**LIVIFEM® TABLETS.**


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7. Selected Safety Information: Contra-indications: Known or suspected hormone-dependent tumours; Known, past or suspected breast cancer – LIVIFEM® increased the risk of breast cancer incidence in a placebo controlled trial. Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer); History of deep vein thrombosis or pulmonary embolism; Severe liver disease; Immunization with a live virus vaccine, or occupational or other exposure to live virus vaccines (e.g. nurses, dentists, veterinarians, health care workers).

**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
We have moved into 2014, the year of our fifth democratic elections and the editorial committee of Menopause Focus takes this opportunity to wish all its readers a peaceful and prosperous 2014.

We are not able to stop the clock ticking along, and we will all age, although, with the advances in medicine, science and technology, women are likely to live longer and healthier lives than any previous generation.

Even though we cannot stop the sands of time, ageing should not be viewed as an illness, and the entities that come with it should be viewed as challenges and not as setbacks. But no matter how well women cope with the many challenges that come about following the menopause, on many occasions I have been reminded by these patients of the age-old adage “ageing is not for sissies”.

Ageing is rife with emotional instability and does not only include fear of losing one’s independence or getting a serious illness, but it may well be associated with tangible debilitating symptoms.

Recent data suggests that roughly two thirds of women complain of cognitive decline, memory issues and forgetfulness or the development of “brain fogginess” as they age. Peter Roos addresses the evolution of these cognitive changes in ageing women and assesses the value of treatment strategies, including the use of hormone therapy during the “window of opportunity” and life style initiatives of which “mental gymnastics”, playing crossword or suduko puzzles etc. seems to be getting more and more emphasis today.

Ageing brings with it a significant increase in likelihood of cancer, but because of advances in screening and treatment strategies, there is an increasing number of gynaecological cancer survivors who will be significantly debilitated by menopausal symptoms after their treatment.

Be it due to personal perspectives, lack of societal and national guidelines or negative publicity, hormone therapy in these patients is considered detrimental and contraindicated. Franco Guidozzi provides a detailed overview of the evidence published within the English literature and shows that there is very little data to oppose the use of hormone therapy among gynaecological cancer survivors.

For a number of reasons, more and more women are delaying having children until they are beyond 40 years of age. Johannes and Lianne van Waart have written an interesting and well balanced article bringing into the ethos, not only the maternal and fetal risks associated with assisted reproductive strategies in peri- and postmenopausal women, but they have also included the ethical and social considerations as well.

On the one hand, it is impressive that the strategies are so successful in a group of women who have such poor ovarian reserve or a uterine milieu that is so inappropriate for conception, but on the other hand, the social and ethical considerations certainly are food for thought.

Treating menopausal women should not take place in a vacuum, and must encompass a holistic attitude. It is not only about hormone therapy, it must also incorporate life style interventions. Weight gain and distribution of adipose tissue in the ageing woman can be notable for a number of reasons, of which decreased activity and diet may be most important, which may well lead to hyperinsulinaemia, diabetes, hypertension, hypertriglyceridaemia and cardiovascular disease, including ischaemic heart disease, stroke and thrombosis. About 50% of menopausal women will die from cardiovascular disease in the USA.

In his second part of the article entitled Postmenopausal Women’s health, Athol Kent elaborates on the role of exercise, dietary intake, fluid intake, concomitant medications, vaccinations and social habits after the menopause. There is much to be said for a healthy diet, exercising at least three times a week, maintaining a BMI < 25, not smoking, drinking plenty of non-alcoholic fluids and keeping an active mind in coping with the menopause. As mentioned earlier, the concept of “mental gymnastics” is receiving more and more attention today.

The final article does not specifically allude to menopausal matters, but addresses an important component of practice which is important. HPCSA is definitely receiving more and more complaints of fraudulent claims and of questionable practice strategies from patients, public at large and medical aids.

Interestingly, a number of practitioners have unfortunately required disciplinarian measures to curb irresponsible and unethical business practices. In this article, Yolande Guidozzi provides a concise overview of desirable business practice and the doctrines that HPCSA have implemented to ensure ethical and appropriate practice in South Africa.

I hope you enjoy reading this edition of Menopause Focus and that you find it enjoyable.
Menopause and cognition

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There has been much written recently about the “window of opportunity”. This theory, also known as the “critical window hypothesis”, suggests that hormone replacement therapy given for vaso-motor symptoms around the perimenopause and in the first 10 years after the final menstrual period may cause a reduction in heart disease and improve cognitive dysfunction later in life. Bone benefits have long been known to exist with hormone therapy.

There are other “windows of opportunity”, probably even more important. These windows are every consultation with midlife women when general health measures, which may modify or reduce the risk of dementia, can be discussed.

Epidemiological studies have shown that women are at a 1.54 increased risk of dementia and Alzheimer’s disease later in life, as compared to men. This information has led to extensive investigation about the effect of oestrogen on the brain and the possible loss of oestrogen in the post menopausal women, being partially causative in the onset and severity of Alzheimer’s disease and other forms of cognitive dysfunction.

Current terminology around abnormalities of cognition include the following:
• Mild cognitive impairment
• Vascular cognitive impairment
• Alzheimer’s disease
• Vascular dementia

The term “all cause dementia” is frequently used, where distinction between Alzheimer’s disease and vascular dementia has not been made. The reason for this is that, until recently, there have been few diagnostic tests for Alzheimer’s disease, which as described by Dr Alzheimer in 1906 consists of the presence of Beta amyloid plaques and neurofibrillary tangles in the brain. This could only be diagnosed by histological examination of the brain in the past.

Ten warning signs of Alzheimer’s
1. Memory loss that disrupts daily life
2. Challenges in planning or solving problems
3. Difficulty completing familiar tasks at home, at work or at leisure
4. Confusion with time or place
5. Trouble understanding visual images and spatial relationships
6. New problems with words in speaking or writing
7. Misplacing things and losing the ability to retrace steps
8. Decreased or poor judgement
9. Withdrawal from work or social activities
10. Changes in mood and personality

These warning signs are obtained from the Alzheimer’s Association website “Know the 10 Signs”, where you will find a more extensive description of these warning signs as well as a comparison with the typical changes of normal ageing.

It is important to recognise that there might be a progression from mild cognitive impairment to dementia or Alzheimer’s disease. It is equally important to recognise that mild cognitive impairment will not always lead to dementia and that memory problems can in fact be a part of natural ageing. It is when a person loses the ability to function normally, either in the workplace or their social environment that the diagnosis of dementia should be made.

The extent of the problem
In the United States, the death rate from various conditions such as heart disease, breast cancer and HIV have been falling over the last decade, whereas the death rate associated with dementia has been increasing significantly. Obviously the fact that we are all living a lot longer contributes to this problem. In one study, 17.8% of women over 85 were found to have dementia and 23.3% had mild cognitive impairment.

It can therefore be seen that it is imperative that the practitioner looking after midlife women should be advising them concerning interventions, which might protect them from dementia or reduce its severity.

Does oestrogen have a biological effect on the brain?
Scientific/biochemical evidence tells us that the brain is rich in oestrogen receptors and that these are particularly plentiful in parts of the cerebral cortex, hypothalamus, pituitary and limbic systems and hippocampus, all of which play an important role in memory. Oestrogen also seems to have an effect on acetylcholine transferase activity and non-amyloidogenic metabolism. It also increases dendritic growth and facilitates synaptic growth and improves glucose metabolism within the brain.

Animal studies have shown that where rats and rhesus monkeys are oophorectomised their function on
memory tests deteriorates and the replacement of oestrogen returns these tests to normal.

Assessment of women who have had their ovaries removed before 45 and not given hormone therapy at the Mayo Clinic shows that there is an increased risk of cognitive dysfunction, compared to women who had their ovaries removed over the age of 50 or women who were given hormone replacement therapy at the time of oophorectomy and continued until the age of 50.

Modern neuro-imaging techniques have shown that hormone therapy will increase hippocampal volume. Photo emission tomography scans done with patients on or off oestrogen have shown improved activity and functional MRI scans showed increased brain activity in subjects on hormone therapy as opposed to those who were not.

These scientific studies, together with epidemiological information that older women are at greater risk than older men, would suggest that oestrogen probably has a role to play in the development of cognitive dysfunction later in life.

**Midlife subjective memory complaints**

There will be few practitioners who look after women in their late 40’s and early 50’s who have not heard these words: “Doctor, I can’t remember a thing, I am sure I am getting Alzheimer’s disease like my mother”!

There is evidence that subjective memory complaints are common in the peri-menopause. This might be due to disruption of the pre-frontal area of the brain causing attentional disruption due to hormonal fluctuations at this time. These memory symptoms are often also associated with depression, anxiety and sleep disturbance, also common symptoms in the peri-menopause. Greendale (2010), in the Study of Women’s Health Across the Nation, found decrements in cognitive performance in women around the menopause. The study showed some improvement following the menopause and also benefits of hormone therapy used prior to the final menstrual period but not later.

This information is useful in order to reassure women that they might well suffer some memory dysfunction around the menopause transition. It is, however, very important to investigate this memory loss if it progresses in order to exclude other causes of memory dysfunction which might have put the women at risk for progression to severe cognitive dysfunction in later life.

**Diagnosis of cognitive disorders**

The diagnosis of cognitive disorders is primarily a clinical one but can sometimes be quite difficult and may require assistance from people specialised in psychiatry, neurology and neuro-psychiatry.

Careful history taking from both the patient and their immediately family or friends will assist in coming to some conclusion.

Obviously a careful history and examination concerning cardiovascular disease, HIV, thyroid disease, vitamin deficiencies, alcoholism and the exclusion of pathologies such as tumours are essential.

The use of the General Practitioners Assessment of Cognition tests (GPCOG) maybe helpful as a simple screening tool to assess whether further investigation and referral is required. This is a questionnaire available on the internet which is simple and has questions for both the patient and the accompanying informant.

Other more complicated neuro-psychological testing and imaging would be performed through a specialist in memory dysfunction and dementia. Tests of verbal memory are often specific for Alzheimer’s disease. These investigations might include brain imaging and there are now biomarkers such as tau protein and Beta amyloid in the CSF which at the moment are used more in research than in clinical practice.

**Can we modify cognitive outcomes?**

There are numerous interventions with varying levels of scientific evidence, which are felt to have beneficial effects on long term cognitive function in the ageing woman.

**Hormone therapy**

Hormone therapy is not indicated for the treatment or prevention of cognitive function.

However, there is growing evidence that hormone therapy used early may well reduce the incidence of Alzheimer’s disease in older women. The WHI study raised concerns about women starting conjugated equine oestrogen and medroxyprogesterone acetate after the age of 60 as this seemed to lead to some cognitive impairment.

In 2002, the same year as the WHI Study was published, the Cache County Study was published, which showed definite reduction in the risk of Alzheimer’s disease in women who had received hormone therapy early in the menopause. Those women who had received hormone therapy had an incidence of Alzheimer’s disease much the same as men. This was significantly less than women who had never used hormone therapy. Further information from this study was published in 2012 confirming the benefit of early hormone usage but raising concern about women who had received hormone therapy later in life. A study published by Whitmer in 2011 precipitated the following response from the International Menopause Society.
“more generally, this research supports the critical window, or timing hypothesis, according to which hormone therapy used by younger women closer to the time of the menopause lowers Alzheimer’s risk but used by the older women more remote from the menopause elevates Alzheimer’s risk”. This response was written by Professor Victor Henderson who has published extensively on matters relating to cognitive function.

“The other windows of opportunity”
When caring for midlife women and older, we should all be doing as much as possible to identify risk factors and give advice about disease modifying interventions.

Risk factors for cognitive dysfunction later in life are: body mass index above 30, atherosclerosis, hyperlipidaemia, hypertension, cerebrovascular pathology and cardiac disorders. All these factors, including diabetes, smoking and binge drinking, increase the risk of developing cognitive impairment. Low levels of education and the APOEe4 allele are also important factors.

It would seem logical that physical exercise has got almost the best evidence for modifying cognitive dysfunction as it clearly benefits all the above risk factors. It appears that physical exercise is helpful in carriers of the APOEe4 allele, the genetic risk factor for Alzheimer’s disease.

Maintaining “brain power” by engaging in social activities, reading and other stimulating pursuits has also been shown to reduce the risk of cognitive dysfunction. Television-watching in excess, however, has shown just the opposite.

References
1. Alzheimer’ Disease, dementia, mild cognitive impairment and the menopause: a “window of opportunity”? Denis A Davey Women’s Health (2013) 9 (3) 279-290
Wom en who have been treated for gynaecological cancer invariably have to face the consequences of oestrogen deficiency, be it due to the surgical resection of the ovaries as part of their treatment strategy, the adjuvant post-operative irradiation, the pelvic irradiation and concomitant chemotherapy given to women with advanced cancer where surgery is not offered or simply because of natural ageing after treatment. These patients will therefore, of necessity, need to make an informed decision on how to treat their menopausal symptoms. Both the psychological and physical symptoms of menopause induced by these treatment strategies appear to be more intense and severe than those of natural menopause. Trinh et al in 2006 showed that the hot flushes, night sweats, vaginal dryness and urinary incontinence experienced by breast cancer survivors are likely to be more severe than those in women not treated for breast cancer irrespective of whether tamoxifen was used or not. Associated stress due to the diagnosis and treatment strategies may further exacerbate the severity.1,2

The use of hormone therapy to treat menopausal symptoms in women who are gynaecological cancer survivors continues to be controversial, highly emotive and challenging, particularly because of the overwhelming opposition to its use by chemotherapists, radiotherapists, and invariably by the surgeons themselves. Most clinicians will not prescribe hormone therapy to these patients because of the underlying fear of the cancer survivors, the insecurity of the medical attendants and the lack of national or societal guidelines and the possibility of litigation should the woman develop a recurrence whilst taking estrogen therapy.

What is the evidence?
The intention of this review is to specifically analyse whether estrogen therapy is a plausible option in women with menopausal symptoms who have been treated for gynaecological cancer, and whether there is a negative impact on disease-free interval or survival amongst these women because of increased incidence of recurrence, metastatic disease or development of a second primary.

Endometrial Cancer
Endometrial cancer is the most common cancer in the developed world, principally affecting postmenopausal women, although about 20-25% of affected women are premenopausal and about 5% will be less than 40 years of age. Patients will invariably have early stage disease because the most common presenting feature is abnormal vaginal bleeding, with about 85% of patients having stage 1 or 2 disease.3,4 Treatment consists of total abdominal hysterectomy, bilateral salpingo-oophorectomy, commonly followed by intravaginal and whole pelvic irradiation. There are a number of studies which have addressed the question of hormone therapy for the treatment of menopausal symptoms in endometrial cancer survivors. In 1986, Creasman analysed retrospectively 47 patients with stage 1 endometrial cancer, who had been given estrogen therapy, because of severe menopausal symptoms post-operatively which was commenced within a median of 15 months after surgery (0-81 months). Estrogen users had a lower recurrence rate (2% vs 15%), a longer disease free interval and overall survival when compared to patients who had not used therapy.5

Four years later, Lee et al published their findings of 44 women who had taken estrogen therapy for a median of 64 months after management of their stage 1 endometrial cancer and compared them to 99 women not taking hormone therapy. No recurrences occurred in the estrogen users while 8% of non-users developed a recurrence.6 There were no recurrences in another two separate retrospective studies published in 1990 by Bryant and Baker respectively involving 20 and 31 endometrial cancer survivors in the two respective studies who were given estrogen therapy after treatment and followed up for 4-16 years.7,8

Chapman et al reviewed 123 women who had been treated for stage 1 or 2 endometrial cancer, of which 62 had used hormone therapy from 8 months after surgery. There was no significant difference in recurrences among the users vs the non-users.9 In 2001, Suriano et al identified 130 women who had used hormone therapy after having been treated for stage I-III endometrial cancer. Among this cohort, 75 matched treatment-control pairs were selected and were matched by using age at diagnosis and stage of the disease. Both groups were comparable in terms of parity, grade of tumour, depth of invasion, histology, surgical treatment, lymph node status, postoperative irradiation and concurrent disease. About half the hormone users were using estrogen only, whilst the other half was using estrogen and progestogens. The hormone users were followed for a mean of 83 months and the non-users for a mean of 69 months. There were 2 recurrences among the users vs 11 recurrences in the non-users (p=0.006).10

In early 2006, Barakat et al published the only randomized study which has addressed whether hormone therapy is safe in endometrial cancer survivors. Even though the study did not reach its accrual goal of 2,108 patients because the
publication of the WHI results made accrual impossible, it was able to randomize 1,236 patients to receive either estrogen or no estrogen therapy after undergoing surgery. The planned duration of hormone therapy vs placebo treatment was 3 years, with an additional 2 years of follow-up. The median follow-up was 35.7 months. The authors concluded that although the study could not definitively refute or support the safety of estrogen therapy in endometrial cancer survivors, it was important to note that the incidence of risk and demise from the disease in the users was low (RR 1.27; 80% CI 0.916-1.77). In late 2006, Ayhan et al published a prospective case-control study which also showed that immediate postoperative use of hormone therapy did not increase the recurrence or death rates in endometrial cancer survivors. Fifty patients were given continuous estrogen and progestogens which was commenced 4-8 weeks after surgery and outcome was compared with a control group with similar characteristics not using hormone therapy. Seven patients stopped taking their hormones, 2 stopped within 24 months, whilst the rest used therapy for at least 24 months for a mean of 49.1 months. At the end of their follow-up, there were no recurrences in both the patients who used hormone therapy for the entire period, as there were no recurrences in those who started therapy but subsequently stopped.

There is very little to support that vaginal topical estrogen is contraindicated in endometrial cancer survivors, even though there are no studies that have specifically addressed this issue. During the initial period of use there does appear to be a mild increase in the systemic estradiol levels, but these levels do not persist, with negligible systemic absorption following estrogenization of the vaginal epithelium.

**Ovarian Cancer**

Management of women with invasive ovarian cancer invariably will include total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and bulk reduction of all tumour deposits followed by adjuvant chemotherapy. Optimal cytoreductive surgery is achieved when residual tumour deposits at the end of the surgery are no greater than 1.5 cm in diameter. The impact of this surgery is the sudden onset of menopausal status in premenopausal or perimenopausal women, who account for about a third of women who develop ovarian cancer. This management strategy is debilitating and was clearly shown in the first study that addressed quality of life in ovarian cancer survivors. Guidoetti interviewed 28 patients on a 3 monthly basis to determine the impact of treatment on 2 domains; activity, daily living, health, support and outlook as the one domain and sexual activity as the second domain. Treatment of ovarian cancer produced significant deterioration in both domains with specific emphasis on behavioral disruption, emotional distress and sexual activity. In 1991, Eeles et al published the first retrospective analysis comparing overall survival and disease free survival in ovarian cancer survivors who did or did not receive hormone therapy after treatment. The end points were measured in 78 patients who used hormone therapy versus 295 who did not. There were no significant difference in survival between women using estrogen therapy and those not using it taking into account stage of disease, differentiation of tumour, histological results and time to relapse. The risk of dying in those using hormone therapy was 0.73 (CI 0.44-1.20) and for disease free interval 0.90 (CI 0.52-1.54). From their study, the authors felt that hormone therapy is unlikely to significantly impact on outcome in users. One year later, Guidoetti and DaPonte published their findings of a randomized study involving 130 women who had been treated for invasive ovarian cancer and were randomized 6-8 weeks after the surgery to estrogent only therapy or no hormone therapy. Nine patients originally randomized to hormone therapy refused or stopped taking their therapy, whilst 5 of the non users commenced taking estrogen hormonal therapy. In the final analysis, disease free interval and overall survival was measured in 59 estrogen therapy users and 66 non users. The median disease free interval was 34 months in users versus 27 months in the non-users respectively, whereas overall survival was 44 months versus 34 months respectively for the two groups. The differences in disease free interval (p=0.785) and overall survival (p=0.354) between the two groups were not statistically significant. Prognostic factors such as stage (p=0.785), differentiation (p=0.53), and suboptimal cytoreductive surgery (p=0.369) did not have an adverse impact on disease free interval when comparing the two groups, as they also had no impact on overall survival (stage p=0.354, differentiation p=0.418 and suboptimal surgery p=0.588). In 2000, Bebar and Ursic-Vrscaj published their analysis of 31 ovarian cancer survivors who received hormone therapy and were followed up for an average of 51 months. Mean duration of hormone therapy was 25 months starting on average about 18 months after surgery. Recurrence occurred in 3 patients at 1, 2 and 10 months after starting hormone therapy, two of which died from the disease. The authors concluded that hormone therapy was not significantly detrimental in ovarian cancer survivors. One year later, the same authors analyzed outcome in 24 patients with invasive serous ovarian cancer who used hormone therapy after surgery. Each patient was compared with 2 patients who did not receive hormone therapy. In the final analysis, there was no difference in outcome.

In 2006, Moscarenhas et al published the 5 year survival of 649 ovarian cancer survivors and 150 survivors with border line ovarian tumours in a prospective nation-wide study according to estrogen therapy before and after diagnosis. After 5 years, 45% of women with ovarian cancer and 93% of women with border line ovarian tumours respectively were still alive. There was no overall difference in 5-year survival in women with ovarian cancer according to use of hormone therapy before diagnosis (HR =0.83, CI 0.48-0.98), whilst analysis according to different hormonal preparations, duration or when commenced after treatment, did not affect survival in women with ovarian cancer. Importantly, the authors of this study noted a
better survival in those women using estrogen therapy than those who did not use hormone therapy (HR=0.57, CI 0.42-0.78). Their conclusion was that hormone therapy before the diagnosis of ovarian cancer did not affect survival after treatment, whilst use after treatment may in fact be associated with improved survival, although they do acknowledge that their latter finding may have occurred because of selection bias.19

Cervical Cancer

Even though estrogen receptors are present in squamous cell cancer tissue, it is not considered an estrogen responsive tumour, with no evidence to support that there is an association with this tumour type and hormonal therapy. Data also does not support any role for estrogen therapy and HPV carriage or replication.20,21 Fertility sparing surgery is an option in very early invasive cervical cancer in women who wish to maintain fertility, although standard treatment is either radical surgery followed by adjuvant chemo-irradiation or primary chemo-irradiation. Metastatic deposits to ovaries are extremely uncommon (0.2%) in Stage 1 and 2 squamous cell cancer, and therefore removal of the ovaries is not advocated. However, if adjuvant postoperative chemo-irradiation is needed, or if this cancer is advanced at initial presentation and primary radiotherapy and chemotherapy is the treatment, not only is there loss of ovarian function, but the irradiation is particularly toxic to the vagina with resulting vaginal stenosis to varying degrees being the result. Use of topical vaginal estrogen early in the postoperative period is important to preserve vaginal function with no evidence to support that topical vaginal estrogen preparations are detrimental to long term survival.22

Vulval Cancer

Cancer of the vulva accounts for about 4% of gynaecological cancers and in about 90% of cases will be squamous cell in nature. Surgical strategies include wide local resection of the cancer or vulvectomy and bilateral inguinal lymphadenectomy in advanced stages. Removal of ovaries is not part of the recommended treatment, but ovarian ablation occurs should postoperative irradiation be necessary. As with the squamous cell cancers of the cervix, cancer of the vulva is not considered estrogen dependent and postoperative hormone therapy in the form of topical vaginal preparations or oral supplementation are not contraindicated and have not shown to impact negatively on outcome.23

Vaginal Cancer

Vaginal cancer is exceedingly rare and accounts for less than 1% of gynaecological cancers. Invariably the cancer will be squamous cell in nature, although even more rarely, in women below 20 years of age who present with vaginal cancer, adenocarcinoma is likely, probably secondary to diethylstilboestrol ingestion by the mother in pregnancy. Surgical resection of the tumour is the primary modality of treatment and removal of the ovaries is not necessary, although postoperative adjuvant irradiation or irradiation as the primary modality of treatment will ablate ovarian function. Squamous cell vaginal cancer is not considered to be estrogen dependent and therefore hormone therapy following treatment is not contraindicated.

Discussion

Gynaecological cancer strikes at the core of femininity and is associated with many distressing and emotive issues in women, other than simply looking at long term survival. Treatment strategies are radical, and as with all cancers, the need for total extirpation of the cancer is the central focus of treatment to try and ensure long term prognosis. There are indeed four groups of gynaecological cancer survivors who will develop menopause as a result of their treatment. There are those who have a bilateral salpingo-oophorectomy at their initial treatment, those who do not have a bilateral salpingo-oophorectomy at primary surgery, but receive post-operative adjuvant irradiation, and those with advanced stage cancer who get primary pelvic irradiation with concomitant chemotherapy and no surgery. All these treatment strategies result in ovarian ablation, and as a consequence the acute onset of menopause. Not only do the surgical and irradiation strategies have their own inherent complications, but the resulting symptoms associated with the menopause are more distressing and debilitating than the symptoms that occur following natural menopause, and invariably will lead to significant hot flushes, night sweats, mood swings, insomnia, dry vagina, decreased libido, urinary symptoms and general malaise. Quite commonly, depression in response to the cancer diagnosis and treatment strategy will compound the symptoms and cause further decline in coping mechanisms. The fourth group of survivors would be those women who had treatment, but became menopausal simply because of natural ageing. Gynaecological cancer survivors will, therefore, not only confront their medical attendants for advice, but also seek options to manage their menopausal symptoms.

It is well known that estrogen therapy is the most effective agent to treat women with such menopausal symptoms, but the greatest concern lurking in the mind of the medical attendants is whether estrogen therapy will impact negatively on the long term outcome in these gynaecological cancer survivors by increasing the risk of recurrences and hence decreasing overall survival. Further indecision in prescribing estrogen therapy is commonly brought about by the fact that many oncologists vehemently oppose the use of hormone therapy in gynaecological cancer survivors, over and above the fact that national guidelines are invariably non-existent or not specific enough to allow one to make an unbiased decision, and there is always the fear of litigation should a recurrence occur. Nevertheless, there is a significant number of studies published in the English literature which supports that estrogen therapy does not increase the recurrence rate or decrease survival rate of gynaecological cancer survivors.24-32 Hormone therapy can be given to women who are vulval, vaginal and cervical squamous cell cancer survivors, and there is very little data to substantiate that
hormone therapy is a problem in women who have been treated for early stage endometrial cancer. There are no data to substantiate that hormones increase recurrences or decrease overall survival in ovarian cancer survivors.

In conclusion, treatment of gynaecological cancer brings with it a significant amount of emotional and physical strain resulting in significant impairment in quality of life. Menopausal symptoms contribute significantly to this distress. In the long-term management of these survivors it should not only be about longevity of life that is the sole priority. Quality of life must also take its place. Estrogen therapy is very effective in eliminating menopausal symptoms and there is no obvious evidence to support that estrogen therapy in survivors of gynaecological cancer is detrimental. It, therefore, does constitute a plausible option when menopausal symptoms prove to be significant.

References

n South Africa the process of oocyte donation in peri- and post-menopausal women is not as common as in Europe and the USA, but the request for donor oocytes in couples where a younger male enters into a relationship with a peri- or postmenopausal female, with or without her own children, is becoming more common. Two very good articles published recently\(^1\),\(^2\) discuss some of the challenges in guiding these couples to make an informed and sound decision in these mostly unique circumstances.

### Success rates of oocyte donation in older women

While the success of donor oocyte IVF (D-IVF) in older pre- and perimenopausal women was firmly established by the early 1990’s, there were some very strong concerns whether or not to offer D-IVF to women with natural menopause over the age of 50. Many clinicians were sceptical of the receptivity of the menopausal normal uterus, even when hormonally prepared, to implantation and development of a normal embryo.

Animal studies demonstrated lower implantation and pregnancy rates with increasing maternal age.\(^3\),\(^4\) However, this phenomenon seemed not evident in a subsequent report in 1992 of even older recipients, including postmenopausal women over 50 years of age.\(^5\) Endometrial biopsies of women of advanced reproductive age that were appropriately primed with hormones before transfer, had normal histological appearance and showed no difference from biopsies obtained from younger women.\(^6\)

In a 10 year review of postmenopausal women at the University of Southern California with a mean age of 52.8 ± 2.9 years, 121 embryo transfers (89 fresh and 32 frozen) using D-IVF were performed and a pregnancy rate of 45.5% with a live birth rate of 37.2% was achieved. These results were no different than rates in younger recipients at the same institute.\(^7\)

The reported success of oocyte donation in women in their 50’s\(^8\),\(^9\) and early 60’s\(^10\),\(^11\) suggests that pregnancy is still possible in almost all women with a normal uterus, regardless of ovarian status, and is determined by the age of the donor, and seemingly not influenced by the age of the recipient.

### Maternal and fetal risks

While oocyte donation is successful in helping older women achieve pregnancy and have babies, it does carry risks. Women of advanced maternal age (AMA, defined as older than 35 years), have long been known to have an increased risk of pregnancy related complications. These include hypertensive disorders, gestational diabetes, abnormal placentation, preterm deliveries, stillbirths and caesarean deliveries.\(^12\)-\(^14\) Studies have also shown that neonates born to AMA women have an increased risk of being small for gestational age, developing respiratory distress syndrome, being admitted to neonatal intensive care units and experiencing a greater overall mortality rate.\(^14\) It is thus not surprising that as maternal age increases above 50, factors contributing to maternal and neonatal morbidity and mortality also increase.

In the largest consecutive series of patients from a single treatment centre, published recently, comprising of 101 deliveries in patients 50 years and older, it was found that no major differences in obstetric and neonatal outcomes occurred compared with patients 42 years and younger, who also fell pregnant through D-IVF.\(^15\)

Perhaps of greater concern are reports of maternal deaths in women undergoing D-IVF. Reports of a cardiac arrest\(^8\) and also a case of maternal death following worsening HELLP syndrome after delivering twins\(^16\) underline the reason for extensive medical screening to be performed prior to performing D-IVF in this population (Box 1).

### Screening recommendations for women over 50 years of age prior to attempting pregnancy.\(^1\)

Medical and reproductive history including general physical examination and pelvic examination.

#### a. Laboratory tests:

- Standard preconception testing and counselling.
- Rubella and varicella titre.
- Full blood count
- Complete metabolic screen
- Fasting lipid screen
- TSH
- Coagulation studies
- Haemoglobin A1c or glucose tolerance test
- Pap smear, testing for *N gonorrhoea* and *C trachomatis*.  
- Infectious disease screen (HIV, Hep B and C testing)
- Stool testing for occult blood

#### c. Imaging

- ECG or Echo of heart (if stress test is abnormal or risk factors exist)
- Mammogram
- Chest X ray
- Transvaginal ultrasound
- Assessment of uterine cavity (hysteroscopy)
- Colonoscopy
- Skin cancer survey

#### d. Mental health and psychosocial assessment

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Optimisation of health should occur preconceptually and involve specialists in internal medicine, fetal maternal medicine and also with the guidance from a psychologist with an interest in reproductive health.

Advanced paternal age has also been associated with chromosomal abnormalities such as Down and Klinefelter syndromes, new dominant mutations resulting in congenital anomalies and an increased risk of autism and schizophrenia in the offspring. Clinical data have been difficult to evaluate because maternal age often increases with that of the male partner. When eggs from a young woman are donated, the impact on abnormalities in the offspring can be evaluated. Two small studies suggest that fertilization, pregnancy, live birth rates and the risks of abnormalities of the offspring, when the male partner is over 50, are identical to those with younger male partners when donor eggs are provided.

**Multiple pregnancies and increased risks**

Limiting the number of multiple pregnancies in older patients by careful selection of embryos for Single Embryo Transfer (SET) is essential in order to lessen complications. Given the potential for serious maternal and neonatal complications resulting from multiple gestation, the American Society for Reproductive Medicine (ASRM) guidelines, with regard to the number of embryos transferred to recipients of donor oocytes, gives very useful guidelines. Transfer of more than one embryo should be a decision taken only after careful discussion between parents to be and the clinician.

**Ethical considerations**

Ethical and psychological issues and infertility treatment: Should we have the ‘right to reproduce’? Are you ever too old to have a baby? Older parenthood raises a variety of important factual and ethical questions. We do not know much about the safety, economic, and psychosocial impact of these emerging practices on children or parents.

**Some more questions asked:**

How do we describe older parenting and fertility treatment? Is it legal and ethical to offer fertility treatment and assisted reproduction to older and post-menopausal women? Should infertility programs discourage, tolerate, or encourage pregnancy in old age? Or, instead, should ethical programs try to discourage and constrain who it is that can bear a child in their later years? None of these questions have received sufficient attention despite the rapid expansion in the numbers of older parents.

Decision makers, medical practitioners, scientists, courts and the public in general are facing new quandaries that involve controversies among profoundly held values.

**Firstly, why do women of later reproductive age want to have children?**

Their motivations vary. New technology exists that permit the creation of children.

- “Forty may be the new thirty.”

- Egg donation makes it possible for older women to have children.
- Older couples will use techniques such as sperm, egg, or embryo donation but keep that fact a secret.

The fact that a certain procedure is technologically possible does not make it ethically right. There are some speed breakers where we should stop and analyse the deep social impact of the latest developed technology before embracing it with open arms.

**Secondly, why is old age an ethical and psychosocial problem?**

The important ethical question is: whether there is an age at which a women should be viewed as “too old” to have a child.

Arguments for age limits for treatment are health risks for older women, social factors and child wellbeing.

1. **Health risks**

Pregnancy and childbirth pose greater risks for older women (discussed earlier). In view of the lack of data about maternal and fetal safety, providing donor oocytes or embryos for transfer to any women over age 55 years, even when she has no underlying medical problems, should be discouraged.

Why pick on women only? Some see sexism when issues of older parenting are raised since most questions arise about older women. Men are not placed at any serious risk by the process of generating sperm. There is some evidence that older men are at risk of creating children with a higher incidence of genetics problems and diseases. The risk to children however is far greater in women than it is in men.

One important concern for the use of IVF in older women may be the age and associated comorbidity of the old mother which may restrict them from being an appropriate parent and this is often seen as an infringement of the resultant child’s rights. We do not know much about the development of children resulting from such services and how they fare with children with comparatively aged parents. From a psychosocial perspective we do know that a child, at least, needs parenting until the age of 15 - 16 years of age, when they reach the young adult stage of life. Thus putting a cap on maternal age of 50 - 55 years when undergoing infertility treatment is something to be considered.

2. **Social Factors and Child Well-Being**

Older and post-menopausal women, who conceive, face a shorter life expectancy. Statistically, those conceiving in their late sixties are more unlikely to see the child to adulthood. Children that lost their parents at a young age are more at risk for stress, depression and drug abuse. Parental loss is one of the most stressful life events for children or adolescents. Parenting imposes both physical and emotional demands, which older parents may have
difficulty meeting. Socially, both parents and their children may experience isolation and stigma from having significantly older parents.

In the South African context it is also culturally appropriate for children to look after, care and support their ageing parent not only physically but also financially. Is it fair to expect a 25 year old to look after parents in their late seventies?

We clearly need more data to fully address these important issues related to safety of both mother and child, and family welfare. Physicians should carefully assess each prospective case, and decide on offering care based upon the merits of the patient’s profile. A psychosocial evaluation of the women and couple is also important to perform during the precycle evaluation. Parenting is emotionally stressful and physically demanding and is reasonable to ensure. The focus should be on attempting to address the complex moral, ethical and psychological issues that confront these unique families.

The ASRM continues to publish both practice and ethical guidelines to responsibly conduct egg and embryo donation. It would serve us all well if everyone involved with assisted reproduction and gamete donation would read them and adhere to their recommendations.

These guidelines are to protect the best interest of children created by technology in new familial circumstances, internationally recognized and to enforce standards for fertility clinics and ethical committees to follow and ought to be enacted in making decisions about treating older parents seeking infertility services.

**KEY POINTS**

- Women considering oocyte or embryo donation because of advanced reproductive age should undergo a comprehensive medical evaluation.
- Medical and gestational risks of AMA should be discussed involving a physician familiar with these risks.
- In view of the lack of data about maternal and fetal safety in D-IVF in women over the age of 55 years of age, D-IVF or embryo donation in even older women should be discouraged (even if no underlying medical problems are present).
- SET should be the standard.
- Prospective parents should be counselled by a psychologist, familiar with fertility, to consider short- and long term parenting and child-rearing issues specific to their age.
- Be honest with older pre- and perimenopausal women that still have regular cycles who might have the wish (and an unrealistic expectation) of having a baby through IVF using their own genetic material. They should be made fully aware of their very slim, if not impossible chance of taking a baby home.

**References**

Nothing is more important than your patients’ health. If we are to be stewards of our patients’ good health as well as treating their pathology, then we need to have data to back up our recommendations for lifestyles that give the best chance of a long and disease-free life. Fortunately there is ample evidence available from erudite articles in reputable journals to assure us that the advice we dispense is accurate.

Diet
The best diet to follow is a mixed intake of carbohydrates, proteins and fats that keep an optimal body mass index.

The aim of any diet should be to provide sufficient nutrients and calories to supply a person with an energy source which is balanced by their output and with vitamins and minerals comparable with health.

Freshly produced food is better for you than processed food with fruit and vegetables forming a high proportion of daily intake. Dairy products are good for you.

All this sounds common sense and hardly worthy of repeating but reading the world’s most eminent medical journals one is struck by the vast intellectual investments in providing the evidence to back these “truisms”. The world is facing an obesity epidemic that threatens to reverse the gains made in healthy longevity that characterised the last century’s medical progress. As professionals we are called on to advise on lifestyle more than ever and what is needed is the evidence to back up sensible behaviour. More and more old people are being studied because their numbers are growing, they are more affluent than in previous generations (which attracts the pharmaceutical companies’ interests) and longitudinal cohort studies are coming to fruition with reliable endpoints well documented.¹

Since we are more likely to die of cardio-vascular disease (CVD) than any other cause, we are, in a sense all high-risk, and so should follow the facts. The data in favour of diet and exercise being the basis of a healthy life are substantial – not some fad or pharmaceutical ploy or what your mother told you (although it appears she was right about eating your greens) but absolutely solid proof that lifestyle trumps medication in anyone’s quest for longevity.

So is the ultimate diet a vegetarian one and if so how does it work? The best direct evidence comes from a prospective investigation comparing vegetarians with non-vegetarians in terms of their cardiovascular health. Over 40 000 women and men living in the United Kingdom were tracked for over 10 years and their incidence of fatal and non-fatal cardiac events monitored and linked to whether they were vegetarians or not.²

The vegetarians had one third less ischaemic cardiac events than non-vegetarians which the authors conclude was due to lowered non-HDL cholesterol and blood pressure differences.

These were not high-risk patients, just ordinary citizens whose diets and lifestyles were observed. One can argue about the strength of observational trials as much as one wishes but in the end someone has to weigh up the evidence and that is usually the advising doctor in consultation with the woman.

So where does all the confusion about fat and cholesterol come from? The answer lies in the fact that it is not total cholesterol levels that necessarily reflect CVD risk. High cholesterol from saturated fat intake is not the “bogey man” that causes CVD. It is rather the small dense particles of low density lipoprotein (LDL cholesterol) that are implicated in CVD risk. These particular particles are in fact responsive to carbohydrate intake.

So cutting out fat, especially saturated fat and replacing it with carbohydrates is not the answer. The United States’ population is now an example of this misguided strategy in that although their fat intake has decreased their obesity rates have rocketed in the last 40 years. They have taken to fructose-filled drinks and large portions of carbohydrate-rich food which is creating citizens plagued by the metabolic syndrome and the medical problems of being overweight which are CVD, endocrinopathies, increased cancer propensity especially in women (breast and uterus), reproductive risks and skeletal pathology.

Sugar which provides too many calories without satiety is the villain of today’s diets being demonised as “pure, white & deadly” with justification.³ It is not the saturated fats or the total cholesterol levels that should be targeted through fad diets or statins for healthy people but excessive carbohydrate overload and lack of exercise.⁴

We cannot medicate our way out of the obesity epidemic since the onus lies with us and our medically knowledgeable advisors who should counsel limited calorie intake of a balanced diet, not smoking and a regular exercise pattern. This is especially true for old people (65 years plus) whose diet quality is associated with their all-cause mortality.

The additional intake of certain foodstuffs is beneficial such as nuts⁵ and chocolate (dark)⁶⁷ with its antioxidants...
so there are treats to be had without guilt but others have been found to be unhelpful. For example diets high in soy products do little for menopausal symptoms and marine derived omega 3 polyunsaturated fatty acids (PUFAs) have had mixed reviews in their place in lowering the risk of all-cause mortality or CVD but have been associated with a decreased risk of breast cancer.

The situation with supplements in addition to a balanced diet in healthy women will always be contentious. Where there are deficiencies in someone’s or a community’s intake then supplementation is necessary — but not otherwise. The so called extras that claim to provide “more health” or vigour or energy or boost the immune system or ward off illness — simply have no medical evidence to back their claims. Imagine if extra substance X could really improve your health or resistance to infection — what a field day the pharmaceutical companies would have.

On the contrary there are rafts of highly reputable papers, studies, reviews and meta-analyses showing categorically that extra vitamins and minerals have no beneficial effects and often that large doses have deleterious effects. Among those demonstrated to have no effect are: Vitamins A, B, C, D and E, folic acid, selenium, iron, copper magnesium, zinc and the “natural cures”.

There may well be placebo effects which make the prescriber or recipient feel better but the actual evidence is lacking.

Drinks

Which drinks are good for us and which are not?

Water is neutral. There is no evidence that dinking “plenty of water” or a specific amount per day is good for you. We have extremely wide ranges of fluid intake — even during normal sporting activities — that allow us to perform optimally. The fad for “energy drinks” is just a ruse to sell commercial fluids to a gullible public as they have no benefit over reasonable hydration.

Bottled water is not environmentally friendly and there is no medical reason why it should be recommended.

Tea and coffee, whether they contain caffeine or are caffeine-free are associated with lowered all-cause mortality at all normal ranges. Up to 6 cups a day are associated with positive health outcomes and there is some evidence that caffeine intake protects against depression and mortality.

Alcohol in moderation has a protective effect on mortality rates through its antioxidant properties and, as part of the Mediterranean diet lowers cardiovascular risks and may even have a joint protecting effect.

There are, however, serious risks in habitual, excessive consumption with cirrhosis, various cancers and anti-social behaviours making it, correctly, the target of public health campaigns, not to mention its teratogenic effects on the developing fetus. While on the topic of deleterious habits, smoking remains the most dangerous of all habits with an average of 10 years of life lost if a person smokes. It is the single most important favour you can do if you can convince one of your patients to quit smoking. Always enquire about it.

The most vilified drinks at present are sugar-sweetened cool drinks which are believed to be central to the obesity epidemic. These products are skilfully marketed to be associated with “good times” by healthy, slim young people while in truth they are ready sources of calories supplied by fructose from corn-syrup which has little appetite suppression.

In the US farmers producing corn-syrup are subsidised by government funds to provide crops at economically competitive prices setting up a cheap supply of sweetening material that gives a “buzz” without satiety sometimes with stimulants added thus pressing all our “quick-fix” buttons, so no wonder the incidence of obesity rises inevitably.

To counter this unhealthy situation more than half of all American states have started food taxes which specifically target sugar-sweetened drinks and many countries are looking to follow their example.

Drugs

There are very few, if any, registered pharmaceutical agents that can improve on nature. Unless people have a diagnosable, symptomatic deficiency or syndrome the drugs available to prevent the natural aging process are few and far between.

Anti-aging agents like exogenous growth hormone do increase lean body mass and reduce fat but they have too many side-effects to ever be considered as long-term medication. Secretagogues have been tried but they do not have the desired changes in bodily proportions or quality of life and made volunteers gain more weight than those allocated to placebo.

Perhaps only aspirin taken prophylactically has been shown to lower the risk of CVD and colo-rectal cancer in healthy people.

There are a number of drugs that are close to being taken by healthy men and women. Take the Polypill for example which contains aspirin 75mg, the ACE inhibitor lisinopril 10mg, the diuretic hydrochlorothiazide 12.5mg and the statin simvastatin 20mg and has been shown to reduce blood pressure and lower cholesterol levels. Although not commercially available it is being touted as a “one-size-fits-all” pharmacological answer to staving off cardio-vascular ailments. It may reduce the statistical risk of certain conditions but there are logistical, legal and moral hurdles to be overcome before it enjoys the blessing of academic endorsement.
The statin wars are now in progress. There are protagonists of “statins for all over 50” who suggest that even low-risk individuals can benefit (statistically) from having their cholesterol levels lowered by the prophylactic intake of statins.

Even the latest Cochrane review came down in favour of “statins for all” but the BMJ pleads for a much more cautious approach citing myopathies and diabetes as side-effects that have been underplayed and the industry sponsorship of the pro-statin trials as reason to doubt the wisdom of blanket prescriptions.19

It is not intended to debate here the role of hormone therapy for the prevention of chronic disorders but suffice it to say that more and more positive aspects are being reported in the literature with which gynaecologists should remain au fait.20

Then what about SERMs like tamoxifen, raloxifene and exemestane21 which are recommended for women at various risks of breast cancer? Again it is up to the physician to know the risk factors of the drug and the patient and be in a position to weigh the benefits and the harms and discuss these with the woman.

Other influences

• Exercise
There is evidence aplenty that exercise is essential for total good health. It wards off obesity, improves every system of the body and beats drugs in almost every level of cardiovascular health and recovery – in short it is the best thing we can prescribe and our patients can take.22 When last did you prescribe – by a written script to be taken – for exercise in a sedentary patient?

• Vaccinations
People over the age of 65 years have been proven to benefit from annual influenza vaccinations whether they live independently or in communal surroundings and should be appropriately advised.

• Social habits
There is much to be said for keeping an active mind to stave off cognitive decline and socialising to maintain if not reverse affect changes, again with recent data to back up what we have always suspected.

The ultimate healthy postmenopausal woman is someone who follows a vegetarian diet with lots of dairy produce and nuts, exercises regularly, has a BMI of 25, does not smoke, drinks alcohol in moderation, decides to take either estrogens with progesterone or SERMs with topical estrogens according to her choice, uses low-dose aspirin daily and consults her trusted physician regularly to have a history taken, a physical examination, advice about the need for screening and reassurance with encouragement “to lead lives of modified hedonism, so that they may enjoy, in the full, the only life they are likely to have.”23

References
18. PILL Collaborative Group. An International Randomised Placebo-Controlled Trial of a Four-Component Combination Pill (“Polypill”) in People with Raised Cardiovascular Risk. PLOS One. 6 (5)e19857.
We are facing a difficult socio-economic climate which has led to an increase in undesirable business practices in healthcare being reported to the Health Professions Council of South Africa (HPCSA).

The HPCSA’s Ethical Rules of Conduct, ethical guidelines and its Policy on Undesirable Business Practices (UBPP) assist health professionals (HPs) to avoid undesirable business practices, such as where a conflict of interests leads to over-servicing, or where perverse incentives are offered, to mention two examples. A conflict of interest arises when a secondary interest (such as financial gain) interferes with the primary interest (the patient). This behaviour amounts to unethical conduct. Consequently, it is even more important to focus on what is in the best interests of patients and HPs to maintain professional autonomy so that the trust required for the patient-practitioner relationship is not undermined.

Acceptable business structures
According to the HPCSA’s UBPP, acceptable business models include solo practice, partnerships and associations between various HPs, as long as all parties are registered under the Health Professions Act. The exceptions to this rule are medical pathologists and radiologists who are required to join only those associated with that discipline. The business arrangement must complete or supplement the health care offered by providing a supportive health care service, or they must all be members of the same profession.

It is also acceptable for a group of HPs to practise as a juristic person (in an incorporated practice), exempted from the operation of the Health Professions Act in terms of s54A. Franchising, too, is per se, not prohibited, as long as the ethical rules of Council are not breached, such as through inappropriate advertising, canvassing, exploitation, fees or commissions.

A HP may form a Closed Corporation to provide administrative services to the practice or outsource the administration of non-professional services, but the HP must ensure that no HPCSA rules are breached by the outsourced entity.

Corporate involvement, which refers to agreements entered into with corporate entities or other persons to provide services to the professional practice, (as opposed to corporate ownership), is allowed if the following conditions are met: HPs must remain responsible for the compliance with HPCSA rules and policies and continue to take responsibility for all business transactions. Consequently, no corporate veil exists for them to hide behind. Fees may not be re-directed to the corporate entity and corporate entities must not coerce HPs to enter into arrangements that breach the ethical rules.

However, a business model which is not acceptable in any form is direct or indirect corporate ownership of a professional practice by a person who is not a registered HP. Therefore, a professional practice may not allow sharing of its profits or income, such as where an income stream is transferred to that person, or shares or an interest is given to that person or where some benefit or inflated fee is paid to a service provider with the intention of facilitating the sharing of profits or income.

Employment of HPs
HPs may be employed by the public sector, universities, training institutions (limited to training and research) and by registered members of the profession. Other employing institutions must apply to HPCSA for accreditation and checking of contracts. However, employment agencies outside of medical practice, such as pharmaceutical companies or medical schemes, do not have to submit an application. Note that a locum tenens may work for a maximum period of 6 months.

A few examples of where conflicts of interest arise are now discussed.

Managed health care
Managed health care remains a controversial arrangement, although gaining in recognition since it was embraced under the regulations of the Medical Schemes Act, 1998 during 2003, and by the Council for Medical Schemes with the release of its Managed Health Care Policy Document in the same year. Most medical schemes now offer managed health care options as cost-saving interventions which tend to be less expensive than the fee-for-service options of the past. The intention behind this option is to influence behaviour and reduce over-servicing. The disadvantage is that the patient’s choice is restricted, as well as the HP’s, with regard to treatment. The managed health care organisations (MCO) use protocols to standardise treatment, as well as formularies to limit the medications that can be prescribed. Disclosure must be made to scheme members of services covered and the extent of cover, or when a service is not covered. The HP must also ensure that cost-saving benefits are passed on to the patient who is the primary sponsor of his or her own care. Patients need to be informed about the implications of this arrangement on their healthcare cover (ie the limitations, co-payments) and HPs must be educated about the implications of this structure on their practices, too.
In this context particularly, the HP’s professional independence should be protected because the HP remains accountable to the HPCSA. Accordingly, the council stresses that schemes’ advisors should not interfere with clinical management. Otherwise they should share the responsibility of treatment outcomes or accrue liability. The clinical guidelines or protocols used by the MCOs must be developed by the HPs themselves, using evidence based medicine as the standard. Contracts between funders and HPs must be based on ethical norms and fair reimbursement, understanding all the stakeholders’ roles in the health care system.

Patients need to be informed of the medically appropriate treatment, regardless of the cost or extent of coverage, because a patient’s welfare remains paramount. Where the HP wishes to vary treatment from that of the scheme or MCO, it should be recorded in writing for the patient. Protection of patients’ confidential information must be ensured as well as their informed consent recorded to share health information with the scheme, as required by law.

**Preferred provider arrangements**

The HPCSA’s policy is that any HP should be allowed to participate in preferred provider networks that meet the professional qualifications, quality of care and competence stipulated. The networks should not be exclusive unless there are compelling reasons for excluding someone. Profiling of a provider is allowed if a transparent and scientific process is used. The criteria should be understandable and a provider may query his/her own profile.

Mechanisms suggested to ensure ethical managed health care arrangements include Quality Audits to uphold quality of care. Peer reviews, practice profiles and utilisation reviews should be implemented to counteract under-servicing and HPs must be aware that capitation arrangements (risk sharing) can lead to under-servicing so avoid them. Charges for services rendered are required to be on a previously agreed rate, not based on a percentage of the HP’s income. Gatekeepers should be appointed with a mechanism for patients to report dissatisfaction at any time. Formularies for prescribing medicines must be based on reasonable costs and best practice principles. Credentialing and accreditation of providers must be transparent and objective, based on qualifications and professional competence.

**Financial interest in hospitals**

During 2009 the HPCSA amended its Rules of Ethical Conduct for Practitioners by lifting the limitation on the amount of shares HPs could own in a private health care institution. Ownership of shares is allowed, provided that shares are purchased at market-related prices, in arm’s length transactions. No terms or conditions must be imposed on the HP that will undermine ethical practice and returns on investment should not be based on patient admissions or meeting other targets related to servicing. Also, appropriate peer review and clinical governance procedures need to be in place to protect patients from over-servicing.

Council requires that it approve the purchase agreement. A form for this purpose is available on the council website. HPs are required to display a conspicuous sign in the waiting room once shares are approved by Council, stating that permission has been obtained to have a financial interest in an unlisted company, laboratory, private clinic or hospital. In addition, a report is to be submitted annually to Council reflecting the number of patients referred by the HP and associates to this facility, as well as to other facilities where no shares are held by the HP or associates.

To avoid conflicts of interest, HPs may not participate in advertising or promoting the health facility in any way.

**Perverse incentives**

The HPCSA defines perverse incentives in its ethical guidelines as any form of compensation, reward or benefit not legally due or which is given to the HP with the understanding that he or she will either engage or not engage in behaviour which may be against the law, in breach of the HPCSA’s ethical rules or may adversely affect a patient’s or group of patients’ interests. The intention is for the person giving the incentive to gain an advantage, payment, benefit or reward. No money, benefit or material consideration may be offered or received which is meant to induce the HP to act or not act, in an unprofessional way, such as over-servicing or over-charging patients.

A HP may not accept commissions or some other material reward in return for the purchase, sale or supply of any goods or substances used in his or her practice. Commissions may also not be paid to anyone for recommending or referring patients.

**Over-servicing**

Over-servicing refers to the supply, provision, administration, use or prescription of any treatment or care, (including diagnostic and other testing, medicines and medical devices), which is medically and clinically not indicated, unnecessary or inappropriate under the circumstances or which is not in accordance with the recognised treatment protocols and procedures, without due regard to both the financial and health interests of the patient.

The HPCSA confirms that over-servicing by HPs in the form of ordering more investigations, procedures or treatment than is strictly required, is a frequent complaint related to contemporary medical practice. HPs may not provide a service or perform procedures that are clinically not indicated nor scientific, or which have been shown through evidence-based reviews to be inappropriate, ineffective or to cause harm.

**Advertising**

The ethical rules related to advertising stipulate that advertisements used by HPs must be truthful. They should
not deceive, exaggerate or mislead.35 When creating an advertisement it is prudent to keep it short and simple. State qualifications, services rendered and relevant contact information. Do not give a personal or professional profile. Be aware that advertising on the internet must comply with the same ethical guidelines of the Council.

HPs may also not canvass or tout. Canvassing refers to drawing attention, through direct contact with prospective clients, to the HP’s personal qualities, superior expertise, quality of service, professional guarantees, or best practice, either through the printed or electronic media or verbally. Touting means conduct which, either verbally or using printed or electronic media, draws attention to the offers, guarantees or material benefits that are not professional services or items but which are linked to them to entice a person to the professional practice.36 Examples are offering gifts, guarantees, or a better life if the service is used.

### Fees

The legal requirements for charging fees as stated in the Health Professions Act37 make it clear that before a service is provided, the HP must inform the patient of the cost of treatment if the patient requests it or when the fee exceeds what is usually charged for that service. The phrase “usual fee” is not defined in the Health Professions Act, however. This requirement is also in line with the NHA’s consent section, which requires that the informed consent process include information related to the cost of treatment before it is commenced.38 Note that split-billing is illegal, where more than one service account is required which can reflect the split in fees, but all parties must receive the same information. This is balance-billing which is the correct approach.39 It is not acceptable to share fees with anyone who has not taken part in the service for which the fee is charged unless the other HP is in his/her employment or is a partner or associate, shareholder or locum tenens.40

The final word on good business practice is summed up in council’s list of the main responsibilities of HPs41 which include acting in the best interests of patients, respecting patient confidentiality, privacy, choices and dignity, maintaining the highest standards of personal conduct and integrity, providing adequate information to the patient for the patient to make an informed decision about health management, ensuring informed consent is given or an adequate alternative, keeping one’s skills and professional knowledge up-to-date, communicating effectively both with patients and other professionals and keeping accurate patient records.

### References

4. The Health Professions Act No. 56 of 1974.
5. HPCSA, Booklet 2, Ethical and Professional Rules, Annexure 6, p33.
6. HPCSA, Booklet 2, Ethical and Professional Rules, Rule 8(1).
8. HPCSA Policy Document on Undesirable Business Practices, as at 22 September 2005, para 2.2.3.
10. HPCSA, Booklet 2, Ethical and Professional Rules, Rule 9(1).
17. HPCSA Policy Document on Undesirable Business Practices, as at 22 September 2005, para. 4.3.
29. HPCSA, Booklet 2, Ethical and Professional Rules, Rule 23A.
31. HPCSA, Booklet 2, Ethical and Professional Rules, para. 7(3).
34. HPCSA, Booklet 5, Over-servicing, Perverse Incentives and Related Matters, Pretoria, May 2008, para. 3.1.
35. HPCSA, Booklet 2, Ethical and Professional Rules, Rule 3.
36. HPCSA, Booklet 2, Ethical and Professional Rules, Rule 1, definitions, as amended and promulgated in Government Gazette 36183 of 1 March, 2013.
37. Health Professions Act No. 56 of 1974, Section 53.
38. National Health Act No 61 of 2003, Section 6(c).
40. HPCSA, Booklet 5, Over-servicing, Perverse Incentives and Related Matters, Pretoria, May 2008, para. 3.10.3; 3.11.
41. HPCSA, Booklet 2, Ethical and Professional Rules, Rule 27A.
Comments by the President

It is always disappointing to hear a colleague who claims to be an expert providing an opinion which is biased, dogmatic and not evidence-based to the public at large through some form of media about hormone therapy and possible adverse outcome. Just recently, this was the scenario on a national television programme pertaining to breast cancer and hormone therapy, where it was implied that hormone therapy is strongly associated with the occurrence of breast cancer. This is simply not true and not based on published data.

It must be remembered that the cause of breast cancer is multifactorial and that cellular changes are influenced by genetics and other local and peripheral processes which we are now just beginning to comprehend. The observational studies have as many showing an increased risk for breast cancer, as there are showing a decreased or no significant change in risk in postmenopausal women using estrogen alone or estrogen and progestogen preparations. The WHI study showed an unweighted risk of 1.24 for estrogen and progestogen, but a risk of 0.77 for estrogen only respectively, for breast cancer.

The Canadian Society of Obstetricians and Gynaecologists has published an excellent overview of relative risks for breast cancer according to how significant the association is between the risk factor and the risk for breast cancer. They have grouped these risk factors into strong (RR: >4), moderate (RR: 2-4) and weak association (RR: 1.1-2) between them and risk for breast cancer. The risk factors that have a strong association include breast cancer in 2 or more first degree relatives, personal history of breast cancer, postmenopausal radiographic breast density and genetic mutations (BRCA 1 and 2). Risk factors that have a moderate association include history of one first degree relative, biopsy proven atypical hyperplasia and high BMD. Risk factors that have a weak association and that have been grouped together include a full term pregnancy >30 years, early menarche <12 years, late menopause > 55 years, no full term pregnancy, never breast fed a child, obesity, long term use of hormone therapy, high alcohol intake and being tall.

This not being sufficient, the Society has also summarised the extra number of breast cancer cases per 1000 women users per year according to risk factors. After 5 years, 10 years and 15 years of hormone therapy, the number of extra cases of breast cancer (absolute numbers) are 2, 6, 12 per 1000 respectively, but that late menopause (beyond 58 years), 2 alcoholic drinks per day, no daily exercise and weight gain (>20 kg) increase the extra cases of breast cancer per 1000 women users by 14, 27, 27 and 45 respectively.

I hope that all medical attendants are circumspect when they discuss hormone therapy with their patients or with the public at large and that the information is not biased, dogmatic or based on personal perspectives. We should always evaluate individual risk benefits ratio for our postmenopausal women and to provide them with the most appropriate intervention based on her symptoms and clinical finding.
Tibolone, a selective tissue estrogenic activity regulator (STEAR), has a tissue-specific mode of action after conversion to three active metabolites following oral ingestion.

Benefits of Tibolone

- Lumbar and hip BMD in women with and without osteoporosis
- Risk of vertebral and non-vertebral fractures in older osteoporotic women (mean age 68.3 years) – LIFT study
- Sexual interest and function (vs. transdermal E2/NETA)
- Vaginal bleeding (vs. oral or transdermal E2/NETA or continuous combined CEE/MPA)
- Breast tenderness/pain (vs. oral or transdermal E2/NETA or continuous combined CEE/MPA)
- Total cholesterol and HDL cholesterol

Time trends for alendronate prescription practices in women with chronic obstructive pulmonary disease and women exposed to systemic glucocorticoids

Brask-Lindemann D, Eiken P, Eskildsen P, Abrahamsen B
Osteoporos Int 2013; 24:1891–1897

Chronic obstructive pulmonary disease (COPD) and systemic glucocorticoid exposure are well-known risk factors of osteoporosis (osteopenia and osteoporosis) and fragility fracture.

68 to 84 % of COPD patients have low bone mineral density (BMD) and osteoporosis is often underdiagnosed and undertreated in these patients.

Systemic glucocorticoid use is associated with rapid and significant bone loss, beginning within the first 3 months of use. This loss appears to be most rapid within 12–18 months, followed by a slower, steady loss and an increased risk of fracture with continued use.

A 12-year nationwide register-based study on alendronate prescription practices in Denmark (388,314 female subjects >50 years old) showed:

- prescription rates of alendronate in COPD patients
- likelihood of filling a prescription for alendronate in prednisolone users
- likelihood of using alendronate with combination of COPD and glucocorticoid exposure
- targeting of alendronate in women with a diagnosis of COPD/women treated with systemic glucocorticoids

Conclusion

This nationwide register-based study on alendronate prescription practices in Denmark shows an increasing targeting of alendronate treatment in patients with COPD and an even stronger trend for patients with systemic glucocorticoid exposure, perhaps indicating increased awareness of well-known and associated conditions.

Updated clinical recommendations for the use of tibolone in Asian women

Huang KE, Baber R on behalf of the Asia Pacific Tibolone Consensus Group
Climacteric 2010; 13:317–327

Tibolone, a selective tissue estrogenic activity regulator (STEAR), has a tissue-specific mode of action after conversion to three active metabolites following oral ingestion.

No cases of endometrial hyperplasia or cancer over 2 years at doses of 1.25 mg and 2.5 mg per day - Tibolone Histology of the Endometrium and Breast Endpoints Study (THEBES)

No increased risk of myocardial infarction

E2=estradiol; NETA=norethisterone acetate; CEE=cyproyterone acetate; MPA=medroxyprogesterone acetate; BMD=bone mineral density; HDL=high density lipoprotein; HRT=Hormone Replacement Therapy

Preferred treatment for postmenopausal women with:

- Increase in breast pain despite HRT dose adjustment
- Increasing mammographic density
- Low libido
- Mood disorders
- Persistent bleeding problems (without histopathology)
FOSAVANCE™
Integrated, updated osteoporosis therapy

FOR THE FIRST TIME in a single, Once-Weekly Tablet¹

Building on the demonstrated Power of FOSAMAX (alendronate 70 mg)

...with the Assurance of a Weekly Dose of Vitamin D¹ (cholecalciferol 2800 IU)

Alendronate is BIOEQUIVALENT in FOSAMAX and FOSAVANCE¹,²

FOSAVANCE™
alendronate/cholecalciferol

Powered for Bone Strength

INDICATIONS: FOSAVANCE is indicated in women for the treatment of postmenopausal osteoporosis to reduce the risk of fractures, including those of the hip and spine (vertebral compression fractures) and to help ensure vitamin D adequacy.

CONTRA-INDICATIONS: FOSAVANCE is contra-indicated in patients with abnormalities of the oesophagus which delay oesophageal emptying, in patients with an inability to stand or sit upright for at least 30 minutes, in patients hypersensitive to any component of the product, in hypocalcaemia and in severe renal insufficiency. FOSAVANCE should not be used during pregnancy or lactation or in paediatric patients.

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.

SIDE EFFECTS: The following common (≥1/100, <1/10) adverse experiences have been reported during clinical studies and/or post-marketing use of alendronate: headache, abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer, dysphagia, abdominal distension, acid regurgitation and musculoskeletal pain.

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

**Selected Safety Information**

**Contraindications:** Known or suspected hormone-dependent tumours; Known, past or suspected breast cancer – LIVIFEM® increased the risk of breast cancer incidence in a placebo-controlled trial. Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer). Increased bleeding of unknown aetiology or increased endometrial hyperplasia. Mammography reveals any abnormalities. Total abdominal hysterectomy: E2/NETA or tibolone may be used in women with hysterectomy. Parenteral gonadotropins: periodic gonadotropin stimulation may be used in conjunction with LIVIFEM® therapy. Known or suspected endometrial hyperplasia or grade I or II endometriosis. Vaginal bleeding of unknown aetiology. Untreated endometrial hyperplasia.

**Warnings:** The use of LIVIFEM® should be avoided until 12 months after the last natural menstrual bleed. If LIVIFEM® is taken sooner than 12 months, the pill regimen of regular bleeding may be increased to reduce irregular bleeding or break-through bleeding during DMPA therapy. Before the use of an apparently unrelated medication due to the possible additive effect. Duration of treatment – Up to 12 months. Periodic examination or testing for breast cancer, as well as possible signs of endometrial hyperplasia. The risk of breast cancer and endometrial cancer is higher than that of women with an intact uterus. The risk of breast cancer is increased in women with a family history of breast cancer and women with breast cancer risk factors. E2/NETA or tibolone may be used in women with hysterectomy. Parenteral gonadotropins: periodic gonadotropin stimulation may be used in conjunction with LIVIFEM® therapy. Known or suspected endometrial hyperplasia. Total abdominal hysterectomy: E2/NETA or tibolone may be used in women with hysterectomy. Parenteral gonadotropins: periodic gonadotropin stimulation may be used in conjunction with LIVIFEM® therapy. Known or suspected endometrial hyperplasia or grade I or II endometriosis. Vaginal bleeding of unknown aetiology. Untreated endometrial hyperplasia.

**Effects:** LIVIFEM® tablets (2.5 mg) exerted specific effects on the following tissues through its active metabolites: Brain, Genital tract and Bone. It effectively relieved vasomotor symptoms in postmenopausal women. It showed a better improvement on sexual function compared to combined HRT. It had a minimal effect on breast tissue vs. combined HRT. It showed a better vaginal bleeding pattern compared to combined HRT. It showed beneficial effects on bone over a ten year treatment period.

**Reference:**

2. Data on file, MSD.

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