using 35 U/ml as the upper limit of normal range, the sensitivity and false-positive rate of a CA-125 value are 50–83% and 14–36%, respectively (38–43). False-negative marker values are common among women with stage I ovarian cancer (sensitivity 50%). False-positive CA-125 values are often found in women with endometriosis, infections, and effusions. Using an upper limit of 50 U/ml, the sensitivity decreases slightly (from 76 to 70%), while the false-positive rate is considerably reduced (from 44 to 33%) (44). It has been suggested that the use of serial CA-125 examinations may decrease the false-positive rate (45).

Table II. Differences between non-suspicious and suspicious ovarian cysts

Non-suspicious ovarian cyst	Unilocular cysts without solid parts or papillary proliferations
Suspicious ovarian cyst	At least two locules, mixed cystic solid or solid (more than 80% solid), bilateral tumor

Risk of malignancy index

The risk-of-malignancy index (RMI) was originally developed to discriminate between benign and malignant pelvic masses in order to refer the women with malignant tumors to gynecology oncology centres (46). Later, the method was validated in women referred to non-specialized gynecologic departments (44,47–49). The RMI is a simple scoring system based on menopausal status (M), ultrasonographic morphology (U), and serum CA-125. Premenopausal status is given a score of 1, and postmenopausal status (more than 1 year of amenorrhea) a score of 4. Unilateral, unilocular, or bilocular tumors on ultrasonography, with no solid parts, no extra ovarian tumor, and no ascites give a score of 1. More complex tumors lead to a score of 4. Both menopausal status and ultrasonography thus give a score of 1 or 4. Serum CA-125 is applied directly into the equation:

$$RMI = M \times U \times CA\text{-}125$$

Using a cut-off level of 200 to discriminate between benign and malignant tumors, RMI has a sensitivity of approximately 80%, the specificity is 92%, and the positive and negative predictive values are 83 and 91%, respectively (47). The original score of 4 has later been modified to a score of 3 both for the menopausal and the ultrasonography score (48).

Treatment

Expectant

In premenopausal women, many cysts are functional and regress without treatment. In a study of 178 premenopausal women with cysts less than 6 cm in diameter and a normal CA-125 value, half of the cysts regressed within 6 months and 73% had disappeared within 75 months of diagnosis (50).

Postmenopausal women may develop functional cysts, and around 50% of all diagnosed cysts disappear within 3–23 months, especially in women younger than 60 years of age (2,20).

Cyst puncture

In a single randomized controlled study including 278 women aged 14–81 years with a unilocular cyst of 4–7 cm, it was not possible, after 6 months of observation, to demonstrate any effect of cyst puncture compared to observation (35). As previously described, puncture should be avoided due to the risk of spillage of malignant cells, which may increase the stage of an ovarian cancer (37).

Treatment with combined oral contraceptive pill

Treatment with combined oral contraceptive pill has been used to suppress ovarian cysts. A registry study (51) showed, that compared to no treatment sequential pills reduced the prevalence of ovarian cysts by 9%, a combined pill with low-dose estrogen by 48% and with high-dose estrogen by 76%. Two case–control studies (52,53) confirmed that mainly monophasic birth control pills reduced the prevalence of ovarian cysts. A review (54) concluded that low-dose monophasic or multiphasic birth control pills have minimal or no effect on the prevalence or development of functional ovarian cysts. A randomized study found expectant management compared to oral contraception for one cycle for ovarian cysts after ovulation induction to be equally effective, as around 74% in both groups experienced complete resolution (55).

If recurrent ovarian cysts are to be treated with birth control pills, a combination pill with a high estrogen dose should be used. The effect of this treatment, however, has not been proven.

Hormonal replacement therapy

Few articles have addressed the issue of hormone replacement treatment (HRT) on ovarian cysts and the results are conflicting. In a study of 564 consecutive, asymptomatic, postmenopausal women, there was no difference in the prevalence of ovarian cysts with or without HRT, except in a subgroup of early postmenopausal women aged 40–55 years, where HRT seemed to significantly reduce the prevalence of ovarian cysts (56). In a screening study of 15 106 women at least 50 years old, a statistically significant higher frequency of ovarian cysts was found during HRT compared to non-users (18).

Surgery

It is essential preoperatively to discriminate between benign and malignant ovarian tumors

to optimize surgical management. Women with malignant cysts or tumors should be operated upon by laparotomy carried out by gynecologic oncologists. Cyst rupture during the operation should be avoided, as this significantly reduces the disease-free survival rate (37). Furthermore, in a patient with a localized ovarian cancer, cyst rupture will change the FIGO stage from IA to IC, and consequently, the patient will have a high risk of adjuvant chemotherapy after surgery.

Premenopausal women with benign tumors should be offered conservative management. The majority of benign ovarian cysts/tumors may be managed laparoscopically (57). In a randomized trial of laparoscopy versus laparotomy in 102 patients (97 premenopausal) with ovarian masses not suspected to be malignant, laparoscopy was associated with a significant reduction in operative morbidity, postoperative pain, and length of hospital stay and recovery, without increasing the risk of spillage of the cyst contents (57).

When operating on a benign lesion, the stripping technique (in which two atraumatic grasping forceps are used to pull the cyst wall and the normal ovarian parenchyma in opposite directions, thus developing the cleavage plane) appears to be a tissue-sparing procedure (58).

Many postmenopausal women will be treated by laparotomy, as there is a higher risk of malignancy in this age group. On the other hand, the reduced operative morbidity, postoperative pain, length of hospital stay, and recovery when laparoscopy has been performed (57) have to be balanced with the risk of malignancy. In most cases, bilateral oophorectomy and often hysterectomy will be performed in postmenopausal women even in the case of benign pathology. In case of malignancy, the women should be treated accordingly.

Pregnancy

The reported incidence of adnexal masses diagnosed on the routine obstetric ultrasonographic examination ranges from one in 80 to one in 2500 pregnancies. Most of the masses are pregnancy-related corpus luteum cysts and resolve by 16 weeks of gestation (59). The ovarian tumors are most often asymptomatic, but due to symptoms or fear of malignancy, one woman with an adnexal mass in 1300 live births will be operated upon during pregnancy (60,61).

Benign tumors make up the vast majority of the ovarian cysts in pregnancy, and half of them are benign cystic teratomas. Malignancy occurs in 1–6% of the cases (60–65).

Ultrasound

Simple cysts <5 cm account for 70–75% of the adnexal masses. In pregnancy, they tend to enlarge up to 7 weeks of gestation and thereafter resolve (66). The remaining 25% of the tumors are complex masses or simple cysts >5 cm, and of these, three quarters will resolve spontaneously (62,67,68). Caspi et al. (69) followed 49 pregnant women with dermoid cysts <6 cm and found that the size remained unchanged and the cyst caused no complications during pregnancy or labor. Bromley and Benacerraf (62) identified 125 pregnant patients with 131 adnexal masses, of which 14 (10.7%) had sonographic characteristics suggestive of malignancy. One of these 14 patients (7%) had an ovarian cancer, and they concluded that sonography in pregnancy has the same predictive value as that in non-pregnant women.

CA-125

Several studies describe elevated serum CA-125 level among pregnant women with normal ovaries. The serum level is particularly high during the first trimester and declines with increasing gestational age, indicating that a higher cut-off level should be used in pregnant as compared with non-pregnant women (70–72).

Methods of treatment

In the discussion of surgery and expectation, fetal and maternal aspects must be considered. The risk of miscarriage in relation to surgery is up to 100% before 7 weeks of gestation and is increased in the first trimester in general (73,74). Emergency surgery seems to increase the risk of abortion and premature delivery (60,64,74). Surgical intervention after 23 weeks of gestation seems to increase the risk of adverse pregnancy outcome (miscarriage, preterm labor, and intrauterine fetal deaths) (61,63).

Emergency surgical intervention seems to be most common in the first trimester and implies more often excision of the affected ovary compared to elective surgery (69,74). Several studies have concluded that laparoscopic cyst excision at 9–17 weeks of gestation appears to be feasible and carries very low morbidity (75,77). Ultrasound-guided cyst aspiration is also described to be almost without complications, but the frequency of recurrence is 30–50% (78–80).

A review by Lachman et al. (81) concludes that laparoscopic surgery in pregnancy in general appears to be safe when performed by experienced practitioners. Akira et al. (82) describe

Table III. Management of ovarian cysts in pre- and perimenopausal and pregnant women (women are considered perimenopausal in this study if less than 1 year after the menopause)

Suspicious cysts and solid tumors should be removed surgically
Non-suspicious cyst with a diameter
<4 cm: no reason for follow up
4–7 cm: estimation of CA-125 followed by an ultrasound scan 3 months later
>7 cm: laparoscopy/laparotomy after determination of CA-125
In pregnancy, surgery before 7 and after 24 weeks of gestation should be avoided

advantages with gasless laparoscopic procedure with extra corporeal ovarian cystectomy compared with laporotomy.

Guidelines

Following discussions among Danish colleagues at a meeting in the year 2002, national guidelines have been worked out (Tables III, IV and *Appendix 1*).

Discussion

Accurate preoperative discrimination between benign and malignant ovarian cysts remains difficult despite recent advances in medical imaging. Reliable prediction of the nature of an ovarian cyst is of crucial importance for treatment. Preoperative detection of malignancy would allow selective referrals to the appropriate centers for optimal care, whereas women with benign cysts could be offered more conservative treatment. The opinion of the affected woman is clearly another important component when the strategy for management of a unilocular cyst is to be settled. RMI is the best discriminator between malignant and benign ovarian tumors described in the literature, but the method has not been subjected to assessment in a randomized trial. However, a significant problem in previously published data on RMI is the relatively poor performance of the index in detecting non-epithelial ovarian cancers, borderline ovarian tumors and early-stage cancers. In a recent study, the RMI was prospectively compared with Tailor's regression model (83), which includes ultrasonographic morphology and transvaginal color Doppler imaging of tumor blood flow. The simple RMI performed better than Tailor's regression model and better than individual demographic (e.g. age and menopausal status), ultrasonographic and biochemical parameters. In the future, the incorporation of tumor blood flow characteristics in risk evaluation models may improve the diagnostic accuracy (27). On the other hand, used in the daily clinic, pretreatment evaluation should be as simple as possible. The RMI has proved useful in optimizing referral of patients with malignant tumors to centralized primary surgery. Women with a RMI below the cut-off level 200, which has given the best sensitivity and specificity at predicting malignancy, may be operated upon by laparoscopic surgery if appropriate. Aspiration of cysts should be avoided, but in rare cases in premenopausal women with several previous abdominal operations and complications, a symptomatic cyst might be punctured, also as a diagnostic input if the symptoms disappear. However, in case of malignancy, the woman's prognosis may have deteriorated to a higher FIGO stage (37).

Several studies indicate that oral contraception prescriptions are unlikely to prevent the development of functional cysts or to hasten their disappearance. The impact of HRT on ovarian cysts needs further clarification.

The diagnosis of ovarian cancer is still one of the hardest tasks in gynecology, and the search for optimal diagnostic tools should continue. Neural network models appear to be encouraging (84), eventhough at this moment complicated scoring systems do not perform a better accuracy of the risk assessment for adnexal masses than the scoring made by the clinicians (85). The initial reports on proteomic patterns in serum to identify ovarian cancers seems promising (86), and in combination with other diagnostic tools give hope for a more multimodal way of diagnosing ovarian cancer. Hopefully thereby discrimination between benign and malignant cysts can be improved, to avoid unnecessary surgery for functional cysts, and to elect the right operating setting for women with ovarian cancer.

Table IV. Management of ovarian cysts in postmenopausal women (more than 1 year after the menopause)

All suspicious cysts and solid tumors should be removed surgically
Non-suspicious, non-symptomatic cysts with a normal CA-125 value and a diameter
<5 cm: Ultrasound and new measurement of CA-125 after 3 months
>5 cm: Operation is recommended, usually at least bilateral salpingo-ophorectomy
With normal ultrasound but elevated CA-125, or with symptoms in spite of benign features, operation is recommended

Acknowledgments

We are very grateful for the invaluable discussions at the Hindsgavl meetings with all our colleagues in the Danish Society of Obstetricians and Gynecologists in Denmark.

References

1. Borgfeldt C, Andolf E. Transvaginal sonographic ovarian findings in a random sample of women 25–40 years old. Ultrasound Obstet Gynecol 1999; 13: 345–50.
2. Bailey CL, Ueland FR, Land GL, DePriest PD, Gallion HH, Kryscio RJ et al.The malignant potential of small cystic ovarian tumors in women over 50 years of age. Gynecol Oncol 1998; 69: 3–7.
3. American Cancer Society: Cancer Facts and Figures – 1998. Atlanta, GA: American Cancer Society, 1998.
4. Stratton JF, Pharoah P, Smith SK, Easton D, Ponder BAJ. A systematic review and meta-analysis of family history and risk of ovarian cancer. BJOG 1998; 105: 493–9.
5. Sutcliffe S, Pharoah PDP, Easton DF, Ponder BAJ. Ovarian and Breast cancer risks to women in families with two or more cases of ovarian cancer. Int J Cancer 2000; 87: 110–7.
6. Okugawa K, Hirakawa T, Fukushima K, Kamura T, Amada S, Nakano H. Relationship between age, histological type, and size of ovarian tumors. Int J Gynecol Obstet 2001; 74: 45–50.
7. Yancik R. Ovarian cancer. Age contrasts in incidence, histology, disease stage, diagnosis, and mortality. Cancer 1993; 71 (Suppl. 2): 517–23.
8. Danish National Board of Health. Cancer Incidence in Denmark. Copenhagen: The Danish National Board of Health, Statistical Office, 1997.
9. Benedet JL, Bender H, Jones H III, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guideline in the management of gynaecologic cancers. FIGO Committee on Gynaecologic Oncology. Int J Gynaecol Obstet 2000; 70: 209–62.
10. Maggino T, Gadducci A, D'Addario V, Pecorelli S, Lissoni A, Stella M et al. Prospective multicenter study on CA-125 in postmenopausal pelvic masses. Gynecol Oncol 1994; 54: 117–23.
11. Olson SH, Mignone L, Nakraseive C, Caputo TA, Barakat RR, Harlap S. Symptoms of ovarian cancer. Obstet Gynecol 2001; 98: 212–7.
12. Amer SA, Li TC, Bygrave C, Sprigg A, Saravelos H, Cooke ID. An evaluation of the inter-observer and intra-observer variability of the ultrasound diagnosis of polycystic ovaries. Hum Reprod 2002; 17: 1616–22.
13. Christensen JT, Boldsen JL, Westergaard JG. Functional ovarian cysts in premenopausal and gynecologically healthy women. Contraception 2002; 66: 153–7.
14. Timmerman D, Valentin L, Bourne TH, Collins WP, Verrelst H, Vergote I. 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: 500–5.
15. Osmers RGW, Osmers M, von Maydell B, Wagner B, Kuhn W. Preoperative evaluation of ovarian tumors in the premenopause by transvaginosonography. Am J Obstet Gynecol 1996; 175: 428–34.
16. Osmers RGW, Osmers M, von Maydell B, Kuhn W. Evaluation of ovarian tumors in the postmenopause by transvaginosonography. Eur J Obstet Gynecol Reprod 1998; 77: 81–8.
17. Ekerhovd E, Wienerroith H, Staudach A, Granberg S. Preoperative assessment of unilocular adnexal cysts by transvaginal ultrasonography: a comparison between ultrasonographic morphologic imaging and histopathologic diagnosis. Am J Obstet Gynecol 2001; 184: 48–54.
18. Modesitt SC, Pavlik EJ, Ueland FR, DePriest PD, Kryscio RJ, vanNagell JR. Risk of malignancy in unilocular ovarian cystic tumors less than 10 centimeters in diameter. Obstet Gynecol 2003; 102: 594–9.
19. Roman LD. Small cystic pelvic masses in older women: is surgical removal necessary? Gynecol Oncol 1998; 69: 1–2.
20. Levine D, Gosink BB, Wolf SI, Feldesman MR, Pretorius DH. Simple adnexal cysts: the natural history in postmenopausal women. Radiology 1992; 184: 653–9.
21. Granberg S, Wikland M, Jansson I. Macroscopic characterization of ovarian tumors and the relation to the histological diagnosis: criteria to be used for ultrasound evaluation. Gynecol Oncol 1989; 35: 139–44.
22. Minaretzis D, Tsionou C, Tziotziotis D, Michalas S, Aravantinos D. Ovarian tumors: prediction of the probability of malignancy by using patient's age and tumor morphologic features with a logistic model. Gynecol Obstet Invest 1994; 38: 140–4.
23. Valentin L, Sladekevicius P, Marsal K. Limited contribution of Doppler velocimetry to the differential diagnosis of extrauterine pelvic tumors. Obstet Gynecol 1994; 83: 425–33.
24. DePriest PD, Varner E, Powell J, Puls L, Higgins R, Shenson D et al. The efficacy of a sonographic morphology index in identifying ovarian cancer: a multi-institutional investigation. Gynecol Oncol 1994; 55: 174–8.
25. Sassone AM, Timor-Tritsch IE, Artner A, Westhoff C, Warren WB. Transvaginal sonographic characterization of ovarian disease: evaluation of a new scoring system to predict ovarian malignancy. Obstet Gynecol 1991; 78: 70–6.
26. Guerriero S, Alcazar JL, Coccia ME, Ajossa S, Scarselli G, Boi M et al.Complex pelvic mass as a target of evaluation of vessel distribution by color Doppler sonography for the diagnosis of adnexal malignancies: results of a multicenter European study. J Ultrasound Med 2002; 21: 1105–11.
27. Kinkel K, Hricak H, Lu Y, Tsuda K, Filly RA. US characterization of ovarian masses: a meta-analysis. Radiology 2000; 217: 803–11.
28. Guerriero S, Mallarini G, Ajossa S, Risalvato A, Satta R, Mais V et al. Transvaginal ultrasound and computed tomography combined with clinical parameters and CA-125 determinations in the differential diagnosis of persistent ovarian cysts in premenopausal women. Ultrasound Obstet Gynecol 1997; 9: 339–43.
29. Acar B, Posaci C, Dicle O, Topuz A, Erten O. Diagnostic value of magnetic resonance imaging in gynaecology. Aust N Z J Obstet Gynaecol 1992; 32: 252–5.
30. Kinoshita T, Ishii K, Naganuma H, Higashiiwai H. MR findings of ovarian tumors with cystic components. Br J Radiol 2000; 73: 333–9.
31. Pretorius ES, Outwater EK, Hunt JL, Siegelman ES. Magnetic resonance imaging of the ovary. Top Magn Reson Imaging 2001; 12: 131–46.
32. Kurtz AB, Tsimikas JV, Tempany CMC, Hamper UM, Arger PH, Bree RL et al. Diagnosis and staging of ovarian cancer: comparative values of doppler and conventional US, CT, and MR Imagining correlated with surgery and histopathologic analysis – report of the radiology diagnostic oncology group. Radiology 1999; 212: 19–27.
33. De Crespigny LC, Robinson H, Davoren RAM, Fortune D. The simple ovarian cyst: aspirate or operate ? BJOG 1989; 96: 1035–9.
34. Moran O, Menczer J, Ben-Baruch G, Lipitz S, Goor E. Cytologic examination of ovarian cyst fluid for the distinction between benign and malignant tumors. Obstet Gynecol 1993; 82: 444–6.
35. Zanetta G, Lissoni A, Torri V, Valle CV, Trio D, Rangoni G et al. Role of puncture and aspiration in expectant management of simple ovarian cysts: a randomised study. Br Med J 1996; 313: 1110–3.
36. Martínez-Onsurbe P, Villaespesa AR, Anquela JMS, Ruiz PLV. Aspiration cytology of 147 adnexal cysts with histologic correlation. Acta Cytol 2001; 45: 941–7.
37. Vergote I, De Brabanter J, Fyles A, Bertelsen K, Einhorn N, Sevelda P et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. Lancet 2001; 357: 176–82.
38. Finkler NJ, Benacerraf B, Lavin PT, Wojciechowski C, Knapp RC. Comparison of serum CA 125, clinical impression, and ultrasound in the preoperative evaluation of ovarian masses. Obstet Gynecol 1988; 72: 659–64.
39. Franchi M, Beretta P, Ghezzi F, Zanaboni F, Goddi A, Salvatore S. Diagnosis of pelvic masses with transabdominal

color doppler, CA 125 and ultrasonography. Acta Obstet Gynecol Scand 1995; 74: 734–9.
40. Malkasian GD, Knapp RC, Lavin PT, Zurawski VR, Podratz KC, Stanhope CR et al. Preoperative evaluation of serum CA 125 levels in premenopausal and postmenopausal patients with pelvic masses: discrimination of benign from malignant disease. Am J Obstet Gynecol 1988; 159: 341–6.
41. Mogensen O, Mogensen B, Jakobsen A. Tumor-associated trypsin inhibitor and cancer antigen 125 in pelvic masses. Gynecol Oncol 1990; 38: 170–4.
42. Patsner B, Mann WJ. The value of preoperative serum CA 125 levels in patients with a pelvic mass. Am J Obstet Gynecol 1988; 159: 873–6.
43. Vasilev SA, Schlaerth JB, Campeau J, Morrow CP. Serum CA 125 levels in preoperative evaluation of pelvic masses. Obstet Gynecol 1988; 71: 751–6.
44. Davies AP, Jacobs I, Woolas R, Fish A, Oram D. The adnexal mass: benign or malignant? Evaluation of a risk of malignancy index. BJOG 1993; 100: 927–31.
45. Zurawski VR, Sjovall K, Schoenfeld DA, Broderick SF, Hall P, Bast RC Jr et al. Prospective evaluation of serum CA 125 levels in a normal population, phase I: the specificities of single and serial determinations in testing for ovarian cancer. Gynecol Oncol 1990; 36: 299–305.
46. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. BJOG 1990; 97: 922–9.
47. Tingulstad S, Hagen B, Skjeldestad FE, Onsrud M, Kiserud T, Halvorsen T et al. Evaluation of a risk of malignancy index based on serum CA 125, ultrasound findings and the menopausal status in the pre-operative diagnosis of pelvic masses. BJOG 1996; 103: 826–31.
48. Tingulstad S, Hagen B, Skjeldestad FE, Halvorsen T, Nustad K, Onsrud M. The risk-of-malignancy index to evaluate potential ovarian cancers in local hospitals. Obstet Gynecol 1999; 93: 448–52.
49. Soegaard Andersen E, Knudsen A, Rix P, Johansen B. Risk of malignancy index in the preoperative evaluation of patients with adnexal masses. Gynecol Oncol 2003; 90: 109–12.
50. Sasaki H, Oda M, Ohmura M, Akiyama M, Liu C, Tsugane S et al. Follow up of women with simple ovarian cysts detected by transvaginal sonography in Tokyo metropolitan area. Br J Obstet Gynecol 1999; 106: 415–20.
51. Lanes SF, Birmann B, Walker AM, Singer S. Oral contraceptive type and functional ovarian cysts. Am J Obstet Gynecol 1992; 166: 956–61.
52. Holt VL, Daling JR, McKnight B, Moore D, Stergachis A, Weiss NS. Functional ovarian cysts in relation to the use of monophasic and triphasic oral contraceptives. Obstet Gynecol 1992; 79: 529–33.
53. Holt VL, Cushing-Haugen KL, Darling JR. Oral contraceptives, tubal sterilization, and functional ovarian cyst risk. Obstet Gynecol 2003; 102: 252–8.
54. Chiaffarino F, Parazzini F, Vecchia CL, Ricci E, Crosignani PG. Oral contraceptive use and benign gynecologic conditions. Contraception 1998; 57: 11–8.
55. 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.
56. Bar-Hava I, Orvieto R, Vardimon D, Manor Y, Weissman A, Nelinger R et al. Ovarian cysts and cyclic hormone replacement therapy: is there an association? Acta Obstet Gynecol Scand 1997; 76: 563–6.
57. Yuen PM, Yu KM, Yip SK, Lau WC, Rogers MS, Chang A. A randomized prospective study of laparoscopy and laparotomy in the management of benign ovarian masses. Am J Obstet Gynecol 1997; 177: 109–14.
58. Muzii L, Bianchi A, Crocé C, Manci N, Panici PB. Laparoscopic excision of ovarian cysts: is the stripping technique a tissue-sparing procedure? Fertil Steril 2002; 77: 609–14.
59. Hill LM, Connors-Beatty DJ, Nowak A, Tush B. The role of ultrasonography in the detection and management of adnexal masses during the second and third trimesters of pregnancy. Am J Obstet Gynecol 1998; 179: 703–7.
60. Hess LW, Peaceman A, O'Brien WF, Winkel CA, Cruikshank DP, Morrison JC. Adnexal mass occurring with intrauterine pregnancy: report of fifty-four patients requiring laparotomy for definitive management. Am J Obstet Gynecol 1988; 158: 1029–34.
61. Whitecar MP, Turner S, Higby MK. Adnexal masses in pregnancy: a review of 130 cases undergoing surgical management. Am J Obstet Gynecol 1999; 181: 19–24.
62. Bromley B, Benacerraf B. Adnexal masses during pregnancy: accuracy of sonographic diagnosis and outcome. J Ultrasound Med 1997; 16: 447–52.
63. Usui R, Minakami H, Kosuge S, Iwasaki R, Ohwada M, Sato I. A retrospective survey of clinical, pathologic, and prognostic features of adnexal masses operated on during pregnancy. J Obstet Gynaecol Res 2000; 26: 89–93.
64. Wang PH, Yuan CC, Chao HT, Yu KJ, Tseng JY, Hung JH et al. Ovarian surgery during pregnancy and puerperium: twelve-year experience at the Veterans General Hospital-Taipei. Zhonghua Yi Xue Za Zhi (Taipei) 1998; 61: 324–31.
65. Zanetta G, Mariani E, Lissoni A, Ceruti P, Trio D, Strobelt N et al. A prospective study of the role of ultrasound in the management of adnexal masses in pregnancy. BJOG 2003; 110: 578–83.
66. Kobayashi H, Yoshida A, Kobayashi M, Yamada T. Changes in size of the functional cyst on ultrasonography during early pregnancy. Am J Perinatol 1997; 14: 1–4.
67. Bernhard LM, Klebba PK, Gray DL, Mutch DG. Predictors of persistence of adnexal masses in pregnancy. Obstet Gynecol 1999; 93: 585–9.
68. Thornton JG, Wells M. Ovarian cysts in pregnancy: does ultrasound make traditional management inappropriate? Obstet Gynecol 1987; 69: 717–21.
69. Caspi B, Levi R, Appelman Z, Rabinerson D, Goldman G, Hagay Z. Conservative management of ovarian cystic teratoma during pregnancy and labor. Am J Obstet Gynecol 2000; 182: 503–5.
70. Aslam N, Ong C, Woelfer B, Nicolaides K, Jurkovic D. Serum CA125 at 11–14 weeks of gestation in women with morphologically normal ovaries. BJOG 2000; 107: 689–90.
71. Bon GG, Kenemans P, Verstraeten AA, Go S, Philipi PA, van Kamp GJ et al. Maternal serum CA 125 and CA 15-3 antigen levels in normal and pathological pregnancy. Fetal Diagn Ther 2001; 16: 166–72.
72. Kobayashi F, Takashima E, Sagawa N, Mori T, Fujii S. Maternal serum CA 125 levels in early intrauterine and tubal pregnancies. Arch Gynecol Obstet 1993; 252: 185–9.
73. Soriano D, Yefet Y, Seidman DS, Goldenberg M, Mashiach S, Oelsner G. Laparoscopy versus laparotomy in the management of adnexal masses during pregnancy. Fertil Steril 1999; 71: 955–60.
74. Wang PH, Chao HT, Yuan CC, Lee WL, Chao KC, Ng HT. Ovarian tumors complicating pregnancy. Emergency and elective surgery. J Reprod Med 1999; 44: 279–87.
75. Moore RD, Smith WG. Laparoscopic management of adnexal masses in pregnant women. J Reprod Med 1999; 44: 97–100.
76. Parker WH, Childers JM, Canis M, Phillips DR, Topel H. Laparoscopic management of benign cystic teratomas during pregnancy. Am J Obstet Gynecol 1996; 174: 1499–501.
77. Yuen PM, Chang AM. Laparoscopic management of adnexal mass during pregnancy. Acta Obstet Gynecol Scand 1997; 76: 173–6.
78. Caspi B, Ben-Arie A, Appelman Z, Or Y, Hagay Z. Aspiration of simple pelvic cysts during pregnancy. Gynecol Obstet Invest 2000; 49: 102–5.
79. Guariglia L, Conte M, Are P, Rosati P. Ultrasound-guided fine needle aspiration of ovarian cysts during pregnancy. Eur J Obstet Gynecol Reprod Biol 1998; 82: 5–9.

80. Platek DN, Henderson CE, Goldberg GL. The management of a persistent adnexal mass in pregnancy. Am J Obstet Gynecol 1995; 173: 1236–40.
81. Lachman E, Schienfeld A, Voss E, Gino G, Boldes R, Levine S et al. Pregnancy and laparoscopic surgery. J Am Assoc Gynecol Laparosc 1999; 6: 347–51.
82. Akira S, Yamanaka A, Ishihara T, Takeshita T, Araki T. Gasless laparoscopic ovarian cystectomy during pregnancy: comparison with laparotomy. Am J Obstet Gynecol 1999; 180: 554–7.
83. Aslam N, Banerjee S, Carr JV, Savvas M, Hooper R, Jurkovic D. Prospective evaluation of logistic regression models for the diagnosis of ovarian cancer. Obstet Gynecol 2000; 96: 75–80.
84. Timmerman D, Verrelst H, Bourne TH, De Moor B, Collins WP, Vergote I et al. Artificial neural network models for the pre-operative discrimination between malignant and benign adnexal masses. Ultrasound Obstet Gynecol 1999; 13: 17–25.
85. Boll D, Geomini PMAJ, Brölmann HAM, Sijmons EA, Heintz PM, Mol BWJ. The pre-operative assesment of the adnexal mass: the accuracy of clinical estimates versus clinical prediction rules. BJOG 2003; 110: 519–23.
86. Petricoin EF, Ardekani AM, Hitt BA, Levine PJ, Fusaro VA, Steinberg SM et al. Use of proteomic patterns in serum to identify ovarian cancer. Lancet 2002; 359: 572–7.

Address for correspondence:
Ulla Breth Knudsen
Department of Obstetrics and Gynecology
Odense University Hospital
DK-5000 Odense C.
Denmark
e-mail: ubk@dadlnet.dk

Appendix 1

Guidelines for pre- and perimenopausal women

The suggested clinical guideline is based on interpretation of the existing, sparse literature. The recommendations have not yet been examined in clinical practice or in randomized trials

It is recommended to perform an ultrasound scan in all premenopausal women suspected of having an ovarian tumor or cyst, and to measure CA-125 in women with suspicious cysts, solid tumors, and non-suspicious cysts of 4 cm or more ($\geq$4 cm)

Suspicious cysts and solid tumors should be removed surgically. These tumors should, until investigated histologically, be considered malignant and peroperative cyst rupture be avoided

Non-suspicious cyst with a diameter

- $<$4 cm: no reason for follow up
- 4–7 cm: estimation of CA-125 followed by an ultrasound scan 3 months later. Regression will be found in 90% of cysts. If not, the cyst should/may be removed. The patient may, however, be observed for up to a year in case of persistence, before operation is offered
- $>$7 cm: laparoscopy/laparotomy after determination of CA-125

Ca-125

- 35–50 U/ml: new determination 3 months later. If CA-125 is then normal ($\leq$35 U/ml), further follow up is not necessary, if the scan is normal. If CA-125 values are unchanged or rising, and a cyst is present, operation must be considered
- $>$50 U/ml on two occasions: if a cyst is present, irrespective of size and morphology, operation must be considered

The RMI value (below or above 200) can be used to decide the operation method and elect the right operating setting

Guidelines for postmenopausal women

All suspicious cysts and solid tumors should be removed surgically. Women with ovarian cysts and symptoms should be operated on as well, in spite of benign features

Non-suspicious, non-symptomatic cysts with a normal CA-125 value and a diameter

- $<$5 cm: Ultrasound and new measurement of CA-125 after 3 months. If the cyst remains unchanged or reduced in size (and non-suspicious), it can be observed up to 12 months. If still present, it may be removed surgically
- $>$5 cm: operation is recommended, usually at least bilateral salpingoophorectomy

With normal ultrasound but elevated CA-125, operation is recommended

Guidelines for pregnant women

The sonographic characteristics used to evaluate ovarian cysts in non-pregnant women can also be used for pregnant women. Conservative management with additional ultrasonographic examinations during pregnancy is preferable in case of asymptomatic simple cysts and dermoid cysts $<$6 cm. If still-present postpartum, surgery should be performed

Serum CA-125 levels are increased in pregnancy, which makes interpretation difficult

Laparoscopic surgery by an experienced gynecologist is recommended rather than laparotomy and elective surgery should be planned. Due to the high extent of spontaneous resolution of the cysts before 16 weeks' gestation, surgical interventions should preferably be done after that time. Surgery before 7 and after 24 weeks' gestation should be avoided