LIVIFEM®

Improved quality of life

Selected Safety Information:

Contra-indications: Known or suspected hormone-dependent tumours; Known, past or suspected breast cancer – LIVIFEM® increased the risk of breast cancer recurrence in a placebo-controlled trial. Known or suspected hypertension – dependent malignant tumours (e.g. medullary thyroid carcinoma). Endometrial hyperplasia - must be excluded before starting treatment.

Warnings: The use of LIVIFEM® should be avoided for at least 12 months after the last natural menarche. If LIVIFEM® is taken sooner than this, the frequency of endometrial bleeding may be increased. LIVIFEM® therapy, because of its apparently delayed endometrium due to some estrogenic products, namely such bleeding is of short duration. Bleeding commencing after 3 months of treatment is recurrent or of longer duration should be investigated. Periodic examinations must be done for endometrial hyperplasia as well as periodic gynaecological examinations. The risk factors for breast cancer include: increasing age, obesity, family history of breast cancer, and oestrogen use. Clinical trials show no increase in the risk of breast cancer in postmenopausal women treated with LIVIFEM®.

Conditions which need supervision: If any of the following conditions are present, have occurred previously, and/or have been associated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with LIVIFEM®. Cautions should be taken in patients with conditions for which oestrogen treatment has been shown to be harmful or has been advised against, for example: medium and high risk breast cancer; a history of breast cancer; a history of endometrial hyperplasia.

Exerted specific effects on the following tissues through its active metabolites: Brain, Genital tract and Bone  
Effectively relieved vasomotor symptoms in postmenopausal women  
_Showed a better improvement_ on sexual function compared to combined HRT  
_Had a minimal effect_ on breast tissue vs. combined HRT  
_Showed a better vaginal bleeding pattern_ compared to combined HRT  
_Showed beneficial effects on bone_ over a ten year treatment period

References:
2. Data on file, MSD.
For full prescribing information refer to the package insert approved by the medicines regulatory authority.

Warnings:

- Known or suspected hormone- dependent tumours; Known, past or suspected breast cancer – LIVIFEM® increased the risk of breast cancer.
- Known or suspected hormone- dependent tumours; Known, past or suspected breast cancer – LIVIFEM® increased the risk of uterine cancer.
- Known or suspected hormone- dependent tumours; Known, past or suspected breast cancer – LIVIFEM® increased the risk of endometrial cancer.
- Vaginal bleeding of unknown etiology; Untreated endometrial hyperplasia.

Selected Safety Information: Contra-indications:

- The use of LIVIFEM® should be avoided until 12 months after the last natural menstrual bleed.
- If LIVIFEM® is taken sooner than 12 months after the last natural menstrual bleed, close supervision is required.
Dr Stephen Jeffrey has written an evidence based paper on the use of topical estrogen therapy in the treatment of stress urinary incontinence (SUI). He rightly points out that although minimally invasive surgical procedures exist for the treatment of SUI, they can occasionally be associated with significant complications. Local estrogen therapy must always be part of the management of SUI, even if the patient is on systemic hormone therapy.

Dr Nicole Jaff’s interesting research on menopause in black South Africans is exciting, especially in an area where little scientific enquiry has been done. As life expectancy increases, the role of the menopausal physician in reducing the increasing burden of non-communicable diseases becomes more relevant. The need for public education on the physiological changes in the climacteric is highlighted. It affords the healthcare provider an opportunity to induce behavioural changes to enhance quality of life.

Prostate cancer is a common affliction of the partners of menopausal patients. Dr Lisa Kaestner has given us an insight into the signs, diagnosis and consequences of treatment of prostate cancer. She makes the point that as care givers, we must firstly do no harm when deciding who to investigate and treat. Our patient’s partner’s health has a direct bearing on how they handle the changes of menopause. Questions on the partner’s health status are vital and mandatory in our consultations.

Hormone treatment is the gold standard for the treatment of the symptomatic menopausal patient. Dr Sid Hirshowitz explores the alternatives in a group of patients where hormone therapy is contraindicated or if the patient declines hormone therapy and prefers alternate medication. This paper is complemented by the information presented in Menopause Matters.

Professor Atholl Kent also discusses the correct place and timing of hormone therapy. The Woman’s Health Initiative Study (WHI) was a brilliant study done in the wrong age group. Nevertheless, it did demonstrate that initiating hormone therapy in women older than 60 years or more than 10 years post menopause carries risks and is best avoided.

Sexual health is a fundamental human right and is linked to quality of life. Age is not a barrier to sexuality and a sexual history is definitely part of a good menopausal assessment.

In conclusion, I would like to thank all the authors for enhancing patient care.

Thank You
Dr S Percy Moodley

Obituary - Dr Samuel (Syd) Shapiro

Dr Samuel Shapiro (Syd) died suddenly a few weeks ago. I guess most of the IMS members did not meet him or even know him, yet he has always been an important key opinion leader in his field of expertise - epidemiology. Syd was affiliated to the Department of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town. IMS officers and board members often consulted with him and used his advices when better understanding of statistics was required. He was always happy to educate the healthcare providers and explain them what could be the biases and pitfalls of the major studies and how to evaluate the strength of the published data. Syd stood firm with his views, criticising the presentation of some results from the Million Women Study and the Women’s Health Initiative, which led to mis-interpretation of relevant data and withdrawal of useful hormone therapy. His opinions how to evaluate the methodology and the mode of statistical analyses in major trials helped our Society when recommendations on postmenopausal therapy were formulated. I had the privilege, as many others, to share with him authorship on articles. I was always grateful to him because during the process of preparation of the papers I was able to learn how to correctly harness epidemiology to achieve better clinical practice. Syd’s beliefs and contributions will not be forgotten. We will not be able to see him again, but his vision will stay with us forever.

Prof Amos Pines MD (Past President, IMS)
How effective is topical oestrogen therapy in the treatment of stress urinary incontinence?

Dr Stephen Jeffery  
Subspecialist urogynaecologist, University of Cape Town  
Head of Department of Urogynaecology and Pelvic floor Reconstruction, Groote Schuur and Vincent Pallotti Hospitals, Cape Town

*Topical vaginal oestrogen cream has been used for decades in the treatment of post-menopausal women with stress urinary incontinence (SUI). This practice has been based on common sense and intuition rather than good evidence. We know that oestrogen plays an important role in the function of the genital and lower urinary tract and oestrogen receptors have been clearly demonstrated in the bladder, urethra, vagina and even the muscles of the pelvic floor.*

1 Iosif et al observed that up to 70% of women relate the onset of their stress incontinence symptoms to the cessation of menses at menopause. Logically, this is associated with a profound reduction in oestrogen levels and hence the ongoing hypothesis that oestrogen replacement may be a useful therapeutic option for stress incontinence.

SUI is a common clinical problem, with a prevalence in women of up to 35%. It is essential to remember that many menopausal women may present with another important cause of urinary leakage rather than SUI. This could be urgency urinary incontinence or mixed urinary incontinence, which is a combination of stress and urgency related leakage. For the purposes of this discussion, we will focus on the role of topical estrogen in stress incontinence.

The management of women with SUI was revolutionised by the invention of the tension-free vaginal tape (TVT) in the late 1990’s. This was followed by the introduction of the transobturator tape (TOT) and most recently the single-incision or mini-slings. It has been reassuring to see numerous studies showing excellent continence outcomes, in excess of 85%, with these devices. While the TVT and TOT are short and minimally invasive surgical procedures, they are occasionally associated with significant complications. These include voiding dysfunction, bladder injury, haematoma and chronic groin pain. Less invasive or non-surgical options therefore remain attractive. Current options include pelvic floor exercises, continence pessaries and possibly local oestrogen cream.

Local oestrogen therapy for stress incontinence is an attractive option for a number of reasons. It is inexpensive, has relatively few adverse effects, and is widely available. It is also easy to use in elderly patients, does not require specialised skill or training and may be an excellent option in incontinence of a milder severity.

It is easier to understand why oestrogen therapy may be a useful in the treatment of SUI when one looks a little closer at the vaginal epithelial skin physiology. Fibroblasts in the vaginal epithelium are one of the main sources of local collagen, producing mainly types I and III. It is important to note that these fibroblasts have both oestrogen and androgen receptors.

After menopause, when there is less oestrogen in the body, skin obviously becomes thinner and trailer. Versi and Cardozo, in and old study in 1998, quantified this and found the collagen content to decrease by 2.1% every post-menopausal year. Falconer et al also showed that in the first five post-menopausal years, collagen types I and III decrease by 30%. This may be due to lower amounts of soluble collagen and a slower turnover and collagen synthesis in postmenopausal tissue.

With age, the collagen fibres have also been shown to become thick and grouped together resulting in weaker connective tissues. Interestingly, matrix metalloproteins 1 and 9 also increase the synthesis of collagenases and gelatinases, the enzymes that break down collagen, and these are more present in postmenopausal skin. This, in turn, results in less collagen synthesis and increased collagen degradation with eventual alteration in collagen forms, resulting in connective tissue with impaired elasticity. Most importantly, there is good data to show that local oestrogen replacement can reverse the physiological changes in tissue.

It makes physiological sense then that post-menopausal oestrogen therapy may be useful in women with SUI, but is there any clinical data to support its use in day-to-day practice? The main finding of the Cochrane review on oestrogen for urinary incontinence in women was that there were proven benefits for the symptoms of urgency urinary incontinence. They also concluded, however, that local oestrogen therapy may have a positive effect on stress incontinence. The authors did qualify this saying that the data came from small trials and the interpretation of the articles was complicated by major differences in trials. There were also large variations in type and dose of oestrogen, the route of administration, type of incontinence and types of populations in studies on SUI.

One of the major issues in the Cochrane review was a discrepant worsening of stress incontinence symptoms in those women receiving systemic treatment oestrogen therapy. The reasons for this negative effect on SUI associated with the systemic compound compared to a positive effect of the local treatment may be explained by the different physiological effects of local
versus systemic treatments. Edwall et al have shown a reduction in the total collagen in post-menopausal women receiving systemic therapy.\(^8\) Other authors have shown an increase in collagen turn-over markers and a decrease in collagen cross-linking in women on systemic therapy.\(^9,10\) This combination of effects may lead to a reduction in bladder neck support in women on systemic therapy and predispose to SUI. The local administration of oestrogen may have an alternative effect since it is able to more easily target the peri-urethral tissues and improve the mucosal seal, which has been shown to play a role in continence.\(^11\) In addition, the effects of local oestrogen therapy on symptoms of vaginal atrophy are undisputed\(^12\) and no doubt play an important role in this group of women. The subjective improvements in symptoms related to stress incontinence may therefore be associated with improvement in vaginal discomfort relating to the treatment of vaginal atrophy.

A recent systematic review on local oestrogen treatment for pelvic floor disorders by Weber et al\(^13\) included 17 eligible studies looking at local oestrogen therapy for urinary incontinence. The Cochrane review that was published in 2012 only included 10 trials. Weber’s review included a total of 3100 participants with treatment ranging from 3 weeks to 12 months. Overall, they found that subjective, objective and urodynamic variables changed in favour of the vaginal oestrogen groups compared to placebo. Interestingly, they found that at urodynamics, maximal urethral closure pressure was greatest in women receiving local oestrogen treatment compared to pelvic floor exercises or electrostimulation.

There is clearly more work to be done to clarify the dose, duration and extent of the effect of local oestrogen on SUI. The South African Menopause Society has been proactive in funding two recent studies that are attempting to answer these questions. One of these was a recently published prospective multi-centre study that was performed in three cities, including Cape Town, Sydney, and Amsterdam.\(^14\) Postmenopausal women with SUI were treated with topical oestriol cream for 6 weeks with the primary subjective outcome of the Patient’s Global Impression of Improvement (PGI-I) scale. The primary objective outcome was vaginal pH. Of the 68 women that were enrolled, half reported improvement on the PGI-I scale and vaginal pH was significantly lower after treatment. No statistically significant differences were found in the other subjective or objective outcomes in this study looking at local oestriol treatment over 6 weeks.

We believe that the duration of treatment of local estrogen therapy may have a significant impact on the outcomes. Therefore, in Cape Town only, a new group of women have been recruited using the same criteria and outcome measures, but with a treatment length of three months. On analysis of this as yet unpublished data [De Nie and Jeffery, personal communication], the longer therapy appears to have had a positive impact on the symptoms on the small number of women recruited. A total of 16 patients were included in this study with 75% of the participants reporting improvement in symptoms on the PGI-I Scale after twelve weeks of treatment. Statistically significant subjective improvements were also found in multiple parameters including the ICIQ-U SF (p=0.0015), IIQ-7 (p=0.000018), UDI-6 (p=0.000216) and Most Bothersome Symptom (p=0.000024). The cough stress test showed a significant reduction with a median reduction in urine loss from 8.6 grams pretreatment to 2.3 grams three months later (p=0.001) Compliance was high with a median of 100%.

Local oestrogen therapy is a safe, inexpensive, non-invasive and widely accessible potential treatment option for SUI in women. The amount of good quality data to support its use in treating women with SUI appears to be growing. The main questions that require answering include dose, type and duration of therapy. An adequately-powered multicentre, placebo-controlled trial is required. This will be of great value in further proving the benefit of this conservative treatment for SUI in postmenopausal women.

References

8. Edwall L, Carlstrom K, Jonasson AF (2007) Endocrine status and markers of collagen synthesis and degradation in serum and urogenital tissue from


Mid-life black South African women appear to have scant knowledge of health risks possibly associated with the menopause transition (MT). Nearly 80% of these women have very little access to gynaecologists and health-care professionals, almost no knowledge of menopause, and generally attend inadequately equipped satellite clinics, understaffed by primary healthcare nurses, who are poorly trained. It appears that these women are a high-risk group for non-communicable diseases, which may be an effect of chronological or reproductive aging, or both. There appear to be no studies addressing the physiological, psychological, psychosocial aspects or health risks of the menopause transition in this group of women. In addition, the manner in which the MT seems to be addressed in many black communities, and lack of information from public health care providers, adds to the opaque nature of the subject.

Almost 80% of women in South Africa are black. In 2013, their life expectancy rose to 61.4 years from 55.2 in 2002. A recent South African National Health and Nutrition Examination Survey (SANHANES) study confirmed that the reported rate of all non-communicable diseases (NCDs) tended to increase with age. The World Health Organization (WHO) estimates that by 2030, 76% of postmenopausal women will live in resource-limited countries. Research shows the MT is accompanied by clear physiological changes, some temporary and others long term, including body composition changes, especially increased abdominal obesity. These changes may increase risk for metabolic syndrome.

The Study of Women Entering and in Endocrine Transition (SWEET) was developed to examine changes in metabolic, hormonal and anthropometric parameters in black urban South African women across the MT. Obesity is widely prevalent amongst mid-life, black South African women and SWEET participants show a high rate of obesity at menopause (68%), but there are few studies analysing the relationship between obesity and the MT in this population.

Studies have found that black African women were more likely to be obese than men, and had multiple risk factors for heart disease including obesity and metabolic syndrome. However, the mid-life women in these studies had not been staged for menopause, so there was little understanding as to whether the MT transition might be related to their health risks, although Western data show a connection between changes during the MT and metabolic syndrome. Vasomotor symptoms (VMS) are a defining characteristic of the MT and research on Western women shows a strong correlation between obesity and increased risk for VMS, and VMS has been linked to an increased risk of cardiovascular disease, but again there appear to be no data on obesity and its effect on the prevalence of vasomotor symptoms in African mid-life women.

There is also very little research accurately staging ovarian aging or determining age at final menstrual period (FMP) in this group of women. Developing countries may not have resources for wide use of blood assays for accurately staging menopause, so it is difficult to determine the overall effect of the MT on health risks in such populations. The high prevalence of diabetes and metabolic syndrome in midlife urban African women has largely been attributed to obesity, but given the strong association between MT and changes in BFD and lean muscle mass reported in non-African populations, the MT may also play a role.

Aims

This article will only describe three of the research questions examined in the study. These are:
1. an exploration of an accurate and reliable method to stage the MT in African women,
2. an examination of body composition changes across MT stages and
3. an investigation of the prevalence and determinants of VMS across the MT.

Methods

The women in SWEET are the biological mothers of children in the Birth to Twenty cohort (BT20), the longest running, longitudinal birth cohort study in Africa. Data for this cross-sectional study was collected over a period of two years. There has been relatively low attrition of the participants and 2,200 mothers of these children are still in contact with the study. Black urban South African women between the ages of 40 to 60 years were randomly recruited from that group. A convenience sample of 902 women was taken, this being the maximum number of women that could be contacted within the timeframe and infrastructural limits of the study, and 200 of those approached were unable to participate, therefore 702 took part.
Bleeding patterns remain the most important criteria in determining reproductive aging. The Stages of Reproductive Aging Workshop + 10 (STRAW + 10) guidelines, which uses internationally recognised criteria for staging reproductive aging, and which were developed by experts in the field,10 were used to determine ovarian aging using bleeding patterns. Follicle-stimulating hormone (FSH) and estradiol (E2) were ascertainment and used as supportive criteria to verify staging accuracy. The 7 stages of ovarian aging are: late reproductive (-3b, -3a); early menopausal transition (-2); late menopausal transition (-1); early postmenopause (+1a, +1b, +1c) and late postmenopause (stage +2). Early and late menopausal transition stages and late postmenopausal stages were combined for the analysis.

Close–ended questions were asked about bleeding patterns to determine MT stage, and these were followed by open-ended questions to clarify menstrual cycle information. Hormone therapy (HT) and contraceptive use were determined, and information on hysterectomy and oophorectomy obtained. Questionnaires were administered in English but where necessary, team members, whose first language corresponded with that of the participant, were trained to translate. The questionnaire included questions on menstrual history, general health and medication, understanding of menopause, educational level, employment and tobacco use including smokeless tobacco use.

Measurements of blood pressure, weight, height, waist and hip circumference were taken, and BMI was calculated. Dual-energy X-ray absorptiometry (DXA) was used to measure fat mass, lean mass, bone mineral density (BMD) and bone mineral content (BMC). Ultrasonography was used to measure abdominal visceral and subcutaneous fat.

A single interviewer administered the internationally validated Menopause Rating Scale (MRS),14 and the prevalence and severity of symptoms, including VMS, were determined, and information on hysterectomy and oophorectomy obtained. A voluntary HIV antibody test was offered to all participants using whole blood collected from a finger prick. If the test was positive, the participant was referred to a local HIV clinic for confirmatory testing. If the test was positive, the participant was referred to a local HIV clinic for confirmatory serological testing, CD4 count and management.

Results

Mean age was 49.2 years with a mean BMI of 33.4, and obesity prevalence of 67.8%. Mean waist circumference was 99.1cms. Only 30% of participants finished high school with or without higher education. The employment level was 57%. Amongst the participants, 404 knew or agreed to have their HIV status measured and 21.3% were HIV positive of whom 55.3% were receiving antiretroviral therapy (ART). Nearly 21% were snuff users and 8.0% of the participants described themselves as previous or current smokers. With regard to menopausal symptoms, 60.1% of the women had vasomotor symptoms (VMS), while 61.7% were experiencing sleep problems.

Menopausal stage was not determined in 112 women due to hysterectomy and contraceptive use. As expected, levels of FSH rose while levels of E2 fell across the MT stages (Table 1).

Risk of VMS peaked at the early postmenopausal transition stages and this increased risk for VMS was attenuated after adjusting for FSH levels (Table 2). The late reproductive group was used as a reference. No significant difference in the prevalence of any of the menopause symptoms was noted between HIV-negative women (n=318) and HIV-positive women receiving antiretroviral treatment (n=47) or not receiving antiretroviral treatment. However, owing to the low number of HIV-positive women, it is possible the study had insufficient power to detect differences in prevalence.

Table 1: FSH and E2 concentrations across menopausal stages

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Menopausal stages (from STRAW+10)</th>
<th>P-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (pmol/L)</td>
<td>-3b &amp; -3a (369)</td>
<td>-2 &amp; -1 (362)</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>7.55 (7.80)</td>
<td>26.2 (52.4)</td>
</tr>
</tbody>
</table>

Data expressed as median (IQR); FSH = follicle stimulating hormone and E2 = estradiol.

Table 2: Logistic regression showing effects of menopausal stage on VMS risk with and without adjustment for FSH

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variable with unadjusted OR (95% CIs); p-value</th>
<th>Adjusted OR (95% CIs); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VasoMOT symptoms</td>
<td>Stage -2 &amp; -1: 1.43 (0.90, 2.28); 0.13</td>
<td>1.22 (0.73, 2.03); 0.44</td>
</tr>
<tr>
<td></td>
<td>Stage +1a, b, c: 1.80 (1.15, 2.81); 0.01</td>
<td>1.12 (0.64, 1.95); 0.68</td>
</tr>
<tr>
<td></td>
<td>Stage +2: 1.13 (0.72, 1.77); 0.59</td>
<td>0.74 (0.41, 1.35); 0.33</td>
</tr>
<tr>
<td></td>
<td>FSH: - - - -</td>
<td>1.01 (1.00, 1.02); 0.02</td>
</tr>
</tbody>
</table>

Stages are as follows: early and late menopausal transition (-2 & -1), early postmenopause (+1a, +1b, +1c), late postmenopause (+2); the reference group is late reproductive (-3b, -3a); the model was adjusted for the following possible confounders, one at a time: estradiol, FSH, BMI and age. Only the model in which an adjustment for FSH affected the outcomes is shown.
There was a tendency for BMI to fall with progression across the MT. Lean mass measures, at all body sites, arm, leg, and trunk, fell significantly across the MT, an effect that was related to rising FSH levels (FSH correlated negatively with total lean mass) (Table 3). There was a strong negative relationship of total body fat mass and total BMC with ART use (Table 3). Whole body BMD fell significantly across the MT and this trend was related to the falling levels of E2 across the MT. In addition, whole body BMC was significantly reduced in women who used snuff when compared to those who did not (Table 3).

Discussion

This study demonstrated that STRAW + 10 criteria were reliable for staging ovarian aging. There was a strong association of MT stage with FSH, E2 and age.

As expected, VMS were strongly associated with the early postmenopause stages, and with increased levels of FSH. The prevalence of VMS in SWEET participants was higher in the late reproductive stage than in some studies using MRS to determine prevalence. This may be explained by cultural differences in the way women describe and perceive hot flushes, as demonstrated in a previous study.

The study demonstrated significant relationships between hormone levels and body composition across the MT. Lean mass fell across the MT stages and appears to be strongly associated with the rising FSH levels.

ART use was associated with lower total fat, as shown in a recent systematic review, where ART was associated with lipoatrophy. The use of ART was also associated with lower BMC and previous studies have also observed a similar association.

There was a non-significant tendency for BMI to become lower across the menopause transition in the cohort, although in many other studies BMI increases across the MT. No relationship was seen between lower levels of E2 and BMI which was well described in a comprehensive review of the literature. This requires further detailed investigation as there may be ethnic differences in the response of adipose tissue to the changing metabolic and hormonal milieu characteristic of the MT. BMD became lower across the MT stages and was associated with the lower E2 levels with progression through the MT. This association has been well documented in other studies. Snuff use was associated with a lower BMD and higher visceral fat, and it is of note that nicotine levels in snuff brands preferred by South African women are stronger than brands in other countries.

A limitation of the study was that it was cross-sectional. In addition, when staging MT using STRAW+10 it was found that bleeding pattern definitions as described therein are technically complicated and participants in the pilot study found the terminology difficult to understand. Therefore, menstrual history and bleeding change-related questions used in the final questionnaire were modified into more basic and open-ended questions to clarify responses. More than two thirds of the participants had very low educational levels, and nearly half of the cohort did not understand the meaning of the term menopause, but participants gave reasonably precise information about bleeding pattern changes, so reproductive aging could be staged using STRAW + 10 criteria.

Staging was confirmed using FSH and E2 trends. Serum samples could not be collected in premenopausal women during the follicular stage of the menstrual cycle (days 2-5), but since ovarian function becomes progressively more dysfunctional in later reproductive and early menopause transition stages, making it more difficult to determine the follicular stage, it was felt that timing of E2 assessment might become less important. In spite of the fact that a timed serum sample was not obtained, the early stages of the MT were characterised by much higher levels of E2 and much lower levels of FSH than observed in women in the early and late postmenopausal stages. Strengths of the study are the large sample number and accurate determination of menopause status. Further positive aspects of this investigation are the wide variety of serum levels of relevant hormones measured, as well as a wide breadth of anthropometric and demographic variables, within a menopausal population group for which no such data were previously available.

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**Table 3: Multivariate regression models for anthropometric measures**

<table>
<thead>
<tr>
<th>Model</th>
<th>Dependent variable</th>
<th>Independent variable with unstandardised β (p-value)</th>
<th>Adjusted R² (p-value) for full model</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Total fat mass (kg)</td>
<td>Use of ART</td>
<td>-3.06 (0.005)</td>
</tr>
<tr>
<td>2</td>
<td>Total lean mass (kg)</td>
<td>FSH (log)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Total BMC (mg/cm²)</td>
<td>Estradiol (log)</td>
<td>20.0 (0.002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage +1a, 1b, 1c</td>
<td>-20.2 (0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage +2</td>
<td>-37.9 (&lt;0.0005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Take snuff</td>
<td>-14.6 (0.04)</td>
</tr>
</tbody>
</table>

Variable coding: employed were compared to unemployed subjects; those who used snuff were compared against those who did not and subjects who used ART were compared with those who were ART naïve; subjects who attended but did not graduate and subjects who graduated high school were compared with those who did not attend; for menopausal stages, stage -3b with -3a was used as the reference group.
Conclusion

STRAW+10 is appropriate for staging menopause in resource-limited countries using information on self-reported bleeding criteria, but validated interviewer questions and simplification of technical terms to improve accuracy are needed. VMS are significantly related to menopausal stage, peaking in the early postmenopausal period. As expected, FSH levels affect the prevalence of VMS across the menopausal stages.

The principal body composition outcomes observed in this study were lower lean mass and BMD in post than in premenopausal women. Lower lean and bone mass in the postmenopausal groups may be related to higher levels of FSH and lower levels of E2, respectively. ART was associated with lower body adiposity whilst snuff use was associated with lower BMD, but higher levels of visceral fat. Both physiological and environmental factors appear to modulate body composition during the MT in this population group. This research has implications for the use of behavioural interventions to lower morbidity and mortality in this population group. Exercise programmes to help maintain lean mass and reduce adiposity and an education campaign to highlight health changes during menopause and to explain the health risks associated with snuff use may be beneficial. In addition, recommendations for the use of ART regimens with a more bone sparing effect may be considered.

Acknowledgements

Professor Nigel Crowther, Professor Shane Norris, Ms. Tracy Snyman, Dr Marketa Toman, the staff of the MRC/Wits Developmental Pathways for Health Research Unit, Department of Pediatrics, Faculty of Health Sciences, the National Health Laboratory Service and University of the Witwatersrand, for assistance with data collection. This study was funded by grants from the Medical Research Council of South Africa (MRC), the National Health Laboratory Service (NHLS), the University of the Witwatersrand Iris Ellen Hodges Cardiovascular Research Trust and the National Research Foundation (NRF) of South Africa. BT20 is funded by the Wellcome Trust.

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12


Prostate cancer is a common disease with a variety of available management strategies. Due to the prolonged course of the disease and, often, the advanced age of those afflicted, it is essential to select a management strategy which optimises survival while limiting treatment-related morbidity. The following article seeks to discuss the diagnosis of the disease and the complications of treatment which affect clinical decision-making in this disease.

**Warning signs**

Prostate cancer is asymptomatic in early stages. Patients often present with symptoms of benign prostatic enlargement and on investigation of the benign condition are diagnosed with prostate cancer. Advanced prostate cancer may present with urinary symptoms similar to benign prostatic enlargement. Poor urinary stream, dysuria, frequency of urination, incomplete emptying of the bladder at urination, nocturia and urgency may occur. In advanced cancer, metastases may cause bone pain (especially in the pelvis and lumbar spine), lymphadenopathy and weight loss.

**Diagnosis**

Screening for prostate cancer is a controversial topic since multiple large studies failed to show that screening improved prostate cancer survival. Currently an individual risk-adapted screening strategy is recommended with careful counselling prior to screening. As prostate cancer has a long disease course, patients with a life-expectancy of less than 15 years are unlikely to benefit from the improved survival gained from early treatment of prostate cancer. The anxiety caused by a cancer diagnosis in a patient unfit for radical therapy should not be underestimated.

Prostate biopsy is also not without complications. Patients with multiple co-morbidities are more likely to encounter the complications of prostate biopsy. Therefore, biopsy should be considered with caution in patients who are unlikely to benefit from treatment if a diagnosis is made. The increase in drug resistant infections following prostate biopsy is of particular concern. Patients who have been treated with ciprofloxacin may harbour ciprofloxacin-resistant bowel flora for months thereafter, limiting its usefulness for biopsy prophylaxis and increasing the risk of sepsis post-biopsy.

If the decision to screen a patient is made it should include a digital rectal examination and a prostate specific antigen measurement.

**Imaging**

Multi-parametric MRI (MP-MRI) has emerged as an extremely helpful tool in prostate cancer. Multi-parametric MRI includes standard anatomical imaging and functional parameters (e.g. dynamic contrast imaging, diffusion-weighted imaging or spectroscopy). It can aid greatly in the diagnosis in patients with multiple negative biopsies to direct subsequent biopsies.

MRI can also be used as a staging tool which can assist in selecting treatment modality. It can be used to identify candidates for nerve sparing prostatectomy. Patients who have had nerve-sparing surgery have been shown to have better post prostatectomy erectile function and continence rates. Although MRI before biopsy has become “standard of care” in some units, it is not recommended for all patients.

MRI/US fusion biopsy is being explored to improve diagnostic accuracy of standard ultrasound guided prostate biopsy. MRI-compatible needle biopsy systems and fully automated MRI-biopsy systems may offer an alternative in future to assist with more accurate biopsies in patients who have had previous negative biopsies.

**Treatment and related impact on quality of life**

**Deferred treatment strategies**

Due to the prolonged disease course in prostate cancer, men with a life expectancy of less than 10 years are not eligible for local curative treatment. A “watchful waiting” strategy can be offered to these patients. This strategy aims to defer treatment until symptomatic progression of prostate cancer thereby delaying the onset of treatment related complications and consequent reductions in quality of life.

Active surveillance is another deferred treatment option which can be offered to appropriately-selected, low risk patients who are candidates for curative therapy. This strategy defers curative treatment until disease progression, thereby postponing the onset of treatment related morbidity. It is a safe strategy with similar oncological outcomes to initial treatment of the cancer. General anxiety and fear of progression may have a significant impact on quality of life in patients on both of...
these deferred treatment strategies. This anxiety seems to be less for patients with favourable clinical parameters and improves after prolonged surveillance.

**Radical prostatectomy**

Low risk prostate cancer can be managed with active surveillance, radical surgery or radiotherapy (external beam or low-dose rate brachytherapy). As oncological outcomes are similar for these treatments, careful discussion with patients is necessary to identify the treatment option with the most acceptable side effect profile.

There appears to be little difference in functional and oncological outcomes between the surgical options (open, laparoscopic and robotic) available.

Although it was hoped that improved vision and precision offered by robotic assisted radical prostatectomy would improve functional and oncological outcomes, there is not much evidence to support this yet.

Radical prostatectomy has a significant impact on urinary continence rates and sexual dysfunction with a great variation in reported rates of these complications. Recovery occurs over 1-2 years with urinary incontinence being worst in the 2 months following surgery. High case volume surgeons seem to achieve better oncological and functional outcomes.

There is an increased risk for incontinence with increasing age which needs to be considered in the selection of treatment modality in older patients.

Although incontinence and erectile dysfunction are mentioned as the two most common complications following surgery, there are numerous other complications which may occur. In a large America study it was reported that 55% of patients had other complications (besides incontinence and erectile dysfunction) after radical treatment for prostate cancer (radiotherapy or surgery) at mean follow up of 5.6 years. Although most of the complications occurred within the first two years they continued to occur at a steady rate up to 10 years. These included procedures for bladder neck contractures, urethral strictures, other surgical complications and rectal bleeding.

**External beam radiotherapy (EBRT) and low dose rate (LDR) brachytherapy**

Brachytherapy uses real-time ultrasound guidance to permanently implant radio-active seeds into the prostate. It is a popular treatment choice in South Africa which, for low risk prostate cancer, has comparable oncologic outcomes to radical surgery and external beam radiotherapy.

Both EBRT and LDR brachytherapy have urinary, gastrointestinal and sexual complications. Urinary frequency and dysuria encountered acutely usually improve after treatment. LDR brachytherapy has a higher incidence of obstructive urinary symptoms than EBRT. Although use of prophylactic alpha-blockers may improve urinary morbidity, transurethral resection of the prostate (TURP) may still be necessary. Prostate volume and pre-existing urinary symptoms should therefore be carefully considered before selecting this treatment modality.

Bowel and rectal symptoms such as rectal urgency, frequency, pain, faecal incontinence and haematochezia occur acutely after radiotherapy but may persist chronically. These gastro-intestinal complications are less severe after LDR brachytherapy than EBRT.

**Androgen deprivation therapy**

Androgen deprivation therapy (ADT) is used as first line management for symptomatic metastatic prostate cancer. Chemotherapy is usually reserved for metastatic castrate resistant prostate cancer (CRPC) when ADT is no longer effective. Androgen deprivation has numerous complications including sexual dysfunction, hot flushes, osteoporosis, metabolic syndrome and fatigue.

**Hot flushes**

Hot flushes are a common and bothersome complication of ADT. Oestrogen and progesterone-based therapies are effective. However, both have significant cardiovascular complications. Serotonin re-uptake inhibitors may also be used but are not as effective as hormonal therapy.

**Osteoporosis**

Lifestyle changes, calcium and vitamin D supplementation are recommended for patients receiving ADT. Bisphosphonates and denosumab, used to reduce skeletal related events in metastatic prostate cancer, have both been shown to reduce fracture risk and improve bone mineral density (BMD) in non-metastatic prostate cancer.

**Metabolic syndrome**

Metabolic syndrome and the associated cardiovascular morbidity are significant contributors to non-prostate cancer related deaths in prostate cancer patients. Exercise and lifestyle management are recommended to reduce these risks.

**Fatigue**

Although anaemia is a common cause which needs to be excluded, fatigue unrelated to anaemia is a common complication of ADT. A recent, phase 2, randomised trial has confirmed the benefit of methylphenidate (Ritalin ®) for fatigue related to ADT.
**New developments**

Docetaxel chemotherapy was previously the first line option for metastatic castrate resistant prostate cancer (CRPC). Abiraterone and enzalutamide are two new drugs which manipulate the endocrine axis which have shown improvements in overall survival in metastatic castrate resistant prostate cancer. Both of these drugs are recommended for patients with a good performance status and minimal symptoms. They combine the convenience of oral treatment and have less severe side effects than chemotherapy. These are but two of numerous new therapeutic options for CRPC.

Second-line chemotherapeutic options have become available and new evidence suggests that up-front chemotherapy with initial ADT confers a survival benefit.

The identification of multiple genetic, epigenetic and protein markers provides hope that in future we will be able to accurately distinguish patients who require aggressive management from those who are unlikely to progress.

**References**

There are many women who may not or who will not consider taking menopausal hormone therapy (MHT) for peri- and post-menopausal symptoms, such as vaso-motor symptoms (VMS). It is therefore necessary to have strategies to not only help these women with their VMS, but also with other conditions, which might be associated with the post-menopausal and ageing process.

Prior to discussion on alternative preparations for the use of MHT, it is prudent to tabulate the conditions in which oestrogen should not be used. If one or more of these pathologies exist, then it is necessary to use alternative non-hormonal therapies.

**Table 1. Contraindications to the use of menopausal hormone therapy**

- Breast Cancer: present or past history
- Porphyria
- Thromboembolic disease
- Active liver disease
- Undiagnosed vaginal bleeding
- Endometrial cancer: depending on stage and grade in consultation with gynaecological oncologist
- Endometriosis: despite the removal of the uterus in pelvic endometriosis it is prudent to add progesterone to estrogen therapy, especially in the first 1 to 2 years
- Current coronary artery disease
- Liver disease
  Severe active liver disease is a contra-indication, as most forms of MHT are metabolised in the liver.

**Thromboembolic disease**
Oral oestrogen should not be used in the presence of thrombo-embolic disease with the associated risk of pulmonary embolism. There is however growing evidence that transdermal oestrogen might not carry any risk of deep vein thrombosis and embolism but this should probably be discussed with the consulting physician.

**Abnormal vaginal bleeding**
Undiagnosed vaginal bleeding should be investigated before the initiation of MHT.

**Previous endometriosis**
It is probably prudent to consider using progesterone together with oestrogen in women who might have residual endometriosis, following removal of their uterus, certainly for the first 1-2 years.

**Coronary Artery Disease**
A number of studies have shown that people with abnormal coronary arteries are at risk of cardiac events in the first 1-2 years after initiating MHT.

**NON HORMONAL MANAGEMENT OF VASO-MOTOR SYMPTOMS**

**Lifestyle changes**
Many lifestyle changes have been recommended, none of them would be considered to do any harm, but few have consistently demonstrated a significant improvement in vaso-motor symptoms in clinical trials.

**Weight loss**
It would seem that weight loss might lead to a significant improvement in VMS.

**Avoiding triggers**
Avoiding hot drinks, spicy foods and alcohol might be
beneficial for some women, but clinical trials have not confirmed this.

**Cooling techniques**

Dressing in layers, avoiding hot indoor interiors and overheated shopping malls and the use of other cooling techniques such as fans, once again seem to benefit some people. However, no clinical trial evidence supports this. This does not mean however that it is necessarily a waste of time to give women this advice.

**Exercise**

Exercise is of course always beneficial, but clinical evidence as to the efficacy of exercising in reducing VMS is mixed.

**Yoga**

There is no clinical evidence that yoga improves VMS, but it does tend to improve a woman’s sense of wellbeing.

**Mind and body techniques**

Cognitive behavioural therapy, mindfulness based stress reduction, paced respiration and relaxation have shown varying benefits in the reduction of VMS. Clinical hypnosis seems to be a promising intervention for reducing VMS.

**Dietary management and supplements**

The use of soy foods and soy extracts is being extensively investigated. Some of the more recent blinded clinical trials have not shown a big benefit with the use of soy isoflavonoids when compared with the placebo. The confounding issue when investigating soy and soy extracts, is that only about 30% of North American women are able to metabolise daidzine to equol which is required if one is to see any benefit from this form of intervention.

**Over the counter supplements and herbal therapies**

There are numerous over the counter products and herbal therapies advertised as helpful in treating VMS. There is very little clinical evidence from placebo controlled trials that these are beneficial.

By far the most commonly used plant remedy is Black Kohosh, which should be used with great care in patients who might suffer from any form of liver disorder and certainly not be used in anything more than the recommended dosage.

When advising patients who ask about these herbal and plant remedies, it is safe to say that you can tell them that there is no evidence that these remedies are superior to placebo. This includes Black Kohosh, Wild Yam, Dongguai, Primrose Oil and Flaxeed as well as Ginseng, Hops and Pollen extract.

**PRESCRIPTION THERAPIES**

**Selective serotonin reuptake inhibitors and serotonin nor epinephrine reuptake inhibitors**

There is growing evidence that these two groups of therapies cause significant improvement in menopausal women. The onset of action is quite quick and so can be assessed in a relatively short amount of time. Venlafaxine 75mg per day is probably the most commonly used SSRI in this country, but when using all these medications, care must be taken to follow the warnings in the companies’ pamphlets, being aware of the possibility of interaction with other drugs.

It should be carefully pointed out that paroxetine and fluoxetine both inhibit CYP2D6, which is responsible for metabolising tamoxifen to its active metabolite. The use of paroxetine and fluoxetine should therefore not be used in breast cancer survivors using tamoxifen.

**Gabapeninoids**

There is evidence that gapapentin at 900mg per day increasing to 2400mg per day is beneficial for VMS. This therapy might also be useful for patients suffering from disruptive sleep. However one must be aware of the side effects of drowsiness, dizziness and impaired balance and co-ordination.

**Clonidine**

Clonidine has been used for many years for VMS and has shown a slight benefit over placebo but is less effective than SSRIs SSNRI’s and gabapentin.

**OTHER TREATMENTS**

**Acupuncture**

Acupuncture has not been shown to be beneficial over sham acupuncture.

**Stellate ganglion block**

Stellate ganglion block using bipivocaine into the anterior cervical spine seems to be showing promise in the management of vaso-motor symptoms, although its exact mechanism of action is unknown.

**OTHER CONSIDERATIONS**

**Vulvo-vaginal atrophy/genito urinary syndrome of the menopause**

Prolonged lack of oestrogen will often result in troublesome vaginal, urinary and sexual problems. There are very few
contraindications to the use of vaginal oestrogen in these circumstances, but it is probably wise to discuss with your breast oncologist the use of vaginal oestrogen in breast cancer survivors on aromatase inhibitors as there might be a conflict of opinion between menopause practitioners and oncologists.

There are numerous vaginal moisturisers and lubricants available, which will benefit women with vaginal symptoms who do not want to use oestrogen therapy.

An interesting but as yet under investigated method of treating genito urinary syndrome of the menopause is intra vaginal laser. We look forward to getting more information about this.

**Osteoporosis**

The relationship between the post menopausal status, hormone therapy and osteoporosis is well known. It is important to discuss this matter with all women, perhaps more so those not on MHT.

Advice concerning exercise, diet and calcium intake should be given to these women. Most people have noticed a current controversy concerning calcium supplementation. It remains necessary for a post menopausal woman to receive 1200mg of calcium per day. The best source of this calcium is from her diet.

There is now a very useful app available on smart phones and Ipads, called the calcium calculator by the IOF (International Osteoporosis Foundation). This allows each individual to work out how much calcium they are getting in their diet per day and topping up to the necessary 1200mg if they are getting insufficient.

The exact dose of Vitamin D supplementation is uncertain and should probably be individualised to each patient.

The prudent use of bone density measurement should be considered and intervention with bone specific drugs instituted if necessary.

**Cardiovascular disease**

It is imperative that any practitioner dealing with women in midlife and beyond gives them advice concerning the prevention of cardiovascular disease.

Advice concerning healthy exercise and diet is necessary as well as the occasional measurement of her cholesterol, fasting blood sugar and obviously blood pressure checks.

**Take home message**

1. Whereas lifestyle interventions have not been shown to significantly improve the experience of VMS, healthy diet and regular exercise improve a sense of wellbeig and are important in helping prevent other conditions such as cardiovascular disease and osteoporosis.
2. “Natural”, herbal and plant remedies have in general not been shown to outperform placebo in the management of VMS. However, some women might feel that they are helped by these products, but should be informed about safety especially in those products which might have an unopposed oestrogenic effect.
3. SSRI’s, SNRI’s, gabapentin all have good evidence for the treatment of VMS.

**References**

1. Position statement
2. RJ Baber, N Pannay, A Fenton and the IMS writing group 2016 IMS recommendations on women’s midlife health and menopause hormone therapy. Climacteric 2016 Volume 16 No 2, 109-150
Non hormonal menopausal treatments

Most American women use non-hormonal remedies to alleviate their menopausal vaso-motor symptoms (Jacob JAMA 2016;315:14-6). Surveys show up to 80% of women use treatments that are not estrogen or progesterone related and the North American Menopause Society has published a position statement on the topic (http://bit.ly/1PSpzxt).

The following are related to vaso-motor symptoms (VMS) relief and are quoted from the abstract of the NAMS document.

Recommended: cognitive-behavioural therapy and, to a lesser extent, clinical hypnoses have been shown to be effective in reducing VMS. Paroxetine salt is the only nonhormonal medication approved by the US Food and Drug Administration for the management of VMS, although other selective serotonin reuptake/norepinephrine reuptake inhibitors, gabapentinoïds, and clonidine show evidence of efficacy.

Recommend with caution: some therapies that may be beneficial for alleviating VMS are weight loss, mindfulness-based stress reduction, the S-equol derivatives of soy isoflavones, and stellate ganglion block, but additional studies of these therapies are warranted.

Do not recommend at this time: there are negative, insufficient, or inconclusive data suggesting the following should not be recommended as proven therapies for managing VMS: cooling techniques, avoidance of triggers, exercise, yoga, paced respiration, relaxation, over-the-counter supplements and herbal therapies, acupuncture, calibration of neural oscillations, and chiropractic interventions.

Incorporating the available evidence into clinical practice will help ensure that women receive evidence-based recommendations along with appropriate cautions for appropriate and timely management of VMS.

Sex & aging

What determines the quality of your life as you age? This seems a reasonable question given the anticipated increasing longevity in most populations and certainly is of interest to geriatricians and should be to gynaecologists who see older patients. Old age officially begins at age 65 years and an article by Flynn & Gow explores the role of sex in senior citizens with a mean age of 74 years (Age Ageing 2015;44:823-8).

The investigators enquired about participation in sexual behaviours namely touching, embracing, kissing, mutual stroking, masturbating and intercourse and the surveyed participants were asked to judge the perceived importance of these activities. The frequency and importance of these sexual encounters correlated positively with quality-of-life scores in this age group.

It would seem that health in general, and sexual health in particular, remain important factors in relationships and quality-of-life determinants well into old age and should be enquired about in consultations.

Hormones for menopausal symptoms

Often in medicine there is enthusiastic adoption of new drugs or practices followed by the finding of adverse effects, and over-reaction when the intervention is underutilised before sanity prevails and the medication or procedure finds its rightful place clinically.

Hormone therapy around the time of the menopause transition is an example of such an intervention that is now finding its correct place for the treatment of worrisome menopausal symptoms. Using hormones for long-term medication of chronic disorders is still under investigation but targeted treatment with hormones for menopausal symptoms is good medicine.

Two of the original Women’s Health Initiative trial investigators (Manson & Kaunitz NEJM 2016;374:803-6) now make a plea for the judicious use of hormone therapy and state that for those “who have moderate-to-severe vasomotor symptoms, a consensus has emerged that the benefits of hormone therapy are likely to outweigh the risks”. They ask for this message to be transmitted to the profession as they feel the topic is poorly understood by trainees entering the clinical arena.

But who was responsible for the adverse publicity that the Women’s Health Initiative trial generated?

In a fascinating article in the O&G Magazine (the Royal Australian & New Zealand College of O&G’s publication) the whole saga is followed as an example of how not to plan, present, publish and publicise research (Baber O&G Mag 2016;18:21-3).
Points to remember about the trial are:

• The trial was set up by the US National Institute of Health (NIH) and cost $725 million
• The NIH is a governmental organisation that is not obliged to share its data with anyone
• One aspect of the investigation was the randomised trial of hormonal therapy (HT)
• The HT trial was set up to assess hormone use in older women, because there was little information about what to expect if HT was started after 60 years old

This seems an odd field to investigate since most women start HT when they experience symptoms but there was observational evidence that HT protected against heart disease and osteoporosis.

With hindsight it would have been better to start the trial at the menopause transition and keep going in older age provided the outcomes looked promising.

Again, looking back it was unwise to give high doses of estrogens to a large group of women with a mean age of 63 years. Their raised risk of cardiovascular disease was well-known and the predictable happened with an increased number of cardiovascular events.

• The investigators were aware of possible age-related differences in when therapy was initiated and the results were supposed to be reported in age cohorts
• The results were released as a single batch which was in breach of this protocol

The data were due to be presented in women from 50 to 59 years and then separately form 60 years and beyond but the chief investigator is reported to have said “NIH was going for high impact with the goal to shake up the medical establishment and change their thinking about hormones”.

This he set about doing with results that have subsequently been proved premature, indefinite or wrong. The statistics were given out in relative risk format rather than absolute risk which confused reporters and the public. To compound the situation the NIH refused to make the data available to outside academics or the companies that made the drugs. The NIH themselves eventually relooked at the facts and started publishing different outcomes for different age groups. It is likely that non-involved academics would have seen the holes in the methodology years earlier and provided a more balanced picture.

The result of the NIH announcements was an immediate drop in all hormone prescriptions. It has been calculated that following the WHI trial, in the United States alone, 91 000 women died prematurely because of avoidance of estrogen therapy.

Doctors have responded to this “disgraced” therapy by not prescribing HT which for women in their 50s who would have a lower risk of dying compared with those not taking HT. For those taking estrogens alone the reduction in coronary heart disease, the commonest cause of death in this age group, is significantly reduced as is the risk of breast cancer.

Women have instead chosen to use complementary medicines and bio-identical hormones which have neither proven efficacy nor safety.

It is salutary that members of the original investigatory group are now (in 2016) trying to correct the unfortunate set of circumstances begun 15 years ago.

Menopausal “timing hypothesis”

Much of the concern of interpreting hormonal therapy (HT) around the time of the menopause transition and cardiovascular health appears to depend on when HT is initiated. The original observational studies showed clear benefits whereas the randomised trial showed differing results. The observational studies looked at the cardiovascular effects of women using HT for symptoms whereas the randomised trials looked at prevention and the participants were not recently “transitional” but at least a decade postmenopausal.

The timing hypothesis suggests that once the estrogen receptors in the cardiovascular system (CVS) are no longer stimulated by high levels of estrogen, they become refractory and cannot function in a way that is protective against atherosclerosis. On the other hand, if estrogens are started close to the menopause transition, their positive effect could be maintained.

To investigate this hypothesis scientists took 2 groups of healthy women and gave them oral estrogen plus vaginal progesterone or placebo. The difference between the groups was that one group was recently menopausal while the other group was at least 10 years postmenopausal. Both groups were studied in terms of an accepted marker of CVS health, namely carotid-artery intima-media thickness. After 5 years of the trial, those who were started on HT within 5 years of their menopause transition had a slowed deterioration in their artery thickness than those who were started long after their menopause (Hodis et al NEJM 2016;374:1221-31).

This suggests that estrogen receptors are less able to respond to estrogens if there is a long delay between a woman’s menopause and when HT is started. It does not prove that estrogens initiated near the menopause transition prevent CVS events but it does give a biophysical explanation of a mechanism of action for clinical results.
Confirmed International Faculty and topics:

**Prof Pauline Maki (USA)**
- The ageing female brain; a roadmap to success
- Menopause; stress and anxiety

Dr. Pauline M. Maki is Professor of Psychiatry and Psychology at the University of Illinois at Chicago. Dr. Maki’s research over the last 15 years has focused on women’s mental and cognitive health. Dr. Maki received her PhD in experimental psychology from the University of Minnesota in 1994. Dr. Maki is Immediate Past President of the North American Menopause Society (NAMS), a member of the NAMS Board of Trustees, the Chair of the NAMS Research Affairs Committee, and the Director of the NAMS Mentorship Program. She has numerous publications on hormones and cognitive function, won a number of NIH awards for her research and service, serves on executive committees for several women’s health advisory boards, and is a frequent international and national speaker on women’s cognitive health.

**Dr Nick Panay (UK)**
- Menopause, natural selection or modern disease?
- Premature Ovarian Insufficiency (POI) – an International Registry
- Compounded Bio-identical Hormones and the way forward

Dr Nick Panay is a consultant gynaecologist and subspecialist in Reproductive Medicine and Surgery at Queen Charlotte’s & Chelsea Hospital and Chelsea & Westminster Hospital in London as well as Honorary Senior Lecturer at the Imperial College in London. He has a special interest in Reproductive Medicine and Surgery and Menopause and Menstrual Disorders. As director of the West London Menopause and PMS Centre at Queen Charlotte’s & Chelsea & Westminster Hospitals, he heads a busy clinical research team which publicises widely, presents at scientific meetings and trains health professionals at all levels. Much of his teams research has focused on improving the understanding and management of premature menopause, PMS, new HRT preparations and complementary therapies. He is currently the Editor-in-chief of Climacteric (The Journal of the International Menopause Society) and is on the editorial boards of the Journal of Obstetrics and Gynaecology and Journal of Family Planning and Reproductive Healthcare.

**Dr Maria Shapiro (Canada)**
- GSM/VVA: Underestimated, Under diagnosed and Under treated
- Approach to the Ongoing care of the Breast Cancer Survivor

Dr. Shapiro completed medical school at McGill University and trained at the University of Toronto for her Masters of Health Science in Community Health and Epidemiology. She trained in Family Medicine and is certified by the Canadian College of Family Practice. She concluded her specialty training in Preventive Medicine and Public Health, receiving her Fellowship from the Royal College of Physicians and Surgeons of Canada. She holds a Fellowship in Family Medicine and is a North American Menopause Society credentialed menopause specialist and NAMS President Elect.

**Dr Suresh Kumarasamy (Malaysia)**
- Care of the menopausal endometrium
- Menopause Hormone Therapy (MHT) and breast cancer

Dr Suresh Kumarasamy obtained his postgraduate qualifications in Obstetrics and Gynaecology from both the University of Malaya and the Royal College of Obstetricians & Gynaecologists, London. He obtained further sub-speciality training in Gynaecological Oncology at the Northern Regional Gynaecological Oncology Centre, United Kingdom as well as the Department of Cancer Medicine, University of Sydney, Australia. He is a Fellow of the Royal College of Obstetricians and Gynaecologists, London as well as a Fellow ad eundem of the Royal College of Physicians of Ireland. He has an academic appointment as Adjunct Clinical Professor at Penang Medical College. Dr Suresh lectures frequently at national and international meetings in his areas of expertise. He is a council member of the Asian Society of Gynaecological Oncology, Chair of the Gynaecological Oncology Sub-committee and Past President of the Obstetrical & Gynaecological Society of Malaysia and Editorial Advisory Board member of the Journal of Gynaecological Oncology. He is also a member of the Malaysian Menopause Society. He has served on a number of Ministry of Health Malaysia committees and industry global, regional and national advisory boards.

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All enquiries contact Alison on 082 5538201 or info@menopause.co.za
AMS’s ongoing commitment to continuing medical education moves on through 2016.

There will be a number of CME meetings around the country given by your most favourite speakers. The topic for these talks will be about the management of the Peri Menopause.

For many of us, not to mention those women in the menopause transition, this can be a tricky clinical problem. The mere inconsistency of the symptoms from irregular menses to intermittent flushes and sweats, which all threaten to get better and then return are extremely troublesome for many women. Throw in memory dysfunction, tiredness and difficult partners and you can understand a degree of unhappiness!!

Our excellent speakers will help you unravel these issues in such a way that the women you care for will benefit from this shared knowledge.

Plans For SAMS Conference 2016 are in advanced stages (see details on page 21) We have all been students at some stage in our lives and understand the need for tertiary education so that a country can have educated professionals serving the nation. This education should be available to rich and poor alike.

You may ask what this has to do with SAMS 2016. We had hoped to have the SAMS meeting this year at a UCT venue as UCT was the medical school where Prof. Denis Davey and Prof. Wulf Utian started the first Mature Women’s clinic in the world.

As we know the students at universities around the country organized legitimate and acceptable action promoting access of education to the less financially fortunate. Most of us supported them, but unfortunately, non students got involved and caused major disruption and damage to university property. We have been unable to be reassured that the venue we had booked will not be affected in November and have therefore changed to the Double Tree Hilton.

For those of you who attended the UCT Gynaecology Update last year DO NOT BE ALARMED. The UCT team had less than two weeks to make these changes last year. We have had most of the year so that the glitches with parking, access and lecture space will all be perfect.

Look forward to seeing you in November.

Peter Roos.

Comments by the President

South African Menopause Society

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.

Become a SAMS Member today and enjoy the benefits:

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SAMS boasts a multidisciplinary membership of menopause experts from diverse healthcare fields. Join SAMS to keep up to date with developments in this field.

Membership fee is R120 per annum. Contact the SAMS Secretariat at: info@menopause.co.za or call Alison Shaw on 082 5538201 for more details.
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DOSAGE AND DIRECTIONS FOR USE: The recommended dosage is one 70 mg/2800 IU tablet once weekly. The tablet must be taken at least one-half hour before the first food, beverage or medication of the day with plain water only. The patient should not lie down for at least 30 minutes and until after their first food of the day.

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Showed a better vaginal bleeding pattern compared to combined HRT

Showed beneficial effects on bone over a ten year treatment period

HRT = hormone replacement therapy

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References:
2. Data on file, MSD.

Selected Safety Information

Contra-indications: Known or suspected hormone-dependent tumours; Known, past or suspected breast cancer – LIVIFEM® increased the risk of breast cancer recurrence in a placebo-controlled trial known or suspected pregnancy – dependent malignant tumours (e.g. endometrial cancer); local bleeding or worsening uterine bleeding – consistent with national Collaborative Group on Hormonal Replacement Reviews; biliary stenosis. LIVIFEM® should be discontinued per medical advice if the symptoms occur or deteriorate. Females who have undergone total hysterectomy or tubal ligation may continue using LIVIFEM therapy, because of an apparently decreased endometrium due to some estrogen production. Normally such bleeding is of short duration. Bleeding commencing after 3 months of treatment or recurrent or longer duration should be investigated. Periodic examinations must be done for endometrial hyperplasia, as well as para-uterine or vaginal cancer. The higher risk with long-term treatment, especially in women with a history of breast cancer, should be considered. In the absence of a further risk of breast cancer, a history of endometrial hyperplasia, should be reviewed. Conditions which need supervision: If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with LIVIFEM®: premenstrual tension syndrome; endometriosis; leiomyoma (uterine fibroids); malignancy (e.g. breast cancer); a history of endometrial hyperplasia; varicose veins; stroke; migraine.

Selected Side Effects:

Exerted specific effects on the following tissues through its active metabolites: Brain, Genital tract and Bone

Effectively relieved vasomotor symptoms in postmenopausal women

Showed a better improvement on sexual function compared to combined HRT

Had a minimal effect on breast tissue vs. combined HRT

Showed a better vaginal bleeding pattern compared to combined HRT

Showed beneficial effects on bone over a ten year treatment period

HRT = hormone replacement therapy

For full prescribing information refer to the package insert approved by the medicines regulatory authority.

References:
2. Data on file, MSD.