HRT AND THE MENOPAUSE

Perceptions and opinions about the menopause and possible treatments are changing. Here, Dr Sarah Gray looks at the implications of the recent NICE guidelines and what they mean for GPs

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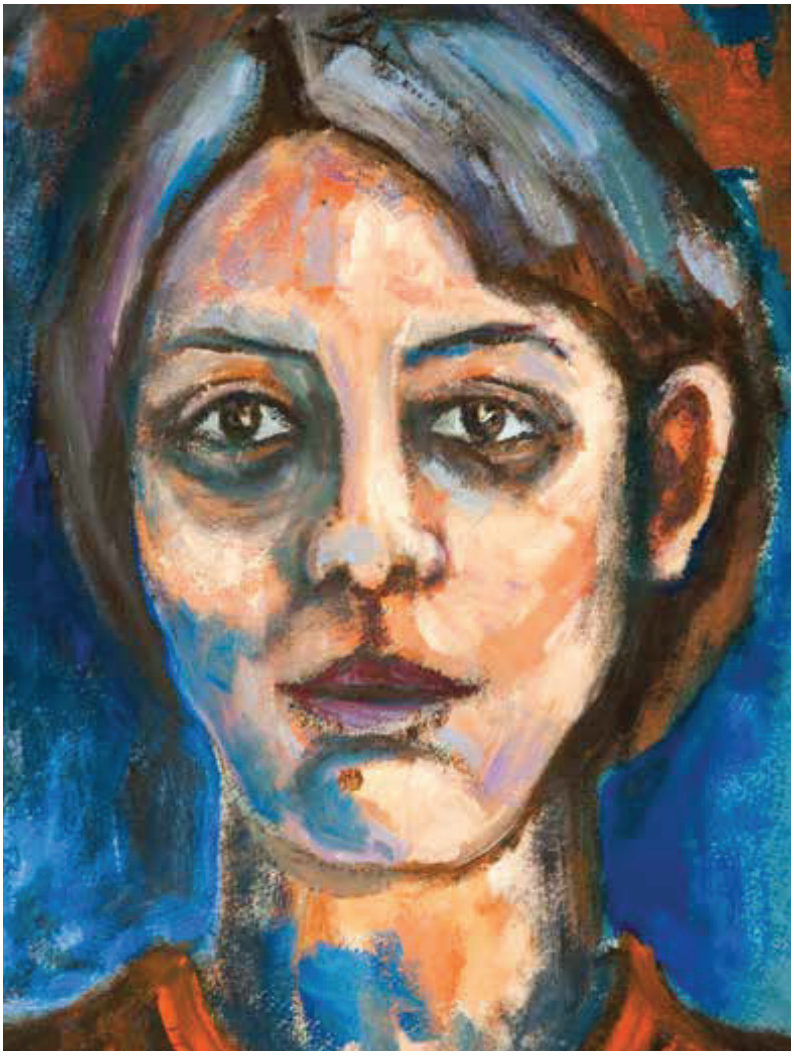
Menopause is technically the last menstruation and is a physiological change that affects every woman. Around this single event is a time of adaptation, with initial wide ranging and then much lower female hormone levels. Associated symptoms are many and individual experience varies from the positive to utter misery.

For more than a decade media and medics have tended to dismiss the negative side of menopause. Publication of large trial results conveyed a message that 'hormones are dangerous', though the evolving evidence did not confirm this. However, many other surveys have shown that many women 'suffer in silence'.



Diagnosing menopause

In November 2015 the National Institute for Health and Care Excellence (NICE) published its review of the evidence regarding the diagnosis and management of menopause. Some key recommendations are discussed below.

Firstly, diagnosis has been confirmed to be a clinical decision in the majority of cases in women over 45 years of age. If more than 12 months have elapsed since a period and having excluded other causes of amenorrhoea, this is diagnostic and no tests are needed. Surgical removal of the ovaries would provide definition but chemotherapy does not as recovery can occur. For younger women the term premature ovarian insufficiency is preferred to premature ovarian failure. For 1% of women this can occur spontaneously before the age of 40. Where no cause is identified it is possible to have a fluctuating and unpredictable pattern of ovarian function and sporadic ovulation can occur. For this reason the term failure is inappropriate.

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After hysterectomy, endometrial ablation or suppression due to a levonorgestrel intrauterine system (LNG IUS) it is not possible to use bleeding as a marker of ovarian function. In such women aged over 45, menopausal symptoms can be used as the diagnostic feature.

When evidence is important, a minimum of two raised follicle-stimulating hormone (FSH) levels (>30miu/ml) taken 4-6 weeks apart can be used to indicate a consistent state of poor ovarian response. NICE suggest that FSH can be considered in women aged 40-45 with symptoms that include a change in menstrual cycle or in women under 40 in whom menopause is suspected. In early perimenopause there may be fluctuating symptoms but normal FSH at the point of measurement and this should not be used to deny treatment for symptoms that are intrusive. Identification of menopause may be important

for discussion and recommendations of long-term preventative measures.

Consider Alison:
Alison is 48. She stopped the pill at 40 when her husband had a vasectomy. Her periods have been increasingly haphazard over the last 2-3 years and she has now missed two. She has been very hot at night and waking up repeatedly over the last six weeks. She is tired, tearful and struggling to cope, which is worrying her greatly as she is a police officer.

She is clearly in the perimenopause phase. This is the time from onset of cycle change or symptoms until one year after the last bleed. This is a clinical diagnosis. There is no test that will tell her how long it will last.

Two raised FSH levels can be used to support the decision making around stopping progestogen only pills, the subdermal implant or LNG IUS. The advice of the Faculty of Sexual and Reproductive Healthcare (FSRH) is to allow an additional two years of contraception in those women under 50 and one year in those women who are older. Combined hormonal contraception (CHC) and depo-medroxyprogesterone acetate (DMPA) suppress FSH and it is not useful as an indicator with these methods of contraception.

The loss of ovarian function results primarily in a reduction in circulating oestrogen. This can result in:

- Early symptoms – consider as a sensitivity to changing levels
- medium-term effects – mainly urogenital and resulting from the atrophy of the surrounding tissues
- Long-term degenerative consequences.

Early symptoms largely derive from the role of oestrogen within the brain. It is a pervasive neurochemical with roles which include temperature and sleep regulation, mood, memory and cognition. These functions adjust variably to lower oestrogen levels and can result in symptoms. Some women have none and some may have all. These symptoms are not actually related to the oestrogen level *per se* and there is no indication to measure it. Individual symptoms may be mitigated by various therapeutic agents but all reviews, including that of NICE, are consistent in advising that there is no intervention that is as effective as oestrogen replacement for all menopausal symptoms. In the clinical trial situation there is a high placebo response but this reflects both the attention of the clinical trial and the naturally fluctuating nature of many symptoms.

NICE has encouraged women not to 'suffer in silence' but to report symptoms that impact on their lives. They should be offered a discussion to include the options available to them. It may be obvious to a woman with irregular periods and hot flushes that she is menopausal but it is not always the case. A woman with amenorrhoea but an IUS in place who is not sleeping, anxious and tearful might dismiss her vaginal dryness and lack of sexual interest as unrelated and be misdiagnosed as depressed. Low mood at menopause can be treated with oestrogen. NICE advises that SSRIs and SNRIs are not recommended unless women are clinically depressed.

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Menopause and impact upon other health conditions

In primary care it is important to be alert for the potential for menopause to be an underlying cause or contributor to a variety of problems. Recurrent urinary tract infection may be the presenting symptom of urogenital atrophy. Consider asking about vaginal dryness and sexual function. Low dose vaginal oestrogens are highly effective if allowed long enough to work so tell women not to expect improvement for at least six weeks. They have minimal systemic impact and can be offered to all women other than those with hormone dependent cancer when expert consideration is needed. NICE confirmed that the low dose products can be used for as long as a problem is perceived.

In systemic replacement, decide if you will use oral or non-oral delivery. Oral preparations may be seen as having the advantages of convenience and cost while the non-orals avoid gastrointestinal effects and hepatic effects on metabolism, protein binding and interaction with other medicines. Having chosen an oestrogen, its delivery route and dose, progestogen should be added if there is endometrial tissue requiring protection. The low dose vaginal oestrogens do not have a hypertrophic effect but the systemic doses can do and adding progestogen suppresses this. Use progestogen cyclically to give scheduled bleeds if there has been a period within the last year or continuously to give best protection if truly postmenopausal. If starting a cyclical regimen when the menstrual cycle has already become more erratic expect to change to a continuous combined preparation within five years. The Mirena LNG IUS has a license for opposition for four years but the universal expert opinion is that it will be effective for five.

After providing an initial prescription for hormone replacement, agree to review before three months. Treatments include Elleste duet (estradiol, norethisterone), Femoston (estradiol, dydrogesterone) and Utrogestan (progesterone). Consider symptom relief, tolerance of the regimen and reprise the risk analysis. Modify as appropriate but once settled, annual review is recommended. Do check blood pressure, not because the HRT will affect it but it is a factor in the background risk analysis. Cardiovascular risks are not contraindications

provided that they are optimally managed and factored into the decision making regarding regimen.

With the loss of ovarian function, there is an accelerated loss of bone that lasts 3-5 years before reducing to a lower sustained rate. If this occurs early there are implications for bone fragility at young age. Both hip and vertebral fracture are painful and affect function. Hip fracture is followed by 20% mortality in the first year. Post-menopausal osteoporosis is multifactorial and one of the recommended risk assessment tools such as FRAX should be used to assess fracture risk.

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Recommendation has swung in the last 25 years but oestrogen has been restored to a treatment option for women under 60. It has always been the only available option for prevention of bone loss. It has evidence of fracture risk reduction at all sites and while there is some accelerated loss after it is stopped the benefit of fracture reduction can still be seen 10-15 years later.

Early loss of ovarian function was identified 40 years ago as linked to an increased risk of coronary artery disease. It would appear that this can be mitigated and potentially avoided by maintaining oestrogen through replacement. Trial data has been very confusing but it has been identified that time since menopause is crucial and that if started within 10 years of the menopause there is no increase and probably a decrease in coronary events and death. No trials have been conducted in women with early menopause but both cohort studies and extrapolation are strongly suggestive of protection. The headlines that caused the misunderstanding resulted from the inclusion of women aged up to 79 in trials. Those over 20 years from menopause treated with oral oestrogen had an increase in events in the first year of use. These women will already have had diseased coronary arteries and it is proposed that the conjugated estrogens used resulted in plaque rupture.

Oral oestrogen undergoes extensive first pass hepatic metabolism and in this process there is an effect on the coagulation cascade. Oral oestrogen at standard dosage is associated with approximately a doubling of the risk of venous thromboembolism. Transdermal oestrogen at up to standard dose (50mcg/day patch) does not show this effect though there is some effect at higher doses. Patches and gels are recommended for women already at risk and NICE suggests consideration at a BMI >30.

Most perimenopausal women have a low risk of stroke. There is no significant increase according to a Cochrane Review even with oral HRT in those less than 10 years after menopause, but some increase after that.[1] Non oral oestrogen (ie, patches and gels) does not show an effect at standard dose. Women who do have risks and particularly those with migraine or arrhythmia should be offered a non-oral oestrogen.

HRT and cancer

HRT is not carcinogenic. Cancers have initiation factors such as age, genetics, environmental exposure and promotion factors. Those which are hormone sensitive (receptor positive) will grow and become detectable more rapidly when hormone levels are higher. For breast cancer the time from nuclear change to detection can be 10 years. At five years there is an effect of HRT, which is similar in scale to that of 2 units of alcohol a day and less than obesity. There are suggestions that these are simply being seen earlier and that long-term there are no more. NICE asks us to tell women that no more of them will die of breast cancer having taken HRT.

The situation regarding ovarian cancer is less clear. There is some evidence suggesting an effect on some types of ovarian cancer and suggesting possibly one extra case per 1,000 women at 5 years. This is a factor to discuss when counselling.

There is no arbitrary limit to treatment, which can be continued for as long as perceived benefit outweighs risk. The aim as a prescriber is to use the lowest dose that works in the most favourable regimen for the patient's profile and this may change over the years. Women who lose their ovarian function early should be offered HRT for bone protection (and advantage for heart and cognition) even if they have no symptoms. Continuation to typical age of menopause is no greater risk to breast than physiological production. This even applies to high risk women with BRCA1 and 2 genes who opt for risk reducing bilateral salpingoophorectomy. These women can have their symptoms managed and risk averted without losing the breast benefit of the procedure.

Summary

NICE states repeatedly that if you are out of your depth ask an expert. There is no consistent network of menopause services or specialists so find out who offers advice in your area and how to contact them.

Be reassured and you will find managing the menopause to be easy and very rewarding. Women will thank you for 'giving them their life back'.

As for Alison, she was prescribed an oral cyclical HRT preparation and returned three months later for a review. Her symptoms have all improved, she has more energy and fells she has her old life back. She is delighted!

References

1. Cochrane Database Syst Rev. 2015 Mar 10;3:CD002229. doi: 10.1002/14651858.CD002229.pub4.