Managing menopause

Part 2: what are the choices in treatment?

We continue our foray into menopause and its management. Part 1 of this article discussed how differently individual women experience the menopause and the importance of tailoring management accordingly.

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For the woman with menopausal symptoms who requires treatment, the choices are increasing. It is important first to gain an understanding of the woman's attitude towards and experience of medication – both her personal view and the information she has received from her family and friends.

Options for treating menopausal symptoms

The oral contraceptive pill

A woman who is still menstruating and has menopausal symptoms may find the low dose (15 to 20 μg) oral contraceptive pill (OCP) ideal. In addition to relieving symptoms, the OCP can control bleeding problems and provide contraception. The usual contraindications apply (Table 1).

The question then becomes: how long should treatment continue? Some women want to know their hormone status even though it may have little or no impact on management. The time to change from the OCP to either hormone replacement therapy (HRT) or no medication needs to be negotiated. Until there are more research findings to guide the decision, it may be convenient to select, by discussion with the woman, an arbitrary age (such as 50, 52 or 55 years) to change or stop treatment.

Table 1. Contraindications to the low dose OCP

- Smoking
- Obesity
- Hypertension
- A history of thromboembolic disease
- Hypertriglyceridaemia
- Liver disease
- Undiagnosed abnormal vaginal bleeding (until it has been investigated and pathology excluded)

Hormone replacement therapy

If HRT is discussed, it is important to address the misconception that once treatment starts it

IN SUMMARY

- **It is important to gain an understanding of the woman's attitude towards and experience of medication.**
- **Every woman should be offered the choices for the management for her individual postmenopausal problems.**
- **Decision making about management is between the woman and her doctor.**
- **Balance the individual risks and benefits of treatment options with every woman.**
- **Continuing care requires regular visits to reappraise the dynamic situation.**

should be maintained lifelong. A commonsense approach is to review the situation annually. The woman should be advised that it is her choice to stop at any time, but that if she intends to do so it would be helpful to discuss this with you first. The purpose is not to persuade her to continue treatment but to ensure she understands the decision and to help address any concerns.

HRT should consist of continuous oestrogen therapy opposed by a progestogen in women for whom this is indicated (see the section on progestogen below).

Oestrogen

The contraindications for oestrogen therapy are the same as for the OCP (see Table 1).

There is a wide range of oestrogen formulations available – from daily pills, weekly or twice weekly patches, implants and skin gel and, in the future, a spray. For women with urogenital symptoms who do not want or need a systemic therapeutic dose, the vaginal creams, pessaries and rings are useful options.

A less than optimal response to oral oestrogen can initially be managed by increasing the dose of oestrogen. Alternatively, changing to a transdermal or subcutaneous approach and monitoring the serum oestradiol levels may resolve the situation.

The serum oestradiol level should be checked at three months for women with a 50 mg implant and at six months for women with a 100 mg implant. The serum oestradiol level also needs to be checked before every implant is inserted because of the incredible variation in absorption and implant residue. The next implant should be scheduled when the oestradiol is in the low physiological follicular range. In my practice I find that the length of time an implant lasts varies with the individual woman. The range can be from 50 mg every 2 to 3 months to 50 mg every 12 to 18 months. A younger active woman has greater requirements than an older one.

Progestogen

Progesterone should always be included in an HRT regimen in the following situations:

- women with a uterus
- after endometrial ablation
- after a subtotal hysterectomy.

Table 2. Progestogen regimens: daily dose*

Progestogen	Cyclical therapy (12–14 days/month)	Continuous combined therapy
Medroxyprogesterone acetate		
Provera	5–10 mg	2.5–5 mg
Ralovera	5–10 mg	2.5–5 mg
Norethisterone		
Primolut N	1.25–5 mg	1.25 mg
Micronor	0.7–1.05 mg	0.35–0.7 mg
Noriday 28	0.7–1.05 mg	0.35–0.7 mg
Locilan 28 Day	0.7–1.05 mg	0.35–0.7 mg
Levonorgestrel		
Microlut	60–90 µg	30–69 µg
Microval	60–90 µg	30–69 µg
Dydrogesterone		
Duphaston	10–20 mg	10 mg
Cyproterone acetate		
Androcur	5 mg	5 mg

* Progesterone is available in tablets or combined in some patches.

It should also be considered initially after a hysterectomy for endometriosis.

Women who are still menstruating should be prescribed progesterone for 12 to 14 days of the second half of the cycle to prevent bleeding problems.

In postmenopausal women, continuous combined treatment is ideal. There may be light but erratic bleeding during the first three to six months and then the woman should become amenorrhoeic.

Some women choose to have a bleed each month, even after explanation about the nature of the bleeding; this is an individual choice.

A number of progestogens is available (Table 2). There may be individual sensitivity to a given formulation, necessitating a change of drug or regimen.

Options for women intolerant to progestogens

A number of choices has been suggested for a woman with intolerance to progestogen.

Low doses less often. Regimens once every 3 to 12 months have been suggested but are not recommended because the risk of endometrial hyperplasia is significant (see the section on endometrial

continued

Mirena – the levonorgestrel intrauterine device (L-IUD)*

Contraceptive efficacy
Failure rate: overall pregnancy rate <0.2 per 100 woman-years

Ectopic pregnancy
Rare: 0.06 per 100 woman-years (expected rate with no contraception is 1.2 to 1.6 per 100 woman-years)

Menstrual loss
Shorter and lighter – for 82% women at 3 months, in 97% at one year

Absorption
- Endometrium absorbs the levonorgestrel and is unresponsive to oestradiol
- Some absorption into systemic circulation but less than with oral progestogens

Cycle control
- Initial increase in number of days bleeding, although amount of blood loss reduced
- Oligomenorrhoea and amenorrhoea (pregnancy and expulsion of L-IUD should be excluded)

Side effects
Small number of reports. Mainly of:
- Nausea
- Breast tenderness
- Depression (with early use; responds to oestradiol)
- Weight gain
- Functional ovarian cysts (usually regress in 2 to 3 months)

Reversibility
Menses return within 30 days of removal

Cost
$250 at time of writing

Duration of use
5 years

* See product information for further details.

hyperplasia on page 37).

No progestogen and annual check of the endometrium (with ultrasound and histological sampling). A woman who is seeking this treatment option should be referred to a specialist in the field for discussion and monitoring.

Mirena – the levonorgestrel intrauterine device (L-IUD) may prove a good alternative method for endometrial protection, particularly in the perimenopausal woman with bleeding problems and contraceptive needs. The main disadvantage is intermittent light bleeding that may persist for some months. The woman needs to weigh this cost against the long term benefits (see the box on this page).

Endometrial ablation. Currently there can be no guarantee of complete endometrial ablation, despite improved techniques and research into new techniques. Therefore, oestrogen therapy should still be opposed with progestogen after endometrial ablation.

Hysterectomy. A hysterectomy is a last resort for treating menopausal symptoms, but should be considered, especially if the woman also has other problems that may benefit from operative management (e.g. uterine prolapse).

Androgens

Androgen deficiency in women

There is no agreed clinical definition of androgen deficiency in women. Nevertheless, a number of symptoms have been suggested to indicate possible androgen deficiency in women:
- diminished or loss of desire
- reduced general wellbeing
- lack of energy
- depressed mood
- diminished confidence or self-esteem.

No specific level of circulating androgen has been shown to be associated with a particular symptom. It may be that the individual woman is sensitive to a change in hormone level. Whether this age-related response should be treated depends on the effect on the woman's life and her preference in management.

The value of measuring the testosterone level in clinical practice has not been determined. A free testosterone level does not reflect total testosterone production or how much testosterone is unavailable because of high binding by serum hormone binding globulin (SHBG). Since the area is still the subject of research, it would be wise to determine baseline levels of total testosterone, SHBG and the free androgen index (FAI – the ratio of total testosterone to SHBG) before considering treatment.

Possible therapeutic effect of androgens

Several prospective studies of surgically menopausal women have demonstrated that, compared with women treated with oestrogen alone, the addition of testosterone to an oestrogen replacement regimen increases sexual desire, sexual arousal and the frequency of sexual fantasies. However, the role of androgens in managing the menopause is still at an early stage of knowledge and much work is to be done.

Androgenic treatment options

Testosterone replacement therapy. There is no form of testosterone replacement therapy officially available in Australia to treat the loss of libido in women, but several products have been used (Table 3) and others are undergoing clinical trials. For women using testosterone implants, the level should be checked before re-implantation, because the rate of absorption can vary between and even within individuals. In some women the implants are rejected; this can occur even when an oestrogen implant given at the same time is not rejected. A different implant site can then be tried.

Tibolone (Livial). This is a synthetic steroid with oestrogenic, progestogenic and androgenic properties in the one tablet. Tibolone has been in clinical use for

about 10 years, although it has not been widely used because of concern about the decrease in HDL cholesterol. The clinical significance of this effect may be less than initially thought but more results are awaited. Tibolone should only be used from 12 months post-menopause.

Dehydroepiandrosterone (DHEAS). There has been limited research on the use of dehydroepiandrosterone in menopausal women. The data available do not support an improvement in wellbeing or cognition.

Side effects of androgens

It is important to counsel women about the possible side effects of androgenic treatment:

- acne
- hirsutism
- voice changes
- excessive libido.

Care should be taken in prescribing testosterone for women with an obvious androgenic tendency – for example, by asking about the frequency of body hair removal.

Alternative therapies

Many women concerned about using HRT because of possible side effects may seek relief from alternative treatments. In recent years there has been a great deal written about alternative therapies, in particular the phytoestrogens. It is important to weigh up the evidence for these preparations in the same way that the evidence for HRT preparations is assessed. More good quality research is required to confirm the benefits and risks of alternative therapies and their place in management.

What are the problems with using hormones?

The problems with using hormones fall into three main groups, all of which overlap to some extent:

- adherence
- side effects
- risks.

Table 3. Androgen replacement for women

Androgen	Route	Dose	Frequency
Testosterone implant	SC	50–100 mg	6–12 monthly
Nandrolone decanoate	IM	50 mg	2–3 monthly
Testosterone undecanoate	Oral	40 mg	Daily
Tibolone	Oral	2.5 mg	Daily

Adherence

Adherence to treatment remains a problem. Before prescribing any treatment, it is essential to allow adequate time to discuss all issues important to the woman. It is useful to outline which symptoms will definitely be helped by HRT, which might be helped, and for which symptoms the response is uncertain. The woman can then evaluate HRT as a treatment that can benefit some or all of her symptoms, not as a complete panacea.

Side effects

Side effects can range from being a nuisance to being a major problem. Either way, they can give rise to concern about possible underlying disease. While most can be managed with an alteration in the regimen, side effects will often cause a woman to stop therapy of her own volition without discussing it with her medical practitioner.

This action can be pre-empted in part by explaining the possible side effects in advance and suggesting that a return visit for further assessment would be appropriate should side effects occur. Not only does this reassure the woman, it also gives her permission to return for discussion about side effects that trouble her but seem too trivial to warrant a visit to the doctor.

The most frequent reasons given by women for stopping HRT include:

- irregular bleeding
- breast tenderness
- premenstrual symptoms (e.g. bloating)
- weight gain
- lack of benefit
- concern about increased risk of cancer
- concern about possible as yet unknown side effects.

The practical management of some of the side effects include:

- Breast tenderness – reduce the oestrogen dose and increase slowly over 1 to 2 months
- Nausea – take tablets with evening meal or use a patch or gel
- PMS symptoms on progesterone – change preparation or reduce dose
- Persistent oestrogen deficiency symptoms – increase dose or use a patch or gel
- Persistent urogenital symptoms – add local treatment for six months.

Weight gain

Many women worry about weight gain from hormone treatment. However, there is no evidence that HRT causes weight gain in addition to that normally gained at menopause. Some studies suggest that the menopause transition accelerates the selective deposition of intra-abdominal fat and that treatment with HRT prevents the central adiposity. However, there is insufficient evidence to explain a relationship between fat deposition, ageing and hormone effects in the individual woman at the present time.

Fears about cancer

Fears about cancer and other side effects that still cause women concern, even

continued

Findings on ultrasound

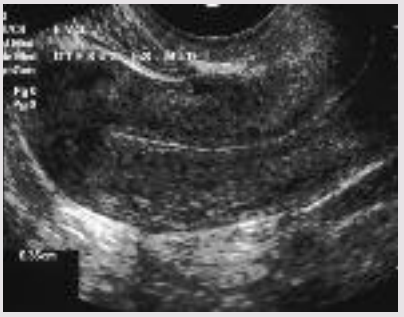

Figure 1. Normal thin proliferative phase endometrium.

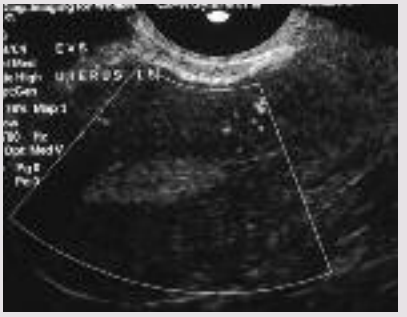

Figure 2. Focally thickened proliferative phase endometrium in a perimenopausal woman. Ultrasound gives excellent anatomical detail but cannot confirm histology. In this case, the differential diagnosis includes benign proliferative change (e.g. polyp or hyperplasia) but endometrial cancer cannot be excluded.

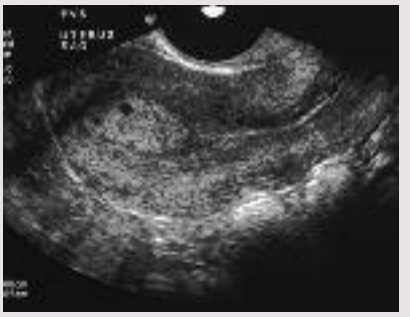

Figure 3. More impressive focally thickened intracavity mass in a postmenopausal woman on HRT.

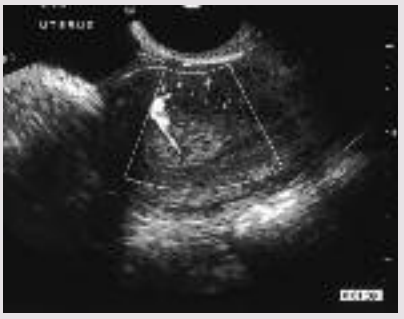

Figure 4. Doppler scan documenting a central vascular core in the same patient as in Figure 3. The appearance is strongly supportive of an endometrial polyp, subsequently confirmed on histology.

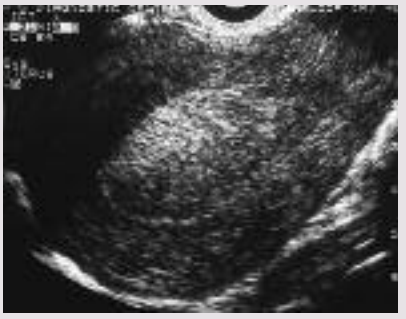

Figure 5. Grossly thickened endometrium in a postmenopausal woman who presented with bleeding. The degree of thickening raises the suspicion of malignancy. There is no clear evidence of invasion, although ultrasound is not able to stage endometrial cancer accurately.

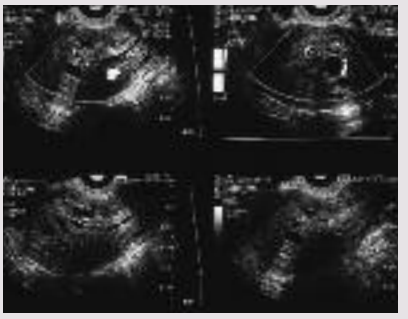

Figure 6. Complex vascular echogenic endometrium with multiple cystic spaces in a postmenopausal woman on tamoxifen. There is no doubt that there is true endometrial change – either cystic hyperplasia or endometrial cancer. Both findings were later confirmed on histology.

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after appropriate explanation, may be sufficient reason to discontinue therapy – the persistent stress may outweigh the benefits of treatment.

Bleeding on HRT

Bleeding is one of the most common causes for lack of adherence to treatment and causes of concern for women. It can be an effect of the oestrogen or the progestogen therapy.

Heavy bleeding on first starting HRT should be investigated. Intermittent light bleeding in a woman on a combined continuous regimen usually settles after the first six months. A pelvic ultrasound examination can check for the endometrial thickness and for specific pathology of the uterus and ovaries (Figures 1 to 6). For a woman on sequential therapy, the time to arrange an ultrasound examination is at the end of an episode of bleeding. When there is a uniform double endometrial thickness of less than

5 mm, there is unlikely to be underlying pathology.

A saline infusion sonohysterography (SIS) is more reliable in excluding focal thickening, polyps or submucous fibroids (see Figures 7a and b). A woman who has any of these changes should be referred for further investigation and histological assessment.

In a woman with persistent light bleeding and a thin endometrium, options for management may include decreasing the progesterone or increasing the oestrogen.

Individual clinicians have many preferred 'tricks' for managing heavier bleeding, such as decreasing the oestrogen, increasing the progesterone or commencing the regimen with a lower dose of oestrogen. However, continuation of the same regimen often produces the same results over time.

Women who have persistent bleeding problems, even with a normal ultrasound report, should be referred for further investigation if the problem is not settled with a change in the regimen.

Women who are troubled by spotting or light irregular bleeding may prefer a cyclical regimen – which results in predictable bleeding – even though continuous combined therapy is more protective to the endometrium in the long term. Occasionally, women continue to have bleeding problems after changing regimens. These women may need to consider the alternatives such as L-IUD, endometrial ablation or hysterectomy.

Hyperplasia

Unopposed oestrogen therapy at moderate or high doses is associated with increased rates of endometrial hyperplasia, irregular bleeding and subsequent nonadherence to treatment.

Oral progesterone use decreases the risk of endometrial hyperplasia and improves adherence. Both sequential and continuous treatment decrease the risk, although there is a suggestion that continuous treatment is more protective in the long term. There is less likelihood of irregular bleeding with the sequential regimen. The duration of progesterone therapy is more important than the daily dose in protecting against endometrial cancer.

Women who have persistent bleeding problems on HRT should be referred for further investigation if the problem is not settled with a change in regimen.

Endometrial hyperplasia is regarded as a precursor of endometrial cancer but progression depends on the type of hyperplasia. Simple hyperplasia without atypia progresses infrequently over a 13-year period to carcinoma. The risk is greater with complex hyperplasia and more likely again with untreated hyperplasia with atypia.

Atrophy

When there is either continuous or too much progesterone, the endometrium becomes decidualised, thin, fragile and atrophic with focal areas of bleeding. The precise mechanism is unclear.

Risks

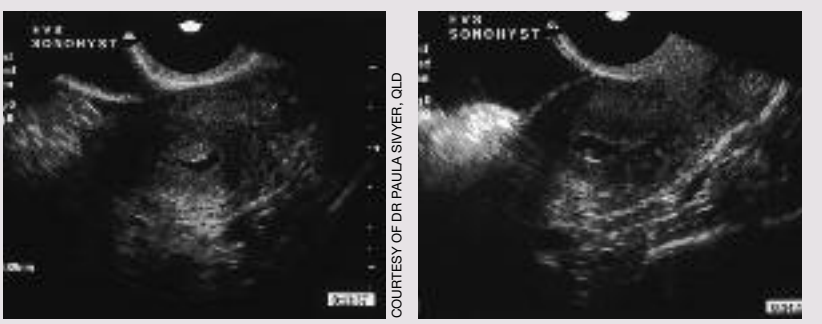
One of the main difficulties with management is explaining to women, in terms that are meaningful, what is meant by risk and benefit (or loss and gain). The concept of relative risk (RR) needs to be explained. It may be useful to give a close comparison. Explain that the association between smoking and lung cancer shows a RR of 12.0 and compare this with the relative risks of HRT (see the box on page 38). Explain also that chance, bias and confounding can confuse the weaker relationship between a disease and a behaviour or treatment. Alternatively, explaining the risk in absolute terms may be more helpful to some women (see the section on thrombosis below).

Thrombosis

The absolute risk of thrombosis in postmenopausal women not taking oestrogen is one in 10,000. This risk increases to 3.6 per 10,000 women in HRT users, and increases further with age.

Venous thromboembolism develops as the result of multiple interactions between nongenetic and genetic risk factors. Inborn risk factors predisposing to thrombosis (most commonly, Factor V – Leiden and prothrombin mutation;

Findings on sonohysterography



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Figures 7a and b. Sonohysterography confirming multiple small echogenic intracavity masses in both the anterior and posterior endometrium. The size of the masses is consistent with multiple polyps.

less commonly, antithrombin III, protein C and S) are present in the majority of patients.

The laboratory screening of thrombosis patients needs to include all of the known genetic risk factors, even if the 'clinical' situation seemingly provides sufficient 'explanation' for a thrombotic event.

Cancer

Endometrial cancer. It became clear in 1975 that the use of unopposed oestrogen was associated with a marked increase in the incidence of endometrial cancer. Adding a progestogen to the therapy for 10 to 12 days a month provides protection to the endometrium, and combined oestrogen–progestogen regimens are now recommended as HRT for women in whom the uterus is intact.

Ovarian cancer. Studies have shown that oral contraceptives with 30 to 50 μg or more of oestrogen reduce the risk of ovarian cancer (estimated risk reduction odds ratio = 0.5). It is not clear whether newer, lower dose (15 to 20 μg) formulations or HRT offer similar protection.

Breast cancer. Considerable controversy has existed regarding the association between HRT and breast cancer in postmenopausal women. It is important to clarify the possible effects of oestrogen. It is not regarded as an 'initiator' (that is, starting a cancer in normal tissue) but may be a 'promoter' (affecting early cancer cells already present). Together with the increased rate of mammography in women on HRT, this may account for the increase in early breast cancers diagnosed in women on HRT. Despite the increase in diagnosis, HRT users generally have a decreased mortality rate after the diagnosis of breast cancer. In my opinion, while not denying the extreme importance and psychosocial effects of breast cancer, the increased risk for breast cancer has been over-emphasised and has become a cause for fear among women. It needs to be put into perspective for the individual woman to balance and trade her own gains and losses in the short and long term.

What about the long term?

Informed decisions

The gold standard for establishing the facts is large, long term, randomised, placebo-controlled trials. The results of two such studies being undertaken in the USA will not be available until 2007 and beyond. In the meantime, we can only explain the current situation to women with the information available.

Each woman needs to use this information, together with her personal information, to assess the weight that she wishes to put on each of the risks and benefits.

Interpreting new information

The enormous surge in publications, both printed and on the web, presents all practitioners with the problem of keeping abreast of the material and of dealing with patients who have found information for themselves.

All medical practitioners have the important role of interpreting new information and explaining it to patients in meaningful terms. The area of menopause is fruitful for research, but can be made difficult by misinterpretation by doctors, media and consumers. Apart from a local expert opinion, reviews and consensus statements from bodies such as the Australian Menopause Society, the RACOG, the RACGP and the NHMRC provide useful information. The Cochrane Collaboration provides a number of menopause articles that review and interpret the literature for practising clinicians.

HRT: the risks and benefits

What is relative risk?

A relative risk (RR) summarises the strength of the association between a factor and a disease. A relative risk of 1 occurs when the incidences are the same in two compared groups (an exposed and a nonexposed group), and is equivalent to no association between the risk factor and the disease. A RR >1 occurs when the risk of disease is higher among those exposed to the factor than those not exposed. The further the RR is from 1, the stronger the association. A RR <1 occurs when the risk is lower among those exposed, a possible protective effect of the factor.

The Table below shows the association between HRT and various conditions.

A relative risk of:

- 1.0 = No association
- <0.5 = Significant decrease in risk
- >2.0 = Significant increase in risk.

A relative risk of 0.5–2.0 is likely to be due to confounding factors or bias (i.e. more likely not to be a real effect).

A relative risk <0.5 or >2.0 is less likely to be due to confounding factors or bias (i.e. more likely to be a real effect).

Table. Association between HRT and various conditions

Condition	Relative risk
Endometrial cancer	9.5*
Thromboembolism	2.1–6.9
Breast cancer	1.35
Bowel cancer	0.80
Alzheimer's dementia	0.71
Cardiovascular disease	0.7

* Taking unopposed oestrogen for 10 years.

Continuing care

Once women have become established on a hormone regimen that suits them, an annual review should be arranged. The situation is a dynamic one. The woman's beliefs, experiences and medical status may have changed. Also, there may be new treatment options and she may want to discuss them. New research may have elicited media coverage that needs to be put into perspective. The clinician needs to be aware of the various factors influencing the woman's initial decision and be prepared to reassess them.

For the woman considering hormone replacement therapy for more than five years, other options for management, not mentioned here, that include the selective oestrogen receptor modulators (SERMS) should be discussed.

Conclusion

The issues around menopause and HRT vary with and for the individual woman. The good news for women and their doctors is that research in the area is ongoing. Choices are increasing all the time, giving more options to individualise management. MT

Last month, Part 1 of this article described the spectrum of menopausal symptoms and advocated a patient-centred approach to management.

Further reading

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