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Oral Ethinyl Estradiol, but not Transdermal 17β-estradiol, Increases Plasma C-reactive Protein Levels in Men

Dear Sir,

The hepatic acute phase reactant C-reactive protein (CRP) is a nonspecific marker of inflammation. CRP can be found in the fibrous plaques of the atherosclerotic arterial wall and levels of CRP are predictive of future cardiovascular events, which suggests that inflammatory processes are part of the etiology of atherothrombosis. Oral use of conjugated equine estrogens and micronised 17β-estradiol, with or without progestin, have recently been shown to increase CRP levels in postmenopausal women. It is unknown whether oral estrogens increase CRP levels in men. In addition, since CRP is of hepatic origin, it may be hypothesized that transdermally administered 17β-estradiol, which has a less strong hepatic impact compared to oral ethinyl estradiol, affects the synthesis of CRP by hepatocytes less strongly than do orally administered estrogens. Therefore, we studied the effects on CRP levels in 30 male-to-female (M → F) transsexuals, aged median 32 years (range 20 to 44) who were open-label randomized to receive either oral ethinyl estradiol 100 μg/day (Lynoral, Organon; n = 15) or transdermal 17β-estradiol (Estraderm TTS 100, Ciba Geigy; n = 15), both in combination with cyproterone acetate 100 μg/day (Androcur, Schering). Eight M→F transsexuals from the oral ethinyl estradiol and 6 from the transdermal 17β-estradiol group were smokers. Ten additional men, aged median 34 years (range 19 to 50), were treated with cyproterone acetate alone. Seventeen female-to-male (F → M) transsexuals, aged median 18 years (range 18 to 37), were treated with intramuscular testosterone esters. At baseline and after (2 and) 4 months, blood samples were obtained without tourniquet after a 12 h fast into evacuated tubes and plasma was separated within one hour and stored at –70° C. CRP was analyzed by a home-made sensitive ELISA, with a lower detection limit of 0.1 mg/L and a upper limit of 10.8 mg/L. Four M→F transsexuals, all from the oral ethinyl estradiol group, were excluded from the analysis because of mild inflammation of the throat in two, of the sinuses in one, and of a molar in one. The right-skewed CRP data were logarithmically transformed before analysis; data are presented as geometric means. An analysis of variance for repeated measurements or t-test for paired samples was used to analyze the effects of cross-sex hormones.

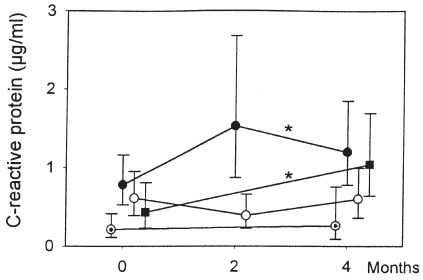

Fig. 1 Plot showing the geometric means (95% confidence interval of the mean) of plasma levels of CRP at base-line and after 2 and 4 months of hormone administration. ● 15 M→F transsexuals receiving oral ethinyl estradiol plus oral cyproterone acetate; ○ 15 M→F transsexuals receiving transdermal 17β-estradiol plus oral cyproterone acetate; ⊙ 10 M→F transsexuals receiving oral cyproterone acetate; ■ 17 F→M transsexuals receiving intramuscular testosterone esters, * $P < 0.05$, by ANOVA test for repeated measurements or *t*-test for paired samples

Baseline mean CRP levels were similar in the two randomized groups using estrogens ($P = 0.40$). After 2 and 4 months of estrogen administration, CRP levels had increased in the oral ethinyl estradiol

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group (by 96 and 54 %; $P = 0.02$), but not in the transdermal 17β-estradiol group ($P = 0.20$; $P = 0.01$ for comparison of oral ethinyl estradiol with the transdermal 17β-estradiol group; Fig. 1). Oral cyproterone acetate administration alone did not affect CRP levels in men ($P = 0.67$; Fig. 1), and parenteral testosterone administration increased CRP levels in women (by 141 %; P = 0.001; Fig. 1).

We conclude that administration of oral ethinyl estradiol was associated with increased CRP levels in men, similar to the effects of oral estrogens in postmenopausal women (5, 6, 9). In contrast, transdermal 17β-estradiol did not affect CRP levels in men. In women with type 2 diabetes mellitus, transdermal administration of 17β-estradiol with oral progestin did decrease CRP levels. Our findings suggest that the stronger hepatic first-pass effect of oral ethinyl estradiol compared to transdermal 17β-estradiol is responsible for the increase in CRP levels. We also observed a potentially harmful increase in CRP levels upon intramuscular administration of testosterone in women, but no decrease upon suppression of endogenous androgens by cyproterone acetate in men. Whether testosterone administration elevates CRP levels also in men, as well as the relevance of these findings for cardiovascular risk, remains to be elucidated.

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The Human Platelet Alloantigen 5 Polymorphism as a Risk for the Development of Acute Idiopathic Thrombocytopenia Purpura

Dear Sir,

Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by thrombocytopenia due to platelet autoantibodies resulting in removal of the opsonized platelets by the reticuloendothelial system. The etiology of ITP remains unknown. However, both genetic and environmental risk factors are implicated. Among genetic risk factors, polymorphisms of the HLA class II antigens, of FcγRIIA expressed on platelets, and more recently of human platelet antigen (HPA) systems have been associated to development of ITP and therapeutic response (1, 2).

The HPA-5 system polymorphism is characterized by a G to A transition at nucleotide 1648 in the glycoprotein Ia of the GpIa/IIa complex, which results in Glu505 to Lys substitution, defining allele a and b, respectively. The GpIa/IIa complex is homologous to very late antigen 2 (VLA-2) appearing on activated T cells that can be upregulated on lymphocytes in response to antigenic stimulation (3). The HPA-5 antigen is the second most common cause of alloimmune platelet disorders (4). The polymorphism of the HPA-5 system has been related to immune-mediated diseases such as chronic ITP or acute vascular rejection of renal grafts (1, 5). In this study we sought to determine whether the HPA-5 polymorphism could be related to development of either acute or chronic ITP.

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