

## The use of 17 $\beta$ Estradiol gel and progestogen tablet for Hormone Replacement Therapy (HRT) in menopause

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### Abstrak

Untuk pengobatan dan pencegahan pada wanita menopause akibat kekurangan hormon estrogen adalah dengan pemberian hormon estrogen yang dikenal dengan istilah hormone replacement therapy (HRT). Cara pemberian HRT yang banyak digunakan adalah berupa tablet. Pemberian tablet akan terjadi metabolisme di usus dan hati. Tablet harus digunakan setiap hari sehingga menimbulkan kebosanan dan menimbulkan gangguan gastrointestinal. Pemberian berupa jel cukup dioles di badan dan tidak terjadi metabolisme di usus dan hati. Pada wanita dengan uterus, estrogen harus dikombinasikan dengan progestogen. Jenis progestogen yang dianjurkan adalah jenis turunan alamiah dan yang memiliki sifat antimineralokortikoid, sehingga tidak menyebabkan retensi cairan. Salah satu jenis progestogen yang tidak menyebabkan retensi cairan adalah nomogestrol acetate. Nomogestrol acetate juga menghambat enzim 17 $\beta$  Hidroksisteroiddehydrogenase tipe 1 sehingga estradiol ( $E_2$ ) tidak dapat diubah menjadi estron ( $E_1$ ). Akibatnya kadar  $E_2$  di dalam jaringan payudara rendah dan dengan sendirinya menurunkan risiko kanker payudara. (Med J Indones 2003; 12: 194-8)

### Abstract

The treatment and prevention of disease in menopausal women due to deficiency of estrogen hormone are done through the administration of estrogen hormone, known as hormone replacement therapy (HRT). The administration of HRT is commonly done through the administration of tablets. However, the administration of tablet will result in metabolism in the colon and liver. Tablets are usually used on a daily basis such that it may lead to boredom and results in gastrointestinal disorder. The administration of gel, on the other hand, is done by applying the gel to the body and therefore metabolism in the colon and liver can be prevented. In women with uterus, estrogen must be combined with progestogen. The type of progestogen recommended is the one with natural derivative and which possesses antimineralocorticoid properties, such that fluid retention can be avoided. One of the types of progestogen which does not result in fluid retention is nomogestrol acetate. Nomogestrol acetate will also inhibit 17 $\beta$  hydrosisteroiddehydrogenase enzyme type 1, such that estradiol ( $E_2$ ) is prevented from being transformed into estron ( $E_1$ ). As a result,  $E_2$  level in the breast tissue is kept at minimum, thereby reducing the risk of breast cancer. (Med J Indones 2003; 12: 194-8)

**Keywords:** 17 $\beta$  estradiol gel, hormone replacement therapy, progestogen, nomogestrol acetate, enzyme.

As a result of deficiency in estrogen hormone in menopausal women, various health problems may occur, either in the long-term or in the short-term. Since its causal factor is deficiency in estrogen hormone, the appropriate therapy is the administration of estrogen hormone from outside the body, well known as hormone replacement therapy (HRT). For the treatment of climacteric complaints, either in pre- or in post-menopause, it is sufficient to administer short-term HRT. However, for prevention

of osteoporosis, coronary heart disease, stroke, dementia, colon cancer, it is necessary to administer long-term HRT (> 5 years).

Although the patient or the physician is well aware of the numerous benefits of HRT, the prevalence of its use is still low. There are a variety of reasons put forward by patients why they do not want it, or do not want to continue using HRT. One of the reasons is (in addition to the fear of cancer) the boredom involved in using HRT tablets everyday.

followed by plaster and cream. Injection and implant are not highly recommended, particularly in women who still have uterus, since it may result in severe bleeding. In addition to boredom, the administration of tablets may also lead to gastrointestinal disorder. Tablets will be absorbed by the colon and in this colon metabolism will be developed by the enzymes existing in the colon lumen. Furthermore, the tablets will reach the liver and a metabolism will in turn be produced by the liver. In addition, tablets, particularly estrogen, will trigger the formation of certain proteins such as angiotensinogen, blood coagulation factor, and certain enzymes. Angiotensinogen will cause hypertension and enhance blood coagulation factor that may result in thrombosis. Enzymes which are formatted may disrupt metabolism of certain medications (oral antidiabetics, oral tuberculostatics, tetracylin) which are accidentally used in conjunction with HRT containing estrogen. Therefore, it is advisable that patients with hypertension and/or history of hypertension, history of embolism, severe varices, history of gall bladder surgery and/or current gall bladder disease, and history of liver disease and/or liver dysfunction, not use HRT in the form of tablets. In patients with the aforementioned abnormalities, or patients who have grown weary of using tablets everyday, HRT in the form of vaginal cream, plaster, or gel (transdermal) can be recommended. It should be noted, however, that such administration of HRT is not achieved through the colon or liver, such that its level in the blood is very high (being prevented from metabolism). Also, doses to be used are relatively low.

In patients who still have uterus, HRT should be administered in combination with progestogen. The purpose of progestogen administration is to prevent endometrial cancer. Although estrogen is administered transdermally, progestogen in the form of cream is still unavailable in Indonesia as yet. It is necessary to know the properties of the type of progestogen tablets to be administered. The most frequently used type is progesterone-derivative progestogen.

Following is a discussion on the administration of transdermal estrogen in gel and the administration of progestogen tablets.

## ESTRADIOL GEL

Gel that contains estradiol is put in a dispenser. (Figure 1).



Figure 1. Method of estrogen gel administration

At one press 0.5 g gel (0.5 mg estradiol) is squeezed out. Early recommended dose is 1.5 mg estradiol (3 x presses).<sup>1</sup> At the first press, the dose is usually not so accurate that it would be best to get rid of it.

In women with uterus, the dose should be combined with progestogen. The combined doses could be administered cyclicly, sequentially, or continually. (Figure 2)

Parts of the skin recommended include abdomen, upper thigh, arm, and shoulder, while breast and mouth, or mucous membrane are not recommended. (Figure 3)

Areas of the skin to be applied must be clean, dry, and without wound. It is not necessary to rub the skin repeatedly, and do not put on clothes too soon. It should be used daily and the sites of application may be interchangeable.

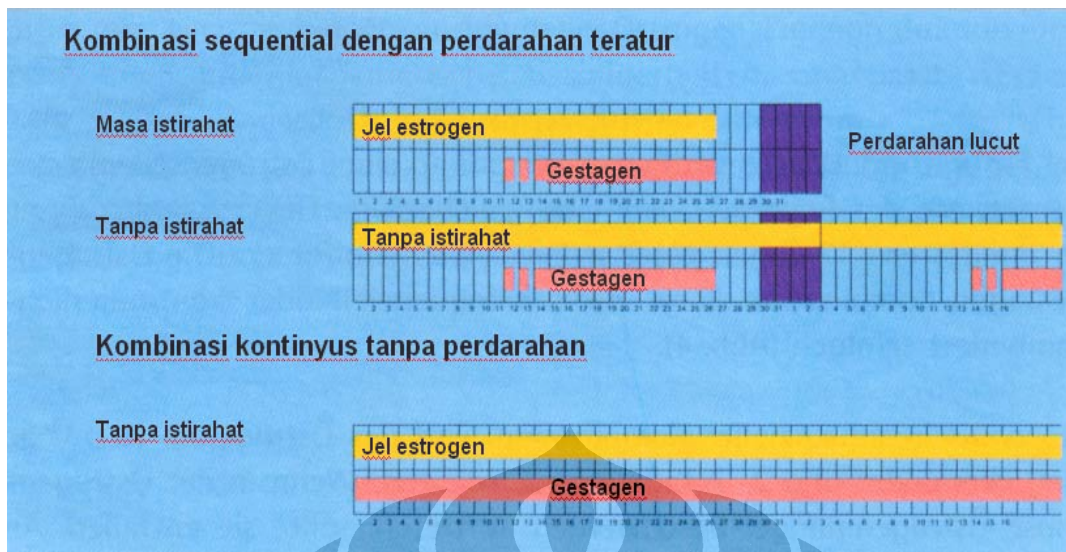


Figure 2. Scheme of estrogen gel administration in HRT

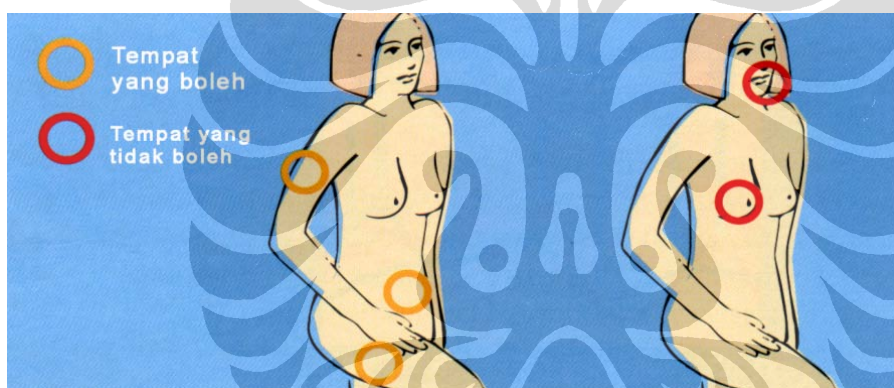


Figure 3. Sites which are recommended and not recommended for application of estrogen gel

**TYPES OF PROGESTOGEN**

The most recommended type is synthetic progestogen which resembles natural progesterone, such as medroxyprogesteron acetate (MPA), nomogestrol acetate, siproteron acetate, didrogesteron, chlormadinon acetate, and magestrol acetate. Natural progesterone is also widely used, but it requires a very high dose (100-200 mg/day). It is not necessary that all types of natural-derivative synthetic progestogen be activated by the liver, such that the liver can be prevented from being overburdened. In addition, natural-derivative progestogen does not affect lipid metabolism. As known, the decrease of HDL

cholesterol and the increase of LDL cholesterol carry the risk of cardiovascular.

Medroxyprogesteron acetate and siproteron acetate possess mineralocorticoid properties which could easily lead to fluid retention. As a result, patients frequently complain of breast pain, headache and swollen leg.

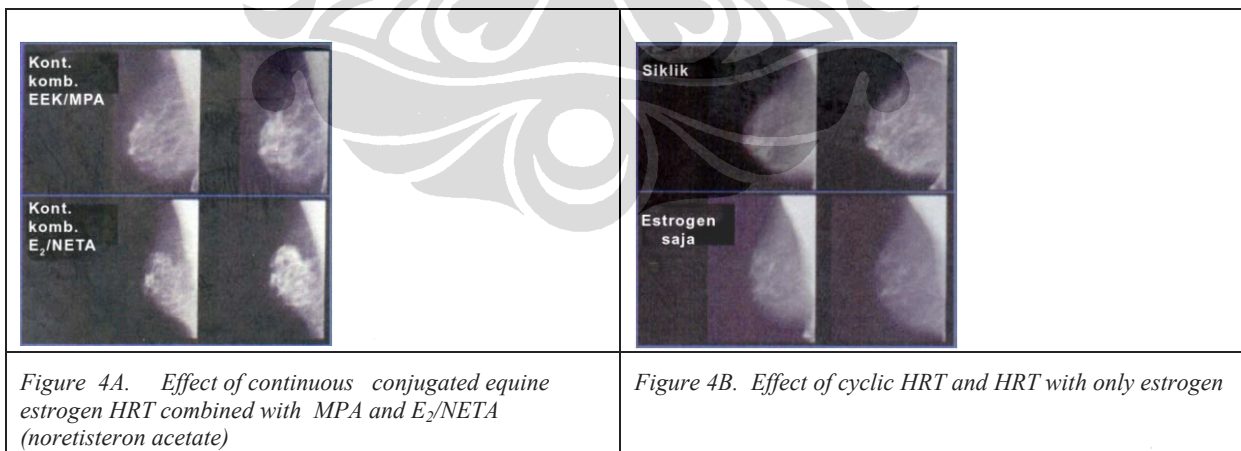
Nomogestrol acetate is new generation natural-derivative progestogen. This type of progestogen has antiminerlocorticoid properties, such that fluid retention can be prevented.<sup>2</sup>

Natural-derivative synthetic progestogen should be activated first by the liver. The types of testosterone-derivative synthetic progestogen include linestrenol,

noretisterone acetate, levonorgestrel, dienogest and desogestrel. This activation process may be disrupted by drugs such as oral antidiabetics, oral tuberculostatics, tetracylin, and ampicillin, and so forth.<sup>3</sup> In the long-term use, it may affect lipid metabolism. Testosterone-derivative synthetic progestogen is widely used as a component in contraceptive pills. All types of testosterone-derivative synthetic progestogen possess strong anabolic properties and do not have any mineralocorticoid effect. Certain types of noretisterons can be aromatized through aromatase enzyme into estrogen, such that they are quite beneficial for the bones, brain and colon; although they are less beneficial for the breast. Noretisterone existing in HRT can triggers aromatase enzyme and 17 beta hydroxysteroid-dehydrogenas enzymes type I and II (17 beta HSD type I and II).<sup>4</sup> Aromatase transforms estrogen into estron ( $E_1$ ). As known,  $E_1$  is a weak estrogen that it does not have any effect on the breast. However, this  $E_1$  will in turn be changed by 17 beta HSD enzyme type I into strong estrogen of estradiol ( $E_2$ ). Furthermore, this  $E_2$  will be transformed by 17 beta HSD type II into  $E_1$ . As a consequence, estrogen level in the breast tissue becomes very high, and on mammography an increase of in the density of breast tissue can be visualized. The administration of only estrogen in post-menopausal women has been found to increase mammographic density by 10-25%, while the administration of combined estrogen and

progestogen (noretisteron acetate, NETA) has been found to increase mammographic density by up to 25-50%.<sup>5</sup> The increase of mammographic density is indicated by an increase in the proliferation of epithelial cells of the breast.<sup>6</sup> Women whose breast tissues show an increase of mammographic density by 60-75% are at risk for breast cancer 4-6 times as high as those who do not show an increase in mammographic density.<sup>7</sup>

Several types of natural-derivative progestogen, such promesgeston, nomogestrol acetate and medrogeston, have powerful ability to inhibit 17 beta HSD enzyme type I, such that  $E_1$  is prevented from being transformed into  $E_2$ . On the other hand, testosterone-derivative synthetic progestogen, such as noretisteron or levonorgestrel and linestrenol, are capable of triggering the activation of 17 beta HSD enzyme type I, thereby transforming more  $E_1$  into  $E_2$ .<sup>4,8,9</sup> Of all types of testosterone-derivative progestogen, only tibolone has the effect to inhibit the activation of 17 beta HSD enzyme type I, and triggers the activation of 17 beta HSD enzyme type II.<sup>10</sup> The enhanced activation of 17 beta HSD enzyme type II will cause even more  $E_2$  to be transformed into  $E_1$ . It has been shown that the administration of tibolone increased mammographic density only by 2-6%<sup>11</sup> (Figures 4a and 4b).





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**ERRATA**

This is to correct a technical error concerning two manuscripts entitled :

1. The effect of fiber diet on colonic cancer formation: the role of butyrate.  
Recently published in vol. 12 # 2, April-June 2003 issue.  
The authorship should read: Ari Fahrial Syam, Daldiyono
2. Idiosyncratic chloroquine retinopathy – a case report.  
Published in vol. 11 # 3, July-Sept 2002 issue.  
The authroship should read: H.Singh, M.Rathee, M.S. Gupta, K. Kishore, S. Singh, J. Singh.

We apologize for the inconvenience.