

Carbohydrate Metabolic Studies After Six Cycles of Combined Type Oral Contraceptive Tablets

Measurement of Plasma Insulin and Blood Glucose Levels

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SUMMARY

Thirty-two normal subjects were studied before and at the end of six cycles of treatment with a combined type of oral contraceptive. The tests involved measurement of blood glucose and plasma insulin levels during an intravenous glucose tolerance test. It was found that the mean blood glucose values were not different in the two groups. There was elevation in the plasma insulin levels in the drug treated group, but the degree of elevation could not be correlated with either familial history of diabetes mellitus or subject's weight change while taking the drug. *DIABETES* 16:590-94, August, 1967.

A previous report described a large prospective study of changes in blood glucose and plasma insulin levels in normal women taking oral contraceptive pills.¹ This paper will present the results of intravenous glucose tolerance tests performed before drug ingestion and during the sixth drug treatment cycle in thirty-two subjects who were receiving 5 mg. Enovid* tablets containing norethynodrel and mestranol.

METHODS

Thirty-two healthy volunteer women, all more than six weeks postpartum, were selected for this study. All gave an adequate dietary history and were not receiving other medications. A complete history was obtained of previous pregnancies, infant birth weights and familial incidence of known diabetes mellitus in either parents or grandparents. No siblings of the subjects had diabetes. Each subject was weighed before each test. Each subject was tested prior to receiving the drug. They were then given 5 mg. Enovid tablets taken in

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*Supplied as Enovid by the G. D. Searle Company, Chicago, Illinois.

the usual cyclic manner and receiving twenty tablets in each cycle. All were then retested on the tablet day 18-20 of the sixth treatment cycle. Thus, in this prospective study, every subject had a pretreatment test to serve as the control.

The test procedure itself has been previously described.¹ Briefly, the tests were all begun before 0900 after an overnight fast. During the test physical activity was limited to sitting. A fasting venous blood sample was drawn, and then 25 gm. of glucose were injected intravenously over a two-minute interval. Blood samples were drawn at 0.25, 0.5, 1 and 2 hrs. after the injection. The blood glucose was measured by the method of Nelson and Somogyi.^{2,3} The plasma insulin was measured by a double antibody radioimmunoassay technic as described by Goetz et al.⁴

As the data consisted of correlated pairs, statistical analysis was made by studying the means and standard errors, the differences, the means of the differences, Student's *t* score, and the probability of occurrence of each *t* score.

RESULTS

Blood glucose

The individual blood glucose values are shown in table 1.

The blood glucose averages are plotted in figure 1 and are shown in table 2. It can be seen that the mean values of the two groups are not different. It should also be noted that some of the individuals have a glucose elevation and some have a decrease after drug therapy but no consistent change is seen for the group data.

Plasma insulin

The individual plasma insulin values are shown in table 3.

The plasma insulin averages are shown in table 4 and the averages plotted in figure 2. It should be noted that all mean values are significantly higher in the drug treated group.

TABLE 1
Individual blood glucose values for the thirty-two subjects before and in the sixth cycle of Enovid treatment

Subject number	Glucose values in mg./100 ml.									
	Control (hours)					Sixth cycle Enovid (hours)				
	F	0.25	0.5	1	2	F	0.25	0.5	1	2
1	79	249	170	88	77	86	241	175	96	66
2	85	211	119	62	82	84	220	167	92	79
3	83	212	131	70	75	94	243	183	142	110
4	64	221	151	71	65	76	207	170	119	81
5	80	262	207	133	76	84	263	226	163	82
6	82	192	133	80	68	87	192	155	116	87
7	88	270	217	133	67	93	255	208	141	89
8	70	261	224	165	83	89	265	205	132	69
9	87	218	135	66	62	71	170	118	76	72
10	93	200	110	73	80	74	182	72	52	77
11	77	216	124	61	66	83	201	154	96	75
12	72	184	89	56	78	77	273	181	72	81
13	78	239	153	63	76	89	202	147	89	87
14	72	234	124	50	59	79	218	138	72	71
15	79	235	203	80	69	92	233	117	58	77
16	85	243	186	114	77	87	260	185	102	72
17	83	225	144	72	77	74	216	155	92	71
18	84	233	194	134	78	85	218	167	92	78
19	79	224	172	107	68	76	199	116	65	72
20	82	237	156	87	71	85	230	149	65	69
21	85	241	144	69	65	75	239	166	87	63
22	78	228	181	112	68	68	230	182	97	64
23	83	265	193	140	68	80	275	198	100	71
24	80	218	160	85	79	74	202	149	95	76
25	88	169	147	85	87	86	205	130	80	84
26	111	235	174	112	91	93	208	120	88	76
27	79	219	151	78	65	75	222	151	78	59
28	74	212	136	71	67	79	224	174	100	75
29	78	193	98	52	76	not valid	210	155	84	87
30	95	230	171	95	76	78	221	124	72	68
31	79	275	219	133	60	75	255	190	114	62
32	85	257	198	121	74	81	237	124	51	72
Mean	82	228	160	91	73	82	226	158	93	76
±S.E.	1.5	4.4	6.3	5.3	1.4	1.3	4.7	5.8	4.6	1.8

Data correlation

In table 5 are shown the patients' family diabetes history and the subjects' weights at each testing. An analysis was made of the correlation coefficients between these variables and the changes in the blood glucose levels or the changes in the plasma insulin levels. No significant correlations were found. The mean weight change was minus one-half pound with a standard error of 1.107 (*t* 0.45, *p* not significant). Only one subject, No. 9, had delivered an infant whose birth weight was greater than nine pounds.

DISCUSSION

Many alterations have been observed in subjects receiving oral contraceptives. Previous studies of blood glucose levels in subjects receiving oral contraceptive drugs have already been reviewed.¹ Generally, these cross-sectional studies have noted more elevated glucose values in the drug treated groups than in the control

TABLE 2

Statistical studies of blood glucose levels in mg./100 ml. before and during the sixth month of Enovid (N = 32)

Time (Hours)	Control					Enovid				
	F	0.25	0.5	1	2	F	0.25	0.5	1	2
Mean	81.8	228.4	159.8	91.2	72.8	81.6	225.5	157.8	93.1	75.7
S.E.	1.5	4.4	6.3	5.3	1.4	1.3	4.7	5.8	4.6	1.8
<i>r</i>	0.111	0.663	0.288	-0.339	1.509					
<i>p</i>	not significant									

groups. Many unsolved questions remain, however, such as: How high will these levels go with prolonged treatment; What type of individual is most susceptible to these alterations; and will the levels return to their pre-treatment values when the drug is discontinued? In attempts to answer these questions, the present long-term

TABLE 3
Individual plasma insulin values for the thirty-two subjects before and during the sixth cycle of Enovid treatment

Subject number	Values in $\mu\text{U./ml.}$										
	F	Control (hours)					F	Sixth cycle Enovid (hours)			
		0.25	0.5	1	2	0.25		0.5	1	2	
1	10	67	18	15	10	22	120	89	56	15	
2	22	150	64	19	13	18	105	96	40	20	
3	28	155	46	28	31	28	135	89	47	29	
4	8	54	31	13	13	10	26	23	20	11	
5	15	38	42	30	17	15	58	49	63	17	
6	8	24	21	12	7	10	19	20	17	13	
7	10	40	30	30	12	18	61	44	40	15	
8	12	45	33	25	26	87	123	90	48	17	
9	11	52	38	15	14	15	47	38	18	14	
10	71	195	54	33	64	71	220	350	75	72	
11	17	61	40	17	20	23	73	45	36	17	
12	25	75	39	21	14	12	140	99	39	11	
13	18	48	47	18	16	20	54	49	28	20	
14	25	32	53	21	16	29	56	45	32	18	
15	11	79	56	122	15	44	72	37	30	12	
16	15	47	30	33	14	25	90	82	52	25	
17	12	110	69	24	15	25	108	76	49	23	
18	10	26	32	31	13	12	32	32	24	12	
19	21	79	54	45	20	30	120	86	75	29	
20	16	57	37	19	8	17	54	47	27	22	
21	39	185	103	42	47	66	400	190	70	49	
22	9	41	45	30	18	17	53	125	39	12	
23	12	52	82	81	36	26	315	218	95	32	
24	25	130	70	28	19	20	74	47	30	20	
25	13	42	34	no sample	21	18	69	46	18	15	
26	20	100	53	33	26	28	260	77	43	30	
27	16	77	52	22	12	21	69	53	36	13	
28	10	35	24	9	9	20	70	58	36	18	
29	13	72	29	13	13	18	105	70	30	18	
30	23	70	82	18	18	8	77	45	28	26	
31	17	62	50	35	14	23	92	65	55	33	
32	11	37	31	31	10	25	105	83	23	25	
Mean	18	73	47	29	19	26*	106*	80*	41*	22*	
\pm S.E.	2	8	3	4	2	3	15	12	3	2	

*Different from the control value at a p value of < 0.01 .

TABLE 4
Statistical studies of plasma insulin levels in $\mu\text{U./ml.}$ before and during the sixth month of Enovid (N = 32)

Time (Hours)	Control					Enovid				
	F	0.25	0.5	1	2	F	0.25	0.5	1	2
Mean	18	73	47	29	19	26	106	80	41	22
S.E.	2	8	3	4	2	3	15	12	3	2
t	2.851	2.804	3.161	2.949	2.760					
p	<0.005	<0.005	<0.005	<0.005	<0.005					

prospective study was initiated.

The present report deals only with the changes in blood glucose and plasma insulin levels after six cycles of drug ingestion. The data reveal that the group blood glucose values do not change. The plasma insulin values

are significantly elevated after six cycles of treatment. This was also demonstrated after one treatment cycle.¹ In order to determine how high these levels will go, studies of longer deviation will be necessary. This alteration is notably contrasted to that demonstrated during the normal menstrual cycle.⁵ A suggestion that high levels are maintained for some time is made from another study. In figure 3 are plotted the data from a subject treated with high doses of this drug for prolonged periods of time as therapy for endometriosis. The blood glucose values are not different, but the plasma insulin levels remain markedly elevated during treatment.

The mechanism producing these metabolic changes is as yet unknown. Frantz and Rabkin have shown that the ambulatory level of human growth hormone can be elevated by giving estrogens.⁶ The steroids of the contra-

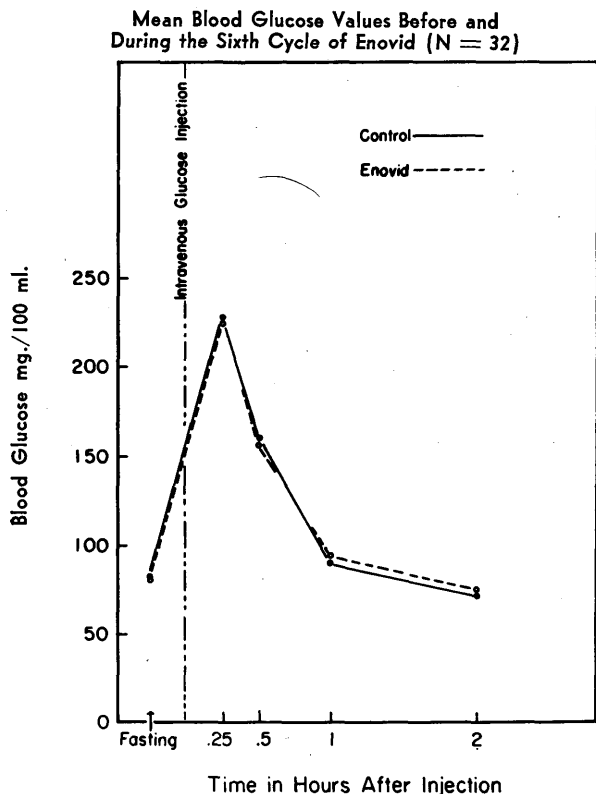


FIG. 1. Mean blood glucose values before and during sixth cycle of oral contraceptive treatment.

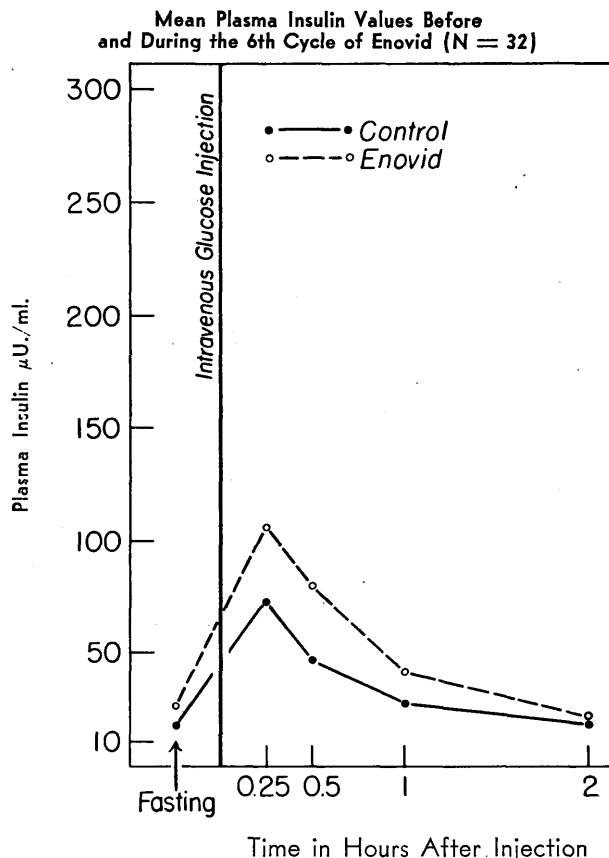


FIG. 2. Mean plasma insulin values before and during the sixth cycle of oral contraceptive treatment.

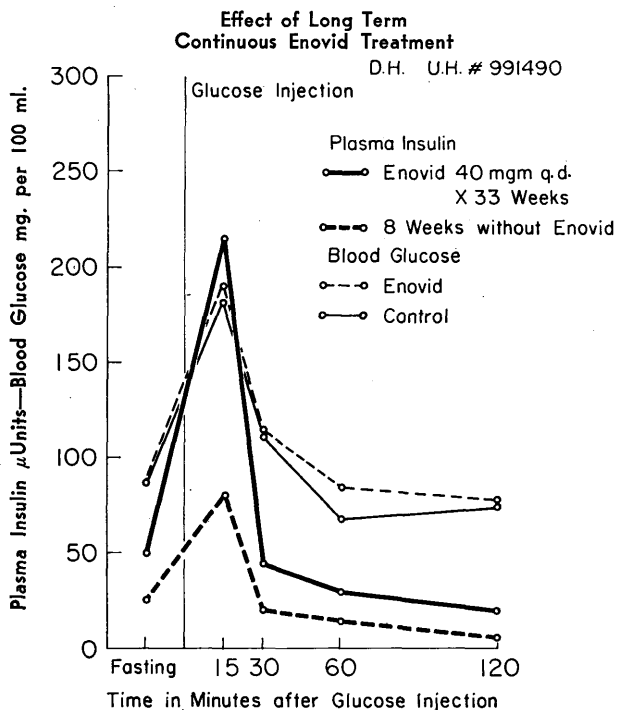


FIG. 3. Blood glucose and plasma insulin levels in a subject treated with long-term continuous Enovid administration for endometriosis.

ceptive tablets could thus be increasing the pituitary output of growth hormone and this in turn could be the active beta cell stimulant. Possibly this could be the mechanism by which the oral contraceptive tablets can alter the insulin levels. Current studies on this problem are underway.

Finally the clinical effects of these changes could be of major importance. The increased incidence of monilial vaginitis in patients taking the combined type of oral contraceptives is possibly a reflection of an altered vaginal carbohydrate milieu.⁷ The systemic effect of this altered metabolism is receiving much speculation.⁸ Any answers, however, must await further studies. It is hoped that from a large prospective study such as the one currently described information will become available concerning risks involved for the subjects treated and also which subjects are at greatest risk.

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TABLE 5
 Familial diabetic history, weight changes for the
 thirty-two subjects studied

Subject number	Weight in pounds		Family history of diabetes mellitus
	Control	Enovid	
1	115	113	+
2	123	121	+
3	145	141	-
4	123	133	+
5	146	134	-
6	190	184	+
7	113	110	-
8	139	140	-
9	120	—	-
10	141	141	+
11	140	140	+
12	122	118	-
13	119	125	+
14	124	124	+
15	125	129	+
16	124	120	-
17	163	170	-
18	136	142	-
19	141	145	-
20	122	125	+
21	114	112	-
22	141	136	+
23	126	124	+
24	170	155	-
25	125	134	-
26	161	161	-
27	131	134	-
28	134	140	+
29	131	142	-
30	131	127	+
31	114	114	-
32	116	120	-

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