Recent advances in hormone replacement therapy

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In view of the benefits of hormone replacement therapy (HRT) and the experience that only 10% of women maintain therapy, it is vital that all doctors are familiar with the pros and cons of HRT, so that women may be correctly advised. Here we discuss new issues and developments in HRT and current views on indications, complications and regimens of treatment.

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In England and Wales there are approximately 10 million climacteric or postmenopausal women (Central Statistical Office, 1991), therefore one in five of the total population is a potential candidate for hormone replacement therapy (HRT) (*Fig. 1*).

Therapy has medical implications in several areas, including depression, ischaemic heart disease (IHD), stroke and thrombosis, osteoporosis, premature menopause, and breast cancer.

Depression

It is generally accepted that the climacteric frequently leads to various unpleasant symptoms, which are optimally treated with oestrogen replacement (Studd et al, 1977). The best characterized of these are hot flushes and vaginal dryness. In addition, a variety of other symptoms, such as insomnia, headaches, dyspareunia, loss of libido, generalized aches and pains, poor concentration, poor memory, irritability and depression, are often associated with the menopause and constitute the less well-defined menopausal syndrome. The emergence of data supporting the theory that fluctuations in oestrogen levels may profoundly influence mood supports the existence of such a climacteric syndrome before the final cessation of periods.

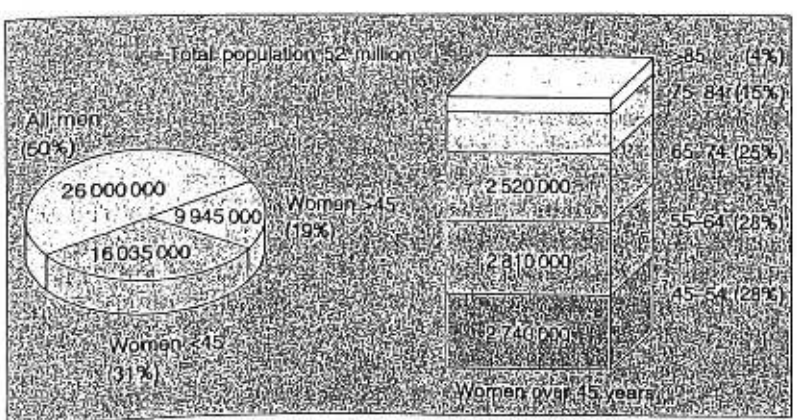

Fig. 1. Number of climacteric and postmenopausal women in England and Wales (Central Statistical Office, 1991).

Changes in the pattern of ovarian hormone secretion are often associated with the development of depression. In premenstrual syndrome (PMS), the mood change is an abnormal response to the physiological changes of the menstrual cycle, but in both postnatal depression and climacteric depression mood change is associated with a major upheaval of ovarian function. These observations suggest that ovarian hormones may modulate mood, a concept in keeping with the generally greater incidence of depressive disorders in women compared with men.

The published data all suggest that oestrogen elevates mood. Oestrogen therapy has been shown to accelerate recovery from postnatal depression (Henderson et al, 1991), to be an effective treatment for PMS, including premenstrual depression (Magos et al, 1986a), and to significantly elevate mood in climacteric depression (Montgomery et al, 1987) (*Fig. 2*). Oestrogen also elevates mood in asymptomatic non-depressed postmenopausal women (Ditkoff et al, 1991), and in high doses is an effective treatment for severe depression (Klaiber et al, 1979). By comparison there is no evidence that either progestogens or progesterone elevate mood. They are not effective treatments for PMS and Magos et al (1986b) have shown that progestogens can cause many of the symptoms of PMS, including depression.

While much collaborative work on the relationship between oestrogen, progesterone and depression remains to be done, it is now time for a wider acceptance by psychiatrists that oestrogen has a role in the treatment of depression in women.

Ischaemic heart disease, stroke and thrombosis

It is regrettable that IHD is still widely regarded as a contraindication to HRT, as this is completely at odds with the published data.

In one of the rare circumstances in

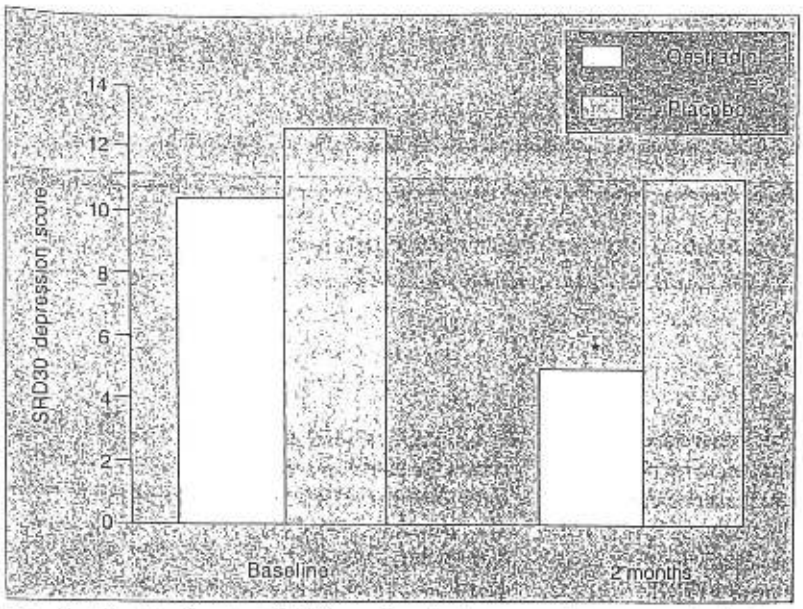

Fig. 2. Effect of oestradiol 50 mg implants on perimenopausal depression (Montgomery et al, 1987). * = significantly different from placebo ($P<0.01$).

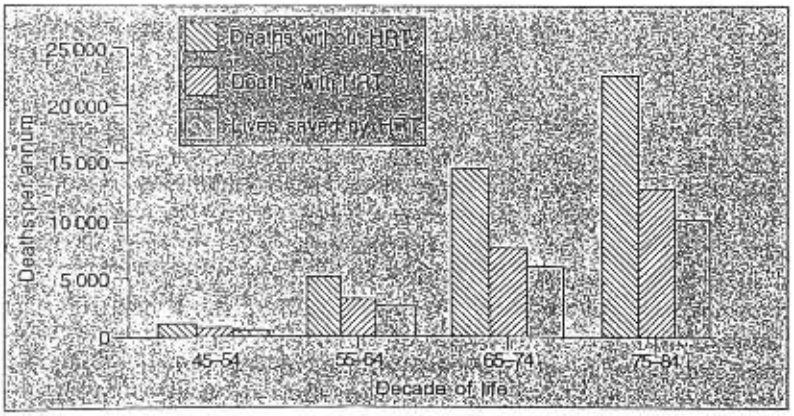

Fig. 3. Potential impact of hormone replacement therapy (HRT) upon annual deaths from ischaemic heart disease.

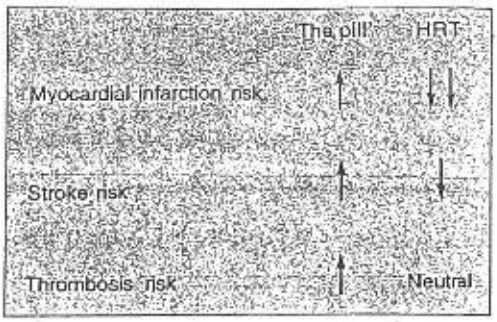

Fig. 4. Differential effects of the pill and hormone replacement therapy upon cardiovascular disease.

which the data are in almost complete agreement, it is clear that HRT markedly reduces the risk of IHD. A recent meta-analysis of 31 published studies found an overall risk ratio for IHD of 0.56 (95% confidence interval 0.5–0.61) for oestrogen users (Stampfer and Colditz, 1991). Even when only the 13 most rigorous studies employing a prospective cohort design were included, the risk ratio for oestrogen users was still 0.58 (95% confidence interval 0.48–0.69). This reduction in risk of IHD is numerically the most significant long-term effect of HRT, because IHD is the greatest cause of death among postmenopausal women. Using the 1990 mortality statistics and population data from the 1981 census, a reduced relative risk of death from IHD among oestrogen users of 0.56 would be translated into a saving of approximately 24 000 lives per annum in England and Wales alone if all postmenopausal women used HRT (Central Statistical Office, 1991; Office of Population Censuses and Surveys, 1991) (*Fig. 3*).

The one theoretical flaw in this epidemiological consensus is that for the last two or three decades HRT may not have been given to patients with a high risk of heart disease. Thus it is possible that these encouraging results are due to selection bias, although the Lipid Research Clinics study found the greatest reduction in cardiovascular mortality among high-risk patients with elevated blood lipid levels (Bush et al, 1987).

Until recently it was thought that oestrogen acted mainly through lipid changes, i.e. by increasing high density lipoprotein and reducing low density lipoprotein cholesterol. Recent data indicate that oestrogen also has other desirable physiological actions. Animal data have shown that oestrogen exerts a direct atheroma-inhibiting action on the arterial wall independently of blood cholesterol (Hough and Zilversmit, 1986). Colour flow Doppler imaging has demonstrated that oestrogen increases peripheral blood flow, both in the uterine artery and in the internal carotid artery (Bourne et al, 1990; Gangar et al, 1991). Oestrogen may also work by modifying carbohydrate metabolism and body fat distribution, both of which are related to IHD risk.

A history of thrombosis is also often regarded as an absolute contraindication to HRT, presumably because it is assumed that postmenopausal HRT has the same thrombogenic potential as the contraceptive pill. This is not the case (*Fig. 4*). There is now worldwide experience of HRT, predominantly oral conjugated equine oestrogens (Premarin), which has not shown any increased incidence of thrombosis; indeed, HRT actually reduces the risk of stroke (Paganini-Hill et al, 1988).

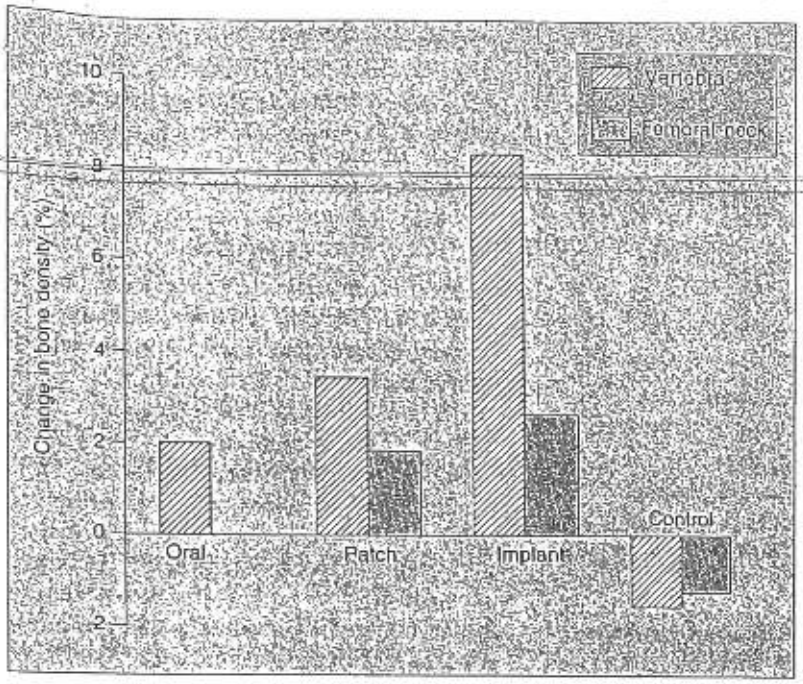

Fig. 5. Increase in bone density achieved with different routes of oestrogen administration (Christiansen and Christiansen, 1981; Lindsay et al, 1976; Stevenson et al, 1990; Studd et al, 1990). Implant = 75 mg; patch = 50 μg; oral = oestradiol 2 mg.

There are several differences between HRT and the combined oral contraceptive pill (COCP) which account for this apparent discrepancy. Most importantly, the synthetic oestrogens in the COCP are four to eight times as potent as the natural oestrogens in HRT at inducing the liver enzyme systems that produce clotting factors (Campbell, 1982). In addition, the dose of oestrogen that is usually employed in HRT is approximately one sixth of that commonly used in the COCP. The avoidance of first-pass hepatic effects by employing a non-oral route of delivery reduces any potential thrombogenic risk even further. While conventional oral HRT results in some minor changes in laboratory measures of clotting function, such as a slight reduction in antithrombin III, no such changes in coagulation, fibrinolysis or platelet function are seen, even with a potent non-oral preparation, e.g. a 50 mg subcutaneous oestradiol implant (Studd et al, 1978).

Thus IHD, or the presence of risk factors for IHD, should be regarded, not as contraindications, but as positive indications for postmenopausal HRT. A history of previous thrombosis need only constitute a contraindication in those rare cases where there is a permanent increase in thrombotic risk, e.g. due to antithrombin III, protein C or protein S deficiency. Where concern exists, non-oral oestrogens such as percutaneous patches or subcutaneous implants should be used in preference to oral therapy.

Osteoporosis

In osteoporosis, bone is normally mineralized but reduced in quantity such that mass per unit volume is reduced. Osteoporosis is a major cause of pain, disability, suffering and death in elderly women. One quarter of white women over the age of 60 years have radiological evidence of vertebral crush fractures, while the combined incidence of fractures of vertebra, femoral neck and forearm in the over-65s is estimated to be 35–40% (Stevenson and Whitehead, 1982). In turn, the financial burden on the health service is considerable, with fracture of the femur being the third commonest reason for occupancy of a non-psychiatric hospital bed in England and Wales.

The tragedy is that postmenopausal osteoporosis is preventable. First, it is well established that oestrogen replacement therapy both prevents the acceleration of bone loss which normally accompanies the menopause (Lindsay et al, 1978) and reduces the subsequent risk of fracture (Keil et al, 1987). Second, oestrogen actually increases bone density, so that oestrogen replacement can be used to correct low bone density in those already at increased risk of fracture. In this respect oestrogen seems to exhibit a dose–response effect. For example, oral oestrogen in general increases vertebral bone density by approximately 1–2% per annum (Lindsay et al, 1976; Christiansen and Christiansen, 1981), whereas the 75 mg oestradiol implant, which achieves oestradiol levels in general at least double those of oral therapy, has been shown to increase vertebral bone density by 8.3% per annum (Studd et al, 1990). The comparable figure for the 50 μg transdermal patch is a 3.5% increase over 12 months (Stevenson et al, 1990) (*Fig. 5*). The finding of a significant correlation between oestradiol level and increase in vertebral bone density by Studd et al (1990) confirms this dose–response relationship.

Oestrogen should be regarded as the benchmark against which all other potential treatments, both prophylactic and remedial, should be judged. Calcium supplements are prescribed as a non-hormonal alternative to oestrogen, but although calcium may be important in early life to establish adequate peak bone mass, there is no evidence that calcium later in life either prevents or treats osteoporosis. Similarly, while undoubtedly able to influence bone mass, physical exer-

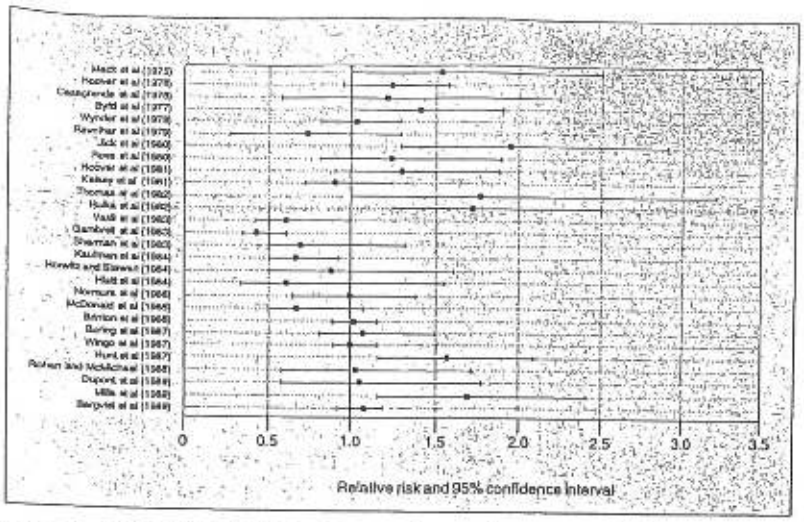

Fig. 6. Disparity of data concerning oestrogen and breast cancer incidence (from Dupont and Page, 1991; references from the figure can be found with original article).

cise alone is not adequate to prevent menopausal osteoporosis. Fluoride increases bone mass, but has been found to increase fracture incidence because of an adverse effect upon bone quality (Lindsay and Cosman, 1990). Calcitonin is able to prevent bone loss but has the major disadvantage of administration by either injection or nasal spray, and it is very expensive. The most interesting non-hormonal approach to date is the bisphosphonate, disodium etidronate (Didronel). This preparation has the convenience of oral administration, is able not only to prevent bone loss but also to increase bone density by approximately 2% per year, and has been shown to reduce the incidence of radiologically detected vertebral fracture (Storm et al, 1990; Watts et al, 1990).

The mechanism by which oestrogen exerts its beneficial effect upon bone mineral and matrix is at present unknown. It does not seem to influence calcium or vitamin D metabolism, but may act indirectly by increasing the activity of calcitonin. Albright et al (1941) believed that postmenopausal osteoporosis was essentially a generalized deficiency of collagen, with loss of the collagenous bone matrix being the principal mechanism. It is known that postmenopausal oestrogen therapy results in a 30% increase in skin thickness and a 34% increase in skin collagen content (Brincat et al, 1985). It is possible that in a similar manner oestrogen increases the collagenous matrix of bone (Studd et al, 1990). This is currently being investigated by means of serial histomorphometric studies on bone biopsy specimens. The possibility that oestrogen may act through collagen holds out the possibility that oestrogen therapy may be able to promote healing of bone in which trabecular disruption has already occurred, and thus be used to treat severe osteoporosis in which bones have already fractured.

Premature menopause and infertility

Cases of premature menopause are usually idiopathic but may also be secondary to surgery, chemotherapy or chromosomal disorders such as Turner's syndrome. While the adverse sequelae of premature withdrawal of oestrogen such as premature osteoporosis and increased risk of IHD should be prevented with appropriate HRT, the personal tragedy of infertility in such women has until recently remained untreatable. The advent of ovum donation in the context of assisted conception has changed that depressing outlook. Abdalla et al (1989) treated 29 women with a mean age of 36 years. Donated oöcytes were fertilized with spermatozoa from the recipient's partner and then frozen until either intrauterine embryo transfer or zygote intrafallopian transfer was undertaken. Pregnancy rates of approximately 30% were achieved, and this success rate has been maintained with 116 pregnancies in 371 couples (Abdalla and Studd, unpublished data). It must be remembered that these are not ageing women trying to cheat nature, but rather women whom nature has cheated.

Breast cancer

The lifetime incidence of breast cancer in the developed world is approximately 10% and any factor that may increase this figure is alarming. Epidemiological evidence that early menarche, late first pregnancy and late menopause are associated with an increased risk of breast cancer has been interpreted as indicating that ovarian hormones, particularly oestrogen, increase the risk of breast cancer.

Unlike the situation with IHD and HRT, where the data are in agreement, there is great disparity among the numerous studies that have sought to investigate the relationship between HRT and breast cancer incidence (*Fig. 6*). Of the 28 studies published since 1972, 19 failed to achieve statistical significance. Of the significant studies, six showed an increased risk of breast cancer with oestrogen use and three a reduced risk. Such data are difficult to interpret. Meta-analysis of all 28 studies

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yields a relative risk of 1.07 for oestrogen users, but the 95% confidence interval of 0.96–1.2 indicates that this difference is not statistically significant (Dupont and Page, 1991). A similar study covering only 16 studies found a relative risk of 1.3 (95% confidence interval 1.2–1.6) but must be criticized because of its selective nature (Steinberg et al, 1991). Perhaps the most obvious conclusion is that there is no evidence of a major increase in the incidence of breast cancer in oestrogen users.

The above data are all concerned with the incidence of breast cancer. While there are few data concerning mortality from breast cancer in oestrogen users, those that exist are of great interest. Even in a study in which the incidence of breast cancer in oestrogen users was increased, Hunt et al (1987, 1990) and Bergkvist et al (1989) reported a reduced mortality from the disease. There are several possible explanations for this apparent discrepancy. First, breast cancer occurring in oestrogen users may have a better prognosis; this idea is supported by the high proportion (68%) of stage I tumours occurring among oestrogen users (Hunt et al, 1987, 1990) and the significantly improved 5-year survival found by Bergkvist et al (1989).

The implication that oestrogen improves prognosis is not necessarily in conflict with known data regarding tamoxifen, as tamoxifen has both oestrogen antagonist and agonist properties. In postmenopausal women it may induce endometrial proliferation and vaginal bleeding, and in some cases hyperplasia and even carcinoma. In addition, it has oestrogen-like favourable effects upon lipid fractions (Love et al, 1991) and, like oestrogen, reduces the risk of myocardial infarction (McDonald and Stewart, 1991).

A second explanation is that the increased level of breast screening by means of palpation and mammography that oestrogen users are subjected to may result in the overdiagnosis of histologically ambiguous lesions (Studd, 1989), or the detection of tumours of very low grade malignancy which otherwise would never have become clinically apparent or would not have done so for many years. In support of the latter concept is the presence of clinically unsuspected in-situ and invasive breast carcinoma at medicolegal autopsy (Nielsen et al, 1987) and the finding by Klemi et al (1992) that, even after adjustment for size, tumours detected by screening were of lower histological and cytological malignancy.

There is a suggestion from epidemiological and cell culture studies that progesterone may increase the risk of breast cancer. These data are confused, but the clinical implications are serious. However, the conclusions remain unconvincing and further work is required to clarify the issue.

It is possible that, in spite of the selection and survival bias of these studies, HRT may be associated with a slight increase in incidence of breast cancer, but that this is balanced by a corresponding reduction in mortality. While the explanation of this paradox remains unknown, the result is that the effect of HRT upon breast cancer is probably neutral.

A difficult question is whether HRT may be given to women who have already had breast cancer. There are no specifically relevant data to give an answer, but in light of the above it seems appropriate to judge each case on its merits and to prescribe HRT where a strong indication exists. Use of oestrogen replacement does not preclude the concomitant use of tamoxifen.

HRT regimens

Progestogens

It has been established practice to give cyclical progestogen with postmenopausal HRT since it was demonstrated that a course of 10–13 days each month could prevent the development of endometrial hyperplasia (Sturdee et al, 1978) and atypical hyperplasia (Paterson et al, 1980). This policy has proved effective in removing the excess risk of endometrial carcinoma associated with unopposed oestrogen therapy (Persson et al, 1989). Unfortunately it has produced unwanted side effects, i.e. cyclical bleeding and progestogenic psychological and physical symptoms.

Withdrawal bleeding is currently the greatest problem with established regimens of HRT. The bleeding may be heavy, prolonged and/or painful, and is probably the major reason for lack of compliance. There are several approaches to this problem. A lower dose of progestogen may be given continuously every day with the aim of rendering the endometrium atrophic — so-called continuous combined therapy. In the long term this type of regimen is very effective, with 95% of women amenorrhoeic at 12 months. In the short term, however, approximately one third of women will discontinue therapy within the first 6 months, mostly because of unacceptable irregular bleeding (Magos et al, 1985). A suitable starting regimen is conjugated

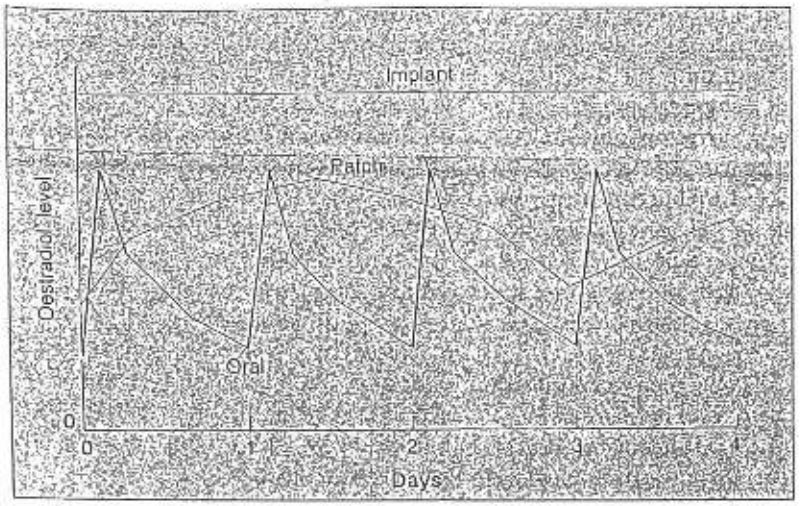

Fig. 7. Short-term variability in oestradiol levels with oral, patch and implant therapy.

equine oestrogen 0.625 mg daily together with norethisterone 1.05 mg. Once amenorrhoea has been achieved, the dose of oestrogen may be increased to 1.25 mg and the dose of norethisterone reduced. The progestogen is conveniently prescribed as the progestogen-only contraceptive Noriday, containing 0.35 mg norethisterone per tablet. As long as the dose of progestogen is low and the total monthly dose is no greater than with cyclical therapy, there appear to be no adverse metabolic sequelae (Christiansen and Riis, 1990). Any bleeding after prolonged amenorrhoea requires endometrial biopsy because of the possibility of adverse endometrial pathology (Leather et al, 1991).

Another option is the new synthetic derivative of norethynodrel, tibolone, which possesses weak oestrogenic, androgenic and progestogenic properties. It has been found to prevent postmenopausal bone loss and to relieve menopausal symptoms (Crona et al, 1988). The claim is that it is not uterotrophic; therefore progesterone is unnecessary and there will be no bleeding. Although true for most women, approximately 15% do experience irregular bleeding. A possible argument against its long-term use is that it may not afford the same protection against IHD as oestrogen because it only possesses weak oestrogenic effects and may reduce high density lipoprotein cholesterol (Bendek-Jaszmann, 1987; De Aloysio et al, 1987). Its use should probably therefore be reserved for medium-term relief of climacteric symptoms where the avoidance of bleeding is paramount.

There may yet be a place in carefully selected women for the use of unopposed cyclical oestrogens, as approximately one quarter of patients on such therapy do not bleed. It may be specifically suitable for the older postmenopausal woman with osteoporosis who refuses to accept any vaginal bleeding, but she must be counselled carefully about the small but real risk of endometrial pathology and be prepared to undergo an endometrial biopsy approximately every 2 years (Leather and Studd, 1990).

Endometrial ablation may have a place in the management of the woman in whom the only progestogenic problem is bleeding. It will render roughly one third of women amenorrhoeic and will reduce the amount of bleeding in almost all (Magos et al, 1991). It does not obviate the need for progestogen as there is likely to be residual endometrium even in those women becoming amenorrhoeic, and in a disquieting number of women troublesome dysmenorrhoea may ensue (Slade et al, 1991). There is probably a much greater place for hysterectomy in the postmenopausal woman taking HRT than is currently realized. In experienced hands the procedure is safe; it guarantees amenorrhoea and completely avoids the need for progestogen.

Unpleasant PMS-like symptoms such as breast tenderness, nausea, headaches, irritability and water retention may occur premenstrually in up to 20% of oestrogen users taking cyclical progestogen (Studd and Magos, 1988). That these symptoms are caused by progestogen and not oestrogen was proved by Magos et al (1986b). Initially a different progestogen such as norethisterone, dydrogesterone or medroxyprogesterone acetate should be used. If symptoms persist it may be acceptable to reduce the number of days for which progestogen is taken, but even a 7-day course is associated with a 3% incidence of endometrial hyperplasia, and some irregular bleeding. Despite such manoeuvres, there will be some women in whom progestogenic symptoms persist with such severity that either treatment is discontinued or a hysterectomy is the preferred option. When using oestradiol implants and cyclical progestogen to treat PMS, Watson et al (1990) found that, in the long term, 10% of women had a hysterectomy because of adverse progestogenic symptoms.

Non-oral oestrogen delivery

One of the main benefits of non-oral oestrogen delivery is that any potential thrombotic tendency is minimized by the avoidance of first-pass hepatic metabolism. There are

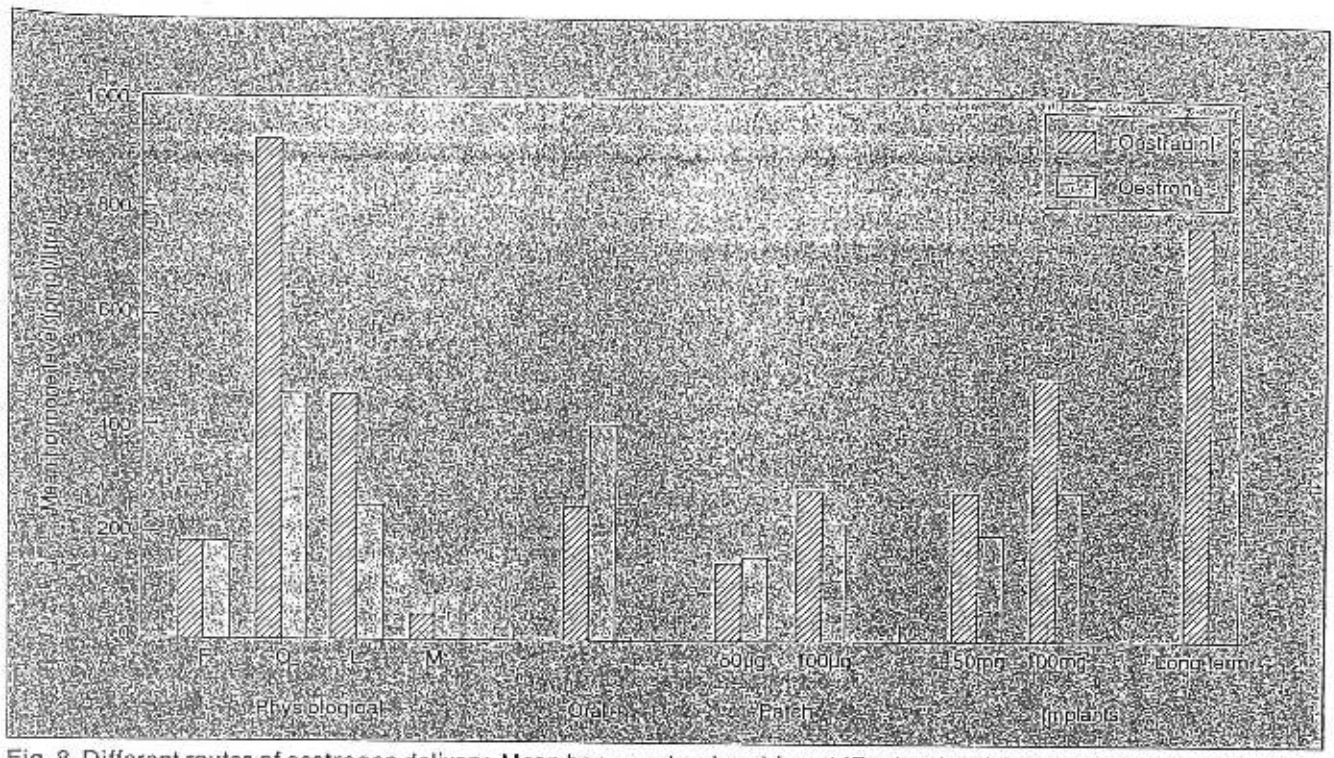

Fig. 8. Different routes of oestrogen delivery. Mean hormone levels achieved (Englund and Johansson, 1977, 1978; Thom et al, 1981; Studd et al, 1990; Stanczyck, 1991). F = follicular; L = luteal; M = menopausal; O = ovarian.

other advantages in that oral oestradiol administration results in a 'roller coaster' 24-hour profile of oestradiol concentration. High levels of oestrogen appear in the systemic circulation within a few hours of ingestion, followed by a steady decline such that levels have fallen to near baseline before the next dose is due. In addition, there is a complete reversal of the physiological 2:1 oestradiol:oestrone ratio so that the latter predominates. In comparison, both transdermal patches and subcutaneous oestradiol implants maintain the 2:1 ratio of oestradiol:oestrone and produce far more stable hormone profiles (Smith and Studd, 1992) (*Fig. 7*).

The first transdermal oestradiol delivery system, Estraderm TTS incorporates oestradiol in an alcohol reservoir contained within an adhesive patch (Padwick et al, 1985; Whitehead et al, 1985). While generally very well tolerated, there are some clinical problems. Young women, particularly, may find the continual wearing of an adhesive patch an embarrassment, and there may also be adhesion problems, especially in hot weather. Perhaps the most common complaint is skin reactions. Minor topical reactions were found in 20% of study weeks by Place et al (1985), while Bellantoni et al (1991) found some irritation at the patch site in 20 of 28 women. These data almost certainly overestimate the size of the problem, but nonetheless skin irritation is a significant problem for a minority of women and in a few may necessitate withdrawal of treatment. Most such skin reactions are thought to be an irritative response to the alcohol in the drug reservoir. New transdermal patches which utilize different technology in order to minimize such skin problems are now undergoing clinical trials, and should be available in the near future.

The administration of cyclical norethisterone transdermally in a combined oestrogen/progestogen patch has recently been reported (Whitehead et al, 1990). Whether this will have any advantage over oral progestogen remains to be seen.

Subcutaneous oestradiol implants, while having the convenience of 6-monthly administration and the improved compliance resulting therefrom, have the added advantage of being able to elevate oestradiol levels higher into the normal premenopausal range than any other currently available route of oestrogen administration, such that the mean oestradiol level of 767 pmol/litre achieved with long-term use is roughly midway between physiological midluteal phase and preovulatory levels (Garnett et al, 1990) (*Fig. 8*). Such oestradiol levels are an advantage in women with low bone density because they achieve a greater increase in bone density over 12 months than do the levels achieved with either oral or patch

therapy. The potential disadvantage is that some women may develop supraphysiological oestradiol levels. Garnett et al (1990) found this so-called tachyphylaxis in only 3% of long-term implant users. Most of these women had been receiving repeat implants at both a higher dose and a shorter interval than recommended, and had a high incidence of psychiatric disorders. It seems that such women require frequent high doses of oestradiol to keep symptoms at bay; this may well be a manifestation of a dose–response effect between oestrogen and mood. In practice, although starting doses may be 75 or 100 mg, eventual maintenance doses should in general be 25 or 50 mg every 5–6 months. If used correctly in this manner by a clinician alert to the potential problem, tachyphylaxis should not occur. Where supraphysiological levels already exist, the correct management is to continue therapy but at reduced dosage until levels fall to within the physiological range. Complete withdrawal of oestrogen would be both unnecessarily harsh and potentially dangerous.

KEY POINTS

- One in every five of the population in England and Wales is a climacteric or postmenopausal woman.
- Oestrogen therapy increases bone density in a dose-dependent manner.
- Oestrogen therapy reduces the risk of ischaemic heart disease by over 40%.
- Contraindications to the oral contraceptive pill such as heart disease, hypertension and thrombosis do not apply to hormone replacement therapy (HRT); indeed, these are indications for HRT.
- The overall effect of HRT upon breast cancer is probably neutral.
- Oestrogen can be effective treatment for climacteric depression and cyclical depression of premenstrual syndrome when approaching the menopause.
- Ovum donation is an effective treatment for the infertility of premature menopause.
- Non-oral oestrogen administration results in more physiological levels and is potentially safer.
- At present the use of continuous combined regimens of HRT or hysterectomy are the best means of avoiding withdrawal bleeding.

Conclusion

The past decade has produced data demonstrating that HRT has even greater benefits than previously thought by those who first recognized the climacteric syndrome as just hot flushes, sweats and vaginal dryness. It is now apparent that the role of HRT in osteoporosis is not merely preventive but also remedial. Evidence is emerging that oestrogen may have a major place in the treatment of depression, and its potential to reduce the incidence of IHD by the order of 40% is probably of greater importance to the prevention of heart disease in women than any other discovery.

Undoubtedly the resumption of menstruation and the cyclical symptoms of monthly progestogen are strong factors, reducing uptake and compliance, but use of continuous combined regimens can avoid this. In view of the potential benefits of HRT, hysterectomy should be more readily offered. Overall the data do not indicate that the risks from breast cancer are increased by HRT.

It is time that gynaecology ceased to be the only branch of the medical profession aware of the importance of HRT. It is time for cardiologists, psychiatrists, neurologists and general physicians to accept that oestrogen replacement has an important role in preventive medicine within their own practice. Every menopausal woman should be offered the potential benefits of HRT, but particularly those with heart disease, depression and osteoporosis. These are the very patients who are often denied HRT for illogical reasons.

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