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Effect of Oral Contraceptive Therapy on the Hypothalamic Pituitary Adrenal Axis in Normal Females as Assessed by Dynamic Tests

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Abstract : The effect of oral contraceptive therapy (OC) of the combined type on the functional integrity of the hypothalamic pituitary adrenal axis (HPA) has been investigated by means of standard dynamic tests. Intravenous insulin stimulation tests, estimation of urinary free corticoids, metyrapone tests for pituitary reserve capacity, and ACTH stimulation tests, have been performed on 25 control and 52 test subjects. The results indicate an impairment of the cortisol response to insulin hypoglycaemia in subjects on OC therapy especially where such therapy has been continued for 5 years or more. However, the response returned to normal within 6 months of discontinuation of therapy. No differences were found between the control and test subjects in respect of responses to the other tests mentioned with the exception of a markedly exaggerated 11-deoxy cortisol (Compound S) response to metyrapone stimulation in the test subjects. This may be explained on the basis of an increase in plasma binding protein concentration provoked by OC therapy. It is concluded that OC therapy especially if long continued has a temporary inhibitory effect on hypothalamic function but no direct inhibitory effect on the adrenal cortex itself.

1. Introduction

The object of the research was to investigate a possible effect on the HPA axis from the use of oral contraceptives, of the "combined type", especially if long continued.

Subjects: All tests were carried out on informed volunteers. 25 control subjects of age group 20-40 years were obtained from University staff and from amongst subjects at the Family Planning Clinic who were fitted with intrauterine contraceptive devices and had never taken the oral contraceptive (OC) pill. 52 test subjects of age group 21-47 years were studied. The duration of therapy was for a continuous period of between 1 and 10 years. The oral contraceptive used was always of the "combined type" and in the vast majority of cases was "Ovulen 50" (the standard pill issued at the Kandy Family Planning Clinic), containing 1 mg ethynodiol diacetate and 50 mcg ethinyloestradiol. All subjects were adjudged to be normal and healthy by a general clinical examination which included urinanalysis, and measurement of haemoglobin concentration and blood pressure.

2. Methods

The following investigations were performed:

i. Intravenous insulin stimulation tests. By the administration of 0.15 i.u. soluble insulin per kg body weight following an overnight fast.[10] The test was performed initially on all 25 control and 52 subjects. Following this, 15 of the test subjects who had been on OC therapy for 5 years or more had the therapy discontinued and the test repeated 6 months after.

Blood was withdrawn into heparinised tubes at 0, 30, 60, 90 and 120 minutes, the plasma separated and stored at -20°C. Plasma cortisol was estimated in all samples by protein binding saturation assay.[17] Blood glucose was measured in every sample by the micro-method of Folin and Malmros, to ensure that a level below 40mg per 100ml was achieved in all cases included in the study.

ii. Estimation of urinary "free" corticoid excretion in 24 hour collections of urine from 15 control and 15 test subjects, by the method of Hsu and Bledsoe,[8] slightly modified. The procedure involved extraction with dichloromethane, acid and alkaline washing, and protein binding assay of the dried extract.

iii. Metyrapone, "Metopirone", tests. On 12 control and 14 test subjects by the method of Liddle *et al.*[12] 750mg metyrapone was administered 4 hourly for one day to each subject and a blood sample taken 4 hours after the last dose. Plasma 11-deoxy cortisol (Compound S) and cortisol (F%) concentration was measured in pre- and post-metyrapone samples, the former by a method based on that of Meikle *et al.*[13] The method differed from the original in that dextran coated charcoal was used as adsorbant and the separation of compound S from cross reacting steroids was achieved by column chromatography using Sephadex LH-20 and a cyclohexane : ethanol, 80 : 20 v/v solvent system.[21]

iv. Corticotrophin (ACTH) stimulation tests. On 6 control and 6 test subjects by the method of Wood *et al*[25] 0.25 mg synthetic ACTH "Synacthen" (Ciba) was administered i.m. and plasma samples taken for cortisol assay at 0, 30, 60, 90 and 120 minutes.

3. Results

I. I. V. Insulin Tests

The plasma cortisol response to insulin hypoglycaemia in the 25 control subjects are shown in Table 1. The mean basal cortisol concentration was 6.52 ± 1.2 (S.D.) mcg 100 ml and the maximum mean value (at 90 minutes) 13.14 ± 3.16 per mcg per 100 ml. When individual responses were considered, the percentage increase of cortisol concentration over basal values was found to be 113.16 ± 32.48% (range 74-195%).

TABLE 1. Cortisol (F) Responses to Insulin Hypoglycaemia in Control Subjects

No.	Age in yrs.	Weight in kgs.	Cortisol μg/100 ml. plasma					% Increase in F concentration
			0	30"	60"	90"	120"	
1	43	40	5.0	5.5	08.9	12.6	11.6	152
2	38	42	5.8	7.6	07.9	10.9	14.2	145
3	25	43	7.5	9.5	16.0	08.9	08.5	74
4	30	40	5.5	6.0	07.4	10.4	09.6	89
5	45	50	5.7	9.2	14.6	14.2	13.6	156
6	38	43	4.6	6.0	10.0	10.0	09.7	117
7	35	46	6.1	6.2	11.4	12.0	11.6	97
8	27	37	7.7	7.9	13.6	14.1	13.2	82
9	30	37	8.1	8.6	15.0	14.6	14.0	85
10	39	44	6.6	9.2	10.4	12.0	11.2	82
11	21	38	5.7	6.1	07.9	10.9	10.6	91
12	30	30	6.6	7.4	09.2	16.2	14.4	145
13	35	45	7.0	8.1	10.4	14.4	13.3	106
14	36	50	10.4	12.4	17.9	24.1	20.6	141
15	29	47	6.8	6.1	11.4	15.2	16.2	171
16	27	44	7.7	10.2	14.5	15.0	14.1	95
17	24	49	6.1	8.2	11.6	12.0	11.7	97
18	26	37	5.5	5.9	10.6	10.2	09.7	93
19	21	39	6.9	6.4	11.1	13.6	13.0	97
20	27	46	7.4	7.1	12.6	12.9	13.7	85
21	34	44	5.7	9.6	14.9	16.8	15.2	195
22	22	52	8.1	9.9	16.0	14.5	14.2	98
23	23	50	5.0	5.1	08.8	09.9	11.6	132
24	27	37	6.9	6.4	11.7	12.4	11.7	79
25	24	45	4.9	5.3	08.0	10.6	10.9	116
		Mean	6.52	7.59	11.69	13.14	12.69	113.16
		S.D.	1.26	1.89	2.83	3.13	2.58	32.48

The results obtained from the initial experiments on the 52 subjects on OC therapy are shown in Table 2. The basal value, 8.33 ± 1.87 mcg/100ml was significantly different from that of the control subjects ($P < 0.001$). The mean maximal value (at 90 minutes) was 12.71 ± 3.90 mcg per 100 ml. The mean percentage increase of cortisol concentration, calculated from each individual response, was 68.87± 44.29%. The difference between this and the value given above for the control group is highly significant, ($P < 0.001$).

TABLE 2. Cortisol (F) Responses to Insulin Hypoglycaemia in Test Subjects

No.	Age in yrs.	Weight in kg.	Duration of OC therapy in yrs	Cortisol responses to i.v. insulin					% Increase of F
				0	30''	60''	90''	120''	
1	40	52	5	6.3	6.1	7.8	6.2	6.0	24*
2	25	47	1	6.2	6.9	10.7	12.1	9.0	95
3	28	36	6	7.1	6.5	9.0	10.2	10.0	44*
4	41	52	5	6.9	8.0	8.7	9.9	9.2	44*
5	39	43	5	7.0	6.5	6.3	9.1	7.8	30*
6	35	56	3	6.5	6.6	14.4	10.4	9.2	121
7	29	42	6	6.0	8.8	7.0	6.0	6.5	15*
8	30	46	4	5.6	7.4	10.7	8.2	8.0	91
9	34	45	8	11.2	13.8	15.9	15.8	18.4	64*
10	33	47	8	9.0	10.0	14.0	11.3	12.0	55*
11	28	46	6	10.5	11.0	12.8	12.7	16.7	59*
12	27	38	4	8.4	11.3	15.5	13.8	11.7	84
13	38	48	4	10.0	10.4	17.5	15.5	15.2	75*
14	29	50	4	10.1	9.4	10.1	15.0	17.6	75*
15	26	43	1	6.6	9.0	18.6	15.5	12.5	181
16	35	44	9	12.0	13.8	15.4	15.4	15.8	32*
17	35	41	8	13.0	13.0	17.5	14.5	13.0	35*
18	27	42	4	11.5	13.6	20.7	22.7	17.6	92
19	47	57	8	11.0	9.9	14.0	16.0	14.0	45*
20	30	51	4	10.8	8.4	18.8	24.6	22.1	127
21	43	42	4	8.0	11.3	11.6	13.0	15.5	94
22	32	53	4	5.6	5.0	6.3	6.2	5.7	11*
23	28	55	8	9.8	11.3	11.5	9.2	8.6	17*
24	39	53	7	8.9	8.1	8.9	9.4	9.7	9*
25	30	57	7	10.0	11.0	9.8	8.8	8.8	10*
26	33	46	3	7.0	8.0	10.2	14.2	9.8	103
27	36	44	3	7.5	9.5	13.0	8.9	8.5	74*
28	32	41	4	5.5	6.0	7.4	10.4	9.6	89
29	30	53	6	8.3	8.1	9.0	13.2	15.2	73*
30	24	52	2	5.0	6.6	10.4	11.0	10.2	120
31	43	40	9	11.1	11.2	10.9	10.2	11.0	1*
32	22	47	3	7.0	7.6	11.4	12.9	11.3	84
33	28	51	4	5.3	7.6	10.1	10.6	10.3	94
34	34	56	7	9.1	10.1	9.4	9.9	10.4	14*
35	27	56	4	7.2	7.6	12.4	14.9	12.1	107
36	40	42	10	8.9	8.6	10.1	10.9	10.0	22*
37	33	47	8	10.4	10.4	13.2	14.6	12.6	40*
38	37	50	6	8.1	9.4	15.6	16.9	14.0	108
39	21	55	1	6.1	7.7	12.9	14.6	15.3	151
40	36	29	5	7.6	8.0	12.9	16.8	14.4	121
41	34	44	6	8.8	9.4	10.9	10.9	10.2	24*
42	24	57	2	8.0	8.9	15.6	20.2	16.4	152
43	22	51	2	6.4	8.1	12.6	13.0	12.2	103
44	35	57	8	9.2	9.0	11.1	11.6	10.7	26*
45	29	49	5	8.8	8.8	9.7	11.2	9.7	27*
46	26	50	4	6.6	7.1	10.0	9.7	8.8	52*
47	29	57	3	7.7	8.2	12.6	15.9	14.6	106
48	33	55	3	8.0	7.7	12.2	17.4	17.4	117
49	45	44	7	10.6	10.0	11.4	10.7	10.7	98*
50	36	48	6	8.6	8.6	11.7	13.0	13.0	98
51	30	42	5	7.9	7.7	9.4	9.6	9.0	22*
52	27	54	4	8.8	9.4	13.0	16.7	18.4	111
			Mean	8.33	8.97	11.96	12.71	12.04	68.87
			S.D	1.87	2.00	3.10	3.90	3.47	44.29

* Denotes impaired response

An examination of the results from the test subjects reveals that 29 of the 52 yield responses that are, in terms of percentage increase of cortisol over basal value, less than one standard deviation below the mean control value; that is, an increase of less than 81 % over basal value. Of these, 24 had been on OC therapy for a continuous period of 5 years or more. Of a total of 27 subjects who had been on OC therapy for this length of time, only 3 yielded normal responses. On the other hand, of 15 subjects who had been on OC therapy for less than 5 years, only 5 yielded responses that could be considered impaired according to the above criteria. It seemed reasonable therefore to break-up the results from the test subjects into 2 groups; those who had been on OC therapy for less than 5 years and those who had OC therapy for 5 years or more.

The results are shown in Table 3. The mean percentage increase in cortisol concentration in Group A (less than 5 years OC therapy) is 100·56 ± 33.48% over basal values. The response is within the normal range as previously defined but is significantly different to that in the control group ($P < 0.1$).

TABLE 3. Cortisol (F) Responses to i. v. insulin in subjects on OC therapy for less than 5 years (Group A) and 5 years or more (Group B)

		F in mcg / 100 ml.					% Increase in F
		0	30′	60″	90″	120″	
Group A	Mean	7.79	8.37	12.47	13.85	12.58	100.56
n = 25	S.D.	0.83	1.88	3.30	4.42	4.01	33.48
Group B	Mean	9.13	9.53	11.25	11.63	11.20	39.66
n = 27	S.D.	1.78	1.98	2.87	2.92	2.87	30.91

Difference between Group A and Control Group significant at p = 0.1
Difference between Group B and Control Group significant at p = 0.0005
Difference between Group A and Group B significant at p = 0.001

The subjects in Group B show a markedly impaired response with a mean percentage increase of cortisol concentration of only 39.66 ± 30.91% over basal values. These subjects also show significantly different responses to those in Group A, ($P < 0.001$).

15 subjects who had previously been on OC therapy for over 5 years and had shown impaired response to i.v. insulin on initial testing had the therapy discontinued and the test repeated 6 months after. The results are shown in Table 4. The mean basal value is 8.85±1.79 mcg per 100ml, which is not significantly different ($t=0.78$) from the the mean basal values calculated for these same subjects while they were on OC therapy, (9.88 ± 3.7 mcg per 100ml).

Two subjects still showed a markedly impaired response to i.v. insulin, in terms of percentage increase of cortisol concentration over basal values, and in two other cases the response was marginally impaired. The mean percentage increase of cortisol concentration, however, is 96.00 ± 24.04 which is within the normal range as derived from the control group.

TABLE 4. Cortisol (F) Responses to i. v. insulin 6 months after discontinuation of OC therapy in subjects who have had OC therapy for five years or more

Subject No.	Duration of OC therapy in years.	Plasma Cortisol mcg/100 ml					% Increase in F Concentration
		0	30''	60''	90''	120''	
3	6	7.4	7.1	16.3	15.1	12.2	120
7	6	6.4	6.8	11.6	12.9	11.8	102
9	8	5.0	4.7	9.4	9.8	7.4	96
10	8	7.7	8.1	13.4	17.5	16.2	127
16	9	8.8	9.6	14.2	15.7	15.6	78*
17	8	11.2	11.0	15.4	15.8	15.5	41*
19	8	9.9	10.2	18.1	16.6	16.0	68*
23	8	10.6	10.0	19.2	22.4	18.9	111
25	7	9.5	9.0	16.2	18.3	15.4	101
31	9	9.0	9.2	15.4	16.8	16.0	89
34	7	8.6	8.8	15.9	17.1	16.3	90
36	10	8.0	7.7	12.9	15.9	15.7	99
37	8	11.6	14.1	20.9	20.4	17.2	76*
44	8	8.8	7.9	19.4	18.2	15.6	107
49	7	10.3	9.4	20.7	24.2	17.6	135
	Mean	8.85	8.91	15.93	17.11	15.16	96.0
	S.D.	1.79	2.13	3.33	3.51	2.79	24.04

*Denotes impaired response.

Differences from control group not significant, $t = 0.57$

II. Urinary "Free" Corticoids

Urinary "free" corticoids excretion in 15 control and 15 test subjects, in 24 hour collections of urine, are shown in Table 5. The mean values in the control group was 45.0 ± 12.35 mcg per 24 hours, and in the treated group 49.27 ± 8.89. The difference between these two values is not significant.

TABLE 5. Urinary free corticoid excretion in control and test subjects

Control Subjects		Test Subjects		
Subject No.	Cortisol mcg/24 hr.	Subject No.	Duration of O.C therapy. (in years)	Cortisol mcg/24 hr.
1	26	2	1	56
3	55	4	5	27
4	63	7	6	44
6	47	8	4	40
8	52	13	4	49
12	41	16	9	49
13	24	20	4	46
14	30	21	4	45
17	33	22	4	38
19	49	25	7	68
20	41	29	6	48
21	50	35	4	61
22	64	38	6	44
24	49	41	6	58
25	51	43	2	56
Mean	45.00	49	7	49.27
S.D	12.35			8.89

The difference between control and test subjects is not significant.

III. Metyrapone "Metopirone" Tests

The results are shown in Table 6. The decrease in cortisol concentration following metyrapone is by 62.64 ± 19.92 % in the control subjects and by 61.33 ± 23.96 in the test subjects. This difference is not significant.

The Compound S response on the other hand is markedly exaggerated in the subjects on OC therapy and is seen in all cases, irrespective of the duration of therapy. Following metyrapone administration, the mean response of Compound S in the control subjects was a plasma concentration of 7.98 ± 2.03 mcg per 100ml, and in the test subjects a plasma concentration of 12.41 ± 2.41 mcg per 100ml. The difference between these two responses is highly significant ($P < 0.001$).

TABLE 6. Cortisol (F) and 11-deoxy Cortisol (S) Responses to Metyrapone

Control Subjects						Test Subjects					
Pre-Metyrapone			Post-Metyrapone			Pre-Metyrapone			Post-Metyrapone		
No.	F	S	F	% Fall in F	S	No.	F	S	F	% Fall in F	S
5	6.0	—	2.6	57	11.4	2	6.5	—	0.5	76	15.9
7	6.6	—	1.1	83	6.8	4	7.2	—	1.1	85	12.4
10	6.0	—	0.5	92	5.6	7	5.6	—	2.6	54	16.4
14	10.0	—	3.1	69	9.2	8	5.9	—	1.0	83	9.9
21	6.1	—	2.0	64	6.1	13	9.4	—	7.1	24	11.6
22	8.8	—	0.5	94	9.6	16	11.7	—	3.9	67	12.0
24	7.2	—	5.1	29	5.5	20	10.2	—	5.0	51	11.9
26*	7.9	—	4.0	49	8.9	21	8.0	—	2.4	70	14.9
27*	8.1	—	2.6	68	9.4	22	6.1	—	2.7	56	9.4
28*	6.8	—	4.6	32	10.1	25	10.6	—	3.0	72	12.6
29*	7.0	—	3.3	53	9.4	29	7.7	—	1.4	82	10.9
30*	6.4	—	2.2	66	8.4	35	7.2	—	2.0	72	15.8
31*	8.8	—	2.2	75	4.9	41	9.1	—	2.9	68	11.6
32*	7.2	—	3.9	46	6.4	43	8.4	—	3.4	60	9.3
Mean	7.35	—	2.62	62.64	7.98**	Mean	8.11	—	2.75	61.33	12.42**
S.D	1.22	—	1.54	19.92	2.03	S.D.	1.90	—	1.79	23.96	2.41

All results as mcg/100 ml plasma.

* Subjects 22 - 32 did not have i.v. insulin stimulation or other tests.

** Difference in compound S response in control and test subjects significant at $p = 0.0005$.

IV. ACTH Stimulation

The results are shown in Table 7. The control subjects show a mean response of plasma cortisol concentration from a mean basal value of 6.50 ± 0.58 mcg per 100 ml to a mean maximal value of 17.73 ± 1.03 mcg per 100 ml. The percentage increase of cortisol concentration over basal value, calculated from each individual response, is 190.16 ± 30.5% (range 145% - 229%). The subjects on oral contraceptive therapy show a mean rise from 7.62 ± 1.89 mcg per 100 ml to maximal value of 17.25 ± 2.76, a percent increase from basal value by 167.33 ± 37.06% (range 107% - 213 %). The difference between the responses obtained from the control and treated groups is not significant ($P < 0.15$).

TABLE 7. ACTH Stimulation Test in Control and Test Subjects

Control Subjects							Test Subjects						
	Plasma Cortisol, mcg/100 ml					% Increase in F		Plasma Cortisol, mcg/100 ml					% Increase in F
No.	0	30''	60''	90'	120''		No.	0	30''	60''	90'	120''	
6	5.7	9.2	16.4	17.3	16.6	203	2	6.9	10.6	16.6	20.4	18.8	196
8	7.6	12.0	18.6	16.4	14.0	145	21	8.4	15.6	21.8	17.4	16.6	160
13	6.2	10.0	15.0	17.2	17.4	181	22	6.0	9.0	12.2	16.2	14.5	170
17	7.0	11.5	19.0	18.8	17.3	171	24	8.2	12.0	15.0	15.0	13.6	158
23	6.6	9.4	14.7	17.9	20.6	212	8	5.5	10.0	17.2	16.2	16.0	213
25	5.9	9.9	14.6	18.8	19.4	229	13	10.7	14.9	22.2	20.6	18.4	107
Mean	6.50	10.33	16.38	17.73	17.55	190.16	Mean	7.62	12.01	16.90	17.25	16.32	167.33
S.D.	0.58	2.18	2.02	1.03	2.29	30.5	S.D.	1.89	2.73	3.02	2.76	1.99	37.06

The difference between the control and test subject responses is not significant ($p = 0.15$).

4. Discussion

The main experimental observations made in this study may be summarised as follows:

1. Subjects on oral contraceptive therapy show significantly elevated basal levels of plasma cortisol as compared to a control group. This elevation is more marked in those who have had OC therapy for 5 years or more.
2. In subjects who had oral contraceptives discontinued after 5 years or more of therapy, basal plasma cortisol values had not fallen to those comparable with values from a control group even at the end of 6 months.
3. Subjects on OC therapy show an impaired response to insulin-induced hypoglycaemia, as judged by increase in plasma cortisol concentration, when compared to normal controls. This effect is also more marked in those who have had therapy for 5 years or more.
4. In subjects who had been on OC therapy for 5 years or more, the cortisol response to insulin hypoglycaemia returned to within normal limits 6 months after therapy was discontinued.
5. No significant differences were seen between the control and treated subjects in regard to urinary 'free' corticoid excretion or in the adrenocortical response to acute stimulation with synthetic ACTH.
6. A markedly exaggerated Compound S response to metyrapone stimulation in all subjects on OC therapy, irrespective of the duration of such therapy, was obtained.

Oral contraceptives are known to produce their effect by depression of the hypothalamic pituitary system.[6] Oestrogens depress FSH secretion and progestins abolish the midcycle peak of LH, although basal values of LH are not affected. Progestins are known to increase and oestrogens to diminish the threshold of excitability of the brain, in a manner dependant on the progestin: oestrogen ratio in the "combined" type of oral contraceptive pill.

Basal a.m. values of plasma cortisol in subjects on OC therapy are known to be increased,[6,16] and this is supported by the findings in this study. In 15 subjects who had OC therapy discontinued after a period of 5 years or more, the mean basal plasma cortisol concentration, 6 months later, was seen to fall in comparison to what it previously was in the same subjects, but was still significantly elevated from normal. This is in agreement with previous findings in which it has been shown that the elevated plasma cortisol values seen in subjects on OC therapy took longer to return to normal on discontinuation of the drug than similarly elevated values seen in pregnancy which rapidly returned to normal following delivery.[5]

In a previous study, the cortisol response to hypoglycaemia induced by insulin infusion were studied in a group of subjects on OC therapy for one year or more. Insulin was infused intravenously at a rate of 22 milli units per minute and the infusion rate doubled every half an hour over a $2\frac{1}{2}$ hour period.[19] A blunted response in regard to both time and magnitude of plasma cortisol increase was observed in the treated group. In the present study, this impaired response is seen in the standard i.v. insulin stimulation test as well, particularly in those who have had OC therapy for 5 years or more.

Conflicting reports on Compound S responses to metyrapone in subjects on OC therapy may reflect differences in techniques employed for the test. Some early reports indicate reduced responses to metyrapone, and impairment of pituitary adrenal function is suggested.[11,15] Other workers,[14] however, report exaggerated responses both to metyrapone administered as in this study, and to a single high dose given at midnight. [24] ACTH responses were also measured and found to be sub-normal, which effect was ascribed to increased hepatic conjugation of metyrapone in the subjects on OC therapy resulting in diminished blood level and therefore insufficient blocking effect on cortisol synthesis at the level of the adrenal cortex.[14] The enhanced compound S response was explained as being due to increased binding capacity of plasma proteins to Compound S provoked by oestrogen administration.[2,14] ACTH has not been measured in this study but the enhanced responses of Compound S in the test subjects is amenable to a similar explanation. It may, however, be mentioned that some recent work seems to suggest an "extra-adrenal" effect of metyrapone in causing inhibition of cortisol binding to plasma protein and reducing the half life of cortisol to about a 6th of the normal value. It is possible that this would apply in the case of Compound S binding to plasma protein as well.

Oestrogen even in low dosage may affect the hepatic enzyme systems controlling cortisol metabolism.[18] On the other hand, only a trivial increase of plasma "free" cortisol is reported in subjects on OC therapy.[4] In the present series, no significant difference is seen in urinary free corticoid excretion rates between control and treated subjects, irrespective of the duration of OC therapy. Although no studies with infusion of exogenous cortisol and estimation of half life has been done, this may be taken as evidence that cortisol metabolism itself is not significantly altered in subjects on OC therapy.

Finally, the normal response to acute administration of ACTH seen in both control and treated subjects would indicate no impairment of adrenocortical reserve capacity resulting from OC therapy, as judged by this procedure.

Plasma cortisol responses to insulin hypoglycaemia and Compound S responses to metyrapone usually parallel each other,[10] but the present investigation reports a situation where these are dissociated, in the case of subjects on OC therapy.

Varying disturbances of pituitary function with OC therapy have been reported. Increased Growth Hormone levels have been found,[23] as also an augmented pituitary TSH response to intravenous TRH.[20] Oral contraceptives are reported to have a depressant effect on lactation, even when this is established.[3] Other reports suggest an effect at hypothalamic level. Certain oral contraceptives do not block the stimulant effect of Luteinising Hormone Releasing Hormone (LH-RH) on the pituitary and may therefore act on the hypothalamus.[9] Amenorrhoea following prolonged inhibition of FSH and LH release by oral contraceptives is considered to be a hypothalamic effect,[22] and galactorrhea with prolonged OC therapy also suggest an effect on the hypothalamus or central nervous system.[7]

In the present study the most striking differences between the control and treated subjects is in the cortisol response to insulin hypoglycaemia, which stimulus is known to act at the level of the hypothalamus. The other differences found, namely, increased basal level of cortisol and enhanced Compound S response to metyrapone, may be explained on the basis of an increase in the concentration of plasma binding protein provoked by OC therapy. Cortisol metabolism does not seem to be altered, nor does there seem to be a direct inhibitory effect on the adrenal cortex. It is open to suggestion therefore that oral contraceptive therapy, especially if long-continued, exerts a depressant effect on hypothalamic function, as judged by the cortisol response to acute insulin hypoglycaemia. This effect is probably a temporary one as evidenced by the series of subjects who had the test repeated 6 months after dissociation of OC therapy yielding essentially normal responses.

This effect is unlike the effect produced by acute administration of dexamethasone which causes complete inhibition of the Compound S response to metyrapone.[13] It is possible that the effect could be further investigated by carrying out dynamic tests of the HPA axis following acute administration of the separate constituents of the OC pill given in large doses over short periods of time. However, this would be difficult in practice and also ethical aspects of this procedure in normal females would be very much open to question. Nevertheless, the results could be further investigated by carrying out dynamic tests of the HPA axis following acute administration of the separate constituents of the OC pill in larger doses over short periods of time.

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