Dietary sodium restriction in the prophylaxis of hypertensive disorders of pregnancy: effects on the intake of other nutrients

Bert JA van Buul, Eric AP Steegers, Henk W Jongsma, Anneloe L Rijpkema, Tom KAB Eskes, Chris MG Thomas, Henk Baadenhuyzen, and Peter R Hein

ABSTRACT Dietary sodium restriction is used in the Netherlands in the prophylaxis of preeclampsia. To study the effects of long-term sodium restriction on the intake of other nutrients and the outcome of pregnancy, 68 healthy nulliparous pregnant women were randomly assigned to either a low-sodium diet (20 mmol/24 h) or an unrestricted diet. The diet was consumed between week 14 of gestation and delivery. The dietary intakes of energy, fat, protein, carbohydrate, sodium, potassium, and calcium were estimated with the dietary-history technique. A low-sodium diet reduced the intake of protein (by ~15 g/24 h), fat (by 20 g/24 h), and calcium (by 350 mg/24 h) and tended to decrease the energy intake (by ~0.7 MJ/24 h). The intakes of carbohydrate and potassium did not differ between the groups. The maternal weight gain was less in the low-sodium group (6.0 ± 3.7 compared with 11.7 ± 4.7 kg). Mean birth weight was not significantly different (3.2 ± 0.5 compared with 3.4 ± 0.5 kg).

KEY WORDS Sodium-restricted diet, pregnancy, prophylaxis of preeclampsia, energy intake, fat intake, protein intake, carbohydrate intake, calcium intake, maternal weight gain, birth weight, body fat mass

INTRODUCTION

During pregnancy many maternal physiologic adaptations have to occur to achieve a good outcome. Nutritional demands are increased. The cumulative specific requirements of protein, fat, and energy throughout pregnancy for a woman gaining ~12.5 kg were theoretically estimated to be, respectively, 925 g, 3825 g, and 355 MJ (84 957 kcal) (1).

Prophylaxis and treatment of hypertensive disorders in pregnancy with dietary sodium restriction has been, in some parts of the world, deeply rooted in the minds of general practitioners, midwives, and obstetricians since the turn of the century (2, 3). Because a low-sodium diet is usually considered to be less palatable in Western society, such a regimen could possibly result in a disadvantageous change in nutritional intake.

In 1986 a Dutch multicenter trial was started to study the prophylactic value of a sodium-restricted diet with regard to the incidence of gestational hypertension. In each of the participating centers additional studies were performed on the pathophysiological effects of the diet. In a previous report of our group on the hemodynamic effects of a low-sodium diet in pregnancy from the 14th gestational week through delivery, the initial results on dietary intake in the first 42 women of the multicenter trial were described. The estimated dietary intake before pregnancy was compared with that between weeks 20 and 28 of pregnancy. In the low-sodium group, the intakes of protein, energy, and carbohydrates were unaltered and fat and calcium intakes were lower than before pregnancy. In the control group, the intake of all of these nutrients was significantly higher during pregnancy (4). To study the effects on nutrition longitudinally, and to make cumulative calculations possible, we decided to analyze dietary intake serially in the group of women that participated in the multicenter trial from 1989 onward in our center.

SUBJECTS AND METHODS

Sixty-eight healthy nulliparous pregnant women with singleton pregnancies who participated in the multicenter trial were included in the study after informed consent was obtained. The other two participating centers in the multicenter trial were the Bosch Medicentrum (Groot Ziekenhuis) in 's Hertogenbosch and the Catharina Hospital in Eindhoven. The experimental protocol was approved by the Committee on Human Experimentation of the University Hospital Sint Radboud in Nijmegen. The study protocol was described previously (4).

All pregnancies were accurately dated by last menstrual period, pregnancy test, and one or two ultrasonic investigations before the 12th gestational week. After an initial check-up around week 12 of pregnancy, women were randomly allocated to either a group with a sodium-restricted diet containing ~20 mmol Na/24 h, or to a group with no dietary restrictions. This random allocation was accomplished by a closed-envelope system. The women in the low-sodium group followed the diet from the 14th gestational week through to delivery. Oral and
written dietary instructions as well as guidance throughout pregnancy were given by a trained dietitian. No salt was to be added during cooking or at the table. Products that contain much sodium by nature were prohibited and replaced by low-sodium alternatives, eg, milk, cheese, butter, and other dairy products. Ready-made products were only allowed if no salt was added during production, eg, canned vegetables, canned fish, instant soups, peanut butter. Bread and other bakery products also had to be unsalted, which are baked without salt by most bakers on request. Low-sodium milk, other dairy products, and other low-sodium products are readily available in Dutch grocery stores because sodium-restricted diets are often prescribed in the management of chronic hypertension.

Thirty-seven women were allocated in the low-sodium group and 31 to the unrestricted group. In the low-sodium group, 12 women were excluded from the trial: 9 women did not want to continue the diet, 1 woman moved to another city, 1 woman developed gestational diabetes mellitus, and 1 woman suffered a subarachnoid hemorrhage. In the unrestricted group, six women were excluded from the analysis: one woman because of intestinal obstruction during pregnancy necessitating surgical intervention and five because insufficient data were obtained. Some dietary data for 6 women in the low-sodium group and 13 women in the unrestricted group in the current report were included in the initial study (4) and some laboratory data from some women in the unrestricted group were also incorporated into three other reports (5-7). For logistic reasons, the serum calcium concentration and urinary calcium excretion were measured only in the last 13 women of the low-sodium group. These data were compared with serial data of an additional group of 28 healthy nulliparous women with an unrestricted dietary intake, who were studied according to the same protocol without estimation of dietary intake.

The dietitian who gave the dietary instructions interviewed the women on seven occasions during pregnancy using the dietary-history technique. This is a standardized, reliable method designed to measure the average nutrient intake of an individual during a considerable period of time (8). The dietary history was completed by a cross-check, which checks for possible omissions and minimizes errors in estimating amounts of food eaten (9). During the first interview in the 12th gestational week, both the food intake before pregnancy and the current intake were assessed. The interview was repeated during weeks 16, 20, 24, 28, 32, and 36. From the collected data, the total daily amounts of ingested energy, fat, carbohydrate, protein, calcium, potassium, and sodium were calculated with the use of food-composition tables (10). The dietitian was instructed to refrain from any comments during the interview regarding the quality of the diet, to avoid any effect of the interview on the food intake during the remainder of the pregnancy.

During the outpatient clinic visits at weeks 12, 16, 20, 24, 28, 32, and 36 of pregnancy and at 6 wk after delivery, the following anthropometric and laboratory indexes were measured or calculated: maternal weight, serum concentrations, and 24-h urinary excretions of sodium, potassium, creatinine, and calcium. The women were weighed on a digital balance (Mettler TE/J, weighing range 2.50–120.00 kg, accuracy 0.05 kg; Mettler Instruments, Greifensee, Switzerland), while wearing light indoor clothing and no shoes. Weighing was also performed weekly between week 36 and delivery to ensure that the interval between the last weighing and delivery was ≤1 wk. Venous blood samples were taken from an antecubital vein after the women had rested for 20 min in the left lateral tilt position. A 24-h urine sample was collected on the day before each outpatient clinic visit. The urinary excretions of sodium, potassium, and calcium are expressed both as mmol/24 h and as a ratio of creatinine excretion (mmol/mmol) to correct for possible inadequate urine collection. To substantiate changes in the protein intake, the urinary excretion of nitrogen was measured with the Kjeldahl method in the last 11 women in the control group and in the last 19 women of the low-sodium group, in week 36 and 6 wk after delivery.

To approximate the prepregnant body mass index (BMI), 2 kg was subtracted from the measured weight in week 12 (1 kg for the clothing and 1 kg for the expected mean weight gain in the first 12 wk of pregnancy (11):

Prepregnant BMI (kg/m²) = (weight_{wk12} - 2)/height²

The change in body fat mass (BFM) between week 12 and term was estimated, on the basis of the difference in maternal weight between week 12 and 6 wk after delivery:

Change in BFM = 0.8 \times (weight_{prep} - weight_{wk12} - 0.36 \text{ kg})

where weight_{prep} is the maternal weight 6 wk after delivery, weight_{wk12} is the maternal weight in week 12 of pregnancy, and the factor 0.36 is the assumed increase of breast tissue. It is assumed that, at 6 wk after delivery, the weight above the weight in week 12 is adipose tissue, that 80% of this tissue is fat, and that no fat is lost in the first 6 wk after delivery (11, 12). The amount of energy that was stored in accreted maternal fat tissue (energy equivalent) was estimated by multiplying the change in BFM by 46 MJ, ie, the amount of energy required for synthesis and storage of 1 kg body fat.

The outcome of pregnancy was evaluated in terms of duration of gestation and birth weights of the babies. The birth weights were classified according to centile curves described by Kloosterman (13).

Statistical analysis

The differences between both groups with regard to population characteristics, pregnancy outcome indexes, nutritional data in the prepregnant period and in week 12 of pregnancy, as well as the anthropometric and laboratory indexes in week 12 and 6 wk after delivery were all tested with the Wilcoxon rank-sum test. Changes within each group in pregnancy compared with prepregnant data, data in week 12, or postpartum results were tested with the Wilcoxon matched-paired rank test. For comparison of the serial data in the diet period between the two groups, a distribution-free test described by Koziol et al (14) was used. This test is suitable for the comparison of response curves when missing values are present. For each variable, some women had one or two missing values at different time points. Differences were considered significant with a P value at the 5% level. Statistical analyses were done by using SAS computer software (SAS Institute Inc, Cary, NC).
RESULTS

Group characteristics and pregnancy outcome

At the moment of randomization, no statistically significant differences were found between the groups with respect to age, weight, height, and BMI. No statistically significant differences were found either, regarding the duration of pregnancy, mean birth weights, and birth weight centiles of the babies (Table 1).

Estimated dietary intake

No significant differences were found between the two study groups in any of the nutritional variables in the prepregnant state, or in week 12 (ie, before the start of the diet in the low-sodium group) (Figures 1–5).

Intakes of energy, protein, fat, and carbohydrates

In both groups, energy intake in week 12 of pregnancy was not different from the prepregnant intake (Figure 1). In the unrestricted group, the average energy intake during pregnancy was higher (by ≈1 MJ/24 h) than in the nonpregnant state (P < 0.01), whereas in the low-sodium group no significant increase was observed during pregnancy. During the dietary period, mean energy intakes were lower (by ≈0.7–0.8 MJ/24 h) in the low-sodium group than in the unrestricted group. This difference, however, was not statistically significant (P < 0.14).

In the unrestricted group, a significant gradual increase in protein intake was observed with a maximal difference of 11 g/24 h between late gestation and prepregnant intake (P < 0.01). In the low-sodium group, protein intake initially decreased after the start of the diet and remained lower than the prepregnant intake. During the diet period, the protein intake was higher (by ≈15 g/24 h) in the unrestricted group than in the low-sodium group (P < 0.01).

In comparison with the prepregnant amounts, the daily fat intake increased significantly by ≈10 g in the ad libitum group (P < 0.01) and fell significantly by ≈15 g in the low-sodium group (P < 0.01). The fat intake was higher (by ≈20 g/24 h) in the ad libitum group in comparison with the low-sodium group (P < 0.01). Both diet groups increased their carbohydrate intakes slightly during pregnancy (P < 0.05). The carbohydrate intake during pregnancy showed no significant differences between the two groups.

Relative contributions of protein, fat, and carbohydrate to the total energy intake

Protein intake supplied between 13% and 16% of the energy intake in both groups. This was not significantly changed by either pregnancy or by the low-sodium diet (Figure 2). Fat intake accounted for ≈40% of total energy in the prepregnant state. In the unrestricted group, no significant change of this percentage during pregnancy was found. The fat percentage

FIGURE 1. Mean (±SEM) energy, protein, fat, and carbohydrate intakes. Broken lines indicate the unrestricted group (n = 25), solid lines the low-sodium group (n = 25). Significance of difference (P) over the diet period is indicated by the horizontal line (Kozial et al; 14). RDA, recommended daily allowances for an average Dutch woman between 20 and 35 y of age, height 1.66 m, weight 60 kg, and moderately active, for the last 6 mo of pregnancy (10).
TABLE 1
Group characteristics and pregnancy outcome

<table>
<thead>
<tr>
<th></th>
<th>Unrestricted diet (n = 25)</th>
<th>Low-sodium diet (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in week 12 (y)</td>
<td>27.9 ± 3.9</td>
<td>29.4 ± 4.1</td>
</tr>
<tr>
<td>Weight in week 12 (kg)</td>
<td>67.3 ± 11.2</td>
<td>70.9 ± 13.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169 ± 6</td>
<td>166 ± 7</td>
</tr>
<tr>
<td>Prepregnant BMI (kg/m²)</td>
<td>22.8 ± 3.6</td>
<td>24.9 ± 4.5</td>
</tr>
<tr>
<td>Duration of pregnancy (d)</td>
<td>277 ± 13</td>
<td>278 ± 13</td>
</tr>
<tr>
<td><strong>Infants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.323 ± 0.360</td>
<td>3.246 ± 0.496</td>
</tr>
<tr>
<td>Birth-weight centiles (number of individuals)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10th</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10th-90th</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>&gt; 90th</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

† ± SD. There were no significant differences between groups.

decreased significantly in the low-sodium group from 41% in the prepregnant period to < 37% in late gestation (P < 0.01). Despite these different patterns, the difference between groups was not statistically significant during the diet period. In the ad libitum group, the percent of energy as carbohydrate remained unaltered, whereas that in the low-sodium group increased from nearly 44% to 50% in late gestation. The difference between the two groups of ±4% was statistically significant (P = 0.04).

Sodium, potassium, and calcium

Sodium intake did not differ between the two groups before the start of the diet. In the unrestricted group, the intake remained the same during pregnancy. In the low-sodium group, the estimated sodium intake decreased to ~20 mmol/d. During pregnancy a significant decrease of ~4 mmol/L was observed in the serum sodium concentration, with no significant differences between the two groups. In the unrestricted group, the urinary sodium excretion remained unaltered, varying from 130 to 150 mmol/24 h. In the low-sodium group, the urinary excretion of sodium dropped during the diet period to values between 20 and 40 mmol/24 h (Figure 3).

No significant differences were found for potassium intake. Serum potassium concentration decreased by ~0.2 mmol/L during pregnancy, with no significant differences between the two groups. The potassium excretion increased during pregnancy in both groups, with no significant differences between the two groups (Figure 4).

The daily calcium intake during gestation in the ad libitum group increased by ~350 mg (8.7 mmol) compared with the prepregnant value (P < 0.01). In the low-sodium group, after an initial fall immediately after the start of the diet, the calcium intake returned to a value similar to the prepregnant amount. During the diet period, the daily calcium intake in the ad libitum group was 300-400 mg (7.5-10 mmol) above that in the low-sodium group (P < 0.01) (Figure 5). The serum concentrations and urinary excretion of the last 13 women in the low-sodium group were compared with serial data derived from 28 other nulliparous women with an unrestricted diet who were studied according to the same study protocol without estimations of dietary intake.

During pregnancy a significant decrease in the serum calcium concentration of ~0.10 mmol/L was observed in the low-sodium group as well as in the additional unrestricted group, compared with the postpartum value. No significant differences were found between the groups. The urinary calcium excretion in the two groups before the start of the diet in week 12 was three to four times as high as that postpartum (P < 0.01). After the start of the diet however, excretion decreased significantly in the low-sodium group (P < 0.01), whereas that in the additional unrestricted group did not decrease. The difference between the groups was significant (P < 0.05) (Figure 5).

The urinary nitrogen excretion at 36 wk of gestation was significantly lower in the low-sodium group than in the unrestricted group. At 6 wk after delivery no significant differences were found (Figure 6). The mean weight gain between week 12 and delivery was 11.7 kg in the control group and 6.0 kg in
DIETARY SODIUM RESTRICTION IN PREGNANCY

Sodium Intake

Serum Sodium

Urinary Sodium Excretion

Urinary Sodium Excretion

the low-sodium group ($P < 0.001$). Six weeks after delivery the mean weight in the ad libitum group was 1.4 kg above that in week 12, whereas in the low-sodium group it was 1.5 kg lower than in week 12 ($P < 0.001$) (Figure 7).

The changes in BFM as estimated with the change in body weight indicated a fat gain in the ad libitum group of $0.80 \pm 2.68$ kg and a fat loss of $1.52 \pm 3.50$ kg in the low-sodium group. The differences between groups was statistically significant ($P < 0.001$).

DISCUSSION

To our knowledge, no data are available in the literature on the use of low-sodium diets in normal pregnancy. The use of sodium-restricted diets in abnormal pregnancy was recently reviewed (15). Widal and Javal (16) and Cramer (17) treated women with severe edema during pregnancy with dietary sodium restriction. De Snoo (3) treated pregnant women with edema who were at risk of developing eclampsia, with hospitalization, bed rest, and a sodium-restricted diet. He demonstrated that after 2 d of treatment the chances of developing eclampsia were negligible. Hamlin (18), Stevenson (19), and Hughes (20) reported a similar decrease in the incidence of eclampsia after the introduction of a low-sodium, high-protein, high-vitamin, and low-carbohydrate diet in combination with increased antenatal supervision. Dieckmann and Kramer (21) advised curtailment of sodium as prophylaxis for edema and, hence, of preeclampsia. Chesley et al (22) demonstrated that in women with excessive weight gain in the early third trimester, treatment with a sodium-restricted diet in combination with forced fluid intake resulted in a decreased incidence of preeclampsia. Robinson (23), however, demonstrated a reduction in the incidence of toxemia in women advised to take more salt during pregnancy as compared with a control group of women advised to reduce sodium intake. The actual compliance with the diets, however, was not checked in this trial. Zuspan and Bell (24) reported that in moderately severely preeclamptic women, dietary salt loading (5 g/d) caused marked sodium retention and a worsening of clinical symptoms. Mengert and Tacchi (25) could not demonstrate any differences in outcome between preeclamptic patients treated with either a high-salt (11 g/d) or a low-salt (2 g/d) diet. However, urinary sodium excretions in this study were similar in the two groups, which suggests poor compliance. Treatment of preeclamptic women with different regimens of salt intake (2, 10, and 25 g/d), did not result in differences in the change of systolic and diastolic blood pressure between the three groups (26). Dietary compliance was not checked in this study.

In a recent analysis of the relation between blood pressure and estimated sodium intake in nonpregnant individuals among 24 populations, the sodium intake ranged from 1 to 370 mmol/d. In six populations the estimated sodium intake was < 30 mmol/d. Blood pressures were lowest in the populations with the lowest sodium intake (27). In nonpregnant individuals,

FIGURE 3. Mean ($\pm$ SEM) sodium intake, serum sodium concentration, urinary sodium excretion, and urinary sodium excretion as a ratio to creatinine excretion. 6PP, 6 wk after delivery. Broken lines indicate the unrestricted group ($n = 25$), solid lines the low-sodium group ($n = 25$). Significance of difference ($P$) over the diet period is indicated by the horizontal line (Kozlak et al; 14).
the physiological sodium need appears to be as low as 1 mmol/d (28).

The present randomized longitudinal study deals with the dietary changes that accompany curtailment of dietary intake of sodium between the 14th wk of pregnancy and delivery in a group of healthy, well-nourished nulliparous women. The compliance with the diet was adequate, as can be concluded from the excretion of sodium in the 24-h urine samples, especially if one considers that these women were outpatient clinic patients who continued their normal activities, which for most of them was a full-time employment throughout a considerable part of pregnancy. Ideally, only the intake of sodium should have changed. However, coinciding with the decrease in sodium intake, we observed a lower intake of fat, protein, and calcium as compared with the unrestricted group. The lower intake of protein was substantiated by a comparable difference in urinary nitrogen excretion in late gestation.

The energy intake during the diet period also tended to be lower in the low-sodium group. Although the energy intake in each group changed in opposite directions after the start of the diet, this did not result in statistically significant differences between the groups, presumably because the baseline energy intake in the low-sodium group tended to be somewhat higher than that in the unrestricted group. This difference agreed with the small difference in mean weight and BMI before pregnancy between the two groups.

Comparison with recommended daily allowances (RDAs; 10) for a moderate active Dutch woman between 20 and 35 y of age, with a height of 1.66 m and a weight of 60 kg, indicates that in both groups the prepregnant diet contained an adequate amount of energy (RDA is 9.1 MJ/d), too much fat (RDA is 84 g/d, supplying ≤ 35% of energy) and protein (RDA is 60 g/d), and an insufficient amount of carbohydrates (RDA is 294 g/d, supplying ≥ 55% of energy). During pregnancy, the women in the unrestricted group increased their energy intake in accordance with the RDA. Protein, fat, and carbohydrate intakes increased equally, so that in comparison with the RDAs, no improvement was observed. In the low-sodium group, however, the energy intake was slightly below the RDA, protein and fat were similar to the RDAs, and carbohydrates were still considerably below the RDA. From an energetic viewpoint, these changes in the diet in the low-sodium group appear beneficial because relatively more energy is derived from carbohydrates and less from fat, although total energy intake was below the RDA. We have no data on basal metabolic rate and total daily energy expenditure, but we assume that no major differences in that respect existed between the two groups because most women in each group continued their normal activities.

Mean weight gain was 12.7 kg (assuming a weight gain of 1 kg in the first 12 wk) in the unrestricted group, including an estimated fat storage of 0.8 kg, whereas in the low-sodium group, mean weight gain was limited to 7 kg with an estimated fat loss of 1.5 kg. Hytten (1) estimated the energy costs of

![FIGURE 4. Mean (± SEM) potassium intake, serum potassium concentration, urinary potassium excretion, and urinary potassium excretion as a ratio to creatinine excretion. 6PP, 6 wk after delivery. Broken lines indicate the unrestricted group (n = 25), solid lines the low-sodium group (n = 25). Significance of different (P) over the diet period is indicated by the horizontal line (Kozioł et al; 14).]
Calcium Intake

Serum Calcium

Urinary Calcium Excretion

Urinary Calcium Excretion

FIGURE 5. Mean (± SEM) calcium intake, serum calcium concentration, urinary calcium excretion, and urinary calcium excretion as a ratio to creatinine excretion. 6PP, 6 wk after delivery. Broken lines indicate the unrestricted group, solid lines the low-sodium group. Significance of difference (P) over the diet period is indicated by the horizontal line (Koziol et al; 14). Data for calcium intake were obtained from 25 women in the low-sodium group and from 25 women in the control group. Data for serum concentration and urinary excretion were obtained from the last 13 women in the low-sodium group and were compared with serial data of 28 other nulliparous woman that were studied according to the same study protocol without the estimations of dietary intake. RDA, recommended daily allowances for an average Dutch woman between 20 and 35 y of age, height 1.66 m, weight 60 kg, and moderately active, for the last 6 mo of pregnancy (10).
Urinary Calcium Excretion

FIGURE 6. Mean (± SEM) urinary calcium excretion/24 h. 6PP, 6 wk after delivery. Control group (unrestricted; n = 11), low-sodium group (n = 19).

The urinary calcium excretion decreased in the low-sodium group whereas no change was observed in the control group. The increment of the urinary calcium excretion was reported previously by others (34). The fact that dietary calcium intake was reduced in the low-sodium group could counteract any possible blood pressure-lowering effects of the restriction of sodium because it has been shown that the risk of gestational hypertension is inversely associated with the oral intake of calcium (35). Furthermore, many studies on the beneficial effects of calcium supplementation on the outcome of pregnancy were published recently. Supplementation with various doses of calcium during pregnancy reduced vascular angiotensin II sensitivity, prolonged the mean duration of gestation, reduced the incidence of premature delivery, lowered blood pressure, and reduced the incidence of gestational hypertension (36–38).

In conclusion, prolonged rigid dietary sodium restriction in pregnancy reduces the intake of fat, protein, and calcium; tends to reduce the energy intake; limits the maternal weight gain; and reduces the maternal fat stores. It has no major effect on birth weight. Obstetricians, general practitioners, and midwives prescribing sodium-restricted diets to pregnant women should be aware of these unwanted side effects, especially in women who already have poor nutritional status before pregnancy. If dietary sodium restriction is considered necessary, then women must be urged not to reduce the intake of calcium-rich foods such as dairy products or to reduce energy intake.

We acknowledge all the participating women, the nursing and laboratory staff, and T de Bon, Department of Statistical Consultation, for the statistical analysis. We thank the reviewers for the constructive recommendations and the suggestion to consider urinary nitrogen excretion.

REFERENCES

10. Lim M, Mathus-Vliegen BMH. Compendium of diet preparations and