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INCREASED CAPILLARY PERMEABILITY FOR PLASMA PROTEINS IN ORAL CONTRACEPTIVE USERS

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ABSTRACT

The transcapillary fluid balance was examined in eleven women before administration of a monophasic oral contraceptive (desogestrel 0.15 mg, ethinylestradiol 0.03 mg), and after three and six months of use. The interstitial colloid osmotic pressure was measured by the "wick" method, and the interstitial hydrostatic pressure by the "wick-in-needle" method in subcutaneous tissue on thorax and leg. During the six-month observation period, the following changes were observed: Plasma colloid osmotic pressure decreased (mean 1.8 mmHg, p=0.047), as well as serum albumin (mean 5.1 g/l, p=0.0006), total protein concentration (mean 2.8 g/l, p=0.0006), hemoglobin (mean 0.5 g/dl, p=0.014) and hematocrit (mean 1.8 %, p=0.047). Blood pressure and body weight remained unchanged, but foot volume showed a significant increase. The colloid osmotic pressure gradient (plasma-interstitium) was significantly reduced. The results indicate an increase in plasma volume in addition to an increased capillary permeability to plasma proteins during oral contraceptive use. We suggest that the observed changes in transcapillary fluid balance is caused by the estrogen component of the oral contraceptive pill.

INTRODUCTION

The "pill" is one of the most thoroughly investigated drugs. However, little attention has been paid to the subjective side effects such as bloatedness which may be one reason for the low continuation rate of oral contraceptives. Cyclic weight gain has not been reported to be different in low-dose oral contraceptive users compared to non-users[1]. Bloatedness may, however, be independent of increased body weight, as it may be explained by redistribution of body fluid between vascular and interstitial compartments.

Fluid exchange between these compartments is regulated by the "Starling forces"[2]: the capillary hydrostatic pressure (Pc), plasma colloid osmotic pressure (COPp), interstitial fluid hydrostatic pressure (Pi), and interstitial fluid colloid osmotic pressure (COPi). Until recently, only

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COPp could easily be measured. Methods are now available for measuring the tissue factors Pi and COPi in humans[3-5]. It is well documented that these methods give a good estimate of Pi and COPi in transcapillary homeostasis[6]. The subjective side effects of OCs are most marked during the first three months, after which they tend to diminish or disappear[7]. The present study describes the effects of low-dose oral contraceptives on transcapillary fluid dynamics during three and six months of use.

MATERIALS AND METHODS

Eleven healthy women, 18 to 26 years of age, with normal menstrual cycles (28 ± 3 days) were included in the study after giving informed consent. The study was approved by the Regional Committee of Medical Human Research Ethics. None of the women used any drugs or hormonal preparations during the three months prior to the study. All were within ± 10 % of ideal body weight.

The examinations were carried out between 8 and 10 a.m., in the follicular phase (cycle day 4-6) before administration of a monophasic oral contraceptive, desogestrel 0.15 mg and etinyloestradiol 0.03 mg (Marvelon, Organon, the Netherlands), and were repeated after three and six months of use (cycle day 17-24), on all occassions after overnight fasting.

Blood pressure was measured by a mercury sphygmomanometer after 30 minutes of rest, and recorded as the average of the last two of three measurements. Blood samples were drawn from an antecubital vein without stasis. Hemoglobin, hematocrit, serum albumin and total protein concentrations were measured by a Coulter Counter analyzer (Coulter Electronics, Hialeah, FL).

Weight was recorded on the same weight scale with the patients wearing standardized clothing. Foot volume was measured by placing each foot in separate steel chambers filled with water (temperature 25° to 30° C) and the spillover was measured.

Interstitial colloid osmotic pressure was determined as described by Noddeland[3] and Øian et al.[4] Six nylon wicks were sewn subcutaneously on the thorax at heart level, and on the leg 10 cm above the lateral malleol. The skin was anaesthetized with 0.1 ml of lidocaine (20 mg/ml, without epinephrine). After one hour the wicks were removed, and the colloid osmotic pressure in the wick fluid was measured by a colloid osmometer with a membrane impermeable to proteins with molecular weights above 30000 daltons.

Plasma colloid osmotic pressure was determined by the same colloid osmometer.

Interstitial fluid hydrostatic pressure was measured by the wick-in-needle technique described by Fadnes et al.[5] A sterile cannula filled with nylon filaments, and connected to the pressure transducer by a tube filled with physiological saline was inserted subcutaneously at the level of the implanted wicks, and the hydrostatic pressure recorded.

Statistical methods

Overall differences between measurements prior to administration (Time 1), after three (Time 2), and six months of use (Time 3) were evaluated by repeated measures analysis of variance (univariate tests). In addition, Persons correlation analyses were used. A p-value less than 0.05 was considered significant.

RESULTS

The main findings during the six months of study are presented in Table I and Table II.

During the first three months, a significant reduction in hemoglobin (mean 0.7 g/dl, p=0.013), hematocrit (mean 2.3%, p=0.044), serum albumin concentration (mean 4.5 g/l, p=0.0028), and serum protein concentration (mean 3.2 g/l, p=0.0083) was observed. These changes are illustrated in Figure 1. Foot volume increased (each foot mean 92.5 ml, p=0.002), whereas weight and blood pressure remained unchanged. The COPp showed a slight decrease (mean 1.1 mm Hg, p=0.08), but the COPi and Pi both on the thorax and on the leg did not change.

During the last three months, hemoglobin, hematocrit, serum albumin, and serum protein concentration did not decline further, and the foot volume remained unchanged, as did plasma colloid osmotic pressure.

The transcapillary colloid osmotic pressure gradient (COPp-COPi) was significantly reduced on the leg (mean 2.7 mm Hg, p=0.004) during the six-month period, but only insignificantly on the thorax (mean 2.0 mm Hg, p=0.10). The individual changes in the colloid osmotic gradients on the thorax and on the leg are shown in Figure 2.

A correlation analyses were performed between the changes in foot volume, serum albumin, and serum protein versus the measured Starling forces. From Time 1 till Time 2 no significant correlations were observed between these variables. From Time 2 till Time 3, however, there was a significant negative correlation between the change in foot volume and the COPi on the thorax (r=-0.817, p=0.0021). The change in serum protein was significantly and negatively correlated with the change in the COPi both on the thorax (r=0,844, p=0.0021) and on the leg (r=0.748, p=0.0127). In addition, the change in serum albumin showed a significant positive correlation with the COPi on the leg (r=0.851, p=0.0018). On the thorax the correlation was almost significant (r=0.606, p=0.0634). Alterations in serum protein were significantly correlated with the COPp (r=0.640, p=0.0465).

DISCUSSION

Oral contraceptives induced significant changes in transcapillary fluid balance. The COPp, serum albumin and total protein concentrations were significantly reduced; in addition, significant reduction both in hemoglobin and hematocrit were observed. This could reflect an in-

Table I. Weight, blood pressure, and foot volume before oral contraceptive use (Time 1), and after three (Time 2), and six months (Time 3) in 11 women (mean ± SE)

	Group mean values			
	Time 1	Time 2	Time 3	Significance
Blood pressure (mm Hg)				
- systolic	112.2 ± 2.4	114.7 ± 2.7	113.6 ± 2.5	p=0.46
- diastolic	69.4 ± 3.2	66.3 ± 2.0	68.4 ± 1.8	p=0.61
Weight (kg)	58.7 ± 2.7	58.8 ± 2.6	58.0 ± 2.7	p=0.78
Volumetry (ml)				
- right foot	1130 ± 68.8	1227 ± 41.6	1229 ± 57.6	p=0.002
- left foot	1119 ± 67.1	1207 ± 46.7	1192 ± 56.3	

Table II. Changes in plasma colloid osmotic pressure (COPp), interstitial colloid osmotic pressure (COPi), and interstitial hydrostatic pressure (Pi) before oral contraceptive use (Time 1), after three months (Time 2), and six months (Time 3) in 11 women (mean ± SE)

	Group mean values			
	Time 1	Time 2	Time 3	Significance
COPp (mm Hg)	22.7 ± 0.9	21.4 ± 0.8	20.7 ± 0.4	p=0.047
COPi (mm Hg)				
- thorax	12.9 ± 0.6	12.6 ± 0.7	13.1 ± 0.5	p=0.51
- leg	9.5 ± 0.9	10.7 ± 0.7	10.5 ± 0.8	p=0.24
Pi (mm Hg)				
- thorax	-1.9 ± 0.4	-3.1 ± 0.8	-1.5 ± 0.5	p=0.24
- leg	-1.6 ± 0.7	-2.2 ± 0.6	-1.0 ± 0.2	p=0.18

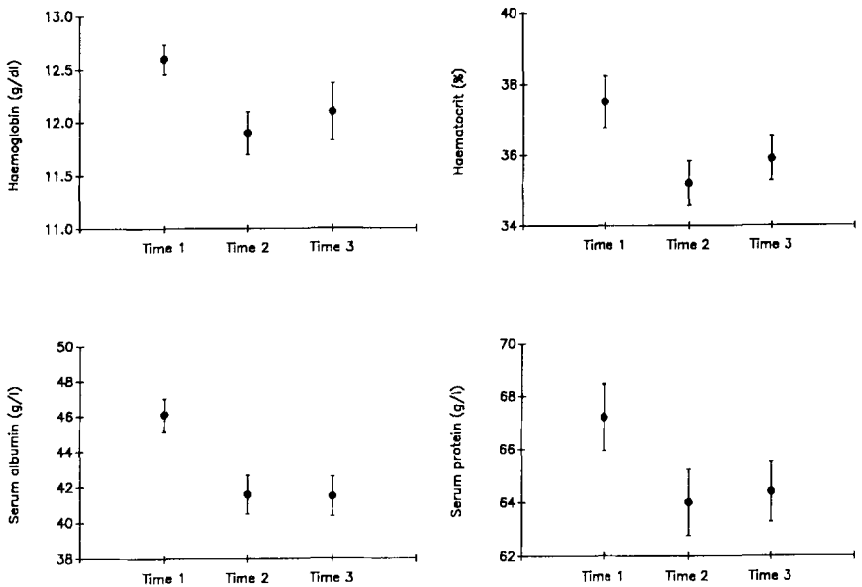

Figure 1. Changes in hemoglobin (g/dl), hematocrit (%), serum albumin (g/l), and serum protein (g/l) concentrations (mean ± SE) before administration of a monophasic oral contraceptive (Time 1), and after three (Time 2), and six months of use (Time 3).

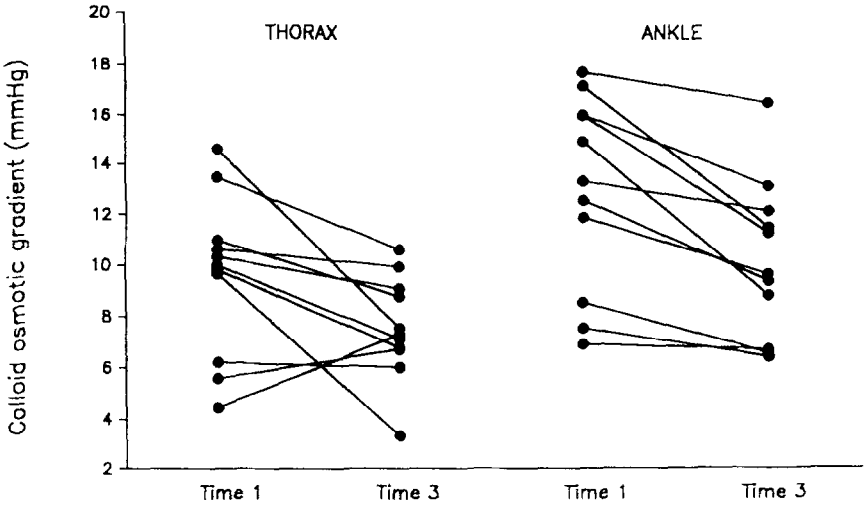

Figure 2. Individual values in colloid osmotic gradient (plasma-interstitium) in mmHg before administration of a monophasic oral contraceptive (Time 1), and after six months of use (Time 3) in 11 women.

creased plasma volume, but the reduction in COPp and serum albumin concentrations are greater (9 % and 11 %, respectively) than the reduction in hemoglobin (5 %) and hematocrit (5 %). Other factors than increased plasma volume must therefore contribute to the fall in plasma colloids, for example reduced protein synthesis and/or increased capillary protein permeability. Oral contraceptives are known to induce changes in liver synthesis, and reduced serum albumin and total protein concentrations are reported[8].

A reduction in COPp will always lead to an increased filtration of fluid from the vascular to the interstitial compartment if not compensated for by changes in one or more of the other "Starling forces". It has been shown in many clinical conditions[9] that a reduction in COPi is an important homeostatic mechanism which prevents a rise in interstitial fluid volume when COPp is reduced. Recently, we reported that during the normal menstrual cycle, from follicular to luteal phase, both COPp and COPi were reduced, thus keeping the colloid osmotic gradient unchanged[10].

In the present study, COPi was not reduced in spite of a fall in the COPp. Consequently, the plasma-to-interstitial colloid osmotic gradient is reduced. This favours transport of fluid from the vascular to the interstitial compartment. The increase in foot volume confirms the rise in net transcapillary filtration. Since COPi remained constant, the interstitial protein mass must also be increased. This can be mediated by either increased capillary protein permeability and/or reduced lymph flow. A reduced transcapillary colloid osmotic gradient (COPp-COPi), as observed in this study, has been associated with increased lymph flow[11]. But, since COPp was reduced, and COPi remained constant, an increase in capillary protein permeability is the most likely explanation.

Recently, we reported that high endogenous estrogen levels in women undergoing ovarian stimulation for in vitro fertilization promote increased capillary protein permeability[12]. The change in transcapillary fluid balance during ovarian stimulation is very similar to the effects observed in this study. The monophasic combination of ethinyl estradiol 0.03 mg and desogestrel 0.15 mg is an estrogen-dominant combination[13]. It is therefore our hypothesis that the estrogen component of oral contraceptives increases the capillary protein permeability.

It is puzzling that no weight gain occurred in spite of an increase in foot volume and probably also an increased plasma volume. This is, however, not necessarily conflicting, and the observations after three and six months of use are consistent. Oral contraceptives are known to have metabolic effects[13], and altered protein metabolism may affect weight and counteract the otherwise expected increase in body weight. A 5 % reduction in hemoglobin and hematocrit corresponds to 100-150 ml increase in plasma volume, and the documented increase in interstitial fluid volume only in the lower legs is as much as 200 ml. If the observed changes were due to water retention alone, a significant weight gain would have been expected.

The most striking changes in the forces regulating transcapillary fluid

balance take place during the first months of oral contraceptive use. The lack of significant correlations between foot volume, serum albumin, and serum protein versus the Starling forces in this period indicates that oral contraceptives induce complex physiological adjustments which not only can be explained by changes in the measured variables. After three months, however, only minimal adjustments are taking place. The significant correlations observed between Time 2 and Time 3 are consistent with the homeostatic process which regulates transcapillary fluid balance; Increased foot volume will imply increased interstitial fluid volume, and consequently reduce interstitial colloid osmotic pressures. Furthermore, changes in interstitial colloid osmotic pressures will parallell changes in serum colloids.

CONCLUSION

After three and six months of use of oral contraceptives, we observed a definite reduction in plasma colloid osmotic pressure, as well as serum albumin and serum protein concentrations. The colloid osmotic gradient was significantly reduced. These findings indicate a slight increase in plasma volume caused by renal fluid retention, and increased capillary permeability to plasma proteins. Most likely these changes are caused by the estrogen component of the oral contraceptives. There was, however, no significant change in body weight. The increase in transcapillary filtration may explain symptoms like bloatedness and a feeling of weight gain in oral contraceptive users.

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