REVIEW

Peri- and post-menopausal incidental adnexal masses and the risk of sporadic ovarian malignancy: new insights and clinical management

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Abstract

Adnexal masses are common among peri- and post-menopausal women. Although ovarian cancer is a significant cause of mortality in menopausal women, large population-based studies demonstrate that the majority of adnexal masses are benign. Despite this, the appearance of an adnexal mass is a concern for the patient and an insight exercise for physicians. In most cases, an adnexal enlargement is an incidental finding, generally corresponding to a benign cyst and easily diagnosed by conventional ultrasound. Exceptionally an ovarian tumour may be malignant and should be treated as early as possible. When conventional ultrasound renders complex morphology other diagnostic tools must be used such as: colour Doppler and functional tumour vessel properties, serum CA 125 levels, nuclear magnetic resonance imaging and in some cases laparoscopy. Several new tumour markers are being studied for clinical application, although there are presently no clear recommendations. Adnexal masses with benign morphological and functional properties must be periodically monitored as an alternative to surgery since malignant transformation is exceptional.

Keywords: Menopause, adnexal mass, ovarian cancer, ultrasound scan, Doppler, CA 125, incidental ovarian cyst

Introduction

Ovarian cancer is the most lethal disease of the female reproductive tract. Risk for ovarian malignancy increases with age, and decreases with pregnancy. Lifetime risk is about 1.6%, while women with affected first-degree relatives have a 5% risk, those with a mutated BRCA1 or BRCA2 gene or hereditary non-polyposis colorectal cancer (Lynch syndrome) have a 25–60% risk depending on the specific mutation [1–3]. Contrary to this, most ovarian cysts are never noticed and resolve without women ever knowing so. Prevalence of ovarian and paraovarian cysts is high in both peri- and post-menopausal women, and while most cases are benign [4–6], other incidental adnexal masses are infrequent [7,8]. Hormonal changes taking place around the menopause may predispose the development of these benign ovarian cysts [9,10].

Proposal for ovarian cancer screening have failed or have not been cost-effective; therefore, aside from clinical trials, screening is not currently recommended in the general populations [11–13]. Routine ultrasound in pre- and post-menopausal women allows diagnosing many ovarian cysts that are devoid of any significant clinical symptom. An incidental ovarian finding produces concern in many women and should be differentiated from ovarian cancer. When a cyst causes symptoms, pain is by far the most common one. This pain may be due to cyst rupture, rapid growth and stretching, intracyst bleeding and/or torsion around its blood supply. The most common type of ovarian cyst is the follicular caused by a follicle growth. Other types include the haemorrhagic or endometrioid. Dermoid cysts are infrequent around the menopause [14]. Ovarian cancer is a silent killer, especially affecting women above 50 years; although presentation is often vague and non-specific, symptoms are definitely present. Therefore, a proper clinical examination and appropriate tests should be carried out upon onset in peri- and post-menopausal
women. This study will update and assess the available evidence concerning the management of incidental adnexal masses around the menopause in otherwise healthy women. Since women with hereditary ovarian cancer risk may also have breast and colon cancer risks and receive special clinical recommendations [15–17], hereditary cancer will not be addressed.

Structure of the human menopausal ovary: focussing on epithelial neoplastic capability

Ovarian plasticity has been postulated to facilitate neoplastic transformation, tumour heterogeneity and the complex pattern of its clinical course [18]. The most common ovarian cancer is the epithelial with three sub-types: mucinous, serous and endometrioid. Germ cell and sex-cord stromal tumours are less frequent types. Epithelial types of cancers derive from the ovarian surface epithelium and its inclusion cysts. Borderline ovarian tumours also arise from the ovarian epithelium and show histological features that are intermediate between benign and malignant tumours. The surface epithelium is embryologically formed from the invagination of the coelomic mesothelium over the gonadal ridges [19], which can migrate into the ovarian stroma to create inclusion cysts. However, cysts can also develop from periovarian and peritubal adhesions [20]. The exposure of an inclusion cyst to the ovarian environment may cause phenotypic changes to the epithelium commonly found in these cysts [21,22]. Metaplastic epithelium may also initiate neoplastic changes which may be, under certain circumstances, the pathway for developing an epithelial carcinoma [23–25]. Characteristics of the epithelium surface of early and advanced ovarian cancer have been classified according to gene expression in attempt to find the causes for cancer progression [26–31]. Despite this, no reasonable explanation for the carcinogenesis process has been elucidated. Serous borderline tumours are a separate category and in most cases probably do not progress to authentic carcinomas [32].

Assessment of the risk of developing ovarian carcinoma has been performed by comparing the histological ovarian features of women with high and low risk. Ovaries removed from women with increased risk of developing ovarian cancer contained atypical features such as: surface epithelial pseudostratification, surface papillomatosis, deep epithelium cortical surface invagination, multiple papillary projections with small cysts, epithelial inclusion cysts, cortical stromal hyperplasia and hyperthecosis, increased follicular activity, corpus luteum hyperplasia or hilar cell hyperplasia [33–35]. An early disruption of the ovarian hormonal balance may exist in women with pre-disposition to ovarian cancer that favours the expression of certain genes and tumour growth [36–38]. However, there are no clear ovarian carcinoma precursors [20,32]. Risk factors for sporadic ovarian cancer include age and a family history of the disease, while increasing parity, oral contraceptive (OC) use, oophorectomy, and breast-feeding have protective effects. Modifiable risk factors for epithelial ovarian cancer include lifestyle ones such as, high body mass index, central obesity, cigarette smoking, alcohol consumption, recreational activities and post-menopausal hormone treatment (HT) [39–49].

In young women, the ovarian surface epithelium is a single layer of mesothelial cells that covers the surface of the ovary, which is cyclically submitted to conspicuous changes due to the ovulatory rupture and repair process. This continuous process produces biochemical changes to date unknown that may favour carcinogenic transformation. There is a large number of biochemical candidates that may initiate genetic alterations and progression, including steroids, cytokines, progestagens, caspases, apoptotic regulators and growth factors [50–52]. The reduction of the number of ovulations due to multiparity or OC use have protective effects against epithelial ovarian cancer risk through the annihilations of repetitive rupture-reparation process in the cell surface ovarian epithelium. Experimental (in-vitro animal studies), epidemiological and clinical evidence have shown that normal ovaries and many ovarian tumours are influenced by endocrine factors that are hormone dependent or may be submitted to HT. However, the relationships between ovarian hormone function and carcinogenesis are still not clear. The presence of oestrogen (ER) and androgen receptors have been documented in a great number of primary ovarian cancers (63% and 69%, respectively), while progesterone receptors are reported in half of tumours and glucocorticoid receptors in up to 88% of ovarian cancers [53–56].

Oestrogen acts on the ovary by the two ER, α and β which are present in the ovary, although ER-β mRNA is the most abundant. Specific roles for each ER at the ovarian level have yet to be established. However, a reduction of ER-β has been suggested to be associated to severity and prognosis of ovarian cancer. The importance of ER signals in the ovarian function has been postulated in the oestrogen depleted aromatase knockout mouse. Although it remains to be determined what genes are regulated by ER-β in the human ovary [57]. Gene expression profile (24 genes) differs in ovarian cancer cell lines with different ER-α and ER-β populations, by adding oestradiol or genistein. It seems that in-vitro oestrogens play a role in ovarian carcinogenesis in association with unidentified cofactors [58]. Molecular factors involved in epithelial ovarian cancer have been studied by microarray techniques to
identify gene expression profiles that participate in cell signalling, proteinase secretion, cell adhesion and proliferation, extracellular matrix formation and apoptosis [59,60]. Clinicopathological correlates have tried to determine malignant disease development, growth, infiltration and progression. However, the mechanisms underlying gene alterations and the specific role of involved proteins remain to be elucidated.

HT use has been related to ovarian cancer risk in post-menopausal women [61–63]. A meta-analysis of 8 cohort and 19 observational studies examined the relation between menopausal HT and ovarian cancer, estimating the risks for less than 5 years, 6–10 and more than 10 years use as 1.02, 1.13 and 1.21, respectively [64]. A more recent systematic review examined a total of 14 publications, including case–control, cohort and randomised studies concerning the use of oestrogen-alone (ET) or oestrogen associated to progestin treatment (EPT) and the risk of ovarian cancer. The use of ET and EPT for 5 years significantly increased this risk (RR: 1.22 and 1.10, respectively) [63]. It seems that progestin addition may slightly reduce cancer risk related to ET. The Danish National Cancer Registry provides interesting information regarding HT and ovarian cancer incidence in a total of 909,946 of women. During a follow up of 8 years, there were 3068 incident ovarian cancers, of which 2681 were epithelial ones. Among current HT users ovarian cancer incidences were 1.38 and 1.44 for epithelial ovarian cancers. Increased ovarian cancer risk was independent of treatment duration, formulations, progestin used and route of administration. It seems that cancer risk disappears more than 2–4 years after HT discontinuation. Incidence rates in current and never HT users were respectively 0.52 and 0.40 per 1000 years [62].

New aspects regarding carcinogenesis are emerging, including the importance of tumour origin and distribution. Thus, it has been postulated that some serous tumours may originate in the fimbria or peritoneum where p53 tumour suppressor gene mutations have been found [65].

**Clinical symptoms of the asymptomatic killer**

It is assumed that early ovarian cancer diagnosis results in better survival and also assumed that stages I and II progress to stage III and IV. However, neither of the two assumptions has been clearly demonstrated. Early stages of ovarian cancers have an insidious onset and cause no or non-specific symptoms. Most women with ovarian cancer have one or several symptoms, including abdominal pain or discomfort, bloating, back pain, urinary urgency, pelvic pain, abnormal genital bleeding and abdominal mass or unjustified weight loss [66–69]. Because of the lack of early symptoms or non-specific nature of these, about two-thirds of patients with ovarian cancer present in FIGO stages III and IV, having tumour dissemination in the abdominal cavity, with or without varying degrees of pleural effusion.

Pavlik et al. [70] have reported the value of clinical symptoms as compared to ultrasound for the early detection of ovarian cancer malignancy. Hence, in a selected group of women, clinical symptoms were correlated with ultrasound vaginal findings, being respectively sensitivity 73% versus 20%. Clinical symptoms have higher specificity (91%) in benign tumours than in malignant ones (74%). In this regard, studied tumours that are negative by both symptom and ultrasound assessment are likely to be benign, and by adding to symptoms information ultrasound malignancy assessment increases sensitivity only 3.3%.

**Ultrasound features of incidental adnexal masses**

The diagnosis of an adnexal mass is usually established by ultrasound. Prevalence of adnexal masses is influenced by the number of scanned women, the inclusion criteria used in each study, and may increase with some endocrine treatments [71,72]. Simple cysts are more common than previously thought (2.5–14%) and are frequently diagnosed incidentally [4,8,73–75]. In many cases, bidimensional (2D) ultrasound examination is sufficient to give a clear diagnosis of benign or malignant ovarian lesions. However, in clinical practice there are many overlapping situations. Thus, some malignancies are detected as simple cyst without a complex morphological image, and contrarily some very complex images may correspond to benign pathological findings.

Three-dimensional (3D) sonography is currently a major development in ultrasound imaging with a significantly higher sensitivity, specificity and accuracy as compared to 2D ultrasound [76]. 3D ultrasound characterises an entire soft tissue volume by storing multiple 2D images. Computer software then rapidly creates a tridimensional image. Despite the fact that 3D ultrasound is gaining clinical acceptance it seems, however, that in routine practice it will not replace conventional 2D ultrasound. Indeed those who support 3D ultrasound vascular assessment for the differential diagnosis of an adnexal mass consider this procedure still under research [74,76]. To improve results, colour Doppler assessment of intratumoural blood flow has been proposed. It is based upon assigning red colour to flow directing toward the transducer and blue colour for flow directing away. Colour Doppler flow imaging is very useful in the detection of uterine adnexal malignancies because of the frequent neovascularisation found...
in these cases [7–9,77,78]. However, considerable overlapping exists between benign and malignant adnexal masses in terms of resistance (RI) and pulsatility (PI) indices. Therefore, colour Doppler RI measurements cannot be used alone for the detection of malignant ovarian tumours. Furthermore, results from ultrasound explorations are highly dependent on individual operator dedication and technical expertise [79]. The use of power Doppler 3D implies new haemodynamic indices, such as the flow index, vascularisation index and the flow vascularisation index, which replace the traditional RI and PI. This allows performing flow volumetric calculations. Vascular tridimensionality may be assessed and the mean vascular density calculated for any tumoral area calculated. In this sense, the most recent technology constitutes the virtual organ computer-aided analysis that allows to automatically obtaining angiographic volumes of spherical or regular structures, as well as of irregular ones.

**Ultrasonographic morphological features of incidental adnexal masses**

The morphological characteristics found at ultrasound may suggest the type of lesion. Complex intracystic ovarian masses, including solid and parietal irregularities, are associated with ovarian carcinoma, suggesting these findings as significant markers of malignancy [4]. Sonographic characteristics of an incidental early ovarian cancer include multilocular or multiple cysts, irregular thick septa or walls, poor-defined borders, papillary growths, solid elements and echogenic components [77,80,81]. Transvaginal sonography has relatively low positive predictive value for ovarian cancer, in some studies with a 10% value in post-menopausal women [81,82]. The presence of a purely solid tumour is highly suspicious of metastatic cancer rather than a primary ovarian cancer [78]. The presence of ascites is suggestive of malignancy but may be related to other causes. Careful examination of the abdominal cavity should be performed to detect the extent of the disease.

Paraovarian (peritoneal inclusion close to the ovary) and paratubal cysts constitute up to 10% of all adnexal masses [83], being more frequent in young women than in menopausal ones. Upon ultrasound examination they may be separately identified from ovaries (76%) as thin walled, anechoic and unilocular cysts. Most usually in these cases ovaries are normal [84]. However, sometimes they display solid nodular areas within the cyst, septations, thick or irregular walls [85,86].

Sonographical features of incidentally detected small ovarian dermoids are better detected by means of transvaginal ultrasound. They generally appear as a solid homogeneous or heterogeneous hyperechoic image, sometimes with a full fluid area and a hyperechoic focus in its wall, an inconstant mixed pattern with solid and liquid areas or calcifications and a frequent posterior or lateral acoustic shadowing [87]. Ultrasonographic morphology has a high accuracy and specificity in differentiating dermoid cysts from other adnexal masses [88].

Ovarian cystadenofibromas are infrequent epithelial tumours that include fibrous stroma as the dominant element and usually appear during the fourth and fifth decade of life. Although in many cases they are simple cysts, sometimes they may have solid and liquid components, therefore simulating upon ultrasound assessment as malignant neoplasms [89]. Ovarian Brenner tumours may also be often incidentally found in women in their 60s, being in 2–5% of cases malignant [90]. During ultrasound assessment, these tumours are in two-thirds of cases solid, multilocular and partially cystic epithelial nests; sometimes affecting both ovaries, and associated to other benign ovarian neoplasms [91].

Borderline ovarian tumours show similar ultrasonographic morphological findings as malignant lesions (89%), including intracystic papillae, diffuse internal echogenicity, intracystic septa, heterogeneous images and a solid pattern [92]. However, neither papillae nor other sonographic features are sensitive ultrasound markers for borderline tumours [93].

**Vascular Doppler assessment of ovarian tumours**

Tumour angiogenesis is an essential part of tumour growth and development. Angiogenesis in early small tumours may be studied with Doppler ultrasound by measuring resistive indices that show the downstream impedance to blood flow within a vessel. Doppler ultrasound findings include: a dominant cyst mass, solid papillary projections and vascularisation. The latter is present in almost half of cases appearing with a typical peripheral pattern and vessels of high blood impedance [72,77–79]. In some cases, malignant tumours display low potential for inducing an angiogenic response or vessels are so small and fail in being detected by color and pulsed Doppler. Specificity for cancer diagnosis may reach 97% and the positive predictive value 91% [94,95]. Nevertheless, overlaps in terms of findings between malignant and benign cases have been long recognised. Medeiros et al. [96] carried out a systematic review to estimate the accuracy of colour Doppler sonography in the diagnosis of ovarian tumours. Diagnosis was confirmed by paraffin-embedded pathology study. The pooled sensitivity was 0.87 (95% CI: 0.84–0.90) and the specificity was 0.92 (95% CI: 0.87–0.90). Receiver operating characteristic curves demonstrated that colour Doppler is a valid tool prior to surgery in predicting the diagnosis
of ovarian tumours. Colour Doppler imaging for borderline ovarian tumours have lower PI and RI compared to benign lesions [92].

3D ultrasound in combination with power Doppler provides better morphologic visualisation of complex ovarian masses (the tumour per se or its vascularisation), significantly improving preoperative diagnostic accuracy of suspected ovarian lesions. A significant problem with power Doppler is that information regarding speed and flow direction is lacking, and the technique is highly dependent on operator expertise. To define an ovarian malignancy the presence of at least two of the following findings have been proposed: irregular branching, vessel diameter changes, microaneurysms and vascular lakes [79].

Paraovarian, paratubal or peritoneal pseudocysts may be diagnosed by 2D and 3D ultrasound. In one retrospective study, pathological paraovarian cyst findings were assessed preoperatively with 2D sonography and power Doppler evaluation. In 30% of cases there were papillary projections within the cyst, and in a quarter of these cases the papillae had blood vessels. Malignancy risk is low in cases without papillary growths; however, when wall proliferations are found this may correspond to borderline ovarian tumours [86].

Assessing the Doppler flow characteristics of dermoid cysts has been intended to differentiate benign ovarian cystic teratoma from malignant cases. Thus, intratumoural blood flow is more frequent in malignant teratomas compared to benign ones. Malignant teratomas usually have RI less than 0.4 and PI less than 0.6, while peak systolic velocity values are similar in benign and malignant teratomas [97]. Ovarian struma ovarii represent 5% of cases of ovarian dermoid cysts, and most women are premenopausal with a mean lesion diameter of 5 cm and normal CA 125 values. Although blood flow signals may be present and low resistance to flow may be more common in struma ovarii, it is difficult to distinguish between struma ovarii and dermoid cysts on the basis of their sonographic appearance [98].

Figure 1 presents the general morphological characteristics of incidental adnexal masses found at ultrasound. Finally, a need to emphasise that there are ovarian cancers that – very early in its development – produce peritoneal dissemination without significant ovarian growth, and therefore, a normal ovarian ultrasound exploration is not synonymous of absence of malignant disease. Van Nagell et al. [99] have clearly established this possibility in their long term ultrasound follow up of the Kentucky cohort.

Tumour markers

Elevation alone of serum tumour markers are not diagnostic, only suggestive of malignancy or related lesions, and some markers are so non-specific that their increase may be associated to benign conditions. Ovarian tumour markers should ideally be specific for each one, indicating what type of cancer is present, or predicting treatment outcome. However, markers may be non-specifically produced in high levels by different cells – ovarian or extraovarian – which suffer various alterations in their biochemical machinery. Unfortunately, a unique and ideal tumour marker is currently not available. Genomic advances may improve ovarian cancer detection in the near future when used with diagnostic imaging.

***CA 125, tumour-associated trypsin inhibitor, α foetoprotein and chorionic gonadotrophin***

Initial optimism for markers such as CA 125, CA 19.9, CA 72-4, CASA, CYFRA and others to be

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**Figure 1.** General morphologic characteristics of incidental adnexal masses in peri- and post-menopausal women according to ultrasound findings.
used in combination with ultrasound, has been confronted because of their non-specific nature in detecting ovarian malignant lesions and borderline tumours [100–103]. Serum CA 125 is the only validated marker for ovarian cancer, and it is useful for follow up purposes and evaluating treatment response or disease recurrence. However, it is not a diagnostic or prognostic marker [104]. The utility of serum CA125 in the identification of early stages of epithelial ovarian cancer is shadowed by the fact that not all cancers display elevated levels [105], and since isolated CA125 values lack adequate sensitivity or specificity [106]. CA 125 screening for the general population is impaired by the low cancer incidence and the high rates of false positive [107]. Several benign gynaecological conditions, such as first trimester pregnancy, pelvic inflammatory disease, uterine fibroids, ovarian cysts, pelvic adhesions and endometriosis may be associated to elevated CA 125 levels [108,109]. These conditions are exceptional in post-menopausal women. Therefore, CA 125 may regain some application in this population for the detection of ovarian malignancies. In addition, serial CA 125 determinations at 3–4 week intervals may detect increases associated to malignant growth. Contrarily benign adnexal masses should not associate to abrupt marker increases but rather stable or diminishing values.

The natural history of ovarian cancer development in relation to changes in serum CA 125 level has been studied in the Shizuoka Cohort Study on Ovarian Cancer Screening. In this study, CA 125 measurement was performed to 396 women with ovarian tumours, TATI has an 89% specificity and 47% (107/228) of patients with non-serous-type ovarian cancers develop secondarily from slightly intervals: 47% (107/228) of patients with non-serous-type ovarian cancers develop secondarily from slightly elevated CA125 level (35 < CA125 < 65 U/ml), with a mean interval of 3.8 years. On the other hand, 75% (126/168) of patients with serous-type ovarian cancer seem to develop suddenly from a normal CA125 level (CA125 < 35 U/ml), with a mean interval of 1.4 years (p = 0.011) [110]. In a small number of cases, ultrasonographic abnormalities associated to normal CA 125 values result in cancer found at surgery [111]. Therefore, depending on the tumour type CA 125 elevation may present a different behaviour and elevation velocity, or even with low values a cancer may be present. These possibilities should be carefully considered when evaluating incidental ovarian masses.

Tumour-associated trypsin inhibitor (TATI) has been considered as a potential polypeptide tumour marker for mucinous ovarian carcinomas, colorectal cancer and other tumours [112,113]. In mucinous ovarian tumours, TATI has an 89% specificity and an 86% positive predictive value for malignancy. However, less than half of ovarian cancers – even at advanced stages – express tissue trypsinogen-1 and 2 and TATI, although TATI tissue expression is an adverse prognostic factor, independent of cancer clinical stage and histological tumour type [114]. In patients with epithelial ovarian carcinoma, using a cut-off of 21 ng/ml TATI had a 63% sensitivity and 72% specificity, as compared – respectively – to 80% and 82% for CA 125 at a cut-off value of 35 U/ml. When measurement of both markers were combined (TATI > 21 ng/ml or CA 125 > 35 U/ml) specificity was 65% [115]. It seems that despite its limitations, CA 125 is the single marker of choice for suspicious epithelial ovarian malignancy. TATI measurement may be helpful as an additional marker in combination with CA 125 when mucinous carcinomas are suspected.

Human α foetoprotein (AFP) and chorionic gonadotrophin are the main tumour markers for germ cell tumours, including ovarian and extragonadal germ cell tumours as well as malignant teratomas of any location. In females, germ cell tumours represent a third of ovarian tumours, but only 1–3% are malignant tumours [116]. These tumours are infrequent in menopausal women. In recent years several messenger RNA AFP isoforms have been described, opening new insights for the development of specific diagnostic possibilities for the cited ovarian tumours [117].

New tumour markers

In recent years concerns have been reported regarding the validation of new biomarkers and risks. Inhibit may complement CA 125 in the assessment of malignant ovarian cancers; although there is limited information since studies have been confined to advanced cases [118,119]. Inhibit is elevated in post-menopausal women with granulose cell tumour and in mucinous epithelial cancers, and less frequently in epithelial serous and endometrioid ovarian carcinoma subtypes [118,120,121]. In peri-menopausal women, inhibit measurements are of less value for ovarian cancer detection because it may be elevated in relation to the menstrual cycle. Serum anti-mullerian hormone levels have been studied for the diagnosis and follow-up of granulose cell tumours [119]. This serum hormone is a more specific parameter than inhibit for granulose cell cancers, since inhibit may also increase in some mucinous epithelial ovarian tumours [122].

Human epididymis protein 4 (HE4) is a protease overexpressed by patients with epithelial ovarian cancers and found elevated in circulating blood [123]. Serum HE4 measurements allow to differentiate epithelial ovarian cancers from benign
prospective clinical studies are needed. However, as authors concluded [I–II], being the highest sensitivity for the endometrium are useful for the detection of early-stage cancer [125, apolipoprotein A-1, transthyretin and transferase [146] have reported that a serum panel including Ca 125 nor HE4, and perhaps combining both markers could be complementary by improving sensitivity for detecting epithelial cancers [130,131].

Mesothelin is a glycoprotein expressed by normal mesothelial cells, and overexpressed in different types of tumors including ovarian carcinomas. It is also a potential target for cancer immunotherapy [132]. Women with diagnosed ovarian cancer show a correlation between high mesothelin levels and chemoresistance and poor survival [133]. It has been postulated that the interaction between mesothelin and CA 125 may be involved in the peritoneal dissemination, although the available information is limited [134]. There are at least three mesothelins, and by means of flow cytometry the most frequent molecule in ovarian cancer cells is mesothelin 1 [135].

Decoy receptor 3 (DcR3) or DD-C248 is a protein member of the tumour necrosis receptor family that prevents apoptosis via direct binding of Fas-ligand. Elevated DcR3 tumour tissue and/or serum levels have been reported in gastrointestinal and ovarian cancers. In advance ovarian cancers with ascites, DcR3 has been associated with negative outcomes [136,137]. B7-H4 or protein DD-O110 is expressed in activated T-cells and is involved in cell mediated immunity [138]. This protein has been demonstrated in ovarian and breast cancer cells using immunohistochemical techniques [139]. Patients with ovarian cancer show elevated serum levels as compared to those with benign gynecological disease or healthy women. The value of B7-H4 measurements seems to rely as a complement to CA 125 determination in the detection of early stage ovarian cancer [140]. Spondin 2 or protein DD-P108 has been demonstrated in prostate and ovarian cancers [136,141].

New diagnostic markers have not yet been validated for clinical use [142–144]. The utility of combining several biomarkers is currently under study. Recent results point out to the fact that a panel of different markers may inform about ovarian cancer existence before symptoms appear [145]. It seems that CA 125, HE4 and mesothelin began to slightly increase some 3 years before diagnosis; however, detectable elevations only were present within the final year before diagnosis. Nosov et al. [146] have reported that a serum panel including Ca 125, apolipoprotein A-1, transthyretin and transferrin are useful for the detection of early-stage cancer (I–II), being the highest sensitivity for the endometrioid subtype. However, as authors concluded prospective clinical studies are needed.

Optimism of these results should be carefully considered to prevent massive testing which later might demonstrate to be cost ineffective, stressful and useless, as occurred in the past. In fact, Anderson et al. [145] insist in the low discriminatory power of their used markers. Although these studies are scientifically encouraging, they are difficult to extrapolate to the early diagnosis and clinical management of ovarian cancer of any individual subject due to the low prevalence of the disease, tumour heterogeneity and the psychosomatic implications of implementing a screening programme with non-standardised tests.

Proteomic technology

Proteomic technology may allow studying new biomarkers for the early diagnosis of malignant and pre-malignant stages. These targets may theoretically be the first step in the development of new diagnostic and therapeutical tools. Tumour tissue, plasma and ascitis samples have been studied to delineate the signals involved in ovarian cancer [147–151]. However, attempts to link genetics, molecular characterisation of the system and clinical measures has not yet been successful [152–155]. There is a need for further developments in serum proteomic analysis to develop more specific screening methods for ovarian cancer and to differentiate from benign lesions.

Magnetic resonance imaging

Although sonography is the primary imaging approach for the diagnosis of adnexal masses, magnetic resonance imaging (MRI) provides additional information on the composition of soft-tissue masses [156–158]. Normal ovaries and dysfunctional cysts have been detailed by MRI at different ages [159]. MRI has a 90–98% overall accuracy for differentiating benign from malignant adnexal tumours. Simple and complex cysts may be clearly identified by MRI with a high degree of precision [160–163]. Benign solid lesions may include fat, haemorrhage or fibrous components. Thus, mature teratomas possessed high fat content and contained derivatives of all three germ layers, although with predominance of ectodermal components [164]. Ovarian fibromas and cystadenofibromas have a dense fibrous tissue [165,166]. Using MRI, paraovarian and paratubal cysts located near the ipsilateral round ligament and the uterus may be separately defined from the ovary [167]. Although preoperative MRI is not free of misinterpretations when correlating adnexal mass images with pathological findings, malignancy diagnosis is often not [168,169].
Clinical management of incidental adnexal masses

Clinical management of an adnexal mass is a controversial issue in gynaecology that depends on the symptoms, ultrasound findings, age and clinical course. Guidelines or algorithms are general clinical recommendations that should be individualised for each patient (Figure 2). Although in peri-menopausal women the prevalence of ovarian cancer is low, adnexal masses (endometriomas or chronic sequel of inflammatory processes) are generally benign. Ultrasound examination may show complex images sometimes with morphological features suggestive of malignancy. Doppler evaluation may be useful along with serum CA 125 determination to establish their nature. Malignancy risk is low in unilocular cysts of up to 10 cm displaying normal tumour marker levels and normal Doppler evaluation. Ovarian malignancies are rare in post-menopausal women yet more common than in younger ones. Simple ovarian cysts of less than 5–6 cm in diameter may stay stable or decrease in size. Although there are no unanimous accepted recommendations for follow up, the characteristics of such cysts may be checked after 4–6 weeks, and at 3, 6 and 12 months. The majority of small cysts will resolve but this may take many months. When size increases or changes from a simple to a complex aspect, complementary evaluation and/or surgery should be considered for both diagnosis and treatment. Unilocular ovarian cysts less than 5 cm – even up to 10 cm – in average diameter were associated with minimal, if not insignificant, risk of ovarian cancer in a follow up period of 5 years in asymptomatic women older than 50 years [4,8,73–76,170]. However, it is unknown if these lesions on the long run progress to an ovarian cancer.

In complex cysts, MRI and/or laparoscopy evaluation may be necessary to define their nature. Variegated masses upon ultrasound exploration or suspected diagnosis of cancer – associated or not to high CA 125 levels – are an indication for surgery and pathological analysis of the adnexal mass. In selected cases, laparoscopy may serve both as diagnostic and therapeutic tools. In some cases, especially when findings are inconclusive, additional assessment at frequent intervals is sometimes necessary. Women using hormone treatment have an increased risk of ovarian cancer [61–64]. These women are likely to be submitted for routine pelvic exams more often than non-hormone treatment users.

The majority of ovarian cancers demonstrate a very rapid growth which may be detectable during a 4- to 6-month period between initial detection and follow-up scanning [8]. Malignancy risk of an adnexal mass has been studied by models combining several of the complementary tests to increase diagnostic efficacy and precision. Thus, the combination of 3D Doppler vascular evaluation, CA 125 measurement and menopause status renders an 88% in the prediction of malignancy with a sensitivity of 99% [171]. However, in some circumstances 3D power Doppler adds little to the correct diagnosis of malignancy [76,172].

Adnexal masses suspicious of cancer may be safely managed by laparoscopy or open surgery, allowing immediate and adequate pathological diagnosis, surgical and systemic treatment, according to the disease stage and other factors. The use of prophylactic oophorectomy has increased in women at high risk for familial hereditary breast and ovarian cancer. Recent studies have shown that it does not only reduce the risk of ovarian cancer yet also appears to decrease breast cancer risk as well. Nevertheless, even after oophorectomy there is still a risk of developing peritoneal serous carcinomas [173,174].

Since the information produced by the different explorations – and at the same time their

![Diagram](image-url)

Figure 2. General clinical assessment of an adnexal mass for asymptomatic peri- and post-menopausal women. Dotted lines represent optional examinations used when there are doubts upon confirming an ovarian cancer.
limitations—patients should know the advantages and risk of a conservative management in complex cysts. Surgery and pathologic study will give assurance in those cases which are not clear or present overlapping benign and malignant features. As in many medical aspects clinical management of adnexal masses should be guided by evidence. Furthermore, clinical management should consider full diagnostic and therapeutic opportunities provided by available tools, not by biased selection of a technique or procedure.

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