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SOME HITHERTO UNREPORTED FINDINGS ON THE EXTRAGENITAL EFFECTS OF PROGESTERONE IN HUMAN FEMALES - A CLINICAL STUDY

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Abstract: 40 women suffering from 'dysfunctional uterine bleeding' (DUB) were treated by progesterone (P) and signs and symptoms of 'extragenital effects' of P were noted. In addition to the previous ones reported from this laboratory, a new crop of effects, which, as far as we are aware of, have never been reported in the literature, were found and included:

(i) Changes in the frequency of EEG waves, (ii) changes in the ECG (iii) changes in psychoanalytical scoring. Further (iv) with most of the parametres, the intensity of the changes showed considerable waning with pasage time, despite the fact that the subjects were still receiving P. Blood P levels similarly fell considerably in the initial phase of the therapy, but recovered to some extent afterwards, despite the continuance of P therapy.

Key words: anxiety blood level of (endogenous) P depression progesterone ECG EEG desynchronization extragenital effects mania ventilatory maximum volume lung function tests peak expiratory flow rate (PEFR) psychoanalytical scoring

INTRODUCTION

Previous reports (1, 2) from this laboratory showed that progesterone (P) causes some extragential effects which included, in human females, signs, like drop of EEG voltage and rise in maximum ventilatory volume (MVV) and in female intact rats, a fall of noradrenalin (NA) concentration in selected areas of brain.

Various neurotransmitters, like NA, 5 hydroxytryptamine (5-HT), dopamine (DA) and gamma amino butyric acid (GABA) are known to be involved in psychiatric disorders like, depression, anxiety, paranoia and mania. Further, the same neurotransmitter may be involved in more than one psychiatric malady. Thus, a fall of NA concentration ([NA]) may cause depression (3) and again NA is involved in the etiology of anxiety (4).

Further, animal studies (5) suggest, that P therapy causes amilieoration of anxiety.

It is possible, therefore, that in the subjects, who receive P for therapeutic purposes, particularly in those who take rather heavier doses, as in the case of patients of DUB, *subtle, subclinical* psychological changes may appear.

In short, circumstantial evidences suggest that P should be etiologically related to such psychiatric problems like anxiety, depression etc. but reports on direct studies in human beings (who are psychologically normal) are lacking.

Also, it was argued that if the EEG, which is a form of electrophysiology of brain, can alter with P, as was reported earlier. It is possible that electrophysiology of heart in the form of ECG can also change.

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Further, many women, like those consuming oral contraceptive pills or users of oral P pills due to DUB, use the drug for long periods. It is necessary to investigate whether the extragenital effects increase or decrease with time although the patients may be still on the drug.

As far as we could see, the literature is silent on these issues and hence with an aim to throw some light, the present work was taken up.

METHODS

Forty women, aged between 15 to 30 years, diagnosed to be suffering from DUB but otherwise healthy, were treated with oral doses of synthetic P. The responsibility of diagnosis and the decision to use P was entrusted on one of us (K.C.De, Associate Prof., Department of Obstetrics & Gynaecology, Medical College, Calcutta). The patients were divided arbitrarily into two groups, viz, Gr. A and Gr. B. Each of Gr. A patients were given an oral preparation of P in the form of Orgametril (lynesterol; 5 mg each tab; Organon), 2 tab BD, on and from the 7th day (of the menstrual cycle) till the 21st day, without any change.

In Gr. B, a loading dose of 8 tablets in divided doses, was given on the 7th day followed by 1 tab daily till the 16th day.

The onset of bleeding was regarded as the Ist day of menstrual cycle.

Laboratory procedures: For EEG, 4 leads were taken, as described previously (1), as follows, (i) 'frontal eyes open' (FEO), (ii) 'frontal eyes closed' (FEC) (ii) 'occipital eyes open' (OEO) (iv) 'occipital eyes closed' (OEC); thus 4 sets of EEG were recorded from each patient in each sitting.

Lung function tests (LUFTS) : Tidal volume (V_T), forced vital capacity (FVC), forced expiratory volume in the Ist second (FEV_1), maximal ventilatory volume (MVV), peak expiratory flow rate (PEFR) were tested by MEDSPIROR (M/S MED SYSTEMS Pvt. Ltd., Chandigarh).

Electrocardiography : A 12 lead ECG was taken. After studying few cases, it was eventually decided to note the following parameters particularly: (i) heart rate (ii) variation of the heart rate, from the minimum to the maximum (ie, intensity of the sinus arrhythmia), (iii) amplitude of the R wave, where R wave is tallest in the precordial leads, (iv) summated values of the tallest R and deepest S waves in the precordial leads.

Blood progesterone levels were estimated by enzyme linked immuno sorbent (ELISA) technic. The kits were supplied by Serono-Diagnostic, Switzerland, Calcutta Agent Dab Chems. Pharma. We used the procedure supplied in their literature.

Psychoanalytical scoring for depression, mania, paranoia and anxiety was done by a set of questionnaire used in a successful Ph.D. thesis of Calcutta University (6). This thesis has used a set of questions (which were already in vogue in the Deptt. of Applied Psychology of Calcutta University) originally developed for the Indian subjects by Murthy (7) who in turn had based on Minnesota Multiple Personality questionnaire (MMPI).

Protocol of the Experiment

Gr. A. All the laboratory procedures mentioned above (viz, EEG, ECG, LUFTs, blood P estimation, psychonalytical scoring) were performed on each patient on the 6th day of their mentstrual cycle and these data served as control (i.e. predrug values). From 7th day the patients started to receive orgametril in 2 tab BD doses and while the drug was on, all the laboratory testings mentioned above were repeated on the 14th day and these values will be henceforth referred as 2nd set of data. The patient continued the drug and a 3rd set of data of the same laboratory tests were collected on the 21st day.

Data obtained on the 14th day (i.e. the 2nd set of data) were compared with those of the control. Thus, each patient served as her own control. Again the 3rd set was compared with the control as well as with the 2nd set.

Gr. B. Laboratory testing for the control values were made on the 6th day of the cycle. On the 7th day, the patient received the loading dose of P as mentioned earlier. On and from the 8th day they continued with 1 tab of orgametril daily. On the 9th day of the cycle, the laboratory testing were repeated (*2nd set of data*). The patient continued with 1 tab orgametril daily. On the 16th day, the 3rd set of data were collected. As with Gr. A, the 2nd and 3rd sets were compared with the control; comparison between 2nd and 3rd set were also made.

Statistical analysis was made by 'paired t test'.

RESULTS

To save space, only the parameters alone which were influenced significantly by P therapy have been shown. These were, (i) EEG (both voltage and frequency), (ii) MVV and PEFR of the LUFTs, (iii) Depression, mania and anxiety of the psychoanalytical scoring, (iv) ECG and (v) Blood P level.

Gr.A. subjects.

Table I shows the effects of P on the different parameters in Gr. A patients. In short, the findings are :

TABLE I : Effects of orgametril (lynestrenol, 5 mg), 2 tab BD dose, in patients of DUB.
Figure in parenthesis indicate the value of p; n = no. of observations.
↑↑, ↑ = Sharp and moderate rise; ↓↓, ↓ = sharp and moderate fall.
W = waning of the intensity 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		*Effect seen on 2nd set of data (collected on 14th day) compared to control*		*Effects seen on 3rd set of data (collected on 21st day) compared to control*		*Comparison, 2nd versus 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 = 13.0±1.94 HZ m_2 = 16.2±2.37 HZ ↑↑ (<0.001)	m_3 = 45.5±4.5 μv ↓ (<0.001)	m_3 = 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 ↓↓ (<0.001)	m_1 = 14.8 ±1.9 HZ m_2 = 16.66±1.98 HZ ↑↑ (<0.05)	m_3 = 51.6±5.74 μv ↓ (<0.05)	m_3 = 14.7±1.57 HZ ↑ (<0.05)	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 = 51.0±4.5 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±4.4μv ↓ (<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 Plevel (n = 30)		m_1 = 4.1±1.37 ng/ml. m_2 = 3.1±1.99 ng/ml ↓↓ (<0.001)		m_3 = 3.3±1.41 ng/ml ↓ (<0.001)		W (<0.001)	

Psychoanalytical scoring (n = 30) Anxiety	m_1 = 10.5±1.4 m_2 = 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 ↓↓ (<0.001)	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
ECG (n = 30) Heart rate	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)
R + S	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)
Tallest	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)

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 desynchronization which recovers later despite the fact that the patient is still using the drug.

LUFTs: In the 2nd set of data, that is initially, the MVV rose but afterwards in the 3rd set of data, the value of MVV became less than the control (i.e., a biphasic response).

The PEFR on the other hand showed a rise initially (2nd set of data) and the rise remained undiminished afterwards (3rd set of data) also.

ECG: In the initial phase (in the 2nd set of data) a bradycardia was noted but this recovered partially, in the 3rd set of data.

P also increased the sinus arrhythmia in the initial phase (2nd set of data) and some recovery was noted in the 3rd set.

The summed up values of the amplitude of the tallest R wave and deepest S wave (referred as R+ S) increased initially but afterwards in the 3rd set the increase was less noticeable. Further, the amplitude of R increased (2nd set) but waned afterwards.

Psychoanalytical scoring: Scores for both anxiety and depression became lower initially (2nd set of data) but afterwards, in the 3rd set, some recovery was noted. With mania, however, in Table I, there was an elevation of the score which did not wane in the 3rd set.

Blood progesterone values became lower in the 2nd set; some recovery took place in the 3rd set.

Gr. B. subjects: Table II shows the effects of P in Gr. B subjects. It will be seen that the trends of changes are broadly (although not identically) similar to those of Gr. A. In mania however there was no change in the score.

TABLE II : Effects of orgametril (lynestrenol, 5mg), 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		*Effect seen on 2nd set of data (collected on 9th day) compared to control*		*Effects seen on 3rd set of data (collectedon 16th day) compared to control*		*Comparison, 2nd versus 3rd set*	
		Voltage	Frequency	Voltage	Frequency	Voltage	Frequency
EEG (n = 10)	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 = 46.2±3.31μv ↓ (<0.05)	m_3 = 11.9±2.64 HZ ↑ (<0.05)	W (<0.01)	W (<0.05)
	OEO	m_1 = 45.9±3.10 μv m_2 = 42.0±4.24 μv ↓↓ (<0.001)	m_1 = 12.7±2.47 HZ m_2 = 15.9±2.76 HZ ↑↑ (<0.001)	m_3 = 45.2±3.13μv ↓ (<0.001)	m_3 = 13.7±3.44 HZ ↑ (<0.001)	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)
LUFTs (n = 10)	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±1.41 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 = 10)		m_1 = 3.5±1.37 ng/ml. m_2 = 2.6±1.4 ng/ml ↓ (<0.05)		m_3 = 2.8±1.33ng/ml ↓ (<0.05)		No change	
Psychoanalytical scoring (n = 10) Anxiety		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	$m_1 = 4.9 \pm 1.51$ $m_2 = 5.0 \pm 1.41$ No change	$m_3 = 4.95 \pm 1.51$ No change	No change
ECG (n = 10) Heart rate	$m_1 = 40 \pm 1.82$/min $m_2 = 2.07 \pm 0.88$/min ↓↓ (<0.001)	$m_3 = 3.5 \pm 1.52$/min ↓ (<0.02)	W (<0.01)
Sinus arrhythmia	$m_1 = 3.3 \pm 0.88$/min $m_2 = 4.5 \pm 1.37$/min ↑↑ (<0.02)	$m_3 = 4.1 \pm 1.2$ ↑ (<0.05)	W (<0.01)
R + S	$m_1 = 22.0 \pm 1.2$ mv $m_2 = 2.2 \pm 1.94$ mv ↑↑ (<0.02)	$m_3 = 22.0 \pm 1.05$ mv No change	W (<0.02)
Tallest R	$m_1 = 12.3 \pm 0.57$ mv $m_2 = 13.8 \pm 2.26$ mv ↑↑ (<0.01)	$m_3 = 12.2 \pm 0.88$ mv No change	W (<0.02)

DISCUSSION

On the basis of our work some broad conclusions can perhaps be taken. These are, P causes (i) some desynchronization (faster rhythm lesser voltage) of EEG (ii) bradycardia, increased sinus arrhythmia and increased amplitude of ventricular complex in ECG (iii) reduction of the scoring rate for anxiety and depression; in short, P causes increased mental stability (iv) fall of endogenous blood progesterone level (v) increase in MVV and PEFR (i.e. increases the efficiency of the respiratory system). Excepting the MVV, all changes become less intensive with progress of time despite the continuance of P (with MVV, the response became biphasic). However, the subjects of Table I develop proneness to mania (according to this work) with P therapy.

In our previous report (1), we reported the voltage drop of EEG but we could not detect a change of frequency of the EEG waves. As far as we are aware, no report has appeared till to date, that P can cause frequency changes in EEG waves. Similarly, we failed to note any reporting of the ECG changes or psychoanalytical scoring (in psychologically healthy women) due to P. The voltage drops were most spectacular in OEC (from 51.1±5.6 μv in 1st set to 42.5±5.74 μv in second set) and FEO (from 53.1±4.3 μv in 1st set to 42.06±5.8 μv in 2nd set) leads (Table I). Although the value of P (0·001) remains same for these differences in OEC and FEO in Table II, the magnitude of the change in Table II compared to those of Table I is less spectacular. The frequency rise with P is consistent, although seen most sharply in OEC (from 13·0±1·94 HZ to 16·2±2·37 HZ) in Table I. Magnitudes of frequency changes in Table II are less spectacular.

It appears many of the changes are beneficial to the subject. Thus, bradycardia means conservation of energy. Improved psychoanalytical scoring may mean that the subject is mentally more stable and is psychologically better adapted to face challenging situations. It may be recalled that progesterone level rises during pregnancy; pregnancy as well as the labor are challenging situations. The rise in MVV and PEFR suggests an improvement of the respiratory efficacy, and this may be of some help during pregnancy.

In a previous report (2) we reported that NA concentration falls in some selected areas of rat brain after P injection, and on the basis, we speculated that P may precipitate depression in human being. However, in this report, our finding reveals that P causes improvement of depression state. The answer to this apparent contradiction may be as follows :

The neurotransmitter, NA is related to the etiology of not only depression but also of anxiety, although how exactly it is involved in the etiology of anxiety is not very clear. There are some evidences that fall of NA activity in the brain can amilcorate anxiety (4). Thus, fall of NA concentration in rat brain, reported in our previous paper (2), may be related to the amilcoration of anxiety seen in the current work [rather than the depression, speculated in the previous report (2)].

The value of *endogenous* serum *P*, *normally,* is minimal during the follicular phase (corresponding to m_1 in our Table I) but normally rises sharply in luteal phase because of the appearance of corpus luteum. In Table I, m_2 and m_3 correspond to the luteal phase. Viewed in this background, the fall of endogenous P level with exogenous P therapy *is to be regarded as very sharp.* It probably indicates that with this dose of exogenous P, ovulation and the formation of corpus luteum stopped.

It is too early to comment on the site of action of P. However, considering, the effects of P on EEG and a report that respiration stimulating effect of P in cat may be of hypothalamic orgin (8), one suspects brain may be a major site of action of P.

Most changes due to P however, wane with time although P continues to be administered. At this stage, its explanation can be only speculative, eg, (i) tolerance or tachyphylaxis against P or (ii) some (unknown) compensatory mechanisms or (iii) manifestation of some delayed effects of P superceding the initial effects and so on.

The standard practice of P therapy for DUB in Calcutta, is to administer P for one cycle. We were not inclined to break the usually routine protocol and therefore we could not study several cycles. However, in a pioneer study like this, study of one cycle gives some rough guidelines, on the basis of which studies on several cycles in future can be made.

Finally, in the previous report (1), we used Primolute N (norethisterone) or Farlutal (medroxy progesterone). The new crop of findings reported in this paper may be due to change of the preparation.

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