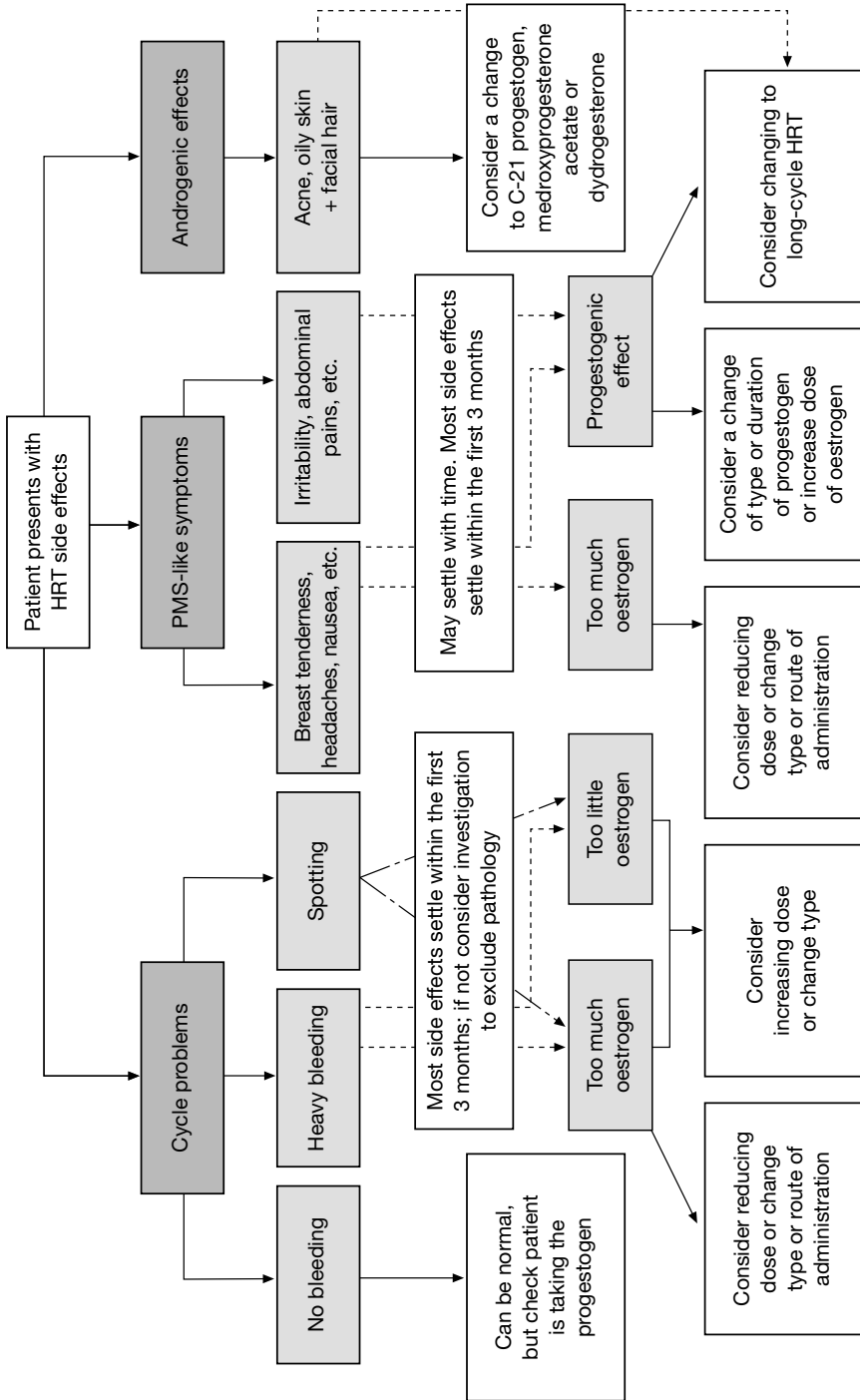


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**Figure 1.2** Side effects of hormone replacement therapy (HRT). (Reproduced with permission from Dr SJ Lee, editor, *Osteoporosis 2000.*)

synthesis of apolipoprotein AI, the main protein component of HDL and HDL<sub>2</sub>. Transdermal estradiol appears to have a less marked effect on HDL-cholesterol than oral oestrogen (Crook *et al.* 1992). However, it does increase HDL<sub>2</sub>, and also causes a reduction in HDL<sub>3</sub>. HDL<sub>3</sub> contains a significant amount of apolipoprotein AII, increased levels of which are associated with vascular lesions in animal models. Thus, a reduction in HDL<sub>3</sub> could theoretically be a beneficial effect for CHD risk.

The type and route of administration of oestrogen determine its effects on triglycerides. As triglycerides may be a particular risk factor for CHD in women, this is of potential importance. Increased endogenous triglyceride levels are associated with low HDL and HDL<sub>2</sub>-cholesterol, insulin resistance and adverse changes in haemostatic parameters. Increased intake of exogenous triglycerides results in increased chylomicron remnants, which themselves are atherogenic. However, oestrogens primarily affect endogenous triglyceride concentrations. Conjugated equine oestrogens cause an increase in triglycerides (Crook *et al.* 1992), an effect that is pharmacological, resulting from the hepatic first-pass effect of this steroid. Orally administered estradiol has a smaller effect on raising triglycerides, although transdermal estradiol causes a reduction in triglycerides (Crook *et al.* 1992), which is a physiological effect of oestrogen.

Progestogens have differing effects on lipids and lipoproteins, depending on their androgenicity and perhaps on their overall dosage (Stevenson 1997). The addition of progestogens to oestrogen therapy has no adverse effect in terms of lowering LDL because, although they increase LDL production, they also increase its clearance. Androgenic progestogens, such as norgestrel, reverse the HDL-raising effect of oestrogen (Crook *et al.* 1992) because they increase hepatic lipase activity. It is not known whether this reduction in HDL reflects any impairment in remnant clearance or in reverse cholesterol transport, so the clinical significance of lowering HDL remains to be determined. In contrast, certain non-androgenic progestogens, such as dydrogesterone, have little negative impact on oestrogen-induced increases in HDL and HDL<sub>2</sub> (Crook *et al.* 1997), whereas others, such as medroxyprogesterone acetate, clearly attenuate the increases. Testosterone-derived progestogens, such as levonorgestrel, decrease triglyceride levels by reducing secretion of very-low-density lipoprotein (VLDL). C-21 progestogens do not prevent the increase in triglycerides induced by oral oestrogens. Thus, combined oestrogen/progestogen HRT may lead to an increase in HDL, but at the expense of an increase in triglycerides, or lead to a decrease in triglycerides at the expense of a decrease, or no increase, in HDL. Which change is more important in terms of CHD benefit remains unknown. When all these changes in lipids and lipoproteins are considered together, however, the various changes seen with most HRT combinations are likely to be beneficial overall, although, in certain situations, some HRT regimens will be potentially more beneficial than others.

Insulin resistance is considered to be a pivotal metabolic disturbance in the pathogenesis of CHD (Godsland & Stevenson 1995). Women with diabetes have a

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