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S 02 (LS 1)

Impact of Various Treatment Regime on Lipid Profile and Clinical Parameters

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The western world and thus also Europe do not so much have a problem of population explosion as one of age explosion. The average life expectancy of women is 80 years, whereas the average menopausal age is 51 to 52 years. Life expectancy has thus doubled in 150 years, but the age of menopause has only risen slightly. The long hormone-free period, but also the distinct advantages of hormone replacement therapy (HRT), which has only a few contraindications and side effects has made HRT highly valuable in prophylactic medicine and there are many ways of applying HRT (2). The same changes will happen in a few years in Thailand and also in whole Asia. With a higher living standard, live expectancy will rise and the hormone free period too. The Thai women life expectancy is now 69.75 years and the average age of menopause 49.5 years.

Cyclo-Progynova (11 tabl. with 2.0 mg estradiol valerate and 10 tabl with 2 mg estradiol valerate + 0.5 mg norgestrel), Progynova (21 table with 1 or 2 mg estradiol valerate) and Climen (11 tabl with 2 mg estradiol valerate and 10 tabl 2 mg estradiol valerate + 1 mg CPA), novels oral hormones for replacement therapy, have been used now for many years in Austria and other European countries. They are well tolerated with only little side effects. All three medicaments contain the most potent human estrogen, 17ß estradiol, as the esterified prodrug estradiol valerate, 2 mg or 1mg/day for the entire cyclic therapy of 21 days (1). The progestogen norgestrel at 0.5 mg and the cyproterone acetate (CPA) at 1mg is added during days 12 to 21. No therapy is administered during the fourth week of the cycle. During this time a menstruation like bleeding is expected.

Cyclo-Progynova and Climen as fixed combinations of estrogen and progestogen, effectively treat climacteric complaints while preventing endometrial hyperplasia and providing endometrial protection subsequently. Early studies showed that administration of exogenous estrogen alone leads to a significant increase in the risk of developing endometrial cancer in non hysterectomized women. However it is now well established that the risk of endometrial hyperplasia, thought to be a precursor of endometrial cancer, can be reduced by addition of a progestogen. The incidence of hyperplasia seems to decrease when progestogen therapy is administered for at least 10 days a month.

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The new medicaments offer the patient following advantages : effective treatment of climacteric complaints or symptoms, prevention of osteoporosis, beneficial effects on lipid metabolism by reduction of LDL cholesterol without decrease of the HDL, so decreasing the risk of cardiovascular disease, and potentially beneficial aspects on carbohydrate metabolism.

Osteoporosis characterized bone porosity, decreased bone mass and increased susceptibility to fractures, is one of the most important manifestations of estrogen deficiency in the white population as well as in Asian population. It can be prevented in long term HRT with 17ß estradiol valerate. All exerts a beneficial influence on bone metabolism and in several studies, it has been shown that postmenopausal bone loss can be halted using estrogen, like Climen, Cyclo Progynova and Progynova in general. It can reduce bone loss and the incidence of osteoporosis related fractures.

Results of recent studies indicate that peroxidation of lipoproteins plays a key role in atherogenesis. Oxidized LDL is cytotoxic to endothelial cells and also is taken up excessively by macrophages, both of which are thought to contribute substantially to the progression of aterosclerotic lesions. Although estrogen in general inhibit the oxidation of lipoproteins, this antioxidant effect is more pronounced with the 17ß estrogen valerate. Climen and Cyclo-Progynova and Progynova showed beneficial effects on the lipid metabolism by reduction of LDL, while HDL cholesterol increased slightly. Triglycerides do not show significant changes. In consequence, the LDL/HDL ratio changes favourably, which lead to a reduction of the cardiovascular risk (3,4).

The incidence of hot flushes decreased by 50% after only one cycle, and only 10% of women reported hot flushes after 12 cycles of treatment. Sweating episodes were reported by 85% of women initially but this number decreased to less 10 after 12 months. The incidence of dizziness dropped to 10% after one years, from the initial reported rate of 37%. Insomnia was reduced from 62% to about 12% and the depression was reported in only 18% of women after 12 cycles, from an incidence of 60%. Similar results are also reported for the other menopausal complaints. The mean blood pressure did not change during the course of the treatment.

Climen with cyproterone acetate (CPA), a 17-hydroxyprogestone progestogen, has an antiandrogenetic effect too. It is similar to the pill diane 35 (ethinylestradiol + 10 mg CPA), but in a much lower concentration. In a relatively high percentage of menopausal women hyper androgenic problems, such as hirsutism and acne, or effluvium occur. In addition to all the other positive benefits of treatment, Climen is an excellent therapy for this problems in premenopause and menopause, resulting from the estrogen induced increase in sex hormone binding globulin(SHBG) levels and the inibiting action of cyproterone acetate on the androgenic effects.

The frequency of adverse events associated with Climen therapy is low, and they are generally mild to moderate in intensity. Some typical examples are breast tension, nausea and edema. All these symptoms decreased to near the baseline reported frequency after 12 cycles. Body weight was found to remain constant in more than 70% of patients or to increase slightly by between 0.5 and 1.0 kg in 4-12 cycles. Slight variations to be attributed to tissue rehydration.

In conclusion, Climen, but also the others Cyclo Progynova and Progynova are well tolerated with a few reported adverse events, and effective as well safe for hormone replacement therapy.

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S 03 (LS 1)

Lipid Profile, Haemostasis and Vasomotor Tone : Effects of Hormone Replacement Therapy on Risk Factors of Cardiovascular Disease

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The menopausal state is associated with changes of several risk markers of cardiovascular disease. Total cholesterol levels rise sharply after menopause, mainly due to a marked increase of the low density lipoprotein (LDL)-cholesterol levels. While high density lipoprotein (HLD)-cholesterol levels are not significantly affected by loss of endogenous estradiol, the potentially cardioprotective subfraction HDL_2-cholesterol levels are markedly reduced in women after menopause. Triglyceride levels are higher in postmenopausal women but this phenomenon appears to be a function of age rather than the hormonal status. While there is evidence that the impact of lipids on the overall risk of arterial risk is considerably lower in Asian women than European women, other risk factors such as reduced fibrinolytic capacity, increased fibrinogen levels and increased vasomotor tone due to reduced endothelial release of nitric oxide (NO) and other vasoactive mediators may be equally important in Asia and Europe.

Hormone replacement therapy (HRT) has been shown to attenuate some of these changes. Cardiovascular benefits of new formulations have been assessed by analyses of these metabolic effects. HRT has been found to reduce total cholesterol levels, particularly the LDL cholesterol fraction. Triglyceride levels were affected differently according to dose and way of administration of the estrogen and the quality of the progestogens component. Effects on fibrinolysis and coagulation appear to be related to the dose of the estrogen component yielding a predominantly profibrinolytic net effect at low estrogen doses and a predominately procoagulant effect at high estrogen doses. All HRT regimen appear to improve NO release. These data suggest that HRT may be equally effective in preventing arterial disease both in the Asian as well as the European postmenopausal population.

Risk of venous disease has recently been linked to congenital predispositions. Particularly the "idiopathic" or "spontaneous" thrombotic episode in postmenopausal women appears to occur mostly in women with such abnormalities of the haemostatic mechanisms. The most important of these conditions (the coagulation factor V Leiden mutation) is frequent among caucasian women (~5%) but unknown among asian women. These data suggest that an increased risk of venous disease as recently described in caucasian women on HRT may not apply in asian users of HRT.

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