Effect of human chorionic gonadotrophin on weight loss, hunger, and feeling of well-being^{1,2}

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Since Simeons (1, 2) introduced his method of treating obesity using human chorionic gonadotrophin (HCG), there has been continuing controversy concerning the effect of HCG on the program. Simeons and his followers have generally not claimed that patients eating 500 kcal daily will lose more weight when receiving HCG. They (2-4) have claimed that patients are less hungry and feel better because of the HCG and are thus more apt to remain in treatment. There have been a number of literature reports of double-blind studies (5-9) concerning the effect of HCG on weight loss. Only one (8) indicated HCG may be of more value than a placebo. However, as pointed out by Gusman (4), most investigators significantly altered Simeons' basic program. Both Simeons and his followers have vociferously maintained that strict adherence to the basics of Simeons' program is essential if HCG is to be useful.

Because of the increasing popularity of Simeons' program, it was felt further attempts should be made to assess, in a doubleblind manner, not only weight loss but the degree of hunger and the feeling of well-being of patients receiving HCG or an identically appearing placebo.

Patients and methods

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One of us (HH), who has an active practice using HCG in weight reduction, did the clinical work. The other (WA) prepared the protocol, labeled the vials of HCG and placebo, and analyzed the results. Forty female patients received, in a modified double-blind manner, either HCG injections or placebo injections. HCG and placebo were prepared by Glogau & Co., Chicago, Illinois, in identically appearing vials. The HCG preparation was prepared in the usual commercial manner. It contained, in addition to HCG, mannitol with monobasic and dibasic sodium phosphates as buffers. The placebo preparation consisted of mannitol with monobasic and dibasic sodium phosphates as buffers. All patients were evaluated for weight loss and other parameters. The code was not broken until the clinical work was completed and the data had all been gathered.

Patient selection

All patients were females 18 years of age or older who had no known serious disease processes requiring significant medications. They were selected from apparently well-motivated patients desiring to enter the HCG program for weight reduction. None was selected who had previously been on Simeons' program. Also excluded from the study were patients who had received appetite suppressants or other weight medications in the 6 weeks prior to the start of the study. None had lost more than 5 lb in the 3 months prior to treatment. No patients were to receive diuretics during the study. Oral contraceptives, estrogen, or thyroid products needed to maintain a euthyroid state could be continued if the patients were receiving them prior to the start of the study. They were neither to be stopped nor started during the study period. Patients known to be pregnant were excluded from the study.

Parameters measured

Blood pressure was taken at the start and at the end of treatment with the patient in a sitting position. The patients were weighed with approximately the same amount of light clothing each day. They were questioned daily about hunger; the responses of those reporting hunger were recorded as "little," "some," or "much." Patients were also asked on each visit how they felt, and the responses were recorded as "excellent," "good," "fair," or "poor."

Injections

Three patients received injections from each vial. Numbers of the three patients to receive injections from each vial were assigned on a random basis before the vials were shipped to the clinical investigator (HH). A series of six vials, of either HCG or an identically appearing placebo, were

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labeled for each trio of patients. Two series of vials, however, had only two numbers on each vial. A new vial was used each 7 days. The study material was kept refrigerated after mixing with bacteriostatic water. Injections were given while cold; at no time did the medications remain at room temperature. Patients were to return to the office 6 days each week for 36 injections (unless the desired weight was achieved prior to this). They received 125 IU of the study material intramuscularly in the upper-outer quadrant of the buttocks on each visit. Injections were discontinued on the days of heavy menstrual flow of a few patients (usually 2 or 3 days). No appetite suppressants or other medications were given. Patients were advised to use no laxatives but were permitted to use a Fleet's or Baxter enema if needed.

Patients were advised to "avoid the use of any and all cosmetics containing fats or oils." They were also to avoid skin contact with other oils or fats. Chewing gum, throat pastilles, vitamin pills, cough syrups, and alcohol were not permitted. The patients were encouraged to drink 8 to 10 glasses of water daily.

Patients were repeatedly advised that absolute adherence to the program was essential. They were told the slightest infractions would slow or stop their weight loss. "The slightest deviation from any of the details will result in utter disaster."

Diet for days of the first three injections⁴

Patients were encouraged to eat all they wished of the foods allowed. No beverages containing caffeine were permitted during this period.

Breakfast and lunch, 1st day. Meat: (all lean) beef, veal, lamb, pork, chicken, turkey, beef or veal heart. Hard cooked eggs. Vegetables: brussels sprouts, cauliflower, green peppers, cucumbers, spinach (not canned), Swiss chard, cabbage, fresh asparagus, tomatoes, kohlrabi. Fruit: apples, oranges, and grapefruit at any time until lunch.

Afternoon of 1st day to noon 2nd day. Patients were to fast after lunch the 1st day until noon the 2nd day. There was no limit on noncaloric, noncaffeine fluids during this period.

Noon 2nd day until noon 3rd day. Patients could have only fruits and vegetables to be selected from the fruit and vegetable groups of the 1st day.

Lunch and evening meal 3rd day. Same as breakfast and lunch of the 1st day.

Diet for remainder of the study period

On the 4th day of injections, the patients were started on a low fat diet of 500 to 550 kcal (no mention was made of calories, however). They were warned "you must not make any changes or substitutions even though you may think they are an improvement or you will be utterly disappointed."

Patients were advised to keep a daily food diary and bring it with them each day. Two meals each day were to be eaten. Meals could be eaten at any time but foods from both meals could not be eaten at the same time. For each meal, one item was to be chosen from each of four food groups, protein, vegetable, bread, and fruit.

Protein group

All meat and fish were to be weighed on a postal scale. Three and one-half ounces (raw weight) were to be eaten at each meal.

1) Meat: Chicken breast (white meat, excluding skin), chicken livers purchased raw and cooked. Veal, in the following lean cuts only: a) sirloin, b) rump roast, c) loin chop. Lean beef hearts, dried chipped beef (3.5 oz). No other beef allowed. All meats and seafoods to be prepared by fat-free cooking.

2) Seafoods: White fish, fresh or frozen, unbreaded, as the following: flat fish (sole, flounder), haddock, pollock, perch, pike, white sea bass, halibut. Shellfish: Lobster, crab, shrimp, only. Irisbrand dietetic canned Cohoe salmon, 3.75 oz (oil must be washed from top). No dried, pickled, or smoked fish, or other seafood allowed.

3) Meat substitutions: Hoop (farmer or pot) cheese, 4 oz mixed with water and seasoning. Occasionally, the whites only of six hard-cooked eggs might be taken as a protein substitute. No cottage cheese was allowed.

Vegetable group

One-half to one cup of one type of the following vegetables at each meal: asparagus, beet greens (not beets), cabbage, celery, chard, chicory, Chinese cabbage, cucumbers, dill-sour pickles (these must be unsweetened), endive, escarole, fennel, kale, lettuce salad, Mung bean sprouts, mushrooms, onions, parsley, red radishes, spinach, string beans, summer squash, tomatoes, watercress. Low calorie dressings containing no more than 1 kcal/tablespoon might be used.

Bread group

Choice of one of the following: one average size bread stick (Grissino), melba toast, Finn crisp cracker (very thin), one square of Norwegian flatbread, or one-third of an English muffin containing 75 kcal or less per muffin (actual calories must be listed on the package).

Fruit group

Choice of one: apple, orange, handful of strawberries (approximately 8 oz), one-half cantaloupe, or one-half grapefruit, one-fourth casaba or honeydew melon, $\frac{1}{2}$ cup sugar-free cooked rhubarb (artificial sweetener permitted), $\frac{1}{2}$ cup of the following (fresh or waterpacked, and/or artificially

⁴ The basic 500- to 550-kcal diet was suggested by Simeons. The specific details of this and the diet for the first 3 days in toto were designed by Peter G. Lindner, M.D., and are reprinted with his permission. sweetened): sliced peaches, apricots, gooseberries, or papaya. One cup D-Zerta gelatine dessert (other sugar-free brands allowed).

The following were also allowed at any time: I) juice of one lemon daily for all purposes; 2) one tablespoon of milk/day; 3) salt, Lawry's seasoning, pepper, vinegar, dry mustard powder, garlic, sweet basil, thyme or seasonings, but no oil, butter, or dressing; 4) any amount of water, black coffee or tea, dietetic soft drinks marked 2 kcal/bottle or less, and artificial sweeteners.

The diet sheet ends with "Any slight change in the above diet rules will result in downright disappointment." The patient was also impressed that he was to lose weight each day or a reason must be found, i.e., fluid retention, dietary digressions, et cetera.

The initial workup included a medical and dietary history, physician examination, and a number of laboratory tests.

Results

Of the 40 patients starting this study, 17 of 20 in the HCG group and 13 of 20 in the placebo group completed 30 or more injections (Table 1). Data on all starting patients were included in the final analyses whenever possible. Final blood pressures and measurements were not obtained on patient 2 of the HCG group who left town due to a death in the family. These data were also unavailable on patients 19, 20, 25, 26, and 33 of the placebo group who dropped out of treatment early. Data concerning hunger in patients 13 and 16 were misplaced and thus not included in evaluating the degree of hunger for this group.

The mean age of the HCG group was 37.8 years (range 18 to 63) and that of the placebo group was 38.4 years (range 21 to 67). The mean height of the HCG group was 64.2 inches (range 60.2 to 70.0), whereas the placebo group had a mean height of 64.0 inches (range 58.5 to 67.5).

Weight loss data on all patients are included in Table 1. The mean starting weight was 6.3 lb greater in the placebo group than in the HCG group. This difference, however, was not significant. The mean weight loss in the HCG group was 19.96 ± 1.63 lb and 11.05 ± 1.29 lb in the placebo group (P < 0.001). The mean percentage of starting weight lost in the HCG group was 11.47 ± 0.58 and 6.77 ± 0.83 in the placebo group (P < 0.001). The mean weight loss per injection was 0.585 ± 0.044 lb in the HCG group and 0.403 ± 0.047 lb in the placebo group (P < 0.025). Fourteen patients lost 15 lb or more in the HCG group and in the placebo group five lost 15 lb or more.

The change in mean systolic and diastolic blood pressures during treatment was not significant in either group at the P = 0.05 level (Table 2). Patients 2, 19, 20, 25, 26, and 33 were excluded from analysis because of incomplete data.

In the HCG group, $76.6 \pm 3.30\%$ of the daily responses indicated little or no hunger. In the placebo group, $48.7 \pm 4.44\%$ of the daily responses indicated little or no hunger (P < 0.001) (Table 3).

Of the daily responses of patients in the HCG group, $86.5 \pm 2.66\%$ indicated they felt "good" to "excellent" as compared with 70.0 \pm 3.82% of the responses in the placebo group (P < 0.001) (Table 3).

Discussion

The mean weight loss and the mean percentage of starting weight that was lost were significantly greater in the HCG group than in the placebo group. It seems unlikely that if both groups had followed their diets strictly there would have been a significant difference in weight loss between the groups. Advocates of this method, including Simeons (1-4) feel that with HCG the patients are less hungry and generally feel better. Responses to daily questioning regarding hunger and feeling of well-being in this study are consistent with these views. It thus seems probable that the increased weight loss of the patients on HCG was related to the fact that they followed more closely the dietary instructions than did the placebo group.

Of the four reports of double-blind studies in the literature, only the study of Lebon (8) showed a significantly greater weight loss in the HCG group than in the placebo group (P < 0.05). The results of our study were quite unexpected by the author responsible for study design because the results of our initial study were negative, as have been most double-blind studies reported in the literature.

There was strict attention given to limiting

dietary fat. Simeons (3) pointed out that beef was allowed on this program. All fats American beef, which is feed lot fattened, contains much more fat than Italian beef. No beef other than beef hearts or dried chipped

were markedly restricted. Even cosmetics containing fats were curtailed, although it is difficult to see how this would affect the pro-

TABLE 1 Starting weight and weight loss

Patient no.	Age, years	Height, inch e s	No. of injections	Starting weight, lb	Loss, lb	Percent body weight loss	Loss, lb, per injection	
HCG group			-					
1	26	64.5	36	177.5	31.75	17.9	0.882	
2	23	63.5	32	149	13.25	8.9	0.414	
5	18	64.5	28	141.5	11.5	8.1	0.411	
7	27	62.25	36	135	11.25	8.3	0.313	
	51	70	36	222.5	20		0.556	
8						9.0		
9	36	64	36	156.5	14.5	9.3	0.403	
14	43	68	36	280	41.5	14.8	1.153	
15	57	64	36	141.5	17.5	12.4	0.486	
18	22	65.5	36	166.5	20.25	12.2	0.563	
21	59	66	33	165.75	21	12.7	0.636	
22	51	62	35	259.25	18.25	7.0	0.521	
23	34	63	35	164.75	22.25	13.5	0.636	
28	37	66	36	144.25	17.75	12.3	0.493	
29	47	62	36	151	17.75	11.3	0.472	
30	34	62	36	180	22	12.2	0.611	
32	21	65	32	123	13.25	10.8	0.414	
34	38	64	36	221.75	28.75	13.0	0.799	
36	33	62.5	28	171.25	21	12.3	0.750	
38	36	64.5	22	137.5	14.5	10.5	0.659	
40	63	60.25	36	145.75	18.75	12.9	0.521	
Mean				171.7	19.96ª	11.47ª	0.5855	
SEM					±1.63	±0.58	± 0.044	
Placebo group								
3	65	66	36	160.75	11.25	7.0	0.313	
4	48	64.5	36	234.5	15	6.4	0.417	
4	34	62.5	27	147	3.75	2.6	0.139	
-					8.25			
10	57	61	35	146.25		5.3	0.236	
11	67	62	36	141.5	9.50	6.7	0.264	
12	52	64	36	159.75	11.25	7.0	0.313	
13	48	58.5	36	139	20.5	14.7	0.569	
16	25	67	36	163.75	22	13.4	0.611	
17	53	60	36	152.75	18.5	12.1	0.514	
19	24	67	20	210	12.75	6.1	0.638	
20	33	64	20	136.5	4.5	3.3	0.225	
24	51	64	31	155	9.25	6.0	0.298	
25	22	67.5	13	159.25	2.5	1.6	0.192	
25	21	67	4	197	4.25	2.2	1.062	
			· · ·				0.493	
27	32	65	36	179.25	17.75	9.9		
31	35	67.5	36	148	9.25	6.3	0.257	
33	28	62	9	166.75	3	1.8	0.333	
35	27	63	35	149	13.75	9.2	0.393	
37	22	62.5	27	157.75	12.75	8.1	0.472	
39	25	64.5	36	195.75	11.25	5.7	0.313	
Mean				165.4	11.05ª	6.77ª	0.403*	
SEM		1			±1.29	±0.83	± 0.047	

• Difference between the HCG and placebo groups, significant at P < 0.001. ^b Difference between the HCG and placebo groups, significant at P < 0.025.

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TABLE	2
Blood p	ressure

	Mean starting b	lood pressure	Mean final blood pressure			
	Systolic	Diastolic	Systolic	Diastolic		
HCG Placebo	$ \begin{array}{r} 120.7 \pm 4.70^{\circ} \\ 122.1 \pm 2.87 \end{array} $	$77.4 \pm 1.80 79.2 \pm 2.16$	$\frac{115.1 \pm 3.89}{120.0 \pm 2.92}$	$72.5 \pm 1.65 \\ 78.0 \pm 2.50$		

Patients 2, 19, 25, 26, and 33 were excluded from analysis because final blood pressures were not obtained.

^a SEM.

TABL	.E 3
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Percentage of all daily patient responses of hunger and feeling of well-being

	Hunger				Feeling			
	None	Little	Some	Much	Poor	Fair	Good	Excellent
HCG	32.8	43.7	16.5	7.0	0.5	13.0	63.2	23.3
	$76.6^{a} \pm$	2.60%	23.4ª ±	= 3.30	13.54	± 2.66	86.5"	± 2.66
Placebo	15.6	33.1	33.9	17.4	6.1	24.0	49.6	20.3
	48.7ª ±	4.44	51.3ª ±	= 4.44	30.04	\pm 3.82	70.0ª	± 3.82

Patients 13 and 16 were excluded from hunger analysis because these data were unavailable.

^a Difference between HCG and placebo group, significant at P < 0.001. ^b SEM.

gram as there is no evidence in the literature that fats are absorbed through the skin. It does, however, seem possible that such extreme measures may have impressed the patients with the necessity of curtailing their dietary fat intake.

A number of physicians using HCG in this manner feel that once the HCG is mixed with diluent it must not be allowed to stand at room temperature and, even when refrigerated, activity is uncertain after 1 week. In this study, each vial was refrigerated and used only 1 week after mixing. The material was injected cold.

HH saw the patients only at the time of the initial and final visits. His office assistants, who were quite enthusiastic about the program, saw the patients 6 days each week. Patient charts were reviewed periodically by HH and his assistants during the course of treatment. The patients had 125 IU HCG (or equivalent placebo) injected deep im in the buttocks on each visit, with the exception that no injections were given to a few patients on the days they experienced heavy menstrual flow. The patients were required, however, to report 6 days each week whether or not an injection was received.

Laxatives and other medications (with the exception of aspirin) were to be avoided if at all possible. Three patients received other medications. All were in the HCG group. One was on birth control pills (no. 2), one on estrogen (no. 15), and one on thyroid (no. 5). The patient on thyroid was retained in the study for the sake of completeness, although the dosage of desiccated thyroid which the patient was taking prior to the start of the study was reduced from 2 grains to 1 grain on the 12th day of the study. It is doubtful this change in dosage significantly affected the patient's weight loss.

Except for receiving the study injections, the subjects were treated in a manner similar to that used in treating HH's regular patients receiving HCG. At any given time, the study patients constituted only a small portion of the patients receiving injections at HH's office.

As we concur with Albrink (10) that all

starting patients should be included in the analyses rather than only those completing treatment, we have included all starting patients.

The placebo used in our study was as nearly like the HCG preparation as possible with only the HCG itself missing. Thus, the HCG and placebo preparations should have been essentially indistinguishable on the basis of appearance or the local sensation of the patient who received the injections.

In addition to the study reported here, we have also completed a double-blind study involving patients of four physicians using Simeons' programs modified to varying degrees. Three of these physicians had had little or no experience with the use of HCG in weight reduction. None of their programs approached the rigidness of the program considered in detail in this report. For instance, one physician allowed some patients to administer their own HCG injections at home. One physician at times gave injections three times/week and one gave injections five times/week.

Physicians were allowed to use diets of their own choosing, as these patients were seen in the course of their regular practice. None of these four physicians insisted on the patient's absolute attention to detail in contrast to the physician whose practice is reported here. This is particularly true in regard to the restriction of fat intake.

The dropout rate was high in all practices involved in the initial study. When weight loss was analyzed for each practice, there was no significant difference between the HCG and placebo groups in any practice. Combined data from all four practices revealed 28 patients were on HCG and 32 on the placebo. The mean number of visits in the HCG group was 18.0 and 18.5 in the placebo group (36 visits possible).

When all starting patients were analyzed, the mean weight loss in the HCG group was 6.8 lb and 6.5 lb in the placebo group. This difference in weight loss was not significant. Thus, it appears that insistence on strict adherence to details is correlated with success (even in the placebo group).

In these four studies and the study presented here only females were included. Because males tend to lose larger amounts of weight, we felt including a few males in each group was undesirable. A large enough series of males needs to be studied so the results in males can be analyzed in a statistically meaningful way.

Fleigelman and Fried (11) injected 50 IU HCG daily intraperitoneally for 7 days into rats. Controls received 0.2 ml saline. The rats were killed after 7 days. The levels of three enzymes involved in linking glycolysis to the esterification and synthesis of fatty acids were assessed. There was an 85%, 35%, and 48% reduction in the adipose tissue levels of alpha-glycero-phosphate dehydrogenase (AGPD), lactic dehydrogenase (LDH), and glucose-6-phosphate dehydrogenase (G6PD), respectively. Liver levels of G6PD and muscle levels of AGPD were also significantly reduced. These enzymes play significant roles in directing lipid synthesis. If these reductions in enzyme levels are in turn responsible for a decrease in the rate of fatty acid synthesis, a possible enzymatic basis for the finding in our present study is suggested.

The extraction method used in preparing HCG from pregnant human urine is similar to the extraction method used for the preparation of urogastrone, a hormone inhibiting gastric secretion (12, 13). These authors report HCG preparations cause inhibition of gastric secretions even when the gonadotrophal activity of HCG preparations is destroyed. Ghosh (14) reported different activity rates for gonadotrophic and antisecretory effects in rats when two purified gonadotrophin preparations were assayed. In addition, van Hell et al. (15) have presented evidence that HCG preparations may be fractionated into a number of HCG components differing from each other in biological potency, electrophoretic mobility, and sialic acid content.

It is conceivable that the activity of HCG preparations in regard to weight reduction could be related to a specific HCG fraction or fractions, or to urogastrone, or other unknown urine components extracted by this method. If this were the case, such "fat mobilizing" activity levels might vary considerably in different preparations and batches of HCG. This might in part explain the variability in results in various reports where HCG has been used. Another possible explanation of negative results might be the loss of activity of HCG with time after mixing especially if not refrigerated. It is probable in most studies that an individual patient received injections from a single vial which, after mixing, would be a minimum of 6 weeks old by the time of the final injection.

The 500- to 550-kcal eating plan needs supplementation of certain items such as calcium to make it nutritionally complete. However, in the interest of simplicity, supplements were not included in the present study.

Whether the long-term results of weight loss using single or multiple courses of HCG injections are better than the usual dismal long-term results of weight reduction needs objective examination. It seems doubtful such would be the case unless the physician involved continued to work vigorously with the patient in the re-education of eating patterns.

The strict requirement that the patient must follow meticulously the various aspects of the program seems almost ritualistic. Whether certain aspects of this ritual are necessary for success when HCG is used remains to be seen. Proponents generally insist a minimal intake of dietary fats is necessary. The emphasis on strict attention to all details may at least motivate the patient to more careful restriction of his daily food intake.

It is interesting to note that HH's patients who were given a placebo lost more on the average than either the HCG or placebo patients of the other four practitioners (11.05 lb versus 6.8 and 6.5 lb, respectively). It therefore appears that HCG used in a casual program of weight reduction, as it often is in a general practice, is of no value. The fact that HH's placebo patients lost more weight in a 6-week period than most physicians' patients do on other diets and/or medications is in itself interesting. Certainly, the psychological impact of receiving a daily injection which the patient believes in is important.

It is hoped other investigators will repeat this study. The insistence on strict adherence to a low fat, low calorie eating plan seems critical. Ideally, each patient should have six or seven individual weekly vials that would make blinding more complete than in this study. Each vial should be kept refrigerated after reconstitution with bacteriostatic water, and should not be used longer than 1 week. Patients selected should be sufficiently overweight to assure they will not reach their desired weight before the termination of the study.

Summary

Twenty female patients on 500- to 550kcal diets receiving daily injections of 125 IU of human chorionic gonadotrophin (HCG) were compared with 20 female patients on 500- to 550-kcal diets receiving placebo injections. Patients in both groups were instructed to return for daily injections 6 days each week for a total of 36 injections (unless desired weight was achieved prior to this). The HCG group lost significantly more mean weight, had a significantly greater mean weight loss per injection, and lost a significantly greater mean percentage of their starting weight. The percentage of affirmative daily patient responses indicating "little or no hunger" and "feeling good to excellent" was significantly greater in the HCG group than in the placebo group. Additional investigation of the influence of HCG on weight loss, hunger, and well-being seems indicated.

We wish to acknowledge the valuable assistance of Lynne Stone who was responsible for carrying out the details of the study on a daily basis.

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