

# Recent advances in hormonal replacement therapy

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## Abstract

**There are various methods of hormonal replacement therapy (HRT). The oral route has been used for over 3 decades. Despite its proven efficacy by this route, dose related adverse effects is a major drawback due to hepatic first pass metabolism. In recent years, a number of non oral-routes which avoid hepatic first pass metabolism, have been used in hormonal replacement therapy (H.R.T.). These include intramuscular depot injections, subcutaneous implants, vaginal creams and pessaries. Recently transdermal patches known as the transdermal therapeutic system (T.T.S.) contains estradiol known as Estraderm and System; this contains micronized 17 $\beta$  estradiol, which is an outgrowth of the ongoing evolution of transdermal delivery system.**

*Keywords: Hormonal replacement therapy (H.R.T.); Transdermal therapeutic system (T.T.S.) Estraderm; System.*

## Introduction

As women reach menopause, usually by 45 years of age, there is a decrease in ovarian activity resulting in Hormonal imbalance. This Hormonal changes cause vasomotor instability, mood and sleep disturbances, vaginal atrophy, difficulties with memory, concentration and increase risk of other health problems such as osteoporosis and coronary artery disease. Fortunately, advances in hormonal replacement therapy (H.R.T.), also known as estrogen replacement therapy, helps women to suffer less of these symptoms and health risks. There are various methods of taking the hormones. The oral route is the most common H.R.T. delivery method. Despite the proven efficacy of oral route, 60-90% of oral estrogen is converted to estrone in the gut wall and liver. Thus relatively high doses of estrogen is required to compensate for conversion to estrone, which cause dose related adverse effect. A number of non oral estrogen delivery method, which avoid hepatic first pass metabolism, has been found to be effective in treating menopausal symptoms and inhibiting bone resorption. These include intramuscular depot injection, vaginal creams, pessaries and subcutaneous implants.<sup>1</sup> The most recent method is the transdermal patches known as "Estraderm and System."

Transdermal estradiol, which avoids hepatic first pass metabolism, elevates circulating concentrations of estradiol in a dose dependent manner in postmenopausal women in the range observed in premenopausal women at the early to mid follicular stage.<sup>2</sup> Transdermal estradiol 0.1 mg and oral estradiol valerate 2 mg raised plasma estradiol concentrations to comparable values.<sup>3</sup> In addition transdermal estradiol does not markedly elevate plasma estrone concentrations and estradiol: estrone plasma ratio is maintained approximately at the same level as found in premenopausal women.

Transdermal estradiol seems to have comparable effect as oral route in relieving vasomotor symptoms, vaginal atrophy and osteoporosis. However various studies have shown that transdermal estradiol does not affect plasma lipid and lipoprotein concentrations.<sup>4</sup> Lipid and lipoprotein change appears to be less marked with transdermal estradiol than with oral estrogen. Further studies are indicated to clarify the effects of long-term transdermal estradiol therapy on plasma lipids and to assess the impact on the incidence of cardio vascular disease in postmenopausal women.

Transdermal estradiol delivery system is a thin adhesive patch consisting of a drug reservoir where estradiol is held in ethanolic solution, between an occlusive backing layer and a rate controlling

microporous membrane. The drug is thus delivered at a constant and predictable rate to the skin surface for percutaneous absorption into the systemic circulation. The 3 sizes of estradiol patch currently available are 5, 10, and 20 cm<sup>2</sup>, containing 2, 4, 8 mg of drug respectively and are designed to release estradiol at a rate of 0.2/mg/cm<sup>2</sup>/h. Maximum plasma estradiol concentrations are attained in post menopausal women within 2 to 8 hours of application of transdermal delivery system to intact skin.<sup>5</sup>

The rate of absorption of the drug solution applied directly to a skin surface can vary according to the properties of the particular skin site. The transdermal delivery system is designed to overcome this problem by delivering drug to the skin surface at a rate less than the slowest rate of skin absorption. Therefore the site application would not be expected to make any difference to the rate of drug absorption. However, Schenkel *et al* <sup>6</sup> reported that absorption of estradiol from 0.25 mg or 0.05 mg patch was comparable whether the patch was applied to the abdomen, buttocks, lower back, lateral thorax or upper arm, there was a significant difference between absorption from the abdomen (100%) and upper thigh (87%).

The recommended initial dosage of transdermal estradiol is 0.05 mg daily which may be increased in cases of inadequate response after 2 to 3 weeks treatment or decreased, if breast discomfort or breakthrough bleeding occurred. For maintenance therapy, the lowest effective dose should be used. Treatment may be continuous or may be given in 4 week cycles (3 weeks on / week off). Sequential progestogen treatment should be administered for 10-12 days/a month to patients with an intact uterus. Estraderm should be changed twice weekly. The chief limitation of Estraderm relate primarily to local intolerance. Most notably, the alcohol excipients in the patch reservoir, have in some cases caused local irritation and discomfort, which may lead to discontinuation of therapy. In fact, it has been reported that as many as 40% of patients have dermatologic reactions, which are severe enough to require termination of therapy in between 2.5% and 7.2% of cases.<sup>7</sup> The newer method of transdermal therapeutic system is System.<sup>8</sup> The key feature that differentiates the two patches is the method by which the drug is released. In Estraderm, the estradiol is dissolved in alcohol contained within a discrete drug reservoir. Here the patch appears to be wrinkled and bulky. In contrast, the active drug in System is incorporated with a non-alcohol based matrix and cause less local irritation and discomfort.

#### **Advantages of transdermal therapeutic system (T.T.S.) over oral route are as follows:**

- I. Avoids hepatic first pass metabolism, so estradiol is not converted to estrone as in the oral route where there is 60-90% conversion to estrone. Therefore dose related adverse effect is avoided.
- II. Estrone levels are not elevated to the extent as in oral route to enhance increased levels of renin substrate, Sex Hormone Binding Globulin (S.H.B.G.), Thyroxine Binding Globulin (T.B.G.) and Cortisol Binding Globulin. It has been speculated that these effects might contribute to development of hypertension, gall bladder disease and thrombosis.
- III. Continuous absorption obviates 'peaks and troughs' and there is sustained physiological level of estrogen in plasma lipids.
- IV. Direct absorption of estradiol through skin also results in estradiol: estrone plasma ratio which more closely approximates with that found in premenopausal women.
- V. The development of transdermal estradiol, with a non alcohol based matrix has decreased adverse effect of local irritation and discomfort significantly.
- VI. Convenient to use, especially the recent transdermal estradiol System.

Advantage of transdermal therapeutic system (T.T.S.) over implants are that once implanted, they cannot be removed, and high peak levels of estradiol is observed after implantation, therefore physiological levels of estrogen is not maintained. Disadvantage of vaginal cream is inconvenient for users and its efficacy not proven in the long-term use.

## Conclusion

With increasing life expectancy, many women will spend more than one third of their life span in the post-menopausal state. There is increased awareness of the problems of post-menopausal osteoporosis and vasomotor instability, together with recognition of less risk of endometrial hyperplasia when progestin is coadministered with estrogen. In view of convenience to use transdermal therapeutic system, it provides more physiological profile of estrogen and less side effects with some limitation as cost and need for oral progestogens in woman with intact uterus. Nevertheless, it represents a recent advance in hormonal replacement therapy.

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