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A STUDY OF EXTRA GENITAL EFFECTS OF ESTROGEN AND PROGESTERONE

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Abstract : Although some extragenital effects (EGEs) of the female sex steroids (FSS) have been known for fairly long time, serious research on it has been taken up only in recent time. This paper has tried to explore the EGEs of Estrogen (E) and Progesterone (P).

This study was based on human beings as experimental subjects. In this clinical study, three further subdivisions were made :

(i) Patients of dysfunctional uterine bleeding (DUB) who were therapeutically advised to use orally ingestible synthetic P tablets. These subjects were studied for any P induced changes in the psychoanalytical score, EEG, lung function tests (LUFTs), ECG; their blood Female sex steroid levels were also measured.

(ii) Another group of women suffering from perimenopausal syndrome were given synthetic E tablets and the E induced changes (if any) of the same above mentioned parameters were studied.

(iii) A third group consisting of healthy women were given oral contraceptive pills (OCP) containing both E and P and the above mentioned parameters were studied to see whether the OCP could cause any change.

The results have been discussed. Attempts have been made to see whether our findings give any hint of any mode of action of the FSS studied and so forth.

Key words : female sex steroids, progesterone, estrogen, extragenital effects

INTRODUCTION

For quite some time it has been known that the gonadal hormones have extragenital effects (1, 2, 3). Such behavioral patterns as *aggressiveness* or *defence of the territory* has long been noted as sign of androgenicity in the male animals. Conversely, 'enticement' was regarded as a part of feminine behavior in the animal world. After the introduction of oral contraceptive pills (OCP), the exploration

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of the extragenital effects of female sex steroids like estrogen and progesterone received a shot in the arm. In the beginning, such studies concentrated on effects like hypertension, hypercoagulability of blood, hyperlipidemia etc., but psychological effects did not escape attention. However, many areas of darkness exists in this field. The present work has tried to illuminate some of these dark areas. We worked on the extragenital effects of estrogen and progesterone on subjects who were receiving these agents for therapeutic purposes as well as on subjects who were on OCP containing both estrogen and progesterone.

METHODS

I. Extragenital effects after progesterone therapy

Forty women subjects suffering from dysfunctional uterine bleeding (DUB) who had been advised to take progesterone (at Eden Hospital, Medical College, Kolkata) were studied. EEG, spirometry, ECG, psychoanalytical scoring and blood progesterone (endogenous) level were done before the start of progesterone treatment (firstset or pre-treatment data). After collection of pre-treatment data, each of the subjects was given drugs according to the dosing schedule (see below). Second and third sets of data on the same parameters were collected while the subjects are on treatment. Second and third sets of data were compared individually with those of the first set applying paired *t* test. Comparisons were made between second and third sets of data as well.

Two dosing schedules were used :

(i) Schedule 1 : Subjects received progesterone in the form of Lynestrenol (Orgametril) 5 mg tab, 2 tab orally twice daily from the 7th day of the menstrual cycle (onset of bleeding being regarded as the 1st day of the cycle). First (pre-treatment), second, and third sets of data were collected on 6th, 14th, and 21st days of the cycle respectively.

(ii) Schedule 2 : A loading dose of 8 tablets of Lynestrenol 5 mg in divided dose on 7th day of the cycle followed by lynestrenol 5 mg 1 tablet daily till 16th day of the cycle (D_8 to D_{16}). First, second, and third sets of data were collected on the 6th, 9th, and 16th days of the cycle.

For EEG, bipolar leads of FEO (frontal, eyes open), FEC (frontal, eyes closed), OEO (occipital, eyes open), and OEC (occipital, eyes closed) were taken.

Lung functions measured were — (1) maximum ventilatory volume (MVV), (2) peak expiratory flow rate (PEFR), (3) tidal volume (V_T), and (iv) forced vital capacity (FVC). Measurements were done by an electronically operated spirometer (Medspiror, M/s Med Systems Pvt. Ltd, Chandigarh).

The psychoanalytical scores measured were those for mania, depression, schizophrenia, and anxiety. The scoring was based on Murthy (4).

Serum progesterone measured was endogenous progesterone. The measurement was done by ELISA technique, the kits being obtained from Serono-Diagnostic, Switzerland.

II. Estrogen and its extragenital effects

The protocol, in principle, was the same as that followed with progesterone. Subjects were given ethinyl estradiol (lynoral, organon) 0.05 mg 1 tab once daily from D_5 to D_{25}. Only one menstrual cycle was observed. Altogether 10 women aged between 44 to 50 years, otherwise healthy were selected. The subjects were sufferers of perimenopausal syndrome i.e., they were suffering from signs and symptoms which were perceived due to the approaching menopause. How ever, none of them reached the actual menopause (i.e., stoppage of menstrual flow) although all of them were suffering scantly menstrual flow in addition to the other signs and symptoms. Ethinylestradiol is the major estrogen in premenstrual women. It is not very effective when given orally. Addition of 17α ethinyl group enhances oral activity. Though it has similar action as estradiol. And other estrogen preparations like estradiol hemisuccinate, estradiol valerate, estradiol benzoate, estradiol phenyl proprionate, estradiol succinate. 17β estradiol estriol (Evalon) etc. are now available in the market. Ethinyl estradiol was most orally effective, cheap and only abundantly available estrogen during the period when the work was done. It is contrasy to mention that lynoral tablet containing 0.05 mg of ethinyl estradiol in the dose of 1 tablet once daily from D_5 to D_{25} of menstrual cycle is standard recommended dose for Indian women at perimenopausal age group. Consent of the subjects was taken regarding the therapy.

III. OCP and extragenital effects

A total number of 10 healthy women subjects, age between 18 to 28 years, were studied. A combined oral contraceptive pill (OCP) i.e., an OCP containing both E and P were used.

Drug used : Novelon (ethinyl estradiol 0.03 mg + desogestrol 0.15 mg tablets) Dose : 1 tablet once daily from D_5 to D_{25}. Data Collection : 1st set : 5; 2nd set : 14; 3rd set : 21.

1. Study	Extragenital effects (EGEs) of progesterone	EGEs of E	EGEs of OCP
2. Drug used	Orgametril (Lynoestrenol) 5 mg, tablet	Lynoral (ethinyl estrodiol) 0.05 mg tablet	Novelon (ethinyl estradiol 0.03 mg + Desogestrol 0.15 mg tablets
3. Dose	either, loading dose followed by 1 tab O.D. or 2 tablet B.D. from the beginning	1 tablet O.D.	1 tablet O.D.
4. Type of the subjects	DUB sufferers	Perimeno-pausal syndrone suffers	Healthy
5. Data collection	Uniform dose / loading dose		
1st set	7 / 6	5	5
2nd set	14 / 9	14	14
3rd set	21 / 16	21	21

RESULTS AND DISCUSSION

I. Progesterone. Progesterone causes some extragenital effects on CNS; respiratory and cardiovascular system. One notable feature is, the values (of the parameters), which changed due to progesterone therapy gradually tend to return towards the control (pre-treatment) value in majority of cases despite the fact that the progesterone therapy was still continuing.

1. EEG. Voltage falls and frequency rises in 2nd set of data but the changes regress to some extent in the 3rd set of data. Thus, initially there is a sort of dysynchronization which recovers later despite the fact that the patient is still using the drug. (vide Table Ia and Ib). There was a fall in EEG voltage and rise in frequency (ie, a faster rhythm and lower amplitude) in the initial phase of exogenous progesterone therapy (10). The lowering of amplitude has been

TABLE Ia: Effects of orgametril (lynestrenol 5 mg) 2 tabs BD dose in patients of DUB. Figure in parentheses indicate the value of p; n = no. of observations. ↑↑,↑ = sharp and moderate rise; ↓↓,↓ = sharp and moderate fall. w = waning of the intensify in 3rd set (compared against 2nd set) seen. m_1, m_2, m_3 = mean value of 1st set (control), 2nd set, and 3rd set respectively.

	Parameter	*Effects seen on 2nd set of data collected on 14th day compared to control (1st set)*		*Effects seen on 3rd set of data collected on 21st day compared to control (1st set)*		*Comparison 2nd set Vs. 3rd set*	
		Voltage	*Frequency*	*Voltage*	*Frequency*	*Voltage*	*Frequency*
EEG (n = 30)	OEC	m_1=51.1±5.6 μv m_2=42.5±5.74 μv ↓↓ (<0.001)	m_1=13.1±1.94 HZ m_2=16.2±2.37 HZ ↑↑ (<0.001)	m_3=45.5±4.5 μv 45.5±4.5 μv ↓ (<0.001)	m_3=13.9±2.94 HZ 13.9±2.94 HZ ↑ (<0.001)	W (<0.001)	W (<0.001)
	OEO	m_1=51.9±4.98 μv m_2=51.0±4.8 μv ↓↓	m_1=14.8±1.9 HZ m_2=16.66±1.98 HZ ↑↑	m_3=15.6±5.74 μv ↓	m_3=14.7±1.57 HZ ↑	W (<0.01)	W (<0.05)
	FEC	m_1=52.0±3.6 μv m_2=48.9±3.6 μv ↓↓ (<0.001)	m_1=16.0±1.78 HZ m_2=17.8±1.97 HZ ↑↑ (<0.001)	m_3=15.0±4.45 μv ↓ (<0.001)	m_3=16.1±1.79 HZ ↑ (<0.001)	W (<0.001)	W (<0.001)
	FEO	m_1=53.1±4.3 μv m_2=42.06±5.8 μv ↓↓ (<0.001)	m_1=13.0±1.78 HZ m_2=14.6±1.67 HZ ↑↑ (<0.001)	m_3=47.5±4.4 μv ↓ (<0.001)	m_3=13.6±1.91 HZ ↑ (<0.001)	W (<0.001)	W (<0.001)
LUFTs (n = 30)	MVV	m_1=103.13±10.7 l/m m_2=110.73±13.8 l/m ↑↑ (<0.001)		m_3=99.5±14.1 l/m ↓ (<0.001)		Reversal of effect (<0.001)	
	PEFR	m_1=2.97±1.14 l/m m_2=3.34±1.2 l/m ↑↑ (<0.001)		m_3=3.71±1.19 l/m ↑↑ (<0.001)		No change of effect	

Serum P level (n=30)	m_1=4.1±1.37 ng/ml m_2=3.1±1.99 ng/ml ↓↓ (<0.001)	m_3=1.3±1.41 ng/ml ↓ (<0.001)	W (<0.001)
Anxiety (n=30)	m_1=10.5±1.4 m_1=7.46±1.3 ↓↓ (<0.001)	m_3=8.6±1.17 ↓ (<0.001)	W (<0.001)
Depression	m_1=5.3±1.2 m_2=2.66±1.2 ↓↓	m_3=4.93±1.4 ↓ (<0.05)	W (<0.001)
Mania	m_1=4.7±1.49 m_2=4.9±1.48 ↑ (<0.001)	m_3=4.9±1.74 ↑ (<0.001)	No change
Heartrate(n=30)	m_1=72.8±2.2/min m_2=72±3.08/min ↓↓ (<0.001)	m_3=72.4±2.9/min ↓ (<0.001)	W (<0.001)
Sinus arrhythmia	m_1=3.16±0.94/min m_2=3.9±1.2/min ↓↓ (<0.001)	m_3=3.86±1.12 ↑ (<0.001)	W (<0.001)
Tallest R	m_1=12.36±0.615 mv m_2=13.33±0.909 mv ↑↑ (<0.001)	m_3=12.66±0.186 mv ↑ (<0.001) (<0.001)	W (<0.001) (<0.001)
R + S	m_1=21±0.2 mv m_2=22±1.42 mv ↑↑ (<0.001)	m_3=21±1.21 mv ↑ (<0.001)	W (<0.001)

TABLE Ib: Effects of orgametril (lynestrenol 5 mg) loading dose followed by 1 tab daily ↑↑,↑ ↓↓↓ W = as Table I : n = no. of subjects : m_1, m_2 & m_3 as in Table I.

Parameter	*Effects seen on 2nd set of data collected on 9th day compared to control*		*Effects seen on 3rd set of data collected on 16th day compared to control*		*Comparison 2nd set Vs. 3rd set*	
	Voltage	*Frequency*	*Voltage*	*Frequency*	*Voltage*	*Frequency*
OEC	m_1=47.9±3.24 µv m_2=44.0±4.24 µv ↓↓ (<0.001)	m_1=11.7±2.47 HZ m_2=12.4±2.30 HZ ↑↑ (<0.05)	m_3=m_3= 46.2±3.31 µv ↓ (<0.05)	W 11.9±2.64 HZ ↑ (<0.05)	W (<0.01)	(<0.05)

OEO	m_1=45.9±3.10 µv m_2=42.0±4.24 µv ↓↓	m_1=12.7±2.47 HZ m_2=15.9±2.76 HZ ↑↑	m_3=45.2±3.13 µv ↓	m_3=13.7±3.44 HZ ↑	W (<0.001)	W (<0.001)
FEC	m_1=47.9±3.24 µv m_2=44.0±4.24 µv ↓↓ (<0.001)	m_1=14.7±2.47 HZ m_2=17.9±2.76 HZ ↑↑ (<0.001)	m_3=47.2±3.13 µv ↓ (<0.02)	m_3=15.7±3.44 HZ ↑ (<0.001)	W (<0.001)	W (<0.001)
FEO	m_1=48.9±3.16 µv m_2=46.9±4.29 µv ↓↓ (<0.001)	m_1=13.7±2.47 HZ m_2=15.2±2.40 HZ ↑↑ (<0.05)	m_3=47.2±3.19 µv ↓ (<0.05)	m_3=14.0±2.64 HZ ↑ (<0.05)	W (<0.01)	W (<0.05)
MVV	m_1=102.9±7.97 l/min m_2=106.8±8.8 l/min ↑↑ (<0.001)		m_3=10.0±8.29 l/m ↓ (<0.05)		Reversal of effect (<0.01)	
PEFR	m_1=2.8±1.14 l/s m_2=4.4±0.94 l/s ↑↑ (<0.01)		m_3=2.9±1.15 l/s No change		W (<0.02)	
Serum P level (n=30)	m_1=3.5±1.37 ng/ml m_2=2.6±1.4 ng/ml ↓↓ (<0.05)		m_3=2.8±1.33 ng/ml ↓ (<0.05)		No change	
Anxiety (n=30)	m_1=12.5±1.45 m_2=10.2±0 ↓↓ (<0.10)		m_3=12.1±1.79 ↓ (<0.10)		W (<0.02)	
Depression	m_1=5.3±1.52 m_2=4.21±2.21 ↓↓ (<0.05)		m_3=4.8±1.82 ↓ (<0.10)		W (<0.05)	
Mania	m_1=4.9±1.51 m_2=5.0±1.41 ↑ No change		m_3=4.95±1.51 No change (<0.001)		No change	
Heart rate (n=30)	m_1=40±1.82/min m_2=2.07±0.88/min ↓↓ (<0.001)		m_3=72.4±2.9/min ↓ (<0.02)		W (<0.01)	
Sinus arrhythmia	m_1=3.3±0.88/min m_2=4.5±1.37/min ↑↑ (<0.02)		m_3=4.1±1.2 ↑ (<0.05)		W (<0.01)	
Tallest R	m_1=12.3±0.57 mv m_2=13.8±2.26 mv ↑↑ (<0.01)		m_3=12.2±0.88 mv No change		W (<0.02)	
R + S	m_1=22.0±1.2 mv m_2=2.2±1.94 mv ↑↑ (<0.02)		m_3=22.0±1.05 mv No change (<0.001)		W (<0.02)	

previously reported (4) but, as far as we are aware of, the faster thythm has never been reported. However, later on the effect of progesterone began to be blunted despite the continuation of the drug.

At this stage, the explanation of appearance of faster thythm lower voltage (characteristic of α block) is not easy. At best it can only be highly speculative :

(a) it should be understood that many drugs can produce desynchronization (faster thythm, lower voltage) of EEG waves and, by itself, it is not of great significance; (b) genesis of EEG itself is very poorly understood which makes the rationalization of changes noted even more difficult; (c) EEG waves are strongly influenced by RAS (reticular activating system) activity. Our animal experiments (5) suggest that many monoaminergic nerve tracts (constituting the RAS) are strongly influenced by the progesterone therapy. This leads to suspicion that RAS activity itself is altered by progesterone. Further speculation at this stage is not permitted as we know so little about the functions of the monoamines. For example in depression some persons sleep more whereas some persons develop insomnia.

Although the explanation is not forthcoming, the EEG changes give an impression that progesterone, notwithstanding the fact that it should work against epilepsy (see below), causes more alertness of the person. This is highly interesting because many of the antiepileptic drugs act by potentiating GABA activity (6) which (on theoretical grounds) should lead to drowsiness. Progesterone, unlike the classical antiepileptic drugs, thus appears to cause mild increase of altertness of the mind in its initial phase of therapy.

2. At psychological level, there is reduction of scoring for anxiety and depression. Progesterone elevates the level of GABA as well as that of 5th in the brain and reduced metabolites of progresterone, viz., 3α pregnan–20 one exhibit GABA against like effect (7). Elevation of GABA level should reduce the level of anxiety and, in fact, most anxiolytic drugs act via this mechanism. Teleologically, reduction of anxiety and depression are desirable developments in pregnancy — a condition when progesterone concentration in the body tissue becomes high. Incidentally, a report from another laboratory shows progesterone has anxiolytic effects on rats (8).

3. Synthetic Progesterone causes rise of maximum ventilation volume (MVV), though it subsequently shows rise of PEFR. On the respiratory system, progesterone increase MVV and PEFR (9). This suggests that progesterone causes increase in respiratory efficiency. With the growth of the size of the fetus one would expect respiratory embarrassment and increased respiratory efficiency appears to be telelogically desirable.

4. ECG tracings suggest that progesterone produces bradycardia, increased sinus arrhythmia, and increased amplitude of ventricular complex. Bradycardia causes conservation of energy.

Most of the effects however are, to some extent, blunted with time, that is, a sort of tachyphylaxis develops. However, most effects, although blunted to some extent, persist. Cause of tachyphylaxis, at this stage, can only be speculative : this can be due to a (i) compensatory phenomenon, (ii) a sort of pharmacokinetic or pharmacodynamic tolerance, and so on.

5. The level of endogenous progesterone fell very sharply with exogenous progesterone therapy. This suggests that the production of endogenous progesterone virtually stopped which indicates that the formation of corpus luteum stopped with this dose. In short, when progesterone is used in this dose ovulation probably stops.

In a previous report (5) from this laboratory, it was reported that lower doses of progesterone failed to produce the extragenital effects although higher doses were successful. In the current work it was noted that the trend of changes were similar whether a loading dose followed by maintenance dose was used or some dose was used throughout the cycle.

II. Estrogen and III OCP. Broadly speaking, the current work shows that when used in the doses mentioned, no appreciable extragenital effects develop no matter whether estrogen alone or combined OCP are used. This of course does not rule out that estrogen or OCP (combined pill) has—any extragenital effects because they may appear with changes of dosing schedule. However, as estrogen is a recognized carcinogen, a change in the dose schedule was not risked. Also, ethically, change in the dose schedule in the OCP was not justified. (vide Table No. II and III).

TABLE II : Effects of estrogen on different parameters.

	Effects seen on 2nd set of data collected on 14th day compared to control (1st set)		*Effects seen on 3rd set of data collected on 21st day compared to control (1st set)*		*Comparison 2nd set Vs. 3rd set*	
EEG (n = 10)	*Voltage μv*	*Frequency HZ*	*Voltage μv*	*Frequency HZ*	*Voltage μv*	*Frequency HZ*
OEC	57.4±4.2	11.2±.8	57.4±4.2	11.2±.8	57 ±4.3	11±.8
	↓	↓				
	57±4.3	11±.8	57.4±4.2	11.2±.8	57.4 ±4.2	11.2±.8
	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
OEO	58.6±4.6	10.6±.84	58.3±4.3	10.6±.84	58.3 ±4.3	10.3±.95
	↓	↓				
	58.3±4.3	10.3±.95	58.6±4.6	10.6±84	58.6 ±4.6	10.6±.84
	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
FEC	58.2±4.4	11.9±1.3	58.2±4.4	11.9±1.3	57.6 ±1.3	11.7±1.34
	↓	↓				
	57.6±4.5	11.7±1.34	58.2±4.4	11.9±1.3	58.2 ±4.4	11.9±1.3
	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

FEO	57.7±5.1 ↓ 57±4.9 N.S.	12.1±1.1 ↓ 11.8±1.14 P≤05	57.7±5.1 ↓ 57.5±4.8 N.S.	12.1±1.1 ↓ 12.1±1.1 N.S.	57 ±4.9 ↓ 57.5 ±4.8 N.S.	11.8±1.14 ↓ 12.1±1.1 N.S.
Anxiety (n=10)	6.2±1.4 ↓ 5.9±1.4 N.S.		6.2±1.4 ↓ 6.1±1.3 N.S.		5.9±1.4 ↑ 6.1±1.3 N.S.	
Anxiety						
Depression	4.2±.8 4.6±.7 N.S.		4.2±.8 4.4±.7 N.S.		4.6±.7 4.4±.7 N.S.	
Mania	3.3±.8 3.6±.97 N.S.		3.3±.8 3.3±.8 N.S.		3.6±.97 3.3±.8 N.S.	
Heart rate (n=10)	71.5±.97/min ↓ 71.1±1.12/min N.S.		71.5±.97/min ↓ 71.4±1.07/min N.S.		71.1±1.12/min ↑ 71.4±1.07/min N.S.	
Sinus arrhythmia	2.8±8 L/min 2.8±8 L/min N.S.		2.8±8 L/min 2.8±8 L/min N.S.		2.8±8 L/min 2.8±8 L/min N.S.	
Amplitude (R)	11.4±1.17 mv ↓ 10.9±1.3 mv N.S.		11.4±1.17 mv 11.4±1.17 mv N.S.		10.9±1.3 mv 11.4±1.17 mv N.S.	
Sigma	20.5±.7 mv ↓		20.5±.7 mv ↓		20.1±.57 mv	
(R + S)	20.1±.57 mv N.S.		20±47 mv N.S.		20±47 mv N.S.	
LUFTs (n = 10) M.V.V.	108.6±4 L/min (1st set) 107.7±3.9 L/min (2nd set) N.S.		108.6±4 L/min (1st set) 107.8±3.6 L/min (3rd set) N.S.		108.6±4 L/min (1st set) 107.8±3.6 L/min (3rd set) N.S.	
P.E.F.R.	2.6±5 L/sec 2.6±5 L/sec N.S. (pg/ml)		2.6±5 L/sec 2.6±97 L/sec N.S. (pg/ml)		2.6±5 L/sec 2.6±97 L/sec N.S. (pg/ml)	
Serum estrogen level (n = 10)	161.8±15.3 (1st set) ↓ 69.8±11.01 (2nd set) P<.001		161.8±15.3 (1st set) ↑ 214.3±17 (3rd set) P≤.001		69.8±11.01 (2nd set) ↑ 214.3±17 (3rd set) P<.001	

TABLE III: Effects of OCP on different parameters.

	Effects seen on 2nd set of data collected on 14th day compared to control (1st set)		*Effects seen on 3rd set of data collected on 21st day compared to control (1st set)*		*Comparison 2nd set Vs. 3rd set*	
EEG (n = 10)	*Voltage μv*	*Frequency HZ*	*Voltage μv*	*Frequency HZ*	*Voltage μv*	*Frequency HZ*
OEC	58.3±1.87	11.1±.38	58.3±1.87	11.1±.38	58.5 ±1.69	11.8±.42
	58.5±1.69	11.8±.42	53.3±1.87	11.3±.37	58.3 ±1.87	11.3±.37
	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
OEO	60.3±1.87	11.4±.27	60.3±1.87	11.4±.27	57.5 ±1.75	12.8±.48
			↓			
	57.5±1.57	12.8±.48	56.9±1.46	10.8±51	56.9 ±1.46	10.8±.51
	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
FEC	59.3±1.87	12.2±1.49	59.3±1.8	12.2±.42	55.6 ±1.89	13.7±.42
		↓				
	55.6±1.87	13.1±.42	56.8±1.8	12.9±.35	56.8 ±1.89	12.9±.35
	P<.05	N.S.	N.S.	N.S.	N.S.	N.S.
FEO	59.8±1.95	12.4±.31	59.8±1.95	12.4±.3	55.8 ±2.25	14.1±.31
	↓	↑				
	55.8±2.25	14.1±.31	57.2±2.4	12.9±.4	59.2 ±2.46	12.9±.46
	P<.05	P<.05	N.S.	N.S.	N.S.	N.S.
MVV	109.7±1.88 L/min		98.4±3.8 L/min		118.2±2.33 L/min	
	↑		↓		↓	
	118.2±2.33 L/min		109.7±1.88 L/min		98.4±3.8 L/min	
	P<.001		P<.001		P<.001	
PEFR	2.5±.17 L/sec		2.5±.17 L/sec		3.5±.17 L/sec	
	3.5±.17 L/sec		3.25±.29 L/sec		3.25±.29 L/sec	
	N.S.		N.S.		N.S.	
Serum	ng/ml		ng/ml		ng/ml	
Progesterone	3.3±.17		3.3±.17		3±.17	
level	3±.17		3.4±.21		3.4±.21	
	N.S.		N.S.		N.S.	
Serum	pg/ml		pg/ml		pg/ml	
estrogen	47.5±1.64		47.5±1.64		69.3±5.30	
	↑		↓		↑	
level	69.3±5.38		1.67±5.77		167.7±5.77	
(n = 10)	P<.001		P<.001		P<.001	
Anxiety	6.6±.64		6.6±.64		6.6±.64	
	6.6±.69		7.1±.69		7.1±.69	
	N.S.		N.S.		N.S.	
Depression	3.7±.45		3.7±.45		3.8±4.46	
	3.8±.46		4±.57		4±.57	
	N.S.		N.S.		N.S.	

LUFT

Mania	2.5±.37	2.5±.37	2.6±.4
	2.6±.4	2.7±.39	2.7±.39
	N.S.	N.S.	N.S.
Heart rate	72.1±.4/min	72.1±.4/min	70±.26/min
	↓	↓	↓
	70±.26/min	68.7±.3/min	68.7±.3/min
	P<.02	P<.01	N.S.
Sinus	2.7±.21/min	2.7±.21/min	3.08±.16/min
	↑	↑	
arrhythmia	3.08±.16/min	2.89±.17/min	2.89±.17/min
	N.S.	N.S.	N.S.
	11.1±.46 mv	11.1±4.6 mv	12.4±.43 mv
	↑		
Amplitude (R)	12.4±.43 mv	11.1±.35 mv	11.1±.35 mv
	N.S.	N.S.	N.S.
Sigma	21.3±.45 mv	21.3±.45 mv	28.3±.42 mv
	↑		↓
(R + S)	23.3±.42 mv	21.1±.43 mv	21.1±.43 mv
	P<.05	N.S.	P<.05

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