Menopausal transition and incontinence

The concept of menopausal transition stages is being more carefully studied and will no doubt be adopted into the obstetric and gynaecological lexicon. To help clinicians understand the terminology, the following definitions are offered:

- premenopause – the time of regular hormonal patterns with less than 3 months of amenorrhoea and no menstrual irregularities in the previous year
- early perimenopause – less than 3 months of amenorrhoea with some menstrual irregularities in the previous year
- late perimenopause – 3 to 11 months of amenorrhoea
- postmenopause – 12 consecutive months of amenorrhoea.

The menopausal transition stages are determined by history, and their duration is personal to each individual. Using these terms, health care workers can describe the physiological changes experienced by women more clearly, and a study in the USA has tracked a cohort of women annually for 6 years to help establish the normal distribution of events. It is called the study of Women's Health across the Nation (SWAN) and has recruited over 3 000 women with excellent (80%) retention rates over the entire trial.

Waetjun *et al.* report on urinary incontinence in the group, with interesting results (*Obstet Gynecol* 2009; 114: 989-998). Women describe a slight increase in incontinence from the premenopause to the early menopause. The actual figures are from 16% to 18% for any incontinence. From early to late perimenopause genuine stress incontinence decreases, but urge incontinence is unchanged. From late perimenopause to postmenopause reporting of both stress and urge incontinence decreases, with the figure for any incontinence now at 8%.

The researchers believe that the initial increase may be due to 'over-reporting' of a worrisome symptom while other untoward events are being experienced, as increasing body mass index and the development of diabetes frequently accompany the transition years in American women. Their overall finding – that incontinence decreases significantly as a symptom through the menopause years – will be reassuring to clinical practice advisors. Since factors such as being overweight and the optimal management of diabetes are modifiable, positive steps in terms of lifestyle can be strongly reinforced.

Hormone use and ovarian cancer

Most studies have found an increased risk of ovarian cancers in woman using hormone therapy postmenopausally. Research does not suggest differences in risk with different preparations – oestrogen only or combined with progesterone – or routes of administration, but does indicate a uniform non-accumulating risk with duration of use. Now a national study from Denmark provides further information on nearly a million women over the past decade (Morch *et al.*, *JAMA* 2009; 302: 298-305). Unsurprisingly most of the tumours detected were epithelial cancers, and the increased risk of current hormone users compared with never-users showed an incidence rate ratio of 1.38. Once a woman stopped hormone use her risk dropped as follows – 0 - 2 years = 1.22, 2 - 4 years = 0.98, 4 - 6 years = 0.72 and more than 6 years = 0.63.

In the perspective of absolute risk the increase is small, amounting to 0.12 per 1 000 years or 5% of all ovarian cancers in the study, so it is another factor to be taken into account when assessing the risks or benefits of hormone use.

HRT and lung cancer

The Women's Health Initiative trial continues to produce data in new spheres. There are continued *post hoc* analyses between the women who received oestrogen plus progesterone and those allocated to placebo.

Because oestrogens are associated with modulating effects on lung cancers it seemed prudent to look at the deaths from this disease in hormone takers and tcontrols (Chlebowski *et al.*, *Lancet* 2009; 374: 1243-1251). Of 16 000 women recruited and followed up for 8 years, 113 died of lung cancer, 73 in the HRT group and 40 in the placebo group. On closer analysis it appears that oestrogens affect survival (not the incidence of the cancer), and more specifically longevity, in those with non-small-cell lung cancer.

Self-evidently this reinforces the fact that women should not smoke, and nor should older women without symptoms be given oestrogens.

Approaches to osteoporosis

Bone mineral density depends on the balance between osteoblast and osteoclast activity. Osteoblastic activity is a function of age and endogenous anabolic substances, but only one medication marketed for treatment of osteoporosis works by stimulating new bone formation – the parathyroid hormone teriparatide. All the others – the so-called anti-resorptives, such as the bisphosphonates, selective oestrogen receptor modulators (SERMs), oestrogens and calcitonin – work by tempering osteoclast activity, which slows the resorptive process.

Now another contender is being tested. A new approach uses a human monoclonal antibody against a key molecule that mediates osteoclastic development, activity and survival. It is called denosumab and neutralises the receptor activator of nuclear factor kB ligand (RANKL), thus slowing bone degradation (Khosla, *NEJM* 2009; 361: 818-820). Trials in postmenopausal women and in men receiving androgen-deprivation therapy for prostate cancer have shown denosumab to be effective in maintaining mineral density and preventing fractures.

The research is novel and follow-up is only over 3 years, so problems with immune system effects may yet surface but so far have not arisen. Such is the order of magnitude of the morbidity caused by osteoporosis that these 'brave new world' agents are being developed and tested (Smith *et al.* and Cummings *et al.*, *NEJM* 2009; 361: 745-755 and 756-765).

Osteoporotic vertebral fractures

Osteoporotic vertebral fractures are common, affecting about one in four people. Women are more vulnerable than men and the mean age of occurrence is about 80 years. The natural history is that these fractures heal, but some result in chronic pain requiring long-term measures that can include hospitalisation.

Since the estimated expenditure on osteoporotic vertebral fractures is $15 billion annually in the USA alone, any means of enhancing recovery would be welcome (Weinstein, *NEJM* 2009; 361: 619-621). One mechanism is the injection of 'medical cement' directly into the compression fracture site. This is called vertebroplasty, and the cement used is polymethylmethacrylate (PMMA). It is claimed that the procedure brings immediate stability and pain relief, but randomised trials have been lacking.

Now two studies have been published that include sham injections versus active PMMA injections (Buchbinder *et al.* and Kallmes *et al.*, *NEJM* 2009; 361: 557-568 and 569-579). Both showed no difference between vertebroplasty and sham injections, which again brings into sharp relief the dangers of band-wagoning new therapies without proper evidence.

Zoledronic acid and bone loss

Postmenopausal women are susceptible to bone loss. There is a continuum from low bone mass, through osteopenia to osteoporosis, with concomitant increasing risks of fracture. The considerable morbidity and mortality associated with such fractures makes their prevention a major public health objective, and pharmacological agents offer much in the way of protection.

Estimation of the risk of fracture can be reasonably accurately calculated using the computer algorithm FRAX (www.shef.ac.uk/FRAX/), or advice can be obtained from www.nof.org/professionals/clinicians_guide for informed patients.

All management starts with prevention, which includes exercise, calcium and at least 800 IU vitamin D per day in older women. When treatment is required oestrogens are of value, but their long-term use is a matter of personal perspective. Bisphosphonates work, but their track record for being taken consistently orally is patchy so the intravenous form – zoledronic acid – given on an annual basis is being investigated. McClung *et al.* conducted a trial over 2 years matching 5 mg zoledronic acid against placebo and found unequivocal evidence of bone loss prevention for the active medication (*Obstet Gynecol* 2009; 114: 999-1007).

As the population ages more tailored treatments will need to be devised, and 12-monthly infusions appear a viable option.

Breast cancer survivors on aromatase inhibitors (AIs) constitute another group at risk from bone loss. AIs may prove superior to tamoxifen for recurrence prevention and regular IV zoledronic acid has been shown to be superior to intermittent use in bone mass preservation. It seems promising, so formal publications are awaited with interest (32nd Annual San Antonio Breast Cancer Symposium: Abstract 4083, presented 11 December 2009).

Treating chronic pelvic pain

Chronic pelvic pain is a major problem in gynaecology. By definition it is said to occur if it has been present for at least 6 months and has no 'actionable' pathology as proven by laparoscopy and/or ultrasound. It can be constant or cyclical and can be associated with menstruation or intercourse. It is common, occurring as frequently as asthma or back pain, and significantly reduces a woman's quality of life.

Pelvic somatic pain is thought to be conveyed through nerve complexes and parasympathetic ganglia in the uterosacral ligaments. Theoretically, ablation of those nerve trunks by laser or electro-diathermy should offer pain relief. The procedure is called laparoscopic uterosacral nerve ablation (LUNA). It has become widely used as a complement to diagnostic laparoscopy, but its efficacy has never been tested by a randomised trial. The publication of the LUNA Trial Collaboration conducted in 18 UK hospitals now makes good this deficit in our knowledge (Daniels *et al.*, *JAMA* 2009; 302: 955-961).

The researchers allocated nearly 500 women to LUNA or no LUNA at the time of laparoscopy without disclosing to the patients whether they had received the ablation or not. All participants were followed up on 6 occasions over the next 5 years. There was an initial general improvement over the first 6 months in both groups, which the authors attribute to the reassurance derived from being told that no serious cause had been found for their pain. Thereafter no differences were found in pain relief or quality of life in the women who had the LUNA procedure compared to those who did not – in any of the multiple analyses at any time duration.

This is an important negative finding, as LUNA is not without its risks and costs. It is to be hoped that these results will discourage the use of a potentially dangerous manoeuvre that has no scientific proof of benefit.

Diet and Alzheimer's disease

There may be a link between a healthy diet and a decreased risk of developing Alzheimer's disease. Two articles and an editorial in *JAMA* point in this direction, with a Mediterranean diet plus exercise playing a role in protecting against cognitive decline in late life (Scarmeas *et al.*, 2009; 302: 627-637, Feart *et al.*, 2009; 302: 638-648 and Knopman, 2009; 302: 686-687).

A Mediterranean diet consists of a high intake of plant food such as fruit, nuts, legumes and cereals as well as fish, moderate wine consumption, and little red meat and poultry, with olive oil being the primary source of mono-unsaturated fat.

Exercise is measured in metabolic equivalents (METs) of physical activity, which represent energy consumption while participating in aerobics, jogging, bicycling, swimming, playing ball games, hiking, walking, dancing, golfing, bowling, and gardening.

The studies showed advantages of both diet and exercise in staving off mental regression. The fact that a Mediterranean diet is associated with greater longevity, reduced risk of cancer and cardiovascular disease as well as neurodegenerative disease should give us all cause to re-look at our own, and our patients', lifestyles.

Pregnancy rates after OCs

There are many anecdotal stories about rebound or delayed fertility after stopping oral contraceptives (OCs). The low oestrogen dosages and newer progestins all have excellent contraceptive profiles and cycle control, and now a large European study confirms their safety in terms of post-OC fertility.

Cronin *et al.* (*Obstet Gynecol* 2009; 114: 616-622) tracked nearly 60 000 OC users, including those on drospirenone pills, to determine their satisfaction with their contraceptive efficacy and their chances of pregnancy after stopping. About 20% achieved a pregnancy in their first cycle after cessation and 80% after one year, irrespective of the type of OC they were taking. These data are comparable to women wishing to conceive but not having been on OCs. Naturally women are older when they stop contraception than when they started, and age has an effect on fecundity. OC use does not positively or negatively affect age-appropriate fertility.

Postmenopausal lifestyle

It is clear that a woman's lifestyle can modify her health after the menopause. This may seem self-evident, but the data appearing in the journals are impressive.

Adiposity

In affluent societies longevity is increasing, with a quarter more people living to 75 years or older than a century ago. Life expectancy in the USA has now reached an all-time high of 78 years for the population. Will this trend continue, or will the march of adiposity halt or even reverse the statistics? Certainly being overweight or obese is now much more common, with 66% of women in the USA falling into this category today compared with 15% 30 years ago.

Looking at the effects of a raised body mass index (BMI) on health in older women, Sun *et al.* (*BMJ* 2009; 339: b3796) showed that being overweight in midlife reduces a woman's chances of enjoying optimal health in old age. This was a large study of over 17 000 nurses who were healthy, in their 50s and lived at least another 20 years, and it revealed an inverse linear relationship between BMI and health. The more overweight the women were, the lower their chances were of a healthy old age, or put another way, an obese woman has 80% lower odds of a healthy survival than a lean woman.

Exercise

It has long been known that women who exercise regularly have a lowered risk of breast cancer postmenopausally. The risk reduction is about a third, but exactly when and how much exercise is needed remains unanswered. To help resolve the 'timing and intensity' query, Peters *et al*. (*BMC Cancer* 2009; 9: 349) asked over 100 000 women about their physical activity and linked it to their propensity for developing breast cancer.

It is clear that moderate to vigorous exercise in late adulthood offers the greatest protection. The last decade premenopausally seems the most critical, and the research reinforces the notion of breast cancer risk being modifiable by lifestyle. The mechanism is probably by a combination of lowering sex hormone levels, modulating insulin metabolism and reducing chronic inflammation. Another benefit of keeping fit.

While on the subject of breast cancer, it seems that women who experience breast tenderness on starting hormone replacement therapy may be more at risk from breast cancer than those who do not develop symptoms. Looking back on symptoms reported by women in the active treatment arm of the Women's Health Initiative study, Crandall *et al.* (*Arch Intern Med* 2009; 169: 1684-1691) concluded that new-onset tenderness was associated with an increased risk of breast cancer. Self-reporting of tenderness compared with no tenderness gave women a hazard ratio of 1.5, which aligns it with other indicators of risk assessment in the Gail model.

What women experience at the menopause may give important clues as to their future risk profile. History-taking and advice about lifestyle are crucial in the perimenopausal period.

Hot flushes and HRT

The causes of hot flushes are imperfectly understood. However, it is known that hypo-oestrogenism at the time of the menopause leads to intermittent cutaneous arteriolar vasodilatation. This effect is readily reversed by oestrogen medication.

It has been postulated that 'oestrogen hypersensitive' women may have different cardiovascular risk profiles (and possibly osteoporosis risk profiles) to women who experience fewer oestrogen-sensitive symptoms. They may also be more sensitive to hormonal therapy. The Woman's Health Initiative trial did show that oestrogens given well past the menopause adversely affected some women's cardiovascular status, and one explanation was that the oestrogen was delivered too late or after the 'window of opportunity', when the resetting of cardiovascular function had taken place. A second explanation may be that women have innately different cardiovascular risk profiles that become apparent in their responses to oestrogen deprivation.

Working on this second supposition, Tuomikoski *et al.* from Finland (*Obstet Gynecol* 2009; 114: 777-785) carried out tests on the cardiovascular effects of oestrogens on two groups of women within 2 years of their menopause. The two groups were those with intolerable hot flushes defined as 7 or more per day ('flushers') or those with mild, tolerable flushes defined as 2 or less per day ('non-flushers'). The researchers did indeed find that the two groups responded differently to exogenous oestrogens as tested by pulse wave analysis and endothelial function parameters.

The 'flushers' had favourable cardiovascular responses to oestrogen therapy, but the 'non-flushers' demonstrated more unfavourable cardiovascular responses to oral oestrogen treatment. The authors suggest this may partly explain the ambiguities in the results between observational trials and randomised trials. It may be that profiles, both symptomatic and laboratory, will assist clinicians advising on who should and should not remain on hormone therapy.

Vasomotor symptoms and mortality

Night sweats at the time of the menopause are unpleasant symptoms. Although they may present concurrently with hot flushes, they may have different mechanisms of origin. It may be that the two symptoms reflect differing vasomotor sensitivities, and these in turn could be prognostic factors for later cardiovascular disease.

This possibility was observed by Svartberg *et al.*, who followed up a group of women for 20 years and related symptom complexes to cardiovascular survival (*Menopause* 2009; 16: 888-891). Three-quarters of their recruits experienced hot flushes, but only 40% of these had night sweats. Those who had the sweats turned out to have a third less risk of all-cause mortality.

This may be a chance finding or illustrate a differing propensity to risk in response to falling oestrogens. Either way, it could be a compensatory thought for those suffering from these unpleasant menopausal events. Perhaps there are sub-groups of women whose cardiovascular systems behave differently perimenopausally. Work from Finland suggests that women who have severe vasomotor symptoms benefit from hormone replacement therapy, while those without severe symptoms are vulnerable to hormonal side-effects – especially if they take oral oestrogens (Tuomikoski *et al.*, *Obstet Gynecol* 2009; 114: 777-785).

Over-screening?

The point of screening is to move the detection of a serious disease 'upstream'. This means detecting aberrations closer to when the process starts, so that interventions can prevent progression. But this presumes that early deviations always progress to more sinister levels, and that interventions are harmless.

Patently both inexorable progression and risk-free interventions are false suppositions. But these facts are lost when a high profile 'celebrity' dies of cervical cancer at age 27. The cry goes up from the public and the profession for more screening, more often and at an earlier age.

It is vital to remember that screening is a two-edged sword. Routine mammography and cervical screening can detect early disease, but there are other considerations. In both cervical and breast cancer we are aware that early changes can be self-limiting.

The latest data on breast cancer screening indicate that one-third of interventions in response to abnormal mammography result in unnecessary procedures. Women are enduring lumpectomies, mastectomies, chemotherapy or radiotherapy, which are over-treatments – hardly trivial insults.

We know a great deal about the aetiology of cervical cancer and recognise that HPV is initially a short-lived infection. Nobody would recommend screening for the virus in teenagers, although this is when a considerable proportion of infections occur. It would cause havoc. Similarly, many cytological changes are difficult to interpret as 'premalignant', and if the threshold is set too low the result would be overwhelming referrals for colposcopy. Recent research shows early triaging to be counterproductive. In developed countries no screening should start before the age of 25 years, as the maximum benefit is in women aged 35 to 65.

The problem is that there will always be outliers – the few very young or very old who escape the net and cause over-reaction. There is also the cost of screening to be considered. Personal time off work, the employment of screeners, cytologists and all the transport and administrative staff in the industry, not to mention the allocation of public time, money and resources. We would all do well to remember that the net should not be made so fine that it cannot the dragged through the water.

Screening for breast and cervical cancer can cause harm. Never mind the physical harm, too much screening is robbing the public of one of its most precious possessions – that of a sense of wellbeing (references: Jorgenson and Gotzsche, *BMJ* 2009; 339: b2587; Saaieni *et al.* and the TOMBOLA Group, *BMJ* 2009; 339: b2948, b2546, b2548, b2549; Spence, *BMJ* 2009; 339: b2937).

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