CLINICAL IMPRESSION AND ULTRASOUND FEATURES IN THE PREOPERATIVE EVALUATION OF OVARIAN MASSES

by

DR CHEONG YEE TSING

Dissertation Submitted In
Partial Fulfilment Of The
Requirements For The Degree Of
Master Of Medicine
(Obstetrics and Gynaecology)

UNIVERSITI SAINS MALAYSIA
NOVEMBER 2001

TABLE OF CONTENTS

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Objektif Untuk menilai kebolehan ultrasound dan gambaran klinikal dalam membezakan ketulan ovari samada benign atau malignant.

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Keputusan 120 orang pesakit dimasukkan ke dalam kajian ini setelah mengeluarkan 6 pesakit yang tidak mempunyai patologi ovari. 97 pesakit (81%) telah mempunyai ketulan ovari benign manakala 23 pesakit (19%) mempunyai ketulan ovari malignant. Gambaran klinikal telah menunjukkan kadar sensitiviti dan spesifisiti yang tinggi, diikuti oleh skor ultrasound 2 hingga 5 dalam membezakan antara ketulan ovari benign atau malignant. Kedua-duanya mempunyai sensitiviti dan spesifisiti yang lebih dari 70% dan ianya lebih tinggi dari ultrasound.

Kesimpulan Ujian klinikal dan ultrasound adalah kaedah yang boleh dilakukan dalam menilai ketulan ovari sebelum pembedahan dilakukan. Ketepatan diagnostik boleh dipertingkatkan dengan adanya penanda tumour atau ultrasound yang lebih jitu. Tetapi ini adalah lebih sukar dan lebih mahal untuk dilakukan.

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An adnexal mass often involves ovarian substance because of the propensity of the ovary for neoplasia. Although the overwhelming majority of adnexal masses are benign, it is important to determine preoperatively whether a patient is at a high risk for ovarian malignancy so that the appropriate preparation and intervention can be planned.

Ninety percent of all ovarian tumours are benign, although this varies with age. Among surgically managed cases, the frequency of malignant tumours is 13% in premenopausal women and 45% in postmenopausal women. The lifetime risk of developing ovarian cancer is 1.4% which is higher than that for either cancer of the cervix (1.25%) or the endometrium (1.1%). Deaths from ovarian

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cancer outnumber those from carcinoma of the cervix and body of the uterus combined (Anderson *et al.* 1997).

The presumptive diagnosis of an ovarian mass will often determine the type of surgery and the preoperative preparation required, and may influence selection of the institution and the seniority and expertise of the surgeon (Davies *et al.* 1993). The prognosis for women with ovarian cancer may be greatly influenced by appropriate first line surgery (Oram & Jacobs 1987; Gillis *et al.* 1991). The initial laparotomy is not only important for the accurate determination of the extent of disease, but also the best opportunity for maximum debulking (Hacker 1987).

If the clinician could accurately differentiate a malignant from a benign mass, patients with masses believed to be malignant could seek proper oncologic consultation preoperatively. At the time of operation, the appropriate incision would allow careful staging. The preoperative diagnosis of ovarian cancer might reduce the need for repeat laparotomies and could lead to referral to or consultation with gynaecologic oncologists capable of proceeding with radical procedures. This surgery demands specific skills and experience. The amount of residual malignant tissue after primary surgery is among the best prognostic factors in ovarian cancer (Levin *et al.*

1993). Therefore, accurate preoperative prediction of the benign or malignant character of an ovarian tumour is essential for optimal preoperative and intraoperative surgical management, which may provide, in the case of malignancy, the best chance of a long disease free interval and cure (Schutter *et al.* 1994).

Minimal access surgery (MAS) has become an important part of the gynaecologist's repertoire, especially when used for removing a persistent or symptomatic benign ovarian cyst (Mettler *et al.* 1993; Parker & Berek 1993). However, if there is a suspicion of malignancy, most gynaecologists would perform a laparotomy via a midline incision. The incidence of finding a malignant cyst at MAS in women where preoperative investigations wrongly suggested that the mass was benign ranges from 0.04% to 3.7% (Peterson *et al.* 1990; Hulka *et al.* 1992; Nezhat *et al.* 1992; Canis *et al.* 1994). The role of MAS in early ovarian cancer has not been clearly defined. It may be detrimental to survival of the patient if the laparoscopic management results in inadequate staging, the piecemeal removal of a potentially curable early stage cancer, or suboptimal clearance of tumour in more advanced disease (Crawford *et al.* 1995).

In spite of the known benefits of thorough surgical staging and cytoreductive surgery, many women do not receive appropriate

treatment at the time of the initial surgical diagnosis (Young *et al.* 1983). This is partly because of the skilled and lengthy surgery that radical cytoreduction often requires and partly a consequence of the difficulty in making an accurate preoperative diagnosis of ovarian cancer. It is postulated that methods of improving the preoperative diagnosis of ovarian malignancy would lead to more women receiving first line surgery from appropriately trained and experienced personnel, either locally or after referral to a gynaecologist with a special interest in gynaecological oncology (Davies *et al.* 1993).

An accurate preoperative diagnosis of ovarian cancer and a method for better preoperative discrimination of patients with an ovarian mass are therefore of great value and much needed.

The standard evaluation for adnexal masses includes history, physical examination and ultrasound. In an international multicenter study conducted by Schutter *et al.* (1994), the individual accuracy of pelvic examination, ultrasound and serum CA 125 in discriminating between benign and malignant pelvic masses among postmenopausal patients was approximately the same (76, 74 and 77%, respectively). Buist *et al.* (1992) assessed the diagnostic potential of pelvic examination, the study showed that

the test accuracy of pelvic examination (70%) was even better than that for computed tomography and ultrasonography (both 65%) and magnetic resonance imaging (50%).

Ultrasound examination of the pelvis and abdomen has become the standard diagnostic test for evaluating adnexal masses and is by far the most commonly used imaging modality for evaluation of a patient suspected of having ovarian malignancy. Its principal value in this setting involves confirming the mass, differentiating ovarian from uterine or tubal origin, delineating the internal appearance of the mass, and defining any associated abdominal findings. It is being explored as a screening method for carcinoma of the ovary, in the attempt to detect early disease. The overall rate of false positive was 9.3% and the likelihood of a positive scan being a primary ovarian cancer was 1:67 (Campbell *et al.* 1989).

Whether ultrasound can differentiate between benign and malignant pelvic masses has been the subject of many studies. Scoring systems have been evolved to reduce the number of false positives. One of the scoring systems used (Davies *et al.* 1993) where ultrasound scans were performed and assessed for the following features suggestive of malignancy: multiloculated cysts; evidence of solid areas; bilateral lesions; presence of ascites and

evidence of metastases. An ultrasound score of 3 (when two or more of the above features were noted) achieved a sensitivity of 87%, specificity of 74% and positive predictive value of 58%.

The serum CA 125 test is a helpful expedient in the diagnosis and monitoring of epithelial ovarian carcinoma. Einhorn *et al.* (1986) have suggested that preoperative serum CA 125 levels may be of value in differentiating a benign from a malignant pelvic mass. However, CA 125 as a single parameter does not distinguish sufficiently benign from malignant masses preoperatively, because it can be elevated in menstruating women, during pregnancy, by liver cirrhosis, and in heart failure (Niloff *et al.* 1984). Raised serum CA 125 levels are also found in association with benign ovarian cysts, endometriosis and pelvic infection.

Finkler *et al.* (1988) assessed the diagnostic procedures: serum CA 125, clinical examination and ultrasound interpretation and they found that in conjunction with such tests, measurement of serum CA 125 significantly increased diagnostic accuracy and may thus have an important role in the preoperative evaluation of women with ovarian masses.

Due to the limited budget in our centre, tumour markers are not routinely done to all patients presented with an adnexal mass. However, evaluation of the patient using clinical judgement and ultrasound scan can be applied easily in our centre.

The purpose of this study is to evaluate the ability of ultrasound findings and clinical impression to discriminate a benign from a malignant mass in patients presented to the gynaecology department with an ovarian mass. Sensitivity, specificity, positive and negative predictive values were calculated for tests used in patients undergoing surgical exploration of ovarian masses.

Literature Review Of The Ability Of Other Methods To Discriminate A Benign From A Malignant Ovarian Mass

Trans-vaginal ultrasonography, Doppler ultrasound and Serum CA 125 have all been shown to be important diagnostic tools in the preoperative evaluation of ovarian masses. However, due to the limited budget and unavailability of the facility in our center, the use of these tests are not possible in all patients presented with an ovarian mass.

Trans-vaginal ultrasonography

Since the mid-1980s, with technical advances in instrumentation and imaging, trans-vaginal ultrasonography has gained in popularity. The advantages of this approach are two-fold:

1. The ultrasound transducer is closer to the objects of interest and not separated from them by layers of fat and muscle. The pelvic organs can therefore be studied with higher ultrasound frequencies, producing images of greater resolution and enhanced quality.
2. The need for a full bladder is obviated.

Although trans-vaginal ultrasonography has better resolution than abdominal ultrasonography and provides detailed images of the ovaries and masses confined to the true pelvis, there are some disadvantages to trans-vaginal ultrasonography. It is more invasive and postmenopausal vaginal atrophy may limit access and patient acceptability.

The ultrasound frequencies used improve resolution, but decrease penetration to 10cm. Thus ovaries situated high or lateral in the pelvis, or greatly enlarged so that they are no longer in the pelvis, may not be seen on scan. Co-incident abdominal palpation or bimanual pelvic examination (or a trans-abdominal scan) should ensure that such ovaries are detected (Timor-Tritsh *et al.* 1988).

With the advent of high-frequency trans-vaginal ultrasonography, new opportunities are presented to better define ovarian lesions. Scoring system using trans-vaginal sonographic characterization of pelvic/ovarian lesions has been developed to maximize the discrimination between benign and malignant entities. Test results have improved using trans-vaginal ultrasound examination compared with the transabdominal method (Sassone *et al.* 1991).

Doppler

Whilst ultrasound imaging has provided a non-invasive method of studying ovarian morphology, pulsed Doppler combined with real-time ultrasound (the duplex method) has the potential to examine patterns of blood flow and hence of identifying functional changes. The duplex technique will show a low pulsatility index (PI) in arteries with vascular impedance.

Colour combined with pulse Doppler has been used to investigate the pelvic circulation under various physiological and pathological conditions (Kurjak *et al.* 1989). Changes in vascularity (which may be an indication of malignancy) can be identified as fluctuating areas of colour. Applying pulsed Doppler to these areas gives a measurement of blood flow and impedance. Previous studies have shown that ovarian malignancy may be associated with characteristic patterns of flow in the newly formed vessels within the tumour (Bourne *et al.* 1989; Kurjak *et al.* 1989, 1991).

It has recently become possible to obtain colour Doppler signals using a trans-vaginal probe. This technique not only assesses morphological features of malignancy, but also functional changes that may be asscociated with malignancy such as the presence of neovascularisation. Two studies have shown that ovarian cancers

may be distinguished from benign adenomas using this technique (Kurjak *et al.* 1989; Bourne *et al.* 1989).

With the introduction of trans-vaginal colour Doppler ultrasound in gynaecology, it is now possible for us to evaluate the haemodynamics in benign and malignant tumours. Earlier reports suggested that pulsatility index (Bourne *et al.* 1989) or resistance index (Kurjak *et al.* 1990) might represent independent parameters allowing the differentiation of benign from malignant tumours. More recent evidence from the analysis of larger populations suggests that neither pulsatility index nor resistance index are sufficient parameters for the preoperative classification of tumours, if taken singularly. Kurjak *et al.* (1993) highlighted the importance of a multiparameter evaluation including the number and location of vessels.

Most malignancies are characterized by a central location of vessels. These malignant tumours tend to initiate tumour neovascularity in the centre of the lesion whereas peripherally located vessels probably originate from pre-existing host vessels. The detection of centrally located vessels is therefore highly predictive of malignancy. New scoring systems should therefore include parameters such as conventional morphology, the location

of vessels, their arrangement and haemodynamics (Kurjak *et al.* 1993).

The techniques of pulsed and colour Doppler play an increasingly important role in the differential diagnosis of a pelvic mass and will probably serve to improve the specificity of ultrasound for ovarian cancer (Davies & Oram 1991). Although the accuracy of differentiation between ovarian carcinoma and benign pelvic masses might be further improved by the technique of Doppler ultrasound with colour flow imaging (Bourne *et al.* 1989; Kawai *et al.* 1992; Weiner *et al.* 1992), this technique requires expensive technology and thus will not be immediately available to most of the centres.

Tumour markers

Quantitative and qualitative changes in numerous circulating substances have been associated with epithelial ovarian cancer. This may reflect an alteration in ovarian function or surface molecular structure , or a 'general' response to malignancy (Smith & Ol 1984b, Bast & Knapp 1987).

Changes in circulating enzymes (van Kley *et al.* 1981; Awais 1978; Gauduchon *et al.* 1983; Cramer *et al.* 1989), hormones (Heinonen *et al.* 1982; Backstrom *et al.* 1983), non-specific inflammatory proteins (Lukomska *et al.* 1981), placental and fetal antigens (Donaldson *et al.* 1980; Nouwen *et al.* 1985; Doellgast & Homesley 1984) have all been identified in women with ovarian cancer. Examples of the serum markers for ovarian cancer are as follows:

Enzymes

1. Galactosyl transferase
2. Alpha 1-fucosidase
3. Amylase
4. Lactic dehydrogenase
5. Cystine aminopeptidase

Feto-placental markers

1. Alpha-feto protein
2. Human chorionic gonadotrophin
3. Placental alkaline phosphatase
4. Carcinoembryonic antigen

Hormones

1. Progesterone
2. Oestrogen

Miscellaneous

1. Circulating immune complexes
2. d-dimer of fibrin

Using monoclonal antibody techniques, antigen with improved specificity and sensitivity for epithelial ovarian cancer has been defined – though the ultimate tumour-specific antigen remains elusive. The tumour marker shown to combine the highest sensitivity and specificity for the disease has been CA 125 which is also the most extensively studied ovarian tumour-associated antigen (Bast *et al.* 1983).

CA 125

CA 125, a high molecular-weight glycoprotein, is recognized by a murine monoclonal antibody, OC 125. Immunohistochemical studies have demonstrated CA 125 expression to be a feature of cells derived from the embryonal coelomic epithelium and Mullerian duct (Kabawat *et al.* 1983) and both benign and malignant pathologies affecting tissues with these embryological origins have been associated with increased CA 125 expression (Niloff *et al.* 1984).

Serum CA 125 levels measured by radioimmunoassay are greater than 35U/ml in over 80% of women with epithelial ovarian cancer (especially of the non-mucinous type) (Bast *et al.* 1983; Hawkins *et al.* 1989). Bast *et al.* (1983) have also shown that only 1% of healthy female blood donors have serum CA 125 levels of greater than 35U/ml. However, raised serum CA 125 levels are also found

in association with benign ovarian cysts, endometriosis and pelvic infection in addition to cancers of the endometrium, fallopian tube, breast and colon. Consequently, the accuracy of CA 125 measurement in differentiating benign from malignant pelvic pathology is limited (Niloff *et al.* 1984).

In view of the association of CA 125 with pathologies other than ovarian cancer and therefore a low specificity and low positive predictive value, methods of improving its specificity are being investigated.

CA 125, clinical examination and ultrasound

In the study by Finkler *et al.* (1988), the ability to differentiate a malignant from a benign ovarian mass was assessed for the following diagnostic procedures: serum CA 125, clinical examination and ultrasound interpretation. Results of diagnostic tests in combination were most informative. CA 125 added predictive value to each of the other diagnostic tests used in this study.

The study conducted by Tingulstad *et al.* (1996) showed superiority of CA 125 over ultrasound and menopausal status in their ability to discriminate a benign from a malignant pelvic mass. At cut-off level

of 70U/ml, CA 125 has a sensitivity of 70%, specificity of 95% and positive predictive value of 87% in predicting malignancy. Results from other studies also showed that serum CA 125 estimation improved the accuracy of diagnosing ovarian cancer preoperatively when combined with pelvic ultrasonography (Gadducci *et al.* 1988) or menopausal status (Vasilev *et al.* 1988).

CA 125 and other tumour markers

Combinations of CA 125 with other tumour markers for discriminating between benign and malignant diseases have also been used (Gadducci *et al.* 1991).

The use of a panel of monoclonal antibodies directed against a spectrum of tumour-associated antigens is being reviewed as a method of improving the specificity of serum CA 125 for ovarian cancer. These antigens may be different epitopes on the same complex or totally separate antigens.

At Duke University Medical Centre, United States, Bast *et al.* (1990) looked for CA 125, CA 15-3, TAG 72, PLAP, HMFG 1, HMFG 2 and NB/70K expression in serum from patients with known ovarian cancer and from women with a 'false positive' elevation of CA 125. His findings indicate CA 15-3 and TAG 72 to be the more

useful antigens for differentiating benign from malignant disease. Serum levels of all three antigens were elevated in 77% of women with ovarian cancer compared with only 5% of women with benign disease. The improved specificity for ovarian cancer using the combination of serum CA 125, CA 15-3 and TAG 72 has been confirmed by others. Einhorn *et al.* (1989) found 98% specificity for malignancy when serum levels of all three antigens were raised, compared with 83% for CA 125 used as a single test.

The increase in specificity using such a method may however occur at the expense of sensitivity. A fall in sensitivity for ovarian cancer to 53% has been documented using a combination of serum CA 125, CA 15-3 and TAG 72 (Jacobs *et al.* 1990).

A general conclusion of several studies (Soper *et al.* 1990) is that some additional information can be obtained from combinations of serum tumour markers but that other diagnostic modalities are needed for optimal and correct preoperative judgement of a pelvic mass.

There has been recent interest in developing scoring systems to improve the preoperative discrimination between benign and malignant ovarian masses (Davies *et al.* 1993). Most scoring

systems have included either tumour markers (Cruickshank *et al.* 1987; Vasilev *et al.* 1988; Einhorn *et al.* 1989; Bast *et al.* 1990) or ultrasonography (Deland *et al.* 1979; Hermann *et al.* 1987).

A study by Jacobs *et al.* (1990) of 143 women undergoing surgery for a pelvic mass assessed age, ultrasound score, menopausal status, a clinical impression score and the serum CA 125 level as discriminators between benign and malignant ovarian disease. The most useful individual criteria were the serum CA 125 level and the ultrasound score.

In order to improve the accuracy in discriminating benign from malignant ovarian disease, Jacobs *et al.* (1990) defined a risk of malignancy index (termed RMI). The RMI being the product of the serum CA 125 level (U/ml), the ultrasound score (U) and the score for menopausal status (M):

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

Postmenopausal status was defined as more than one year of amenorrhoea or age older than 50 years in women who had had a hysterectomy. Women who did not meet these criteria were classified as premenopausal. The ultrasound examination was performed via the abdominal route with the full bladder technique.

The presence of a multilocular cystic lesion, solid areas, bilateral lesions, ascites and intra-abdominal metastases, scored 1 point each. A total ultrasound score (U score) was calculated for each patient.

Based on the data obtained, the RMI was calculated for each patient. The calculation was based on a simplified regression equation where total ultrasound score of 0 gave U = 0, score 1 U = 1, and score ≥ 2 U = 3; premenopausal status gave M = 1, postmenopausal M = 3. The serum level of CA 125 was applied directly into the calculation.

A RMI of 200 achieved a high sensitivity of 85% and a specificity of 97% for diagnosing ovarian cancer. Davies *et al.* (1993) undertook a study to verify the accuracy of RMI in discriminating benign from malignant ovarian disease. Tested on a new population of women, the RMI retained the high sensitivity for diagnosing ovarian cancer seen in the original report describing its derivation. The study confirmed that the RMI is more accurate than the individual criteria in diagnosing ovarian cancer, and was comparable with other scoring systems.

The main advantage of the RMI, compared with other approaches such as blood flow characterization with Doppler ultrasound (Bourne *et al.* 1989; Kurjack *et al.* 1989; Fleischer *et al.* 1991; Kurjack *et al.* 1991; Weiner *et al.* 1992) or the use of a panel of different tumour markers (Einhorn *et al.* 1986; Vasilev *et al.* 1988; Zi-Xia *et al.* 1988; Gadducci *et al.* 1992; McGuckin *et al.* 1992; Jacobs *et al.* 1993), is that the RMI can be applied easily in less specialized departments of gynaecology.

MATERIALS AND METHODS

Participants of the study were women admitted consecutively to the Department of Gynaecology, Hospital Tengku Ampuan Afzan, Kuantan, Pahang for surgical exploration of an ovarian mass between 1st February 1999 and 31st January 2000. Among those women who presented with a pelvic mass at the Department of Gynaecology, Hospital Tengku Ampuan Afzan, Kuantan, Pahang between 1st February 1999 and 31st January 2000, 126 women were diagnosed to have ovarian mass. The method of detection was either by physical examination or by ultrasonography. They were subsequently admitted for surgical exploration of the ovarian mass and these 126 consecutive patients were enrolled in the study.

A standardized data sheet was used to record clinical and test data (see Appendix). Data collected on each patient included age, parity, ethnic group, family history of ovarian cancer, menopausal status, usage of oral contraceptive pills, clinical impression, ultrasound interpretation and final pathologic diagnosis.

Family history of ovarian cancer was defined as one or more first degree relatives with ovarian cancer. Postmenopausal status was defined as women with menopausal symptoms and more than one year of amenorrhoea or age older than fifty years in women who had had a hysterectomy. Women who did not meet these criteria were classified as premenopausal.

The clinical impression of the ovarian mass was judged based on history and physical examination, both general and pelvic. The clinical assessment and physical examination were performed by the participating consultant gynaecologist. The examination was considered to be abnormal when a palpable mass of any size was found to be clinically distinguishable as being separate from the uterus and gastrointestinal tract. The participating clinician was specifically asked to define the ovarian mass as either benign or malignant without knowledge of the ultrasound interpretation. Report of clinical impression of the ovarian mass as either benign or malignant was then recorded preoperatively in all cases.

All women admitted for surgical exploration of ovarian masses had an ultrasound scan done preoperatively within one week before surgical exploration. All ultrasound scans were performed by consultant gynaecologists or under their supervision using a