

adults with peptic ulcers.<sup>7</sup> This could be due to the fact that not all patients underwent regular follow-up endoscopy after apparent healing. In adults it is now well known that many relapses are entirely asymptomatic and it is possible that the same applies in children. After initial diagnosis and treatment, no patient subsequently presented with complications of gastro-intestinal bleeding or perforation. It would seem that the consequences of missing an asymptomatic relapse in childhood are rarely serious.

In conclusion, although relatively infrequent, peptic ulcers in childhood are probably more common than generally realised. Diagnosis of the condition presents a challenge and demands a high level of awareness if diagnostic delays are to be avoided. Despite a high index of suspicion some children will present for the first time with features related to intestinal blood loss without preceding symptoms. Earlier diagnosis in these will remain impossible. In children with abdominal pain the diagnosis must always be considered and probably the most valuable clinical clues are localised epigastric tenderness and anaemia. Failure to consider this possibility in children presenting with abdominal pain may lead to a considerable

delay in reaching the correct diagnosis. The confirmatory diagnostic investigation of choice is upper gastro-intestinal tract endoscopy. Where this is not available a barium meal examination remains an alternative but false-negative studies occur in a significant number of cases in childhood.<sup>6</sup>

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## Human chorionic gonadotrophin and weight loss

### A double-blind, placebo-controlled trial

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#### Summary

Low-dose human chorionic gonadotrophin (HCG) combined with a severe diet remains a popular treatment for obesity, despite equivocal evidence of its effectiveness. In a double-blind, placebo-controlled study, the effects of HCG on weight loss were compared with placebo injections. Forty obese women (body mass index  $> 30 \text{ kg/m}^2$ ) were placed on the same diet supplying 5000 kJ per day and received daily intramuscular injections of saline or HCG, 6 days a week for 6 weeks. A psychological profile, hunger level, body circumferences, a fasting blood sample and food records were obtained at the start and end of the study, while body weight was measured weekly. Subjects receiving HCG injections showed no advantages over those on placebo in respect of any of the variables recorded. Furthermore, weight loss on our diet was similar to that on severely restricted intake. We conclude that there is no rationale for the use of HCG injections in the treatment of obesity.

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Obesity is a common disorder with a strong association with heart disease, diabetes mellitus, gallbladder disease and pulmonary disorders.<sup>1-5</sup> In many societies it is also associated with a desire to be thin, and many obese individuals are desperate for an effective method of weight loss and weight maintenance.

Of the many forms of treatment currently available, the use of low-dose injections of human chorionic gonadotrophin (HCG) combined with a severe diet has been popular since 1954.<sup>6</sup> However, only two studies have obtained conclusive evidence that HCG is effective in the treatment of obesity.<sup>7,8</sup>

In contrast, it has been reported that placebo injections are as effective as HCG in the treatment of obesity.<sup>9,10</sup> Despite the equivocal evidence relating to the effectiveness of the regimen, the use of HCG in the treatment of obesity remains popular. A further reservation for the use of HCG is the use of a very-low-kilojoule diet (2100 kJ) as proposed by Simeons,<sup>6</sup> which could produce cardiac and metabolic problems<sup>11</sup> and is not suitable for long-term maintenance treatment.

Simeons<sup>7</sup> and Gusman<sup>8</sup> claimed that HCG promotes patient compliance, decreases appetite, facilitates sustained weight loss, causes differential weight loss from waist and hips, and releases free fatty acids from depot fat. Gusman<sup>8</sup> also reported that HCG injections caused no adverse side-effects. Stein *et al.*,<sup>12</sup> however, reported that one previously infertile patient became pregnant while receiving a course of low-dose HCG injections. He advised warning all patients receiving HCG for weight loss to take adequate precautions to prevent pregnancy, even if they had previously been infertile.

The purpose of this study was to test the validity of the purported additional benefits of HCG in the treatment of obesity, using a 'prudent diet' of 5000 kJ per day instead of the usual very-low-kilojoule diets.

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## Subjects and methods

Ethical approval was obtained to conduct a double-blind, placebo-controlled trial on forty obese white women (body mass index (BMI)  $> 30 \text{ kg/m}^2$ ) randomly selected from volunteers responding to an advertisement in a local newspaper. Subjects were advised that they would be randomly assigned to one of two groups of 20, and that they would only be informed of what injections they had received on conclusion of the study. One group received injections of HCG 125 IU in 0,2 ml diluent, in accordance with the recommended dosage,<sup>12,13</sup> while the control group received injections of 0,2 ml saline (placebo). Subjects were all in good health, as determined by a medical history and examination before commencing the study. One subject had previously been treated with HCG, more than 1 year before this study.

The drugs were prepared separately and dispensed in a double-blind manner utilising a subject code number that was only broken on completion of the course. Fresh HCG solution was prepared every 3 days and the solution was stored at  $4^\circ\text{C}$  at all times; individual HCG and saline injections were prepared daily from their respective vials. Intramuscular injections into the lateral upper arm were given at the same time each day, 6 days a week for 6 weeks. They were given by a project leader in order to ensure administration of the treatment. To be included in the results, patients had to have received a minimum of 34 of the 36 injections.

Side-effects of the drugs were reported and recorded daily. On completion of the programme, subjects were required to quantitate their experience of pain, both during and after administration of the injections, on a digital scale of 1 - 5 (1 = no pain; 5 = very painful).

All subjects were placed on the same balanced diet supplying 5000 kJ per day. Compliance with the diet was assessed using detailed daily food intake records completed by the subjects for the 2 weeks before commencement of the course, the first 2 weeks of the course and the final 2 weeks. For each 2-week period, 3 days (2 weekdays and 1 weekend day) were randomly selected; the average daily energy intake was then calculated and taken to represent the average intake over the 2-week period.

Once a week, all subjects attended a lecture on topics such as the causes and treatment of obesity and behavioural changes associated with obesity and its treatment. Subjects were weighed before this weekly lecture.

For the assessment of serum lipid profiles, venous blood samples were drawn after a 12-hour fast at the start and on completion of the course. Body circumferences were measured at the start and end of the course by the same examiner using standard measuring sites and techniques.<sup>14</sup> Using abdomen, thigh and calf circumferences, body fat percentage was then calculated according to the method of Katch and McArdle.<sup>14</sup>

Subjects also completed a psychological questionnaire specifically designed to assess psychological status, including mood and self-image. Variables were measured on a graded scale of 1 (never) to 5 (always); the lower the score, the more positive the psychological status. Subjects were also requested to mark their hunger level on a continuum ranging from 'all the time' through 'sometimes' to 'never'; the level of hunger was inversely related to the recorded score.

The Wilcoxon matched-pairs signed rank test was used for comparisons within groups (intragroup), while the Mann-Whitney *U*-test was used for intergroup comparisons.

## Results

Of the original 40 participants, 7 (4 from the saline group and 3 from the HCG group) did not meet the minimum require-

ments for the course. Only the results for the participants who successfully completed the course (16 in the saline group and 17 in the HCG group) are reported. Values are expressed as mean  $\pm$  standard error of the mean.

### Average daily energy intake

Fig. 1 illustrates the average daily energy intake for the two groups for the 2 weeks before the study, the first 2 weeks and the final 2 weeks. During the first 2 weeks energy intake was significantly reduced ( $44,6 \pm 5,5\%$  and  $44,1 \pm 5,5\%$  for the saline and HCG groups respectively) ( $P < 0,001$ ). This decrease in daily energy intake was maintained for the 6-week period, although there was a slight increase in the energy intake of both groups in the last 2 weeks ( $12,9 \pm 9,2\%$  and  $29,4 \pm 7,3\%$  for the saline and HCG groups respectively). Although this increase was significant in the HCG group only ( $P < 0,05$ ), the differences between the two groups were not significant at any stage during the study.

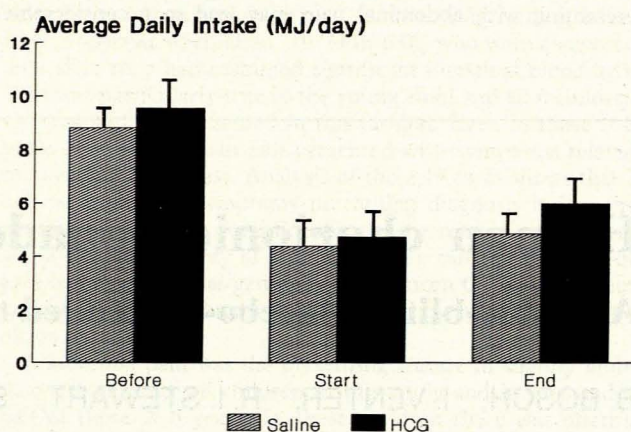


Fig. 1. Daily energy intake (mean  $\pm$  SE) was calculated from food intake records (see 'Methods').

### Body mass, BMI and body fat

The initial, final and percentage changes in body mass, BMI and body fat for the two groups are shown in Table I. All values were significantly lower ( $P < 0,001$ ) at the conclusion of the study.

Fig. 2 illustrates average weekly body mass for both groups over the 6-week study period. There were no differences between the groups in body mass, BMI or percentage body fat at any stage of the trial.

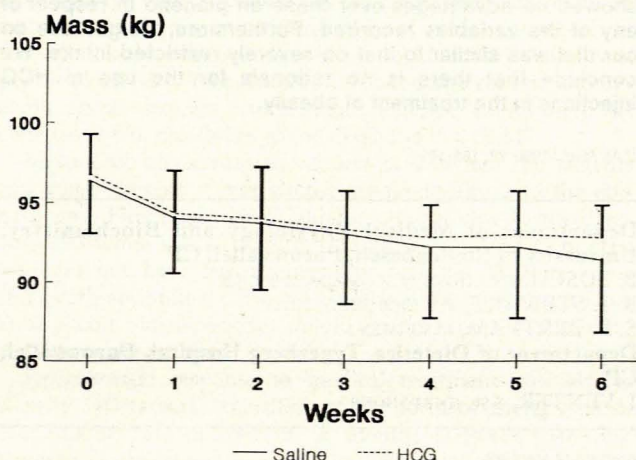


Fig. 2. Body mass (mean  $\pm$  SE) recorded weekly.



TABLE I. BODY MASS, BMI AND BODY FAT MEASUREMENTS

	Start	End	Decrease (%)
<b>Body mass (kg)</b>			
Saline	96,0 ± 2,7	91,4 ± 2,7*	4,9 ± 0,6
HCG	96,0 ± 2,6	92,8 ± 2,7*	3,4 ± 0,7
<b>BMI (kg/m)</b>			
Saline	34,79 ± 1,09	33,13 ± 1,12*	4,9 ± 0,6
HCG	35,47 ± 0,77	34,28 ± 0,82*	3,4 ± 0,7
<b>Body fat (%)</b>			
Saline	40,3 ± 1,3	37,0 ± 1,7*	8,4 ± 2,1
HCG	41,5 ± 1,3	38,3 ± 1,3*	7,5 ± 1,5

Final values significantly different from the start:

\* $P < 0,001$ .

### Body circumferences

All body circumferences decreased significantly over the trial period in both groups, the most significant reductions occurring in the trunk and thigh regions. There were no significant differences between the groups at any stage of the study, and specifically there was no significant additional reduction of either waist or hip circumferences as a result of HCG administration (Table II).

### Lipid profile

Serum lipid concentrations are summarised in Table III. Only blood cholesterol levels were significantly reduced in both groups, decreasing from slightly above the normal reference range (3,8 - 5,7 mmol/l) to within the upper limits thereof. Although the initial high-density lipoprotein (HDL)/total cholesterol ratio was significantly higher ( $P < 0,05$ ) in the

HCG group, the percentage changes in this ratio and in the HDL/low-density lipoprotein (LDL) cholesterol ratio were not significantly different between the groups. The mean HDL/total cholesterol ratios for both groups of women were unchanged and remained normal ( $> 0,20$ ) throughout the study.

Although blood triglyceride concentrations tended to decrease in all subjects over the 6-week period, changes were not significantly reduced and values remained within the upper limits of the normal range (0,97 - 1,97 mmol/l).

Fasting triglyceride and uric acid levels were similar in both groups, and remained unchanged for the duration of the study.

### Psychological profile

The psychological questionnaire measured mood and self-image on a scale of 1 (never) to 5 (always), and the lower the

TABLE II. BODY CIRCUMFERENCES (cm)

	Start	End	Decrease (%)
<b>Neck</b>			
Saline	36,7 ± 0,4	36,2 ± 0,4*	1,3 ± 0,3
HCG	36,9 ± 0,5	36,0 ± 0,4**	2,3 ± 0,6
<b>Shoulder</b>			
Saline	117,0 ± 1,3	115,0 ± 1,4*	1,7 ± 0,5
HCG	117,8 ± 1,6	116,2 ± 1,5*	1,4 ± 0,4
<b>Arm</b>			
Saline	37,3 ± 0,5	36,4 ± 0,5*	2,3 ± 0,6
HCG	37,7 ± 1,0	36,7 ± 0,9*	2,4 ± 0,5
<b>Chest</b>			
Saline	116,3 ± 2,1	112,9 ± 2,1**	3,0 ± 0,4
HCG	114,6 ± 2,1	112,6 ± 2,2**	1,7 ± 0,5
<b>Abdomen</b>			
Saline	104,0 ± 2,6	99,8 ± 2,8**	4,2 ± 0,7
HCG	103,5 ± 2,7	99,0 ± 2,5**	4,3 ± 0,8
<b>Hips</b>			
Saline	121,5 ± 2,5	116,9 ± 2,6**	3,8 ± 0,5
HCG	122,9 ± 1,7	119,6 ± 1,7**	2,7 ± 0,4
<b>Thigh</b>			
Saline	69,1 ± 0,8	66,5 ± 1,0**	3,8 ± 0,5
HCG	71,8 ± 1,1	69,5 ± 1,2**	3,1 ± 0,5
<b>Calf</b>			
Saline	41,4 ± 0,7	40,8 ± 0,7*	1,3 ± 0,4
HCG	41,2 ± 0,6	40,6 ± 0,6*	1,3 ± 0,3

Final values significantly different from the start:

\* $P < 0,05$ .\*\* $P < 0,001$ .



TABLE III. LIPID PROFILE

	Start	End	Decrease (%)
<b>Total cholesterol (mmol/l)</b>			
Saline	6,22 ± 0,28	5,79 ± 0,27*	- 7,50 ± 2,64
HCG	5,81 ± 0,27	5,27 ± 0,26*	- 8,88 ± 2,02
<b>HDL/total cholesterol</b>			
Saline	0,24 ± 0,01	0,24 ± 0,01	+ 0,46 ± 3,26
HCG	0,30 ± 0,02†	0,29 ± 0,02	- 2,77 ± 2,92
<b>HDL/LDL cholesterol</b>			
Saline	0,40 ± 0,03	0,39 ± 0,03	- 1,15 ± 4,05
HCG	0,55 ± 0,06	0,50 ± 0,04	- 6,00 ± 4,02
<b>Triglycerides (mmol/l)</b>			
Saline	1,84 ± 0,23	1,52 ± 0,20	- 15,63 ± 6,35
HCG	1,58 ± 0,23	1,39 ± 0,19	- 7,95 ± 6,67
<b>Uric acid (mmol/l)</b>			
Saline	0,29 ± 0,02	0,29 ± 0,02	+ 3,11 ± 2,78
HCG	0,30 ± 0,01	0,32 ± 0,02	+ 3,36 ± 2,72

Final values significantly different from the start:

\*P &lt; 0,01.

Significant inter-group difference:

† P &lt; 0,05.

TABLE IV. PSYCHOLOGICAL PROFILE

	Start	End	Improvement (%)
<b>Mood</b>			
Saline	18,6 ± 1,1	17,2 ± 1,5	4,8 ± 8,1
HCG	19,4 ± 1,0	17,9 ± 1,4*	9,6 ± 3,4
<b>Self-image</b>			
Saline	22,6 ± 1,3	20,4 ± 1,4	9,2 ± 4,4
HCG	20,6 ± 1,2	18,1 ± 1,8*	15,1 ± 4,3
<b>Hunger level</b>			
Saline	3,7 ± 0,6	5,8 ± 0,4*	133,0 ± 43,7
HCG	3,9 ± 0,5	6,5 ± 0,5**	225,6 ± 84,0

Final values significantly different from the start:

\*P &lt; 0,05.

\*\*P &lt; 0,01.

score the more elevated was the mood and the more positive the self-image. Although mood was elevated and self-image was more positive ( $P < 0,05$ ) at the end of the study in the HCG group only, there were no significant differences between the two groups with respect to percentage change (Table IV).

Hunger, on the other hand, was measured on a scale of 1 (always) to 10 (never), with the result that the recorded score was inversely related to the level of hunger. On conclusion of the study, the perception of hunger was significantly and equally reduced in both groups.

### Side-effects

No major side-effects were reported on daily questioning or in response to a written questionnaire on completion of the course. Minor side-effects reported included headaches (saline 1, HCG 2), insomnia (saline 1), pruritus (saline 1) and temporary nocturia (HCG 1). These side-effects were present for less than 3 days and only occurred during the first week. None of the subjects developed infections at the injection sites at any stage of the course or in the 2 weeks after the study.

There was no difference in the pain experienced by the two groups. On a scale of 1 (no pain) to 5 (extreme pain), the perceived pain levels were  $1,63 \pm 0,81$  and  $1,94 \pm 1,24$  for the saline and HCG groups respectively.

### Discussion

The major finding of this study was that HCG was no better than placebo (saline) in promoting weight loss. Furthermore, none of the claimed additional benefits, namely increased compliance, decreased appetite and differential weight loss from the hips and thighs, could be substantiated.

### Critique of the study

In this study, a diet supplying 5 000 kJ per day was used instead of the very-low-energy diets of 2 100 kJ per day<sup>6-8,13</sup> originally proposed by Simeons in 1954.<sup>6</sup> It has recently been shown that very-low-energy diets lower the resting metabolic rate,<sup>15</sup> thus making weight loss more difficult. Furthermore, a prudent diet supplying 5 000 kJ per day was selected because we have previously shown<sup>16</sup> that it produces an average weekly weight loss of 0,5 - 1,0 kg but is not associated with the cardiac and metabolic abnormalities that can occur with very-low-energy diets.<sup>11</sup> An additional benefit was that it was a balanced diet that subjects could safely continue on completion of the course.

In spite of the higher energy equivalent of our diet, average weight loss over 6 weeks, both for the saline group ( $5,0 \pm 0,5$  kg) and for the HCG group ( $4,1 \pm 0,6$  kg), compares favourably



with weight loss reported by previous workers over a similar period of time. Craig *et al.*<sup>13</sup> reported a total average weight loss of 2.9 kg (HCG) and 4.0 kg (saline) using a modified Simeons diet (2300 kJ per day), while Frank<sup>17</sup> reported weight loss of 5.6 kg (HCG) and 5.1 kg (saline) for subjects on a diet supplying 4300 kJ per day. It would seem therefore that there is no particular advantage in prescribing very-low-energy diets.

Furthermore, when the average weight loss in the present study is compared with the loss reported<sup>16</sup> on this diet alone ( $7.0 \pm 1.8$  kg), on the diet combined with an exercise programme ( $7.0 \pm 1.9$  kg), or on the diet combined with lecture therapy ( $6.3 \pm 0.9$  kg), it is seen that the injections, whether of placebo or HCG, had no added effect on weight loss.

Thirty-three of the initial 40 subjects completed the course of injections despite the inconvenience of daily attendance for this administration. Three subjects had to withdraw owing to circumstances beyond their control, but the other 4 subjects absconded. This drop-out rate is similar to those recorded by Craig *et al.*<sup>13</sup> and Stein *et al.*<sup>12</sup> but it is significantly lower than the 35 out of 66 recorded by Frank,<sup>17</sup> in whose study injections were administered every other day as opposed to daily. On first examination, it does not appear that daily contact with project leaders has an added advantage with respect to weight loss. However, if it is assumed that subjects who absconded did not lose weight, the average weight loss in the Frank investigation would be significantly lower than in the studies where subjects received injections daily. Thus it would appear that daily contact promotes compliance and adherence to the regimen.

## Analysis of the results

The various claims made that HCG assists in weight loss by promoting patient compliance, decreasing appetite and causing differential weight loss from the waist and hips could not be substantiated by our findings.

Firstly, patient compliance with the diet, as measured by recorded food intake, was good throughout the course in both the placebo and the HCG groups, and no advantages of the HCG could be established. In fact, although there were no significant intergroup differences, intake increased significantly in the HCG group over the last 2 weeks of the study. However, average daily values remained significantly lower than those recorded before commencement of the study.

Although the improvement in mood and self-image was statistically significant only in the HCG group, the percentage changes of the two groups were not different. The elevated mood and more positive self-image may be ascribed to the consistent weight losses experienced by these volunteers. Furthermore appetite, as indicated by the level of hunger, was significantly reduced in both groups, in spite of the large reduction in average daily kilojoule intake. Simeons' claim<sup>6</sup> that dietary compliance was assisted by HCG injections as a result of reduced hunger and a more positive mood could therefore also not be substantiated in this study.

No supportive evidence was found for the claim that HCG enhances differential weight loss from the waist and hips as reflected by body circumference measurements. The fact that there were no intergroup differences in fasting triglyceride levels mitigates against the claim that this alleged differential weight loss is mediated by an enhanced depot fat mobilisation.

Minimal pain from the injections was experienced by both groups, thus concurring with Gusman<sup>8</sup> that, despite the many injections administered ( $> 1500$ ), there were no major side-effects or infections.

## Conclusions

None of the claims made in support of HCG as an aid to weight loss could be substantiated in this study. Therefore, the only reason for giving injections would be to motivate the patient through daily contact with the administrator, and through regular dietary follow-up. However, since the administration of injections combined with diet provided similar, if not identical, effects to combination of a 5000 kJ diet with weekly lectures,<sup>16</sup> the use of daily injections in itself does not appear to contribute to weight loss. We therefore conclude that there is no rationale for using this particular form of therapy in the treatment of obesity.

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