Sex hormone binding globulin, cortisol binding globulin, thyroxine binding globulin, ceruloplasmin: changes in treatment with two oral contraceptives low in oestrogen

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Summary: It is generally assumed that the oral contraceptives cause the carrier proteins to change. Notoriously this effect is used to evaluate indirectly their estrogenicity/gestagenicity ratio. In order to assess the residual intrinsic androgenic activity of two new 19-norderivative components, Desogestrel (DG) 150μg and Gestodene (GD) 75μg, both in association with Ethinylestradiol (EE) 30 μg, Sex Hormone Binding Globulin, Thyroxine Binding Globulin, Ceruloplasmin and Free Androgen Index (FAI), were studied in 40 young normally cycling healthy volunteers, matched for body mass index and age. The participants were randomly assigned to either EE-DG or EE-GD treatment. A marked significant increase in all the carrier proteins was found. Conversely, the values for FAI decreased significantly. The changes in the two groups were substantially of the same magnitude.

These results are an indirect confirmation of the well-known negligible receptor binding affinity of the two progestogen in vitro, also supporting for these compounds the lack of relevant androgenic effects.

INTRODUCTION

It is well known that oestrogens characteristically induce a rise in transport proteins (TP), such as Sex Hormone Binding Globulin (SHBG), Corticosteroid Binding Globulin (CBG), Ceruloplasmin (CP), Thyroxine Binding Globulin (TBG), by increasing the rate of their synthesis in the liver ([1, 2]). Limited to the SHBG only, this effect can be counteracted, to a different degree, by gestagens, strictly according to their relative androgenic potential, as expressed by the specific oestrogenity/gestagenicity ratio ([3, 4]). Therefore the evaluation of the TP modifications could indirectly reflect both the intrinsic androgenity (interaction with SHBG increase) and oestrogenicity (entity of TP increase) of combined oral contraceptives (OC). In this connection, the study of the carrier system could also represent an adequate criterion for the preliminary choice of a proper OC in the perspective of a suitable therapy for hyperandrogenism, for instance in idiopathic hirsutism and in micropolycystic ovary syndrome.

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MATERIAL AND METHODS

In order to verify indirectly the residual androgenic activity of two newly 19-no-derivative gestagens, namely Desogestrel (DG) and Gestodene (GD), both of them in association with Ethinylestradiol (EE), 40 healthy non-obese eumenorrheic volunteers were studied in relation to the transport system (SHBG, CBG, CP, TBG) to the Total Testosterone (TT) values; the Free Androgen Index (FAI), expressed as percent TT/SMBG molar ratio, was also determined. All the women were divided into two groups of 20, matched as closely as possible by age, body weight, dietary and smoking habits, and were randomly assigned to either the EE (30 μg) - DG (150 μg) or the EE (30 μg) - GD (75 μg) protocol. The above parameters were evaluated before (in the follicular phase, at days 3 to 6) and after six months of treatment (within a week from the completion). SHBG was measured by Irma kit provided by Farmos Diagnostica, Finland); TT, CBG and TBG were determined by RIA kits, purchased respectively from Diagnostic Products Corporation (USA), Medgenix (Belgium), and Behringwerke AG (Germany); CP was assessed by immunonephelometry (Behring nephelometer, Germany). All samples were analyzed in duplicate and in a unique run for each patient. Statistical analysis was performed using Student's t test for paired data, and the values were expressed as Mean ± SD.

RESULTS

The data obtained showed, in both groups, a marked percentage increase in all the carrier proteins, practically of the same magnitude, together with a similar reduction in TT and FAI values.

No discernible side-effect was recorded in course of therapy; particularly, body weight as well as blood pressure did not change significant in relation to pretreatment values. The occurrence in 5 women (2 of EE-DG and 3 of EE-GD protocol) of intermenstrual bleeding (spotting) at the beginning of the treatment, disappeared within at most months from the start.

DISCUSSION

Our results, as far as the evidence of properly enhanced SHBG levels are concerned, are clearly in good agreement with the well-known slight estrogen prevalence of two compound studied, whose effects on the transport mechanisms are quite superimposable: moreover, these reports agree with the concomitant positive changes in FAI values. From a clinical point of view, it is of particular interest that every change in this integrated functional index would seem quite properly to reflect the correspondent improvement of clinical score in hyperandrogenism ([5]). The modifications in the other carrier proteins (CBG, CP, TBG) are undoubtedly an expression of the correlated value of the oestrogenici-

Table 1. – *Values of SHBG, CBG, TBG, CP, TT, FAI, before (A) and after (B) EE-DG and EE-GD treatment.*

		EE (30 μg) - DG (150 μg)		EE (30 μg) - GD (75 μg)	
		A	B	A	B
SHBG	nmol/L	40±17	207±121 (*a*)	39±13	139±67 (*g*)
CBG	ug/ml	37±12	87±17 (*b*)	34±9	84±29 (*h*)
TBG	ug/ml	23±4	36±7 (*c*)	21±3	31±4 (*i*)
CP	mg/dl	26±3	45±7 (*d*)	27±4	44±5 (*l*)
TT	ng/ml	0.8±0.2	0.6±0.2 (*e*)	0.8±0.3	0.7±0.2 (*m*)
FAI		9.6±7.2	1.5±1.0 (*f*)	9.6±10	2.5±2.9 (*n*)

(*a*) $p=0.0000078$; (*b*) $p<10^{-6}$; (*c*) $p<10^{-6}$; (*d*) $p<^{-6}$;
(*e*) $p=0.0014$; (*f*) $p=0.00002$; (*g*) $p=0.0000028$; (*h*) $p=0.0000013$;
(*i*) $p<10^{-6}$; (*l*) $p<10^{-6}$ (*m*) $p=0.033$; (*n*) $p=0.00045$.

ty/gestagenicity ratio of the compounds studied and would confirm their greater oestrogenicity, at least in comparison with formulations containng LN. Therefore, the effects on SHBG levels and the corresponding decrease in FAI values seem finally to strengthen what has been reported in many experimental studies concerning the relative binding affinity of the two gestagens for the estrogen, androgen, and progestogen receptors ([17]). This issue would account particularly for the almost negligible biological androgenic activity of DG and GD as well as their high « selectivity index », as expressed by the elevated « affinity progesterone receptor/affinity androgen receptor ratio » ([8]). Accordingly, we can draw a well defined conclusion as to the high effectiveness and adequacy of OC containing DG and GD with regard, more properly, to the therapy of hyperandrogenism.

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