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Editorial

Professor Franco Guidozzi
President of SAMS, Editor

Despite the advances in imaging modalities, early diagnosis of ovarian cancer still eludes us. The vast majority of women with ovarian cancer will, unfortunately, have advanced stage disease at the time of their initial presentation. Unlike cervical cancer, ovarian cancer does not have a clearly defined pre-malignant phase and, therefore, the question begs “Can we screen for ovarian cancer?” Tracey Adams addresses this very issue and clearly emphasizes that screening for ovarian cancer is still not a reality. Despite the implementation of varying morphologic scoring modalities, including a panel of tumour markers, 4 large trials involving about 300,000 women support that screening for ovarian cancer is not plausible. Even though the studies have different designs and their methodologies cannot be directly compared, the Kentucky trial, The Japanese Trial, The Prostrate, Lung, Colorectal and Ovarian Cancer Screening Trial and the United Kingdom Collaborative Trial on Ovarian cancer Screening (UKCTOCS) clearly show that for every true ovarian cancer so-called detected by screening, between 10-35 women will require a laparotomy. Surprisingly, this was 3 laparotomies for every cancer in the UKCTOCS, but even within this study, the screening tools were not sensitive or specific enough support that screening for ovarian cancer is a reality. Is the menopausal an occupational health issue? In a thought provoking article, Theo Kopenhager looks at the impact of menopause on working women, a subject that has received scant attention in the medical literature. Not only can menopausal symptoms impact negatively on the quality of life of working women between 50-60 years of age, but the added burden of co-morbid diseases, emotional instability, need to care for other family members, death of a partner or the “empty nest syndrome” will invariably compromise coping mechanisms even further. Today, not only are women likely to work harder, live longer and retire later, they are likely to work longer hours, have shorter breaks and have less vacations. There are no “quick fixes” but Theo appeals to employers to take cognisance of the predicament, show compassion, tolerance and understanding and institute strategies in the workplace to accommodate the symptoms associated with the “hormonal roller coast”.

Alice Shaw is a keen athlete and has very ably addressed bone health in the female runner. Stress fractures are common in runners and account for about 10% of all running injuries. It does seem paradoxical that the young female runner is reported to have lower bone density than sedentary age matched controls, yet volleyball and basketball players have a 35% higher bone density than controls. Studies suggest that it is nutritional deficiency that is of paramount concern in female runners, which may be responsible for the decrease in bone formation and the increased bone resorption. The recommended caloric intake per day should be 30 kcal/kg lean body weight. The younger female athlete is not only at risk of lower bone density, particularly of the spine, she is also likely to have menstrual irregularities. Simply regulating the menstrual function by using hormonal correction does not necessarily correct the bony deficiency without the appropriate amount of nutrition. Improving bone health in a young female runner mandates that appropriate amount of calories are consumed whenever she is training, competing or exercising.

The International Federation of Gynecology (FIGO), under the able direction of Professor Ian Fraser, have established a new classification for abnormal vaginal bleeding from menarche to menopause. The primary aim for the new classification was to remove the entity previously entitled dysfunctional uterine bleeding, menorrhagia, metrorrhagia, define abnormal uterine bleeding pattern according to etiology and standardize the modalities of diagnosis and treatment. The acronym PALM-COEIN was processed over a five year combining the inputs from 17 countries and brings into the new classification the role played by Polyps, Adenomyosis, Leiomyoma, Malignacy, Coagulopathy, Ovulatory dysfunction, Endometrial, and Iatrogenic not yet classified. Shastra Bhoora has managed to deal with a difficult subject and has provided a well written article which has 2 algorithms for the evaluation of women who present with abnormal vaginal bleeding from menarche to menopause. FIGO has every intention to simplify understanding abnormal vaginal bleeding, but I sense it is going to a long time before PALM-COEIN takes priority and we elect to no longer utilize the old terminology.

Ultrasound imaging of an adnexal mass is more helpful with a view to the need for surgical intervention than the role of ultrasonography in screening for ovarian cancer. Douglas Dumbrill has provided an excellent appraisal, not only for the role of ultrasound examination of adnexal masses and the significance of the findings, but has managed to make this article extremely reader-friendly by including wonderful images substantiating the approach one should take in trying to determine whether the findings on ultrasound imaging support the need for surgical intervention. He has summarized well the salient findings of the International Ovarian Tumour Analysis, the largest on-going study involving 20 centres in 20 countries looking into the ultrasound diagnosis of adnexal pathology. There will obviously be laparotomies that are deemed necessary and are associated with benign pathology, but if one adheres strictly to the recommendations, as described in this article, the likelihood of missing malignant pathology is significantly reduced. A meaningful article with great “visual aids”.

Happy reading!
Screening for ovarian cancer in the general population

Dr Tracey Adams
Department of Obstetrics & Gynaecology, Gynaecological Oncology Unit, Groote Schuur Hospital University of Cape Town

Abstract: Ovarian cancer is not the commonest gynaecological malignancy. However it is the most devastating as it has the highest case fatality ratio. The majority of patients present with advanced disease with a five year survival of 20-30%. Over the last decade, there have been numerous studies that looked at screening in the general population. The aim of these studies was to create a stage shift in detection of ovarian cancer in order to improve survival. This review article summarises the methods used in screening as well as the recent trials over the last decade.

Background

There are 225 000 cases of ovarian cancer diagnosed annually worldwide and the incidence rates are highest in developed countries such as the United States of America and Northern Europe (1 in 70). The incidence is much lower in Africa and Asia.1 Although not the commonest gynaecological malignancy, ovarian cancer has the highest case fatality ratio as 70% of women present with advanced disease with a five year survival of 20-30%.2

It is known that 80-85% of ovarian cancers are epithelial in histological origin and the majority of these are of serous histological subtype, which has the poorest outcomes.1

Why screening in the general population?

If disease is confined to the ovary, the five year survival is greater than 90%. The rationale behind screening is that by early detection of ovarian cancer, long-term survival can be improved. The aim is thus a “stage shift”.

Topics to be discussed:

• Tumour markers
• Ultrasound
• Combined tests
• Ovarian screening trials
• Controversies
• The future?

Tumour Markers

CA-125

This was first discovered by Bast et al in 1981 as a protein thought to be elevated in more than 80% of cases of epithelial ovarian cancer.3 We now know that it is elevated in less than 50% of cases with stage 1 ovarian cancer.2 It has a poor specificity especially in younger patients, and there are a number of conditions where the CA-125 may be elevated. (See Table 1)

It is suggested that the measurement of CA-125 in an individual patient over time is better than a single measurement to improve the estimation of a patient’s risk of ovarian cancer. This is referred to as the ROC algorithm. A retrospective study by Skates et al in 2003 found that the sensitivity of CA-125 was 86% if the ROC was used, compared to a sensitivity of 62% for a single CA-125 measurement.4

HE-4 (Human Epididymis protein 4)

This tumour marker was discovered in the 90’s. It is among the most frequently upregulated genes in epithelial ovarian cancer based on gene expression profiles. Its main benefit is its use in the younger premenopausal woman where CA-125 has low sensitivity and specificity, as HE-4 is not elevated in endometriotic lesions.5

Other tumour panels

There are a range of tumour markers used together in panels such as CA-125, leptin, prolactin, osteopontin and IGF-2. These tumour panels increase sensitivity by 5-10% but with an associated decline in specificity.1

Table 1: Conditions associated with elevated CA-125

<table>
<thead>
<tr>
<th>Physiological</th>
<th>Menses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Benign gynaecological</td>
<td>Endometriosis</td>
</tr>
<tr>
<td></td>
<td>Fibroids</td>
</tr>
<tr>
<td></td>
<td>Pelvic inflammatory disease</td>
</tr>
<tr>
<td>Benign non-gynaecological</td>
<td>Appendicitis</td>
</tr>
<tr>
<td></td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td>Peritonitis</td>
</tr>
<tr>
<td></td>
<td>(any peritoneal irritation)</td>
</tr>
<tr>
<td>Non-gynaecological cancers</td>
<td>Breast cancer</td>
</tr>
<tr>
<td></td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td></td>
<td>Colon cancer</td>
</tr>
<tr>
<td></td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Gynaecological cancers</td>
<td>Ovarian, fallopian</td>
</tr>
<tr>
<td></td>
<td>Primary peritoneal cancer</td>
</tr>
<tr>
<td></td>
<td>Endometriial cancer especially if extra-uterine spread</td>
</tr>
</tbody>
</table>

Menopause Focus 5

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Combination of HE-4 and CA-125

The 2 tumour markers can be used as a method of triage to identify low and high risk groups especially in the younger woman. An elevated CA-125 without an increase in HE-4 would suggest advanced endometriosis. On the other hand, an elevated HE4 with a normal CA-125 may suggest the presence of ovarian or other types of cancer.

Ultrasound

Transvaginal ultrasound is superior to transabdominal scans. If a mass is identified, the following features are characterized:

1. Morphology: complex masses with solid, papillary or a multiloculated appearance is more concerning (See Table 2).
2. Vasculature: it has been suggested that an increased blood flow in a mass is indicative of the presence of a malignancy. These findings have been inconsistent in studies and the benefit of dopplers is limited.
3. Volume: studies in healthy women have established the upper limit of ovarian volume as:
   - 20cm³ in premenopausal women
   - 10cm³ in postmenopausal women
4. Suggested algorithm: See Table 3

Combined tests

The Risk of Malignancy Index (ROMI) combines CA-125 and morphological features on ultrasound to triage which patients require referral to a gynaecological oncologist:

\[
\text{ROM} = \text{CA125 value} \times \text{menopausal status} \times \text{morphology.}
\]

- Score =1 if premenopausal or 3 if menopausal.
- 1 if no or 1 morphologically suspicious feature or score of 3 if 2/more suspicious features.
- A score of > 200 implies a significant risk.

Ovarian Screening trials

There have been 4 trials on ovarian cancer screening in the general population published over the last decade:

- Kentucky trial
- Japanese trial (Shizuoka Cohort Study of Ovarian Cancer Screening)
- PLCO (Prostate, lung, colorectal and ovarian cancer screening trial)
- UKCTOCS (United Kingdom Collaborative trial on ovarian cancer screening)

The Kentucky trial

The Kentucky trial was published in 2007 by Van Nagell et al. During 1987-2005, 25,327 asymptomatic women were screened annually with transvaginal ultrasound. The aim was to determine the efficacy of annual transvaginal ultrasound as a screening method for ovarian cancer.

---

Table 2 - Morphology Index used in the Kentucky Trial

<table>
<thead>
<tr>
<th>TUMOR VOLUME</th>
<th>TUMOR STRUCTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;10 cm³</td>
</tr>
<tr>
<td>1</td>
<td>10-50 cm³</td>
</tr>
<tr>
<td>2</td>
<td>&gt;50-100 cm³</td>
</tr>
<tr>
<td>3</td>
<td>&gt;100-200 cm³</td>
</tr>
<tr>
<td>4</td>
<td>&gt;200-500 cm³</td>
</tr>
<tr>
<td>5</td>
<td>&gt;500 cm³</td>
</tr>
</tbody>
</table>

Table 3 - Algorithm used in the Kentucky Trial

- Transvaginal Sonography (TVS)
  - Normal
  - Abnormal
  - Repeat TVS one year
  - Repeat TVS 4-6 weeks
  - Repeat TVS one year
  - Morphology indexing
  - Ca-125 Color Doppler Proteomics
  - Unilocular cystic tumor < 5 cm with a normal serum Ca-125
  - Persisting complex tumors, or persisting cystic tumors with an elevated Ca-125
  - Surgery

---
The criteria for an abnormal ultrasound involved looking at ovarian volume and a morphology index. Each mass was given a score from 1-10 according to increasing morphologic complexity and volume.

Women with a persisting complex mass or a persisting cystic mass with an elevated CA-125 were offered surgery.

**Results of the Kentucky trial**

The mean age of the women was 56 years of age. There were 364 women (1.4%) who underwent surgery. Of these, 44 women had primary ovarian cancer. It was found that most ovarian malignancies had solid or papillary features on transvaginal ultrasound with a mean morphology index of 6. Of the 44 ovarian cancer patients, 28 had stage 1 disease, 8 had stage 2 and a further 8 women had stage 3 disease. There were 9 patients who developed ovarian cancer within 12 months of a negative screen (false negatives) and 51 true positives (44 with primary ovarian cancer and 7 women with metastatic cancer to the ovary). Of note, there were 313 women with a false positive test (benign cysts). In conclusion the Kentucky trial found that annual transvaginal ultrasound as a screening test had moderate sensitivity and a low positive predictive value as only 14% of persisting masses were malignant. This was not a randomised control trial. However, they compared the recruited women to 380 patients with ovarian cancer who were entered into the register between 1987-2005 (controls). In this study it was found that annual transvaginal ultrasound decreased disease stage detection as 82% of women with ovarian cancer detected by screening had stage 1 and 2 disease compared to 34% on the control group (p< 0,0001).

**The Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS)/ Japanese study**

This was the first prospective randomised control trial in ovarian cancer screening and it was published in 2008. It was designed to study the effect of annual transvaginal ultrasound and blood tests viz CA-125 from menopause in a screened versus a control group. All asymptomatic postmenopausal women resident in Shizuoka were eligible. These women were recruited between 1985-1999 and were randomised to an intervention (41 688 women) and control group (40 799 women) and followed up for an average of 9.2 years. The intervention group received annual transvaginal ultrasound and CA-125. Ultrasound was simplified as normal (<4cm, normal in appearance), category 1 (> 4cm in size, simple cyst) or category 2 (> 4cm in size, complex mass).

**Results of the SCSOCS**

There was no significant difference in the number of women with ovarian cancer detected in the screened versus the control group (27 versus 32 patients). It was found that 33 surgical procedures were required to detect one case of ovarian cancer and also 8 additional cancers were detected outside of screening. The stage distribution between the two groups was different but not statistically significant.

**The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)**

The PLCO was a randomised controlled trial designed to determine the effect of specific cancer screening tests on cause-specific mortality. The findings of the ovarian arm of this trial was published in 2011. Women between the age of 55-74 years were recruited into either an intervention group/annual screening (39 105 women) or usual care (39 111 women) in 10 centres in the United States. Screening involved CA-125 and transvaginal ultrasound at baseline then repeat ultrasound annually for an additional 3 years and repeat CA-125 for an additional 5 years. Ultrasound was regarded as abnormal if ovarian volume was > 10cm3, together with any solid or papillary projections or mixed components.

The primary endpoint was ovarian cancer mortality and secondary endpoints included:

- Ovarian cancer incidence
- Cancer stage
- Survival
- Potential harms of screening
- All-cause mortality

The median follow-up was 12.4 years. There was no statistically significant difference in the incidence of ovarian cancer in the screened versus the usual care group (212 cases of ovarian cancer in the intervention group versus 176 cases in the usual care group RR1.21 CI 0.99-1.48). There was also no difference in mortality between the two groups. There were 118 deaths in the screened group versus 100 deaths in the usual care group (RR 1.18 CI 0.91-1.54).

The stage distributions were similar between the two groups with stage 3 and 4 comprising the majority (69% in the intervention group and 78% in the usual care group). In terms of screening-related harms, 45% of women in the screened group with ovarian cancer had a major complication (including infection, blood loss, bowel injury etc.) compared to 52% in the usual care group. More importantly, in those cases where surgery was performed for benign cases (false positives), there were 20.6 complications per 100 operations.

**The United Kingdom Collaborative Trial on Ovarian Cancer Screening (UKCTOCS)**

This was based on the work published by Jacobs in 1999 which suggests that screening sequentially with CA-125 and ultrasound (multimodal screening/MMS) can result in a survival benefit. This involves repeat/sequential CA-125 and the rate of change is used to assess risk.
The UKCTOCS is thus far the largest randomised controlled trial in ovarian cancer screening (includes 202,638 postmenopausal women aged 50-74 years). It was also designed to assess the effect of screening on mortality.

The prevalence data was published in 2009 and the mortality data is to follow in 2014/2015. It is a 3 armed trial randomised in a ratio 2:1:1 which includes:

- No treatment (N= 101,359)
- Annual CA-125 with ultrasound as a second line test (MMS, N=50,640)
- Annual screening with ultrasound (N= 50,639)

Results of the prevalence study of the UKCTOCS

Of 98,308 women screened, 942 (0.95%) underwent surgery - 8.7 in the ultrasound group for every one woman in the MMS group.

The number of operations in the MMS group was significantly lower (p< 0.005).

Benign pathology was found in 834 women (47 MMS, 787 USS). There was no difference in the detection of ovarian/tubal malignancies (42 MMS, 45 USS). The MMS group required 2.3 operations per case of ovarian cancer versus 18.8 operations per case of cancer in the USS group.11

Summary of the above studies

All the studies have different study designs and methodologies and cannot be directly compared. The studies do, however, substantiate that in screening programmes, an awful amount of laparotomies need to be performed in patients suspected of having ovarian cancer to actually find a true ovarian cancer. (See Table 4)

Back to basics: Is screening in ovarian cancer justified?

Table 5 reminds us of the basic principles of a good screening test.

### Table 4: Summary of ovarian cancer screening trials

<table>
<thead>
<tr>
<th>Study design</th>
<th>Van Nagell and colleagues, 2007</th>
<th>Kobayashi and colleagues, 2008</th>
<th>PLCO, 2005</th>
<th>UKCTOCS USS group</th>
<th>UKCTOCS MMS group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening strategy</td>
<td>Single-arm prospective study</td>
<td>RCT with one screening strategy in study group</td>
<td>RCT with one screening strategy in the study group</td>
<td>RCT with two screening strategies in the study group</td>
<td>RCT with two screening strategies in the study group</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Physical exam, ultrasound and CA125</td>
<td>Ultrasound and CA125</td>
<td>Ultrasound</td>
<td>CA125 interpreted by ROC algorithm</td>
<td></td>
</tr>
<tr>
<td>Number of women screened †‡</td>
<td>25327</td>
<td>41688</td>
<td>28816</td>
<td>48227</td>
<td>50078</td>
</tr>
<tr>
<td>Mean number of screens per woman</td>
<td>4.8</td>
<td>5.4</td>
<td>1 (first)</td>
<td>1 (first)</td>
<td>1 (first)</td>
</tr>
<tr>
<td>Number of women who had surgery</td>
<td>364</td>
<td>903</td>
<td>570</td>
<td>845</td>
<td>97</td>
</tr>
<tr>
<td>Primary epithelial ovarian and tubal cancers (ICD-10 C56, C57.0)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of women with primary epithelial ovarian and tubal cancers</td>
<td>39</td>
<td>27</td>
<td>27</td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>Interval (missed) cancers diagnosed within 1 year of screen</td>
<td>9</td>
<td>8</td>
<td>†</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Apparent sensitivity</td>
<td>81%</td>
<td>77%</td>
<td>†</td>
<td>85%</td>
<td>89%</td>
</tr>
<tr>
<td>Operations per cancer listed above detected</td>
<td>9.3</td>
<td>33.0</td>
<td>21.1</td>
<td>18.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Number of borderlines or low malignant potential tumours</td>
<td>10</td>
<td>†</td>
<td>9</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Outcome measure: primary invasive epithelial ovarian and tubal cancers (within 1 year of screen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apparent sensitivity</td>
<td>76.3%</td>
<td>†</td>
<td>†</td>
<td>75.0%</td>
<td>89.5%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.7%</td>
<td>†</td>
<td>98.4%</td>
<td>98.3%</td>
<td>99.9%</td>
</tr>
<tr>
<td>Number of operations per cancer detected</td>
<td>9.3</td>
<td>†</td>
<td>21.1</td>
<td>35.2</td>
<td>2.9</td>
</tr>
<tr>
<td>% of stage I/II cancers among screen-detected cancers</td>
<td>82.1%</td>
<td>†</td>
<td>22.2%</td>
<td>50.0%</td>
<td>47.1%</td>
</tr>
</tbody>
</table>

Excludes primary peritoneal cancers non-epithelial neoplasms to allow comparison with Kobayashi et al, 2008. † Cannot be calculated owing to an absence of data ‡ Absent data.
Furthermore:

There are no specific identifiable precancerous lesions in ovarian cancer. Also, there are new classifications that have been proposed. These include dividing ovarian cancer into type 1 and type 2 ovarian cancers. Type 1 cancers are described as slow-growing, forming a continuum starting with cystadenoma benign tumours, subsequently developing towards borderline and finally invasive tumours. These include low-grade serous carcinomas, mucinous, endometrioid, clear cell and malignant Brenner tumours. Type 2 ovarian cancers, on the other hand, evolve quickly, have a greater propensity for metastases and include high grade serous carcinomas, carcinosarcomas and poorly differentiated carcinomas.

It has recently been proposed that ovarian cancer is actually a heterogenous disease which cannot be lumped into the 2 tier classification described above. There are 5 different types based on histopathology and molecular genetic alterations or mutations. These include high grade serous, endometrioid, clear cell, mucinous and low grade serous carcinomas. These different histological subtypes thus each have a different response to chemotherapy and prognosis.

### Table 5: Criteria for screening

<table>
<thead>
<tr>
<th>Features</th>
<th>Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease significantly impacts on public health</td>
<td>YES (high case-fatality ratio)</td>
</tr>
<tr>
<td>Disease must be prevalent/common</td>
<td>NO</td>
</tr>
<tr>
<td>Must be able to detect a high proportion of cases in the preclinical state</td>
<td>NO</td>
</tr>
<tr>
<td>Safe and easy to administer</td>
<td>YES (bloods and scan)</td>
</tr>
<tr>
<td>High sensitivity</td>
<td>NO</td>
</tr>
<tr>
<td>High specificity</td>
<td>NO</td>
</tr>
<tr>
<td>Inexpensive</td>
<td>YES/Questionable</td>
</tr>
<tr>
<td>Medical treatment of the condition must be widely available</td>
<td>NO (surgery not available in all settings)</td>
</tr>
</tbody>
</table>

In conclusion

There is currently insufficient evidence to support screening for ovarian cancer in the general low-risk population. The way forward in combating this devastating disease would be genetics with a focus on the development of personalised medicine.

**References**

Working women and the menopause

Dr Theo Kopenhager
Gynaecologist, Park lane Clinic, Johannesburg and Council Member, SA Menopause Society

The effects of the menopause on working women has received scant attention in the medical literature. This is certainly a deficiency considering the increasing number of older women in the workplace. All women who reach the 5th decade will experience the menopause. Because of the prevailing economic climate, it is common for many women to continue working to an older age, and for many to return to work when family commitments allow this.

Reliable statistics relevant to menopausal women in the South African work place are not readily available. In the United Kingdom, women comprise 47% of the workforce. More than 3.5 million of these women exceed 50 years in age, and comprise 45% of the over-50 workforce. This number is steadily increasing.1

In the United States, women's presence in the workforce has increased 44% in the last 25 year. Here, too, there is a tendency for more women to continue working beyond the age of 50 years. In 2010 the U S Congress Joint Economic Committee declared that the US economy is dependent on working women.2

Definition of working women

Women today are found in virtually any form of employment including heavy physical labour, especially in parts of Africa and Asia. The United Kingdom and United States statistics pertain to women in the following occupations: professional, scientific and technical activities, education, information and communication, finance, administration, business, wholesale and retail trade, industry, usually light but also heavy, agriculture and defence.3

The challenges of working during the menopause

The most recognisable challenges result from the decline in hormones associated with the menopause transition with irregular menses, and then eventual amenorrhoea. Initially there may be ‘hormonal chaos’ followed by the well known menopausal symptoms associated with decreased quality of life, namely hot flushes and night sweats, urogenital atrophy, sleep disturbances, mood changes and difficulties with concentration and memory. Certain diseases are more common during this period including osteoporosis, coronary artery disease, large bowel cancer and macular degeneration.

Menopause tends to occur at a challenging time in many women’s lives. Chronic personal health issues become more common and their risk increases with age. Women at this age are often responsible for the care of chronically ill or disabled partners or parents. Child care, either their own, or grandchildren may be a factor in their lives, especially if these children are socially problematic. On the other hand the ‘empty nest syndrome’ may have a negative effect on quality of life. A significant number of women bear the greater burden of domestic responsibility and may need to work at the same time.3

All studies point out that a significant number of women found it difficult to cope with work during this time of their life. Poor concentration, tiredness, poor memory, depression or feeling low and lowered confidence are frequently cited. Hot flushes are a major source of distress especially for those who work in hot or poorly ventilated environments, attend formal meetings or during formal presentations.3

The menopause is an occupational health issue. Employers have been slow to recognise that menopausal women may need special support and consideration in order to remain as productive as they were.4

Studies on menopausal women’s experience in the workplace

The vast majority of these studies are conducted by, or on behalf of labour unions, and do not appear in medical journals. These studies are, however, no less interesting, informative or valuable. In order to try and be brief, the findings of these studies have been presented in point-form.

Working through the change: Health and safety and the menopause

In this study, the TUC5 surveyed 500 industrial safety representatives. The study found that:

- 45% of company managers did not know of the existence of menopause related problems.
- 35% of workers reported embarrassment in discussing their menopause problems with managers, especially if these managers were either younger than them or male.
- 30% of managers were critical of menopause related sick leave.
- 20% of workers reported criticism, ridicule and even harassment on broaching these problems.
Menopausal subjects in the study claimed that working exacerbated the following symptoms:

- Hot flushes (53%)
- Headaches (46%)
- Tiredness and lack of energy (45%)
- Sweating (39%)
- Anxiety attacks (33%)
- Aches and pains (30%)
- Dry skin and eyes (29%)

Menopausal subjects in the study claimed that symptoms were exacerbated by certain work conditions:

- High temperatures in the work place (66%)
- Poor ventilation (50%)
- Work related stress (49%)
- Poor or non-existent toilet and rest facilities
- Lack of access to cold drinking water
- Inconvenient working hours

Women’s experience of working through the menopause

This study explored “women’s experience of working through the menopause” and found the following:

Most women were generally ill prepared for the consequences of the menopause and even more poorly equipped to manage menopause symptoms at work.
- The majority of women felt in need of advice, support and information regarding the menopause and how to cope with symptoms at work. These women felt this information should be provided by their employers.
- Many women felt that work places and work practices are not designed to accommodate menopausal women.
- Women in general were not comfortable disclosing their health problems to their managers, particularly if these were younger than them, or were male.
- Some women worked extremely hard to hide their self-perceived shortcomings resulting from menopause symptoms.
- Only half of the women who took time off to deal with their menopause symptoms disclosed the real reason in their sick-leave applications.
- Over half of the women in the study were unable to negotiate flexible working hours which they felt would facilitate their ability to handle the discomfort of their symptoms.
- As a consequence a number of women contemplated resigning or applying for part-time employment but were concerned about the effect of this on their careers.
- Almost half of the sample reported no form of temperature control in their work places. Some could not open windows, or if they could, this often caused interpersonal difficulties with colleagues.
- Many women described strategies to cope with hot flushes such as the use of personal fans, layers of clothing or bringing a change of clothing to work.
- 75% of women in the sample reported using hormone therapy to alleviate their symptoms and allow them to manage their work load. In over 90% of these women hormone therapy was effective.

The impact of menopausal symptoms on work ability

This cross-sectional study looked at the impact of menopausal symptoms on the ability to perform effectively at the workplace. The premise was that if menopausal symptoms interfere with quality of life, will they also interfere with consistency and quality of work output?

Two hundred and eight women aged 44 to 60 years were recruited. All worked for a hospital and home-care organisation in the Netherlands. Each subject was required to complete a questionnaire that included:

- **The Work Ability Index (WAI)**
  This is a survey of self-reported work ability relative to past performance, job demands, current diseases and recent illness related absences. Higher WAI scores denote better work ability.
- **The Greene Climacteric Scale (GCS)**
  This is a 21 item survey of menopausal symptoms and their severity. These include psychological symptoms such as difficulty in concentrating, mood changes and depression and somatic symptoms such as headache, dizziness and joint pain and vasomotor symptoms i.e. flushes and sweats. The higher the GCS the more severe the menopausal symptoms.

A significant negative correlation was found between total GCS and WAI scores which clearly indicated that the more severe the menopausal symptoms the poorer the general work ability.

An analysis of the GCS subscales was interesting in that the psychological and somatic symptoms, but not the vasomotor symptoms, significantly correlated with a low WAI. This indicated that contrary to all other surveys, in this study, flushes and sweats were not bothersome to most of the women.

The fact that this article appears in the journal ‘Menopause’ may give it gravitas that it probably does not deserve. The study sample was small and the response rate only 24%, possibly because of the fear of the participants of intimidation or negative repercussions if they were found to be taking part in the study. The significance of the study results is therefore questionable. Despite the fact that the majority of the study subjects dismissed hot flushes...
as “not bothersome”, the results of this study indicate that psychological and somatic menopause symptoms had deleterious effects on work ability and increased absenteeism. Sarrel, in an editorial remark in the same journal, points out that the confusion following the publication of the WHI study in 2002, caused many women to discontinue hormone therapy, thus increasing the severity of menopausal symptoms and decreasing the capacity to function effectively in the workplace.7

Coping with menopause in the workplace8

Zachos opines that we work harder, live longer and retire later. Today’s competitive business atmosphere requires longer work hours, shorter breaks and less vacation. Zachos asks the question “how are women with menopause coping in the ever competitive workplace?” Zachos, however, does not answer the question.

Legal aspects concerning the problem

Menopause should be considered an occupational health issue. As such, this issue would fall under the ambit of a number of laws in all industrialised countries, e.g. The Health and Safety at Work Act and The Equalities Act of 2010 in the United Kingdom.

In South Africa menopause women in the workplace are relatively adequately protected by the Constitution. In the chapter on BILL OF RIGHTS, the section on Equality 9(1)” Everyone is equal before the law..... the section on Equality 9(3) “ There may be no unfair discrimination.....” the section on Labour Relations, 23(1) “Everyone has the right to fair labour practices”, and the section on The Environment, 24(1) “Everyone has the right to an environment that is not harmful to their health or wellbeing”.

The role of employers

Women should expect and receive support and assistance during this difficult time at work.

• Managers, risk managers and safety officers must be made aware of the effects of the menopause on work. They should be trained to make the necessary adjustments to support struggling women.
• Employers must display a positive attitude to the menopause by incorporating it into a wider health awareness campaign. This should help to prevent embarrassment in menopausal workers.
• Issues arising at work as a result of the menopause should be appropriately handled. These should preferably be handled by older female human resources, welfare or safety managers so as to avoid embarrassment to the workers. There should be an adequate number of these managers with whom the female workers can interact.
• Sickness absence procedures must be flexible to cater for menopause-related illness. Women should experience no detriment as a result of this.
• Flexible working times should be introduced to allow menopausal women breaks when needed.
• Work environments should not exacerbate menopause symptoms. Issues of importance here are ambient temperature control, ventilation, accesses to cool water and clean toilet facilities.

Many women may enter menopause at the prime of their productive lives. It would be of advantage to employers to retain these women for their skill, knowledge, experience and loyalty. This will require thought, planning, consideration and effort, but will in the final analysis benefit both sides.

References

1. United Kingdom Office of National Statistics, 2010
2. United States Joint Economic Congress, 2010
7. Sarrel PM. Women, work and menopause. Menopause 2012 March; 19:250
Bone health and the female runner

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Exercise is associated with increased bone density. Volleyball and basketball players have been reported to have a bone density 35% higher than controls. Tennis players have a higher bone density in the dominant arm. It seems paradoxical that the young female runner is reported to have lower bone density than sedentary age matched controls.

The female athletic triad was a term coined in the early 1990’s to explain this phenomenon. The triad originally was described as eating disorders, amenorrhea and osteoporosis. It is now understood to be more of a continuum between normality and pathology. The nutritional aspect includes an energy deficit. The food intake is often normal in comparison to non-active individuals but is not sufficient for the amount of exercise being performed. This may be intentional or unintentional. Young runners often have high scores on eating disorder questionnaires, suggesting abnormal body perception as seen with anorexia nervosa.

Menstrual irregularity and not amenorrhea is now used to evaluate these athletes. This would include oligomenorrhea and amenorrhea. Oligomenorrhea is defined as 4-9 cycles a year and amenorrhea as less than 3 cycles per year.

Osteoporosis cannot be defined in the same terms as in the postmenopausal female. It is important to use the Z score and not a T score. It is recommended that a Z score below -2.0 in premenopausal women be reported as low bone density below the expected range for age. A Z score less than 1.0 in an athlete requires evaluation.

Studies in young female runners have shown that oligomenorrhea is common. Runners with eumenorrhea have bone densities equivalent to their sedentary counterparts but runners with oligomenorrhea have lumbar spine bone densities 5-15% below that of non-active controls. The femoral neck is less affected. Risk factors include a previous stress fracture, low bone density and menstrual irregularities. There are also biomechanical factors that contribute such as peak hip adduction and rear foot eversion.

Stress fractures are common in runners and account for 6-14% of all running injuries. The tibia is most commonly affected. Risk factors include a previous stress fracture, low bone density and menstrual irregularities. There are also biomechanical factors that contribute such as peak hip adduction and rear foot eversion.

Runners with oligomenorrhea have a low estrogen, low FSH and a very low LH. It would seem logical that oral contraceptive pill or hormonal treatment would be the treatment of choice. In a review of 9 studies, oral contraception prevented further bone loss but did not increase bone density to that of age matched controls. Stress fractures were not significantly reduced. Hypoestrogenic states increase bone turnover with increased bone resorption and formation.

Bone markers suggest that in runners, as with anorexia nervosa, bone formation is depressed and resorption increased. This would then infer that nutritional management is of more importance. Nutritional studies in these runners point to an energy deficit. It has been shown that diets including low fat dairy and potassium rich fruit and vegetable diets are associated with less menstrual irregularities. A detailed analysis of the diet needs to be performed in young runners. At least 30 kcal/kg lean body weight must be consumed per day as well as providing sufficient protein, iron and dairy.

The Canadian Multicentre Osteoporosis Study determined that in females, peak mass in the lumbar spine is achieved between 33 and 40 years and in the hip between 16-19 years of age.

Cobb et al reported a study of 91 competitive female athletes, running at least 40 miles per week, aged between 18 and 25 and not having used oral contraception in the last 6 months. A questionnaire assessed training regimen and menstrual history. Nutrient intake was assessed and an Eating Disorder Inventory (EDI) was used to screen for eating disorders. Height, weight, bone mineral density (BMD) at the left proximal femur, spine, whole body and body composition were measured. Thirty six per cent of the women had oligomenorrhea including 10% with amenorrhea. This group ran 18% more miles per week than the women with eumenorrhea. Twenty three women had elevated EDI scores and 65% of this group had oligomenorrhea as compared to 25% of the 67 women with normal EDI scores. BMD was 5%, 6% and 3% lower at the lumbar spine, total hip and whole body respectively in the oligomenorrhea group. Six per cent of this group had osteoporosis as defined as a T score less than 2.5 and forty eight per cent were osteopenic at the lumbar spine.

In the group with eumenorrhea there was no osteoporosis but 26% had osteopenia of the spine. Interestingly the runners were not particularly lean. The women with oligomenorrhea had on average 22% body fat and there was no difference in weight between the two groups.

Stress fractures were not significantly reduced. Hypoestrogenic states increase bone turnover with increased bone resorption and formation.
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It is important to know what happens to these athletes over time.

Kaga et al compared 13 high school female long distance runners aged 15-17 to 7 adult athletes aged 21-25 years. Height, weight and total body fat were similar in both groups. Lumbar spine bone density was significantly higher in the high school group. Lumbar spine BMD was low in reference to reference values of young adults. Total BMD and femur BMD were higher in the adult group. Menstrual irregularity decreased lumbar spine and femur bone density in the younger group but had no effect on bone density of the older group. This group was very small.

Hind et al evaluated the bone density of premenopausal elite athletes on two occasions, 5 years apart. Twenty three elite athletes were available for testing. Five were using oral contraception. Mean age at the first examination was 24 years. Lumbar spine and total body BMD significantly improved over 5 years. The major factor associated with this was the restoration of menses. Importantly the study showed that bone density improved, although the running volume was not significantly decreased. The Z score of the lumbar spine improved from -1.1 to -0.7 at follow up. Bone density of the lumbar spine should improve during this time as peak bone mass is attained in the fourth decade. The increase was more than expected compared to age matched controls.

Fanning et al did a 10 year follow up of BMD in competitive perimenopausal runners. Fifteen master female runners between 40-50 years were evaluated by Dexa (dual energy xray absorptometry) and re evaluated 10 years later. The median age was 46 at baseline and the median duration of competitive running was 11 years. At baseline hip BMD T score was 0.8 and Z score 1.6. Lumbar spine T score was -0.8 but equal to age matched controls, Z score -0.1. After 10 years hip T score fell to -0.2 but was higher than age matched controls Z score 0.5. There was little change in the lumbar spine. Since most of the runners would have become menopausal during this time there was good preservation of bone density overall.

Andreoli et al looked at post menopausal ex-elite athletes. Forty eight women were included aged 54-73. The athletes had competed at international and national level. They still participated in their sport on average 4-5 hours a week. Twelve were swimmers and twelve runners. There were 24 age-matched controls who did less than 1 hour exercise a week. Most were not using hormone therapy. There was no difference in height, weight and body mass index between the groups. The BMD of the lumbar spine was highest in the runners and significantly higher than the sedentary controls. Femur BMD was significantly higher in both groups of athletes than controls.

It would appear from these studies that lumbar spine bone density is a problem in the younger female athlete. If the runner continues to compete there is eventually a beneficial effect. It may be that the athlete with low bone density is forced to stop because of stress fractures. However, these small studies do indicate that improvement can occur with age.

In conclusion, the younger female athlete is at risk of low bone density particularly of the spine. Coaches must be aware of the female triad and make sure that the nutritional intake is adequate. Menstrual irregularity should be an indication to assess diet.

References

The International Federation of Obstetrics and Gynaecology (FIGO) approved a new FIGO classification system which illustrates the causes of abnormal uterine bleeding (AUB) in non-gravid reproductive women and incorporating women with abnormal bleeding from menarche to menopause.

The acronym PALM-COEIN was processed over a five year period combining the inputs from seventeen different countries representing the various world geographies. The new classification and nomenclature aims to enable collaborative research, and improve the assessment and management of AUB in clinical practice.

Abnormal Uterine Bleeding (AUB)

AUB is bleeding from the uterine corpus that is abnormal in regularity, volume, frequency or duration and occurs in the absence of pregnancy.

Vaginal bleeding is considered normal when any of the following is apparent:

- Onset of menses at 16 years old with secondary sexual characteristics
- Menstrual cycle length is between 24-35 days
- Menstrual duration 2-7 days
- Menstrual flow 20-80mls per menses with an average of 35mls

AUB has been divided into two classes, acute AUB and chronic AUB. Acute AUB is an episode of heavy bleeding that requires immediate intervention. It may occur spontaneously or within the context of chronic AUB. Bleeding that is present for most of six months, is unpredictable and excessive, is classified as Chronic AUB.

The primary changes now proposed to standardise nomenclature are shown in the following:

<table>
<thead>
<tr>
<th>Current Term</th>
<th>To be replaced by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysfunctional uterine bleeding</td>
<td>Coagulopathy, endometrial dysfunction and ovulatory disorders</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>Heavy menstrual bleeding</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>Intermenstrual bleeding</td>
</tr>
</tbody>
</table>

The PALM-COEIN classification

The PALM aspect of the acronym refers to the discrete structural entities that can be measured visually with imaging techniques, such as sonography and histopathology testing while COEIN categories are unrelated to structural abnormalities. The entities of PALM-COEIN structurally related to the uterus include:

- **Polyp**
- **Adenomyosis**
- **Leiomyoma**
- **Malignancy and hyperplasia**
- **Coagulopathy**
- **Ovulatory dysfunction**
- **Endometrial**
- **Iatrogenic**
- **Not yet classified**

It is key to note that the classification does not include AUB as a result of the pathological conditions of the lower genital tract.

A further description is applied to diagnose AUB to a lower level of detail, only in the AUB-L group. The entities of PALM COEIN structurally related to the uterus include:

**Polyp AUB-P**

Polyps are epithelial proliferations that comprise of variable components i.e. vascular, glandular, fibromuscular or may be connective tissue in origin. AUB-P includes both endometrial and endo-cervical polyps, which are usually benign, although a small minority may have malignant features. The polyp is confirmed on ultrasound or hysteroscopy. The variables for consideration are based on polyp dimension, location, number, morphological and histological features. The definitive management includes polypectomy.

**Adenomyosis AUB-A**

AUB-A is the presence of glandular endometrial tissue within the myometrium (muscle) of uterus. The classification promulgates that the minimal criterion is identification of adenomyosis on ultrasound testing or magnetic resonance testing.

**Leiomyoma AUB-L**

The preferred term for myoma or fibroids is leiomyoma or benign fibromuscular tumors of the endometrium. An ultrasound investigation is the minimal criteria for
diagnosis. The AUB-L group is the only category thus far that has a secondary classification system that divides leiomyomas into “submucosal” and “others” as illustrated in the list below.

The leiomyoma secondary classification system categorises lesions as “submucosal” and “others”.

- Submucosal types are:
  - 0 (pedunculated intracavitary),
  - 1 (< 50% intramural),
  - 2 (≥ 50% intramural),

- Other types are:
  - 3 (contacts endometrium, 100% intramural),
  - 4 (intramural),
  - 5 (subserosal ≥ 50% intramural),
  - 6 (subserosal < 50% intramural),
  - 7 (subserosal pedunculated)
  - 8 (includes cervical or parasitic and other lesions not related to the myometrium)

- The leiomyoma classification does not yet include the size of the uterus, single longest measurement, location, and number of lesions.

Malignancy and hyperplasia AUB-M

AUB-M is relatively uncommon in the late reproductive perimenopausal age group, but should always be considered as a potential cause of AUB. The new AUB-M classification does not replace the WHO and FIGO classifications of endometrial hyperplasia and neoplasia.

The entities of PALM COEIN structurally NOT related to the uterus and part of the COEIN acronym include:

Coagulopathy AUB-C

Coagulopathy, disturbances of haemostasis, occur in approximately 13% of women with AUB, heavy menstrual bleeding. The commonest cause is von Willebrand disease. The screening tool put forward by the ACOG to identify women with coagulation deficiencies, includes:

- Heavy menstrual bleeding since menarche
- 1 of the following:
  - Post partum hemorrhage
  - Surgery related bleeding
  - Bleeding associated with dental work
- 2 of the following:
  - Bruising 1-2 times a month
  - Epistaxis 1-2 times a month
  - Frequent gum bleeding
  - Family history of bleeding symptoms

Ovulatory AUB-O

Ovulatory dysfunction can lead to amenorrhea or heavy menstrual bleeding and may be as a result of endocrinopathies e.g. polycystic ovarian syndrome, hypothyroidism, hyperprolactinaemia, mental stress, obesity, anorexia, weight loss as in extreme physical activity i.e. athletes, iatrogenic causes or at the extremes of age, namely, adolescence and the menarche or the transition to menopause. The menstrual cycle is often irregular and unpredictable.

AUB-O is a common cause of AUB in perimenopausal bleeding owing to anovulatory cycles in the months before menopause because of luteal phase defects. Luteal phase defects may shorten the menses (there is corpus luteal insufficiency in the second half of the cycle and, therefore, decreased concentrations of oestrogen and decrease progesterone) or prolong the menses (there is a persistent corpus luteum and, therefore, increased progesterone changes in the first half or the cycle, the proliferative phase). The term dysfunctional uterine bleeding, therefore, is no longer used.

Menstrual dimensions that should be evaluated are:
- Regularity: Is the menstrual cycle irregular, regular or absent
- Frequency: Is the menstrual cycle frequent, normal or infrequent
- Duration: Is the menstrual cycle prolonged, normal or shortened
- Volume: Is the menstrual cycle heavy, normal or light

Endometrial AUB-E

Endometrial disorders are likely to occur when other abnormalities are excluded in the presence of normal ovulatory function. The menstrual cycle is often regular and predictable in contrast to the AUB-O group. An endometrial cause of AUB may owe to deficiencies in the local production of vasoconstrictors such as endothelin-1 and prostaglandin F2α and/or due to accelerated lysis of endometrial clots because of an excess of plasminogen activator and vasodilators such as prostaglandin E2 and I2.

Other factors that may contribute to HMB is incomplete repair of the endometrium at menstruation, owing to endometrial inflammation or infection (especially with Chlamydia trachomatis). Endometritis should be considered in patients who present with AUB in the postpartum period, post abortal period and in patients who present with pelvic inflammatory disease, especially in young teenage patients. Failure of the graafian follicle to ripen or rupture results in AUB-E.
Iatrogenic AUB-I

Iatrogenic causes include ‘breakthrough bleeding’ (the major component of AUB-I) during use of single or combined gonadal steroid therapy, intrauterine systems or devices (especially the levonorgestrel-releasing intrauterine device), systemic agents that may interfere with dopamine metabolism or anticoagulant drugs. These agents may directly impact on the endometrium or influence ovulation. Gonadal steroid therapy, i.e. oestrogens, progesterone and androgens impact on the hypothalamic-pituitary-ovarian axis as well as on the endometrium directly.

Drugs that cause abnormal uterine bleeding.1

- Anticoagulants
- Antidepressants (SSRIs/TCAs)
- Acetylsalicylic acid
- Hormone replacement therapy
- Tamoxifen
- Phenothiazines
- Corticosteroids
- Thyroxine
- Contraceptives
- Herbs: ginseng, ginkgo, soy products

Not yet classified AUB-N

The AUB-N category includes rare and ill defined conditions that are not included in PALM-COEI. The causes of AUB-N are, for example, chronic endometritis, arteriovenous malformations, and myometrial hypertrophy.1

Clinical implications

Acute Bleed

Obtain urgent haemodynamic stability, which may include active resuscitation and adhering to facility specific protocols. Ovulatory function, potential related medical problems, medications and lifestyle factors should be thoroughly reviewed in every patient that presents with AUB. Management plans should consider the patient’s desire of fertility as well as relevant biochemistry and imaging.

The evaluation pathway of abnormal uterine bleeding is shown in Figure 1.1

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**Figure 1: Uterine evaluation for diagnosis**

Uterine evaluation

- Enhanced risk for hyperplasia/neoplasia
  - Enhanced risk for structural abnormality
    - Office endometrial biopsy
      - Adequate specimen
        - Yes
          - Atypical hyperplasia or hyperplasia/neoplasia
            - Yes
              - Management of AUB-M
            - No
              - AUB-E or O
                - Yes
                  - Hysteroscopy ± biopsy
                - No
                  - Saline infused sonography
                    - Target lesion
                      - Yes
                        - Can’t assess
                          - Consider MRI
                    - No
                      - Normal cavity
                        - TVUS
                          - Yes
                            - Management of AUB-Lsm, AUB-P, AUB-A
                          - No
                            - Management of AUB-E or O
Laboratory tests that should be considered include:

- **Initial laboratory tests:** Full blood count, blood type and cross match, pregnancy test
- **Disorders of haemostasis:** PTT, PT, activated partial thromboplastin, fibrinogen, Von Willebrand factor antigen, Factor VIII
- **Other laboratory test:** TSH, LFTs, iron studies, chlamydia trachomatis

The medical treatment options are included in Table 2.3 Surgical methods, non-invasive and invasive, are not included i.e. endometrial ablation, myomectomy, hysterectomy etc. The surgical management options would pertain to each specific AUB-cause and the patients profile. The surgical treatment of choice will, therefore, follow facility specific protocols and guidelines.

### Table 2: Medical Treatment Strategies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Dose Schedule</th>
<th>Contraindications</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated equine estrogen</td>
<td>25mg IV</td>
<td>Every 4-6 hrs for 24 hrs</td>
<td>Breast cancer, Previous VTE, liver dysfunction</td>
<td>72%</td>
</tr>
<tr>
<td>Combined oral contraception</td>
<td>Monophasic pill containing 35 micograms of ethinyl estradiol</td>
<td>Three times per day for 7 days</td>
<td>Cigarette smoking, hypertension, thromboembolic disease, ischaemic heart disease, liver disease</td>
<td>88%</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>20mg po</td>
<td>Three times per day for 7 days</td>
<td>Thromboembolic disease, breast cancer, liver disease</td>
<td>70%</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>1 -1.5g orally</td>
<td>Three times per day for 5 days</td>
<td>Thromboembolic disease, not more than 7 days, risk of thrombosis formation is very uncommon</td>
<td></td>
</tr>
</tbody>
</table>

**Chronic Bleed**

The algorithm for chronic AUB (Figure 2) offers a structured approach to the evaluation of chronic AUB.3

**Conclusion**

There are a number of disorders that manifest as AUB.

The PALM-COEIN classification has been implemented to improve the evaluation of AUB in all the female age groups. It is still new and will soon be the standardised method of AUB assessment and interpretation world wide. FIGO has propigated to review PALM-COEIN every 3 years to enhance its value and it will therefore be continually revised and improved.

### Figure 2: Assessment of AUB

**References**

1. Munro M.G., Critchley H.O.D., Broder M.S., Fraser I.S. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in non-gravid women of reproductive age. Int J Gynecol Obstet 2011;113:3-13
With the increased use of ultrasound in medical practice it is common to find asymptomatic ovarian cysts. In the PLCO (prostate, lung colon and ovary) screening trial in women over 50 years of age, 21% were shown to have an ovarian cyst. The vast majority were benign, but 15% were described as 'complex'. Ultrasound is a useful first line investigation for discriminating between benign and malignant masses. A confident diagnosis of benign pathology in an asymptomatic patient would minimise further unnecessary expensive investigations (e.g. diagnostic laparoscopy) and possible complications. Conversely a malignancy would require prompt treatment in the hands of an appropriately skilled gynaecologist without unnecessary delay.

Ultrasound has been used in a number of ways to improve our diagnosis. These include morphological scoring systems, colour Doppler imaging, computer scoring systems, risk of malignancy index, pattern recognition and more recently the international ovarian tumour analysis (IOTA) studies.

**Morphological scoring systems**

Granberg et al published his seminal paper 25 years ago in which he described cysts as being unilocular, unilocular/solid, multilocular, multilocular/solid or solid. This classification is the basis of morphological scoring system used today. Granberg reported a sensitivity of 82% and a specificity of 92% in diagnosing ovarian malignancy. To date there have been over 80 published papers all looking at differing scoring systems.

**Risk of malignancy (RMI)**

The risk of malignancy index (RMI) is one of the most used and familiar predictive models to define malignancy, and in the UK it has also provided a means of triaging patients with adnexal masses into low, moderate or high risk categories. Depending on the level of risk they would be referred to the appropriate oncology centre for definitive treatment. See Table 1

**Pattern recognition/subjective assessment/grey scale assessment**

Many adnexal masses have a typical appearance on ultrasound which can be easily recognisable to the examiner. This so called pattern recognition/grey scale/subjective assessment, especially when performed by experienced examiners, is seen as the “gold standard” or best way of characterising ovarian masses. Valentine et al have reported a sensitivity of 88-98% and a specificity of 89-96%.

---

### Table 1 B rules Unilocular ovarian cyst

- **Ultrasound score**
  - 1 multilocular cysts
  - 3 (solid areas, bilateral, ascites, metastases)
- **CA 125**
- **Menopausal status**
  - 1 premenopausal
  - 2 postmenopausal

---

**Endometrioma**

- Unilocular cyst
- Thin walled
- Content low level echogenicity
- “ground glass” appearance
- Internal septations in 10-30%
- Poorly vascularised wall

**Dermoid**

- Rokitansky nodule (hyper-echogenic “white ball”) with acoustic shadowing
- Hyper-echogenic lines
- Fluid fluid levels
- Prominent echogenic clots
International Ovarian Tumour Analysis (IOTA)

The International Ovarian Tumour Analysis (IOTA) is the biggest ongoing study (20 centre in 20 countries) looking into the ultrasound diagnosis of adnexal pathology. Kauser et al have recently published an excellent paper on the IOTA studies so far.\textsuperscript{6} The principal IOTA investigators aimed to study a large cohort of patients from different centres/countries in Europe using standard ultrasound protocols with the aim of developing rules and models to study ovarian pathology.

In phase 1 of the IOTA trial, 11 possible models were evaluated and the best performing ones (logistic regression one and logistic regression two (LR1/LR2) were tested prospectively and compared to RMI and CA-125.\textsuperscript{7}

LR 1 has 12 independently predictive variable for cancer (see Table 2) whilst LR2 has 6 variables (see Table 3) Both of these options are available as part of the astria ultrasound reporting package and have been shown to be comparable to complex statistical models.

Simple Rules

A further innovation of IOTA are the simple ultrasound based rules for the diagnosis of ovarian cancer. Timmeran et al has shown in another excellent publication, that by using simple B and M rules, one can confidently classify masses as either benign or malignant.\textsuperscript{8} (see Table 4)

If one or more B-rules apply then a mass is benign. If 1 or more M-rules apply then the mass is malignant. If neither of the rules or both are applicable then the mass cannot be classified and would then undergo pattern recognition/subjective evaluation.

<table>
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<th>Table 4: B-Rules</th>
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<tr>
<td>• Unilocular cyst</td>
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<td>• Presence of solid components &lt; 7 mm</td>
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<td>• Acoustic shadowing</td>
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<tr>
<td>• Smooth multilocular tumour &lt; 100mm</td>
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<td>• No blood flow</td>
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<th>Table 5: M-Rules</th>
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<td>• Irregular solid tumour</td>
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<td>• Ascites</td>
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<tr>
<td>• 4 or more papillary structures</td>
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<tr>
<td>• Irregular multilocular solid tumour &gt; 100 mm</td>
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<td>• Strong blood flow</td>
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When the simple rules were applied to the IOTA dataset then similar results to pattern recognition were found in 75% of the masses. In the remaining 25% only pattern recognition achieved a good result. LR1/2 and RMI also performed poorly in this inconclusive group.

By applying a two stage procedure for cases of inconclusive masses i.e. simple rules followed by pattern recognition, one could reach a sensitivity of 90% and specificity of 93%. Fewer stage 1 malignancies were misclassified than with the RMI algorithm and, therefore, the RCOG adopted these rules into their greentop guidelines on adnexal masses.\textsuperscript{9}

In summary, IOTA has developed two main approaches for the classification of ovarian masses. The first uses the logistic regression models 1 and 2 which continue to show good test performance on external validation. This, however, does need the Astria reporting package. Alternatively the simple rules can be applied to 75% of adnexal masses and is well suited to busy outpatient clinics with ultrasound facilities.

Table 2: Logistic regression 1 (LR1)

- Personal history
- Current HRT
- Age
- Diameter of lesion
- Pain during examination
- Ascites
- Blood flow within solid papillary projection
- Solid tumour
- Maximum diameter of solid component > 50 mm
- Irregular internal cyst walls
- Acoustic shadows
- Doppler colour score

Table 3: Logistic regression 2 (LR2)

- Age
- Ascites
- Blood flow within solid papillary projection
- um diameter of solid component > 50 mm
- Irregular internal cyst walls
- Acoustic shadows

Results from IOTA phase 1 and 2 showed that LR1 had a high sensitivity of 92% and specificity of 87% and LR2 a sensitivity of 92% and specificity of 86% respectively. When LR1, LR2, RMI and CA-125 were plotted on a receiver operating curve (ROC) for pre- and post-menopausal women, the area under the curve (AUC) demonstrated a diagnostic advantage of LR1 and LR2 over RMI and CA 125.
Figure 1: B-rules Unilocular ovarian cyst

Figure 2: B-rules presence of solid components < 7 mm

Figure 3: B rules acoustic shadowing

Figure 4: B rules multilocular tumour < 100 mm

Figure 5: M-rules Irregular solid tumour

Figure 6: M-rules - ascites
The current IOTA recommendation is that the simple rules or logistic regression should be adopted as the principal test to characterise masses as both outperform RMI.

Pattern recognition, especially by an expert, remains the best current method of discriminating between benign and malignant masses.

References

Comments by the President

In March of this year, the American College of Obstetricians and Gynecologists Committee of Practice published their opinion pertaining to the impact of breast tissue density on mammography and the value of subsequent investigations in the management of women with dense breast tissue. Having read the bulletin a few times, I must say, I am now even more confused than before, when it comes to the question of increased breast tissue density.

On the one hand, 18 states within the USA have enacted the “Dense Breast Tissue Notification Law”, whilst a further 10 states have laws pending to make these notifications obligatory. These notifications must now be sent to all patients who have been found on mammography to have dense breast tissue. I have included the Notification Law enacted by the state of California which states “Your mammogram shows your breast tissue is dense. Dense breast tissue is common and is not abnormal. However, dense breast tissue can make it harder to evaluate the results of your mammogram and may also be associated with an increased risk of breast cancer”.

The committee also states that about 8% of the general population will have extremely dense breasts and who will have a 1.4 relative risk for breast cancer compared to women with average breast density. About 39% of women will have heterogeneously dense breast tissue and these women have a 1.2 relative risk for breast cancer. Screening sensitivity falls from 88% in breast composed almost entirely of fat tissue to 62% in women with extremely dense breast tissue, whilst it is 69% in women with heterogeneously dense breasts. Despite having included all this their bulletin, The Committee then concludes that there is no evidence to support that alternative screening techniques, such as tomosynthesis, thermography, or adjunctive methods, such as ultrasonography or magnetic resonance imaging, improve breast cancer mortality in asymptomatic women with no other risk factors. The committee does state that digital mammography has been shown to be more effective than film mammography in women with extremely dense breast.

I am now concerned whether anything short of digital mammography is acceptable to screen for breast cancer. If we do not accept this as the gold standard, what is the impact going to be on the public healthcare costs and the medical aid providers? Frequent recalls for alternative imaging options, repeat mammograms or invasive diagnostic procedures because of the poor sensitivity of the more commonly performed film mammogram in screening for breast cancer in low risk women will have a significant financial impact on healthcare costs.

I am surprised that screening mammography has managed to stay under the litigation radar even though there are so many pitfalls.

SAMS Mission Statement

The South African Menopause Society (SAMS) is one of South Africa’s leading nonprofit organisations that is dedicated to promoting women’s health during midlife and beyond, through the understanding of menopause. It boasts a membership of over 190 leaders in the field (including clinical and basic science experts from medicine, nursing, sociology, psychology, nutrition, anthropology, epidemiology and education). This allows SAMS to be the dominant resource on all aspects of menopause to both healthcare providers and the public.

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References: