FEATURE

Women, hormones and heart disease

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Despite evidence suggesting that endogenous oestrogen partly accounts for the delay in the onset of cardiovascular disease in women, the results of large trials designed to determine whether exogenous oestrogen reduces cardiovascular risk have been disappointing.

Cardiovascular disease (CVD) is the leading cause of death in women in Australia and the risk increases markedly with advancing age and postmenopausal status.[1] There is considerable evidence that endogenous oestrogen protects women from heart disease and contributes to the 10-year delay in the onset of CVD in women compared with men. For this reason, there has been much interest in hormone therapy (HT) as a possible treatment for the prevention of CVD as well as an effective treatment for menopausal symptoms.

Postmenopausal HT

Basic science studies and numerous animal models provide good biological evidence that oestrogens can exert antiatherogenic effects via both systemic effects on circulating factors and direct effects on the heart and blood vessels.[2,3] A large body of evidence from

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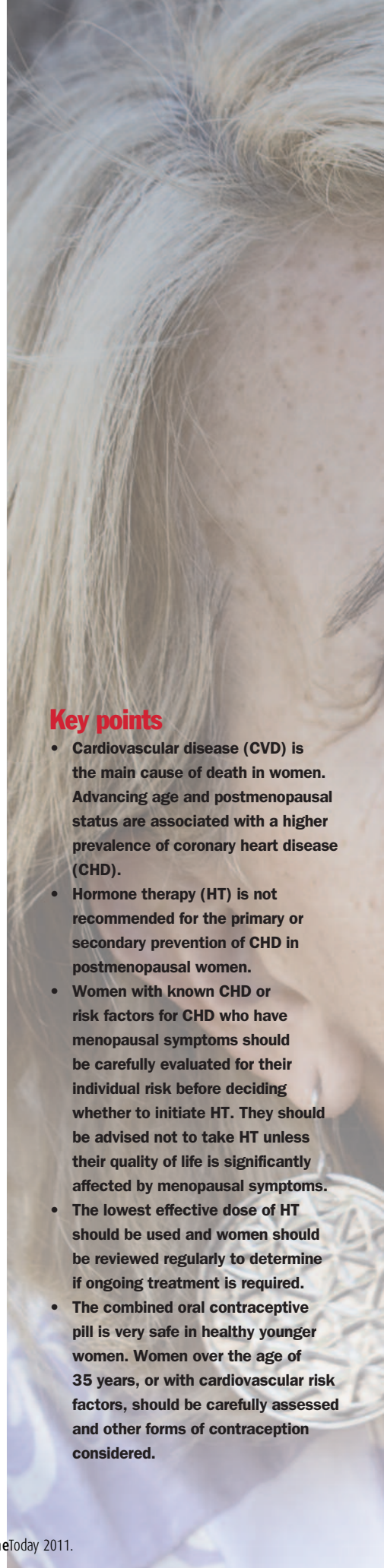

Key points

- **Cardiovascular disease (CVD) is the main cause of death in women. Advancing age and postmenopausal status are associated with a higher prevalence of coronary heart disease (CHD).**
- **Hormone therapy (HT) is not recommended for the primary or secondary prevention of CHD in postmenopausal women.**
- **Women with known CHD or risk factors for CHD who have menopausal symptoms should be carefully evaluated for their individual risk before deciding whether to initiate HT. They should be advised not to take HT unless their quality of life is significantly affected by menopausal symptoms.**
- **The lowest effective dose of HT should be used and women should be reviewed regularly to determine if ongoing treatment is required.**
- **The combined oral contraceptive pill is very safe in healthy younger women. Women over the age of 35 years, or with cardiovascular risk factors, should be carefully assessed and other forms of contraception considered.**

observational studies conducted up to the early 1990s suggested that long-term postmenopausal HT provides cardiovascular benefits and a reduced risk of osteoporosis and fractures in postmenopausal women.[4] These studies also found a slightly increased risk of breast cancer and significantly more venous thromboembolism (VTE) in HT users. Initially, it was generally believed that the benefits outweighed the risks, and the evidence from these large observational studies contributed to the high levels of HT prescription during the 1990s, when HT was often prescribed for both menopausal symptoms and its possible cardioprotective effect.

HT and secondary prevention of CHD

The encouraging results of large observational studies in postmenopausal women stimulated great interest in HT and the possibility that it could be beneficial in the secondary prevention of CHD. The Heart and Estrogen/Progestin Replacement Study (HERS), published in 1998, studied 2763 postmenopausal women (average, age 67 years) with known heart disease.[5] The investigators found that the use of oestrogen plus a progestogen did not prevent further heart attacks or death from CHD over a four-year period, despite a beneficial effect on lipids. There was a 50% excess of coronary events in the first year in the treated group and a lower rate from the third year onwards. These results led the study investigators to postulate that the early negative outcomes might be attributable to an immediate adverse effect of HT, such as a prothrombotic effect, that was gradually outweighed by a beneficial effect on the progression of atherosclerosis.

The HERS caused much controversy and consternation at the time and following its publication, clinicians became much more circumspect about prescribing HT in women with known, or at high risk of, heart disease. The focus in secondary prevention moved to other medications such as statins, antiplatelet agents and angiotensin-converting enzyme (ACE) inhibitors, all of which were proven to be of benefit in men and women with CHD.

HT and primary prevention of CHD

Despite the disappointing results from the secondary prevention trial, there was still interest in HT with respect to primary prevention of CHD. The Women's Health Initiative (WHI) was a large, randomised trial conducted to determine whether HT provided cardiac protection and whether it increased the risk of breast cancer in postmenopausal women without known CVD.[6] It included 27,000 postmenopausal women in American (average age, 63 years), and initial results were published in 2002. It showed that after five years of combined oestrogen and progestogen therapy, there was an expected small increase in breast cancer and VTE, and a reduction in fractures. However, there was also an unexpected increase in CVD. The publication of the second paper from the WHI in 2004, analysing results for oestrogen-only users, showed a reduction in fractures, no increase in CVD, no increase in breast cancer and the expected increase in VTE.[7]

Subsequent to its publication, controversy arose with respect to the WHI's applicability to women just entering menopause. The study included predominantly older women and only a tiny percentage (3.5%) of the women was aged between 50 and 54 years, the age when women usually make a decision regarding initiation of HT. Reanalysis of the subgroup of women starting HT between the ages of 50 and 59 or less than 10 years after the onset of menopause showed a trend towards a reduction in all-cause mortality and CHD. In this subgroup, oestrogen plus some progestogens slightly increased the risk of breast cancer, whereas oestrogen alone did not. Thus it appears that for women initiating HT at the time of their menopause, the risks are few.

In summary, there is no evidence that HT is effective in the primary prevention of CHD in women over the age of 50, or has a role in the secondary prevention of CHD. It is important to note, however, that most of the evidence has been obtained using conjugated equine oestrogens and medroxyprogesterone acetate taken orally. The impact of newer generation hormones, different delivery mechanisms and variable dosage regimens is still uncertain. Transdermal patches have no thrombotic effect nor any impact on stroke rates, but there are no long-term data on their effect on breast cancer risk.

Who is suitable for HT?

- The main indication for menopausal HT is the treatment of menopausal symptoms.
- HT is generally safe in younger postmenopausal women, without any associated increase in cardiovascular risk, but it should not be initiated in women over the age of 60 years except after thorough breast and cardiac evaluation and discussion with the patient about the risks versus benefits. It may be indicated in certain situations.
- The benefits and risks of HT should be decided on an individual basis, including the woman's overall health and her cardiovascular and cancer risk, including her family history of heart disease and breast and gynaecological cancers.
- Patients should be commenced on the lowest possible dose of oestrogen (and progestogen if they have not had a hysterectomy) and the treatment should be continued only as long as required for symptom relief. The need for ongoing treatment should be reviewed annually.

Oral contraceptive pill and CVD

Contraceptive hormones, most commonly prescribed as combined oral contraceptives (OCs), are widely used to prevent pregnancy and in older women to manage perimenopausal symptoms. As with HT, there are many basic science, animal, and human studies which suggest that oestrogens in contraceptive hormones have antiatherosclerotic effects.[8] However, there are no randomised, controlled trials of OCs with cardiovascular end-points to guide clinical practice in contraceptive hormone use.

OC formulations have evolved considerably over the past few decades. First-generation OCs contained 150 μg of ethinyloestradiol compared with 50 μg in the second-generation pills and 20 to 35 μg in most of the currently available preparations, although preparations containing 40 and 50 μg ethinyloestradiol are still available and prescribed.

The progestogen component of the OC pill has also changed. The first-generation progestogens were replaced by more potent second-generation compounds that allowed lower doses to be used, and the third- and fourth-generation progestogens commonly used today have fewer androgenic and metabolic effects.

Contraceptives can also be delivered by nonoral routes, such as transdermal patches, injection, implant or via a vaginal ring. It is not known whether the route of administration of contraceptive hormones has any differential effect on cardiovascular outcomes. For current users of newer generation OC formulations, there is no indication of an increased risk of myocardial infarction (MI), but there is a persistent increased risk of VTE, particularly in smokers.

OCs and cardiovascular risk factors

Blood pressure

Most studies on blood pressure in normotensive women have shown a small but significant increase in blood pressure associated with combined OC use. The magnitude of blood pressure increase appears to be related to both the dose of oestrogen and the type of progestogen used. Newer progestogens such as drospirenone, which has antimineralocorticoid diuretic effects, appear to have less effect on, and may actually lower, blood pressure when used in combination with oestrogen.

Hypertension can be precipitated by OC use and first-line management is to stop the OC pill. Blood pressure may reduce to normal levels, when other forms of contraception should then be considered. If blood pressure remains elevated or the use of an alternative form of contraception is not feasible, the OC may be continued and antihypertensive therapy initiated. Since the renin–angiotensin system is implicated in OC-induced hypertension, ACE inhibitors may be particularly effective. In difficult cases, specialist referral should be made.

Summary of hormonal contraceptive prescribing guidelines for women with elevated cardiovascular risk*[8]

Hypertension Monitor BP and if controlled after starting, OC may be continued. If BP not well controlled, alternative methods such as progestogen-only pills or IUD may be started.
Dyslipidaemia LDL-C >4.14 mmol/L or multiple cardiac risk factors: use alternative nonhormonal contraceptive methods, such as an IUD.
Diabetes Diabetes type 1 or 2, OC is only appropriate for use in otherwise healthy, nonsmokers <35 years of age. Otherwise progestogen-only contraception or IUD may be started.
Smoking Smoking and >35 years of age: use alternative nonhormonal contraceptive methods, such as an IUD. Smokers <35 years of age are not addressed.
Obesity Obesity (BMI >30 kg/m^2): use alternative nonhormonal contraceptive methods such as progestogen-only contraception or IUD. Obesity is felt to be an independent risk factor for VTE.
Women older than 35 years of age Healthy, nonsmoking women: use of OC with <50 µg ethinyloestradiol remain safer than pregnancy, and can be continued until 50 to 55 years of age or until menopause after reviewing risks and benefits.

ABBREVIATIONS: BMI = body mass index; BP = blood pressure; IUD = intrauterine device; LDL-C = low-density lipoprotein cholesterol; OC = oral contraceptive; VTE = venous thromboembolus.

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Smoking

Although the overall incidence of smoking is in decline, 15% of women in Australia continue to smoke.[1] Earlier studies found that the risk of MI was increased in current OC users, especially in those who smoked. Recent studies have not found OC use to be an independent risk factor for MI; however, American guidelines suggest using alternative forms of contraception in women who are over 35 years of age and smoke.[9]

Lipids

OCs have a small, variable effect on the lipid profile. On the whole, newer generation OCs slightly increase total cholesterol, HDL cholesterol and triglyceride levels and slightly reduce the LDL cholesterol level. The extent to which the lipid profile is altered depends on the doses and types of oestrogen and progestogen used, and also the delivery route. Transdermal contraceptive hormone delivery is relatively less potent than oral delivery.

Glucose tolerance and diabetes mellitus

Contraceptive hormones can affect glucose tolerance and diabetes control, but to a very small extent. Generally, OCs are considered safe in women under the age of 35 years who have diabetes.

Current hormonal contraceptive prescribing guidelines for women at elevated cardiovascular risk

The American College of Obstetrician and Gynecologists (ACOG) have developed guidelines for prescribing hormonal contraceptives in women with medical conditions. These specifically address the use of OCs in women with cardiovascular risk factors such as hypertension, dyslipidaemia, diabetes, smoking, and obesity, as well as in women older than 35 years of age (see the box on this page).[8]

Summary

Postmenopausal HT is not indicated for the primary or secondary prevention of CHD. HT initiated at the time of menopause appears very safe from the cardiovascular point of view, but should be continued only as long as required for symptom relief. It should not be initiated in older women, except in specific circumstances.

Current guidelines indicate that, as with all medication, contraceptive hormones should be selected and initiated by weighing the risks and benefits for the individual patient. Women aged 35 years or older should be assessed for cardiovascular risk factors, including hypertension, smoking, diabetes, nephropathy, and other vascular diseases, including migraine, before they start using OCs. **CT**

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