Review Article

Benefits and limitations of ultrasonographic evaluation of uterine adnexal lesions in early detection of ovarian cancer

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Summary

Ovarian cancer is the most frequent cause of death from gynaecological malignancies in the Western world. Most cases of epithelial ovarian cancer are detected at late stages and the resultant overall five-year survival is poor. However, when epithelial ovarian cancer is detected with the disease confined to the ovary the prognosis is favorable. Transvaginal gray-scale ultrasonography and colour Doppler assessment of blood flow have been evaluated as methods to predict risk of malignancy in ovarian tumours. In order to reduce the number of unnecessary surgical procedures for uterine adnexal tumours, ultrasonomorphologic scoring systems have been developed, assigning numerical ultrasonographic parameters of the tumours. However, the positive predictive value of these scoring systems is low and this is due to the fact that the appearance of many benign ovarian lesions overlaps with that of malignant disease. In addition, some ovarian malignancies are ultrasonographically detected as simple cysts without exhibiting a complex morphology. Moreover, the cut-off size of uterine adnexal tumours for surgical intervention in the early detection of cancer is not yet well determined. The application of colour blood-flow imaging is very helpful in the detection of uterine adnexal malignancy because of the presence of neovascularization in malignant tumours. When gray-scale ultrasonography detects the presence of septum or papillary projections or solid components in uterine adnexal lesions and Doppler flow is present within these lesions malignancy is likely. However, the detection of vascularity within the papillary projection of a malignant tumour may not be detected when it is very small. When colour-flow imaging is used in premenopausal patients attention is needed to avoid confusion of luteal flow with flow of cystic lesions. Initial reports using pulsed Doppler ultrasonography showed high sensitivity and specificity in the detection of ovarian cancer when levels of the resistive index (RI) less than 0.4 and levels of the pulsatility index (PI) less than 1 were used. Subsequent studies have shown considerable overlap of RI and PI rates between benign and malignant uterine adnexal masses, suggesting that pulsed Doppler ultrasonography is not an independent indicator for malignancy. Serum CA-125 levels have been used in conjunction with ultrasonography to identify as many of the false-positive results in order to avoid unnecessary surgery. In postmenopausal women with a uterine adnexal mass the combination of physical examination with serum CA-125 levels and pelvic ultrasound scan seems to improve the sensitivity and specificity of predicting adnexal malignancies. In contrast, in premenopausal women the consideration of CA-125 levels with Doppler ultrasonographic findings might confuse the differential diagnosis of ovarian masses. In conclusion, accurate selection of patients with uterine adnexal tumours for surgical intervention is not provided by pelvic ultrasonography. Pelvic ultrasonography as a screening method for the early detetection of ovarian cancer should be probably limited to those women who are at increased risk for development of ovarian cancer and not in the general population.

Key words: Ovarian neoplasms; Ovarian cancer; Adnexa uteri; Pelvic masses; Cysts; Transvaginal; Ultrasonography; Screening test; Diagnostic accuracy.

Introduction

Ovarian cancer is the most frequent cause of death from gynaecological malignancy in the Western world [1]. The majority of ovarian cancers are sporadic. For women in the U.S., the overall lifetime risk of developing ovarian cancer is 1.4% to 1.8% [2]. The risk of ovarian cancer increases from 15.7/100,000 at age 40 years to 54/100,000 at age 75 years [1] and over one-third of cases occur in women over 65 years [4]. The majority of ovarian malignancies in women under 25 years are non-epithelial, usually from germ cells [5].

Women with a family history of epithelial ovarian cancer represent a high-risk population. Kerlikowske *et al.* estimated that women with over one relative with ovarian cancer are at a 3.1 times increased risk compared to the general population [6]. True hereditary ovarian cancer syndromes account for less than 10% of

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ovarian cancer cases [4]. Lynch *et al.* have described three hereditary ovarian cancer syndromes where affected members tend to present with disease approximately ten years earlier than the general population (45-50 years old vs 59-62 years old): (a) Site-specific ovarian cancer, where ovarian cancer is expressed in multiple female members of the genetic lineage; (b) hereditary breast-ovarian cancer syndrome, where both breast and/or ovary cancers are present in family members; and (c) Lynch syndrome II or hereditary non-polyposis colon cancer (HNPCC) in which a genetic tendency to develop ovarian, endometrial and colon cancers can be demonstrated in the pedigree [7].

Most cases of epithelial ovarian cancer (70-75%) are detected only after there has been regional or distal metastasis with the resultant overall 5-year survival approximating 15%. However, if epithelial ovarian carcinoma is detected when the disease is confined to the ovary (Stage I), the 5-year survival approximates 90% [5]. Therefore, ovarian cancer should be diagnosed by a suitable test or examination at an early stage. This test or examination should have both high sensitivity (the probability of the test being positive in individuals with disease) and high specificity (the probability of the test being negative in those patients without the disease). Physical examination has been proven to be of limited value, especially in small tumours, and is very inaccurate in predicting whether a given adnexal mass is benign or malignant unless there are associated findings of disseminated disease such as ascites or palpable intra-abdominal masses [8]. Rulin and Preston found that pelvic examination detected only 71% of ultrasonographically detected masses less than 5 cm in diameter and fared only slightly better (76%) when the mass was 5-10 cm in diameter; 10% of masses larger than 10 cm were missed on pelvic examination [9]. Transvaginal gray-scale ultrasonomorphology, and colour blood-flow ultrasonographic imaging have been evaluated as methods to predict risk of malignancy in ovarian tumours. However, the use of transvaginal ultrasonography into diagnostic gynaecology has dramatically increased the number of surgical procedures for ovarian tumours [10]. Here all the limitations of pelvic ultrasonography for the evaluation of ovarian masses as regards the early detection of ovarian cancer will be considered.

2. Ultrasonographic detection and characterization of uterine adnexal lesions

The introduction of vaginal ultrasound probes has enhanced our ability to look in detail at structures in the pelvis. These higher frequency transducers produce a significant improvement in image resolution [11]. Alterations in ovarian size or volume may be an early indication of ovarian malignancy. The upper limit of normal ovarian volume for premenopausal women is 20 cm^3 and 8 cm^3 to 10 cm^3 for postmenopausal women. Ovarian volume decreases after menopause, and ovarian volume in women over 70 years of age is in the range of 1 cm^3 to 1.8 cm^3. Any ovarian enlargement for age, exceeding twice the volume of the contralateral side is considered suspicious by ultrasonographic criteria [12-15]. However, ovaries with size in the normal range are not seen all the time by transvaginal ultrasonography. DiSantis *et al.* reported that only 76% of normal ultrasonographically premenopausal ovaries and 20% of normal ultrasonographically postmenopausal ovaries were seen when transvaginal ultrasonography was used alone [16]. In contrast, some other authors reported better results [17, 18].

Adnexal masses are ultrasonographically diagnosed on the basis of standard criteria. Simple cysts in premenopausal women are usually of functional origin due to failure of involution of the follicle or the corpus luteum. They present with a smooth well-defined thin wall, increased through transmission and lack of internal echoes, septations or mural nodules [19, 20]. In haemorrhagic cysts the presence of clots make the ultrasonic pattern variable. Sonographic criteria includes a specific pattern of multiple fine interdigitating septations giving a fishnet appearance (Figures 1a, 1b) or a whirled pattern of clotted blood associated with sharply marginated thin walls and enhanced through sound transmission. Ruptured cysts may be associated with fluid in the Douglas pouch [12, 20]. A paraovarian cyst is suggested when a unilocular cystic adnexal mass with a regular wall and a good through-transmission is separated from the ipsilateral ovary [21]. Benign serous cystadenoma appears as a cystic mass containing clear fluid, with thin internal septa. Wall nodulations are not frequent. Benign mucinous cystadenoma is strongly suggested when the mass is multi-

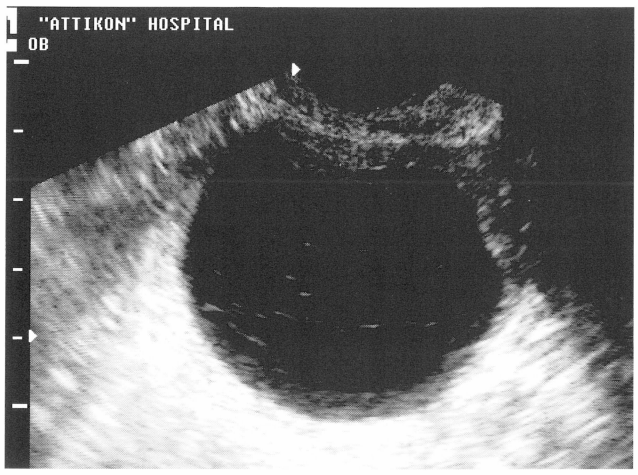


Fig. 1a

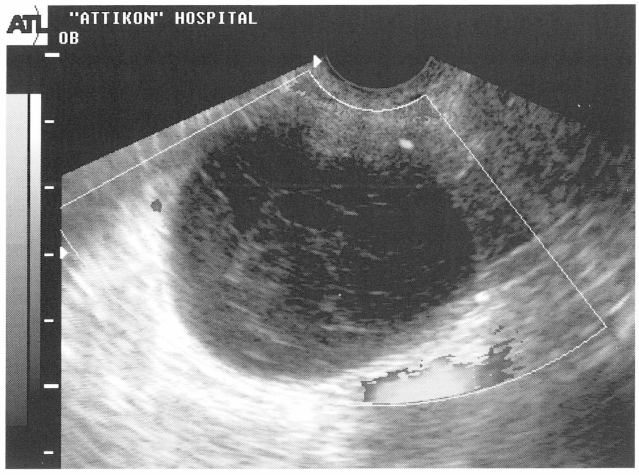


Fig. 1b

Figure 1. — Heamorrhagic ovarian cyst in a 32-year-old patient.
1a. Gray-scale trasvaginal ultrasonography shows a cyst with internal thrombus and fibrin strands.
1b. Colour-flow imaging shows absence of blood flow inside the cyst; the lesion is ultrasongraphically considered as benign.

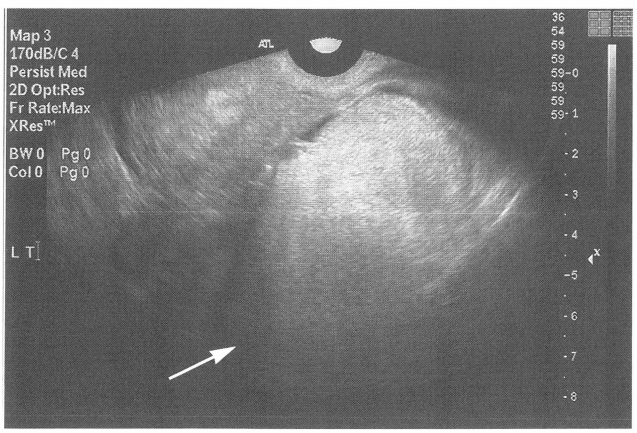


Figure 2. — A transvaginal ultrasound scan of a left parasagittal highly echogenic adnexal mass containing mostly fat (arrow) with the typical appearance of a dermoid cyst. Dermoid cyst was confirmed by histopathology.

locular and contains liquids of different echogenicities, although multilocutated serous cystadenomas and endometriomas can have the same presentation [21]. Ultrasonographic characteristics of mature cystic teratomas (dermoid cysts) include the presence of fat-fluid levels, a hyperechoic mural nodule (dermoid plug) (Figure 2), or areas of calcification [20]. An intensely hyperechoic mass within the ovary is also indicative of a dermoid cyst (Figure 3). Ovarian endometrioma is suggested when a mass, more or less round, with homogeneous low-level echoes (of lesser echogenicity than myometrium) and an internal irregular shaggy wall is found (Figures 4, 5). Homogeneous echogenic blood clots appearing as echogenic foci lying against the inner wall support the diagnosis when they are curvilinear or slightly separated from the wall [21]. Ovarian sclerosing stromal tumour is usually ultrasonographically detected as a pelvic mass with mixed heterogeneity and without focal calcifications [22]. Ovarian fibromas are more commonly solid, with an echogenicity close to myometrium. These tumours may resemble cystic echogenic masses and subserous leiomyomas when the ipsilateral ovary cannot be detected [21]. A subserous uterine leiomyoma is suggested when the echogenicity of the mass is close to that of myometrium and when the mass is separated from the ovaries. A calcified locus within the mass supports the diagnosis. The mass could be homogeneous or slightly heterogeneous, with thin, multiple acoustic shadows without a hyperechoic focus [21]. Ultrasound findings in pelvic inflammatory disease vary according to the severity of the disease. In early conditions, ultrasound may be normal [12]. Sonographic criteria of pyosalpinx include identification of a tubular fluid-filled mass separated from the ovary (Figures 6a, 6b). Thickened epithelial mucosal folds are helpful in establishing the tubal origin (Figure 7). Layering of echogenic debris is suggestive of blood or pus. The ultrasonographic findings of tubo-orarian abscesses are not specific [23]. Varras *et al.* analyzed retrospectively the ultrasonographic findings of 25 women in whom the presence of tubo-ovarian abscess was confirmed by surgery and histopathology. Presence of a mass was found in all cases. The maximum diameter of the mass was 5 cm in two cases and between 5 cm and 10 cm in 23 cases. The mass was demonstrated at the anatomic position of the ovary in 21 cases (84%) and at the cul-de-sac in four cases (16%). The mass

Fig. 3

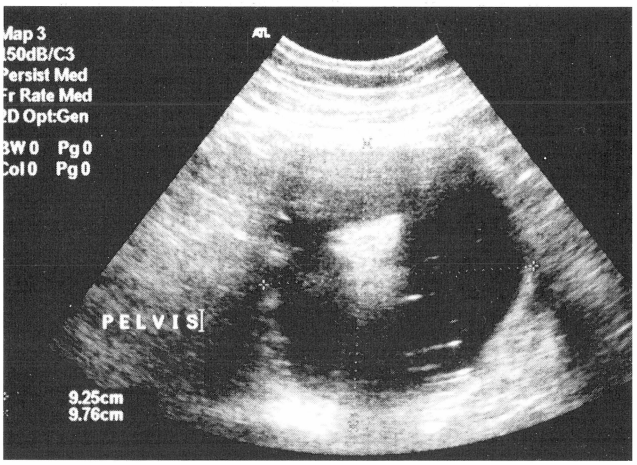


Fig. 4

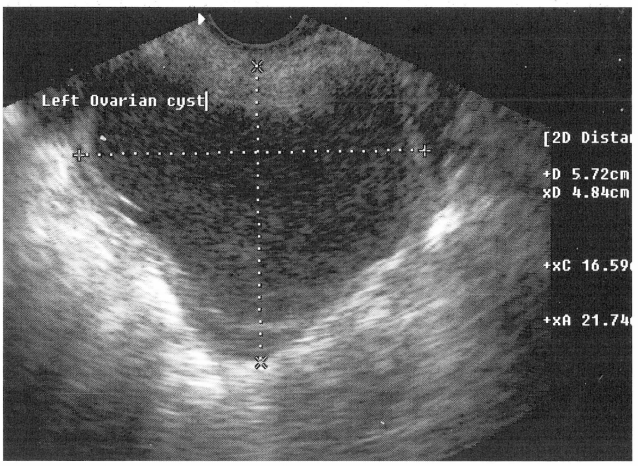


Fig. 5

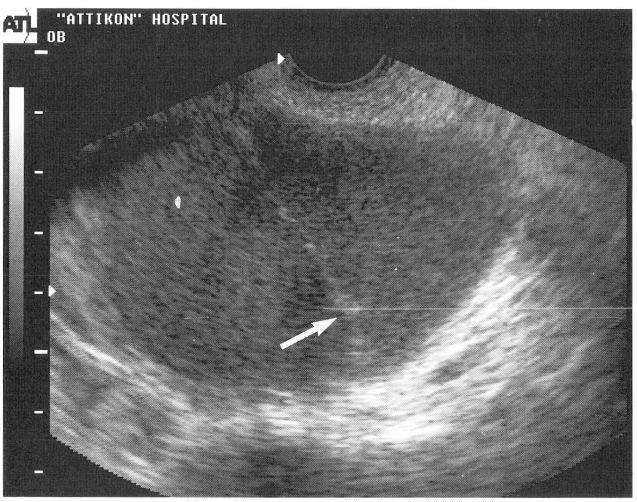


Figure 3. — A transvaginal ultrasonogram of a solid-cystic tumour is presented. The intensely hyperechoic mass within the cyst indicates a dermoid cyst. Dermoid cyst was confirmed by histopathology.

Figure 4. — Ovarian endometrioma of the left ovary in a 43-year-old patient: coronal endovaginal ultrasound scan shows diffuse dispersion of low-level echoes within the cyst. Preoperative levels of CA-125 were 115 IU/ml (normal < 33 IU/ml).

Figure 5. — Endometrioma of the left ovary: at conventional transvaginal ultrasonography septum within the cyst was observed (arrow), which represents residual ovarian tissue.

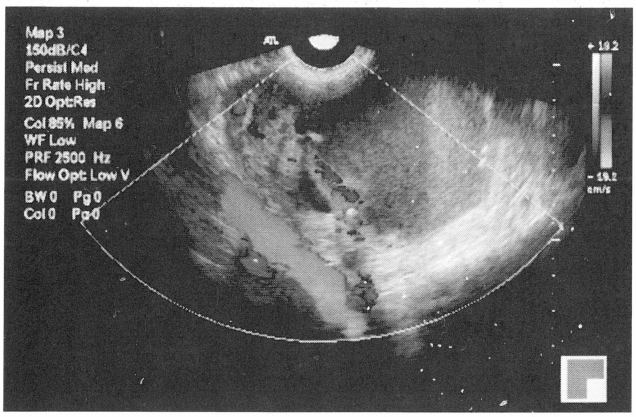
was a simple cyst in two cases (8%), in four cases (16%) it was a thickened tube-shaped structure with multiple internal echoes, in 15 cases (60%) it was a mixture of cystic and solid elements (Figure 8a) and in four cases (16%) it was cystic with diaphragms (Figure 8b). Pyosalpinx with fluid-fluid levels was found in two cases. Fluid in the cul-de-sac was found at a rate of 48% [23].

The presence of any of the following morphologic features is suggestive of a borderline or malignant tumour: (i) an echogenic structure against the wall of the cyst, suggesting vegetation; (ii) a large, irregular homogeneous or heterogeneous echogenic structure suggesting an irregular solid portion with or without degenerative changes; (iii) an irregular thickened (> 3 mm) wall or septum [21]. Also, the presence of ascites and involvement of the liver are suggestive of malignancy [24]. Malignant germ cell tumours are predominatly solid, while ovarian metastases have a variable appearance and are most frequently from breast cancer, colon cancer, gastric cancer and lymphoma [12].

3. Sonomorphologic scoring systems of uterine adnexal masses for identification of ovarian cancer

Various sonomorphologic scoring systems, which assign numerical ultrasonographic parameters of the adnexal tumours have been developed in order to differentiate between benign and malignant neoplasms in pre- and postmenopausal women. Some of these parameters are: (1) size of the tumour; (2) structure of septa; (3) solid components; (4) papillary projections from the outer rim of the mass; (5) thickness of septa; (6) wall thickness of mass; and (7) echogenicity. In terms of the connection of tumour size with the risk of malignancy it has been found that 27% of tumours ≥ 9 cm in diameter were malignant [10]. The presence of septa, creating a multilocular pattern, increases the likelihood of cancer in an ovarian mass [25]. The thickness of septa seen has received some attention, with various authors suggesting that septa thicker than 3 mm is a hallmark of malignancy [25]. Solid components are also suggestive of malignancy. Granberg *et*

Fig. 6a



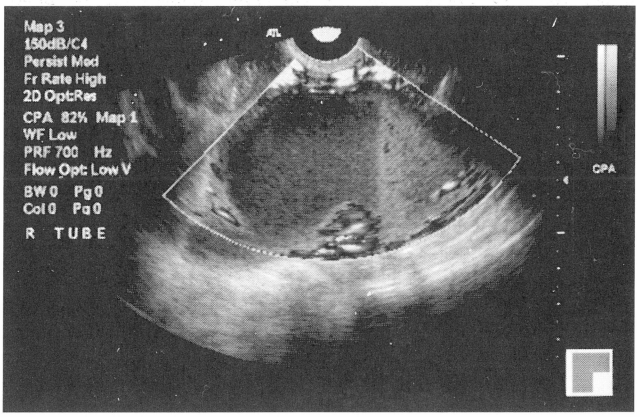


Fig. 6b

Figure 6.
6a. Demonstration of pyosalpinx on the right; the right ovary has an ambiguous appearance. The internal pelvic vessels and a small amount of fluid around the ovary are demonstrated.
6b. The pyosalpinx is seen as a thickened tube-shaped mass. Also fluid-fluid levels within the mass and abundant blood flow in its periphery can be observed.

Fig. 7

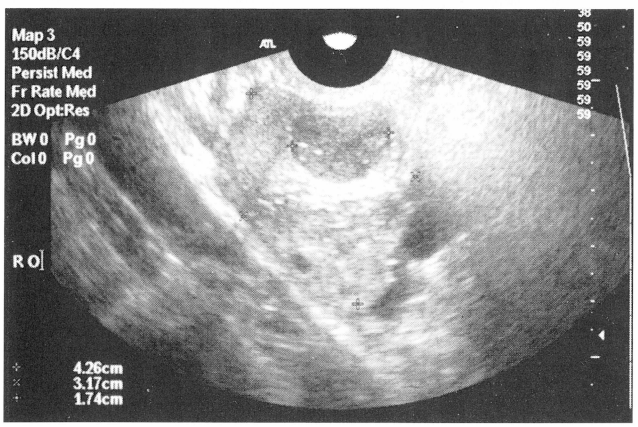
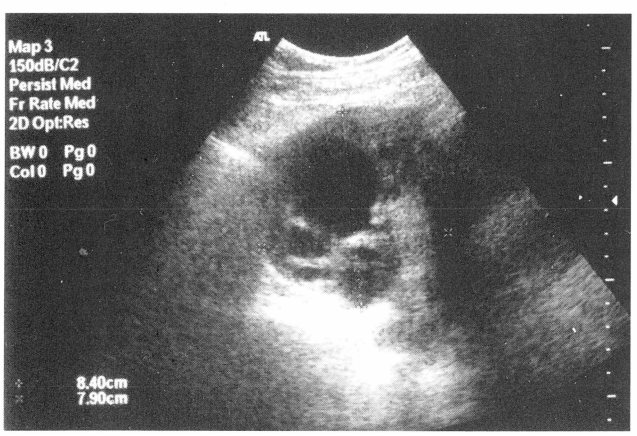


Figure 7. — Right pyosalpinx with ambiguous appearance of the right ovary (transvaginal ultrasonography).

Fig. 8a



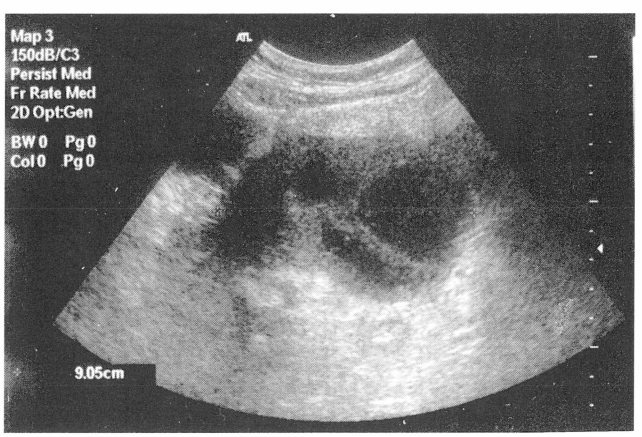
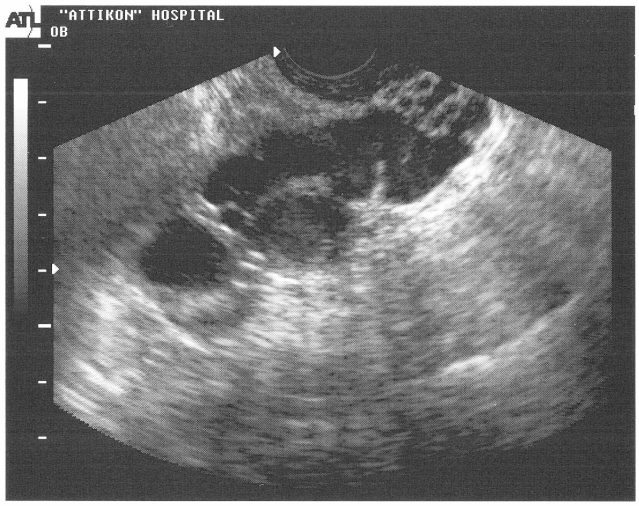


Fig. 8b

Figure 8. — Two cases of tubo-ovarian abscesses.
8a. Right tubo-ovarian abscess: Ultrasonographic appearance of a pelvic mass with cystic and solid elements (abdominal ultrasonography).
8b. Left tubo-ovarian abscess: Ultrasonographic appearance of a pelvic mass with internal confines and diaphragms (abdominal ultrasonography).

al. reported 8% (20/229) of cancers in multilocular tumours without solid components and 70% (147/209) of malignancies in multilocular tumours with solid components [26]. Osmers *et al.* found that on a single transvaginal sonogram, the estimated risk of malignancy in cysts with solid components was 17% in premenopausal women; in postmenopausal women two-thirds with such tumours were found to be malignant [10]. As regards the papillary projections from the outer rim of the mass and the possibility for ovarian malignancy Granberg *et al.* found that 73 of 79 (93%) tumours with such excrescences were malignant [26]. Sassone *et al.* assigned four morphologic characteristics of adnexal masses (inner wall structure, wall thickness, characteristics of septa and echogenicity) according to the likehood of defining a malignant tumour. Tumour morthology scores varied from 4 to 15 and a score of 9 was used to distinguish benign from malig-

Fig.9a



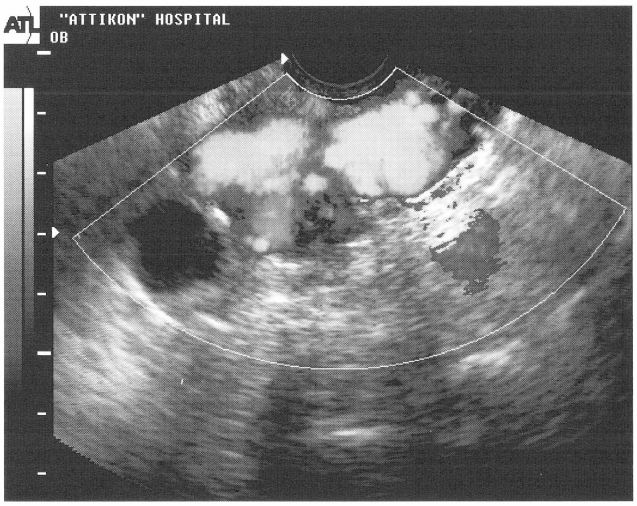
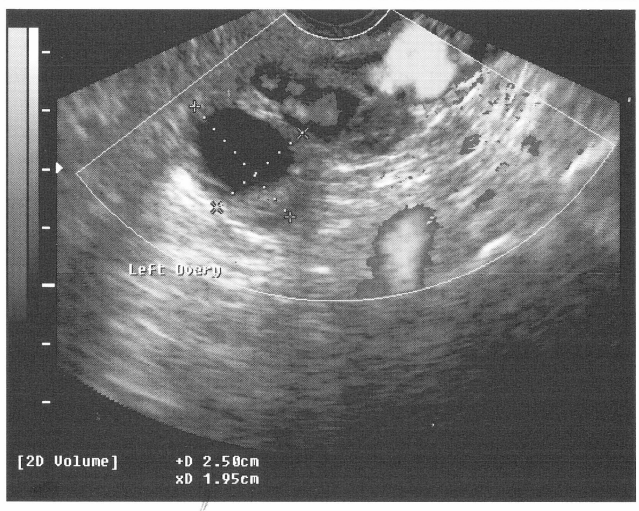


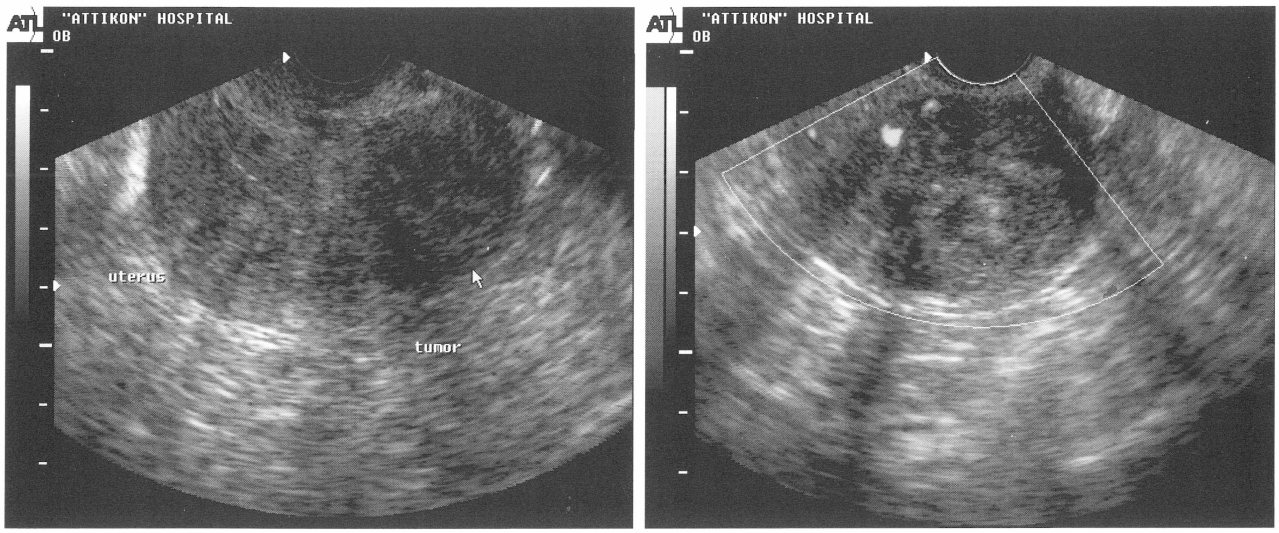
Fig. 9

Fig. 9c



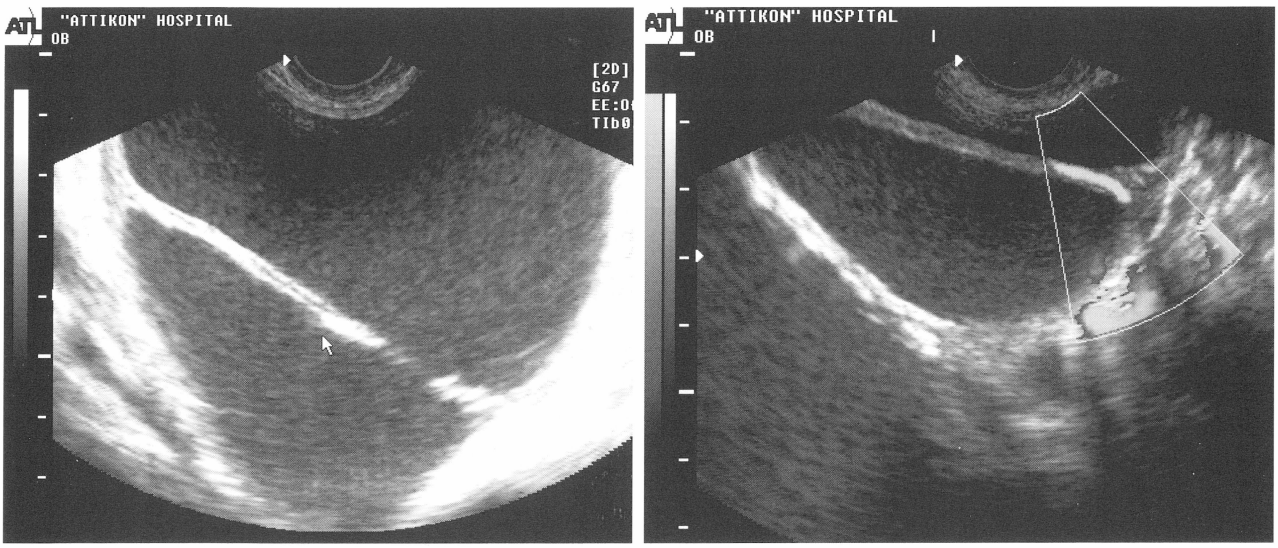
Figures 9. — Pelvic varices.
9a. A complex pelvic lesion is found by gray-scale ultrasonography.
9b. Pelvic varices are detected by colour-flow imaging.
9c. The ovary measures 2.5 x 1.95 cm.

nant tumours. The researchers applied this scoring system in 143 patients undergoing surgery for clinically detected pelvic masses. Twenty of these patients had ovarian cancer. Using a morphology score of ≥ 9 as indicative of cancer, malignant ovarian tumours were distinguished from benign lesions with a specificity of 83%, a sensitivity of 100%, a positive predictive value (PPV) of 37% and a negative predictive value (NPV) of 100%. The PPV of this scoring system was hampered by high-scoring masses such as teratomas, fibroma-thecomas and endometriomas [27]. DePriest *et al.* developed a morphology index based on tumour volume, wall structure and septa structure. Ovarian tumour volume was calculated using the prolate ellipsoid formula: (width x height x thickness x 0.523). A point scale (0-4) was developed within each category to specific criteria with the total points per evaluation varying from 0 to 12. Sonographic data on 121 patients undergoing exploratory laparotomy for ovarian tumours were evaluated using this model. Eighty ovarian tumours had a morphology index score of < 5 and all were benign; the NPV was 100%. In addition, many of the benign conditions associated with the highest morphology index values such as pelvic inflammatory disease or corpus luteum cysts occurred almost exclusively in premenopausal women. Using a morphology index ≥ 5 as indicative of malignancy, this system had a positive predictive value of 45% in postmenopausal patients. Wall structure was the most reliable morphologic criterion in distinguishing ovarian cancer form benign lesions. All ovarian cancers had a papillary projection or solid component protruding from the inner wall of the tumour [28]. Bourne *et al.* reported the findings of a screening study for ovarian cancer among women with a strong family history of the disease. In women with a persistent ovarian mass, the application of a morphology score as a second-stage test led to a significant reduction in false-positive test results (53 to 6). However, this was at the cost of failing to detect an early-stage cancer [29].



ig. 10a Fig. 10b

Figures 10.
10a & 10b. A solid mass in contact with the uterus with internal blood flow. The differential diagnosis includes subserosal uterine fibroid or solid ovarian mass. Surgery and histopathology demonstrated the presence of a subserosal uterine fibroid.



ig. 11a Fig. 11b

Figure 11. — **11a & 11b.** Cystic lesion with low-level echoes and thick septa (arrow) with vascularity suggestive of malignancy. Histopathology showed a mucinous borderline ovarian tumour.

Summarising the above data, the ultrasonomorphologic scoring systems of uterine adnexal lesions do not allow a reliable prediction of the presence of ovarian cancer. The low positive predictive value is due to the fact that the appearance of many benign lesions overlaps with that of malignant disease [30]. In addition, ultrasonomorphologic assessment of adnexal masses is complicated by the fact that simple ovarian cysts detected in both pre- and postmenopausal women do not exhibit a complex morphology [10]. Osmers *et al.* found that 0.8% of ovarian malignancies presented as simple cysts [10]. Moreover, the cut-off size of the ovarian tumour for surgical intervention is not well determined. One can assume that the larger the tumour the greater the risk for ovarian cancer, but this does not mean early detection of ovarian cancer as it has been found that 59% of all ovarian malignancies were between 3 and 9 cm [10].

4. Colour and power Doppler imaging for evaluation of uterine adnexal masses

The use of colour blood-flow ultrasonographic imaging in the pelvis has some diagnostic benefits. First of all, colour blood-flow imaging is used to distinguish cysts from vessels. Figures 9a, 9b and 9c demon-

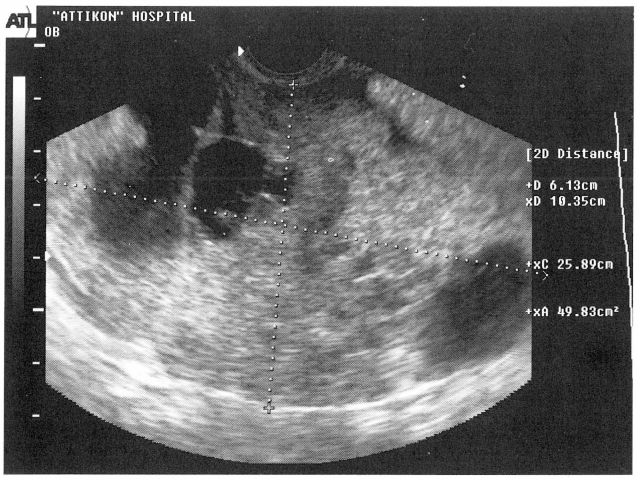
strate the benefits of colour blood-flow imaging in the differential diagnosis of varices from uterine adnexal lesions. In addition, colour blood-flow imaging can be used to evaluate uterine adnexal masses in patients suspected of having torsion. The theory behind Doppler ultrasonography of the adnexal vessels in suspected ovarian torsion is that Doppler ultrasonography will show a decrease or absence of blood flow in these vessels resulting from the mechanical torsion of the ovarian vessels [31]. Peña *et al.* assessed the predictive value of Doppler ultrasonography in the diagnosis of ovarian torsion in ten patients who were managed surgically. The authors found that Doppler ultrasonographic findings were normal in 60%, whereas 20% revealed decreased Doppler flow (decrease in vascular flow to the ovary) and 20% revealed absent of Doppler flow (absence of vascular flow to the ovary), suggestive of torsion. In this study, Doppler ultrasonography missed the diagnosis 60% of the time [32]. This is in agreement with the findings of Lee *et al.* in which the presence of normal arterial and venous flow was confirmed in 57% of cases of surgically confined adnexal torsion (16 out of 28) [33]. These findings are explained by the degree of vascular compromise. As is known, ovarian torsion initially interferes with the venous and lymphatic circulation and, if unrelieved, progresses to occlusion of the arterial circulation. Therefore, persistent arterial flow cannot rule out a diagnosis of early or incomplete torsion of the ovary. The specific indication for complete occlusion of both venous and arterial vessels is the absence of flow to the ovary detected by colour Doppler ultrasonography. Fortunately, malignant ovarian neoplasms are less likely than benign ovarian neoplasms to undergo adnexal torsion. Varras *et al.* found malignant adnexal tumours in association with adnexal torsion in 9% of cases [34] and this finding is in agreement with the results of other studies. In 85% of the cases of twisted uterine adnexae the patients were under 50 years old [34]. Possible explanations for the low probability of malignant ovarian neoplasms found in twisted uterine adnexal structures are the following: (i) malignant ovarian tumours are less common than benign ovarian tumours; (ii) most patients with uterine adnexal torsion are premenopausal; (iii) malignant ovarian tumours adhere to local structures by inflammation or adhesions or local invasion and therefore uterine adnexal torsion is not possible.

Colour blood-flow imaging can be used to further characterize the nature of tubo-ovarian abscesses. Varras *et al.* estimated the blood flow in the periphery of tubo-ovarian abscesses and found it to be rich in 90% [23]. However, in cases with abundant flow in the periphery of a pelvic mass the possibility of tubal or ovarian malignancy should be taken into consideration. The clinical condition of a patient with a tubo-ovarian abscess such as fever, leukocytosis and elevated erythrocyte sedimentation rate is helpful for the differential diagnosis. However, many patients harboring a tubo-ovarian abscess may present with a normal temperature and white blood count. Therefore, following-up these patients, if they are not operated on, is needed to reduce the possibility of misdiagnosing a malignant lesion [23].

In addition to the above-mentioned applications of colour blood-flow imaging, it is useful in distinguishing solid ovarian tumours, such as fibromas or thecomas with a homogeneous and hypoechoic appearance in gray-scale ultrasonography from adnexal cysts such as endometriomas by showing flow within the solid mass [30] (Figures 10a, 10b). In the case of endometriomas blood flow may be present around the periphery of the cyst or within septations of the cyst, which may represent residual ovarian tissue surrounded by endometriomas [30]. However, the septated appearance of endometriomas makes differentiation from malignancy impossible. Figure 1b shows the absence of blood flow inside a haemorrhagic ovarian cyst.

In cases of uterine adnexal malignancy colour blood-flow imaging is very helpful for the detection of malignancy, because of the presence of neovascularization in malignant tumours [24]. When gray-scale ultrasonography detects the presence of septum or papillary projections or solid components in a uterine adnexal lesion and Doppler flow is present within these legions, malignancy is likely [30]. Figures 11a and 11b demonstrate a mucinous borderline tumour of the right ovary with thick septa and vascularity within them suggestive of malignancy. Also, Figures 12a, 12b and 12c show a clear-cell adenocarcinoma of the left ovary detected as a multilocular cystic mass containing solid elements with increased vascularity at the periphery and the center of the echogenic portions suggestive of malignancy. However, the lack of detectable blood flow by means of colour Doppler does not exclude ovarian malignancy [35, 36]. It has been suggested that detection of vascularity within malignant tumours may be related to the size of tumor papillary projections with decreased detection of internal flow if papillary projections are smaller than 1 cm [12]. However, one important limitation for

g. 12a



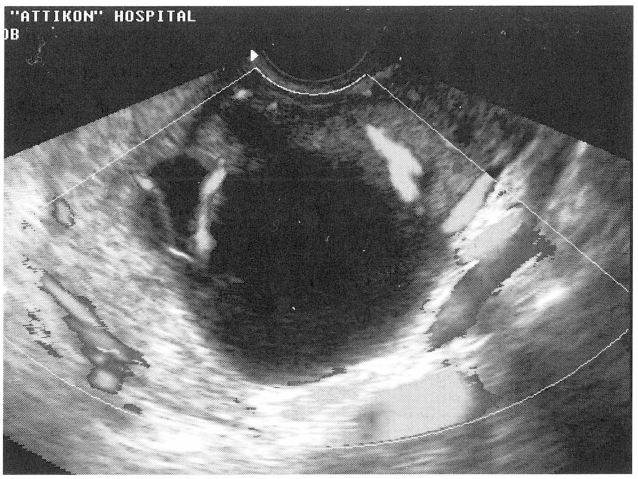
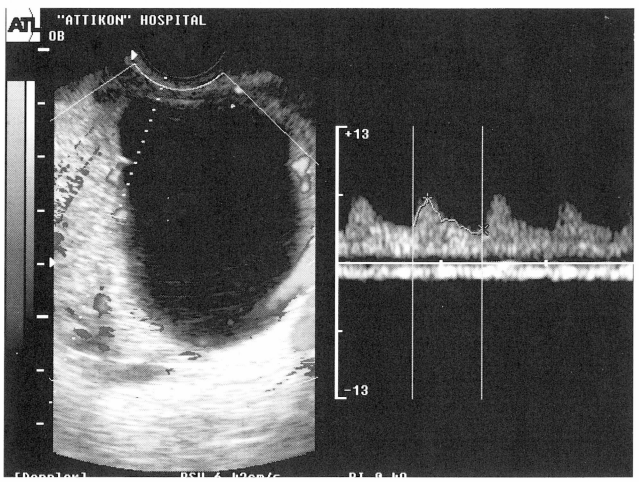


Fig. 12b

g. 12c



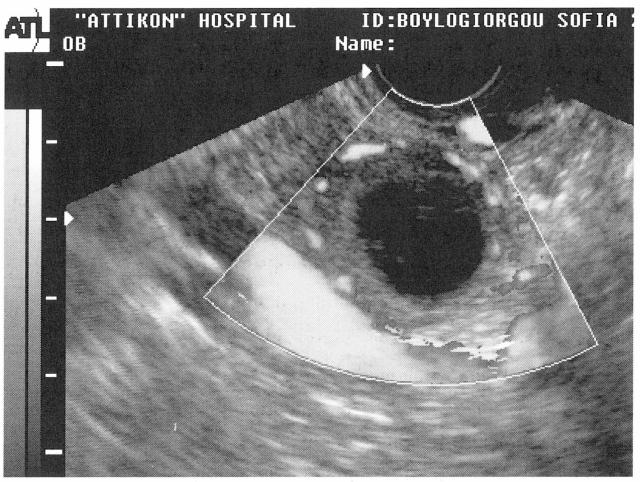


Fig. 13

Figure 12. — Clear-cell adenocarcinoma of the left ovary in a 67-year-old patient. Preoperative levels of CA-125 were 120 IU/ml (normal < 33 IU/ml).
12a. Conventional ultrasonography shows a 10.4 cm multilocular cystic mass containing solid elements which suggest malignant tumour.
12b. Color-flow imaging shows increased vascularity at the periphery and at the center of the echogenic portions, making diagnosis of a malignant tumour more certain.
12c. The pulsality index (PI) is lower than 1.0 (PI = 0.73) indicative of malignancy.
Figure 13. — Colour-flow imaging outlining the corpus luteum represents the neovascularity of the peripheral rim in a 25-year-old woman. Also the internal pelvic vessels are demonstrated.

the application of colour blood-flow imaging in detecting ovarian cancer is that, angiogenesis is typically present with normal corpus luteum development [30]. Figure 13 presents the corpus luteum in a 25-year-old woman; the colour blood-flow imaging outlining the corpus luteum represents the neovascularity of the peripheral rim. Therefore, to avoid confusing luteal flow with flow of other cystic masses women of menstrual age should be ultrasonographically examined in the first ten days of their cycle [30].

Pulsed Doppler techniques allow sampling of blood flow within the vessels. In Doppler velocimetry, the flow velocity waveform obtained from a target vessel is assessed according to standard parameters: resistive index (RI) and pulsatility index (PI). RI is peak systolic velocity minus end-diastolic velocity divided by peak systolic velocity. PI is peak systolic velocity minus end-diastolic velocity divided by mean velocity [12]. The vessels in benign ovarian lesions generally have significant peak systolic flow and a high PI. In contrast, vessels supplying ovarian malignancies lack muscular intima and there is a low impedance to flow within them. Initial reports using pulsed Doppler showed high sensitivity and specificity for detection of ovarian cancers. As a result, a PI < 1.0 (Figure 12c) and RI < 0.4 were considered as indicative of malignancy. Kurjak *et al.* noted that the RI values were > 0.4 in 99.8% of 624 benign ovarian tumours, and RI

values were < 0.4 in 96.4% of 56 malignant ovarian tumours [37]. Using colour flow Doppler, Weiner *et al.* evaluated the blood flow to 53 ovarian masses prior to laparotomy. These authors reported that there was a low impedance to flow as evidenced by a PI of ≤ 1.0 in 16 of 17 malignant ovarian tumours. In contrast, the PI was > 1.0 in 35 of 36 benign ovarian tumours [38]. However, subsequent studies have shown considerable overlap of RI and PI ratios in benign and malignant masses. Tekay and Jouppila performed Doppler flow studies in 72 patients suspected of having an adnexal tumour on conventional sonography. These authors could not find significant differences between the mean PI and RI values in benign and malignant ovarian tumours [39]. Bromley *et al.* found that the addition of Doppler flow studies to an ultrasonographically determined morphology index did not significantly improve prediction of malignancy [40]. The overlap in PI and RI values between benign and malignant ovarian tumours, and the expense of this procedure, make its routine use in the evaluation of pelvic tumours impractical [41]. In addition, this method is time-consuming because a recording from a single high-resistance vessel within the tumour is not sufficient but multiple samples should be taken and the lowest value should be selected [12, 30]. Therefore, pulsed Doppler sonography cannot be used as an independent indicator of malignancy, but it may provide supplemental information that is useful in benign versus malignant differentiation [12].

5. Ultrasound pelvic scan in combination with other screening methods

It is clear that an additional test or examination is needed in conjunction with ultrasonography to identify as many of the false-positive results as possible to avoid unnecessary surgery [24]. Tumour markers have been used to differentiate benign from malignant uterine adnexal tumors; the most used is CA-125 assay [42]. Serum CA-125 levels are increased in patients with different stages of epithelial ovarian cancer and patients with serous, mucinous, endometrioid, clear cell, and undifferentiated carcinomas of the ovary [43]. CA-125 assay has proved its value especially in monitoring therapy and early detection of recurrent ovarian cancer after complete remission [43]. Several studies have evaluated the combination of serum levels of CA-125 and ultrasound in diagnosing ovarian malignancy. Malkasian *et al.* compared the diagnostic accuracy of serum CA-125 at various cut-off values, along with menopausal status, in patients with known pelvic masses. They determined that serum CA-125 had a sensitivity of 78% and specificity of 97% for the detection of malignancy when values in postmenopausal women were ≥ 65 IU/ml. In premenopausal women, a similar cut-off produced a sensitivity of 60% and specificity of 89%. The prevalence of malignancy was 63% in the postmenopausal group and just 15% in the premenopausal group [42]. Gadducci *et al.* evaluated the efficacy of serum CA-125 levels as a means to identify ovarian cancer in 344 patients undergoing laparotomy for clinically apparent ovarian masses. Serum CA-125 ≥ 35 IU/ml had a specificity of 67.3% and a positive predictive value of 47.1%. However, over three-fourths of the patients with ovarian cancer in this study had advanced-stage disease [44]. Jacobs and Bast, in a review of the literature, found that serum CA-125 is elevated > 35 IU/ml in only 50% of patients with Stage I ovarian cancer [45]. Some investigators examined the specific role of serum CA-125 levels and colour Doppler ultrasonography in the evaluation of ultrasonographically suscpicious adnexal masses. Kawai *et al.* found that colour Doppler was more specific than CA-125 (79% for colour Doppler ultrasonography versus 46% for CA-125) with similar sensitivity (75% for colour Doppler sonography vs 72% for CA-125) [46]. Also, Alcázar *et al.* found that the specificity of colour Doppler ultrasonography was significantly higher than CA-125 (84% for colour Doppler sonography vs 68% for CA-125); the sensitivity was similar for colour Doppler ultrasonography (88%) and for serum CA-125 levels (84%) [8]. Strigini *et al.* compared the diagnostic accuracy of transvaginal ultrasonography, colour blood-flow imaging and serum CA-125 assay in pre- and postmenopausal women undergoing laparotomy for a clinical diagnosis of an adnexal mass. They found that the diagnostic accuracy of the tests in discriminating a benign from a malignant mass was dependent on menopausal status. In premenopausal women, all malignant masses were correctly identified by means of transvaginal ultrasonography, with a very high specificity (97%). In these women the accuracy of transvaginal ultrasonography was significantly better in comparison with either serum CA-125 assay ($p < 0.05$) or Doppler study ($p < 0.002$). The accuracy of transvaginal ultrasonography was significantly lower in postmenopausal than in premenopausal patients ($p < 0.05$), whereas the menopausal status did not significantly modify the accuracy of

serum CA-125 assay and Doppler study [47]. Jacobs *et al.* suggest that ultrasound scan combined with CA-125 assay and menopause status yield a sensitivity of 85% and a specificity of 97% in diagnosing malignant lesions [48]. Thus, in premenopausal women the specificity of CA-125 assay is low, as serum CA-125 levels are elevated in benign conditions such as endometriomis, benign ovarian cysts, pelvic inflammatory disease and during menstruation [8]. In premenopausal women considering CA-125 levels with Doppler ultrasonographic findings could cloud rather than clarify the differential diagnosis of ovarian masses [25]. However, in postmenopausal patients with an adnexal mass the combination of physical examination with serum CA-125 levels and pelvic ultrasound scan seems to improve the sensitivity and specificity in predicting uterine adnexal malignancy [24, 49].

6. Screening for ovarian cancer

Ovarian cancer screening in the general population has been performed using ultrasound examination of the female pelvis (particularly transvaginal ultrasonography) and serum tumour marker determinations, but at present it is an experimental technique [50].

The Kentucky group published their transvaginal ultrasonography results from 14,469 women enrolled in the University of Kentucky Ovarian Cancer Screening Program. Women participating in the study were recruited through media campaigns and via communications through civic organizations. Eligibility criteria included (i) all women ≥ 50 years of age and (ii) women ≥ 25 years of age with a documented family history of ovarian cancer in at least one primary or secondary relative. *BRCA1* and *BRCA2* testing was not performed as part of the trial. Postmenopausal was defined as the absence of menses for a minimum of 12 months. Any woman with a known ovarian tumour or a personal history of ovarian cancer was excluded from this investigation. Criteria for abnormality included an ovarian volume in excess of 20 cm^3 for premenopausal women and an excess of 10 cm^3 for postmenopausal women. In addition, any cystic ovarian tumour with a solid or papillary projection into its lumen was considered abnormal. Women with an abnormal screen underwent a repeat scan in four to six weeks. Patients with a persistently abnormal second scan had a serum CA-125 determination, tumour morphology indexing and Doppler sonography. Morphology indexing was performed according to the classification of DePriest *et al.* [28]. The investigators performed 57,214 scans to identify 11 epithelial invasive ovarian carcinomas, three borderline ovarian tumours and three granulosa cell tumours. A total of 11 Stage I tumours were identified: five invasive ovarian carcinomas, three borderline ovarian tumours and three granulosa cell tumours. Also, the authors found that a negative ultrasound examination was imperfect, as four women developed Stage II or III ovarian cancer within 12 months of a normal scan. Two of these patients had Stage II disease and two patients had Stage III disease. The authors appropriately note that a major limitation of transvaginal architectural screening is that ovarian cancer arising from ovaries of normal size and structural appearance can be undetectable. In addition, the investigators found an additional four women who presented with Stage III disease more than 12 months after a negative scan. If these latter patients were excluded, the sensitivity for detection of all stages of ovarian cancer was 81% (17/21). The positive predictive value for transvaginal ultrasonography was 9.4%. In this study persistent ovarian cysts or masses had a low likelihood of malignancy (9.4%) [17].

Adonakis *et al.* investigated the effectiveness of the combination of pelvic examination and serum CA-125 determination, as a screening method for the early detection of ovarian cancer in 2,000 women over 45 years old, without any evidence of adnexal disease. When either the findings of the pelvic examination were ambiguous or positive, or the serum CA-125 levels were > 35 IU/ml, further investigation including ultrasonography and surgical intervention was done. Among 174 women with clinical findings of adnexal disease there were 15 (8.62%) who had serum CA-125 levels > 35 IU/ml. Among 18 women with elevated serum CA-125 levels (> 35 IU/ml) there were 15 women (83%) who had clinical findings of adnexal disease. In 15 women further investigation was suggestive of adnexal disease and surgical exploration revealed three cases of malignancy: one case of serous invasive ovarian cystadenocarcinoma Stage Ia, one case of borderline ovarian tumour and one case of metastatic carcinoma from the right kidney. The other 12 women had benign adnexal masses or pelvic endometriosis. This combined approach had a sensitivity of 100%, specificity of 99.7% and PPV of 22% [51].

Bourne and Campell's group screened 1,601 women (age 17-79) with a family history of ovarian cancer by transvaginal sonography and colour Doppler imaging. Transvaginal sonography served as a primary screen, with colour Doppler imaging and morphology index reserved as secondary tests in those women with persistently abnormal transvaginal findings. Sixty-one patients (3.5%) were ultimately believed to have a positive screen and were referred for surgical exploration. Six ovarian cancers (five Stage I, three of which were borderline histology, and one Stage III) and 48 benign ovarian masses were found. In seven women no abnormality could be identified at surgery. The screening procedure had an apparent detection rate of 100%, a specificity of 96.5% and a positive predictive value of 9.8%. When the investigators coupled their secondary test results with their transvaginal findings, the specificity rose to 99.1 and the positive predictive value to 29% [29]. Therefore, ovarian screening programs should probably be limited to those women clearly identified to be at significant increased risk compared to the general population [5].

6. Management of an ultrasonographically detected ovarian mass

Once the presence of an ovarian mass is established, the crucial decision regarding management is whether to observe the patient or proceed with surgical removal [49]. During the reproductive years, the majority of ovarian simple cysts with diameter less than 10 cm in asymptomatic patients should be followed expectantly, as 70% of these cysts will resolve [49]. Cysts of more than 12 cm diameter are unlikely to benefit from a repeat scan because they constitute only 0.5% of all functional tumours, but 30% of all premenopausal malignancies [10, 52]. A follow-up scan after a period of four to six weeks enables the detection of spontaneous regression in functional cysts and reduces the likelihood of unnecessary surgical intervention [10]. High-dose contraceptive pills do not appear to cause significant remission rates of functional cysts, but remain a common practice [10, 49]. Persistence of the mass or change in ultrasonographic characteristics to a more complex mass or evidence of possible malignancy, such as ascites are indications for surgery [49].

During the postmenopausal period, especially within the first five years, a significant number of functional cysts is observed due to acyclic residual ovarian activity during this period. Consequently, these women should have a repeat scan after four to six weeks. In general, operative histological clarification of even a simple ovarian cyst after menopause is recommended. Also, when complex cystic tumours are detected in postmenopausal women, in spite of the risks associated with surgery, operative therapy should be carried out [10].

Several investigators have aspirated ovarian cysts in an attempt to avoid operative intervention [25]. However, cysts recur in 44% to 63% [53-56]. Cytology from cyst fluid aspirates is clinically unreliable, having a specificity of 100% in one large study but sensitivity and NPV of only 26% and 76%, respectively [57]. Irrigation of the cyst cavity does not improve these disappointing figures [58]. Cysts yielding blood fluid present diagnostic problems, as one series reported a case of cystadenocarcinoma that was misinterpreted cytologically as a propable endometrioma [59].

The appropriateness of employing minimally invasive methods such as laparoscopy in pre- and postmenopausal women with ovarian masses is in dispute [10]. However, many surgeons are now using a laparoscopic approach in the management of adnexal masses. The benefits of the laparoscopic approach include reduced hospital stay, less pain, and shorter recovery. In patients younger than 40 years cystectomy should be attempted, while in women older than 40 years, oophorectomy is probably a safer choice because of the increased incidence of malignancy [49]. Visible gross features of malignancy include size, surface excrescences, dense adhesions, ascites and peritoneal lesions in other areas of the abdomen. When malignancy is suspected, full-staging laparotomy should be done. The probability of finding a malignancy in an ovarian mass is extremely low (about 1%) and two thirds of those encountered can be determined to be malignant by their gross characteristics seen at laparoscopy [25]. If all preoperative and intraoperative criteria for benign disease are met, the ovarian cyst can be drained and opened for inspection and frozen-section biopsy is needed [25]. In order to reduce the risk of tumour spill, appropriate plastic sacs during laparocopic cystectomy or oophorectomy can be used [60].

Apart from the use of pelvic ultrasonography for the early detection of ovarian cancer, cul-de-sac aspiration for peritoneal cytology assessment has been employed. However, the aspiration failed to show a significant impact on early detection of ovarian cancer because of the lack of success in performing it and the low sensitivity. The presence of oncogene mutations in malignant peritoneal fluids of human ovarian ade-

nocarcinomas may have value in the early diagnosis of ovarian carcinomas. Varras *et al.* showed for the first time the pattern of point mutations at codon 12 of K-*ras*, H-*ras* and N-*ras* genes, using polymerase chain reaction and restriction fragment length polymorphism analyses in 47 malignant cytologic specimens of ovarian adenocarcinoma peritoneal fluids; 47% of the samples were found to carry a point mutation at codon 12 of the K-*ras* gene. However, point mutations at codon 12 were found in 14% of cystadenoma peritoneal fluids. Therefore, further studies are required to determine the genetic alterations taking place in human ovarian adenocarcinoma peritoneal fluids which may increase the sensitivity of cul-de-sac aspiration for the early detection of ovarian cancer [61].

In conclusion, accurate selection of patients with uterine adnexal tumours for surgical intervention is not provided by transvaginal ultrasonographic scans. In women who are at a significantly increased risk of developing ovarian cancer, pelvic ultrasonography should be used as a screening method but not in the general population.

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