



Variations of Sex Hormones across the Menstrual Cycle: Correlations to Depressive Symptoms, Hostility, Lipidemic and Haemostatic Factors

Ioannis Syros^{1,2*,3}, Liapi C¹, Kolaitis G², Gourna C¹, Papageorgiou C⁴ and Chrousos PG⁵

¹Department of Pharmacology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

²Department of Child Psychiatry, School of Medicine, National and Kapodistrian University of Athens, Aghia Sophia Children's Hospital, Athens, Greece

³Child and Adolescent Psychiatry Unit, Sotiria, General Hospital, Athens, Greece

⁴Psychophysiology Laboratory, 1st Department of Psychiatry, School of Medicine, National and Kapodistrian University of Athens, Aiginiteion Hospital, Athens, Greece

⁵1st Department of Pediatrics, School of Medicine, National and Kapodistrian University of Athens, Aghia Sophia, Children's Hospital, Athens, Greece

Abstract

Background: Exogenous sex hormones affect lipid metabolism and haemostasis, as well as psychological aspects of the personality but the information on the interrelationships regarding the endogenous hormones is limited.

Objective: In the present study we examined the association between sex hormones, lipidemic profile, haemostatic activity, and symptoms of hostility and depression at 3 phases of the menstrual cycle in 59 healthy young women (22.95 ± 2.83 mean age ± SD).

Methods: Blood was drawn at follicular (FL), mid luteal (ML) and late luteal (LL) phase. At each visit, students completed the Zung Depression Scale and the Hostility and Direction of Hostility, and following variables were measured: a) Estradiol (E₂), Testosterone (T), Free Testosterone (FT), Δ₄-Androstenedione (Δ₄A), b) Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides c) PT and APTT, AT III, Proteins C and S, Plasminogen and Fibrinogen. Pearson's and Spearman's rank correlation were used to determine the relation between variables. P<0.05 was considered significant.

Results: Aspects of hostility were mostly positively correlated with androgens especially in FL and ML phase. Ratio T/E₂ positively correlated with depression scores and the direction of hostility, in the ML and LL phase, respectively. FT positively correlated with triglycerides across the cycle while the ratios T/E₂, FT/E₂ and Δ₄A/E₂ appear to influence fibrinogen and protein C levels but not premenstrually. E₂ levels do not seem to essentially modulate lipid levels and haemostatic factors across the menstrual cycle.

Conclusion: The relations between sex hormones and the tested psychological and biological factors in the young female population generally appear to differ markedly across the cycle, while the effect of endogenous hormones on these factors may be different comparatively to exogenous ones. Therefore, in order to evaluate them, the menstrual cycle effect should be taken into consideration.

Keywords: Sex hormones; Menstrual cycle; Depressive symptoms; Hostility; Lipids; Hemostasis

Introduction

Sex hormones influence not only purely biological functions, such as lipid metabolism and haemostasis [1,2], but also emotional, behavioral and cognitive functions. [3-6]. There has been a great interest in defining correlations between gonadal hormones and depressive symptoms or hostile behavior. In particular, hostility is enhanced by exogenous testosterone supplements [7,8] and ameliorated by estrogens [6], however, data regarding the effect of endogenous sex hormones on hostility are limited, mostly due to small size samples of male populations examined. [9-11]. Furthermore, evidence indicates an ameliorative role of estrogen in depressive disorders, [12-14] yet the relation between endogenous sex hormones and depressive symptoms remains controversial [15-19].

Exogenous sex hormones clearly modulate lipid metabolism [20-23], however, the effects of endogenous steroids remain unclear [24-28]. Administration of estrogens, has been related to increased fibrinolytic activity [29,30], along with decreased fibrinogen levels [30,31], while androgens in premenopausal women or women under hormone therapy (HT) have been associated with a decline in fibrinolytic activity [32]. It has been proposed that the cyclical variability of ovarian steroids during the menstrual cycle in premenopausal women might be consistent with changes in serum lipid levels [33,34], in haemostatic variables [24,35,36] as well as in mood changes [37]. Cyclical hormonal

variability across the menstrual cycle could thus serve as a natural model in order to: A) Test the above relations and to increase our understanding of the biological pathways that possibly mediate these links. B) To clarify if the endogenous sex hormones affect the above noted biological and psychological variables in a contiguous manner in relation to exogenous ones. C) To show if the phases of menstrual cycle could influence the above relations, so it would be necessary to take this factor into account when considering these links.

Therefore, in the present study we examined the association between endogenous sex hormones, haemostatic activity, the lipidemic profile and hostility and depressive symptomatology at each phase of the menstrual cycle in healthy young women.

***Corresponding author:** Ioannis Syros, MD, PhDc, Department of Child Psychiatry, School of Medicine, National and Kapodistrian University of Athens, Aghia Sophia, Children's Hospital, Athens, Greece, Tel: +306972735958; E-mail: jonsir9975@yahoo.com

Received: September 24, 2018; **Accepted:** October 03, 2018; **Published:** October 15, 2018

Citation: Syros I, Liapi C, Kolaitis G, Gourna C, Papageorgiou C, et al. (2018) Variations of Sex Hormones across the Menstrual Cycle: Correlations to Depressive Symptoms, Hostility, Lipidemic and Haemostatic Factors. J Neuroendocrinol Res 1: 101.

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Subjects and Methods

Fifty-nine young students (mean age 23.0 ± 2.8 years) were participated, after exclusion from the analysis of women with missed data, ($n=10$). The women received written information on the purpose and procedures of the study and gave informed consent. All of them were interviewed and examined by an internist. All women were physically healthy, free of clinical evidence of cardiovascular disease and were not using medication (i.e., birth control pills or Selective Serotonin Reuptake Inhibitors); they reported regular menses ranging between 27 and 33 days and had no signs of acnea or hirsutism. Clinical examinations included weight, height, blood pressure and electrocardiogram. The Body Mass Index (BMI) was calculated as $\text{weight}/\text{height}^2$ (kg/m^2). Furthermore, the women reported no signs of major symptomatology (clinical depression or any other mental disorder), and were also questioned about premenstrual symptoms. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Sex Hormones, Lipids, Clotting Factors Measurements

Venous blood samples were drawn between 8-10 am, after overnight fasting for at least 12 hours, three times at each cycle: at the follicular phase (FL), mid luteal phase (ML) and late luteal phase (LL), the latter corresponding to the premenstrual phase. The following steroid hormones, lipidemic and haemostatic factors and clotting time tests were determined at each sample as follows.

Steroid hormones

Estradiol (E_2), Testosterone (T), Free Testosterone (FT), Δ_4 -Androstenedione (Δ_4 A) and the ratios T/E_2 , FT/E_2 and Δ_4A/E_2 .

Lipidemic factors

Total cholesterol, LDL-cholesterol, HDL-cholesterol, VLDL-cholesterol and triglycerides.

Factors of haemostasis

Coagulant factor: fibrinogen; fibrinolytic factor: plasminogen; anticoagulant factors: protein S, protein C, ATIII; Clotting time tests: APTT, and PT.

Measurement of Lipidemic and Coagulation Factors

Serum lipid concentrations were measured using biochemical analyzer ILAB 350 of company Instrumentation Laboratory. LDL cholesterol was calculated with the Friedewald equation [38].

Fibrinogen, plasminogen, ATIII, APTT, and PT were analyzed on a DADE-Behring analyzer (with reagents from the same company); protein S and protein C were measured using Elisa. Normal range of Protein S activity is 60-150% and that of Protein C activity is 65-140%.

Hormonal Assay

Serum samples were analyzed to determine the concentration of estradiol, total testosterone, free testosterone and Δ_4 -Androstenedione using a commercial radioimmunoassay kit purchased from DIACEL (DIASource E2-RIA cat. No KIP0629, TESTO RIA cat. No KIP1709, Free-TESTO RIA KIP19000, Androstenedione cat. No KIP 0451). The interassay coefficient of variation was ranging between 3.5% to 4.5% and the interassay CV was ranging between 4-6%.

Assessment of Depressive Symptoms and Hostility

Depressive symptomatology was assessed by the Zung Self-Rating Depression Scale, a 20-item self-report questionnaire, which is widely used as a screening tool covering affective, psychological and somatic symptoms associated with depression [39]. The Questionnaire takes about 10 minutes to complete, and items are framed in terms of positive and negative statements. Each item is scored on a Likert scale ranging from 1 to 4. A total score is derived by summing the individual item scores and ranges from 25 to 80. The scores provide indicative ranges for depression severity that can be useful for clinical and research purposes, but the Zung Scale cannot take the place of a comprehensive clinical interview for making the diagnosis of depression.

Individuals also completed the Hostility and Direction of Hostility Questionnaire (HDHQ) [40]. This assessment instrument represents a measure of hostility and anger, and consists of five subscales: (a) the urge to act out hostility (AH), (b) criticism of others (CO), (c) projected delusional or paranoid hostility (PH), (d) self-criticism (SC), and (e) delusional guilt (DG). The first three subscales are summed to form an extrapunitive score, and the other two are summed to yield an Intropunitive score. The direction of hostility was obtained from the following formula: [$2 \times$ self-criticism+delusional guilt-(urge to act out hostility+criticism of others+projected delusional or paranoid hostility)]. Each subscale score is ranged from 0 to 11, so the total Hostility score ranges from 0 to 55 by summing the five subscale scores. Participants completed these questionnaires immediately before blood sampling at each phase of the cycle.

Statistical Analysis

Data are presented as mean \pm SD. The relations between variables at each phase of the menstrual cycle were determined using the Pearson correlation coefficient (R). The Spearman rank correlation coefficient (RS) was also computed when normality assumption was not satisfied. Comparisons within cycle phases were performed by the one-way analysis of variance (ANOVA) for repeated measures followed by Bonferroni correction for multiple comparisons. When data were not normally distributed, the non-parametric Friedman test was used for comparisons within phases and the Wilcoxon Signed Ranks test for paired comparisons. All reported p-values were considered significant when less than 0.05.

Results

The clinical features of the subjects are shown in Table 1.

Mean values \pm SD of hormonal, lipidemic and hemostatic factors, as well as of the psychometric scores evaluated in FL, ML, LL phases of the menstrual cycle are shown in Table 2.

Tables 3-6 show the statistically significant correlations between lipids, haemostatic factors, hostility, and depressive symptoms and sex hormones, respectively.

Clinical characteristics of subjects (n=59)	
Age	23.0 \pm 2.8(years)
Weight	60.1 \pm 8.0(kg)
Height	164.9 \pm 6.2(cm)
BMI	22.1 \pm 2.7(kg/m ²)
Menstrual cycle duration (range)	27-33 (days)
Menstrual cycle duration	29 (days)

Table 1: Clinical characteristics of the individuals.

	PHASE FL	PHASE ML	PHASE LL
Reproductive hormones			
E2-Estradiol	23.97 ± 19.09	100.39 ± 68.23	57.83 ± 49.66
Testosterone	0.63 ± 0.15	0.76 ± 0.26	0.67 ± 0.17
F- Testosterone	2.27 ± 0.87	2.79 ± 1.17	2.26 ± 0.71
Δ4 Androstenedione (ng/mL)	1.95 ± 0.83	2.29 ± 0.78	2.07 ± 0.71
T/E2 (× 10 ³)	0.06 ± 0.07	0.02 ± 0.02	0.02 ± 0.02
FT/E2 (× 10 ³)	0.15 ± 0.13	0.06 ± 0.09	0.06 ± 0.05
Δ4A/E2 (× 10 ³)	0.13 ± 0.17	0.04 ± 0.05	0.05 ± 0.04
Lipids			
Total cholesterol	184.96 ± 30.94	183.90 ± 29.68	185.27 ± 24.78
Triglycerides	65.52 ± 28.31	66.15 ± 19.28	61.47 ± 16.82
HDL-C	54.66 ± 9.30	57.27 ± 9.49	60.00 ± 8.99
LDL-C	117.40 ± 29.47	113.45 ± 29.60	113.08 ± 25.59
VLDL	13.06 ± 5.62	13.22 ± 3.80	12.27 ± 3.37
Haemostatic factors			
PT	13.80 ± 1.29	13.88 ± 1.72	13.92 ± 1.18
APTT	42.04 ± 4.91	44.81 ± 12.58	40.58 ± 5.93
Fibrinogen	2.67 ± 0.76	3.12 ± 1.34	3.11 ± 1.39
AT III	99.07 ± 13.97	100.91 ± 9.46	101.48 ± 10.11
PRC	96.66 ± 17.95	95.07 ± 17.79	92.24 ± 18.05
PRS	46.30 ± 14.88	53.60 ± 9.38	48.75 ± 12.01
Plasminogen	91.78 ± 13.37	96.23 ± 14.06	91.48 ± 12.21
Depression (Zung self-rating scale scores)			
	47.69 ± 8.28	46.57 ± 8.96	46.16 ± 9.68
Hostility (Hostility and Direction of Hostility Questionnaire scores)			
Urgue to act out Hostility (AH)	4.30 ± 1.90	4.06 ± 1.92	4.02 ± 2.14
Criticism of others (CO)	5.41 ± 2.06	5.48 ± 2.26	5.58 ± 2.70
Projected delusional or Paranoid Hostility (PH)	1.76 ± 1.37	1.93 ± 1.35	1.58 ± 1.42
Self Criticism (SC)	3.65 ± 1.96	3.57 ± 2.11	3.94 ± 2.19
Delusional Guilt (DG)	1.78 ± 1.27	1.71 ± 1.40	1.55 ± 1.22
Intropunitive Hostility	11.01 ± 5.74	10.53 ± 6.18	11.05 ± 5.98
Extrapunitive Hostility	11.33 ± 4.17	11.48 ± 4.34	11.16 ± 4.97
Direction of Hostility	-0.55 ± 5.25	-1.04 ± 5.26	0.28 ± 5.11
Total Hostility	16.93 ± 5.90	16.78 ± 6.57	16.69 ± 7.08

Table 2: Mean values ± SD of the biological and psychometric parameters measured. E2: pg/mL, T:pg/dL, FT:pg/ml, Δ4-A:ng/ml, Total Chol, Trigl, HDL-C, LDL-C,VLDL: mg/dl, PT, APTT: sec, Fibrinogen, PrC, PrS, Plasminogen: mg/d.

Notes: Lipidemic factors: For the variables Triglycerides, Total Cholesterol, VLDL, HDL-C and LDL-C, a statistically significant difference was found only for HDL-C between phases FL and LL (p=0.009, Bonferroni correction). Hemostatic factors: For the variables PT, APTT, Fibrinogen, ATIII, Pr C, Pr S and plasminogen, a statistically significant difference was found only for Pr C between phases FL and LL (p=0.043 by the non-parametric Wilcoxon Signed Ranks test).

Discussion

Steroid hormones and lipids

Previous studies revealed that exogenously administered estrogens decrease the total cholesterol and LDL-C levels, increase the production ratio and the metabolic clearance rate of VLDL and increase the HDL-C levels [20-23]. Regarding the effect of exogenous androgens, the most settled and well documented findings until now seem to be the decrease in HDL-C and lipoprotein (a) levels in addition to a less well characterized decline of triglycerides and LDL-C [41,42]. In the present study, E2 does not seem to essentially modulate the lipid levels across the menstrual cycle with an exception for LDL-C, which is inversely correlated to E2 premenstrually. HDL-C seems to be negatively influenced by the ratio FT/E2 and FT, but during the ML period only.

With respect to the effect of endogenous sex hormones on blood lipids and lipoproteins throughout the menstrual cycle, the data so far are inconsistent; some investigators describe that the changes in sex hormones during the cycle induce cyclic modifications in lipid levels

[33,34], while others do not confirm this relation [24,43,44]. The evaluation of the relevant studies has to be done with caution since in most studies sample sizes were small, while the age ranges as well as the variables tested (i.e., peak hormone concentrations versus mean value) were different compared to the present study. In the biocycle study [28] in which 259 premenopausal subjects participated, the authors in an effort to evaluate the association between E2 and lipids on the same day, used acute effects models and revealed an inverse association between the hormone and LDL paralleling our results in the premenstrual phase. In contrast to the bio-cycle study, we did not find any correlation between E2 and TC, HDL and TC/HDL ratios in any phase of the cycle. Two studies involving young and healthy premenstrual women failed to detect a significant correlation between these variables in any of the three menstrual cycle phases [44,45] while Mattson et al. [46], evaluating this relation in four time points across the cycle, determined various significant albeit different correlations in comparison to our study i.e., E2 levels were related to various lipid elements during the follicular, as well as the mid cycle phase, while no correlation was detected during the premenstrual phase [47-49].

Lipidemic Factors	Hormones	Phase			R (p-value)	Rs (p-value)
		FL	ML	LL		
Triglycerides	F-Testosterone	+				0.37 (0.022)
	F- Testosterone		+			0.41 (0.014)
	F- Testosterone			+		0.44 (0.014)
HDL	F- Testosterone		-			-0.39 (0.019)
	FT/E2		-		-0.38 (0.028)	
LDL	E2 Estradiol			-		-0.36 (0.037)
VLDL	F- Testosterone	+				0.41 (0.009)
	FT/E2	+			0.50 (0.001)	
	F- Testosterone		+			0.44 (0.009)
	F- Testosterone			+		0.41 (0.023)

Table 3: Statistically significant correlations between lipidemic factors and sex Hormones ($\alpha=5\%$) in the various phases of cycle (the phase marked by gray denotes the significant correlation). R: Pearson rank correlation coefficient; RS: Spearman rank correlation coefficient; $P < 0.05$ was considered significant.

Notes: In FL phase a positive correlation was found between a) FT and Triglycerides ($R_s=0.37, p=0.022$) and VLDL ($R_s=0.41, p=0.009$), b) the FT/E2 ratio and VLDL ($R=0.50, p=0.001$). In ML phase the following were found: a) positive correlation between FT and Triglycerides ($R_s=0.41, p=0.014$) and FT and VLDL ($R_s=0.44, p=0.009$), b) negative correlation between FT and HDL ($R_s=-0.39, p=0.019$) and FT/ E2 ratio and HDL ($R=-0.38, p=0.028$). In LL phase the following were found: a) FT was positively correlated to Triglycerides ($R_s=0.44, p=0.014$) and VLDL ($R_s=0.41, p=0.023$), b) E2 was inversely correlated to LDL-C ($R_s=-0.36, p=0.037$).

Coagulation Factor	Hormones	Cycle phase			R (p- value)	Rs (p- value)
		FL	ML	LL		
APTT	F-Testosterone	-				-0.613 (0.034)
	FT/E2	-				-0.800 (0.003)
	D4-Androstendione		+		0.599 (0.024)	
Fibrinogen	Testosterone	+			0.612(0.026)	
	F-Testosterone	+				0.569 (0.053)
	D4-Androstenedione	+			0.594(0.015)	
	FT/E2	+				0.627(0.039)
	T/E2		+		0.763 (0.010)	
	FT/E2		+		0.808 (0.008)	
AT III	D4A/E2		+		0.710 (0.010)	
	E2 Estradiol			-	-0.523(0.046)	
PRC	E2 Estradiol		-			-0.521 (0.046)
	F-Testosterone		+			0.618 (0.042)
	T/E2		+			0.727 (0.011)

Table 4: Statistically significant correlations between coagulant/anticoagulant/fibrinolytic factors and sex hormones ($\alpha=5\%$) in the various phases of cycle (the phase marked by gray denotes the significant correlation). R: Pearson rank correlation coefficient; R_s : Spearman rank correlation coefficient.

Notes: In Follicular phase: a) APTT was negatively correlated with FT ($R_s=-0.61, p=0.034$), the FT/E2 ratio ($R_s=-0.80, p=0.003$) and $\Delta 4A$ ($R=0.60, p=0.024$), b) Fibrinogen was positively correlated with T ($R=0.61, p=0.026$), FT ($R_s=0.57, p=0.053$), $\Delta 4A$ ($R=0.59, p=0.015$) and the FT/E2 ratio ($R_s=0.63, p=0.039$). In ML phase: a) Pr C was positively correlated with FT ($R_s=0.62, p=0.042$) and the T/E2 ratio ($R_s=0.73, p=0.011$), b) Pr C was negatively correlated with E2 ($R_s=-0.52, p=0.046$), c) Fibrinogen was positively correlated with T/E2 ($R=0.76, p=0.01$), FT/E2 ($R=0.81, p=0.008$) and the $\Delta 4A/E2$ ratio ($R=0.71, p=0.010$), d) APTT was positively correlated with $\Delta 4A$ ($R=0.60, p=0.024$). In LL phase: a negative correlation was found between ATIII and E2 ($R=-0.52, p=0.046$).

Furthermore, Wall et al. [33] described a positive correlation between E2 levels and HDL-C by testing the correlation between peak E2 levels in the ovulatory phase, and lipids across the whole cycle. Finally, in a study concerning the follicular phase only, described significant correlations between E2 and various lipidemic factors (LDL-C, HDL-C, VLDL) [47].

Furthermore, according to our data, increased FT, and not the total concentration of T, appears to be significantly associated with increased total plasma triglycerides and VLDL at each phase of the menstrual cycle. The literature so far regarding this kind of association is limited and it encompasses studies with dissimilar sample groups. In a study, free Androgen Index, i.e., a marker of FT, was positively correlated with VLDL and LDL particles in a sample of 120 mid-life women [48]. Additionally, in a case control study involving 156 postmenopausal women with carotid atherosclerosis, FAI was also positively correlated to LDL-C as well as to triglyceride levels [26]. Other studies, however, involving postmenopausal women [27], healthy middle aged men [49,50] or men with CHD [51] and diabetes 2 [52,53] were not supportive of the above relations.

The positive interrelation of FT with serum triglycerides and VLDL along the menstrual cycle might support the hypothesis of a potentially atherogenic profile of the free fraction of this hormone in premenopausal women. The positive interrelation of FT with serum triglycerides and VLDL along the menstrual cycle may support the hypothesis of a potentially atherogenic profile of the free fraction of this hormone in premenopausal women. However, based on data so far, the effect of exogenous androgens on lipidemic factors may be different from endogenous ones.

In reference of estrogens, despite the discrepancy of some studies findings compared to ours, as well as the fact that, with the exception of HDL-C, we detected no significant difference for the rest of lipidemic factors levels throughout the cycle, there is still a need to define the phases of the cycle in which blood is collected when assessing the lipid profile in normal premenstrual women [46,54,55]. Additionally, more studies are needed in order to further clarify this issue.

Psychometric parameter	Hormones	Cycle Phase			R (p-value)	Rs (p-value)
		FL	ML	LL		
HDHQ AH	F-Testosterone		+		0.452 (0.006)	
HDHQ CO	F-Testosterone	+			0.377 (0.014)	
	D4-Androstendione		+		0.401 (0.009)	
	T/E2		+			0.350 (0.031)
	D4A/E2		+			0.318 (0.045)
HDHQ PH	Testosterone		+			0.541(0.0004)
	F-Testosterone		+		0.344 (0.039)	
	D4 Androstendione		+			0.464 (0.002)
	T/E2	+			0.339 (0.032)	
	FT/E2	+			0.405 (0.008)	
HDHQ SC	T/E2	+			0.312 (0.049)	
HDHQ DG	D4-Androstendione	-			-0.318 (0.023)	
HDHQ intropunitive	D4 Androstendione	-			-0.277 (0.048)	
HDHQ extrapunitive	Testosterone		+		0.384 (0.017)	
	F-Testosterone		+		0.407 (0.014)	
	D4-Androstendione		+		0.406 (0.008)	
HDHQ direction	D4-Androstendione		-		-0.371 (0.017)	
	T/E2			+		0.385 (0.043)

Table 5: Statistically significant correlations between sex hormones and hostility (a=5%) in the various phases of cycle (the phase marked by gray denotes the significant correlation). R: Pearson rank correlation coefficient; RS: Spearman rank correlation coefficient; P< 0.05 was considered significant.

Notes: In FL phase the following were found: a) positive correlation between HDHQ CO and FT (R=0.45, p=0.013), T/E2 ratio (R=0.34, p=0.032) and FT/E2 ratio (R=0.41, p=0.008), b) positive correlation between HDHQ SC and T/E2 (R=0.31, p=0.049), c) negative correlation between HDHQ DG and Δ4A (R=-0.32, p=0.023) and HDHQ Intropunitive (R=-0.28, p=0.048). In ML phase, the following were found: a) FT was positively correlated with HDHQ AH (R=0.45, p=0.006), HDHQ PH (R=0.34, p=0.039) and HDHQ Extrapunitive (R=0.41, p=0.013) b) Δ4A was positively correlated with HDHQ CO (R=0.40, p=0.009), HDHQ PH (Rs=0.46, p=0.002) and HDHQ Extrapunitive (R=0.41, p=0.008), c) Δ4A was inversely correlated with the Direction of HDHQ (R=-0.37, p=0.016) d) T was positively correlated with HDHQ PH (Rs=0.54, p=0.0004) and HDHQ Extrapunitive (R=0.38, p=0.016), e) T/E2 (Rs=0.35, p=0.310) and Δ4A/E2 (Rs=0.32, p=0.044) were positively correlated with HDHQ CO. In LL phase, the only statistically significant correlation was between the Direction of Hostility and the ratio T/E2 (Rs=0.39, p=0.042).

Psychometric Parameter	Hormones	Cycle Phase			R(p- value)	Rs (p-value)
		FL	ML	LL		
ZUNG (Depression)	E2 Estradiol		-			-0.346 (0.042)
	T/E2		+			0.356 (0.045)

Table 6: Statistically significant correlations between depressive symptoms and sex hormones (a=5%) in the various phases of cycle (the phase marked by gray denotes the significant correlation). R: Pearson rank correlation coefficient; RS: Spearman rank correlation coefficient; P< 0.05 was considered significant.

Notes: In ML phase, Zung score was negatively correlated to E2 (Rs=-0.35, p=0.042), and positively correlated to the T/E2 ratio (Rs=0.36, p=0.045). No other significant correlations were found.

Steroid hormones and haemostatic variables

Although it is well documented that exogenous administration of estrogens and androgens influence procoagulant as well as fibrinolytic pathways [29-32], there is limited information about the correlation between endogenous sex hormones and haemostatic factors. According to our study, in FL phase, androgens appear to increase the coagulant process, especially through their interrelation with fibrinogen. In ML phase, the ratios androgens/estrogens (FT/E2, T/E2 and Δ4A/E2) appear to influence both the coagulant and anticoagulant process, through their positive correlation to fibrinogen levels, as well as to protein C levels, respectively. On the other hand, in premenstrual phase, sex hormones do not seem to modulate essentially the haemostatic factors, while only the negative correlation between the anticoagulant factor ATIII and E2 detected.

Quite a few studies so far have focused on these associations throughout the menstrual cycle, revealing conflicting results, probably because the factors examined in the various studies differed. In particular, in a prospective study, in which 20 healthy premenopausal women participated, attempted to explore the correlation between several endogenous sex hormones with selective haematological factors during the menstrual cycle: the authors determined an inverse relation between the average concentrations of E2 and PAI-1 across the cycle

but, similarly to our work, no significant correlation was found between E2 and fibrinogen [35]. Larsen et al. [36] and Lebech et al. [24], focusing on similar samples, detected a positive correlation between the cyclical fluctuation of progesterone and fibrinogen levels throughout the cycle, but the latter was not affected by E2 variability, in agreement to our results. In several studies in which healthy postmenopausal women participated, the results concerning the relation between fibrinogen and PAI-1 with the endogenous sex hormones varied [25,56,57]. In healthy women at mid-life, a lack of association between the same hormones and fibrinogen was reported, while for fibrinolytic variables, a positive relation with androgens and a negative one with estrogens was shown [58-60]. In two studies, focusing on apparently healthy [61] as well as hyperlipidemic men [62], the same haemostatic variables were inversely affected by the endogenous T, while in young women with PCOS, a positive correlation between fibrinogen and Δ4A, as well as an inverse correlation with E2 was reported [63].

Based on our results as well as the data so far, we could speculate the ratios androgens to estrogens potentially play the most regulatory role in haemostasis across the menstrual cycle, although, in the premenstrual phase, this association seems to significantly weaken. In agreement with the existing literature, estradiol levels do not seem to affect essentially the haemostatic factors throughout the cycle. On

the other hand, the sample characteristics in various studies appear to influence significantly this association.

Sex hormones and hostility

Hostility is a multifaceted psychological construct comprising primarily cognitive and affective dimensions; it is thought to be a potentially 'toxic' characteristic of the type A personality, and has been related to premature mortality as well as to increased incidence of CHD [64,65]. Although hostility is improved by exogenous E2, as shown in several studies of postmenopausal women with racial differences [66,67] and chronically stressed older women-caregivers [68], according to our data, endogenous E2 does not seem to interfere with the expression of hostile behaviour across the menstrual cycle.

Regarding the exogenously administered androgens and hostility, a positive correlation between them has been reported [3,7,8,69]. In the present study total testosterone as, well as its free fraction, were positively correlated with the extroverted forms of hostility, particularly during the ML phase, while a positive association between the T/E2 ratio and the Direction of Hostility in the premenstrual phase was found. The existing studies are scant and contradictory: in some of them, focusing on small samples of healthy men [11,70], on criminals [10] and on female patients diagnosed with anorexia nervosa [9], a positive correlation between endogenous testosterone and hostility is shown, while in others no relation was found [17,71-76]. A possible explanation for the above discrepancies is the use of different questionnaires for the hostility assessment, as well as the different sample population characteristics.

The clinical significance of the present findings is difficult to estimate, but we can speculate that a) testosterone levels might interfere in a more complicated manner with the balance between physiological responding and emotional coping during stressful events than the hostility profile of the individual [75] and b) the ratio T/E2 might be a more essential parameter in the expression of hostile behaviour in the premenstrual phase of menstrual cycle than T or E2 alone. Dougherty et al. [77] investigated the relation between plasma testosterone levels and aggression, a behavioural ingredient of hostility, emphasizing the need to take into consideration the menstrual cycle phases when testing this interrelation. In the present study the findings are in accordance with those of Dougherty since the correlations between androgens and hostility differed markedly across the cycle.

Therefore, the positive correlation between androgens and hostility found in our study, depends either on the aspect of the hostility examined or on the phase of the cycle, showing a selectivity for the FL or the ML phases, since only one correlation was observed in LL phase.

In addition, we could speculate that exogenous androgens affect hostile behaviour in a similar way compared to endogenous androgens, while this is not the case with endogenous estrogens.

Steroid hormones and depressive symptoms

Although the psychotherapeutic effects of exogenously administered estrogens in postpartum, premenstrual and perimenopausal depression [6,12,13] is known, their effect on depressed mood remains a question [14,66,68,78,79]. According to our findings, depressive symptomatology is enhanced by low serum E2 or T/E2 ratio, during the mid-luteal period only. Regarding the association between endogenous E2 and depressive symptomatology across the menstrual cycle, Hengartner et al. [37] suggested no correlation while testing the link in a longitudinal study encompassing two consecutive cycles. The literature is limited, suggesting also no correlation in perimenopausal [15] and postmenopausal women

[16,19]. Halbreich et al. [80] in an attempt to explore the relation between plasma E2 levels in the luteal phase and clinical features of premenstrual changes found a weak correlation between depressed mood and the rate of decrease of E2.

Likewise, the relation between endogenous testosterone and depressive mood remains unclear but our data are in agreement with most of the studies in which no relation between these factors has been observed in younger [17,18,37,81], in perimenopausal [15,19,82-84] and in older women [16,19] or in subjects with eating disorders [85,86]. On the contrary, Santoro et al. [87] and Morsink et al. [88], in a large cohort of apparently healthy middle aged and elderly females respectively, reported a negative correlation between these factors; a similar inverse association was shown in young women with anorexia nervosa [89]. In agreement to the limited existing literature, no relation was found between endogenous Δ 4A and depression in our study [15,17,19,81]. The variability of studied samples as well as the different psychological assessment could explain the diversity of findings so far.

According to our findings, it seems that sex steroids might interfere with the expression of depressed mood at the ML period only. The ratio T/E2, as well as the E2 increase, during this phase of cycle, might play a regulatory role in young women's well-being, in which reportedly positive emotions reach their maximum level [90-92].

Limitations

Findings of this study should be interpreted with caution because of several limitations• depressive symptoms and hostility are difficult to measure and may change over time. Thus, measurement error (plus the fact that our measures refer to a single point in time) may have resulted in important bias toward the null. Furthermore, the reliance on a self-report test to assess the presence of depressive and hostile feelings should be considered with caution. Nevertheless, self-reports are widely used in epidemiological studies and are generally considered satisfactory tools to detect and assess depressive symptoms, as well as hostility feelings [65,92]. Additionally, while the Zung Scale cannot substitute a comprehensive clinical interview, no formal structured interview was used to establish the absence of a psychiatric disorder (e.g., through the MINI-plus, CIDI or SCID). In contrast, psychiatric assessment of participants was based on their personal reference as well as on the brief psychiatric history taken by the internist. Another limitation of this study was the high intra- and inter-individual variations of the biochemical parameters obtained, while due to the cross-sectional design of this research, we can simply no causal relation between the parameters examined. Further research including extended study periods as well as larger sample size groups is necessary to highlight the correlation between the factors studied and the effect of the menstrual cycle on these interactions.

Conclusion

Based on our results, estrogens do not appear to interrelate essentially with lipid levels throughout the cycle, although existing literature does not allow us to draw safe conclusions about whether the menstrual cycle may have to be considered when examining the relationship between these variables. On the contrary, free endogenous testosterone may have an atherogenic role by affecting lipids such as triglycerides and VLDL.

Contrary to the effect of exogenous sex hormones, the ratios of FT/E2 and T/E2 hormone levels across the cycle may play the most important regulatory role on haemostasis, in comparison with the absolute values.

Regarding the correlation of hostility to androgens, it appears to differ significantly across the cycle, stating that one should take into account the phase of the cycle of the individual, as well as the aspect of hostility we seek to study.

Finally, the T/E2 ratio, as well as the low E2 levels, might play an aggravating role in the depressive symptoms of young women in the ML phase, but more studies are needed on this subject, including longitudinal design and larger samples.

Conflicts of Interest

All authors have no commercial associations or disclosures that may pose or create conflicts of interest with the information presented within this manuscript.

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