CARBOHYDRATE METABOLISM IN GYNANOVLAR 21 AND LYNDIOL 2.5 USERS

By

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INTRODUCTION

In a previous study on the effect of the combined steriod contraceptives (Gynanovlar 21 & Lyndiol 2.5) on the adrenocortical activity, it was found that total plasma 17-OHCS increased in users after 3, 6, and 12 months with Lyndiol 2.5 and 6 and 12 months with Gynanovlar therapy.

Cortisol is known to increase blood glucose through gluconeogenesis, and in the presence of well functioning islets of Langerhans a normal blood glucose level is established through increased insulin secretion. Also several investigators reported abnormal glucose utilization after variable periods of contraceptive pill therapy (Spellacy and Carlson, 1966, Peterson et al, 1966, Starup et al, 1967, Beck and Wells, 1969).

To clear this point and to reveal the relationship between the changes in plasma 17-OHCS accompanying pill intake and the blood glucose levels, the effect of these two types of pills (Gynanovlar 21 and Lyndiol 2.5) on carbohydrate metabolism was studied in the same groups investigated before for plasma 17-OHCS after contraceptive therapy for variable periods.

MATERIAL & METHODS

50 healthy women were used for this study, 10 as controls not taking any type of pills, 20 were on Gynanovlar for 3, 6, and 12 months and the other 20 were on Lyndiol 2.5 for the same duration of time.

The characteristics of the control and test groups and the classification of subjects are presented in table 1.

TABLE 1

Charecteristics of the control and test groups

	Control group	Test group	G 21 users	L 2.5 users
Number of Women :	10	40	20	20
Age distribution :				
Between 20—25 years	6	26	9	17
Between 26—30 years	4	14	11	3
Parity : Number of labours :				
1 — 5	6	30	16	14
6 — 10	4	10	4	6
Number of abortions :				
No abort.	5	18	10	8
1 — 3	5	22	10	12
Average body weight in kgm.	69.3	69.4	70.3	68.45

Classification of subjects

	Gynanovlar 21				Lyndiol 2.5			Controls
	3	6	12	M	3	6	12	
No. of cases	5	5	10		5	5	10	10
Per cent	10%	10%	20%		10%	10%	20%	20%

Oral glucose tolerance tests were done to all cases. Blood glucose was measured by the method of Folin and Wu (1920), in the fasting samples as well as after, 30, 60 90, and 120 minutes of ingesting 50 gm. of glucose.

RESULTS

Oral Glucose Tolerance Test (O. G. T. T.) :

Table 2 shows the average blood glucose levels obtained in the different groups of patients. The mean fasting blood glucose levels with either Gynanovlar or Lyndiol were within the normal limits (80—120 mg./100 ml.) Thirty minutes after the glucose stimulus, there was an increase in blood glucose in all groups but the highest response was in the group using the pills for 3 months.

TABLE 2

The mean blood glucose values in the different groups

Pills used	Durat. of tr.	No. of cases	Mean levels (mg/100 ml.)				
			Fasting	30 min.	60 min.	90 min.	120 min.
Gyn. 21	3 M	5	91.2	140.6	120.1	102.2	93.8
Gyn. 21	6 M	5	90.8	134.6	123.4	108.8	96.2
Gyn. 21	12 M	10	96.2	130.0	128.3	113.0	100.0
Lyndiol 2.5	3 M	5	97.2	138.4	152.4	129.4	116.4
Lyndiol 2.5	6 M	5	96.0	132.8	131.0	113.4	98.8
Lyndiol 2.5	12 M	10	89.7	131.2	125.0	111.6	102.4

One hour after the glucose stimulus, the mean values recorded in Gynanovlar users for 3, 6 and 12 months were 120.1, 123.4 and 128.3 mg/100 ml. and in Lyndiol users 152.4, 131.0, and 125.0 mg% respectively indicating that a high response was in the group on Lyndiol 2.5 for 3 months.

After 1.5 hours, the mean values in Gynanovlar users were 102.2, 108.8, 113.0 and in Lyndiol users 129.4, 113.4, 111.6 mg/100 ml. after 3, 6 and 12 months respectively.

After 2 hours, the results in Gynanovlar users were 93.8, 96.2, 100.0 and in Lyndiol users 116.4, 98.8, 102.4 mg/100 ml. respectively. The data show clearly that the mean values obtained were within normal limits in all the groups and that the highest levels were found in Lyndiol users for 3 months.

Also data show that in case of Gynanovlar 21 (Fig. 1), the 12 month users showed a higher mean fasting level and higher mean values after 1 and 2 hours of the glucose stimulus than the other 2 groups of 3 and 6 month users. Also the 6 month users showed higher mean values than the 3 month users after 1 and 2 hours.

In case of Lyndiol 2.5 (Fig. 2), the opposite was found, the 3 month users showed higher mean values than the 6 and 12 month users.

It is of importance also to mention that in spite of the fact that all mean values obtained were within the normal limits, yet 11 cases showed deteriorated glucose tolerance, as evidenced by higher fasting

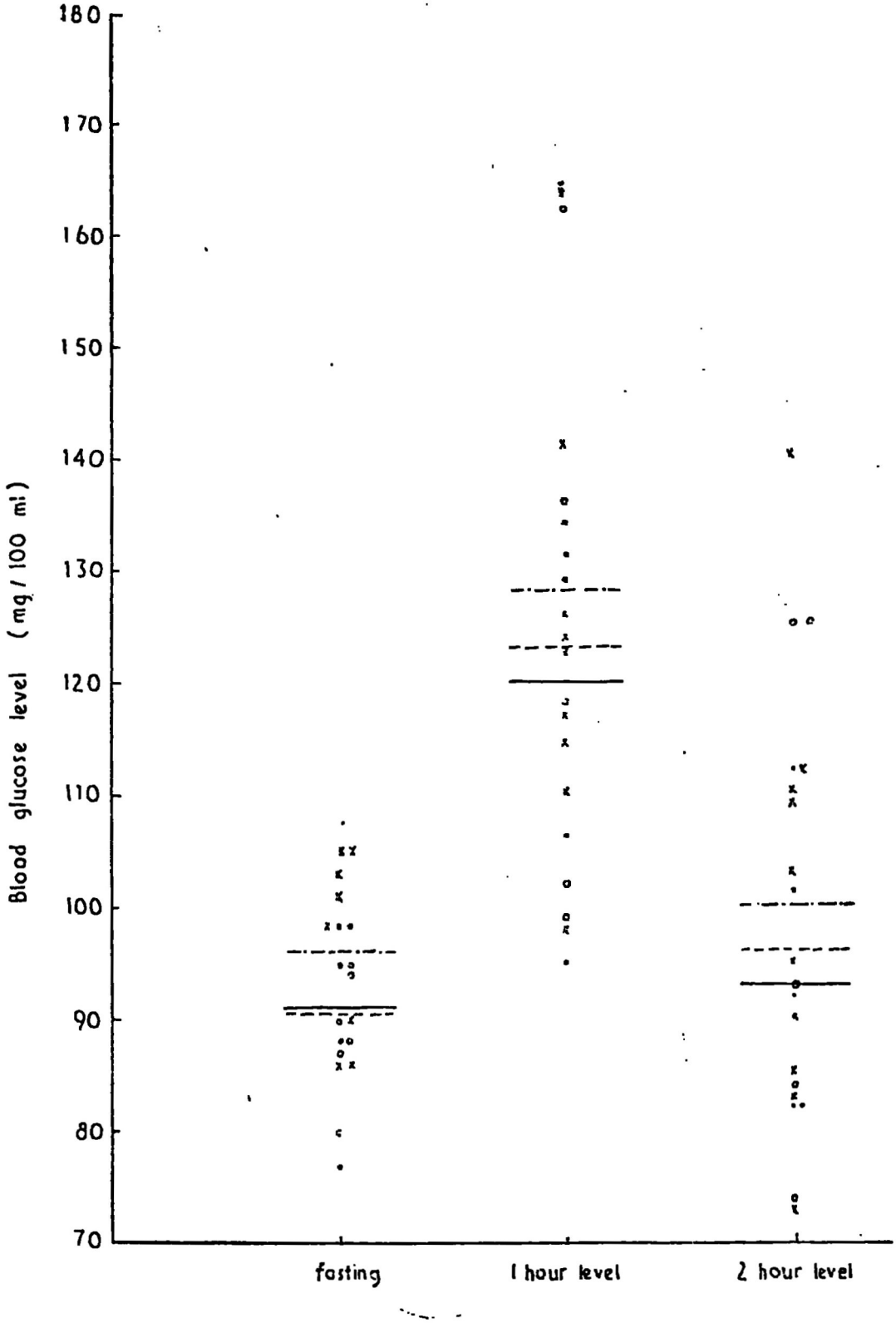

Figure (1) Blood glucose levels in subjects using Gynanevlar 21

. for 3 months ____ Mean
o for 6 months _____ Mean
x for 12 months _ _ _ Mean

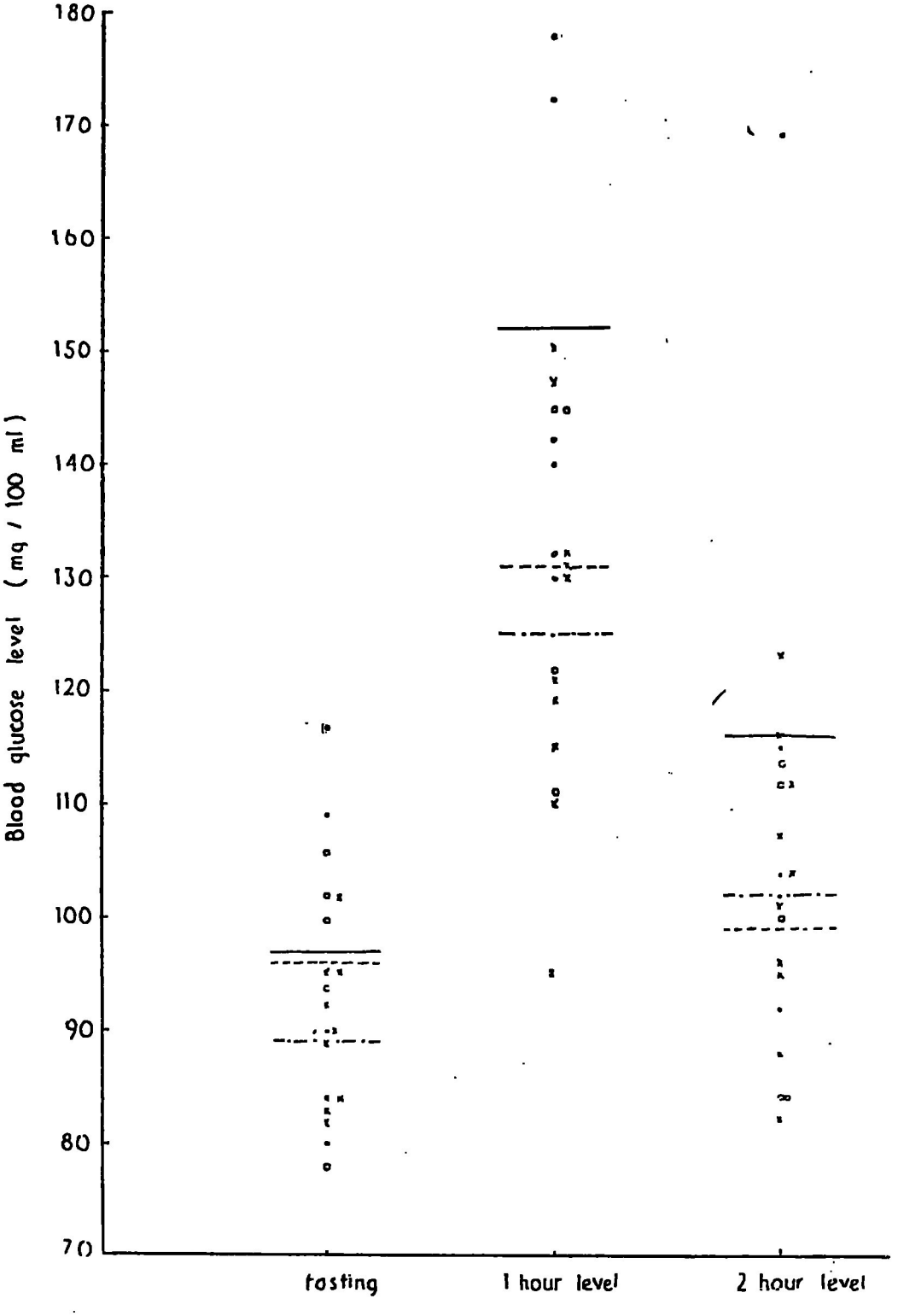

Figure (2) Blood glucose level in subjects using Lyndiol 2.5 .

. for 3 months —— Mean
o for 6 months ----- Mean
x for 12 months -.-.- Mean

blood glucose level, with delayed utilization and hence the level did not return to the fasting level after 2 hours from the glucose stimulus.

These cases represent 27.5% of the total cases investigated. The number of these cases in each group and their percentage are shown in table 3.

TABLE 3

The number of cases with deteriorated glucose utilization in each group and their percentage

Pills ur.	Gynanovlar 21			Lyndiol 2.5			Tota
	3 M	6 M	12 M	3 M	6 M	12 M	
No. of deter.	—	2	3	2	2	2	11
Total	5	5	10	5	5	10	40
%	0%	40%	30%	40%	40%	20%	27.5%

Data table 4 show the blood glucose levels in subjects with deteriorated glucose tolerance. In cases Nos. 3 and 22 using Gynanovlar for 6 months, the fasting blood glucose levels were within normal limits. However, they showed delayed glucose utilization. Case Nos. 15, 27, 38 using Gynanovlar for 12 months showed a slightly higher fasting levels as well delayed glucose utilization. Case No. 38 showed the highest level after 2 hours (140 mg%). In the group using Gynanovlar for 3 months , no cases with deteriorated glucose tolerance were detected. However, cases Nos. 17 and 21 treated with Lyndiol 2.5 for 3 months showed high fasting blood glucose levels (117 and 109) as well as delayed utilization, The highest deteriortion noticed was in case 21 (fasting level 109, reached 180 after 1½ hours and remained at 169 after 2 hours). Two cases on Lyndiol 2.5 for 6 months and 2 for 12 months showed also changes in glucose utilization.

DISCUSSION

As oral contraceptive steriods mimic preganacy in some of their effects, and pregnancy has a known diabetogenic effect, so a diabetogenic action for these steroids is a theoretical possibility. However, non of the cases investigated have shown typical diabetic curves, and the blood glucose levels never exceeded 180/100 ml., and no sugar appeared in the urine in any of the cases. In spite of this 11 out of

the 40 cases investigated showed delayed glucose utilization. In case of Lyndiol 2.5 there was no relation between the number of cases with delayed glucose utilization and the duration of treatment as the percentage of abnormality was 40, 40, and 20 in the 3, 6, and 12 month users respectively. In Gynancular users, the percentage was 0,40, and 30 respectively thus it seems that a certain percentage of women are liable to develop changes in glucose utilization which is not related to the type of pills used or the duration of treatment. Most probably this is due to individual variation, and in this respect it is better to follow up the subject for different periods so as to exclude any difference due to individual variation but it was difficult in the present work to follow up the cases.

TABLE 4

The blood glucose levels in subjects with deteriorated blood glucose levels

Case No	Pills used	Durat.	Fasting	1/2 hr.	1 hr.	1 1/2 hr.	2 hrs.
3	Gyn. 21	6 M	95	145	162	138	125
22	Gyn. 21	6 M	90	154	136	128	125
15	Gyn. 21	12 M	105	138	163	125	110
27	Gyn. 21	12 M	105	159	164	153	112
38	Gyn. 21	12 M	103	103	123	128	140
17	Lyndiol 2.5	3 M	117	142	172	128	104
21	Lyndiol 2.5	3 M	109	175	178	180	169
24	Lyndiol 2.5	6 M	100	123	132	121	114
26	Lyndiol 2.5	6 M	102	163	145	133	112
8	Lyndiol 2.5	12 M	90	165	150	147	123
18	Lyndiol 2.5	12 M	84	121	147	125	116

Taking into consideration the data previously obtained as regards plasma 17-OHCS, 17-KGS, SGOT, SGPT for the 11 cases with delayed glucose utilization (Table 5), the degree of deterioration was not proportionate to the total plasma 17-OHCS. However, the high levels of plasma 17-OHCS recorded for the 11 cases with delayed glucose utilization may be an important factor in causing changes in glucose utilization, but the protein unbound biologically active fraction of cortisol must be determined. Another factor in this respect is the oestrogen component of the pill which is more blamed for the changes in carbohydrate metabolism. Metcalf and Beaven (1963), Nelson et al (1963), Tait and Burstein (1964), Goldman and Ovadia (1969), Vela and Yen (1969) and Spellacy (1969), stated that oestrogens cause abnormal glucose utilization. Nelson (1963), found that oestrogens potentiate the glycosuric effect of administered cortisol in diabetic subjects. He also suggested that a direct effect of oestrogens on carbohydrate metabolism is made apparent by cortisol.

TABLE 5

The different results obtained in the 11 cases with deteriorated oral glucose tolerance curves

Serial No.	Age (years)	Parity	Wt. (kgm)	Pills used	Duration (months)	17-OHCS ug/100 ml	17 KS mg/ 24 hrs.	17 KGS mg/ 24 hrs.	SGOT (units)	SGPT (units)
3	28	6+1	62	Gyn.	6	14.1	4.3	11.3	18	17
22	28	6+2	83	Gyn.	6	34.4	2.1	10.3	10.5	17
15	27	2+0	62	Gyn.	12	45.3	5.2	9.36	18	17
27	24	4+1	71	Gyn.	12	38.2	4.82	6.22	26	23
38	26	4+1	77	Gyn.	12	37.2	3.78	6.78	22	20
17	28	5+1	80	Lynd.	3	26.9	4.6	6.2	12	18
21	24	4+1	62	Lynd.	3	25.1	5.6	9.4	12	22.5
24	26	5+1	63	Lynd.	6	39.2	3.5	1.92	19	10
26	29	6+2	72	Lynd.	6	41.8	4.1	3.63	17	12
8	25	5+0	89	Lynd.	12	37.6	3.2	1.26	10	17
18	23	4+0	64	Lynd.	12	66.9	6.9	8.3	18	27

From the results of the present investigation, one can say that Lyndiol 2.5 being more oestrogenic caused relatively more changes in glucose utilization than Gynanovlar 21, as evidenced by the higher blood glucose values recorded in subjects on Lyndiol therapy. The mean fasting values as well as after 1 and 2 hours after the glucose stimulus in Gynanovlar users for 3, 6 and 12 months were below the corresponding mean values in Lyndiol users for 3 months. That a certain percentage of women shows decreased glucose utilization during treatment with oral contraceptives was mentioned by other workers (Lebherz and Fobes, 1961, Geshberg et al, 1964, peterson 1966, Buchler and warren, 1966, wynn and Doar, 1966, Spellacy and Carlson, 1966, Posner et al, 1967, Goldman et al, 1969, Spellacy, 1969, Spellacy et al, 1971).

As regards the progestogen component of the pill, Beck and Wells (1969), found no difference between the effect of mestranol and ethyndiol diacetate and mestranol alone as regards glucose utilization thus proving that ethyndiol lacks the glycometabolic activity. Muggia et al (1968), found that medroxy progesterone acetate increased the insulin requirements or diabetics during treatment. Halling et al (1967), suggested that 19 nortestosterone derivatives are oestrogenic and may cause changes in carbohydrate metabolism. Spellacy et al (1971), used 2 types of pills containing mestranol but with different progestogen component and found different results as regards their effect on glucose utilization and concluded that the metabolic effects of progestogens or their metabolites are extremely important.

In this respect it must be mentioned that progestogens differ completely from progesterone. Benjamin and Casper (1966), concluded that glucose tolerance improved in a small group of patients treated with progesterone. Thomas (1963), Yen and Vela (1968), and Vela and Yen (1969), found that progesterone caused on changes in glucose utilization.

From the present investigation and the current literature, it is clear that oral contraceptive may have the potential danger of being diabetogenic in certain predisposed individuals. The oestrogen component is more blamed for this effect and it is the tendency nowadays in all factories to decrease the amount of oestrogen in the contraceptive pills to not more than 50 mcg. per pill.

SUMMARY & CONCLUSIONS

Oral glucose tolerance test was done to 50 cases (10 controls not using contraceptive pills, 20 on Gynanovlar 21 and 20 on Lyndiol 2.5 for variable periods-3, 6 and 12 months).

Non of the cases showed a typical diabetic curve. However, 11 out of the 40 cases on the contraceptive pills showed slight delay in glucose utilization.

Taking the mean fasting blood glucose levels as well as 1 and 2 hours after the glucose stimulus for all cases, Lyndiol 2.5 users for 3 months showed higher values than those of Gynanovlar users for 12 months.

The oestrogen component of the pill is more blamed, Lyndiol being more oestrogenic, it caused more changes than Gynanovlar.

The effects of oestrogens and progestogens on carbohydrate metabolism were discussed in view of the current literature.

It is concluded that the pill must be administered with caution in subjects with family history of diabetes or prediabetes. Also it seems ideal that glucose tolerance curves should be done to every case for selection of cases suitable to take the pills and periodic retesting must the basis for continuation of the therapy.

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