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Journal Vol: suppl 233
Journal Issue:
Journal Year: 1980
Article Title: The place of estriol therapy after menopause
Article Author: Utian
Article Pages: 51-56

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Acta Endocrinologica 1980, Suppl. 233: 51–56.

The place of oestriol therapy after menopause

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Abstract. The therapeutic principles covering sex hormone replacement therapy after menopause have undergone profound modification in recent years. Initial optimism regarding benefits, proven and unproven, was followed by deep pessimism because of potential serious adverse effects. Some degree of equilibrium has resulted from the application of risk-benefit and cost-effectiveness formulae to such hormone replacement regimens. Cost-effectiveness analysis in particular has highlighted the fact that different hormones or hormone combinations can markedly affect the therapeutic outcome. The purpose of the present paper is to examine the place of oestriol therapy after menopause based on such risk-benefit analyses. Oestriol, it would appear, has the potential for reduced risk but similar benefit to alternative oestrogen or oestrogen-progestogen combinations. The potential risks and benefits of long-term oestrogen therapy are therefore surveyed from the general standpoint of all oestrogens and the specific role of oestriol alone.

Key words: oestriol, oestrogen therapy, menopause.

The history of post-menopausal oestrogen replacement therapy over the past 20 years has been one of extremes. Use of these potent hormones was at first abused; like vitamins, an attitude prevailed that if a little was good, a lot was better. This initial euphoria, largely based on non-scientific observations, was followed by deep pessimism because of serious potential adverse effects. Fortunately, there now exists a substantial and escalating body of information pertaining to the entire subject, and this is allowing a better scientific perspective of the whole area (Utian 1980).

One aspect gaining increasing acceptance is the recognition that different oestrogens appear to induce different metabolic responses (Utian 1972a, b, 1973). Although these differences are apparently drug-specific and not simply dose-related, considerable difficulty exists in properly differentiating the total drug profile of each therapeutically available substance. Cost-effectiveness analysis appears to be one method of value in making such comparisons.

The purpose of this paper is to survey the role of long-term oestriol therapy after menopause on the basis of cost-effectiveness. It is therefore pertinent to provide a brief background to the above-mentioned methods of analysis.

Some comments on general analytic approaches

Different measures have been designed to assist in decision making in medicine by systematic analysis (Bunker et al. 1977; Weinstein & Stason 1977). One such measure, cost-effectiveness analysis, has been applied to post-menopausal oestrogen therapy (Utian 1978). Such an analysis necessitates the availability of the best current information on both the efficacy of the therapy and its costs, as well as the possible therapeutic risks and the respective costs thereof. Because the available data on the effectiveness of most clinical procedures, oestrogen therapy and menopause included, is often limited, such an analysis is structured to incorporate new

data as it becomes available, and even to suggest areas in need of future research to resolve critical uncertainties. It is inevitable when risks and benefits of any therapy are being evaluated that subjective values have to be involved. Nonetheless, even subjective 'trade offs' can be compared by suitably defined scoring systems.

It should be emphasized that any effective analysis of a therapeutic procedure should be structured to incorporate present and future health benefits or risks and their respective costs. For example, oestrogen therapy should be recognized as a preventative medicine programme with immediate and ongoing costs, but with health benefits and risks that also may be in the future.

The actual calculation of the cost-effectiveness analysis has been described by Weinstein & Stason (1977) and related to oestrogen therapy by Utian (1978). In summary, health care costs are measured in financial terms according to the following formula:

$$\Delta C = \Delta C_{RX} + \Delta C_{SE} - \Delta C_{BENEF} + \Delta C_{RX\Delta LE}$$

where: ΔC = Net health care costs (HCC); ΔC_{RX} =All direct HCC (drugs, physicians, etc.); ΔC_{SE} = All HCC due to side effects of treatment; ΔC_{BENEF} =Savings in HCC due to disease prevention; $\Delta C_{RX\Delta LE}$ = HCC of diseases which would not have occurred had the patient not received treatment.

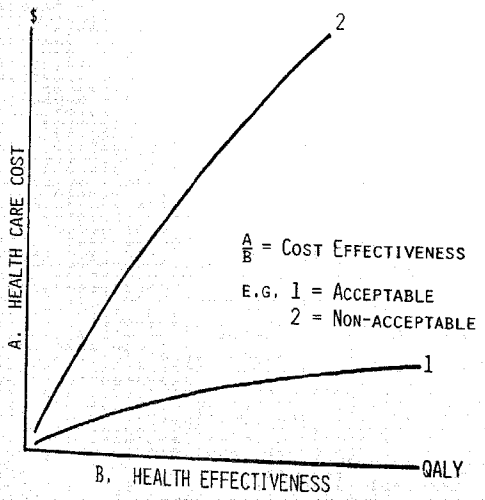

Fig. 1
Cost effectiveness is illustrated as the ratio of health care costs to health effectiveness of the therapy under scrutiny.

Health effectiveness is measured in 'quality-adjusted life years' (QALY), a measure that incorporates changes in survival and morbidity in a single value that reflects trade-offs between them. The methodology for measurement of health effectiveness has been fully described elsewhere (Utian 1978; Weinstein & Stason 1977).

The measure of cost-effectiveness becomes a ratio, the numerator being health care costs and the denominator being health effectiveness. It is then immediately apparent (Fig. 1) that different oestrogens can be directly compared and that such comparisons take both costs and relative effectiveness into account. A drug that is high in risk factors may, for example, generate greater costs over the long term despite having equivalent or superior therapeutic effects in the short term.

Oestriol

Oestradiol, the principal oestrogen of the premenopause, is produced almost totally by direct ovarian secretion. Following spontaneous menopause the levels of oestradiol and oestrone drop, the oestrone to a relatively lesser extent than oestradiol, thus becoming the principal post-menopausal oestrogen. In post-menopausal women oestrone production is principally, if not completely, the result of peripheral aromatization of plasma androstenedione, and not of ovarian or adrenal secretion. The amount of precursor androstenedione does drop after menopause, but the rate of conversion to oestrone increases (Utian 1980).

Oestriol is also a natural oestrogen, but it is principally derived by 16α hydroxylation of oestrone and oestradiol in peripheral tissues and liver. The question of direct ovarian secretion remains to be fully elucidated. Large amounts are of course produced by the feto-placental unit, and oestriol isolated from the urine of pregnant women was the second oestrogenic substance ever described.

Binding studies on different oestrogens tend to suggest that oestriol and oestradiol behave differently to oestrone. The stoichiometric replacement of oestradiol by oestriol in the nucleus indicates that these steroids are associated to the same receptor binding site, whereas oestrone does not *directly* bind to the nuclear receptor (Tseng 1979). Thus when oestradiol and oestrone are both pre-

sent at the target organ oestradiol rather than oestrone binds to the receptor in the nucleus. Theoretical considerations would suggest this to hold true for oestriol and oestrone, but further research is still necessary. Oestradiol does have a greater relative affinity constant for binding sites than oestriol.

A measure frequently used to compare oestrogens is the 'proliferative dose'. This is the total dose that will provide full endometrial proliferation in a previously unstimulated or gonadectomized animal. The proliferative dose of oestriol is 120–150 mg as compared to 60–80 mg for conjugated equine oestrogen, 60 mg for oestradiol valerate, and 2 mg for ethinyloestradiol.

The 'oestrogenicity' of oestrogens cannot be simply related to the dose administered for reasons stated above. Current research is therefore increasingly directed towards defining the specific target organ effects of different oestrogens, endogenous or exogenous, in equivalent 'doses'. These target organ responses could be advantageous or disadvantageous depending on the metabolic activity generated. Logically, specific oestrogens should be engineered and selected for desirable specific target organ responses. This ideal is far from being achieved. Oestriol has, however, been shown to differ slightly from the broad group of oestrogens as a whole, and it is therefore pertinent to review this aspect.

Potential risks and benefits of oestrogen replacement after menopause

The potential risks and benefits of long-term oestrogen therapy after menopause have been fully reviewed elsewhere (Utian 1980, 1979). These risks and benefits can be summarized for oestrogens in general as follows:

Potential risks

Post-menopausal bleeding.
Unnecessary surgery.
Uterine cancer.
Breast cancer.
Deep venous thrombosis and thromboembolism.
Increase in blood pressure.
Increase in gallstones requiring surgical treatment.
Changes in glucose tolerance.

Potential benefits

Relief of true oestrogen-dependent symptoms (hot flushes and those related to vaginal atrophy).
Prevention of osteoporosis.
The mental tonic effect.
Effect on skin.

Specific risk/benefit ratio of oestriol

The above-listed risks and benefits apply to oestrogens in general as a group of hormones. Any specific hormone that could eliminate or reduce the likelihood of risks yet maintain the benefits would thus come closer to the ideal. Oestriol has been suggested as such a substance. That is, oestriol may have an enhanced cost-effectiveness score or risk/benefit ratio. This favourable situation could result from specific oestriol-induced modifications of some of the above-mentioned factors.

I. *Reduced risk*

Sufficient information exists in the literature to suggest that oestriol does not carry the same degree of risk as other oestrogens for some of the above-mentioned problems. Insufficient information exists to comment at all on blood pressure, gallstones, or glucose tolerance changes.

1. *Decreased likelihood of post-menopausal bleeding and unnecessary surgery*

Post-menopausal bleeding is a real disadvantage of post-menopausal oestrogen therapy for many reasons. It raises a 'cancer scare' in women, and it inevitably leads to diagnostic curettage and perhaps further unnecessary surgery such as hysterectomy. The latter would adversely affect the risk/benefit and cost/effectiveness ratios.

Oestriol has a high proliferative dose and in clinical amounts produces extremely little endometrial response (Heuser & Staemmler 1973). It is therefore rarely associated with post-menopausal bleeding and the concomitant adverse sequelae mentioned above.

2. *Reduced chance of uterine cancer*

The general consensus of the studies linking long-term oestrogen therapy to endometrial cancer is that the annual cancer risk will be increased to between 4 and 8 cases per 1000. These studies have been reviewed (Utian 1980), and the following factors seem to enhance the relationship between oestrogens and cancer:

Duration of therapy.
Dosage.
Continuous unopposed oestrogen administration.
Type of drug.

Oestriol, because of its low stimulatory effect on the endometrium, may have a reduced association with endometrial cancer. (The evidence for this thesis is examined in this publication by Dr. Salmi and by Dr. Klopper.) The relevance of such a reduced risk to the risk/benefit ratio speaks for itself.

3. *Reduced chance of breast cancer*

A possible marginal increase in breast carcinoma in oestrogen treated patients has been reported (Hoover et al. 1976), but has not yet been confirmed. (The subject of breast cancer is dealt with in this publication by Dr. Lemon.)

4. *Decreased risk of deep venous thrombosis and thromboembolism*

Most authorities are in agreement that the oral contraceptive is associated with a definitive risk of venous thrombosis, thromboembolism and possible death (Boston Collaborative Drug Surveillance Program 1973; Vessey & Doll 1968). It is also generally accepted that this risk is causally related and not simply the initiation of an inherent predisposition to thrombosis (Badaracco & Vessey 1974). Some dissension does exist, and this relationship has been questioned (Drill 1972; Drill & Calhoun 1972). It is therefore hardly surprising that far more disagreement exists in the question of a relationship between post-menopausal oestrogen usage and thromboembolic phenomena.

The possibility of thromboembolic risk is extremely important. There would be no advantage in preventing one risk factor, for example osteoporotic fracture, and substituting another, namely thromboembolism.

Preliminary evidence suggests that the risk of thromboembolism may be increased in post-menopausal oestrogen users compared to non-users. This risk appears to be increased in users of synthetic conjugated steroids (ethinyloestradiol and mestranol) (Gow & MacGillivray 1971) as compared to users of conjugated oestrogens (Bolton et al. 1975), oestradiol valerate or oestriol succinate (Toy et al. 1978). The latter finding does seem to be a drug-related response rather than a dose-related effect, in that all the oestrogens thus far incriminated in clinical reports as potential thrombogenics are synthetic compounds with an alkylated side chain which renders their metabolism slow and inefficient.

Several authors have investigated the effects of various oestrogens on coagulation factors, but results thus far have been conflicting. Oestriol, however, appears to exert very little, if any effect on the clotting factors (Toy et al. 1978; Davies et al. 1975).

Large epidemiologic, clinical and laboratory based studies are urgently needed, but at this time oestriol would appear to be one of the safest oestrogens in relation to thromboembolic risk.

II. *Maintenance of benefit*

1. *Relief of true oestrogen-dependent symptoms*

The symptoms that occur during the peri-menopause are the result of an interaction between true endocrine changes and psycho-socio-cultural influences (Utian 1979, 1980). Specific hormone-related symptoms, particularly hot flushes and those related to vaginal atrophy, respond extremely well to all forms of oestrogen replacement therapy (Utian 1972c). This response also holds true for oestriol and oestriol hemi-succinate (Schiff et al. 1978; Tzingounis et al. 1978; Perovic et al. 1975).

2. *Prevention of osteoporosis*

A potent indication for long-term oestrogen therapy has been the prevention of bone resorption with a consequent reduction in osteoporosis and, hopefully, bone fractures. This subject has recently been reviewed in depth (Utian 1980).

Oestriol hemi-succinate in doses of up to 12 mg per day does not appear to prevent bone loss in post-menopausal women (Lindsay et al. 1979). Lindsay et al. have suggested that to be an effective agent for prevention of osteoporosis, oestriol would have to be prescribed in daily doses consid-

erably in excess of 12 mg. Unfortunately at that dose it is likely that undesirable side effects would also increase.

The inability of oestriol to prevent bone resorption is an important deficiency of the substance. It would be of interest to investigate the effect on bone of combinations of oestriol with calcium supplementation, but no such study appears yet to exist.

3. *Mental tonic effect*

The ability of some exogenous oestrogens to stimulate a general feeling of well-being (Utian 1972d) has not been adequately tested with oestriol, and a definitive study in this respect needs to be undertaken.

4. *Increase in skin thickness*

The epidermis becomes thinner after menopause and a decrease in the rate of mitosis has been observed by means of autoradiographic studies after castration (Rauramo & Punnonen 1973). Oestriol succinate causes thickening of the epidermis and an increase in the rate of mitosis (Rauramo & Punnonen 1973). Improvement in skin thickness is clearly an advantage to post-menopausal women and is maintained by oestriol.

Conclusion
The place of oestriol therapy after menopause

Oestriol has been demonstrated to be an oestrogen capable of inducing metabolic responses in oestrogen-receptor containing target tissues, but not always producing identical effects to other oestrogenic substances. In particular oestriol appears to be associated with a reduction in potential adverse responses, notably on the endometrium and blood clotting factors. It does suffer from one major drawback, namely the minimal effect on bone.

The main place for oestriol therapy after menopause would appear to be the patient who requires exogenous oestrogens, but is considered 'high risk' by virtue of absolute or relative contra-indications to such therapy. These factors have been reviewed elsewhere (Utian 1979).

A secondary role for oestriol is identical to that for most of the other oestrogens in popular use, including relief of hot flushes and symptoms related to vaginal atrophy. At this time oestriol would not appear to be indicated in patients receiving oestrogens for inhibition of bone resorption as a prime indication.

The potential to minimize risks yet maintain most benefits places oestriol in a unique category amongst the oestrogens, and supports both its clinical use and further scientific investigation.

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