The South Africa Menopause Society (SAMS)

Menopause Focus

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Contents

Editorial Board

Editorial

Professor Franco Guidozzi
President of SAMS, Editor

This edition of Menopause Focus has six articles, is packed with information and is slightly different to the previous editions.

In the first article, Percy Moodley has managed to put together a well-balanced and plausible approach to sexual dysfunction in menopausal women. So many factors play a role in maintaining healthy sexual activity, many of which are radically affected by menopause. The significant hormonal, physical, psychological and emotional changes that accompany the menopause invariably impact negatively on sexual well-being. Understandably, it is married women who are 3-4 fold more likely to complain of sexual dysfunction than women with no partner, of which the Hypoactive Sexual Desire Disorder is the most common. Vulvo-vaginal atrophy, which is under reported by women, under recognized by health care providers and as a result overwhelmingly under treated, commonly adds to the problem by producing dyspareunia. This article emphasizes the need for estrogen and testosterone therapy as possible therapeutic options and at the same the use of lubricants or moisturizers should they be necessary.

Whenever hormone therapy is administered, it should be given in the lowest dose to minimize complications and side effects. Carol Thomas and Mike Davey address one of the other strategies to maximize benefits but at the same time to minimize complications and side effects, and that is mode of administration. Oral administration is easy and very convenient, but this mode of delivery results in the estrogen undergoing hepatic first pass metabolism. This leads to significant metabolic responses that impact especially on the cardiovascular system, particularly with regards to thrombosis, cardiac disease and stroke. Transdermal delivery of hormone therapy does not lead to hepatic first pass metabolism and hence has a more acceptable side effect profile and a lesser rate of complications. Carol Thomas has not only provided a brief overview of all the possible modes of delivery of both estrogen and progestogens, she has also included a comparison of the most important metabolic effects of the different progestogens used in hormone therapy. Mike Davey has addressed, in more detail, the specific impact of estrogen on the cardiovascular system when it is administered transdermally. His analysis shows that transdermal estrogen has clear advantages over oral estrogen, and may be the choice in older women who wish to continue with hormone therapy, in women with mild hypertension, diabetes, metabolic syndrome, smokers and in obese women.

Whenever women are to initiate hormone therapy they invariably will ask about breast cancer and whether they will put on weight. In the fourth article, Trudy Smith has looked at the literature and shows that although there is some initial weight gain because of fluid retention, hormone therapy is not associated with a significant weight gain. Ageing alone will invariably lead to an increase in intra-abdominal and visceral/waist-to-hip fat. This is a natural physiological response to menopause and all women need to adhere to lifestyle modifications, including dietary calorie restriction and exercise, to curtail the likely increase of body weight. It is guestimated that the majority of women at 50 years of age will weigh what they weighed at the end of their second pregnancy! This well written article is reader friendly and can certainly be given to patients who question the impact their hormone therapy may have on their weight.

The last two articles have been written by Athol Kent and both articles are related to what Athol is writing for the South African Menopause Society as a monthly review known as Menopause Matters. Each month he reviews menopausal matters that have recently appeared in the recent literature and the summaries concentrate on clinical issues, although he does also include pathology and physiology to ensure a scientific basis to the articles. Scientific journalism has become an important component of most journals and it makes interesting reading. Most of the articles do pertain to women of menopausal status, although a fair amount of the topics discussed apply to women's health in general or to the ageing male. Two such articles are included which address gene editing, epigenetics, surgical checklists, PSA testing, cardiovascular disease, breast cancer and women with BRCA gene mutations.

I hope you enjoy reading this edition of Menopause Focus and that you find it meaningful. Happy reading!

An approach to sexual dysfunction in menopausal women

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Female sexual dysfunction (FSD) is a common complaint in menopausal women. It occurs when the quality of the sexual relationship is associated with personal or couple distress. Current research shows that many postmenopausal women have an increased sexual responsiveness as a result of reduced fear of pregnancy, absence of the need for contraceptives and the end of menstrual distress.[1]

Aetiology

It is important not to label the normal age related changes in sexual response as pathology. Sexual problems, however, may be the first sign of an underlying illness, a sign of a deteriorating marital relationship, or a symptom caused by hormone deficiency.[2] FSD has a multifactorial aetiology and even if there is co-existing psychosocial or psychological morbidity, ensuring a normal hormonal milieu is vital for effective management.

HORMONES

Estrogen

The sharp decline in estrogen is the biochemical hallmark of the menopause. The resulting vaginal atrophy often leads to dyspareunia with a subsequent decline in libido. Estrogens play an essential role in sexual function. These hormones are responsible for the alleviation of hot flushes leading to better sleep patterns, less fatigue and the prevention and treatment of atrophic vulvovaginitis. Appropriate estrogen replacement may be enough to reverse a negative sexual cascade, although estrogen therapy only does not appear to increase libido.

Androgens

All androgens decrease with age. In premenopausal woman, the ovaries and adrenals together account for 50% of the total testosterone production. The remaining 50% comes from the conversion in the skin, liver and adipose tissue of androgenic precursors derived from the adrenal gland and ovary.[3]

Despite the continued production of testosterone by the ovaries, total testosterone levels decline due to decreased production of adrenal androgen precursors which are available for peripheral conversion. In surgical menopause, the loss of ovarian production results in dramatically reduced levels.

Only 1 to 2% of testosterone is free and physiologically active due to sex hormone binding globulin (SHBG) binding strongly to testosterone. The bound fraction includes 66% tightly bound to SHBG and 33% weakly bound to albumin.[3]

This whole topic is complicated by the difficulty in measuring testosterone, especially in females. Weakly bound testosterone can easily dissociate from albumin at tissue level. Therefore, serum levels may not accurately define dynamics at a cellular level.

The dramatic fall in testosterone levels with a surgical menopause may add to atrophy of the female genitalia.[4] Free testosterone enters the genital smooth muscle cells and is converted to dihydrotestosterone by 5 alpha reductase. The dihydrotestosterone then binds onto the androgen receptor and translocates to the nucleus. It influences transcriptional activity of certain genes which will code for growth factors that maintain the adult form of the genital structures. The loss of this effect results in regression to the pre-pubertal state.

Specific Conditions

Vulvo-vaginal Atrophy (VVA)

Atrophic vaginitis is under-reported by women, under-recognised by health care providers and therefore under-treated.[5] The latter is regrettable as effective treatments are available with minimal side effects.

VVA is a progressive symptom in the climacteric as opposed to other menopausal symptoms which may be self limiting. It is important to also remember that one third of women with VVA suffer vaginal symptoms despite systemic hormone treatment.[6]

The International Menopause Society (IMS) statement on postmenopausal vaginal atrophy issued on World Menopause Day October 18th 2010 recommends the following.[7]

- Treatment should be started early before irrevocable atrophic changes have occurred
- Treatment needs to be continued to maintain the benefits (noting chronicity of condition)
- All local estrogen preparations are effective and patient preference will often dictate choice of treatment
- Delay in starting local treatment will reduce the degree of response
- An initial loading dose to stimulate receptors followed

by a maintenance dose once or twice a week
- Additional progesterone is not required as the low amounts of estrogen absorbed when administered correctly does not stimulate the endometrium

Alternatives to local estrogen therapy include intravaginal DHEA (phase 3 clinical trials), ospemifene tablets (a new selective estrogen receptor modulator),[8] TSEC (bazodixifene plus conjugated equine estrogens)[9] and vaginal moisturizers.

Vaginal moisturizers hydrate the vaginal mucosa and have to be used several times a week. They improve the balance of intracellular fluids in the vaginal mucosa and some may restore the acidic vaginal pH.

Vaginal lubricants provide comfort during sexual activity. They should ideally be silicone or water based. Lubricants prevent irritation and potentially avoid mucosal tears, thus preventing pain with coitus and leading to an improvement in all domains of sexual activity.

Breast cancer survivors, especially those on aromatase inhibitors, have severe VVA. Sexual activity if desired is an important part of the rehabilitation process. The above modalities used appropriately will optimise sexual function and lessen emotional distress and improve psychosexual adjustment.[10]

Hypoactive Sexual Desire Disorder (HSDD)

The commonest sexual dysfunction in the climacteric is HSDD.[11] The hypothesis to consider is what role the lowered testosterone in the climacteric contributes to the HSDD. The reduced levels of testosterone in postmenopausal women are associated with a loss of libido, decreased sexual activity, diminished feelings of wellbeing and fatigue. If the latter causes personal or interpersonal distress, testosterone therapy is an option. This applies especially to the scenario of a patient who has had a bilateral oophorectomy where there is a sudden precipitous drop in hormone levels.

Before we ascribe HSDD to be purely hormonal in aetiology, we have to exclude other causes. They include psychosocial issues, psychological disorders, mental conditions and pharmacological agents. This involves taking a detailed history and allowing the patient time to express herself to care givers with a non-judgmental attitude towards sexual issues.

Testosterone therapy for women is a complex and ongoing debate. The European Union approved the use of the Tesosterone Transdermal Patch (TTP) (intrinsa) in 2007. In clinical practice, testosterone therapy can be safely used after excluding other causes of HSDD and informing patients that it is still off-label therapy in South Africa. Owing to the unavailability of TTP in South Africa, testosterone implants could be used at a dose of 40 milligrams. The dose is repeated at 4 to 6 months if there has been a definite response. Response can only be assessed 2 weeks after insertion of implant. There is no point continuing androgen therapy in the absence of a change in HSDD. In patients who request implants at intervals of less than 4 months, it is advisable to measure the free testosterone index, and only repeat the dose if the level is in the lower quartile of the normal range. Unfortunately, the implants have recently also been removed from the market and are no longer available in South Africa.

Testosterone therapy is usually given to patients after ensuring that they are well estrogenised. However, the recent ADORE study confirmed the efficacy of TTP in treating HSDD in naturally menopausal women with or without concomitant estrogen therapy use.[12] Thus, testosterone therapy may have a place even in patients in whom estrogen therapy is contraindicated.

Appropriate candidates for testosterone therapy include patients with premature ovarian insufficiency, surgical menopause, adrenal insufficiency and hypopituitarism.[13] Androgens heighten response to psychosexual stimulation. They also cause external genitalia to become more sensitive leading to more consistent sexual gratification. Overall, it induces a greater sense of well being.

Alternatives to testosterone therapy include tibolone (livifem) and DHEA. Tibolone does have weak androgenic activity and does not increase SHBG (sex hormone binding globulin)[14] Dehydroepiandrosterone (DHEA) is a neurosteroid with a wide range of functions. The role of DHEA in the improvement of sexual function is controversial and we await more studies.[15]

The sexual function of the partner is vital and the appropriate questions have to be asked. With many therapies being available for male sexual dysfunction, early referral of the male sexual partner may be indicated. It is also important to emphasise intimacy even if penetrative sex is not possible. Couples need to be informed of accessories that can aid the sexual response to enable them to gain access if so desired.

Relationship duration also influences sexual satisfaction. Sexual activity and satisfaction decline with increased duration of the relationship.[16]

Conclusion

Sexual health is a fundamental human right. Age must not be a barrier to sexuality. Skill is needed to identify the subset of patients who will benefit with hormonal enhancement. Practitioners entrusted with the care of patients in the climacteric have to develop their abilities in sexual medicine in order to provide comprehensive care.

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Modes of delivery of hormone therapy in menopausal women

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More than a decade has passed since the publication and the resulting havoc caused by the Women's Health Initiative study (WHI)[1]. Although there are numerous questions that remain unanswered, studies like the Kronos Early Estrogen Prevention Study (KEEPS) has lent credence to the concept of a window of opportunity for some of the benefits of initiation of hormone therapy close to the onset of menopause. Among early menopausal women, neither conjugated oestrogen tablets, nor an oestradiol transdermal patch system, both given with a progestogen, change the rate of progression of atherosclerotic cardiovascular disease, as measured by carotid intima media thickness (CIMT).[2]

There is also increasing evidence that lower hormone therapy doses have better risk and side effect profiles while still ensuring symptom relief and bone integrity.[3]

Other than timing of hormone therapy use and dose, the modes of administration of hormones have started to receive attention since WHI in the quest for the lowest, effective dose with the best safety and lowest side effect profile.

Oestrogen with or without Progestogen

The main difference between the use of oral and transdermal hormone therapy administration used to be geographical with prescription habits in North America favouring oral hormone therapy, while European doctors favoured transdermal hormone therapy use. This disparity is set to change as reflex prescribing habits are replaced with more individualised approaches based on patient risk assessment.

The risks of oral oestrogens include a higher and significant risk of venous thrombo-embolism (VTE) which was considered to be a class effect until the publication of the Estrogen and Thromboembolism Risk (ESTHER) study in 2003.4

When transdermal oestrogen is chosen, patient choice, views about medication, especially hormone therapy, and convenience may influence whether oestradiol is prescribed in patch or gel form.

In 1999 Utian et al reported a statistically significant improvement of vasomotor symptoms in women treated with patches delivering 50 and 100 µg oestrogen daily from week 2 onward and from week 3 onward in patches delivering 25 µg.[5]

The effect of transdermal oestrogen dose on bone turnover was found to be similar to oral oestrogen preparations. Low (0.025 mg/day) and standard (0.050 mg/day) doses of transdermal oestradiol displayed similar efficacy in controlling bone turnover in postmenopausal women.[6]

Transdermal hormone therapy use is associated with a significantly lower incidence of increased mammographic breast density and breast tenderness compared with oral hormone therapy. Of women using transdermal hormone therapy, 39.1% had no change in breast density compared to 15.7% for women using oral hormone therapy. Only 4% of women using transdermal hormone therapy had a large increase in density (425%) compared to 15.7% of women using oral hormone therapy. Oral and transdermal norethisterone acetate (NETA) use have comparable risks for breast cancer and the dose or route of administration of NETA in oestrogen progestogen therapy does not modify the risks for breast cancer.[7]

The risk of gallbladder disease and cholecystectomy seems to be significantly lower among women using transdermal hormone therapy in the UK Million Women Study and the study by Racine et al.[8]

Early results and recent meta-analyses showed that VTE risk among hormone therapy users, including women at high thrombotic risk, depended on the route of oestrogen administration. Oral, not transdermal oestrogens, were associated with an increased risk of VTE. Recent studies suggested that concomitant progestogens could also be an important determinant of the VTE risk in postmenopausal women who used hormone therapy and that there may be a role for micronised progesterone. In addition to the improved VTE risk when entero-hepatic metabolism is avoided, there is growing evidence that the dose of oestrogens could also play a role in determining VTE risk among oral oestrogen users.[9] Low dose transdermals are also not associated with stroke.[10]

Brynhilsen et al performed a randomised controlled trial to demonstrate the effects of 2 year transdermal continuous combined low-dose oestradiol (0.025 mg/day) and norethisterone acetate (0.125 mg/day) on lipid/lipoprotein profile and coagulation/fibrinolysis. A transdermal patch delivering 0.025 mg oestradiol and 0.125 mg norethisterone acetate daily had a positive overall effect on lipids and significantly lowered factor VII, Antithrombin-III and fibrinogen. Lower total cholesterol levels and a higher ratio of HDL cholesterol to total cholesterol were observed on active treatment. These results pointed to a possible benefit of this

low-dose continuous combined hormone therapy on cardiovascular health.[11]

Sarrel[12] and Hodis[13] have recently reported that many women died prematurely or unnecessary by avoiding oestrogen therapy entirely.

Utilising the four primary outcomes of the WHI E+P arm (cardiovascular disease risk, cerebrovascular disease risk, venous thromboembolism risk, and breast cancer risk), and a compilation of the published epidemiological literature on these endpoints and transdermal oestradiol and/or micronized progesterone, a hypothetical reanalysis was conducted assuming that oral conjugated equine oestrogens and oral medroxyprogesterone acetate (MPA) as in the WHI E+P arm were replaced by comparable doses of transdermal oestradiol and oral micronized progesterone.

Statistical methods to ascertain the attributable risk of venous thromboembolism, and subsequent cardiac or cerebrovascular events for transdermal oestradiol versus oral conjugated equine oestrogens, were imputed into the WHI primary outcomes. The result demonstrated a marked decrease in venous thromboembolism and likely decreases in cardio- and cerebro-vascular thrombosis depending upon the baseline age and risk profile. Substituting micronized progesterone for MPA in this analysis would have resulted in a negligible increase in breast cancer risk.[14]

Other Methods of Oestrogen Administration

Implants

Hormonal implants are now of historical interest only as they are no longer available. The advantage of a long-acting method came at the disadvantage of a non-physiological initial hormonal serum peak.

Vaginal

Oestrogen vaginal creams, rings or pessaries are available for the effective treatment of vulvovaginal atrophy and urogenital ageing in the 15% of women who, despite systemic hormone therapy use, may suffer from sexual dysfunction, urinary symptoms, like overactive bladder and recurrent urinary tract infections and vaginal dryness. Based on current evidence, there is no need to provide progestogen opposition for endometrial protection in women who use local vaginal oestrogen for longer than 6 months.[15]

Progestogens and progesterone

Oral

The route of administration of progestogens may not be the only factor influencing progestogen choice as progestogens are not homogenous as a group. (Table 1)

Table 1

Classification	Oestrogenic	Androgenic	HDL cholesterol	LDL cholesterol	Glucocorticoid	Glucose intolerance	Anti-androgenic	Anti-meralcorticoid
Progesterone	-	-	-	-	(+)	-	(+)	+
Dydrogesterone	-	-	⇧	⇩	-	-	-	(+)
NETA	+	+	⇧	⇩	-	⇩ ⇩	-	-
MPA	-	(+)	⇧	-	+	⇩	-	-
Drosperinone	-	-	- / ⇩	⇩	-	-	+	+

Sturdee DW,MacLennan AH. Reducing the problems of the progestogen. Climacteric 2006;9: 241–3

Transdermal

Progesterone absorption through the skin is variable and there is a dearth of information pertaining to the efficacy and safety of Mexican Yam derived progesterone creams sold without prescription, regulatory control and assessment in women who use it. The information available should not be relied on to support its use in preventing endometrial hyperplasia and/or cancer because of lack of any evidence.

Vaginal

Reproductive health experts have until recently had most experience with vaginal progesterone administration, but it offers an additional route of administration for women, with the main side effect of some vaginal leakage from the micronized progesterone capsules. Vaginally inserted progesterone has a 40-fold higher bioavailability than oral administration allowing for lower doses.[17]

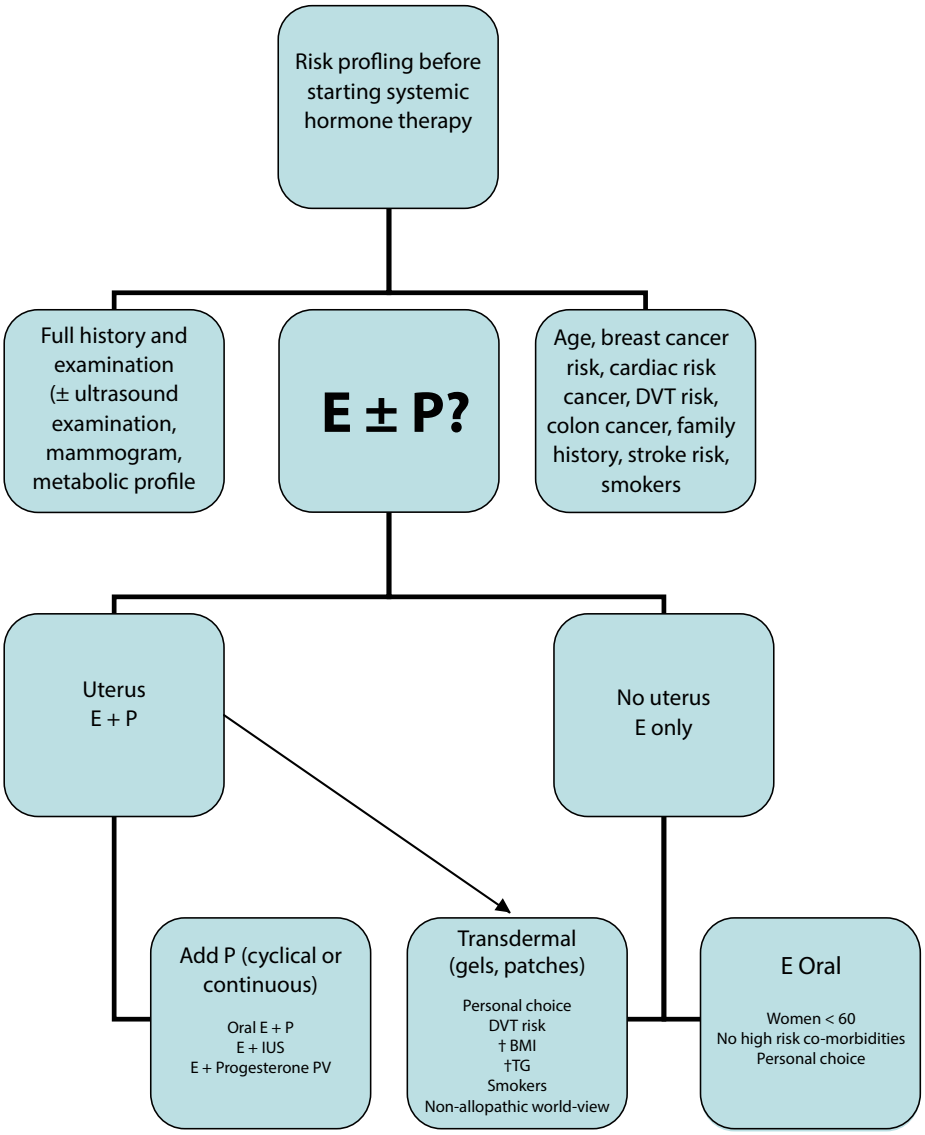
Intra-uterine

Local intra-uterine progestogen administration with the levonorgestrel intra-uterine system, Mirena®, has become an effective means of decreasing the increased risk of systemic progestogen administration and adds another option for non-hysterectomised women.

Testosterone

Registered, commercially available testosterone products for women are not available in South Africa and any current use of testosterone in any form of administration is off-label, sporadic and not standardised with no available data to support its use.

Figure 1: Decision making about route of administration of hormone therapy



Conclusions

In the absence of significant co-morbidities, oral, preferably low dose, hormone therapy forms part of the essential armamentarium in the approach to the successful, optimised management of the menopausal transition, especially in women close to their final menstrual period. Understanding the advantages and disadvantages of different modes of administration of hormone therapy allows the clinician to present the most appropriate, targeted hormone therapy management plan to women, after a clinical assessment supported by appropriate investigations. Transdermal administration of hormone therapy is associated with less adverse events than oral administration, particularly with respect to cardiovascular adverse events. In addition, transdermal hormone therapy does not significantly increase the risk of thromboembolic disease. The transdermal route is, therefore, more suited to women at high risk for cardiovascular events.[18] Local oestrogen is effective in maintaining vaginal integrity. By ensuring that women are risk assessed for co-morbidities, cardiac and breast health threat of progestogens can be minimised by considering characteristics, dose and modes of administration of individual progestogens.

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Transdermal estrogen - a first-choice option in hormone therapy

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The Women's Health Initiative study, first published in 2002,[1] raised concerns about the overall health benefit ratio of menopausal Hormone Therapy (HT). The original publication suggested more harm than benefit, showing increased risk of coronary heart disease, stroke, breast cancer, and venous thrombosis. The concern caused to patients and medical practitioners resulted in a significant drop in the number of women taking HT. Subsequent publications from WHI[2] and re-analyses of other studies, such as the Nurses Health Study,[3] have highlighted that in younger recently menopausal women, there is in fact a decrease in overall coronary heart events and a 30% decrease in overall mortality in users of HT.

The WHI study investigated the use of an oral estrogen, conjugated equine estrogen (CEE), in hysterectomized patients and used with medoxyprogesterone acetate (MPA) in non-hysterectomized patients. The surprising results in the original WHI publication lead to an increased focus on alternative ways of using HT. These included using lower doses, using different estrogens and progestins, and using estrogen transdermally instead of orally.

This paper will focus on the potential health advantages of transdermal over oral estrogen.

In South Africa, transdermal HT is available in the form of patches and gels. Both estrogen only and combined estrogen/progestin patches are available. If the transdermal estrogen is used in non-hysterectomized patients, the progestogen has to be provided separately as a tablet.

The major benefits of transdermal estrogen are as a result of it not undergoing hepatic first pass metabolism. A large amount of the estrogen administered orally, be it CEE or estradiol, is converted to estrone during absorption though the gut wall. It is then further metabolized in the liver. During this process it has a significant effect on clotting factors that lead to an increase in thrombosis risk. It also affects lipoproteins and other cardiovascular risk markers. Transdermal estrogens, by avoiding hepatic first pass metabolism, do not have these effects.

Effect on thrombosis

Oral estrogens affect many clotting factors during hepatic first pass metabolism, but the major effects leading to increased thrombosis risk are the effects on coagulation inhibitors and on thrombin:

- Oral estrogen negatively affects coagulation inhibitors. Antithrombin (AT III) levels are decreased by oral estrogen.[4] Oral estrogen also increases Activated Protein C (APC) resistance.[4] APC is a potent thrombosis inhibitor and by increasing resistance to this protein, its thrombosis inhibitory activity is markedly decreased.
- Oral estrogens increase the rate of thrombin production and increase peak levels of thrombin,[5] again resulting in an increase in thrombosis risk.

Numerous studies, as well as WHI, have confirmed the increased risk of thrombosis with oral estrogens.

In the WHI estrogen and progestin arm,[6] the relative risk (RR) of thrombosis was doubled compared with placebo (RR 2.06 CI 1.57-2.70). Importantly, the effect of other risk factors for thrombosis such as age, weight and Factor V Leiden were enhanced by E/P therapy. In patients aged 60-69 years the RR was 4.28, in obese patients it was 5.69, and in patients who were Factor V Leiden positive it was 6.69.

In a recent meta-analysis[7] of observational studies, the RR of thrombosis for oral estrogen was 2.5 (CI 1.9-3.5), whilst for transdermal estrogen it was 1.2 (CI 0.9-1.7).

A case control study[8] (155 patients and 381 controls) compared transdermal and oral estrogen as regards risk for deep vein thrombosis and pulmonary embolus. Transdermal estrogen did not increase the risk for either condition. Adjusted odds ratios for DVT were 3.2 and 0.8 for oral and transdermal E. For pulmonary embolism they were 3.8 and 0.8 respectively.

A further case control study, the Estrogen and Thrombo-Embolism Risk (ESTHER) study[9] supported these findings with the risk being doubled for oral estrogen and not increased with transdermal estrogen. This study also looked at the effect on patients with additional risk factors for thrombosis. As with the WHI study, the increased risk of thrombosis was compounded in patients with prothrombin mutations[10] and in obese patients.[11] There was no compounding of the risk with transdermal estrogen.[10,11] The Menopause Estrogen and Veins (MEVE) cohort study[12] looked at whether oral and transdermal estrogen further increased risk of thrombosis in patients with a previous deep vein thrombosis. There was no compounding of the effect with transdermal estrogen (RR 1 CI 0.4-2.4) whereas with oral estrogen it was dramatically increased (RR 6.4 CI 1.5-27.3).

Stroke

WHI[13] showed an increase in ischaemic stroke risk with the use of oral estrogen (RR 1.31 CI 1.02-1.68). This increase in risk was present in all age groups. A meta-analysis of 28 RCT's[14] showed a similar increase (RR 1.29 CI 1.13-1.47). A nested case control study[15] comparing transdermal and oral estrogen found an increased risk similar to that seen in WHI with oral estrogen (RR 1.28 CI 1.15-1.41). The increased risk was seen with all doses. With transdermal estrogen there was no increased stroke risk (RR 0.95 CI 0.75-1.20). The risk was, however, dose dependent. When administered in "usual" or low doses (≤50µg) the RR was 0.81 (CI 0.62-1.05). With higher doses the risk was increased (RR 1.89 CI 1.15-3.11).

Coronary Heart Disease

There are no significant clinical studies comparing oral and transdermal estrogen as regards coronary heart disease. A Danish cohort study did, however, suggest a lower risk for myocardial infarction with unopposed transdermal estrogen than with unopposed oral estrogen. The RR with the use of oral estrogen was 0.98 (CI 0.90-1.96) whereas with transdermal estrogen it was 0.62 (CI 0.42-0.93). The difference between the two forms of therapy was significant (p=0.04)

There are numerous differences in cardiovascular intermediate endpoints which point to advantages with transdermal estrogen use, particularly in higher risk patients. Oral estrogens have some beneficial effects on lipoproteins in that they decrease total and LDL cholesterol and increase HDL cholesterol.[17] Triglyceride levels are, however, increased with oral estrogen and this may be of significance in patients with the metabolic syndrome which in itself is a high risk factor for coronary heart disease. Small particle LDL levels are also increased with oral estrogen[18] and this decreases the oxidative susceptibility of LDL which would be considered a negative effect. This does not occur with transdermal estrogen. Similar to oral estrogen, transdermal estrogen lowers total and LDL cholesterol, but unlike oral estrogen, it lowers triglycerides.[19]

Other differences between oral and transdermal estrogen suggest that transdermal estrogen has a better cardiovascular profile. Oral estrogens increase the inflammatory marker C reactive protein (CRP).[20] This is another effect of hepatic first pass metabolism. Raised CRP is, however, an independent risk factor for cardiovascular disease in women.[21] Transdermal estrogen does not increase CRP levels. Oral estrogen also increases another acute phase protein, serum amyloid A (SAA), which is an adverse risk factor in postmenopausal women.[22] Transdermal estrogen does not have this effect.

Other advantages of transdermal estrogen

Effect on breast tissue

There are no clinical studies comparing oral and transdermal estrogen as to their effect on breast cancer. A prospective randomized clinical study on 77 women randomized to receive either sequential CEE/MPA or transdermal estradiol gel/micronized progesterone showed less breast cell proliferation and therefore less breast density with the transdermal estrogen/micronized progesterone regimen.[23] It has also been shown that the above two regimes differ in their effect on gene regulation with the transdermal estrogen /micronized progesterone regime again having a more favourable profile.[24]

Effect on hepatic proteins

The increase of Sex Hormone Binding Globulin (SHBG) seen with oral estrogen use lowers free testosterone levels. This can have a negative impact on libido. This is not seen with transdermal estrogen. Patients complaining of a low libido whilst using oral estrogen should be changed to a transdermal preparation.

Thyroid Binding Globulin (TBG) levels are also increased with oral estrogen and a change in thyroid replacement dose may be needed. Again this is not seen with transdermal preparations.

Conclusions

The discussion above shows that transdermal estrogen has some clear advantages over oral estrogen, particularly in higher risk patients such as the older woman who wishes to continue with HT, patients with mild hypertension, diabetes or metabolic syndrome, smokers, and in obese patients. Given the many advantages of transdermal administration we should offer this form of HT as a first choice to all patients being considered for HT. In so doing we may lower the risk of adverse events and further increase the benefit vs risk profile with the use of HT in our management of menopausal patients.

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Weight gain in the menopause

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Obesity is increasing in incidence globally and is a big concern to many women as they transition to menopause. There has been a rapid epidemiological change in weight gain in South Africa with the prevalence of obesity now up to 30% in women aged 30 to 59.[1] The shift in population from a rural to urban environment has been associated with significant lifestyle changes and increased availability of foods high in fat and carbohydrates. Easy access to fast foods has also resulted in obesity. The effects of obesity are vast and include diabetes mellitus, cardiovascular disease, stroke and hypertension. Obesity is also related to an increase in dementia and malignancies such as endometrial, breast and colon cancer. Overweight women have a higher incidence of osteoarthritis and this adds to their inability to exercise.[2] Women in comparison to men are protected from heart disease prior to the menopause because of the anti-arthrogenic effect of estrogen which changes as women transition to menopause, especially if there are changes in body habitus, fat distribution and weight.

Computed tomography (CT) and magnetic resonance imaging (MRI) have shown that there is an accumulation of intra abdominal fat in postmenopausal women compared to premenopausal women.[3] This increase in abdominal fat is said to be due to the decrease in estrogen levels, even though the androgens remain steady, resulting in a decrease in resting metabolic rate coupled with decrease in physical activity. In animal models, estrogen has been shown to inhibit food intake. Waist circumference closely corresponds to cardiovascular disease and dyslipidemeia. The waist-to-hip ratio, which increases with menopause, is associated with an increase in visceral fat, a good indicator of the metabolic syndrome. Abdominal obesity is defined as a waist-to-hip ratio (WHR) of above 0,85 in females. WHR has been found to be a better predictor of mortality in older people than body mass index BMI or waist circumference alone.[4] The controversy regarding age, menopausal status and lifestyle behaviours which contribute to "the middle age spread" still prevails. This may all be a function of chronological aging itself. A study in Scotland followed premenopausal women over time to their menopause and found that the increase in weight gain did not differ between those that remained premenopausal over the study period and those that became menopausal in that same period of time.[5] Interestingly, rural women in Mauritius were less likely to have abdominal obesity (27%) compared to urban women in the perimenopause. This was thought to arise because of increased physical activity and less calorie containing diet because of socioeconomic status.[6] There is no doubt that the waist circumference in relation to the last menstrual period does increase.

Is weight gain a function of hormonal change that occurs with menopause or is it the result of aging? Most studies show a progressive weight gain of 0,5kg annually as we age, suggesting that this increase is due to aging rather than menopausal transition.[7] In the SWAN study (Study of Women's Health Across the Nation) women of 5 ethnic backgrounds were investigated and it was found that the median weight gain was 2,1 kg and was unrelated to menopausal status.[8] The perimenopausal phase is associated with an increase in abdominal girth and redistribution of fat to an android pattern rather than a gynaecoid distribution. Women with an increase in abdominal girth are subsequently at risk of an unfavorable lipid profile and cardiovascular disease. This intra-abdominal fat acts as an endocrine organ and it secrets substances, which increase the risk of metabolic syndrome, insulin resistance and Type 2 diabetes. Sex hormone binding globulin in postmenopausal women is negatively associated with adipose tissue and insulin resistance and this is independent of estrogen and androgen levels.[9]

What does seem to be important is the level of physical activity related to weight gain and abdominal circumference. The SWAN study showed that women who decreased their level of activity at midlife were associated with a much higher weight gain over time.[8] What does appear to be evident is that while an increase in activity does contribute to less weight gain, there still appears to be an increase in abdominal girth. Several studies have attributed this to changes in diet in the midlife with an increase in carbohydrate intake.

Several other factors are associated with obesity such as urbanization, poor education, parity, early marriage and family history of obesity. Depression is also associated with an increase in weight gain. Women in the perimenopausal phase are at higher risk of depression and as a result this further contributes to obesity. Second generation antidepressants, which are frequently used in peri- and postmenopausal women, contribute to weight gain. The most commonly used antidepressants that cause an increase in weight are clozapine (Clozaril), imipramine (Tofranil) and amitriptyline (Elavil). These drugs have an effect on the satiety centre and are involved in cholesterol and fatty acid biosynthesis. The SSRIs particularly lead to weight changes of which weight gain is more common than weight loss. Antidepressants, which do not cause weight gain, are ziprasidone (Geodon) and buproprion (Wellbutrin, Zyban). Apart from depression, overweight women suffer from psychosocial issues and the percentage of women with sexual dysfunction in the menopause is significantly higher in menopausal women with a high BMI. The treatment of metabolic syndrome and weight loss improves sexual function in these women.

The age of menopause is largely genetically determined and obesity has a strong genetic link. The Penn Ovarian Aging Study found that a high body mass index is associated with a later menopause. In obese women, enzymes such as aromatase and 7 beta hydroxysteroid dehydrogenase are increased in activity and consequently estradiol levels are elevated. A weight fluctuation of 5kg and an increase of BMI was also associated with a late menopause. Women who consume more alcohol, smoke and eat meat also have a later menopause. Despite the later menopause and the higher estradiol levels, women who are obese at the menopause have more severe symptoms. A reduction in abdominal circumference and weight in obese menopausal patients improves symptoms such as hot flushes, joint pain and sleep disturbances.[11]

In the Global Longitudinal Study on osteoporosis in women, it was found that obese women were twice as likely to fracture ankles and hips than women with a normal BMI and this contradicts previous belief that obese women loose less bone.[12] This is probably due to the fact that obese women are more likely to have other comorbidities such as diabetes, asthma and emphysema and are less likely to do weight bearing exercise.[12]

Most women believe that hormone therapy (HT) increases weight. A Cochrane review, published in 1999, and updated in 2011, showed that unopposed estrogen had no effect on weight gain when compared to women not on hormone therapy. There was insufficient data when the researchers looked at hip to waist ratio and body fat composition.[13] This non effect on weight gain lasted at least 48 months in the WHI review and dose of hormone therapy also did not appear to affect BMI. Patients on high doses of estrogen and or estrogen and progesterone did not appear to differ from those on lower doses. When combined hormone replacement therapy, continuous combined or sequential therapy was studied, there did not appear to be a difference in weight gain in women taking hormone therapy compared to women not on HT. Hip to waist and body fat composition also remained the same. HT, however, has favorable effects in that it decreases central adiposity. Oral estrogen when compared to transdermal estrogen had a small but significant increase in fat mass but it appears to cause an overall improvement in insulin sensitivity and decreases the development of type 2 diabetes.[13]

Perimenopausal and menopausal women should be encouraged to undertake a moderate physical activity of at least 60 min a day to ensure a normal weight. The elderly are prone to loss in muscle and bone mass. Resistant exercise has been shown to decrease intra-abdominal fat, improve lean mass and decrease the incidence of osteoporosis. An increase in physical activity by one hour a week can result in a 4cm loss in inta abdominal fat.[14] There is no doubt that exercise also decreases hypertension and type 2 diabetes.

A diet low in carbohydrates has been suggested to improve a decrease in central obesity and decreases type 2 diabetes. Ideally, any diet that restricts calories should not result in loss of protein. Weight control is essential in counseling peri-menopausal women and is critical to decreasing menopausal symptoms and improving general health. Contrary to belief, hormone replacement therapy does not add to the increase in weight gain, but may rather decrease accumulation of abdominal fat. Metformin is a useful drug for selected overweight individuals in the menopause and will treat insulin resistance and patients with type 2 diabetes. There is however no substitute for healthy eating and exercise.

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Gene editing and epigenetics

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Gene editing is a new expression to come out of the genomic lexicon.

For those qualifying in the last century, there are a considerable number of terms that were not familiar in the medical schools when they graduated that are now being used to describe genomic research. There are a plethora of original articles appearing in the major journals about genetic progress, biochemical manipulations and immunological responses all describing medicine at a molecular level.

Some of these articles are difficult to understand but they are chosen for publication as they represent the world's foremost medical research. Some are so esoteric as to be incomprehensible to the average clinician but others are instructive and give glimpses of new horizons. Terms are becoming assimilated into medicine that we will have to understand if we want to keep up with these trends. An example is gene editing in a paper by Tebas et al (NEJM 2014;370:901-10). It gives a glimpse of what can be done in the field of HIV therapy.

Scientists studying the way in which the HIV virus gains access to cells paid particular attention to a rare group of individuals who appeared to be resistant to HIV infection. Although the subjects had lifestyles which would make them highly likely to become HIV positive they remained infection free, so probing their genome could provide clues to HIV defence mechanisms that might have clinical application.

They discovered that the HIV virus gains entry into cells using 2 receptors. The first is a transmembrane protein called CD4 [CD 4 stands for cluster of differentiation 4 and describes a particular glycoprotein that is found on the surface of certain cells.

The best known of these cells are the T helper immune cells – now known as CD4 cells for short. Their count is used as a measure of the HIV infection process]. The second is a co-receptor protein called CCR5. However, the HIV resistant people had an unusual defect in the gene responsible for encoding the CCR5 coreceptor. The genetic defect blocks the normal receptor function of the CCR5 protein. Without the CCR5 working properly, the HIV virus cannot gain entry to the cell. The people who were resistant had a naturally occurring genetic defect (a homozygous deletion defect). This defect did not appear to affect other functions of the CD4 cells so they were HIV resistant but otherwise immunologically functional.

Armed with this knowledge the researchers studied a cohort of people who were HIV positive and who were being successfully treated with antiretroviral drugs. These volunteers had viral counts of zero and CD4 counts between 500 and 1000 per mm^3 and were in stable health and had normal CCR5 function.

They drew blood from these volunteers and extracted CD4 cells for "editing". Editing is a process whereby a particular portion of a gene sequence is cut out and replaced by a modified "rejoined" sequence. This is sophisticated genetic engineering but it was applied to the volunteers' harvested CD4 cells, in this case manipulating [or "knocking out"] the CCR5 gene thus rendering these cells artificially resistant to HIV entry. After editing, the cells were infused back into the donor's own circulation and the situation was monitored.

The scientists found that the modified CD4 cells functioned normally so they took the volunteers off their antiretroviral drugs. This allowed an HIV viraemia to ensue – and they noted that the modified CD4 cells lasted significantly longer than other unmodified circulating CD4 cells. In other words they had created HIV resistant cells by gene editing. In this experiment the volunteers had higher CD4 counts than the controls and therefore greater immunity while the modified cells survived thus effecting some, albeit temporary, therapeutic advantage. This proof-of-concept trial may encourage experimentation with genetically edited haemopoetic stem cell transplants and other strategies to combat HIV.

Another two contributions in the same journal illustrate genetic research directly related to Obstetrics & Gynaecology (Caburet et al NEJM 2014;370:943-9 and Huang et al NEJM 2014;370:1220-6).

In the first, the researchers identified a genetic defect in a family where the women had a high incidence of ovarian failure. Premature ovarian malfunction occurs in about 1% of the population but only a few of these women can have a genetic component identified. This research work has pin-pointed the particular locus of a defect that will be catalogued as a reference site to be explored in other women who present with a premature menopause.

The second involved a family where sisters were infertile without explanation. Genetic investigations showed abnormal gene coding for glycoproteins comprising the zona pallucida which have nutritional and protective functions for early embryos.

By investigating, recording and sharing the genetic sequencing of affected individuals or families it may be possible to build libraries of information which identify women who carry seriously debilitating disorders.

The genetic story is just beginning.

Epigenetics is another word that needs to be understood from the genomic lexicon. Epigenetics is the study of factors that cause genetic activity NOT attributable to DNA inheritance. That is, how the environment modifies the way genetic information is expressed.

The presence of a specific genetic sequence does not automatically result in a direct effect.

The fact that a sequence is present and associated with, say hypertension, does not mean that person will develop hypertension. Epigenetic factors play a role in whether the genetic material will result in a clinical outcome.

These factors, that modify gene expression, work by adding to or subtracting from the proteins that the gene encodes. For example a gene locus linked to mortality is affected by biochemical changes (like methylation) that allow it to function (be expressed) normally. If the environment does not allow this methylation to occur then the gene and its encoded proteins function incorrectly and this malfunction is associated with an increased risk of mortality. The particular locus (F2RL3) and its methylation malfunction is strongly associated with smoking. This may explain why smokers have raised mortality rates (Zhang et al J Int Epidem 2014; doi:10.1093/ije/dyu006).

Epigenetics is one of the reasons genomics is not a straight-forward science. It represents Nurture in the old "Nature versus Nurture" concept. Another complicating factor is the combination of genes required for a syndrome to manifest. Complex diseases like hypertension and diabetes require a number of genes to be present before they develop into a clinical picture. There are very few single defects [single nucleotide polymorphisms – SNPs or snips] that are responsible for diseases.

This is where whole genome sequencing runs into trouble. People who have their genome sequenced always discover incidental findings that are uninterruptable. These are called incidentalomas. Incidentalomas cause havoc because although they are abnormal, nobody knows what they mean – yet. There are about 4 million in everyone's genetic makeup, so the full interpretation of every genetic variation is a long, long way off.

Uterine morcellation

As minimally invasive surgical techniques expand in scope and style, notes of caution need to be sounded. One such issue is the spread of an unanticipated uterine malignancy by morcellation of myometrial tissue within the abdominal cavity.

Electric morcellators shave or slice uterine (or other) tissue into strips that can be removed via laparoscopic portals thus enabling large organs to be extracted through small apertures. This makes enlarged uteri – from fibroids or adenomyosis – accessible to minimally invasive techniques whether manually or robotically approached.

Warnings have now been made public in the United States about cases where undiagnosed uterine sarcomas that have been morcellated within the abdomen inadvertently spreading malignant debris, the presence of which was not suspected. This is thought to "up-stage" the cancer and worsen the prognosis of an already aggressive tumour (Hampton JAMA 2014;311:891-3 and Kho & Nezhat JAMA 2014;311:905-6).

Although leiomyosarcomas are rare, their morcellation and spread intraperitoneally is a concern so tissue isolation within a bag prior to dissection may provide a safe alternative and is being explored. In the meanwhile informing patients of the potential harms is being advocated rather than calling for the entire abandonment of the procedure. The debate continues.

Surgical checklists

Do you operate in your gynaecological practice?
Does the theatre in which you operate have checklists? Are they adhered to?

Surgical safety checklists have been shown to reduce errors, complications both intraoperative and post-operative and hospital stays plus assisting with team-building. The reports are there for all to read starting with the seminal article 5 years ago by Haynes et al. (NEJM 2009;360:491-9) which showed up to half of all complications are avoided by introducing, and the correct use, of check-lists.

If these innovations save lives and help avoid non-fatal mistakes, surely they should be made compulsory, as they have been in some parts of the UK, the Netherlands and regions of Canada?

But human error is a complex phenomenon. We perform better when we are being observed (which is the Hawthorne effect) and we do not take kindly to being coerced into routines that are thrust upon us. And so it is with surgical checklists. Yes, their strict and full use does lead to fewer complications but how this occurs bears investigation. Where the effects have been investigated it appears that communication, team building, full implementation, hospital infrastructure and personality attitudes and collaboration underpin

success or failure (Leape NEJM 2014;370:1063-4 and Urbach NEJM 2014;370:1029-38).

Surgical skill and technique are important but outcomes depend on other factors which are usually under the control of others with whom we need to collaborate for optimal results. That is the lesson of ticking the boxes of surgical safety checklists.

PSA testing again

The American confusion with prostate-specific antigen (PSA) testing continues. PSA levels were originally used to monitor prostate cancer treatment responses and were never intended to be adopted as a screening test. Swept up by a tide of enthusiasm to "do the right thing" American men were encouraged to have annual PSA screening and arbitrary normal levels were set. It soon became apparent that many "benignly enlarged" neoplastic prostate glands were being diagnosed as cancerous that men would have "died with but not from".

The harms of such over-diagnoses and over-treatments left many men worse off than if they had not embarked on a screening programme in the first place. Observational data and recent randomised trials have failed to provide clear direction for medical science to supply evidence-based reasoning on PSA screening. On balance screening causes more harms than benefits and fewer and fewer national organisations recommend its use. In the US some societies suggest "shared decision making" but none overtly support testing. One of the most influential groups (The US Preventative Services Task Force) has finally stated PSA testing should not be offered to men of average risk.

Now a Review of the Evidence has been published in JAMA by Hayes & Barry (2014;311:1143-9) distilling all the articles available and concluding "Only men who express a definite preference for screening should have PSA testing."

In the writer's opinion this is outrageous. If there is no clear medical evidence in favour of testing (which there cannot be if the authors say doctors' opinions should be neutral) then how can a doctor "agree with the patient's wishes"? Surely as the person entrusted with the man's wellbeing the profession should say there is no evidence in favour, but there are harms, so on balance is it better not to be tested? The advice from the UK is clear – PSA testing is not in equipoise – it is on balance harmful, so do not offer it or agree to carry out the test (Wilt & Ahmed BMJ 2013;346:f325).

Surely, it is time for US doctors to stop abrogating their responsibilities and say "we don't know but first do no harm and don't take a PSA test"?

Cardiovascular disease

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More women will die of cardiovascular disease than from any other cause. The best documented risk factor for CVD is raised blood pressure which is strongly associated with coronary heart disease, heart failure, stroke and vascular dementia. Hypertension over a long period of time is a powerful predictor of future cardiac events so the measurement of a woman's BP is an essential part of her physical examination at any age (Sarafidis & Bakris JAMA 2014;311:471-2).

There is ample evidence that lowering a raised BP is preventative of later CVD and the risk of death. So at what level of BP should action be taken? Clear guidelines have been issued by an expert group in the United States. (The Joint National Committee – James et al JAMA 2014;311:507-20) and are likely to be the accepted standard worldwide. For people of otherwise low-risk the numbers are:-

- Younger than 60 years a BP of greater than 140/90 should be treated
- Those older than 60 years a BP of greater than 150/90 should be treated

Treatment should in the first place be lifestyle changes with smoking cessation, weight reduction, exercise and a healthy diet. Thereafter medication is indicated initially with thiazide-type diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers.

Recently there has been a spate of articles on the advantages of lowering low-density lipoprotein levels. If lipoprotein levels are too high then lowering them with statins reduces the risk of CVD and death. The problem is the level at which healthy people should be considered at risk and statin therapy initiated. Should statin commencement be based on a series of factors that give a composite risk of developing CVD over the next 10 years or biochemical levels?

The American guidelines issued by their College of Cardiology recommend the risk assessment approach with an at-risk percentage of 7.5% of developing a CVD problem in the next 10 years being the point above which high-intensity statins are recommended and the range of 5 to 7.4% that which statins should be considered. The most widely accepted means of assessing CVD risk is a composite algorithm called QRISK. It is accessible at www.qrisk-2013.org and quantifies age, BP, smoking, cholesterol, BMI, ethnicity, deprivation, family history and co-morbidities.

These are applicable to asymptomatic people and the numbers potentially involved are enormous. World-wide this would amount to more than a billion people. If accepted by society on the encouragement of their medical advisors then every person in every community in every country would need to be assessed and those at risk "statinised" according to their composite score – which would be "one of the greatest achievements or one of the worst disasters of medical history (Ioannidis JAMA 2014;311:463-4).

Apart from patients who have atherosclerotic disease and/or diabetes, the latest American guidelines categorise 2 other groups based on their biochemical risk. The first consists of adults with low density lipoprotein levels of greater than 190mg/dl and the second adults older than 40 years who have low density lipoprotein levels between 70 and 190mg/dl plus a 7.5% or greater 10 year risk of atherosclerotic CVD. People with a 5 to 7.5% risk should be considered to statin therapy.

Needless to say the stakes are high both financially and socially with the benefit/harms ratios very much in the eye of the beholder. Who knows which statin takers will benefit by not suffering CVD? Their numbers must be weighed against those who will be laid low by the detrimental side effects like myalgia and diabetes. The statin wars are well under way!

Breast cancer and CVD

If women are asked "what is most likely to kill you?" the two commonest answers are breast cancer and heart disease. The fact that CVD is 10 times more likely to be a woman's cause of death than breast cancer does not seem to change perceptions about the risk of each.

This misperception could have much to do with publicity, fear and femininity as well as the concept of being a woman. This social "drawing together in sisterhood" of women around symbols provides strong identity factors that tend to thrust images into their consciousness and increase their importance. The impact is then translated into numerical significance.

Feared or dramatic events which make the news are likely to be remembered and appear more frequent occurrences than more mundane incidents (Dobelli R. The art of thinking clearly. 2013. Sceptre pp 203-4) Breast cancer can also be viewed as an assault on an exclusively feminine icon and therefore something against which all women should rally – a tribal threat response (Kahan et al J Empir

Legal Stud 2007;4:465-505). The American reaction to data on mammography in 40 to 50 year olds doing more harm than good was not well received, despite its intellectual rigour and the vast majority of US women polled said they would continue to have mammograms despite the evidence. Rosenbaum (NEJM 2014;370:595-7) suggests that emotional responses and "visceral allegiances" play a larger role than is accepted in decision making about choices affecting health.

Cardiovascular health is vastly more important than mammograms and all ways of conveying such messages should be explored and used to guide lifestyle choices. Protecting against breast cancer: Any woman can reduce her chances of developing breast cancer by leading a healthy lifestyle of not smoking or being overweight, by eating healthily and exercising regularly. But some women will remain at high risk because of a family history, like having 2 or more blood relatives with the disease, a mother or a sister who developed breast cancer before the age of 50 years or a mother or a sister who had bilateral tumours. There are also those who inherit the specific BRCA1 and 2 mutations which can be screened for by genomic testing.

Prophylactic mastectomies are the most effective preventative measure, although the less radical is hormone therapy, usually tamoxifen or raloxifene, which are anti-estrogenic and lower breast cancer risk by 50% and 40% respectively. The problem is side effects both consisting of hypo-estrogenic symptoms or haematological disorders. Another biochemical approach is to block the conversion of endogenous androgens to estrogens which is driven by the aromatase enzyme. Inhibitors of this enzyme are exemestane and anastrazole, both of which are used to prevent breast cancer recurrence as part of a postmenopausal woman's chemotherapy.

The results of a 5 year study have recently been published describing anastrazole's role as a prophylactic agent in high risk women (Cuzick et al Lancet 2014 doi:10.1016/S0140-6736(13)62292-8). This was an international placebo controlled trial with nearly 2000 women in each arm – the IBIS II study – and the results were "as good as we could have hoped for" according to the lead author. Only 2% of the anastrazole group developed breast cancer compared with 4% in the control group (hazard ratio of 0.47, 95% CI 0.32 – 0.68). This provides strong evidence in favour of anastrazole's use in post-menopausal women at high risk of breast cancer.

Mammography – a Canadian study

Twenty five years ago a Canadian study was started comparing screening for breast cancer by mammography with screening by physical examination. Nearly 90 000 women between 40 and 60 years old were randomised to receive 5 annual mammograms, or no mammograms – the control group. All participants had 5 annual breast examinations and the primary outcome was mortality from breast cancer 7 years later and 25 years later (Miller et al BMJ 2014;348:g366).

The results showed no difference between the 2 groups. The hazard ratio of death associated with mammography was 1.05 (95% CI 0.85 – 1.30). There were overdiagnoses in the mammogram group of 22% which the authors describe under "Harms". Kalager et al (BMJ 2014;348:g1403) in an editorial question the wisdom of mammography programmes in the face of ongoing evidence that it is improved treatment and not screening that is lowering breast cancer mortality rates. They agree with the Canadians that screening mammography rationale needs to be urgently reassessed but fear this is unlikely to happen because "governments, research funders, scientists and medical practitioners may have vested interests in continuing activities ....." Lest JASS be queried for not having an opinion on mammography, here it is: JASS's editor does not support screening mammography for low-risk women at any age.

BRCA mutations & treatment

Normally BRCA 1 & 2 genes suppress the risk of breast cancer. Women who have abnormal genetic sequencing at these sites are said to carry the BRCA 1 or 2 "gene mutation" and have a 5 times higher risk of developing breast cancer than women who do not have the mutation. Their lifetime risk is 60% with an additionally increased risk of ovarian cancer.

Most women with the BRCA mutation only find out this propensity when they are already diagnosed with the malignancy and then undergo investigation. They have a much greater chance of cancer in their remaining breast than women without the BRCA 1 or 2 mutations.

So should these women have the other breast removed at the same time as their original surgery, in other words, a prophylactic contralateral mastectomy?

Data now published by Metcalfe et al (BMJ 2014;348:g226) demonstrate that the additional surgery would considerably reduce such a woman's risk of death from breast cancer. The researchers have shown in BRCA positive women with breast cancer, 88% will survive for 20 years if they have bilateral mastectomies whereas 66% will survive if they have a unilateral mastectomy.

Women facing such decisions face enormous dilemmas (Michels BMJ 2014;348:g1379) but at least there are reliable statistics to assist their choices.

BSO at hysterectomy

It has long been a contentious issue whether a woman's ovaries should be removed at the time of hysterectomy for benign disease. Especially in older women there are arguments in favour of bilateral salpingo-oophorectomy

(BSO) on the grounds of reducing future risk of developing ovarian cancer (Jacoby et al Arch Int Med 2011;171:760-8) but the ongoing endocrine production of postmenopausal ovaries suggests advantage to their preservation.

Now a large study has found that retaining the ovaries at surgical removal of the uterus may protect against the possible development of diabetes in the future (Appiah et al Diabetic Care 2014;37:725-33). It is accepted that ovarian hormones regulate glucose and insulin sensitivity so it is feasible that BSO would influence later diabetic status. After a follow-up of a decade there was indeed a difference in diabetic incidence in women who had their ovaries removed and the general population (Hazard Ratio 1.57, 95%, CI 1:03-2.41) after adjustment.

The researchers make the case for these endocrinological aspects to be taken into account when surgery is being planned. Chronic conditions may be influenced so cancer risk is certainly not the only consideration. A woman's life-time risk of ovarian cancer is 1.2%

South African Menopause Society NEWS

Comments by the President

There have been a number of excellent congresses this year and I have had the privilege of participating in two of them. In May, the International Menopause Society had their World Congress in Cancun, Mexico, which was attended by over 2500 delegates and had over 400 oral and poster presentations. IMS has gone from strength to strength and produced a congress that was not only in a wonderful environment but it had a most informative scientific programme delivered by a superbly assembled powerhouse faculty. David Archer and Susan Davis are to be congratulated for putting together such a meaningful scientific programme. How thinking has changed from the dark days following WHI. The programme had a strong emphasis on present day perceptions pertaining to the heart, brain, breast, thrombosis and sexual function in menopausal women, and more and more is positive! There was much discussion about screening for breast cancer, with as many presentations in favour as presentations opposing routine screening. South Africa has produced some extremely notable and highly reputable figures in the world of menopausal women, with Wulf Utian, Morris Notelowitz, Ernst Sonnendecker and Denis Davey being just a few to mention. There is another who most definitely now joins these ranks, and that is Tobie de Villiers. Tobie has been the President of the International Menopause Society for the last 3 years and his swan song was the congress. Tobie runs a very successful practice in Cape Town, yet he has managed to lead IMS "from the front", has been prolific in producing scientific articles, is an accomplished researcher and an international expert in bone health and has become a very much in demand as an international and local speaker. He gave a magnificent van Keep Memorial lecture at the congress which outlined the road taken from yesteryear today with view to bone health in menopausal women. He has been magnificent. Tobie deserves every bit of praise heaped on him, as well as our deepest gratitude, for how well he "flew our flag" in the international arena these last 3 years. Tobie continues to be on the executive committee of IMS for another 3 years as past president.

It is no mean feat organizing national conferences, but from our local perspective, Stellenbosch University, under the guidance of Gerhard Theron and Tinus Kruger, managed to give us an exceptional SASOG Congress, which had all the elements; great lectures, great food and great entertainment. A wonderful congress enjoyed by over 750 delegates and over 60 trade companies. I thoroughly enjoyed the Margaret Orford Lecture delivered by Professor AP van Niekerk from Stellenbosch University in which he gave a thought provoking presentation pertaining to the ethical boundaries of advanced reproductive technology. A most enjoyable congress and our special gratitude to Gerhard Theron and his team for an outstanding event.

Oscar Shimange, Trudy Smith and Theo Kopenhager are hard at work organizing the next National South African Menopause Society Congress which will take place on 26-28 February 2015 at the Sandton Convention Centre. The scientific programme is exciting and I urge all interested in menopausal women's health to diarise these dates and attend. There will be 4 workshops on the Thursday preceding the start of the congress which will have significant practical value.

I wish all our readers a happy viewing of the world cup and may the best team win.

Franco Guidozzi

SAMS Mission Statement

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

SAMS Congress 2015

26-28 February 2015
Sandton Convention Centre, Johannesburg
Please diarise. More details to follow.

Become a SAMS Member today and enjoy the benefits:

- Monthly Electronic Newsletter Menopause Matters
- Bimonthly faxed Newsletter News by Fax
- Menopause Focus every 3 months
- Regular scientific meetings featuring acknowledged experts in the field
- Discounted registration fees at SAMS conferences
- Guidelines and updates on international menopause related issues

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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